Clinical Trial Protocol
BB-RSP-301

A One Year, Open-label, Study to Evaluate the Safety and Tolerability of Risperidone Implants as a Maintenance Treatment in Patients with Schizophrenia

RISPERIDONE IMPLANT

Date:

Version 4: Amendment #3: July 15, 2016

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IND#: 110143

Sponsor:

Braeburn Pharmaceuticals Inc.

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1. SPONSOR AND KEY PERSONNEL CONTACT INFORMATION

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2. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Braeburn Pharmaceuticals	
Name of Investigational Product: Risperidone Implant	
Name of Active Ingredient: risperidone	
Study Title: A One Year, Open-label, Study to Evaluate the Safety and Tolerability of Risperidone Implants as a Maintenance Treatment in Patients with Schizophrenia	
Principal Investigator: David Walling, Ph.D.	
Study Centers: Up to 15 centers **Countries:** United States	
Study Period: Estimated date first subject enrolled: 15-Mar-2016 Estimated date last subject completed: Oct-2017	**Phase of Development:** Phase 3
Objectives: The primary objective of the trial is to evaluate the 48-week safety and tolerability of Risperidone Implants as maintenance therapy in subjects with schizophrenia. Safety and tolerability will be measured by the incidence of psychotic symptoms exacerbation/impending relapse, PANSS, CGI-I, CGI-S, adverse events, vital signs, clinical laboratory, physical exam and ECG findings, Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Scale (SAS) and Investigator assessments.	
Study Design: Open-label maintenance study of two consecutively administered 6 month Risperidone Implants in the treatment of subjects with schizophrenia.	
Methodology The study consists of a Screening Period, a Conversion Phase, a 48-week Maintenance Treatment Phase and a Follow-up Visit. ***Screening Period (Up to Six Weeks):*** Eligibility for the study will be determined during the Screening period. The Screening period will include psychiatric and medical evaluations, screening tests, physical examination/medical history and other assessments to establish whether the patient meets the inclusion/exclusion criteria for the study. During the Screening period, subjects will be washed out of all prohibited concomitant medications. Subjects receiving an antipsychotic other than oral risperidone (4 mg/day), long acting risperidone injection (37.5 mg/dose), Invega® (6 mg/day)or Invega® Sustenna® (156 mg dose) will be required to enter the Conversion Phase. To enter the 48-week Maintenance Treatment Phase, subjects are required to be taking only one antipsychotic medication: risperidone. Subjects who are receiving oral risperidone (4 mg/day), long-acting risperidone injection (37.5 mg/dose), Invega® (6 mg/day) or Invega® Sustenna® (156 mg dose) at the time of Screening will be eligible to directly enter the 48-week Maintenance Treatment Phase. All other eligible subjects will enter the Conversion Phase.	

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Conversion Phase (Two to Six Weeks):
During the weekly visits in the Conversion Phase, subjects will cross-titrate from other antipsychotic(s) to oral risperidone therapy over a minimum of 2 - 6 weeks. The objective of the oral conversion Phase is for all subjects to achieve an oral risperidone dose of 4 mg by the end of Week 6 of the Conversion Phase.

Maintenance Phase (48 Weeks):
At the beginning of the 48-week Maintenance Treatment Phase, all subjects will receive Risperidone Implants (two, 360 mg or three, 300 mg 6-month implants, each containing risperidone). Oral dosing with risperidone will continue for one day after the subject has received the Risperidone Implants. During the Maintenance Phase, subjects will be evaluated in the clinic and at any unscheduled visits for signs of exacerbation of psychotic symptoms/impending relapse as defined in Section 9.3.1. Subjects (or their caregiver) will be contacted by phone periodically throughout the trial to check-in on the subjects in between on-site visits. The appearance of any clinically significant signs of exacerbation of psychotic symptoms/impending relapse criteria will result in withdrawal from the trial. Additionally, any subject withdrawn for lack of efficacy in the Maintenance Phase per the Principal Investigator has to meet at least one of the criteria for exacerbation of psychotic symptoms/impending relapse.

Number of Subjects (Planned):
Screening Phase – approximately 250 subjects.
Conversion Phase – It is anticipated that approximately 120 subjects will enter the Conversion Phase.
Maintenance Phase – approximately 140 subjects will be implanted.

Study Population: Patients with a diagnosis of schizophrenia as defined by DSM-5 criteria.

Inclusion/Exclusion Criteria:

Inclusion Criteria during Screening Period:

1. Subject has provided written informed consent.
2. Male and female subjects 18 to 70 years of age, inclusive, at time of informed consent.
3. Subjects with a current diagnosis of schizophrenia as defined by DSM-5 criteria and a history of the illness for at least 2 years prior to screening (as per subject, family, healthcare provider, and/or by previous medical records).
4. Subject is assessed by the Investigator to be symptomatically stable with regard to his or her psychiatric condition at screening and baseline.
5. Subject must be stable on their current antipsychotic medication for at least 30 days prior to screening.
6. Subject has identified a caregiver or personal contact with whom the subject has significant contact with at least once per week.
7. Subjects who have shown a previous response to antipsychotic treatment (other than clozapine) in the past year, according to the Investigator's opinion.

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8. Subjects who are currently being treated with one or two antipsychotics other than clozapine, and who, in the Investigator's judgment, require chronic treatment with an antipsychotic medication and would benefit from treatment with Risperidone Implants.

   Note: Subjects taking oral risperidone (4 mg/day), long-acting risperidone injection (37.5 mg/dose), Invega® (6 mg/day) or Invega® Sustenna® (156 mg dose) at the time of Screening can be directly enrolled into the Maintenance Phase of the study.
9. Subjects who meet the following criteria:
   a. Outpatient status
   b. PANSS Total Score ≤ 80, and if PANSS score at baseline increases by ≥ 20% change from screening, the subject cannot participate in the study.
   c. PANSS scores of ≤ 4 on all of the following items:
      • Conceptual disorganization
      • Suspiciousness
      • Hallucinatory behavior
      • Unusual thought content
      • Hostility
   d. CGI-S ≤ 4 (moderately ill)
   e. Lack of clinically significant suicidal ideation or behavior in Investigator's judgment
10. Subjects who are able to understand the nature of the trial and follow protocol requirements, have the ability to read and understand the written word, and who can be reliably rated on assessment scales.
11. Subjects who have completed adequate washout (5 half-lives unless otherwise specified) of prohibited concomitant medications, including mood stabilizers and strong inducers or inhibitors of CYP2D6 activity, prior to receiving oral risperidone or implant Risperidone.
12. Subject has completed washout of 42 days for any fluoxetine containing compound.
13. Female participants (if of childbearing potential and sexually active) and male participants (if sexually active with a partner of childbearing potential) who agree to use a medically acceptable and effective birth control method throughout the study. Medically acceptable methods of contraception that may be used by the participant and/or his/her partner include abstinence, birth control pills or patches, diaphragm with spermicide, condom with spermicide, intrauterine device (IUD), surgical sterilization, or progestin injection. All females of childbearing potential must have a negative serum pregnancy at the screening visit.

    Females of non-childbearing potential must meet the following:
    a. Have medical documentation of surgical sterility OR
    b. Be post-menopausal, defined as 12 consecutive months of amenorrhea and confirmed by a Follicle-Stimulating Hormone (FSH) test.
14. Subject has a body mass index (BMI) ≥18.5 and ≤38.0 kg/m^2.
15. Subject is assessed by the Investigator to be symptomatically stable with regard to pre-existing medical conditions as evidenced by medical history, non-clinically significant

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findings on physical examination, vital signs, clinical laboratory evaluations (hematology, serum chemistries, and urinalysis) or 12-lead electrocardiogram (ECG). Subjects may continue on their current prescribed medication regimens to control pre-existing medical and psychiatric conditions (other than schizophrenia) including the use of prescribed PRN medications.

Inclusion Criteria at entry into the Risperidone Implant 48-week Maintenance Treatment Phase

The subject is tolerating oral risperidone 4 mg/day in the Conversion Phase or the subject directly enters the 48-week Maintenance Treatment Phase because they are receiving at Screening either oral risperidone (4 mg/day), long-acting risperidone injection (37.5 mg/dose), Invega® (6 mg/day) or Invega® Sustenna® (156 mg dose) and meets the following criteria:

a. Outpatient status
b. PANSS Total Score ≤ 80 (if PANSS score at baseline increases by ≥ 20% change from screening, the subject cannot participate in the study)
c. PANSS scores of ≤ 4 on all of the following items:
   • Conceptual disorganization
   • Suspiciousness
   • Hallucinatory behavior
   • Unusual thought content
   • Hostility
d. CGI-S ≤ 4 (moderately ill)
e. Lack of clinically significant suicidal ideation or behavior in Investigator's judgment

Exclusion Criteria

1. Known hypersensitivity or allergy to lidocaine or any local anesthetic agent of the amide type (local anesthetic used during implant and explant procedures).
2. Known sensitivity to polyurethane.
3. Reports or reveals a presence of clinically significant skin disorders (such as, but not limited to, skin cancer, psoriasis, eczema, or atopic dermatitis), and/or evidence of recent sunburn, scar tissue, tattoo, open sore, body piercing or branding at the intended implantation site that would interfere with the implantation procedure or interfere with implant site assessments as determined by the Investigator.
4. History of abnormal scar formation or family history of keloid formation.
5. Subjects with a current DSM-5 diagnosis other than schizophrenia, including schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, amnestic or other cognitive disorders. Also, subjects with borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder are excluded.
6. Subjects experiencing acute depressive symptoms within the past 30 days, according to the Investigator's opinion, that required treatment with an antidepressant.

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7. Subjects considered by the Investigator to be at imminent risk of suicide or injury to self, or subjects who within the past 6 months prior to Screening have attempted suicide, or who within the past 3 months prior to Screening have had active suicide ideation (positive answers to item 4 or 5 on the C-SSRS).
8. Subjects with schizophrenia that are considered resistant/refractory to antipsychotic treatment by history.
9. Subjects with a history of failure to clozapine treatment or response to clozapine treatment only.
10. Subjects with a documented history of failure to respond to an adequate dose of risperidone or paliperidone treatment including long acting injectable formulations.
11. Subjects with a significant risk of violent behavior or a significant risk of committing suicide based on history or Investigator's judgment.
12. Subjects who currently meet DSM-5 criteria for substance use disorder (moderate or severe); including alcohol and benzodiazepines, but excluding caffeine, nicotine, and marijuana.
13. Females who are breast-feeding or will be breast feeding during the course of the study, and/or who have a positive serum pregnancy test result prior to receiving trial medication.
14. Subjects with uncontrolled hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days).
15. Subjects who have a clinically significant history or evidence of a medical condition that would expose them to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial, including but not limited to hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, hematologic, or immunologic disease as determined by the clinical judgment of the Investigator.
16. Subjects with epilepsy or a history of seizures, except for a single childhood febrile seizure, post traumatic, alcohol withdrawal, etc. A subject with a history of any seizure activity will have their case discussed with the medical monitor prior to subject's study enrollment.
17. Subjects with a positive drug screen at screening for drugs of abuse without a prescription, excluding marijuana, will be discussed with the medical monitor. If the subject has a second positive drug screen during the Screening Phase, the Conversion Phase, or at Maintenance Baseline, the subject will be excluded from the trial.
18. The following laboratory test, vital sign, and ECG results are exclusionary:
    a. Platelets $\leq 75{,}000/mm^3$
    b. Hemoglobin ≤ 9 g/dL
    c. Neutrophils, absolute $\leq 1000/mm^3$
    d. Aspartate aminotransferase > 3x upper limit of normal
    e. Alanine aminotransferase > 3x upper limit of normal
    f. Creatinine ≥ 2 mg/dL
    g. Diastolic blood pressure > 105 mmHg

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h. QTc > 470 msec for females and QTc > 450 msec for males using the QTcF (Fridericia) correction

NOTE: Consultation with the medical monitor may allow for retesting. In addition, subjects are excluded if they have any other clinically significant abnormal laboratory tests, vital sign results, or ECG findings that, in the Investigator's judgment, are medically significant or would impact the safety of the subject or the interpretation of the trial results. Criteria are provided in the protocol to assist Investigators in their assessments of results that are potentially medically significant, depending on the subject's medical history and clinical presentation. Abnormal results for laboratory parameters or vital signs will be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. If a repeated ECG has a triplicate corrected QTcF $\leq$ 470 msec for females on the correction that was initially > 470 msec, or if a repeated ECG has a triplicate corrected QTcF $\leq$ 450 msec for males on the correction that was initially > 450msec, the subject could be included in the trial.

19. Subject is HIV positive.
20. Active hepatitis. Subjects with no viral load, no acute inflammation and no clinical necessity for therapy will be allowed, at the discretion of the Investigator.
21. Subjects with a history of an allergic hypersensitivity to antipsychotic agents.
22. Subjects with a history of significant intolerance or who are refractory to antipsychotic agents.
23. Subjects with a history of neuroleptic malignant syndrome.
24. Subjects with clinically significant tardive dyskinesia at screening [any one AIMS item (1-7) with a score >2].
25. Subjects likely to require prohibited concomitant therapy during the trial (see Section 8.6.1).
26. Subjects who require current use of agents that are strong inhibitors (e.g. quinidine) and inducers (e.g. carbamazepine, phenytoin, rifampin, and phenobarbital) of cytochrome P450 2D6.
27. Subjects who have received any investigational agent in a clinical trial within 30 days prior to screening; for investigational drugs with an elimination half-life greater than 15 days, this time period will be extended to 60 days.
28. Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness, or who have ongoing legal issues that could affect their ability to continue to participate in this trial.
29. Subjects who have been hospitalized, including hospitalization for psychosocial reasons, for more than 30 days total in the last 60 days prior to entry into the Screening Phase.
30. Electroconvulsive therapy within 180 days prior to entry into the Screening Phase.
31. Any other finding that, in the Investigator's opinion, would present undue risk to the subject or may confound the interpretation of study results.

Reference Therapy, Dosage and Mode of Administration:

Risperidone Implants inserted every 24 weeks (see Instructions for User)

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Oral risperidone 4 mg (Conversion Phase)

Duration of Study: 14.5 Months

Screening: 45 days

Conversion Phase: 2 - 6 weeks

Maintenance Phase: 48 weeks

Criteria for Evaluation:

Primary Endpoints:

1) Safety parameters will be monitored throughout the study by collection of vital signs, clinical laboratory evaluations, ECGs, physical examinations, implant site assessments, extrapyramidal symptom assessments (EPS), Columbia Severity Scale assessments (C-SSRS), Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), and Barnes Akathisia Scale (BARS), and adverse event (AE) monitoring.
2) Time to discontinuation due to all causes
3) Mean change from baseline to endpoint in PANSS Total Score
4) Mean change from baseline to endpoint in Clinical Global Impression of Severity (CGI-S)
5) Mean change from baseline to endpoint in PANSS positive and negative subscales
6) Mean CGI-I score at endpoint

Secondary Endpoint:

The secondary endpoint of the trial will be the incidence of psychotic symptom exacerbation/impending relapse in the 48-week Maintenance Treatment Phase, defined as meeting any of the following 4 criteria:

1) Clinical Global Impression of Improvement (CGI-I) of ≥ 5 (minimally worse)

AND

- an increase on any of the following individual Positive and Negative Syndrome Scale (PANSS) items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, hostility) to a score > 4 with an absolute increase of ≥ 2 on that specific item since baseline **OR**
- an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, hostility) to a score > 4 and an absolute increase of ≥ 4 on the combined five PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, hostility) since baseline **OR**

2) Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), but excluding hospitalization for psychosocial reasons **OR**
3) Clinically significant suicidal ideation or behavior in Investigator's judgment **OR**
4) Violent behavior resulting in clinically relevant self-injury, injury to another person, or property damage

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Exploratory Endpoint 1) Pittsburgh Sleep Quality Index (PSQI)
Statistical Methods (Data Analysis):
The safety results will be based on the safety population that will include all subjects who receive study medication. The efficacy results will be based on intent-to-treat population that will include all enrolled subjects. The efficacy measures will be summarized at baseline and over time. The safety assessments and AEs will be summarized appropriately.

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5-HT2	5-hydroxytryptamine receptor type 2
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
AIMS	Abnormal Involuntary Movement Scale
AUC	Area Under the Curve
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
C_{max}	Concentration (maximum)
C_{ave}	Concentration (average)
C_{min}	Concentration (minimum)
C_{ss}	Concentration (steady state)
C_{trough}	Concentration (trough)
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CRF	Case Report Form (may include electronic data capture systems or paper forms)
C-SSRS	Columbia-Suicide Severity Rating Scale
D2	Dopamine receptor type 2
dL	Deciliter
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EKG	Electrocardiogram
EPS	Extrapyramidal symptoms
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone

GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for User
IND	Investigational New Drug
IRB	Institutional Review Board
Mg	Milligram
Msec	millisecond
NF	National Formulation
NSAID	Non-steroidal anti-inflammatory
PANSS	Positive and Negative Syndrome Scale
PRN	As needed
PR	Pulse Rate
PSQI	Pittsburgh Sleep Quality Index
QT_c	Q wave, T wave, corrected value
QT_cB	Q wave, T wave, corrected Bazett
QT_cF	Q wave, T wave, corrected Fridericia
SAE	Serious adverse events
SAS	Simpson-Angus Scale
SOC	System organ class

5. INTRODUCTION

5.1. Background

Schizophrenia is a debilitating mental illness estimated to affect 1% of the United States (US) population (Diagnostic, 2000). Men and women are equally affected by the disease although men usually present with the illness in their late teens or early 20s whereas women usually present 10 years later in their late 20s or early 30s (Schultz et al., 2007). The neurotransmitter dopamine is thought to play an important role in the disease as drugs that increase dopamine neurotransmission induce psychosis similar to the positive symptoms of schizophrenia; almost all of the treatments for schizophrenia act to decrease dopamine neurotransmission (Freedman, 2003). Schizophrenia is characterized by positive and negative symptoms as well as disorganized thought which is manifested in patient's speech and behaviors (Diagnostic, 2000). Positive symptoms include hallucinations, voices that converse with, or about the patient, and delusions.

Negative symptoms include lack of emotion, loss of will or drive, and social withdrawal. Disorganized behaviors may lead to difficulty for patients to live normal lives, which includes preparing meals, maintaining employment, or interacting with friends, family, and colleagues (Diagnostic, 2000). The life-long nature of schizophrenia requires long-term treatment and usually involves pharmacological, psychological, and psychosocial treatment strategies. The aim of long-term treatment is to maintain symptom stability, adequately treat any increases in symptoms, maintain or improve daily function and quality of life, and to prevent relapse (Harrison, Goa, 2004). Patients with schizophrenia generally have impaired insight and do not recognize that they have the illness. This lack of insight leads to poor or partial compliance with prescribed medication, which in turn results in reduced treatment efficacy (Urquhart, 1994), earlier relapses, higher psychiatric admissions (Valenstein et al., 2002), reduced quality of life, increased suicide rates (Herings, Erkends, 2003), and a shortened life expectancy (Schultz et al., 2007).

One of the patient-driven reasons for noncompliance is the patient's inability to adhere to daily dosing on a long-term basis. Current depot formulations of antipsychotics only provide medication coverage up to one month. A formulation such as Risperidone Implant provides therapeutic dose levels of risperidone over 6 months and should further enhance patient compliance and therefore improving patient outcomes.

Risperidone, the active pharmacological agent in the Risperidone Implant, was first marketed by Janssen Research Foundation under the brand name Risperdal® (IND 20-272) and was approved in the United States in 1993 and in Europe in 2008 to treat schizophrenia (Van Peer et al., 1996). The mechanism of action of risperidone is believed to be through blockade of both the serotonin 5-hydroxytryptamine receptor type 2 (5-HT2) and dopamine type 2 receptor (D2) (Page et al., 2010).

For adults with schizophrenia, the effective dose range of oral risperidone tablets is 4 to 16 mg/day with a target dose of 4 to 8 mg/day. Extensive experience with risperidone supports favorable efficacy and tolerability with relatively little weight gain, less extrapyramidal side

effects, and the absence of anticholinergic effects compared to older antipsychotic agents (Keks, Culhane, 1999).

Risperidone Implant utilizes a novel drug delivery implant technology (polyurethane polymer technology), that was developed by Endo Pharmaceuticals Solutions Inc. in order to deliver a wide range of drugs and small molecules for an extended period of time. The Risperidone Implant is a subcutaneous implant composed of 300 mg or 360 mg USP grade risperidone, National Formulation (NF) grade croscarmellose sodium, NF grade stearic acid, and biomedical grade polyurethane (Tecoflex® EG-80A). Tecoflex EG-80A is an aliphatic, polyether-based polyurethane membrane that controls the rate of risperidone release. The dimensions of the implant are approximately 38 mm long with an outside diameter of approximately 4 mm. Risperidone is delivered systemically via passive diffusion at an anticipated release rate of 1.2 to 1.5 mg/day (based on 6-month dog data) for a period of up to 6 months (RISI-TR-10-007, Endo Pharmaceuticals, Braeburn Pharmaceuticals, 2010). This release rate is expected to result in achieving similar steady-state trough levels from a 4 mg/day oral dose of risperidone.

The Risperidone Implant is a reservoir-type drug delivery system in which risperidone pellets are enclosed within a sealed, cylindrical polymer membrane, made of Tecoflex EG-80A. The polymer membrane controls the rate of diffusion of the drug substance to provide the release appears superficially to be a pseudo-zero-order however a more detailed analysis of models development is presented in a separate report. The polymer membrane is not intended to exert therapeutic effects although it acts to improve product delivery via controlled release of the drug substance.

The proposed initial indication for the Risperidone Implant is maintenance treatment of schizophrenia in adults. The Risperidone Implant may offer significant advantages over risperidone oral tablets and long-acting depot formulations of antipsychotics (i.e., Risperdal® Consta®) including: 1) reduced pain, anxiety, and risk of infection associated with frequent IM injections; 2) ability to remove the implant if treatment needs to be discontinued urgently, which is not possible with the depot injectable formulation; 3) improved patient compliance, which is expected to lead to improved functional outcomes and reduced relapse rates and EPS; 4) improved convenience for patients and healthcare providers due to less frequent clinic visits; and 5) reduced healthcare costs because of improved functional outcomes, reduced relapse rates, reduced clinic visits for drug dosing, and reduced hospitalizations.

Study EN3342-101 was the first in human study of Risperidone Implants and investigated the pharmacokinetics of a single dose strength implant (375 mg total risperidone; estimated to deliver 1.2-1.5 mg risperidone daily). Patients with schizophrenia participating in the study (n=6) were required to receive a stable 4 mg daily dose of oral risperidone prior to implant placement. The first patient's implant was removed 1 month post-implantation and subsequent patient (n=5) implants were left in place for 3 months.

Plasma concentration of risperidone and its active metabolite 9-OH-risperidone were measured at various time points to determine the pharmacokinetic parameters of the active moiety (risperidone +9-OH risperidone) responsible for risperidone's clinical effects.

Safety was assessed as were pharmacodynamics measures including the Clinical Global Impressions scale and the Positive and Negative Syndrome Scale (PANSS) for schizophrenia.

Following the 4 mg oral dose, the average risperidone C_{trough} concentration was 1.97 ng/mL and 9-OH risperidone was 16.40 ng/mL and the total active moiety (risperidone + 9-OH risperidone) C_{max} and C_{trough} concentrations were 54.36 ng/mL and 18.37 ng/mL, respectively. T_{max} of total active moiety occurred at 2.5 hours following the oral risperidone dose and the AUC_{0-24h} of total active moiety was 681.52 ng/mL•hr. After implantation, the risperidone C_{ave} at 1 month and 3 month were 6.30 ng/mL and 4.42 ng/mL, respectively (with 9-OH risperidone having 12.33 ng/mL and 9.4 ng/mL, respectively). The PK values for the active moiety demonstrated C_{ave} values of 18.62 ng/mL and 14.19 ng/mL for the 1 month and 3 month implant period, respectively. The average AUC_{3-30d} of total active moiety was 540.12 ng/mL•hr and 1262.50 ng/mL•hr for AUC_{3-90d}. For all 6 subjects, the EN3342 (Risperidone Implant) C_{ave} was 81.3% of the oral (C_{trough}) level and 27.5% of the C_{max} values following a daily 4 mg oral dose of risperidone.

In this study there were no serious adverse events (SAEs), nor any discontinuations due to an adverse event (AE). Treatment-emergent adverse events (TEAEs) were either mild or moderate in severity.

CGI-I, CGI-S, PANSS scores were all little changed from baseline and remained stable throughout the 3-month implantation period.

Study EN3342-102 investigated the pharmacokinetics of 3 implant dose strengths (480 mg. n=10 patients, 720 mg n=10 patients, and 960 mg n=10 patients) over a 6 month implantation period. 30 total patients with schizophrenia received implants.

Patients receiving the 480 mg implants were previously stabilized on a 4 mg daily oral dose of risperidone.

Patients receiving the 720 mg implants were previously stabilized on a 6 mg daily oral dose of risperidone.

Patients receiving the 960 mg implants were previously stabilized on an 8 mg daily oral dose of risperidone.

Plasma concentrations of risperidone and its active metabolite 9-OH-Respiridone were measured at various time points to determine the pharmacokinetic parameters of the active moiety (risperidone + 9-OH risperidone) responsible for risperidone's clinical effects.

Safety was assessed as were pharmacodynamics measures including the Clinical Global Impressions scale and the Positive and Negative Syndrome Scale (PANSS) for schizophrenia.

Comparison of oral risperidone and the Risperidone Implants demonstrate that while C_{max} and C_{avg} were higher, C_{trough} for oral risperidone was more comparable to C_{ss} for EN3342 implants at respective dose levels.

The plasma concentrations after 4 mg oral risperidone showed C_{max} of approximately 18 ng/mL for risperidone and approximately 35 ng/mL for 9-OH risperidone and C_{trough} of approximately 2 ng/mL for risperidone and 18 ng/mL for 9-OH risperidone. Additionally, the C_{ave} for the 480 mg risperidone Implant was approximately 5 ng/mL for risperidone and approximately 14 ng/mL for 9-OH risperidone.

Four subjects (13.3%) in the safety population experienced SAEs during the study; 1 subject each (10.0%) in the 480 mg and 720 mg groups and 2 subjects (20.0%) in the 960 mg group. The SAEs were chest pain and pulmonary embolism in the 480 mg group, Psychotic disorder in the 720 mg group, and Psychotic disorder and Schizophrenia in the 960 mg group.

Four subjects experienced adverse events leading to discontinuation. They were Sluggishness and Psychotic disorder in the 960 mg group.

Injury, poisoning and procedural complications were the most common types of TEAEs overall, followed by general disorders and administration site conditions, psychiatric disorders, gastrointestinal disorders, and musculoskeletal and connective tissue disorders. The most common TEAE overall was injection site pain. Injection site haemorrhage, incision site oedema, anxiety and psychotic disorder were also relatively common. Implant site pain, device difficult to use and weight increased were less common, while other TEAEs were each reported in only 1 or 2 subjects, overall.

There were no marked differences in patterns of TEAEs between the 3 treatment groups. Overall, 36.7% of subjects had TEAEs considered to be related to the study drug; and treatment-related TEAEs were somewhat more common in the 2 higher dose groups. Anxiety was the most common TEAE overall, followed by weight increased, sluggishness and device difficult to use.

Most subjects had TEAEs that were considered mild or moderate in severity; the incidence of moderate TEAEs did not appear to be dose-related, although the incidence was slightly higher in the EN3342 960 mg group.

Implantation-related TEAEs (implant site pain, device difficult to use, device breakage and implant site pruritus) were relatively uncommon (<10% of subjects). Incision-related TEAEs (incision site pain, incision site oedema and incision site complications) were somewhat more common, within incidences ranging from 6.7% to 40.0% of subjects overall.

Generally, this safety profile was consistent with what has been observed either with oral risperidone or the implantation procedure itself.

CGI-I and CGI-S scores showed little variation from baseline and remained stable over the 6 month implantation period. PANSS scores were slightly decreased from baseline and remained stable throughout the 6 month implantation period.

5.2. Study Rationale

The current trial is a pivotal Phase 3 trial designed to evaluate the safety and tolerability of the Risperidone Implants (two, 360 mg or three, 300 mg 6-month implants each containing risperidone) administered to adult subjects with a diagnosis of schizophrenia as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). To enter the 48-

week Maintenance Treatment Phase, subjects are required to be taking only one antipsychotic medication: risperidone. Subjects who are receiving oral risperidone (4 mg/day), long-acting risperidone injection (37.5 mg/dose), Invega® (6 mg/day) or Invega® Sustenna® (156 mg dose) at the time of Screening will be eligible to directly enter the 48-week Maintenance Treatment Phase. All other eligible subjects will enter the Conversion Phase with the goal of the stabilizing subjects on 4 mg of oral risperidone.

Subjects who achieve stability during the 2 - 6 week Conversion Phase are eligible to enter the Maintenance Phase and will receive Risperidone Implants (two or three 6-month implants each containing risperidone).

The Risperidone Implant has the ability to improve patient compliance and can therefore decrease the time to relapse and frequency of relapse by delivering a therapeutic dose of risperidone. Two 360 mg Risperidone Implants (720 mg total dose) will deliver, over 24 weeks, comparable C_{min} plasma levels of oral risperidone 4 mg/day. Three 300 mg Risperidone Implants (900 mg total dose) will deliver, over 24 weeks, comparable C_{avg} plasma levels of oral risperidone 4 mg/day. Risperidone 4 mg/day is considered a therapeutic dose in the long term treatment of schizophrenia.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of the study is to evaluate the 48-week safety and tolerability of Risperidone Implants as maintenance therapy in subjects with schizophrenia. Safety and tolerability will be measured by the incidence of psychotic symptoms exacerbation/impending relapse, PANSS, CGI-I, CGI-S, adverse events, vital signs, clinical laboratory, physical exam and ECG findings, AIMS, BARS and SAS rating scales and Investigator assessments.

6.2. Overall Study Design and Plan

This is an open-label maintenance study of two consecutively administered 6 month Risperidone Implants in the treatment of subjects with schizophrenia.

The study consists of a Screening period, a Conversion Phase, a 48-week Maintenance Treatment Phase and a Follow-up Visit.

Screening Period (Up to Six Weeks):

Eligibility for the study will be determined during the Screening period (a maximum of 45 days). The Screening period will include psychiatric and medical evaluations, screening tests, physical examination/medical history and other assessments to establish whether the patient meets the inclusion/exclusion criteria for the study. During the Screening period, subjects will be washed out of all prohibited concomitant medications.

Subjects receiving an antipsychotic other than oral risperidone (4 mg/day), long acting risperidone injection (37.5 mg/dose), Invega® (6 mg/day) or Invega® Sustenna® (156 mg dose) will be required to enter the Conversion Phase.

To enter the 48-week Maintenance Treatment Phase, subjects are required to be taking only one antipsychotic medication: risperidone. Subjects who are receiving oral risperidone (4 mg/day), long-acting risperidone injection (37.5 mg/dose), Invega® (6 mg/day) or Invega® Sustenna® (156 mg dose) at the time of Screening will be eligible to directly enter the 48-week Maintenance Treatment Phase. All other eligible subjects will enter the Conversion Phase.

Conversion Phase (Two to Six Weeks):

During the weekly visits in the Conversion Phase, subjects will cross-titrate from other antipsychotic(s) to 4 mg/day of oral risperidone therapy over 2 - 6 weeks. The objective of the oral Conversion Phase is for all subjects to achieve an oral risperidone dose of 4 mg/day by no later than the end of Week 6 of the Conversion Phase.

Maintenance Phase (48 Weeks):

At the beginning of the 48-week Maintenance Treatment Phase, all subjects will receive Risperidone Implants (two, 360mg or three, 300mg 6-month implants each containing risperidone). Oral dosing with 4 mg Risperidone will continue for one day after the subject has

received the Risperidone Implants. During the Maintenance Phase, subjects will be evaluated per schedule of events in the clinic and at any unscheduled visits for signs of exacerbation of psychotic symptoms/impending relapse as defined in Section 9.3.1. Subjects (or their caregiver) will be periodically contacted by phone between visits per the Investigator's discretion to determine whether or not the scheduled visit should be moved to an earlier time, based upon the subject's clinical need. The appearance of any of the signs of exacerbation of psychotic symptoms/impending relapse criteria will result in withdrawal from the trial. Any subject withdrawn for lack of efficacy in the Maintenance Phase per the Principal Investigator has to meet at least one of the criteria for exacerbation of psychotic symptoms/impending relapse.

6.3. Discussion of Study Design

The study design is intended to evaluate the safety and tolerability for Risperidone Implants in patients with chronic schizophrenia who would benefit from long-term treatment. Two or three Risperidone Implants are inserted every 24 weeks and deliver comparable plasma exposure level of oral risperidone 4 mg/day.

This is a multi-center, open-label study. Screening procedures will be completed during a period of up to 45 days, after which, eligible subjects, aged 18-70 years, will enter into a Conversion Phase or the Maintenance Treatment Phase. Subjects will receive Risperidone Implants twice for 24 weeks each. The second implant will occur in the opposite arm of the originally implanted arm. If the risperidone implants are expelled from the subjects' arm, the subjects will have the risperidone implants removed from the arm and new risperidone implants will be placed into the opposite arm. When the subjects return for their second implant, the subjects will have the risperidone implants implanted into the originally implanted arm. Subjects will be seen per the schedule of events for the duration of the study.

7. SELECTION OF STUDY POPULATION

Approximately 250 subjects will be screened and approximately 140 subjects will be implanted during the Maintenance Phase. Enough subjects will be enrolled to complete 100 subjects and subjects who enter the Maintenance Phase will receive two or three Risperidone Implants twice during the 48 week trial period. The study is planned to recruit at approximately 15 sites in the United States. See Section 11 for a discussion of sample size.

7.1. Inclusion Criteria

Subjects must meet each one of the following inclusion criteria at Screening in order to be eligible for participation in the study:

Inclusion Criteria during Screening Period:

1. Subject has provided written informed consent.
2. Male and female subjects 18 to 70 years of age, inclusive, at time of informed consent.
3. Subjects with a current diagnosis of schizophrenia as defined by DSM-5 criteria and a history of the illness for at least 2 years prior to screening (as per subject, family, healthcare provider, and/or by previous medical records).
4. Subject is assessed by the Investigator to be symptomatically stable with regard to his or her psychiatric condition at screening and baseline.
5. Subject must be stable on their current antipsychotic medication for at least 30 days prior to screening.
6. Subject has identified a caregiver or personal contact with whom the subject has significant contact with at least once per week.
7. Subjects who have shown a previous response to antipsychotic treatment (other than clozapine) in the past year, according to the Investigator's opinion.
8. Subjects who are currently being treated with one or two antipsychotics other than clozapine, and who, in the Investigator's judgment, require chronic treatment with an antipsychotic medication and would benefit from treatment with Risperidone Implants.

   Note: Subjects taking oral risperidone (4 mg/day), long-acting risperidone injection (37.5 mg/dose), Invega® (6 mg/day) or Invega® Sustenna® (156 mg dose) at the time of Screening can be directly enrolled into the Maintenance Phase of the study.
9. Subjects who meet the following criteria:
   a. Outpatient status
   b. PANSS Total Score ≤ 80, and if PANSS score at baseline increases by ≥ 20% change from screening, the subject cannot participate in the study.
   c. PANSS scores of ≤ 4 on all of the following items:
      • Conceptual disorganization
      • Suspiciousness
      • Hallucinatory behavior
      • Unusual thought content

- Hostility

d. CGI-S ≤ 4 (moderately ill)
e. Lack of clinically significant suicidal ideation or behavior in Investigator's judgment

10. Subjects who are able to understand the nature of the trial and follow protocol requirements, have the ability to read and understand the written word, and who can be reliably rated on assessment scales.
11. Subjects who have completed adequate washout (5 half-lives unless otherwise specified) of prohibited concomitant medications, including mood stabilizers and strong inducers or inhibitors of CYP2D6 activity, prior to receiving oral risperidone or implant Risperidone.
12. Subject has completed washout of 42 days for any fluoxetine containing compound.
13. Female participants (if of childbearing potential and sexually active) and male participants (if sexually active with a partner of childbearing potential) who agree to use a medically acceptable and effective birth control method throughout the study. Medically acceptable methods of contraception that may be used by the participant and/or his/her partner include abstinence, birth control pills or patches, diaphragm with spermicide, condom with spermicide, intrauterine device (IUD), surgical sterilization, or progestin injection. All females of childbearing potential must have a negative serum pregnancy at the screening visit. Females of non-childbearing potential must meet the following:
    a. Have medical documentation of surgical sterility OR
    b. Be post-menopausal defined as 12 consecutive months of amenorrhea and confirmed by a Follicle-Stimulating Hormone (FSH) test.
14. Subject has a body mass index (BMI) ≥18.5 and ≤38.0 kg/m^2.
15. Subject is assessed by the Investigator to be symptomatically stable with regard to pre-existing medical conditions as evidenced by medical history, non-clinically significant findings on physical examination, vital signs, clinical laboratory evaluations (hematology, serum chemistries, and urinalysis) or 12-lead electrocardiogram (ECG). Subjects may continue on their current prescribed medication regimens to control pre-existing medical and psychiatric conditions (other than schizophrenia) including the use of prescribed PRN medications.

Inclusion Criteria at entry into the Risperidone Implant 48-week Maintenance Treatment Phase

The subject is tolerating oral risperidone 4 mg/day in the Conversion Phase or the subject directly enters the 48-week Maintenance Treatment Phase because they are receiving at Screening either oral risperidone (4 mg/day), long-acting risperidone injection (37.5 mg/dose), Invega® (6 mg/day) or Invega® Sustenna® (156 mg dose) and meets the following criteria:

a. Outpatient status
b. PANSS Total Score ≤ 80 (if PANSS score at baseline increases by ≥ 20% change from screening, the subject cannot participate in the study)
c. PANSS scores of ≤ 4 on all of the following items:
    - Conceptual disorganization
    - Suspiciousness

- Hallucinatory behavior
- Unusual thought content
- Hostility

d. CGI-S $\leq$ 4 (moderately ill)
e. Lack of clinically significant suicidal ideation or behavior in Investigator's judgment

7.2. Exclusion Criteria

1. Known hypersensitivity or allergy to lidocaine or any local anesthetic agent of the amide type (local anesthetic used during implant and explant procedures).
2. Known sensitivity to polyurethane.
3. Reports or reveals a presence of clinically significant skin disorders (such as, but not limited to, skin cancer, psoriasis, eczema, or atopic dermatitis), and/or evidence of recent sunburn, scar tissue, tattoo, open sore, body piercing or branding at the intended implantation site that would interfere with the implantation procedure or interfere with implant site assessments as determined by the Investigator.
4. History of abnormal scar formation or family history of keloid formation.
5. Subjects with a current DSM-5 diagnosis other than schizophrenia, including schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, amnestic or other cognitive disorders. Also, subjects with borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder are excluded.
6. Subjects experiencing acute depressive symptoms within the past 30 days, according to the Investigator's opinion, that required treatment with an antidepressant.
7. Subjects considered by the Investigator to be at imminent risk of suicide or injury to self, or subjects who within the past 6 months prior to Screening have attempted suicide, or who within the past 3 months prior to Screening have had active suicide ideation (positive answers to item 4 or 5 on the C-SSRS).
8. Subjects with schizophrenia that are considered resistant/refractory to antipsychotic treatment by history.
9. Subjects with a history of failure to clozapine treatment or response to clozapine treatment only.
10. Subjects with a documented history of failure to respond to an adequate dose of risperidone or paliperidone treatment including long acting injectable formulations.
11. Subjects with a significant risk of violent behavior or a significant risk of committing suicide based on history or Investigator's judgment.
12. Subjects who currently meet DSM-5 criteria for substance use disorder (moderate or severe); including alcohol and benzodiazepines, but excluding caffeine, nicotine, and marijuana.
13. Females who are breast-feeding or will be breast feeding during the course of the study, and/or who have a positive serum pregnancy test result prior to receiving trial medication.
14. Subjects with uncontrolled hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days).

15. Subjects who have a clinically significant history or evidence of a medical condition that would expose them to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial, including but not limited to hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, hematologic, or immunologic disease as determined by the clinical judgment of the Investigator.
16. Subjects with epilepsy or a history of seizures, except for a single childhood febrile seizure, post traumatic, alcohol withdrawal, etc. A subject with a history of any seizure activity will have their case discussed with the medical monitor prior to subject's study enrollment.
17. Subjects with a positive drug screen at screening for drugs of abuse without a prescription, excluding marijuana, will be discussed with the medical monitor. If the subject has a second positive drug screen during the Screening Phase, the Conversion Phase or at Maintenance Baseline, the subject will be excluded from the trial.
18. The following laboratory test, vital sign, and ECG results are exclusionary:
    a. Platelets $\leq 75{,}000/mm^3$
    b. Hemoglobin ≤ 9 g/dL
    c. Neutrophils, absolute $\leq 1000/mm^3$
    d. Aspartate aminotransferase > 3x upper limit of normal
    e. Alanine aminotransferase > 3x upper limit of normal
    f. Creatinine ≥ 2 mg/dL
    g. Diastolic blood pressure > 105 mmHg
    h. QTc > 470 msec for females and QTc > 450 msec for males using the QTcF (Fridericia) correction

    NOTE: Consultation with the medical monitor may allow for retesting. In addition, subjects are excluded if they have any other clinically significant abnormal laboratory tests, vital sign results, or ECG findings that, in the Investigator's judgment, are medically significant or would impact the safety of the subject or the interpretation of the trial results. Criteria are provided in the protocol to assist Investigators in their assessments of results that are potentially medically significant, depending on the subject's medical history and clinical presentation. Abnormal results for laboratory parameters or vital signs will be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. If a repeated ECG has a triplicate corrected QTc $\leq$ 470 msec for females on the correction that was initially > 470 msec, or if a repeated ECG has a triplicate corrected QTcF $\leq$ 450 msec for males on the correction that was initially > 450msec, the subject could be included in the trial.
19. Subject is HIV positive.
20. Active hepatitis. Subjects with no viral load, no acute inflammation and no clinical necessity for therapy will be allowed, at the discretion of the Investigator.
21. Subjects with a history of an allergic hypersensitivity to antipsychotic agents.
22. Subjects with a history of significant intolerance or who are refractory to antipsychotic agents.
23. Subjects with a history of neuroleptic malignant syndrome.

24. Subjects with clinically significant tardive dyskinesia at screening [any one AIMS item (1-7) with a score >2].
25. Subjects likely to require prohibited concomitant therapy during the trial (see Section 8.6.1).
26. Subjects who require current use of agents that are strong inhibitors (e.g. quinidine) and inducers (e.g. carbamazepine, phenytoin, rifampin, and phenobarbital) of cytochrome P450 2D6.
27. Subjects who have received any investigational agent in a clinical trial within 30 days prior to screening; for investigational drugs with an elimination half-life greater than 15 days, this time period will be extended to 60 days.
28. Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness, or who have ongoing legal issues that could affect their ability to continue to participate in this trial.
29. Subjects who have been hospitalized, including hospitalization for psychosocial reasons, for more than 30 days total in the last 60 days prior to entry into the Screening Phase.
30. Electroconvulsive therapy within 180 days prior to entry into the Screening Phase.
31. Any other finding that, in the Investigator's opinion, would present undue risk to the subject or may confound the interpretation of study results.

7.3. Qualification Criteria

Each subject will receive a subject identification number after they have signed informed consent. The number will consist of seven digits, where the first two digits are the country number, the second set of two digits is the site number, and the third set of three digits is the patient number. Every subject must sign informed consent prior to any study procedures being conducted. All subjects who are consented will also have their data entered into the electronic data capture (EDC) system. Subjects who are screen failures will only need to have informed consent information, demographics, and reason for screen fail entered.

Subjects will enter either the Conversion or Maintenance Phase after all screening procedures have been performed and eligibility to continue in the study is confirmed. Eligibility will be assessed again at the Baseline Visit for the Maintenance Phase (the end of the Conversion Phase Visit can also serve as the Baseline Visit for the Maintenance Phase). Once eligibility is confirmed, all subjects will receive two or three Risperidone Implants on entry into the Maintenance Phase.

7.4. Removal of Subjects from Therapy or Assessment

A subject is free to withdraw his/her consent and discontinue participation in the study at any time for any reason.

A subject should be considered for withdrawal from the study in the instance of occurrence of psychotic symptom exacerbation/impending relapse in the 48-week Maintenance Treatment Phase, defined as meeting <u>any</u> of the following 4 criteria:

1) Clinical Global Impression of Improvement (CGI-I) of ≥ 5 (minimally worse)

AND

- an increase on any of the following individual Positive and Negative Syndrome Scale (PANSS) items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, hostility) to a score > 4 with an absolute increase of ≥ 2 on that specific item since baseline **OR**
- an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, hostility) to a score > 4 and an absolute increase of ≥ 4 on the combined five PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, hostility) since baseline **OR**

2) Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), but excluding hospitalization for psychosocial reasons **OR**

3) Clinically significant suicidal ideation or behavior in Investigator's judgment **OR**

4) Violent behavior resulting in clinically relevant self-injury, injury to another person, or property damage

NOTE: If the investigator believes this is not a true exacerbation of schizophrenia, upon consultation with the medical monitor the subject may be continued and brought back for an additional assessment of stability within 7 days. If the aforementioned criteria persist after 7 days, the subject should be withdrawn. Additionally, any subject withdrawn for lack of efficacy in the Maintenance Phase per the Principal Investigator has to meet at least one of the criteria for exacerbation of psychotic symptoms/impending relapse.

A subject may also be discontinued from the study, at the discretion of the Investigator and/or sponsor, for any of the following reasons:

- Entered the study in violation of the protocol;
- Safety reasons, including adverse event(s) (AEs);
- Use of unacceptable concomitant medication(s);
- Non-compliance or major protocol violation;
- It is not considered in the best interest of the subject to continue;
- Pregnancy; (NOTE: All positive urine pregnancy test results are confirmed by a 2nd urine pregnancy test. Treated subjects with 2 positive urine tests will discontinue treatment, be withdrawn from the trial, and an immediately reportable event form will be completed).
- Multiple positive urine drug screen or breath alcohol tests. Investigator will use clinical judgment and should discuss with medical monitor. One positive drug screen for drugs of abuse without a prescription, excluding marijuana, during the study will be discussed with the medical monitor. If the subject has a second positive drug screen, the subject will be excluded from the trial;
- Administrative reasons (e.g., termination of enrollment or study).

The Investigator must maintain a record of all subjects who discontinue from the study prior to completion; the reason(s) for study discontinuation will be documented. In the event that a subject chooses to withdraw from the study, the Investigator should make a reasonable attempt to

obtain and record the reason(s) for withdrawal, if possible, although the subject is not obligated to provide such a reason.

In the event that a subject is discontinued while at the clinical site, the early termination procedures shown in the Schedule of Assessments (Table 3) should be performed prior to discharge from the study site. For any case of early discontinuation (whether or not the subject is at the clinical site), the Investigator should ask the subject to return for the Follow-up visit procedures, provided that the subject has not withdrawn consent for those procedures. If a subject refuses to complete early termination procedures and/or the Follow-up visit, this information will be recorded. The implants should be removed whenever possible from all subjects who discontinue in the study

7.5. Study Restrictions

In addition to the inclusion/exclusion criteria described in Section 7, the subject must agree to abide by the following study restrictions:

Fasting the evening prior to blood tests

No recreational drug use

Limiting alcohol use

No blood donations

8. TREATMENTS

8.1. Treatment Administration

Following confirmation of a signed informed consent document, eligibility and entry into the Conversion Phase or Maintenance Phase:

Conversion Phase - Subjects will be converted from their current antipsychotic to oral risperidone 4 mg/day over a minimum of 2 and a maximum of 6 weeks.

Maintenance Phase – approximately 25% of the subjects will receive 2-360 mg and approximately 75% 3-300 mg Risperidone Implants at Baseline (Implant Day) and week 24.

Subjects meeting the criteria to enter the Maintenance Phase will receive Risperidone Implants twice for up to 48 weeks of treatment total.

8.1.1. Implant Insertion and Removal Procedures

All Risperidone implants will be implanted and removed by trained clinicians. The Sponsor will institute the Risperidone Implant Clinical and Procedure Training and Evaluation program to ensure that clinicians who perform the implant insertion and removal procedures meet competency standards. The Sponsor will also provide an Implant Insertion/Removal Instruction for Use slide deck and live training on the instructions for aseptic subdermal insertion and removal of Risperidone implants. Following each implantation the physician will complete a User Input Survey to assess the performance of the investigational Insertion Tool.

Prior to Maintenance Phase, Baseline (Implant Day), subjects will take their oral antipsychotic that day as prescribed and for one day after. In addition, subjects should discontinue any non-steroidal anti-inflammatory (NSAID) or aspirin-containing medications one week prior to and bathe the day of insertion and removal of implants.

Details on Insertion/Removal procedures and training will be provided in the Instructions for User (IFU) and live implant training. Subjects should be monitored closely for AEs and vital signs for at least 30 minutes following insertion by medically qualified study staff.

Subjects will have their implants removed at the end of the Maintenance Phase. If the subject withdraws early or completes the study the implants will be removed during the End of Treatment Visit or as soon as explantation can be scheduled. Should the subject choose to leave the study early and has not had their implants removed due to inability to contact the subject and schedule an appointment, or for whatever reason, the sponsor may utilize a third party to locate the subject to ensure the implants can be removed. Implant removal procedures are described in detail in the IFU. If, upon removal, the Implanting Clinician has difficulty locating the implants, ultrasound may be used to facilitate their localization.

8.2. Identity of Investigational Product(s)

The Risperidone Implant is a sterile subcutaneous implant composed of 6, 60 mg USP grade risperidone pellets (360 mg implant) or 5, 60 mg USP grade risperidone pellets (300 mg implant), Tecoflex EG-80A, an aliphatic, polyether-based polyurethane membrane that controls the rate of risperidone release. The dimensions of the implant are approximately 38 mm long with an outside diameter of approximately 4 mm. The release rate of two 360 mg Risperidone Implants (720 mg total dose) is expected to result in comparable C_{min} steady-state trough levels from a 4 mg/day oral dose of risperidone. The release rate of three 300 mg Risperidone Implants (900 mg total dose) is expected to result in comparable C_{avg} steady-state trough levels from a 4 mg/day oral dose of risperidone.

Each implant is individually packaged in a foil-lined, heat-sealed pouch. Pouched implants are labeled and packaged into an individual Subject Kit (Box). All Implant Kits used in the Maintenance Phase will contain 2, 360 mg or 3, 300 mg Risperidone Implants. Commercially available oral risperidone 2 mg and 4 mg will be provided to subjects in the Conversion Phase.

All containers/packages /boxes of study drug will be clearly labeled with study-specific information meeting all the applicable regulatory/institutional requirements.

8.2.1. Handling, Storage, and Accountability

All study drugs will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions provided to the research site, and applicable regulations.

All Subject Kits should be stored at room temperature (15–25°C / 59–77°F) in a secured area and in accordance with applicable laws, regulations and institutional requirements.

Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed, the running inventory, and the unused quantities returned to the Sponsor's drug supply vendor at the end of the trial. All unused supplies will be checked against the drug accountability records during the study and/or at the end of the study. Subjects will be instructed to return all unused study drugs to the clinical site (oral risperidone; Conversion Phase).

Following implant removal, appropriate disposal of all implants is outlined in the Study IFU.

8.2.2. Dispensing and Administration

The study drug will be dispensed or administered according to applicable standard operating procedures. Details regarding the preparation and administration of the study drugs will be outlined in a study-specific procedure. Only eligible subjects participating in the study will receive the study drug. Only authorized research site staff may supply or administer the study drugs. Once dispensed, study drug may not be relabeled or reassigned for use by other subjects.

8.3. Selection of Doses

Approximately 25% of the total number of subjects enrolled will have two, 360 mg Risperidone Implants inserted. The approximate remaining 75% of the total number of subjects enrolled will have three, 300 mg Risperidone Implants inserted. Two 360 mg Risperidone Implants (720 mg total dose) will deliver, over 24 weeks, comparable C_{min} plasma levels of oral risperidone 4 mg/day. Three 300 mg Risperidone Implants (900 mg total dose) will deliver, over 24 weeks, comparable C_{avg} plasma levels of oral risperidone 4 mg/day. Risperidone 4 mg/day is considered a therapeutic dose in the long-term treatment of schizophrenia. Based on the CATIE study the average daily dose of risperidone is 3.9 mg per day (Lieberman et al, 2005; Lehman, et al., 2004). The study was initiated by implanting patients with two, 360 mg (720 mg total dose) Risperidone Implants with the understanding that the 720 mg Risperidone Implants would deliver, over 24 weeks, comparable C_{min} plasma levels of oral risperidone 4mg/day. After thorough PK modeling, it was later determined, after the study was initiated, that three, 300 mg (900 mg total dose), over 24 weeks, would deliver approximately C_{avg} plasma levels of oral risperidone 4 mg/day. The target dose of the Risperidone Implants is to deliver approximate C_{avg} plasma levels of oral risperidone 4 mg/day and that dose is three, 300 mg (900 mg total dose). Oral risperidone 1 mg to 4 mg/day will be administered at the investigator's discretion in the Conversion Phase.

8.4. Selection and Timing of Dose

During the Conversion Phase subjects will be tapered off their current antipsychotic and titrated to oral Risperidone 4 mg/day administered in the morning without regard to meals. On Baseline of the Maintenance Phase each subject will have two or three Risperidone Implants inserted in the upper portion of one arm. Baseline procedures and insertion of the Risperidone Implants may take place over 24 hours if necessary, but it is preferable that all Baseline procedures occur on the same day as insertion of the Risperidone Implants. On week 24/Day 168 (±4 days) of the Maintenance Phase, the currently inserted Risperidone Implants will be removed and subjects will receive two or three new Risperidone Implants in the opposite arm depending on what dose they received originally.

8.5. Blinding

The entire study is open-label so subjects, physicians, and sponsors will know what product the patients are administered during the course of the study.

8.6. Prior and Concomitant Therapy

All non-study medications, including prescription, over-the-counter, or herbal therapies, used by the subject will be documented for the 45 days prior to Screening and throughout the study. The Investigator will determine if the prior/concomitant medication(s) affect the patient's/subject's eligibility to participate or continue to participate in the study. Any medication the patient takes between Screening and the end of the study, other than the study drug, is considered to be a

concomitant medication. All concomitant medications must be recorded in the electronic case report form (eCRF). Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

8.6.1. Permitted, Prohibited, and Restricted concomitant medications

Medications Prohibited During the Trial

- Potent Cytochrome P450 2D6 inhibitors (fluoxetine, paroxetine, bupropion, quinidine, cinacalcet, ritonavir) and inducers (e.g. carbamazepine, phenytoin, rifampin, and phenobarbital) are prohibited during any Phase of the study. (NOTE: Any fluoxetine containing compound must be washed out for 42 days)
- The use of investigational drugs will be restricted for at least 30 days (or 5-times the half-life of the drug, if known and longer) prior to first study drug administration and throughout the study. NOTE: for investigational drugs with an elimination half-life greater than 15 days, this time period will be extended to 60 days
- Mood stabilizers will be tapered and discontinued in the Screening Period at least 7 days prior to either the Conversion or Maintenance Phase. Mood stabilizers are not permitted during any of the Phases of the study.
- Nutritional supplements and nonprescription herbal preparations with central nervous system effects (e.g., St. John's Wort, omega-3 fatty acids, kava extracts, gamma-aminobutyric should be tapered and discontinued at least 14 days prior to the end of the Screening Period and are not permitted in any of the Phases of the study.

Medications Restricted During the Trial

- Benzodiazepines are allowed during all Phases of the study up to a maximum of 6 mg/day of lorazepam or equivalent.
- Anticholinergics $\leq$ 4 mg/day benztropine or equivalent for EPS are permitted during all Phases of the study.
- Propranolol (for akathisia or tremor) up to a maximum of 60 mg/day is permitted during all Phases of the study.
- Subjects should discontinue any non-steroidal anti-inflammatory (NSAID) or aspirin-containing medications one week prior to insertion and removal of Risperidone implants.
- Antipsychotics are allowed during the Screening Period but are tapered off and converted to oral risperidone during the Conversion Phase. No antipsychotics, other than the Risperidone Implants are permitted during the Maintenance Phase, with the following exception:

  In the instance that the investigator believes that the subject is not experiencing a true exacerbation of schizophrenia (see Section 7.4 above), a supplemental antipsychotic may be used for a maximum of 7 days upon consultation with the medical monitor.

Medications Permitted During the Trial

- Non-benzodiazepine sleep aids are permitted during all Phases of the study

- Non-sedating antihistamines (e.g., loratadine, cetirizine) are the treatment of choice for allergies.

On a case-by-case basis, the Investigator is permitted to allow the use of some concomitant medications, for example, to treat an AE, as long as the Investigator determines that the medication will not affect the patient's/subject's safety or study integrity (e.g., topical medications). Whenever possible, the Investigator should obtain approval from the sponsor's medical monitor prior to administering the medication.

8.7. Treatment Compliance

Subjects will receive implants twice during the study. Subjects will receive 2-360 mg or 3-300 mg Risperidone Implants at the Baseline of the Maintenance Phase and will receive 2 or 3 Risperidone Implants after approximately 168 days (+/- 4 days) in the Maintenance Phase. The implants are inserted into the subject's arm, alternating arms, by a trained study staff member.

During the Conversion Phase subjects will be dispensed a sufficient quantity of oral risperidone to last until the next scheduled study visit (+/- 3 days). Compliance with oral study medication will be monitored by tablet counts. Subjects who are noncompliant with oral study medication, in the Investigator's judgment, are to be counseled on the importance of adhering to the daily administration schedule.

9. STUDY PROCEDURES AND ASSESSMENTS

All study assessments will be performed at the visits and time points outlined in the Schedule of Assessments (Table 1, Table 2, Table 3); the following sections outline the details and procedures associated with the assessments. Other logistical considerations (e.g., sequence of events, assessment windows) will be outlined in study-specific procedures.

Table 1: Schedule of Assessments – Screening and Conversion Phase

Procedure	Screening (-45 days)[a]		Conversion Phase[b,c] (± 3 days)					
		Conversion Day 1°	Week 1 (Day 7)	Week 2 (Day 14)	Week 3 ° (Day 21)	Week 4 ° (Day 28)	Week 5 ° (Day 35)	Week 6 ° (Day 42) / Baseline Maintenance Phase
Written informed consent[d]	X							
Inclusion/Exclusion Criteria	X							X
Medical / Psychiatric history	X							
Antipsychotic medication history[e]	X							
Assessment of substance dependence	X							
Physical examination[f]	X							X
Height	X							
Weight, BMI[g]	X	X						X
Vital signs[h]	X	X	X	X	X	X	X	X
Hematology and chemistry[i]	X	X						X
Urinalysis	X	X						X
HIV, Hepatitis B/C	X							
Pregnancy test[j]	X	X						X
Urine drug screen[k]	X	X		X		X		X
Breath alcohol test[k]	X	X		X		X		X
12-Lead ECG[l]	X							
Concomitant medications	X	X	X	X	X	X	X	X
Adverse Events[m]	X	X	X	X	X	X	X	X
C-SSRS (Baseline)[n]	X							
C-SSRS (Since Last Visit)[n]		X	X	X	X	X	X	X

Procedure	Screening (-45 days)[a]		Conversion Phase[b,c] (± 3 days)					
		Conversion Day 1[e]	Week 1 (Day 7)	Week 2 (Day 14)	Week 3[e] (Day 21)	Week 4[e] (Day 28)	Week 5[e] (Day 35)	Week 6[e] (Day 42) / Baseline Maintenance Phase
4 mg oral risperidone administration		X	X	X	X	X	X	X
Pittsburgh Sleep Quality Index (PSQI)	X							X
SAS	X	X		X		X		X
Barnes Akathisia Scale	X	X		X		X		X
AIMS	X	X		X		X		X
PANSS[p]	X	X		X		X		X
CGI-S	X	X		X		X		X
CGI-I								X[q]

[a] Screening procedures could be performed any time between Day −45 and Day 1 of the Conversion Phase or Baseline of the Maintenance Phase.
[b] Subjects who are receiving monotherapy with protocol accepted doses of oral risperidone, long acting risperidone injection, Invega® or Invega® Sustenna® as their current antipsychotic treatment at screening can proceed directly to baseline of the Maintenance Phase after screening.
[c] The last visit in the Conversion Phase will serve as the Baseline visit for the Maintenance Phase.
[d] Informed consent will be obtained prior to any trial-related procedures.
[e] All antipsychotic medications used within 45 days of screening and any approved long-acting antipsychotic depot formulations given within the one cycle plus 14 days prior to screening (e.g., 2-week cycle plus an additional 14 days for risperidone long-acting injection) or investigational long-acting antipsychotics given within 60 days of screening will be recorded. In addition, the Investigator will record details of the cross-titration that will occur during the Conversion Phase to bring about a stable transition from previous antipsychotic treatment(s) to oral risperidone.
[f] A full physical examination will be performed with the exception of the genitourinary (GU) body system.
[g] BMI will be calculated in kg/m2 from the screening height and baseline weight using one of the following formulae, as appropriate: Weight (kg) ÷ [Height (m)]^2 or Weight (lb) ÷ [Height (in)]^2 x 703.
[h] Vital sign measurements includes body temperature, systolic and diastolic blood pressure, respiratory rate and pulse rate. Blood pressure cuff should be used on the opposite arm of the implant for at least 2 weeks after implant day.
[i] Subjects should fast for a minimum of 10 hours prior to blood draws for screening laboratory assessments. If no fasting blood samples are obtained initially for determining eligibility for the trial, a fasting blood sample should be drawn prior to enrollment.
[j] A serum pregnancy test for βhCG is performed at screening for all women of childbearing potential. Subjects with a positive result are excluded from the trial. Urine pregnancy tests could be performed at any point during the trial if pregnancy is suspected. All positive urine pregnancy test results are confirmed by a 2nd

urine pregnancy test. Treated subjects with 2 positive urine tests will discontinue treatment, be withdrawn from the trial, and an immediately reportable event form will be completed.

[k] A urine drug screen and a breath alcohol test are required at the designated times, but either or both can be conducted at any time during the Phase at the discretion of the Investigator.

[l] ECG recordings will be obtained and evaluated at the investigational site to determine the subject's eligibility and to monitor safety.

[m] Adverse events will be recorded starting at the screening visit.

[n] The C-SSRS (Baseline Version) will be completed for all subjects at the baseline visit; the C-SSRS (Since Last Visit Version) will be completed for all subjects at all subsequent visits as scheduled.

[o] These weekly visits are not required if subject is stable on oral risperidone and meets eligibility requirements for the Maintenance Phase.

[p] PANSS is required at the designated times, but can be conducted at any time during the Phase at the discretion of the Investigator.

[q] Reference point for CGI-I is the baseline of the Maintenance Phase (i.e., last visit of the Conversion Phase or Screening Phase).

Table 2: Schedule of Assessments – Maintenance Phase: Baseline – Week 24

Procedure				Maintenance Phase (Visits ± 4 days)[k]									
	Baseline[a]	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 16	Wk 20	Wk 22	Wk 24
Inclusion/Exclusion Criteria	X												
Phone contact[b]						X		X				X	
Assess criteria for exacerbation of psychotic symptoms/impending relapse			X		X		X		X	X	X		X
Physical examination[c]	X												X
Weight, BMI[d]	X								X				X
Vital signs[e]	X		X		X		X		X	X	X		X
Hematology and serum chemistry[f]	X								X				X
Urinalysis	X								X				X
Urine pregnancy test[g]	X				X		X		X	X	X		X
Urine drug screen[h]	X								X				X
Breath alcohol test[h]	X								X				X
12-Lead ECG													
Concomitant medications	X	X	X	X	X		X		X	X	X		X
Adverse Events	X	X	X	X	X		X		X	X	X		X
Implant palpation and site examination		X	X	X	X		X		X	X	X		X
C-SSRS (Since Last Visit)	X		X		X		X		X	X	X		X

Procedure				Maintenance Phase (Visits ± 4 days)[k]									
	Baseline[a]	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 16	Wk 20	Wk 22	Wk 24
4 mg oral risperidone administration	X[L]												
Study drug implantation / explantation	X[m]												X[m]
SAS	X				X		X		X	X	X		X
Barnes Akathisia Scale	X				X		X		X	X	X		X
AIMS	X				X		X		X	X	X		X
PANSS[i]	X								X				X
CGI-S	X		X		X		X		X	X	X		X
CGI-I[j]	X		X		X		X		X	X	X		X
Pittsburgh Sleep Quality Index (PSQI)	X				X		X		X	X	X		X

[a] The end of the Conversion Phase visit will serve as the Baseline for the Maintenance Phase; therefore, all evaluations noted for "End of the Conversion Phase or Baseline Maintenance Phase" will be performed on the day of administration prior to insertion of the Risperidone Implants. The baseline procedures prior to implanting can occur over 24 hours if necessary, although it is preferred that all procedures occur on the same day as insertion of the Risperidone Implants.

[b] Phone contacts can be made to the patient at the discretion of the Investigator throughout the course of the study. At Week 6, 10, 22, and 30 in lieu of a phone call, an on-site visit can be made to perform the following procedures: C-SSRS, AE and concomitant medication assessment, implant palpation and site examination, vital signs collection, assess criteria for exacerbation of psychotic symptoms/impending relapse.

[c] A full physical examination will be performed with the exception of the genitourinary (GU) body system.

[d] BMI will be calculated in kg/m^2 from the screening height and baseline weight using one of the following formulae, as appropriate: Weight (kg) ÷ [Height (m)]^2 or Weight (lb) ÷ [Height (in)]^2 x 703.

[e] Vital sign measurements includes body temperature, systolic and diastolic blood pressure, respiratory rate and pulse rate. Blood pressure cuff should be on the opposite arm of the implant for at least 2 weeks after implant day.

[f] Subjects should fast for a minimum of 10 hours prior to blood draws for laboratory assessments.

[g] Urine pregnancy tests could be performed at any point during the trial if pregnancy is suspected. All positive urine pregnancy test results are confirmed by a 2nd urine pregnancy test. Treated subjects with 2 positive urine tests will discontinue treatment, be withdrawn from the trial, and an immediately reportable event form will be completed.

[h] A urine drug screen and a breath alcohol test are required at the designated times, but either or both can be conducted at any time during the Phase at the discretion of the Investigator.

[i] PANSS is required at the designated times, but can be conducted at any time during the Phase at the discretion of the Investigator. If relapse occurs or PI suspects that patient will relapse, PANSS should be conducted.
[j] Reference point for CGI-I is the baseline of the Maintenance Phase (i.e., last visit of the Conversion Phase or Screening Phase).
[k] Baseline is Day 1 of the Maintenance Phase. Week 2 is Day 14, Week 4 is Day 28, Week 6 is Day 42, Week 8 is Day 56, Week 12 is Day 84, etc.
[L] Oral risperidone (4 mg) should be administered on baseline day and for one day after implantation.
[m] Subjects should remain on site for at least 30 minutes after the implant has been inserted.

Table 3: Schedule of Assessments – Maintenance Phase: Week 26 – Follow-Up

Procedure				Maintenance Phase (Visits ± 4 days)[k]							
	Wk 25	Wk 26	Wk 27	Wk 28	Wk 30	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48 ET/ Impending relapse	Follow-Up Visit +14 to +28 days after Wk 48
Inclusion/Exclusion Criteria											
Phone contact[b]					X						
Assess criteria for exacerbation of psychotic symptoms/impending relapse		X		X		X	X	X	X	X	
Physical examination[c]										X	
Weight, BMI[d]							X			X	
Vital signs[e]		X		X		X	X	X	X	X	
Hematology and serum chemistry[f]							X			X	
Urinalysis							X			X	
Urine pregnancy test[g]				X		X	X	X	X	X	

Procedure				Maintenance Phase (Visits ± 4 days)[k]							
	Wk 25	Wk 26	Wk 27	Wk 28	Wk 30	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48 ET/ Impending relapse	Follow-Up Visit +14 to +28 days after Wk 48
Urine drug screen[h]							X			X	
Breath alcohol test[h]							X			X	
12-Lead ECG										X	
Concomitant medications	X	X	X	X		X	X	X	X	X	X
Adverse Events	X	X	X	X		X	X	X	X	X	X
Implant palpation and site examination	X	X	X	X		X	X	X	X	X	X
C-SSRS (Since Last Visit)		X		X		X	X	X	X	X	
Study drug explantation										X	
SAS				X		X	X	X	X	X	
Barnes Akathisia Scale				X		X	X	X	X	X	
AIMS				X		X	X	X	X	X	
PANSS[i]							X			X	
CGI-S		X		X		X	X	X	X	X	
CGI-I[j]		X		X		X	X	X	X	X	
Pittsburgh Sleep Quality Index (PSQI)				X		X	X	X	X	X	

[a] The end of the Conversion Phase visit will serve as the Baseline for the Maintenance Phase; therefore, all evaluations noted for "End of the Conversion Phase or Baseline Maintenance Phase" will be performed on the day of administration prior to insertion of the Risperidone Implants.

[b] Phone contacts can be made to the patient at the discretion of the Investigator throughout the course of the study. At Week 6, 10, 22, and 30 in lieu of a phone call, an on-site visit can be made to perform the following procedures: C-SSRS, AE and concomitant medication assessment, implant palpation and site examination, vital signs collection, assess criteria for exacerbation of psychotic symptoms/impending relapse.

[c] A full physical examination will be performed with the exception of the genitourinary (GU) body system.

[d] BMI will be calculated in kg/m2 from the screening height and baseline weight using one of the following formulae, as appropriate: Weight (kg) ÷ [Height (m)]^2 or Weight (lb) ÷ [Height (in)]^2 x 703.
[e] Vital sign measurements includes body temperature, systolic and diastolic blood pressure, respiratory rate and pulse rate. Blood pressure cuff should be used on the opposite arm of the implant for at least 2 weeks after implant day.
[f] Subjects should fast for a minimum of 10 hours prior to blood draws for laboratory assessments.
[g] Urine pregnancy tests could be performed at any point during the trial if pregnancy is suspected. All positive urine pregnancy test results are confirmed by a 2nd urine pregnancy test. Treated subjects with 2 positive urine tests will discontinue treatment, be withdrawn from the trial, and an immediately reportable event form will be completed.
[h] A urine drug screen and a breath alcohol test are required at the designated times, but either or both can be conducted at any time during the Phase at the discretion of the Investigator.
[i] PANSS is required at the designated times, but can be conducted at any time during the Phase at the discretion of the Investigator. If relapse occurs or PI suspects that patient will relapse, PANSS should be conducted.
[j] Reference point for CGI-I is the baseline of the Maintenance Phase (i.e., last visit of the Conversion Phase or Screening Phase).

9.1. Demographics and Other Baseline Characteristics

9.1.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the participant by the Investigator or designated study personnel. The participant must provide written informed consent on an ethics-approved informed consent form (ICF), prior to performing any study-related procedures.

9.1.2. Demographics

The following demographics will be recorded: age (birthdate), sex, race, and ethnicity.

9.1.3. Medical History

A complete medical history will be taken for each patient at Screening (Visit 1) in accordance with the Schedule of Assessments (Flow Chart Table 1). General medical history information will be recorded in the eCRF and will include information relating to any prior or existing medical conditions.

9.1.4. Medication History and Alcohol/Drug Use

All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) taken by the subjects during the 45 days prior to Screening will be recorded in the source documentation as medication history.

All antipsychotic medications used within 45 days of screening and any approved long-acting antipsychotic depot formulations given within the one cycle plus 14 days prior to screening (e.g., 2-week cycle plus an additional 14 days for risperidone long-acting injection) or investigational long-acting antipsychotics given within 60 days of screening will be recorded. In addition, the Investigator will record details of the cross-titration that will occur during the Conversion Phase to bring about a stable transition from previous antipsychotic treatment(s) to oral risperidone.

DSM-5 modules will be included as a part of drug/alcohol use history and used to screen for substance use disorders.

9.2. Eligibility Review and Randomization

Prior to conversion and implantation, subjects must meet all inclusion and not meet any exclusion criteria as outlined in Section 7.1 and 7.2.

The Investigator or designee must document that the subjects meet each individual criterion via a signed note or eligibility and clinical stability checklist during Screening. Signatures on these documents must be dated on or before the date of study drug administration in the Maintenance Phase.

9.3. Study Assessments

9.3.1. Primary Endpoints

1) Safety parameters will be monitored throughout the study by collection of vital signs, clinical laboratory evaluations, ECGs, physical examinations, implant site assessments, extrapyramidal symptom assessments (EPS), Columbia Severity Scale assessments (C-SSRS), Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), and Barnes Akathisia Scale (BARS), and adverse event (AE) monitoring.
2) Time to discontinuation due to all causes
3) Mean change from baseline to endpoint in PANSS Total Score
4) Mean change from baseline to endpoint in Clinical Global Impression of Severity (CGI-S)
5) Mean change from baseline to endpoint in PANSS positive and negative subscales
6) Mean CGI-I score at endpoint

9.3.1.1. Positive and Negative Symptom Scale

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

1) Positive Subscale (7 positive symptom constructs: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility)
2) Negative Subscale (7 negative symptom constructs: blunted affect, emotional withdrawal, poor rapport, passive/apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking)
3) General Psychopathology Subscale (16 symptom constructs: somatic concerns, 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)

All efforts will be made to ensure that the same rater administered the PANSS for a given subject and the number of raters within each trial center is kept to a minimum. Instructions for administering this instrument will be provided to the site. All raters will be required to demonstrate interrater reliability before rating subjects in this trial. A copy of the PANSS assessment with complete rating criteria is required as source documentation. Qualified raters will be required to demonstrate rating proficiency on the PANSS prior to being certified to rate subjects in the trial to ensure continued interrater reliability through the duration of the trial.

PANSS is required at the designated times, but can be conducted at any time during the Phase at the discretion of the Investigator. If relapse occurs or PI suspects that patient will relapse, PANSS should be conducted.

9.3.1.2. Clinical Global Impression – Severity

The severity of illness for each subject will be rated using the CGI-S scale. To assess CGI-S, the rater or Investigator will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" Response choices included: 0 = not assessed; 1 = normal, not ill at all; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients.

9.3.1.3. Clinical Global Impression – Improvement

The efficacy of trial medication will be rated for each subject using the CGI-I scale. 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 to the subject's condition at baseline of the appropriate Phase. In other words, the reference point is the end of the Conversion Phase/baseline of the Maintenance Phase for assessments made during the Maintenance Phase. Response choices included: 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.

9.3.2. Secondary Endpoint

The secondary endpoint of the trial will be the incidence of psychotic symptom exacerbation/impending relapse in the 48-week Maintenance Treatment Phase, defined as meeting any of the following 4 criteria:

1) Clinical Global Impression of Improvement (CGI-I) of ≥ 5 (minimally worse)

AND

- an increase on any of the following individual Positive and Negative Syndrome Scale (PANSS) items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, hostility) to a score > 4 with an absolute increase of ≥ 2 on that specific item since baseline **OR**

- an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, hostility) to a score > 4 and an absolute increase of ≥ 4 on the combined five PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, hostility) since baseline **OR**

2) Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), but excluding hospitalization for psychosocial reasons **OR**

3) Clinically significant suicidal ideation or behavior in Investigator's judgment **OR**

4) Violent behavior resulting in clinically relevant self-injury, injury to another person, or property damage

9.3.3. Exploratory Endpoint

1) Pittsburgh Sleep Quality Index (PSQI)

9.4. Safety Assessments

Safety monitoring will be performed throughout the study for all subjects.

9.4.1. Adverse Events (AEs) and Serious Adverse Events (SAEs)

The Investigator and research site staff are responsible for the detection, documentation, classification, reporting, and follow-up of events meeting the definition of an AE or serious adverse event (SAE). An AE can be any unfavorable and unintended sign (including a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

All AEs will be recorded in the AE eCRF, regardless of causality or severity, following informed consent (at Screening) until the end of the Follow-up period of the study. Pre-existing conditions, diseases, or disorders are not considered AEs unless there is a change in intensity, frequency, or quality.

Appropriate medical intervention should be provided and, if necessary, implants may be removed as clinically indicated.

9.4.1.1. Adverse Event Reporting

All AEs must be entered on the AE CRF, regardless of causality or severity. AEs include new AEs, worsening baseline conditions, clinically significant laboratory findings, disease-related signs and symptoms that were not present at baseline, and any events or findings that the Investigator feels are clinically significant.

Disease-related signs and symptoms that are present at baseline should not be recorded as AEs unless they worsen in severity or increase in frequency.

Information collected concerning AEs will include the following:

Name of the event

Onset date

Resolution date

Severity (i.e., mild, moderate, or severe)

Relationship to study drug

Action and outcome

Relationship to insertion / removal procedure

Seriousness of event

All AEs will be documented and followed from the time the subject has signed the ICF until 14 days after the End of Treatment Visit (i.e., implant removal). All unresolved AEs will be followed for a minimum of 14 days after the participant's final study visit, unless the Investigator's judgment dictates otherwise, the event has resolved or stabilized before the 14-day period, or the participant is lost to follow-up. Serious AEs and AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization.

9.4.1.2. Serious Adverse Events and Serious Unexpected Adverse Events

An SAE is any untoward medical occurrence that at any dose:

Results in death;

Is life-threatening (at the time of the event);

Requires inpatient hospitalization or prolongation of existing hospitalization;

Results in persistent or significant disability/incapacity; or

Is a congenital anomaly/birth defect.

An Important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A serious and unexpected AE is an SAE that is not identified in nature, intensity, or frequency in the risk information set out in the Investigator's Brochure/Product Monograph of the drug.

All AEs requiring hospitalization or prolongation of a pre-existing hospitalization should be reported as SAEs unless they occur greater than 30 days after the End of Treatment Visit. Date and time of hospitalization should be captured.

9.4.1.2.1. Serious Adverse Event Reporting

Serious Adverse Events (SAEs) must be reported to the Sponsor or designee within 24 hours of knowledge of the event. All SAEs that occur while a subject is receiving study drug and within 30 days following the End of Treatment Visit are reportable within 24 hours.

The procedure for reporting an SAE is as follows:

Within 24 hours of knowledge of the event, the site must contact the Sponsor (or designee) by telephone or facsimile to report the event.

The initial report should include all information known at the time of the report (additional information can be reported as discovered). Do not delay the initial reporting in order to obtain resolution or follow-up information.

The site will enter into the electronic database (or fax, if the database cannot be accessed for any reason) an SAE report, or similar form, that includes the following information, as available:

- Subject ID
- Basic demographic information (age, gender, weight)
- Outcomes attributed to the event (death, life-threatening hospitalization [new or prolonged], disability, congenital anomaly, required medical intervention to prevent permanent impairment/damage, etc.)
- Onset date and severity of the event
- Brief description of the event including frequency and severity of symptoms leading to diagnosis
- List of relevant test results and lab data
- Any other relevant history
- Dates of implantation and removal, if applicable
- Whether the study drug was discontinued
- Investigator's assessment of causality

The Medical Monitor or another representative of the Sponsor may contact the Investigator to request additional information regarding the event or to confirm information. All SAEs will be entered on the AE eCRF. The same nomenclature should be used on both the SAE report and the AE eCRF.

Specific instructions for SAE reporting and a copy of an SAE report form will be provided to the sites.

The Investigator is responsible for the complete and timely reporting of all SAEs to the Sponsor (or designee), reporting pertinent follow-up information on the SAE, and notifying the appropriate IRB / Independent Ethics Committee (IEC) of the occurrence of and details surrounding the event. In the event there is a question as to whether the AE is serious, the event should be reported.

9.4.2. Pregnancy

Urine pregnancy tests could be performed at any point during the trial if pregnancy is suspected. All positive urine pregnancy test results are confirmed by a 2nd urine pregnancy test. Treated subjects with 2 positive urine tests will discontinue treatment, be withdrawn from the trial, and an immediately reportable event form will be completed.

Pregnancies among trial participants should be reported to the Sponsor or designee as soon as possible after learning of the event. Follow-up information will be obtained where possible (with the consent of the participant or their partner) regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant (30 days post-birth).

9.4.3. Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood and urine samples will be performed at a selected central laboratory, with the exception of urine pregnancy tests that are conducted at the study site. The central lab will generate laboratory reports and forward them to the clinical site in a timely manner. It is the responsibility of the Investigator to review and sign all lab reports expeditiously, in order to document appropriate safety monitoring of study subjects. The Investigator should sign and date each lab report concurrent with her or his review, and should indicate the clinical significance of each abnormal/flagged value by noting "NCS" (not clinically significant) or "CS" (clinically significant), for example. Notations indicating that a value is clinically significant should also include a brief description of the underlying disease or condition that is associated with the value, e.g., "CS/mild anemia." In general, abnormal, clinically significant laboratory values are expected to be associated with an item recorded in medical history or with an AE.

Blood and urine samples will be collected, processed, and shipped according to instructions from the safety laboratory. Additional laboratory samples may be taken at the discretion of the Investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety. Specific hematology, coagulation, biochemistry, and urinalysis assessments are listed in Table 4.

Table 4: Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Hemoglobin	Sodium	pH
Hematocrit	Potassium	Specific gravity
Red blood cell (RBC) count	Calcium	Ketones
White blood cell (WBC) count	Glucose (fasting)	Protein
White blood cell differential	Carbon Dioxide	Glucose
Platelet count	Chloride	Urobilinogen
	Creatinine	Blood
	Total protein	Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*
	Blood urea nitrogen	
	Phosphorus	
	Albumin	
	Total bilirubin	
	Alanine aminotransferase (ALT)	
	Aspartate aminotransferase (AST)	
	Gamma-glutamyl transferase (GGT)	
	Lactic dehydrogenase (LDH)	
	Alkaline phosphatase	
	Triglycerides	
	Total cholesterol	
	HDL (high-density lipoprotein)	
	LDL (low-density lipoprotein)	
	HDL/Total Cholesterol	
	Follicle stimulating hormone [a]	

[a] Postmenopausal women at Screening only.

In addition to the clinical laboratory tests, pregnancy testing for the presence of β-human chorionic gonadotropin will be performed for all women of childbearing potential. Serum pregnancy tests will be performed at the screening visit, and must be negative prior to study entry. Results of all scheduled urine pregnancy tests will be reported and determined to be negative prior to study continuation and/or dosing.

A blood sample for a serology panel testing for hepatitis B surface antigen, anti-hepatitis C antibodies, and HIV will be performed for all subjects. Only subjects with negative viral serology tests will be eligible for the study. Positive results will be managed according to local regulatory requirements and the site's standard operating procedures.

Any value outside the normal range will be flagged for the attention of the Investigator, who will indicate whether or not a flagged value is of clinical relevance. If one or more values are

questionable, the test(s) may be repeated. If the result of any test (or repeat test, if done) is indicated as clinically relevant in the samples taken during the Screening Period, the subject will not be enrolled into the trial without the permission of the medical monitor. In addition, follow-up unscheduled laboratory assessments are performed on clinically relevant abnormalities. Unscheduled laboratory tests may be repeated at any time at the discretion of the Investigator for appropriate medical care.

The following laboratory test results were exclusionary:

1) Platelet count ≤ 75,000/mm3

2) Hemoglobin ≤ 9 g/dL

3) Neutrophil count, absolute ≤ 1000/mm3

4) Aspartate amino transferase (AST) > 3 x upper limit of normal

5) Alanine aminotransferase (ALT) > 3 x upper limit of normal

6) Creatinine ≥ 2 mg/dL

In addition, subjects are excluded if they have any other abnormal laboratory test result at screening that, in the Investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the trial results.

9.4.4. Urine Drug Screen and Breath Alcohol Testing

Urine drug screens will test for the following drugs of abuse: barbiturates, opiates, amphetamines, cocaine, phencyclidine (PCP) and benzodiazepines.

Breath alcohol testing will be performed according to the site's standard operating procedures. If there is any doubt or concern regarding alcohol use, research site staff may request a breath test for alcohol measures at any time during the study.

9.4.5. Vital Signs

The following vital signs will be assessed in accordance with the Schedule of Assessments (see Table 1, Table 2, Table 3):

- Blood pressure, sitting (systolic and diastolic; mmHg);
- Pulse rate (beats per minute), sitting;
- Body temperature (oral °C).
- Respiratory rate (breaths/min),

Vital signs will be measured at all study visits after allowing the patient to rest in a sitting position for at least five minutes. The blood pressure cuff should be put on the opposite arm of the implant for at least 2 weeks after implant day.

9.4.6. 12-Lead Electrocardiograms

Twelve-lead electrocardiograms (ECGs) will be performed in accordance with the Schedule of Assessments (Table 1, Table 2, and Table 3). ECGs will be performed after the subject has been resting in a semi-supine position for at least 5 minutes. The ECG variables will include ventricular heart rate and the PR, QRS, QT, QTcB and QTcF intervals. The ECGs will be signed and dated by a medically-qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant. In general, abnormal, clinically significant ECGs are expected to be associated with an item recorded in medical history or with an AE.

Additional 12-lead ECGs may be obtained at the Investigator's discretion and are always to be obtained in the event of an early termination. The ECGs are evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The ECG should be repeated if any results are considered to be clinically relevant.

A screening ECG finding of QTc > 470 msec for females and QTc > 450 msec for males using the QTcF (Fridericia) correction is exclusionary (see exclusion criterion #18 in Section 7.2). In addition, subjects are excluded if they had any other abnormal ECG finding at screening that, in the Investigator's judgment, are medically significant in that it would impact the safety of the subject or the interpretation of the trial results.

9.4.7. Physical Examination

Physical examinations will be performed in accordance with the Schedule of Assessments (Table 1, Table 2, and Table 3). A complete physical examination will be conducted with the exception of the genitourinary (GU) body system at Visit 1 (Screening) and the End of Study Visit.

9.4.8. Physical Measurements

Height will be measured at Screening while body weight/BMI will be recorded at Screening, and at scheduled time points (Table 1, Table 2, and Table 3) throughout the Conversion and Maintenance Phases. The following guidelines will aid in the standardization of these measurements:

• The same scale should be used to weigh a given patient throughout the study.

• Scales should be calibrated and reliable; scales should be zeroed just prior to each patient's weigh-in session.

• Weight should be recorded before a patient's meal (if applicable) and at approximately the same time each day.

• A patient should be minimally clothed (i.e., no shoes or heavy over garments).

The BMI (kg/m^2) will be calculated from the screening height and the weight at the current visit using one of the following formulae, as appropriate: Weight (kg) ÷ [Height (m)]^2 or Weight (lb) ÷ [Height (in)]^2 x 703.

9.4.9. Implant Site Examination and Wound Care

Subjects will receive written instructions that explain how to care for the surgical site after implant insertion and removal. Subjects should be informed about care of the implant site and implant site safety, educated about situations where they should seek medical attention, and queried about implant-related AEs. Copies of the wound care information sheets must be reviewed and approved by each site's IRB, prior to providing them to subjects.

Implant site assessments will include monitoring for signs and symptoms of infection, (e.g., pain, tenderness, swelling, erythema, exudate) and tolerability. The presence of the implant will be assessed by palpation in addition to the visual examination at the times indicated in the Schedule of Assessments (Table 2, Table 3). Clinically significant infection, as deemed by the Investigator, resulting from the implant site assessment will be recorded as AEs. If there is scarring, abnormal bleeding, infection etc., at the implant location, non-identifying pictures of the implant location may be taken. If an infection develops at the implant site, the subject will be withdrawn from the study and the implant will be removed. The infection will be treated in accordance with standard medical practice. Once the implant has been removed the subject will be restarted on his/her pre-implant regimen. Additionally, ultrasounds may be performed at the discretion of the Investigator to confirm implant location.

If there is any evidence of removal or attempted removal of the implants, or if the subject confirms the removal of some or all of the implants, the subject will be withdrawn from study and any remaining implant will be removed.

If an expulsion of an implant(s) occurs, and the subject appears to be compliant and wants to continue with the study, the current implant site will have all implants removed and new implants (same dosage strength as original) will be implanted into the opposite arm. If an expulsion occurs, sites are to contact the medical monitor to discuss if oral risperidone should be given to the patient prior to the following implantation.

The Investigator will inform the Sponsor's Medical Monitor of any clinically significant findings related to implant assessments.

9.4.10. Other Assessments

9.4.10.1. Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored throughout the trial using the Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicide events and suicidal ideation and a post baseline "Since Last Visit" evaluation that focuses on suicidality since the last trial visit. The baseline C-SSRS form will be completed at Screening. The "Since Last Visit" C-SSRS form will be completed at all subsequent visits.

9.4.10.2. Simpson-Angus Scale (SAS)

The SAS 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 is rated on a 5-point scale, with a score of one representing absence of

symptoms, and a score of 5 representing a severe condition. The SAS Total Score is the sum of the scores for all 10 items.

9.4.10.3. Abnormal Involuntary Movement Scale (AIMS)

The AIMS 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) are observed unobtrusively while the subject is at rest (e.g., in the waiting room), and the Investigator also makes global judgments on the subject's dyskinesias (items 8 through 10). Each item is 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 addresses the subject's dental status. 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 through 6, extremity movements; and item 7, trunk movements).

9.4.10.4. Barnes Akathisia Rating Scale (BARS)

The BARS consists of 4 items related to akathisia: objective observation of akathisia by the Investigator, subjective feelings of restlessness by the subject, subject distress due to akathisia, and global evaluation of akathisia. The first 3 items are 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 is 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 are observed while they were 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) are also rated. Subjective phenomena are to be elicited by direct questioning.

9.4.10.5. Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score. (Buysse et al., 1989)

10. DATA QUALITY ASSURANCE

This study will be conducted under Good Clinical Practice (GCP) and all applicable regulatory requirements. To ensure compliance, the sponsor or designee may conduct a quality assurance audit, as outlined in Section 10.2.

Actions to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centers; the review of protocol procedures with the Investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use (where applicable); the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as the periodic site monitoring by the sponsor. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples. The sponsor or designee will review source documents for accuracy and completeness during on-site monitoring visits and after their return to the sponsor; any discrepancies will be resolved with the Investigator, as appropriate.

Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in Investigator site termination and regulatory authority notification.

10.1. Data Collection

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, participant diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This study will use electronic data capture (EDC). At a minimum, all data required by the protocol should have supporting source documentation for entries in the EDC system, unless that data can be recorded directly in the EDC system or other device.

All CRFs will be completed by the site staff prior to review by the sponsor's monitor or designated representative. The sponsor's monitor or designated representative will review all source records on-site and compare them to the data collected on the CRF. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture system maintains a full audit trail.

10.2. Study Auditing and Monitoring

Monitoring of the study site (including, but not limited to, reviewing CRFs for accuracy and completeness) will be performed by the sponsor's monitor or designee. The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the sponsor, a regulatory authority, and/or an institutional review board (IRB) may visit the site to perform audits or inspections, including the

drug storage area, study drug stocks, drug accountability records, participant charts and source documents, and other records related to study conduct. The purpose of the sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether the study-related activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, the site's standard operating procedures, GCP guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact the sponsor immediately if contacted by a regulatory agency regarding an inspection.

11. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

11.1. Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan, which will be completed prior to database lock. This document will include more detail of analysis populations, summary strategies, and analysis methodologies. Changes to the statistical analysis plan in the methodologies used for the clinical study report (CSR) will be discussed in the clinical study report.

11.2. Analysis Populations

The study analysis populations will consist of

Enrolled Population: All subjects enrolled into the study.

Safety Population: All subjects who received at least one dose of study medication

Intent-to-treat population: All enrolled subjects.

11.3. Planned Analyses

11.3.1. Subject disposition

Subject disposition will be summarized for the enrolled population, including the number and percent of subjects who are included in each population, who completed the study, and who drop out the study prematurely with the reasons for early termination.

11.3.2. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the enrolled population as well as for the safety population.

11.3.3. Prior and concomitant medication

Prior and concomitant medication will be summarized for the safety population.

11.3.4. Analysis of Safety Assessments (Primary Endpoints)

Study drug exposure will be summarized for the safety population. The following safety measures will be summarized over time:

1) Columbia Severity Scale assessments (C-SSRS), Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), Barnes Akathisia Scale (BARS) and Pittsburgh Sleep Quality Index (PSQI).
2) Time to discontinuation due to all causes
3) Mean change from baseline to endpoint in PANSS Total Score
4) Mean change from baseline to endpoint in Clinical Global Impression of Severity (CGI-S)

5) Mean change from baseline to endpoint in PANSS positive and negative subscales
6) Mean CGI-I score at endpoint

Treatment emerging adverse events are AEs that occurred on or after the first dose of study medication and on or before the last dose of study medication. SAEs that occurred within 4 weeks after the last dose of study medication will also be included.

Adverse events will be coded by primary system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), and summarized by number and percent of subjects in each primary SOC and preferred term. Summaries of these AE subsets will be presented for relationship to trial drug, intensity, seriousness, AEs or SAEs leading to discontinuation. Frequencies for deaths and hospitalizations will also be summarized.

Data for clinical laboratory tests, ECG, vital signs, and physical and implant site examinations will be summarized using standard descriptive and change from baseline statistics. Shift tables and tabular summaries of abnormalities will be provided, where appropriate.

Medications will be coded using the World Health Organization Drug dictionary and summarized using descriptive statistics.

By-subject listings will be provided for all safety data.

11.3.5. Efficacy assessment

The secondary endpoint of the trial will be the incidence of psychotic symptom exacerbation/impending relapse in the 48-week Maintenance Treatment Phase, defined as meeting any of the following 4 criteria:

1) Clinical Global Impression of Improvement (CGI-I) of ≥ 5 (minimally worse)

AND

- an increase on any of the following individual Positive and Negative Syndrome Scale (PANSS) items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, hostility) to a score > 4 with an absolute increase of ≥ 2 on that specific item since baseline **OR**
- an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, hostility) to a score > 4 and an absolute increase of ≥ 4 on the combined five PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content, hostility) since baseline **OR**

2) Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), but excluding hospitalization for psychosocial reasons **OR**
3) Clinically significant suicidal ideation or behavior in Investigator's judgment **OR**
4) Violent behavior resulting in clinically relevant self-injury, injury to another person, or property damage

11.4. Determination of Sample Size

The sample size of approximately 140 subjects will enter the Maintenance Phase to achieve the goal of having 100 subjects with 48 week exposure.

12. STUDY ADMINISTRATION AND INVESTIGATOR RESPONSIBILITIES

Additional details may be outlined in the Clinical Study Agreement (CSA) between the sponsor and the investigational site.

12.1. Regulatory and Ethical Considerations

12.1.1. Ethical Conduct of the Study

The Investigator will conduct the study in accordance with GCP and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the sponsor's representatives and/or regulatory authority's representatives at any time.

12.1.2. Regulatory Authority and Ethics Approval

The investigational site's IRB must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB prior to enrolling participants into the study; written approval from the committee must be received by the sponsor before drug will be released to the Investigator. The Investigator is responsible for submitting all protocol or ICF changes and SAE reports to the IRB according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

In accordance with applicable local regulatory requirements, the Investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her research site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the Investigator and not of the sponsor. The sponsor will be provided with copies of all notifications sent to the IRB.

All relevant correspondence from the IRB will be forwarded by the respective study site to the sponsor in a timely fashion.

In accordance with applicable local regulations, the sponsor or designee will obtain approval from the appropriate regulatory agency prior to a site initiating the study in that country or jurisdiction.

12.1.3. Subject Informed Consent

The Investigator (or authorized designee) will ensure that the participant is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject will receive an IRB-approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided in a language understandable to the participant and must not include any language that waives the participant's legal rights. Prospective participants must also be informed of their right to withdraw consent without prejudice at any time during the study. If the participant chooses to participate, he/she must sign the ICF before any study-related procedures are performed.

Significant changes to the protocol or product safety information may require a revision of the ICF, which must be reviewed and signed by all applicable study participants.

The time that informed consent is obtained must be documented. The Investigator must maintain the original, signed ICF in the participant's source documents. A copy of the signed ICF must be given to the study participant.

12.2. Privacy and Confidentiality

The Investigator is responsible for complying with applicable privacy regulations, per his or her jurisdiction. Only information identified in this protocol will be collected. The information collected will only be used for the purposes identified in this protocol.

To ensure anonymity and to limit disclosure, participants will be assigned a unique identifier at their first assessment. This identifier will be cross-referenced in the participant's chart. The identifier will not contain any potentially identifiable information. An identifier log will be maintained, linking each participant's name to the corresponding identifier. This log will be stored at the research site in a secure location.

The knowledge gained through this study is the property of the sponsor. The sponsor, representatives and affiliated companies of the sponsor, the IRB, and regulatory agencies (such as the United States Food and Drug Administration [FDA]) may inspect medical records related to the study to check the validity and accuracy of the data gathered in this study. Participant medical records (with participant's initials and/or date of birth) may be copied. Confidentiality of participant records will be maintained except where release of information is required by law.

The results of this study will be reported in such a manner that participants will not be identifiable in any way. Published reports or presentations will refer to grouped data or coded individual data and not to any identifiable individuals. Study reports sent to the sponsor or drug regulatory agencies will not include participant names.

By signing the ICF, the participant consents to the collection, access, use, and disclosure of his or her information as described in the ICF document. If a participant withdraws consent, some of the subject's information may still be collected, used, and disclosed by those involved in this study, per applicable laws.

By signing this protocol, the Investigator affirms that he or she will maintain in confidence information furnished to him or her by the sponsor and will divulge such information to his or her respective IRB or IEC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of the sponsor. Please refer to the Clinical Study Agreement (CSA) for details.

12.3. Study and Site Closure

Upon completion of the study, all study data will be provided to the sponsor following review of site study records for completeness, and data clarifications and resolutions. Accounting,

reconciliation, and final disposition of used and unused study drugs, treatment codes, and emergency code break envelopes will be performed, as applicable.

In addition, the sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. The sponsor will promptly inform any other Investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons and will inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator will inform the IRB promptly and provide the study participants with the reason for the suspension or termination. If the study is prematurely discontinued, all study data will be returned to the sponsor.

12.4. Regulatory Documents and Records Retention

The Investigator is responsible for creating and/or maintaining all study documentation required by 21 CFR 50, 54, 56 and 312, ICH E6 section 8, as well as any other documentation defined in the protocol or CSA. The Investigator must provide key documents to the sponsor prior to the start of the study. A complete list of required regulatory documents will be supplied by the sponsor or its representative.

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study for whichever of the following is the longest period of time:

A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or

A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.

The sponsor will notify Investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by the sponsor that the entire clinical investigation (not merely the Investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application/Clinical Trial Authorization or request for marketing approval (New Drug Application/Marketing Authorization Application).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the sponsor.

12.5. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study.

The term “Investigator” used throughout this protocol refers to the principal Investigator and/or qualified sub-Investigators. However, the Investigator may delegate responsibilities to other investigational site personnel. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff have been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the investigational site.

12.6. Protocol Amendments

Approval of a protocol amendment by the Investigator’s IRB must be obtained before implementation of the protocol amendment, unless a change is necessary to eliminate an apparent immediate hazard to the participant or when the change involves logistical or administrative aspects of the study. The protocol amendment must be signed and dated by both the sponsor and the Investigator. The sponsor or designee will submit protocol amendments to the appropriate regulatory authorities, if required.

12.7. Financial Disclosure

Clinical Investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR § 54.2, a clinical Investigator is a listed or identified Investigator or sub-Investigator who is directly involved in the treatment or evaluation of research participants. The term also includes the spouse and each dependent child of the Investigator. In addition, Investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

13. INVESTIGATOR PROTOCOL AGREEMENT PAGE

A ONE YEAR, OPEN-LABEL, STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF RISPERIDONE IMPLANTS AS A MAINTENANCE TREATMENT IN PATIENTS WITH SCHIZOPHRENIA

Version: 4.0

Date: 15-JUL-2016

I have read the protocol and agree that it along with the related Clinical Trial Agreement contain all the details necessary to carry out the study. I will conduct this study according to the protocol and will complete the study in the time agreed. Potential additions or modifications to the study will be by mutual written agreement between the Sponsor and me and will be documented and filed, if required, with the Institutional Review Board and the Food and Drug Administration.

I will provide copies of the protocol and other pertinent information to all individuals responsible to me who will assist in the study.

The Sponsor will have access to source documentation from which case reports have been generated.

Principal Investigator's Name
(please print or type) _____

_____ _____

Principal Investigator's Signature Date

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