BB-PK-103

A PHASE II, OPEN-LABEL PHARMACOKINETIC STUDY IN SCHIZOPHRENIC PATIENTS ON A STABLE DOSE OF 4 MG ORAL RISPERIDONE TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF RISPERIDONE AND 9-HYDROXY (OH)- RISPERIDONE WHEN RISPERIDONE IS ADMINISTERED WITH A SIX MONTH IMPLANT

Date:

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Sponsor:

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SYNOPSIS

Name of Sponsor/Company: Braeburn Pharmaceuticals	
Name of Investigational Product: Risperidone Implant	
Name of Active Ingredient: Risperidone	
Title of Study: A PHASE II, OPEN-LABEL PHARMACOKINETIC STUDY IN SCHIZOPHRENIC PATIENTS ON A STABLE DOSE OF 4 MG ORAL RISPERIDONE TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF RISPERIDONE AND 9-HYDROXY (OH)- RISPERIDONE WHEN RISPERIDONE IS ADMINISTERED WITH A SIX MONTH IMPLANT	
Study center(s): Study will be conducted at approximately 2 centers within the United States.	
Study Period (Planned): Estimated date first subject enrolled: October 2015 Estimated date last subject completed: February 2017 Estimated date last subject completed in safety extension: August 2017	**Phase of Development**: 2
Objectives: <u>Primary</u>: The primary objective of this study is to characterize the pharmacokinetics of 6-month Risperidone Implants containing 300 mg risperidone each compared to an oral 4-mg risperidone tablet. **<u>Secondary</u>:** • To explore the efficacy of Risperidone Implant as assessed by the Positive and Negative Syndrome Scale (PANSS) • To explore the safety of Risperidone Implant as assessed by vital signs, clinical laboratory evaluations, electrocardiograms (ECGs), physical examinations, implant site assessments, extrapyramidal symptom (EPS) assessments, Columbia Suicide Severity Scale (C-SSRS) assessments, Abnormal Involuntary Movement Scale (AIMS), Simpson Rating Scale (SAS), Barnes Akathisia Scale (BARS), and adverse event (AE) monitoring.	

Name of Sponsor/Company: Braeburn Pharmaceuticals
Name of Investigational Product: Risperidone Implant
Name of Active Ingredient: Risperidone
Methodology: The study will be a 6 month, open-label, multiple center study in approximately 60 stable subjects diagnosed with schizophrenia or schizoaffective disorder to evaluate the safety, tolerability, and pharmacokinetics of risperidone and 9-OH-risperidone following implantation of two or three, 300 mg Risperidone Implants. It will be followed by a 6 month safety extension for subjects who agree to receive a second implant. Subjects who are diagnosed with schizophrenia or schizoaffective disorder according to DSM-V and are stable on a daily 4 mg oral dose of risperidone for at least 8 weeks will be recruited into the study. Subjects will be implanted with two or three 300 mg Risperidone Implants. Approximately the first 10 subjects will receive two 300 mg implants; approximately 50 additional subjects will receive three 300 mg implants. All implants will be placed in the inner aspect of the upper arm. Samples for determination of plasma concentrations of risperidone, 9-OH-risperidone and the active moiety (risperidone plus 9-OH-risperidone) will be obtained prior to and after insertion of the Risperidone Implants. The additional 50 subjects who receive the three 300 mg implants will stay in the treatment center for 7 days prior to and 7 days post implantation of the initial Risperidone Implants. Subjects can check in up to 16 days prior to allow flexibility for subject check in. Safety monitoring and pharmacokinetic sampling will be conducted during the in-house period of the study. Scheduled outpatient visits, that will include safety monitoring and pharmacokinetic sampling, will be conducted for the remainder of the implantation period. After 6 months, the first implants will be explanted and subjects may be implanted (at their same dose level) with two or three additional implants for an additional six months in the same site in a safety extension. Again, scheduled outpatient visits that will include safety monitoring will be conducted for the remainder of the implant period. A subset of study participants (approximately 15 subjects) will also have pharmacokinetic sampling during the 7 days following reimplantation, as well as throughout the remainder of the study. A subset of approximately 10 subjects who are re-implanted during the safety extension will be followed with serial monthly ultrasounds for 6 months to characterize ability of high resolution ultrasound to localize implanted rods. Following explantation of the second set of Risperidone Implants, each subject will be converted back to his/her pre-implant oral risperidone dosing regimen. **Number of Subjects (Planned)**: Approximately 10 subjects will receive the two 300 Risperidone Implants (600 mg risperidone) and approximately 50 subjects will receive three Risperidone Implants (900 mg risperidone). A subset of approximately 15 subjects in the 900 mg risperidone group will have additional pharmacokinetic sampling during the 7 days following re-implantation, as well as throughout the remainder of the safety extension.

Name of Sponsor/Company: Braeburn Pharmaceuticals
Name of Investigational Product: Risperidone Implant
Name of Active Ingredient: Risperidone

Diagnosis and Main Criteria for Inclusion:
Inclusion Criteria:

1. Subject (and/or a subject's authorized legal representative) has provided written informed consent
2. Subject has been on a stable dose of 4 mg of oral risperidone for at least 8 weeks
3. Meets the following criteria that is related to subject's stability on current 4 mg risperidone:
    a. Outpatient status
    b. PANSS Total Score ≤ 80 at screening and if PANSS score at baseline is ≥ 20% change from screening, the patients cannot participate in the study.
    c. A score of ≤ 3 on the following PANSS items:
        • Conceptual disorganization
        • Suspiciousness
        • Hallucinatory behavior
        • Unusual thought content
4. Subject has identified a caregiver or personal contact with whom the subject has significant contact with at least once per week
5. Subject is male or female between 18 to 60 years of age.
6. 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, intrauterine device (IUD), surgical sterilization, condoms with spermicide, or progestin injection. All Females of childbearing potential must have a negative serum pregnancy test at the Screening visit. All females of non-child-bearing potential must have the following documentation:
    a) Medical documentation of surgical sterility OR.
    b) Are post-menopausal defined as 12 consecutive months of amenorrhea and confirmed by a Follicle Stimulating Hormone (FSH) test
7. Subject has a diagnosis of schizophrenia or schizoaffective disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) criteria
8. Subject has a body mass index (BMI) ≥18.5 and ≤35.0 kg/m^2
9. Subject is assessed by the Investigator to be symptomatically stable with regard to his or her psychiatric condition at screening and baseline
10. Subject is assessed by the Investigator to be symptomatically stable with regard to pre-existing medical conditions as evidenced by medical history, 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.

Name of Sponsor/Company: Braeburn Pharmaceuticals

Name of Investigational Product: Risperidone Implant

Name of Active Ingredient: Risperidone

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. Hospitalized or required acute crisis intervention for exacerbation of symptoms of Schizophrenia or Schizoid Disorder in the 60 days prior to admission as determined by the Investigator
4. Subject has a history of suicide attempt in the last year, or in the opinion of the investigator is currently at imminent risk of suicide
5. Reports or reveals a presence of clinically significant skin disorders (such as, but not limited to, skin cancer, psoriasis, eczema, or atopic dermatitis), 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
6. History of abnormal scar formation at insertion site or elsewhere on the body or family history of keloid formation
7. Has a current or recent (within 12 months) DSM-V diagnosis of moderate or severe substance use disorder (except for tobacco use disorder) or has a positive urine drug screen for prohibited substances at screening.
8. Have impaired hepatic (ALT/AST >1.5 times higher than the upper limit of normal) or renal function (eGFR<50 mL/min)
9. Previously defined hypersensitivity to risperidone
10. History of neuromalignant syndrome (NMS)
11. Electroconvulsive therapy within 6 months of admission
12. Requires current use of agents that are strong inhibitors and inducers of cytochrome P450 2D6
13. Current diagnosis of Acquired Immune Deficiency Syndrome (AIDS) and active hepatitis. Subjects with no detectable viral load, no detectable acute inflammation and no clinical necessity for HIV therapy will be allowed, at the discretion of the Investigator.
14. Participation in the treatment phase of a clinical study or receipt of an investigational drug within 30 days prior to study drug administration on Day 1; for investigational drugs with an elimination half-life greater than 15 days, this time period will be extended to 60 days
15. Prior participation in a risperidone study within the last 6 months
16. Involvement in the planning and/or conduct of the study (applies to both Braeburn staff or staff at the investigational site)

Name of Sponsor/Company: Braeburn Pharmaceuticals
Name of Investigational Product: Risperidone Implant
Name of Active Ingredient: Risperidone
17. History of difficulty with phlebotomy procedures
Investigational Product, Dosage, and Mode of Administration: 2x or 3x Risperidone Implant 300 mg risperidone, 4 mg, oral tablet
Reference Therapy, Dosage, and Mode of Administration: None
Duration of Treatment: Approximately 56 weeks, up to 50 weeks of Risperidone Implant.
Criteria for Evaluation: Pharmacokinetics: Blood samples for pharmacokinetic assessment of risperidone and 9-OH-risperidone plasma concentrations will be obtained for the oral risperidone dose and for the Risperidone Implants. The following pharmacokinetic parameters will be determined for risperidone, 9-OH-risperidone, and active moiety (risperidone + 9-OH-risperidone) after the 4 mg oral dose of risperidone on Day -1: AUC_{0-24h}, C_{avg}, C_{max}, C_{trough}, and T_{max}. The following parameters will be determined for risperidone, 9-OH-risperidone and active moiety following the Risperidone Implants: $AUC_{3\text{-}180\ days}$, $AUC_{3\text{-}t}$ (where t represents the duration of pharmacokinetic sampling in subjects not completing the 180 day sampling schedule), AUC monthly for each month of the 6 month periods, C_{avg} monthly for the each month of the 6 month period, $C_{avg\ 3\text{-}180\ days}$ and $C_{avg\ 3\text{-}t}$. The C_{avg} values for risperidone, 9-OH-risperidone and active moiety over time will be calculated as their respective AUC value divided by the number of days over which the data was collected. In the event a subject discontinues during the implantation period $AUC_{3\text{-}t}$ and C_{avg} will be assessed, if determined evaluable by the pharmacokineticist. Efficacy Assessment: Positive and Negative Syndrome Scale (PANSS) will be summarized using appropriate descriptive statistics for pharmacokinetic population. Safety: 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 Suicide Severity Scale assessments (C-SSRS), Abnormal Involuntary Movement Scale (AIMS), Simpson Rating Scale (SAS), and Barnes Akathisia Scale (BARS) and adverse event (AE) monitoring.

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Name of Active Ingredient: Risperidone

Statistical Methods:
Approximately 40 will provide over 90% power to establish that implant is non-inferior to the oral 4 mg dose of risperidone. In the sample size calculation it was assumed that the true ratio was 1.1 and the coefficient of variance (CV) was less than 0.45. These assumptions were based on internal data. Therefore, approximately 50 subjects will be enrolled to ensure approximately 40 subjects completing the study assuming that the drop rate is less than 20%.

Analysis Populations: Safety population will consist of all subjects who have received any study medication.

The pharmacokinetic (PK) population will consist of subjects who receive 4 mg oral risperidone daily and the Risperidone Implant.
Pharmacokinetic Analyses: All pharmacokinetic results (concentration and pharmacokinetic variables) will be summarized using appropriate descriptive statistics where applicable. The total active moiety will be considered the primary interest. The ratios of Risperidone Implant C_{avg} over oral $C_{max,}$ over the oral C_{avg} and over the oral C_{trough} will analyzed based on log-transformed scales using an ANOVA model with treatment effects. The two sided 95% confidence intervals will be presented.
Safety/Tolerability Analyses: The frequency of AEs will be tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred terms and treatment for each cohort. The maximum intensity and frequency of AEs will also be summarized by treatment and cohort.
Vital sign measurements, clinical laboratory evaluations, assessment of implant site, EPS assessment and ECGs will be summarized by treatment and study day (visit) using descriptive statistics or frequency distribution, as appropriate.

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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
5-HT2	5-hydroxytryptamine receptor type 2
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
API	Active Pharmaceutical Ingredient
$AUC_{0\text{-}24h}$	area under the plasma concentration-time curve from time zero to 24 hours post-dose of the oral tablet (Day -1 dose)
$AUC_{3\text{-}180days}$	area under the plasma concentration-time curve from Day 3 to 180 post-implantation
$AUC_{3\text{-}t}$	area under the plasma concentration-time curve from Day 3 to the last collected sample (post-implantation) for subjects who do not complete the 180 pharmacokinetic sampling period
BARS	Barnes Akathisia Rating Scale
BLQ	Below the limit of quantification
BMI	Body mass index
C_{avg}	average steady-state concentration
C_{max}	observed maximum concentration
C_{ss}	plasma concentrations at steady-state
C_{trough}	trough concentration
CNS	Central nervous system
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P-450 system
CYP3A4 - 2D6	Cytochrome P450, family 2, subfamily D, polypeptide 6
D2	Dopamine receptor type 2
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	Electrocardiogram
eCRFs	electronic case report forms
EDC	electronic data capturing
EM	Extensive metabolizers
EPS	Extrapyramidal symptoms
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
anti HCV	Hepatitis C Antibody
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

IM	Intramuscular
IRB	Institutional Review Board
LC-MS/MS	liquid chromatography-tandem mass spectrophotometry
LOE	Lack of efficacy
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NF	National Formulation
NMS	neuromalignant syndrome
OTC	Over-the-counter
PANSS	Positive and Negative Syndrome Scale
PK	Pharmacokinetics
PM	Poor metabolizers
PT	Preferred term
SAE	Serious adverse event
SAS	Simpson-Angus Scale
SC	Subcutaneous
SOC	System organ class
T_{max}	Time to maximum concentration
ULN	Upper limit of normal reference range

1 INTRODUCTION

1.1 Background

Schizophrenia is a chronic debilitating mental illness, which is estimated to affect 0.4% to 0.71% of the population (Goldner et al., 2002). 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 (Castle et al, 1991). The course of schizophrenia is typically characterized by episodes of psychotic behaviors occurring at varying intervals between periods of relative symptomatic stability. The symptoms may involve multiple psychological realms, such as perception (hallucinations), ideation, reality testing (delusions), thought processes (loose associations), feeling (flatness, inappropriate affect), behavior (catatonia, disorganization), attention, concentration, motivation (avolition, impaired intention and planning), and judgment. These psychological and behavioral characteristics are associated with a variety of impairments in occupational or social functioning. Although there can be marked deterioration with impairments in multiple domains of functioning (e.g., learning, self-care, working, interpersonal relationships, and living skills), the disorder is noted for great heterogeneity across persons and variability within persons over time.

Patients with schizophrenia usually do not return to baseline functioning, and there is often further deterioration after each relapse. Prevention of future exacerbations is a critical goal of therapy, and patients who stay on continual treatment are more likely to achieve better outcomes. 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 their prescribed medication which in turn results in reduced treatment efficacy, earlier relapses, higher psychiatric admissions, reduced quality of life, increased suicide rates, and a shortened life expectancy. An estimated 50% of patients do not adhere to prescribed medication regimens for a variety of reasons. The lack of compliance leads to increased morbidity, decreased quality of life, and consequently, an associated increase in healthcare costs. 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 antipsychotic 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 improve patient outcomes

Risperidone, the active pharmacological ingredient (API) in the Risperidone Implant, was first marketed by Janssen Research Foundation under the brand name Risperdal® (NDA 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). Risperidone is also marketed by the Janssen Research Foundation as a depot intramuscular injection under the brand name Risperdal CONSTA® (NDA21-346). Three dosage strengths are marketed (25 mg, 37.5 mg and 50 mg) given every 2 weeks; following this regimen, plasma concentrations during the dosing interval are maintained within the range achieved by oral therapeutic doses of risperidone. The steady state average exposure of the 25 mg and 50 mg intramuscular depot injections (Risperdal CONSTA) and the corresponding daily administration of 2 mg and 4 mg oral tablets, respectively, were comparable.

Risperidone Implant utilizes a novel drug delivery implant technology (polyurethane polymer technology), that had been 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 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 50 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, 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.

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 6 mg/day.

Additional information about the Risperidone Implant can be found in the Investigator’s Brochure/Prescribing Information.

1.1.1 Summary of Nonclinical Findings and Safety

The endocrine, central nervous system (CNS), and cardiovascular effects of risperidone have been characterized as part of the original Risperdal® New Drug Application (NDA 20-272) (Risperdal NDA 20-272, 1993). The safety and efficacy of risperidone have also been demonstrated in acute, sub chronic and chronic toxicity, reproductive and developmental toxicity, genotoxicity, and carcinogenicity studies in support of the original Risperdal NDA 20-272 (Risperdal NDA 20-272, 1993). Findings in these studies were consistent with the proposed mechanism of action, i.e., antagonism of 5-HT2 and dopamine receptor type 2 (D2) of risperidone.

Comprehensive biocompatibility testing of Tecoflex EG-80A implant was performed in

accordance with ISO 10993 requirements for a permanent, tissue contact implantable biomaterial. Testing included acute toxicity, genotoxicity, local tolerance, cytotoxicity, implantation, and pyrogenicity. Extracts of blank Tecoflex EG-80A were not systemically toxic, mutagenic, cytotoxic, or pyrogenic, and did not elicit a dermal sensitization response. Extracts of blank Tecoflex EG-80A were not irritating when injected intradermally in rabbits and subcutaneous (SC) implantation of empty Tecoflex EG-80A implants for up to 6 months in dogs, 4 weeks and 6 months in rats , or 36 weeks in rabbits were very well tolerated systemically, and did not elicit an adverse local reaction.

The safety of risperidone and empty (blank) Tecoflex EG-80A implant was demonstrated in the 3- and 6-month toxicity studies in Beagle dogs. There was no systemic toxicity observed with empty (blank) Tecoflex EG-80A implants in both studies. In both studies, findings related to the perturbations of the pituitary-reproductive axis, consistent with the previously reported effects of risperidone, have been observed with Risperidone Implants. In the 3-month dog toxicity study, chronic inflammation (mild to severe) was noted microscopically at the implantation site in 1 of 8 blank Tecoflex EG-80A animals and two (2) of 8 Risperidone Implant animals. The inflammatory changes were consistent with infection, and not indicative of a local reaction to Tecoflex.

In the 6-month dog toxicity study, blank Tecoflex implant-related findings included local dark red area noted at primary necropsy in one animal, mild to severe fibrosis, minimal to mild chronic-active inflammation, and minimal to moderate hemorrhage at the implant sites. At the end of recovery, only mild fibrosis and minimal brown pigment were observed microscopically in 1 out of 4 blank implant animals, indicating local implant site recovery. At the primary necropsy, dark red and yellow areas at the implant site were observed in 1 male in the risperidone group. These observations were considered potentially related to the implant. Microscopic findings of mild to severe fibrosis, minimal hemorrhage, minimal to mild chronic-active inflammation, and minimal to mild brown pigmentation at the implant sites were noted in the risperidone group. At the end of recovery, only minimal fibrosis and mild brown pigment were observed in 1 out of 4 risperidone group animals, indicating local implant site recovery. These findings indicate implant biocompatibility with no toxic leachables and no biodegradation of either blank Tecoflex or risperidone-containing Tecoflex implants. No particles or foreign body reaction to particulate were identified in any of the implant sites indicating that biodegradation, by any mechanism, with loss of integrity of the devices was not present. Histological evaluation of the recovery necropsy implantation sites and recovery necropsy-incision sites showed no inflammation, granulation tissue, foreign body reaction, or fibrous capsule formation. These findings indicate reversibility of the inflammatory and wound healing responses following removal of the implant, and no persistence or delayed occurrence of test article-related effects.

The effects of age, moderate and severe renal impairment, and liver disease on the pharmacokinetics of risperidone and 9-OH-risperidone have been evaluated (Snoeck et al., 1995). The elimination rate and clearance of 9-OH-risperidone was reduced in the elderly and patients with renal disease because of a diminished creatinine clearance, while the PK of risperidone in the elderly and cirrhotic patients were comparable to those in young patients. The total clearance of oral risperidone was reduced in patients with renal disease. Based on the pharmacokinetics of the active moiety, a dose reduction and a cautious dose titration in the

elderly and in patients with renal disease is recommended (Snoeck et al., 1995). In patients with cirrhosis of the liver, the single-dose pharmacokinetics were comparable to those in healthy young subjects, thus no dose adjustment is required.

1.1.2 Pharmacokinetics and Drug Metabolism in Humans

The PK and metabolism of the active ingredient risperidone, has been extensively studied in human subjects, patients with schizophrenia, and patients with bipolar disorders. In addition, the PK of risperidone has been evaluated in subjects with impaired hepatic and renal function (Snoeck et al., 1995).

Risperidone metabolism in humans, as well as in rats and dogs, results in the formation of an active metabolite, 9-OH-risperidone. In humans, this metabolite has a different PK profile (longer half-life: 20 hours versus 3 hours compared with risperidone), but has in vitro pharmacological and potency profiles comparable to that of risperidone (Mannens et al., 1993). For this reason, the sum concentrations of risperidone and 9-OH-risperidone are generally considered the "active drug moiety."

The hydroxylation of risperidone to the 9-OH metabolite is catalyzed mainly by cytochrome P-450 system (CYP) 2D6, a polymorphically expressed CYP in humans. The ratios of risperidone to 9-OH-risperidone in plasma and urine differ in humans phenotyped as extensive metabolizers (EMs) or poor metabolizers (PMs) of debrisoquine or dextromethorphan (Mannens et al., 1993; Huang et al., 1993).

Following an oral dose of ^{14}C-risperidone to healthy subjects, Mannens et al., 1993 found that in the urine of EM subjects, only 3.5% of the dose was the parent compound, while 30% of the dose was recovered in the urine of PM subjects (Mannens et al., 1993). Although the primary elimination pathway of risperidone is through metabolism, the active metabolite 9-OH-risperidone is primarily eliminated by renal excretion. In urine, 9-OH-risperidone represented 32% of the dose in the EM, but only 8% in the PM. Other metabolites, of far less importance, were detected in urine. Only 3% to 5% of the dose could be identified as glucuronide conjugates in urine, indicating that glucuronidation is a minor metabolic pathway (Mannens et al., 1993).

After intravenous dosing, risperidone plasma concentrations fell in a biphasic manner with a distribution half-life of 6 minutes followed by a terminal half-life of 3 hours in EM and 17 to 22 hours in PM. The apparent volume of distribution of risperidone (1.1 L/kg) was independent of the metabolic phenotype. Renal clearance of risperidone represented 3% of the total clearance in the EMs (394 mL/min), and about 20% of the total clearance in the PMs (54 mL/min) (Huang et al., 1993). Although the clearance of risperidone differed by 7-fold between EMs and PMs, the plasma AUC and also the clearance of the active moiety differed only by 20% between PMs and EMs because the EMs extensively form the active metabolite (Van Peer et al., 1996). The terminal half-life of the active moiety averaged 20 hours (Huang et al., 1993).

The effects of age, moderate and severe renal impairment, and liver disease on the pharmacokinetics of risperidone and 9-OH-risperidone have been evaluated (Snoeck et al., 1995). The elimination rate and clearance of 9-OH-risperidone was reduced in the elderly and patients with renal disease because of a diminished creatinine clearance, while the PK of risperidone in the elderly and cirrhotic patients were comparable to those in young patients. The

total oral clearance of risperidone was reduced in patients with renal disease. Based on the pharmacokinetics of the active moiety, a dose reduction and a cautious dose titration in the elderly and in patients with renal disease is recommended (Snoeck et al., 1995). In cirrhotic patients, the single-dose pharmacokinetics was comparable to those in healthy young subjects, thus not requiring dose adjustment.

1.2 Previous Human Experience

Endo has completed two clinical studies, first a 3-month first in human Phase 1 study (EN3342-101) in 6 subjects diagnosed with schizophrenia whose disease was maintained with a daily 4 mg oral dose of risperidone. In this study there were no serious adverse events (SAEs), or discontinuations due to an AE occurred. Adverse events were reported in five (5) of the 6 enrolled subjects. There was 1 treatment-emergent adverse event (TEAE) of erectile dysfunction. The AE reported included incisional site pain, paresthesia, and hypoesthesia in the arm of the implantation, constipation, arthralgia, join swelling, worsening of extrapyramidal disorder, worsening of schizophrenia, and suicidal ideation. The PK data indicated that the active moiety C_{ave} from the risperidone Implant over a 3-month period averaged approximately 77% of the subjects' oral risperidone C_{trough} level. The implants used in Risperidone Implant-101 contained 375 mg risperidone.

The second study was another Phase 1 study with a 6-month in duration in 35 subjects (EN3342-102) study, including 5 subjects who only received oral risperidone and discontinued prior to receiving EN3342 implants, and there were 10 subjects each in the 480 mg, 720 mg, and 960 mg Risperidone Implant doses/treatment groups. The most common TEAE overall was injection site pain (40.0%), which occurred in 1 subject (10.0%) in the EN3342 480 mg group, 7 subjects (70.0%) in the 720 mg group and 4 subjects (40.0%) in the 960 mg group. Injection site hemorrhage, incision site edema, anxiety and psychotic disorder were also relatively common (occurring in 13.3%) of subjects overall. Implant site pain, difficult device use and weight increased were reported in 10.0% of subjects overall, while other TEAEs were each reported in only 1 or 2 subjects, overall. There was no discernible difference in patterns of TEAEs between the 3 treatment groups, other than possibly a higher incidence of implantation-type events in the 720 mg group, and a higher incidence of psychotic disorder in the 960 mg group (30.0% of subjects vs. 10% in the 720 mg group and 0% in the 480 mg group). Comparison of oral risperidone and the Risperidone Implants demonstrate that while C_{max} and C_{avg} were higher in oral risperidone, C_{trough} for oral risperidone was more comparable to C_{ss} for EN3342 implants at respective dose levels.

Summary of Selected Pharmacokinetic Parameters of the Active Moiety (risperidone + 9-OH-risperidone) (Pharmacokinetic Population)

Treatment Group	Oral risperidone				EN3342
	C_{max} (ng/mL)	AUC_{0-24h} hr*(ng/mL)	C_{avg} (ng/mL)	C_{trough} (ng/mL)	C_{ss} (ng/ml)
480 mg EN3342 (4 mg oral)	53.3	724.6	34.4	19.6	19.1
720 mg EN3342 (6 mg oral)	82.8	1203	56.2	29.7	31.0
960 mg EN3342 (8 mg oral)	80.6	1177	54.9	32.8	32.7

$AUC_{0\text{-}24h}$=area under the concentration versus time curve from time 0 to 24 hours after oral dose; C_{avg}=average steady-state concentration; C_{max}=observed maximum plasma concentration; C_{ss}=plasma concentration at steady-state; C_{trough}=plasma concentration at 24 hours following an oral dose risperidone.

1.3 PK Model Summary

All PK data (risperidone, 9-OH-risperidone, and total active drug) from study EN3342-102 could be modeled. Total active drug concentration (risperidone + 9OH-risperidone) is the best representation of compound activity. EN3342 PK data show an immediate release of risperidone once implanted consistent with a single day's dose, then constant (the release appears superficially to be a pseudo-zero-order however a more detailed analysis of models development is presented in a separate report) delivery of risperidone over a 180-day period. PK modeling comparisons of EN3342 three 300 mg Risperidone Implants (900 mg risperidone) to daily oral risperidone 4 mg dosing suggests EN3342 maintains concentrations above C_{trough} and below C_{max}, and comparable to C_{avg} over 180 days and which is being tested in this clinical study.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Primary Objective

The primary objective of this study is to characterize the pharmacokinetics of 6-month Risperidone Implants containing 300 mg risperidone each compared to an oral 4-mg risperidone tablet

2.2 Secondary Objectives

The secondary objectives are:

- To explore the efficacy of a Risperidone Implant as assessed by the Positive and Negative Syndrome Scale (PANSS)
- To explore the safety of Risperidone implant as assessed by vital signs, clinical laboratory evaluations, electrocardiograms (ECGs), physical examinations, implant site assessments, extrapyramidal symptom (EPS) assessments, Columbia Suicide Severity Scale (C-SSRS) assessments, Abnormal Involuntary Movement Scale (AIMS), Simpson Rating Scale (SAS), Barnes Akathisia Scale (BARS), and adverse event (AE) monitoring.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan: Description

The study will be a 26 week, open-label, multiple sites, Phase 2 study in stabilized subjects with schizophrenia or schizoaffective disorder to evaluate the PK of risperidone its active metabolite, 9-OH-risperidone and the active moiety (risperidone plus 9-OH risperidone) following implantation of the Risperidone Implants. A 24 week safety extension will follow. Subjects diagnosed with schizophrenia or schizoaffective disorder who are stable on a daily dose of 4 mg oral risperidone will be recruited into the study.

Subjects will be implanted with two or three 300 mg Risperidone Implants. All implants will be placed in the inner aspect of the upper arm. Plasma concentrations of risperidone and the active moiety will be measured prior to placement of the Risperidone Implants, throughout the first 6-month implantation period

The subjects will check into the clinic 16 to 7 days prior to implantation for the two or three 300 mg Risperidone Implants and check-out 7 days' post implantation of the Risperidone Implants. Safety monitoring and PK sampling will be conducted during the in-house period of the study. Scheduled outpatient visits, that will include safety monitoring and PK sampling, will be conducted for the remainder of the implantation period. After 6 months, the first implants will be explanted and subjects may be implanted (at their same dose level) in the same location in the arm with two or three 300 mg Risperidone Implants for an additional 6 months in the safety extension. Again, scheduled outpatient visits that will include safety monitoring, will be conducted for the remainder of the implant period. A subset of subjects in the PK group (approximately 15 subjects) will have pharmacokinetic sampling during the 7 days following reimplantation, as well as throughout the remainder of the study in the extension. Following explantation of the second Risperidone Implants each subject will be converted back to his/her pre-implant oral risperidone dosing regimen. The four non-PK run in subjects who received the three 300 mg implant checked in up to 4 days and a minimum of two days prior to implantation.

The treatment design for those subjects receiving 600 mg or 900 mg is illustrated in Table 1 and the schedule of study evaluations is provided in Table 3. The treatment design for the non-PK run in subjects who received 900 mg is illustrated in Table 2 and the schedule of study evaluations is provided in Table 3.

3.1.1 Overview of Treatment

Informed consent must be obtained prior to the initiation of all screening and study specific procedures. During screening and prior to admission to the research center, subjects will be evaluated against the inclusion and exclusion criteria to determine eligibility. Subjects stable on 4 mg oral risperidone will be admitted to the research center at any time from Day -16 to Day -7 (for the two 300 mg and the three 300 mg implants). Subjects receiving the three 300 mg implants will be admitted to the research center at any time from Day -4 to Day -2 (enrollment is complete for this non-PK run in group).

- Day – 16 to Day -7 (or Day -4 to Day – 2): subjects admitted to the research center for in-house confinement period, eligibility confirmed, and admission procedures conducted
- Day – 16 to Day -7 to -1 (or Day -4 to Day -2): subjects will receive their once daily oral dose of risperidone in the AM
- Day -7 to -2: daily PK sampling, before daily 4 mg oral risperidone dose for all of the PK run in dose groups.
- Day -1: serial PK sampling begins prior to oral risperidone administration for all of the PK run in dose groups.
- Days 1 to 7: Daily PK sampling will continue 2 hours post implantation
- Day 7: subjects released from research center following completion of all Day 7 study evaluations
- Outpatient visits: Weeks 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24
- Weekly phone calls from sites to patients on non-inpatient visit weeks
- Week 26: Risperidone Implant explantation and implantation of the second 6-month Risperidone Implant in the same location for the safety extension
- Week 26 Days 1 (PK subset of subjects only): PK sampling 2 and 6 hours post implantation
- Week 26 Days 2 to 7 (PK subset of subjects only): Daily PK sampling
- Week 26 Day 7 (PK subset of subjects only): subjects released from research center following completion of all Day 7 study evaluations
- Outpatient visits: Weeks 28, 32, 36, 40, 44, and 48
- Week 48: Risperidone Implant explantation
- Follow-up visit/EOS: week 50

Table 1: 600 mg and 900 mg Treatment Design

Days -7 to – 1	Day -1	Day 1	Days 1-7	Weeks 2 – 26	Week 26	Week 26 Days 1-7	Weeks 28 – 48	Week 48	Week 50
Check-in to CPU/Oral Dosing (Variable Check-in: Day -16 to Day -7, to permit flexibility in subject check-in schedule).	Oral PK Profile/ Safety Assessments	Risperidone Implant Administered	PK/Safety /Efficacy Assessments Check-Out of CPU (Day 7 only)	PK/Safety/ Efficacy/ Assessments (Weekly, Bi-Weekly with weekly phone calls on non-on site visit weeks)	Initial Risperidone Implant Removed and Second Risperidone Implant Administered in the same implant site	PK subset subjects only: PK/Safety Assessments Check-Out of CPU (Day 7 only)	PK/Safety / Efficacy/ Assessments	Second Risperidone Implant Removed	Follow-Up Visit
Subject Confined Total 14 days (With variable check-in up to 23 days)				Outpatient	Outpatient	Inpatient	Outpatient	Outpatient	Outpatient

Table 2: 900 mg Non PK Run-in Treatment Design (Enrollment for this group is complete)

Days -2 to – 1	Day 1	Days 1-7	Weeks 2 – 26	Week 26	Weeks 28 – 48	Week 48	Week 50
Check-in to CPU/Oral Dosing (Variable Check-in: Day -4 to Day -2, to permit flexibility in subject check-in schedule).	Risperidone Implant Administered	PK/Safety/ Efficacy Assessments Check-Out of CPU	PK/Safety /Efficacy/ Assessments (Weekly, Bi-Weekly with weekly phone calls on non-on site visit weeks)	Initial Risperidone Implant Removed and Second Risperidone Implant Administered in the same implant site	PK/Safety / Efficacy/ Assessments	Second Risperidone Implant Removed	Follow-Up Visit
Subject Confined Total 9 days (With variable check-in up to 11 days)			Outpatient	Outpatient	Outpatient	Outpatient	Outpatient

Table 3: 600 mg and 900 mg Schedule of Study Evaluations: Screening through Day 7

Phase	Screening	Risperidone Oral Dosing			Risperidone Implant TREATMENT						
DAY	-28 to -8	-16 to -7	From day after Check-in to -2	-1	1	2	3	4	5	6	7
Informed Consent	X										
Demography	X										
Inclusion/Exclusion Criteria	X	X									
Psychiatric/Medical History	X	X									
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination	X[a]										
HIV/Hepatitis Screen[b]	X										
Substances of Abuse Urine Screen[c]	X	X									
Clinical Laboratory Tests[d]	X										X
Serum Pregnancy Test/FSH	X	X									
12-lead Electrocardiogram	X	X									X
Vital Sign Measurements[e]	X	X	X	X	X	X	X	X	X	X	X
PANSS	X	X[f]			X						X
AIMS		X									X
SAS		X									X
BARS		X									X
C-SSRS (Baseline)	X										
C-SSRS (Since Last Visit)											X
4 mg Oral risperidone Administration		X	X	X	X						

[a] PE exam to include, general appearance, skin, head and neck (including eyes, ears, nose, and throat), lymph nodes, thyroid, musculoskeletal/extremities (including spine), cardiovascular, lungs, abdomen and neurological systems, height, weight

[b] It is the Investigator's responsibility to understand and comply with all laws and regulations that apply to HIV, Hepatitis B, and Hepatitis C and testing of blood. Hepatitis B/C and HIV testing is required unless a site's IRB prohibits such testing.

[c] Urine dipstick test only

[d] Subjects should be fasting for at least 8 hours prior to all laboratory evaluations.

[e] Consists of blood pressure, heart rate after 5 minutes of rest in the supine position, temperature and respiration rate at Screening; blood pressure, heart rate at all other time points.

[f] If PANSS score at baseline is ≥ 20% change from screening, the patients cannot participate in the study.

Phase	Screening	Risperidone Oral Dosing			Risperidone Implant TREATMENT						
DAY	**-28 to -8**	**-16 to -7**	**From day after Check-in to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
PK Sample Collection[g, h]		X[h]	X[h]	X[h]	X	X	X	X	X	X	X
Risperidone Implant Insertion					X						
Implant user survey					X						
Assessment of Implant Site[i]					X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Confinement to Research Center		X	X	X	X	X	X	X	X	X	X
Discharge from Research Center											X

[g] PK samples will be drawn at pre-dose during days -7 to -1 then at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24 after dosing on Day -1

[h] On implant day, PK samples will be drawn pre-implantation, 2 and 6 hours post implant, then daily from day 2 to day 7 at approximately the same time each day.

[i] Implant site assessments will include monitoring for signs and symptoms of infection, (e.g., pain, tenderness, swelling, erythema, exudate), expulsion, and tolerability. The presence of the implants will be assessed by palpation in addition to the visual examination at the times.

Table 4: 900 mg Non-PK run-in group - Schedule of Study Evaluations: Screening through Day 7 (Enrollment complete for this group)

Phase	Screening	Risperidone Oral Dosing	Risperidone Implant TREATMENT						
DAY	**-28 to -3**	**-4 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Informed Consent	X								
Demography	X								
Inclusion/Exclusion Criteria	X	X							
Psychiatric/Medical History	X	X							
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X
Complete Physical Examination	X[j]								
HIV/Hepatitis Screen[k]	X								
Substances of Abuse Urine Screen[l]	X	X							
Clinical Laboratory Tests[m]	X								X
Serum Pregnancy Test/FSH	X	X							
12-lead Electrocardiogram	X	X							X
Vital Sign Measurements[n]	X	X	X	X	X	X	X	X	X
PANSS	X	X[o]	X						X
AIMS		X							X
SAS		X							X
BARS		X							X
C-SSRS (Baseline)	X								
C-SSRS (Since Last Visit)									X
4 mg Oral risperidone Administration		X	X						
PK Sample Collection[p]		X	X[p]	X	X	X	X	X	X
Risperidone Implant			X						

[j] PE exam to include, general appearance, skin, head and neck (including eyes, ears, nose, and throat), lymph nodes, thyroid, musculoskeletal/extremities (including spine), cardiovascular, lungs, abdomen and neurological systems, height, weight

[k] It is the Investigator's responsibility to understand and comply with all laws and regulations that apply to HIV, Hepatitis B, and Hepatitis C and testing of blood. Hepatitis B/C and HIV testing is required unless a site's IRB prohibits such testing.

[l] Urine dipstick test only

[m] Subjects should be fasting for at least 8 hours prior to all laboratory evaluations.

[n] Consists of blood pressure, heart rate after 5 minutes of rest in the supine position, temperature and respiration rate at Screening; blood pressure, heart rate at all other time points.

[o] If PANSS score at baseline is ≥ 20% change from screening, the patients cannot participate in the study.

[p] On implant day, PK samples will be drawn pre-implantation, 2 and 6 hours post implant, then daily from day 2 to day 7 at approximately the same time each day.

Phase	Screening	Risperidone Oral Dosing	Risperidone Implant TREATMENT						
DAY	**-28 to -3**	**-4 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Insertion									
Implant user survey			X						
Assessment of Implant Site[q]			X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Confinement to Research Center		X	X	X	X	X	X	X	X
Discharge from Research Center									X

[q] Implant site assessments will include monitoring for signs and symptoms of infection, (e.g., pain, tenderness, swelling, erythema, exudate), expulsion, and tolerability. The presence of the implants will be assessed by palpation in addition to the visual examination at the times

Table 5: Post-Implantation Outpatient Treatment Period: Weeks 2-26 (All Subjects)

Phase	Risperidone Implant Treatment													
Week	2	3	4	6	8	10	12	14	16	18	20	22	24	26
Brief PE (including weight)							X							X
Clinical Laboratory Tests[r]							X							X
Urine Pregnancy			X		X				X		X			
Serum Pregnancy Test							X							X
12-lead Electrocardiogram														X
Vital Sign Measurements	X	X	X		X		X		X		X			X
PANSS			X		X		X		X		X			X
AIMS			X		X		X		X		X			X
SAS			X		X		X		X		X			X
BARS			X		X		X		X		X			X
C-SSRS (Since Last Visit)	X	X	X		X		X		X		X			X
Risperidone Implant removal														X
Risperidone Implant Insertion														X
PK Sample Collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X[s]
Assessment of Implant Site	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone call to patients	Phone calls to patients will occur on weeks that patients are not attending the site													
Outpatient Visit[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[r] Subjects should be fasting for at least 8 hours prior to all laboratory evaluations. Lipid profile will be measured in addition to all other clinical laboratory tests.
[s] PK sample should be collected approximately 60 minutes prior to explant.
[t] Outpatient visit windows are +/- 2 days.

Table 6: 900 mg PK Subset Subjects Only: Week 26 to Week 27

Phase	PK Sampling Period						
Week 26, DAY	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Prior/Concomitant Medications	X	X	X	X	X	X	X
Vital Sign Measurements[u]	X	X	X	X	X	X	X
PK Sample Collection[v]	X	X	X	X	X	X	X
Risperidone Implant Insertion	X						
Implant user survey	X						
Assessment of Implant Site[w]	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Confinement to Research Center	X	X	X	X	X	X	X
Discharge from Research Center							X

[u] Blood pressure and heart rate only

[v] On implant day, PK samples will be drawn 2 and 6 hours post implant, then daily from day 2 to day 7 at approximately the same time each day.

[w] Implant site assessments will include monitoring for signs and symptoms of infection, (e.g., pain, tenderness, swelling, erythema, exudate), expulsion, and tolerability. The presence of the implant will be assessed by palpation in addition to the visual examination at the times

Table 7: Post-Implantation Outpatient Safety Extension Treatment Period: Weeks 28-50 (All Subjects)

Phase	Risperidone Implant Treatment						
Week	28	32	36	40	44	48	50 - FU
Brief PE (including weight)				X		X	
Clinical Laboratory Tests[x]				X		X	
Urine Pregnancy	X	X	X	X	X	X	
12-lead Electrocardiogram						X	
Vital Sign Measurements	X	X	X	X	X	X[y]	X
PANSS				X		X	
AIMS			X			X	
SAS			X			X	
BARS			X			X	
C-SSRS (Since Last Visit)	X	X	X	X	X	X	
Risperidone Implant removal						X	
Transfer to 4 mg oral risperidone						X	
PK Sample Collection[z]	X	X	X	X	X	X	
Ultrasound[aa]		X	X	X	X	X	
Assessment of Implant Site	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Phone call to patients	Phone calls to patients will occur approximately 2 weeks following each visit						
Outpatient Visit[bb]	X	X	X	X	X	X	X

[x] Subjects should be fasting for at least 8 hours prior to all laboratory evaluations.
[y] Consists of blood pressure, heart rate after 5 minutes of rest in the supine position, temperature and respiration rate.
[z] Subjects in the second implant PK subset only.
[aa] Subjects in the second implant ultrasound subset only.
[bb] Outpatient visit windows are +/- 2 days.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Subject Inclusion Criteria

Inclusion Criteria:

1. Subject (and/or a subject's authorized legal representative) has provided written informed consent
2. Subject has been on a stable dose of 4 mg of oral risperidone for at least 8 weeks
3. Meets the following criteria that is related to subject's stability on current 4 mg risperidone:
   a. Outpatient status
   b. PANSS Total Score ≤ 80 at screening and if PANSS score at baseline is ≥ 20% change from screening, the patients cannot participate in the study.
   c. A score of ≤ 3 on the following PANSS items:
      - Conceptual disorganization
      - Suspiciousness
      - Hallucinatory behavior
      - Unusual thought content
4. Subject has identified a caregiver or personal contact with whom the subject has significant contact with at least once per week
5. Subject is male or female between 18 to 60 years of age.
6. 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, intrauterine device (IUD), surgical sterilization, condoms with spermicide, or progestin injection. All females of childbearing potential must have a negative serum pregnancy test at the Screening visit. All females of non-childbearing potential must have the following documentation:
   a. Medical documentation of surgical sterility OR
   b. Are post-menopausal as defined as 12 consecutive months of amenorrhea and confirmed by a Follicle Stimulating Hormone (FSH) test
7. Subject has a diagnosis of schizophrenia or schizoaffective disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) criteria
8. Subject has a body mass index (BMI) ≥18.5 and ≤35.0 kg/m^2
9. Subject is assessed by the Investigator to be symptomatically stable with regard to his or her psychiatric condition at screening and baseline
10. Subject is assessed by the Investigator to be symptomatically stable with regard to pre-existing medical conditions as evidenced by medical history, 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.

4.2 Subject 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. Hospitalized or required acute crisis intervention for exacerbation of symptoms of Schizophrenia or Schizoid Disorder in the 60 days prior to admission as determined by the Investigator
4. Subject has a history of suicide attempt in the last year, or in the opinion of the investigator is currently at imminent risk of suicide
5. Reports or reveals a presence of clinically significant skin disorders (such as, but not limited to, skin cancer, psoriasis, eczema, or atopic dermatitis), 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
6. History of abnormal scar formation at insertion site or elsewhere on body or family history of keloid formation
7. Has a current or recent (within 12 months) DSM-V diagnosis of moderate or severe substance use disorder (except for tobacco use disorder) or has a positive urine drug screen for prohibited substances at screening.
8. Have impaired hepatic (ALT/AST >1.5 times higher than the upper limit of normal) or renal function (eGFR<50 mL/min)
9. Previously defined hypersensitivity to risperidone
10. History of neuromalignant syndrome (NMS)
11. Electroconvulsive therapy within 6 months of admission
12. Requires current use of agents that are strong inhibitors and inducers of cytochrome P450 2D6
13. Current diagnosis of Acquired Immune Deficiency Syndrome (AIDS) and active hepatitis. Subjects with no detectable viral load, no detectable acute inflammation and no clinical necessity for therapy will be allowed, at the discretion of the Investigator.
14. Participation in the treatment phase of a clinical study or receipt of an investigational drug within 30 days prior to study drug administration on Day 1; for investigational drugs with an

elimination half-life greater than 15 days, this time period will be extended to 60 days

15. Prior participation in a risperidone study within the last 6 months
16. Involvement in the planning and/or conduct of the study (applies to both Braeburn staff or staff at the investigational site)
17. History of difficulty with phlebotomy procedures

4.3 PK Subset Inclusion

Approximately 15 subjects who complete through Week 26 will be included in the PK subset of subjects in the safety extension. These PK subset subjects will remain in the clinic for 7 days after the explants and implant procedure on Week 26. After Week 27, the PK subset subjects will have the same procedures performed as the remaining subjects from Weeks 27 through 48. These subjects will be selected based on order of completion of the Week 26 visit, Investigator judgment, and subject informed consent.

4.4 Subject Withdrawal Criteria

4.4.1 Criteria and Procedures for Discontinuation

Subjects may be discontinued from the study for the following reasons, if deemed appropriate by the Sponsor or Investigator:

- Entered the study in violation of this protocol
- Safety and/or Efficacy reasons as judged by the Investigator and/or Sponsor (see section 10.3 and/or section 9)
- Non-compliance to the protocol as judged by the Investigator and/or Sponsor
- Required the use of a prohibited concomitant medication (see section 5.2)
- Withdrawal of informed consent; any subject who withdraws consent as a result of an AE, regardless of severity or Investigator's opinion, must be reported as a discontinuation due to an AE
- In the Investigator's opinion, it is not in the subject's best interest to continue
- Sponsor decision

The date a subject discontinues, the treatment, and the reason for discontinuation will be recorded in the case report form (CRF). If a subject discontinues from the study, all end-of-study procedures should be conducted. If, however, a subject withdraws consent, no end-of-study procedures are required except the collection of AE information and removal of the implant. This information should be recorded in the CRF. The decision whether to enroll replacement subjects will be made by joint agreement of the Investigator and Sponsor.

When a subject is "lost to follow-up" (i.e., fails to return for study visits), a reasonable effort will be made to contact him/her to determine a reason for the failure to return and encourage the subject to return for removal of the implant. The detailed plan that the research center will follow in attempts to contact a subject that fails to return for a visit is listed below.

In the event a subject misses a scheduled outpatient visit during the study, the following procedures will be conducted to locate the patient:

- The study coordinator will attempt to contact the subject (e.g., phone, email, or text) 4 consecutive weeks in an effort to locate the subject and coordinate his/her return to the research site.
- If unsuccessful in contacting the subject the coordinator will contact the subject's caregiver/emergency contact.
- The study coordinator will contact the treating psychiatrist, therapist, case manager, and all other listed contacts and alert them of the urgency to call the research site 24/7 if they have contact with the subject or can provide a location where the subject can be found.
- Once contact is established, the Investigator will assess the subject's ability to continue in the study.
- If the patient does not contact his/her caregiver, treating psychiatrist, therapist, case manager, or site, the Sponsor will request for a third party to locate the patient to have the implant removed.

All attempts to contact the subject must be documented in the source data.

The subject will be considered lost to follow up if the subject is not successfully located using the plan outlined above and should be identified as "lost to follow-up" in the CRF. However, the research site will request that all listed contacts continue to monitor for the subject and request that they call the emergency numbers if contact is made with the subject. The research site will also continue to monitor their psychiatric network in efforts to locate the subject.

5 TREATMENT OF SUBJECTS

5.1 Identity of Study Drug and Duration of Treatment

5.1.1 Investigational Product, Dosage, and Mode of Administration

Two 300 or three 300 mg Risperidone Implants.

Risperidone, 4 mg, oral tablet

5.1.2 Duration of Treatment

Two or three 300 mg Risperidone Implants will be inserted for a period of up to 26 weeks. An additional set of Risperidone Implants will be inserted for a period of up to 24 weeks as part of the safety extension.

5.2 Concomitant Medications

Subjects will be permitted to continue on their current prescribed medication regimens, including prescribed PRN medications, to treat stable coexisting medical and psychiatric conditions that are not associated with schizophrenia or schizoaffective disorder while enrolled in the study. At entry to the study, if a subject's current medication regimen includes the use of a CYP450 2D6 inducer or inhibitor the Investigator will inform the Sponsor. The Investigator must use caution when prescribing new medications to ensure that they are not inducers or inhibitors of CYP2D6.

The following medications, defined as strong CYP inducers, are excluded from Screening through week 50: carbamazepine, phenytoin, rifampin, and St. John's wort.

Any medication taken by a subject during the course of the study (from Day -7 through week 50) and the reason for use of the medication will be recorded onto the appropriate CRF page. Upon entering the study, each subject will be instructed to report the use of all and any new medication to the Investigator. Subjects will also be instructed about the importance of not taking any new medication (including OTC [over-the-counter] medication) without consulting the Investigator.

5.3 Treatment Compliance

All oral Risperidone will be dispensed by the Investigator or designee and will be administered under supervision. All doses will be recorded in the subject's CRF (dose, route of administration, frequency, date and time of each administration). During the patients in the clinical research facility stay, all efforts will be made to dispense the 4 mg oral risperidone to the patient for administration as close to the same time each day. A mouth and hand check will be performed after each oral risperidone dose administration to ensure treatment compliance.

A Sponsor-trained, licensed physician will insert the Risperidone Implants subcutaneously into the upper, inner aspect of the subject's non-dominant arm between the bicep and triceps. At the completion of the implantation period, the Risperidone Implants will be removed by a Sponsor trained, licensed physician. The date and time of implantation and explantation and the arm that the implant was inserted in will be recorded in the subject's CRF. If the subject is reimplanted, the same site and dose will be used, and the dose, date and time will be recorded. Detailed

instructions for the insertion and removal procedures for the Risperidone Implants will be provided to the Investigator separately.

5.4 Restrictions on Study Subjects

Subjects will be served standardized meals during the confinement periods in the clinical research facility; no other foods will be permitted. A record of the menu served will be maintained. Water is permitted ad libitum throughout the study.

No alcohol containing foods or beverages may be consumed within 24 hours prior to check-in and extending until the subjects are discharged from the study site.

All sexually active females of childbearing potential and all male subjects who are sexually active with a partner of childbearing potential must agree to use a medically acceptable method of contraception throughout the entire study. Medically acceptable methods of contraception for the subject and/or partner include abstinence, birth control pills or patches, diaphragm with spermicide, IUD, surgical sterilization, condom with spermicide, or progestin injection. Additionally, all males treated with Risperidone Implants must avoid donating sperm during treatment and for 3 months following the final explants procedure.

5.5 Randomization and Blinding

5.5.1 Randomization

This is an open-label study that requires no randomization.

5.5.2 Blinding

This is an open-label study that requires no blinding.

6 STUDY DRUG MATERIALS AND MANAGEMENT

6.1 Study Drug

The risperidone Implant drug product is supplied as a sterile implant. The 300 mg Risperidone Implant is composed of 5 pellets of 60 mg risperidone and a membrane composed of aliphatic, polyether-based polyurethane that controls the rate of risperidone release. The implants are manufactured by a Contract Management Organization, Xcelience, Tampa FL.

Commercially available 4 mg risperidone oral tablets will be provided at no cost to subjects and sites from check-in to Day -1.

6.2 Study Drug Description, Packaging, and Labeling

Risperidone Implant is packaged in a sealed clear polyester/foil pouch containing one sterilized implant per package. Each pouch is labeled with a single-panel label containing product description, dose of risperidone contained in implant, lot number and Sponsor name. Each pouch is packaged into a carton with a single-panel label containing protocol number, product description, lot number, storage conditions, caution statement and name and address of Sponsor.

Kits containing all supplies needed for implantation and explantation will be provided.

6.3 Study Drug Storage

Risperidone Implant should be stored at controlled room temperature, i.e., 25°C (77°F); excursions allowed 15°C to 30°C (59°F to 86°F).

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

6.4 Study Drug Preparation

Record the lot number on the CRF prior to opening the pouch. Once the implants pouches are opened, the implants should be used within 1 hour.

6.5 Administration

A Sponsor trained, licensed physician will insert the Risperidone Implants subcutaneously into the upper, inner aspect of the subject's non-dominant arm (between the bicep and triceps). Reinsertions will be made in the same incision location following explantation. Detailed instructions for implantation and explantation procedures will be provided to the Investigator separately. The implantation/explantation kit will contain all the ancillary supplies necessary for implantation and/or explantation of the Risperidone Implants. The implantation and explantation procedure must be performed using aseptic technique and the use of a local anesthetic.

Subjects will be administered their oral risperidone at approximately the same time each morning under direct supervision of the study site personnel. If a subject is on an evening dosing regimen of 4 mg risperidone prior to study entry, the subject will be converted to a morning dosing regimen one week prior to admission to the clinical research center. The dosing regimen a subject will follow once admitted to the research center will be the same regimen they will be converted

back to the day after explantation of the second set of Risperidone Implants.

6.6 Study Drug Accountability

The Principal Investigator is responsible for ensuring that all study medication received at the site is inventoried and accounted for and that dispensed study medication is recorded both in the CRF and in the Study Medication Log. Drug accountability will be verified by the monitor during site visits.

Upon completion of the study and verification of the final study medication inventory by the monitor, a list of all the remaining study medication will be provided to the Sponsor.

The Principal Investigator will not supply the study drug to any person except those named as sub-investigators on Form FDA 1572, designated staff reflected on the Delegation of Authority Log, and consented subjects in this study. Study drug may not be relabeled or reassigned for use by other subjects.

6.7 Study Drug Handling and Disposal

All study medication and kits must be kept in a locked area with access restricted to designated study personnel. After completion of the study, all unused study drug will be returned to the Sponsor. The monitor will provide instructions to the site for the return drug shipment.

7 ASSESSMENT OF PHARMACOKINETICS

7.1 Pharmacokinetic Assessments

7.1.1 Blood Sample Collections

Pharmacokinetic assessments for risperidone, 9-OH-risperidone and active moiety (risperidone plus 9-OH-risperidone) will be performed for all subjects in the study. Samples of venous blood will be obtained according to the clinical research facility standard procedure and collected at the times indicated in the Schedule of Study Evaluations (Table 3-7). PK samples should be drawn from the arm contralateral to the implant. Samples collected within 10% of the specified times will not be considered protocol deviations; however, every attempt will be made by the clinical research facility to collect samples at the specified times. The exact sample collection times will be recorded in the CRF to the nearest minute.

All plasma samples will be placed into a freezer at -20°C or below within 1 hour after collection and further plasma sample handling instructions will be provided and detailed by the central laboratory.

7.1.2 Sample Storage and Shipment

All plasma samples will be stored frozen (at -20°C or below) until they are shipped to the analytical facility. Prior to shipping, the samples will be packed into thermal insulated containers and packed in sufficient dry ice to assure they remain frozen, and are protected from breakage during shipment to the analytical facility. Samples will be shipped by ground courier with appropriate documentation to identify the samples. The samples will be divided into 2 shipments, each containing 1 aliquot of plasma for each time point. The second aliquot will remain at the site until Sponsor notification of the receipt of the 1st sample is received.

The shipment schedule, shipping address, and contact information will be provided to the site in a separate document. The analytical facility will be notified by telephone, fax, and/or email prior to shipment of any samples

7.1.3 Analytical Methodology

A validated liquid chromatography-tandem mass spectrophotometry (LC-MS/MS) method will be used for the determination of concentrations of risperidone and 9-OH-risperidone from the plasma samples. Details of the method validation and sample analysis will be included in the final report.

8 ASSESSMENT OF EFFICACY

8.1 Psychiatric Rating Scales

All assessments will be completed as indicated in the Schedule of Study Evaluations (Table 3-7) by clinicians trained in the use of the rating scales. The number of clinicians who make these assessments should be kept to a minimum. It is most desirable to have only one person making all the assessments for a given day.

8.1.1 Positive and Negative Syndrome Scale (PANSS)

The PANSS is a rating scale used to assess the positive symptoms, negative symptoms, and general psychopathology specifically associated with schizophrenia. The scale consists of

30 items. Each item is rated on a scale from 1 (symptom not present) to 7 (symptom extremely severe). The sum of the 30 items is defined as the PANSS total score and ranges from 30 to 210. The PANSS positive sub-scale and the PANSS negative sub-scale contain seven items of the

30 items, and the scores range from 7 to 49. The PANSS general psychopathology sub-scale includes 16 of the 30 PANSS items, and the score ranges from 16 to 112. To optimize the scales objectivity and standardization a tightly structured interview is important.

9 CLINICAL CRITERION FOR LACK OF EFFICACY

Any subject presenting with signs and symptoms of lack-of-efficacy (LOE) will be evaluated by the Investigator, or designee. LOE will be evaluated using PANSS. The subject will be withdrawn from the study and will be scheduled for implant removal as soon as possible if LOE is determined. Once the implant has been removed, the subject will be restarted on his/her pre-implant oral Risperidone dosing regimen. The Investigator will notify the Medical Monitor and Sponsor of each case of LOE.

10 ASSESSMENT OF SAFETY

10.1 Timing of Safety Assessments

Safety assessments will be obtained throughout the study. The timing of these measurements is detailed in the Schedule of Study Evaluations (Table 3-7). PK samples will be drawn before the 4 mg oral risperidone dose during days -7 to -1 then at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24 hours on Day -1 prior to implantation of Risperidone Implant for the patients that will be implanted with 600 mg (2, 300 mg) and 900 mg (3, 300 mg). The initial four "Non-PK run in" subjects in the three 300 mg implant group will not have PK draws done until the pre-implant draw on Day 1 (this group is no longer enrolling).

On implant day, PK samples will be drawn pre-implantation, 2 and 6 hours post implant, then daily from day 2 to day 7. The following "priority order" will be in effect when more than 1 assessment is required at a particular time point:

- PK blood sampling will take priority over all study procedures unless there is a LOE. The exact time of collection to nearest minute will be documented in the CRF.
- 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 Suicide Severity Scale assessments (C-SSRS), Abnormal Involuntary Movement Scale (AIMS), Simpson Rating Scale (SAS), and Barnes Akathisia Scale (BARS) and adverse event (AE) monitoring will be performed at a similar time per day. The exact time of assessments to nearest minute will be documented in the CRF.

10.2 Safety Parameters

10.2.1 Medical/Medication History and Demographic Information

A detailed relevant medical history and medication history will be recorded for each subject at screening and reviewed/updated upon admission to the clinical research facility to confirm eligibility for the study. Significant medical conditions or conditions that are ongoing (e.g., headache, indigestion, diabetes, hypertension) will be recorded in the CRF. The medication history must identify any known drug allergies, present or history of drug abuse and use of acute or chronic medications.

Demographic information (i.e., age, sex, and race) will be collected for all subjects and recorded on the appropriate CRF.

10.2.2 Physical Examinations

The complete physical examination assessment will be completed at the time points indicated in the Schedule of Study Evaluations (Table 3-7) and will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears, nose, and throat), lymph nodes, thyroid, musculoskeletal/extremities (including spine), cardiovascular, lungs, abdomen and neurological systems. The screening physical examination will also include a measurement of body height and weight (without shoes) for determination of the subject's BMI.

Except for the screening examination, if there has been a change from the previous examination, only that information need be recorded.

10.2.3 Laboratory Evaluations

Subjects should be fasting for at least 8 hours prior to all laboratory evaluations. A complete series of laboratory evaluations (i.e., clinical chemistry, hematology, and urinalysis), substances of abuse screen, virology screen, and serum pregnancy test (female subjects only) will be performed at the screening visit. A complete series of laboratory evaluations (i.e., clinical chemistry, hematology, lipid profile, and urinalysis), substances of abuse screen, and urine and serum pregnancy tests (female subjects only) will be performed in accordance with the Schedule of Study Evaluations on (Table 3-7).

Lipid profile evaluations will be conducted at week 12 and 26, and also 40 and 48 in the safety extension. The required laboratory evaluations are detailed in Table 8.

Test results for the substances of abuse screen, virology screen, and serum pregnancy (females only) will be confirmed negative prior to implant of the Risperidone Implants as indicated in (Table 3-7) documentation will be maintained with the source worksheets; the test results will not be entered into the database.

Table 8: Safety Laboratory Tests to be monitored during the Study

Clinical Chemistry	**Hematology**	**Urinalysis**
Sodium	Hemoglobin	pH
Potassium	Hematocrit	Specific Gravity
Chloride	Red Blood Cell Count	Protein
Carbon Dioxide	White Blood Cell Count	Glucose
Blood Urea Nitrogen (BUN)	White Blood Cell Differential	Ketones
Creatinine	Platelet Count	Urobilinogen
Calcium		Blood
Phosphorus	**Substance of Abuse Screen**[a]	
Albumin	Amphetamines	**Virology**
Total Bilirubin	Barbiturates	Hepatitis C Antibody (anti-HCV)
Aspartate aminotransferase (AST)	Benzodiazepines[b]	Human Immunodeficiency Virus (HIV)
Alanine aminotransferase (ALT)	Cocaine	Hepatitis B surface Antigen
Gamma-glutamyl transferase (GGT)	Phencyclidine (PCP)	
Alkaline phosphatase	Opiates	**Serum/Urine Pregnancy (females of childbearing potential only)**
Lactate dehydrogenase (LDH)	Ethanol (breath test acceptable)	Beta-human chorionic gonadotropin (β-HCG)
Glucose		
Lipid Profile		**FSH (post-menopausal females only)**
Total cholesterol		
HDL (high-density lipoprotein)		
LDL (low-density lipoprotein)		
Triglycerides		
HDL/Total Cholesterol		

[a] Substance of abuse screen will be conducted using urine samples.

[b] Positive results for benzodiazepines are permitted if the subject is on a currently prescribed medication regimen

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, unless a site's IRB prohibits such testing.

It is the Investigator's responsibility to understand and comply with all laws and regulations that apply to the testing of blood for HIV and hepatitis B and C. These laws and regulations may include state laws related to written consent, separate from the ICF for this study, and pre- and post-test counseling.

Any clinically significant abnormalities should be fully investigated and reported as AEs. Whenever possible, the etiology of the abnormal findings will be documented in the CRF. Laboratory results with clinically significantly abnormal values should be repeated for confirmation. Additional tests and other evaluations required to establish the clinical significance or etiology of an abnormal laboratory result or to monitor the course of an AE should be obtained when clinically indicated. In particular, if a clinically significant abnormal result is observed that is not resolved by the final study visit, repeat tests should be performed to document resolution or stability of the abnormality.

The diagnosis associated with any clinically significant laboratory abnormality will be recorded as an AE on the CRF. Recorded AEs should indicate the underlying abnormality or diagnosis (e.g., renal insufficiency) as opposed to the observed deviation in laboratory results (e.g., elevated creatinine).

Any significant laboratory abnormalities that are either serious or unexpected should be promptly reported to the Medical Monitor. Any additional relevant laboratory results obtained by the Investigator during the course of this study will be supplied to the Sponsor.

10.2.4 Vital Signs

Routine vital signs, including blood pressure, heart rate, respiration rate, and oral body temperature will be obtained at the times indicated in the Schedule of Study Evaluations (Table 3-7). Blood pressure assessments should be conducted in the arm contralateral to the implant.

Blood pressure, heart rate and respiration rate will be obtained after the subject is in the supine position for at least 5 minutes. Additional vital signs will be obtained when clinically indicated. Any additional relevant data obtained by the Investigator during the course of this study will be supplied to the Sponsor.

10.2.5 12-Lead Electrocardiograms

A standard 12-lead ECG will be obtained at the times indicated in the Schedule of Study Evaluations (Table 3-7). The ECG will be obtained after the subject has been resting in the supine position for at least 5 minutes. The ECG intervals (PR, QRS, QT, and QTc), heart rate, and ECG findings will be recorded in the CRF. Additional ECGs may be obtained if clinically indicated. A follow-up ECG will be obtained at the Investigator's discretion if any symptom-oriented abnormalities are detected after dose administration. Any additional relevant data obtained by the Investigator during the course of this study will be supplied to the Sponsor. Clinically significant ECG findings will be reported to the Medical Monitor.

10.2.6 Implant Site Assessments

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 Study Evaluations (Table 3-7). Clinically significant findings, as judged by the Investigator, resulting from the implant site assessment will be recorded as AEs. 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 oral risperidone dosing regimen. Additionally, ultrasounds may be performed at the discretion of the Investigator to confirm implant location.

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

10.2.7 Extrapyramidal Symptom Assessments

Safety testing to monitor for signs of EPS will assessed at the times indicated in the Schedule of Study Evaluations (Table 3-7). The assessments will be conducted with the use of the following objective rating scales: Abnormal Involuntary Movement Scale (AIMS), Simpson Rating Scale (SAS), and Barnes Akathisia Scale (BARS).

Assessments will be completed by clinicians trained in the use of the rating scales. The number of clinicians who make these assessments should be kept to a minimum. It is most desirable to have only one person making all the assessments for a given day.

10.2.8 Columbia Suicide Severity Scale

Suicidality will be assessed at the times indicated in the Schedule of Study Evaluations (Table 3-7).

10.3 Early Explantation and Subject Withdrawal Criteria

10.3.1 Suspicion of Implant Breakage

If it is suspected that an implant has been broken or damaged during the insertion procedure the implant will be removed and the subject will be withdrawn from the study. If there is no immediate suspicion of implant breakage or damage during the insertion procedure, subjects will be followed closely during the inpatient stay with assessments of symptoms, vital signs, ECGs, and plasma drug concentrations. Previous experience with implant technology has shown that plasma levels rise more quickly than predicted and to higher levels than expected when an implant is damaged during insertion. The occurrence of EPS and tachycardia have been observed in cases of excessive ingestion of oral risperidone (Page et al., 2010) and these signs and symptoms should be monitored after implantation of the Risperidone Implants.

After discharge from the inpatient phase the following criteria should be followed to identify if an

implant may have been damaged:

- During the outpatient phase of the study all subjects will be instructed to call the site if they have a sudden change in feelings of wellness that may be related to possible exaggerated pharmacologic effects. If a severe or serious adverse event (SAE) is reported within 24 hours following implantation of the Risperidone Implant and is considered at least possibly related to the Risperidone Implant the subject will be withdrawn from the study and have the implant removed.

At the time of explantation, it is expected that the implant will be removed as a single piece. If any breakage occurs, attempts will be made to remove the remaining piece(s). If the remaining piece(s) is not found, the patient will be observed closely for clinical symptoms and plasma drug levels will be monitored for higher than expected levels, and treatment will be provided per standard medical practice.

10.3.2 Subject Manipulation or Attempted Removal of RISPERIDONE IMPLANT

If a subject attempts to remove the Risperidone Implants once implanted, or in any way attempts to manipulate the Risperidone Implants while implanted, the subject will be withdrawn from the study and the implant will be removed.

10.3.3 Documentation of Implant Events

In the event implant breakage is observed, excessive increase or decrease in plasma concentrations is reported, or a subject manipulates or attempts to remove the implant, the Investigator will evaluate the finding, inform the Sponsor, and report any clinically significant abnormality as an AE.

10.4 Recording and Reporting Adverse Events

Throughout the study, AEs will be documented on the appropriate page of the CRF whether or not considered treatment-related. This includes any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to dosing will be recorded as part of the subject's medical history. The Investigator is responsible for assessing the relationship of AEs to the study medication; relationship will be classified as not related, unlikely related, possibly related, or probably related (see section 10.4.1.2 for definitions).

All AEs will be collected by the Investigator from the time informed consent is signed through the follow up visit. This includes any AEs that are ongoing at the completion/termination of the study, and any AEs that start after the last dose of study medication. A follow-up safety visit will be conducted approximately 14 days after discharge from the research center.

All SAEs will be collected from the time the informed consent is signed at screening through the follow up visit. Any SAEs considered related to study medication should be reported to the Sponsor without regards to these timelines.

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study or within 14 days following cessation of the study treatment or premature discontinuation from the study whether or not related to the investigational product, must be reported via email, facsimile or telephone within 24 hours of first being advised of the SAE.

Follow-up information collected for any initial report of an SAE must be reported to the Sponsor or designee within 24 hours of receipt by the Investigator. In the event discussion is necessary call the Medical Monitor.

The Sponsor or designee will determine whether the SAE must be reported within 7 or 15 days to the FDA. If so, the Sponsor (or the Sponsor's representative) will report the event to the FDA. The Investigator will transmit a written report of the circumstances and outcome to the Sponsor as soon as he or she is made aware of the circumstances. The Investigator will report SAEs to the Institutional Review Board (IRB) per IRB policy.

10.4.1 Adverse Event Definitions

An AE is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (e.g., chemistry, ECG, etc.), or worsening of a pre-existing condition associated temporally with the use of the study medication whether or not considered related to the study medication.

A treatment-emergent AE is any condition that was not present prior to treatment with study medication but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

All AEs, including either observed or volunteered problems, complaints, signs, or symptoms must be recorded on the AE page of the CRF, regardless of whether associated with the use of study medication. This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study). AEs should be recorded in standard medical terminology.

The Investigator will evaluate each AE for duration, intensity, and relationship to study medication, record the action taken, and any treatment given. Recurrent symptoms of a chronic pre-existing condition are not considered AEs unless they occur in a worse or unexpected pattern during study drug administration.

10.4.1.1 Intensity of AEs

The intensity (or severity) of AEs is characterized as mild, moderate, or severe:

Mild AEs are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.

Moderate AEs introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

Severe AEs interrupt a subject's usual daily activity and typically require systemic drug therapy or other treatment.

When the intensity category of the AE changes more frequently than once daily, the maximum intensity for the event is recorded. If the intensity category changes after a number of days, then these sub-events or changes are recorded separately (i.e., having distinct onset and stop dates).

10.4.1.2 Relationship to Study Medication

The degree of "relatedness" of the AE to the study drug may be described using the following scale:

Not related indicates that the AE is definitely not related to the study drug.

Unlikely related indicates that there are other, more likely causes and study drug is not suspected as a cause.

Possibly related indicates that a direct cause and effect relationship between study drug and the AE has not been demonstrated but there is a reasonable possibility that the event was caused by the study drug.

Probably related indicates that there probably is a direct cause and effect relationship between the AE and the study drug.

It is the Sponsor's policy to consider "Probable" and "Possible" causality assessments as positive causality. It is the Sponsor's policy to consider "Not" and "Unlikely" causality assessments as negative causality.

Assessments are to be recorded on the CRF and must indicate clearly the relationship being assessed.

10.4.1.3 Serious Adverse Events (SAEs)

An SAE is defined as an AE that:

- Results in death
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)
- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or pre-planned surgery, procedure, or drug therapy does not constitute an SAE unless there is complication resulting in hospitalization prolongation). An AE that results in a visit to an Emergency Room that does not require an inpatient stay is not always classified as an SAE.
- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a patient using the study medication regardless of time to diagnosis)
- Is considered an important medical event

Life-threatening events are defined as events that place the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.5 Procedures in Case of Pregnancy

All pregnancies of a subject or their partner will be reported to the Sponsor using the same reporting timelines as indicated for SAEs in section 10.4.1.3. Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (i.e., spontaneous miscarriage, elective abortion, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs unless the decision to abort was based on a diagnostic test that indicated there was a problem. All outcomes of pregnancy must be reported to the Sponsor on the pregnancy outcomes report form.

10.6 Precautions

It is expected that the Risperidone Implants will have a safety and efficacy profiles similar to risperidone oral tablets and the long-acting IM depot injectable formulation of risperidone. Risperidone is considered to be generally safe and well tolerated. The most common adverse reactions (≥10%) in clinical studies with risperidone oral tablets include somnolence, increased appetite, fatigue, rhinitis, upper respiratory tract infection, vomiting, coughing, urinary incontinence, saliva increased, constipation, fever, Parkinsonism, dystonia, abdominal pain, anxiety, nausea, dizziness, dry mouth, tremor, rash, akathisia, and dyspepsia. Subjects will be monitored closely throughout the study for potential adverse events.

There are no additional risks expected with implantation of the Risperidone Implants beyond those normally encountered during similar minor surgical procedures. A Sponsor-trained, licensed physician, must insert and remove the Risperidone Implants Aseptic technique should be followed at all times during the implant procedure to minimize the chance of infection. Sterile gloves are required at all times throughout the implantation and explantation procedure. The implantation/explantation procedure may result in bruising, pain/soreness/tenderness, skin redness, and swelling at the site of implantation. Subjects will be monitored closely throughout the study for signs and symptoms of implantation site reactions.

The Investigator should treat all adverse experiences in accordance with standard medical practice. Due to the investigational nature of the method of delivery of Risperidone, the AE profile cannot be defined with certainty; all subjects will be carefully evaluated.

Additional information regarding AEs is provided in the Investigator Brochure and the MOP.

10.7 Observation

All subjects will remain in the clinical research facility from approximately Day -7 until discharged by the Investigator at the end of the in-house confinement period. The subjects will be kept under observation during their time in the clinical research facility in a manner consistent with the standard operating procedures of the clinical research facility and as medically indicated.

AEs should be treated in accordance with the standard medical practice. During the course of the study, the overall safety and tolerability of the study medications will be reviewed by the Investigator and Sponsor.

11 STATISTICS

This section describes the statistical methods to be used. These methods may be revised and updated due to reasons such as regulatory requirements or need for further clarifications. The final analysis plan will be documented in a formal statistical analysis plan (SAP) that must be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how data will be presented as well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report will discuss deviations from the SAP, if any.

For bridging the efficacy of the Risperidone Implant to oral risperidone, the mean concentrations after the insertion of the Implants is expected to approximate the mean C_{avg} of oral 4 mg risperidone and not to exceed oral C_{max}. In addition, the average concentrations after the implant is expected to be higher than the oral $C_{trough.}$ The target concentration is to provide consistent levels between the relevant oral C_{trough} and C_{max}, where efficacy and safety could be preserved.

11.1 Sample Size Consideration

Approximately 40 will provide over 90% power to establish that implant is non-inferior to the oral dose of risperidone. . In the sample size calculation it was assumed that the true ratio was at least 1.1 and the coefficient of variance (CV) was less than 0.45. These assumptions were based on internal data. Therefore, approximately 50 subjects will be enrolled to ensure approximately 40 subjects completing the study assuming that the drop rate is less than 20%.

11.2 Analysis Population

The safety population will consist of all subjects who have received at least one dose of study treatment.

The PK population will consist of subjects who receive 4-mg oral risperidone daily and the Risperidone Implants.

The primary PK analyses will be based on the subjects who provide Month 6 PK results.

11.3 Subject Disposition

Subject disposition will be summarized. The overall summary will be comprised of the number and percentage of subjects for each analysis population, as well as the number and percentage of subjects who completed and discontinued early with reasons for discontinuation.

11.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized using appropriate descriptive statistics.

11.5 Concomitant Medications

Medications administered prior to and concomitantly with study treatment will be tabulated and listed.

11.6 Pharmacokinetic Analysis

11.6.1 Calculation of Pharmacokinetic Variables

Pharmacokinetic variables of $AUC_{0\text{-}24}$ (oral dose only), $AUC_{3\text{-}180\ days,}$ (Risperidone Implant only), $AUC_{3\text{-}t,}$ (Risperidone Implant only), C_{max}, C_{trough} and T_{max} (oral dose only), for risperidone, 9-OH-risperidone will be derived. The active moiety will be calculated as the sum of the risperidone and 9-OH-risperidone concentrations at each sampling time point. In order to minimize the contribution that the Day 1 oral dose of risperidone will have on the AUC during implantation, the AUC calculation for the implantation period will initiate 3 days after implantation (Day 3). The concentrations of risperidone, 9-OH risperidone and active moiety on Days 1 to 3 will be summarized to characterize the pharmacokinetics of risperidone and 9-OH-risperidone when changing the oral tablet to implant. The C_{avg} values for risperidone, 9-OH-risperidone and active moiety from the Risperidone Implants will be calculated as the plasma $AUC_{3\text{-}t}$ divided by t-3 (in days). The C_{avg} for the oral tablet will be calculated as the plasma $AUC_{0\text{-}24}$ on Day -1 divided by 24 hours. Actual sample times (relative to the corresponding implantation time) rounded to two decimal digits and negative pre-dose times set to zero, will be used in the computation of the pharmacokinetic variables, rather than scheduled times. Refer to section 11.7 for the handling of missing values.

The definition and method of determination for each pharmacokinetic variable are summarized in Table 9.

Table 9: Pharmacokinetic Variables

Variable	Definition
$AUC_{0\text{-}24hr}$	Area under the concentration versus time curve from time 0 to 24 hours after oral dose; calculated using the linear trapezoid rule.
$AUC_{3\text{-}180day}$	Area under the concentration versus time curve from time Day 3 to 180 days after Risperidone Implant for the subsequent subjects; calculated using the linear trapezoid rule
$AUC_{3\text{-}t}$	Area under the concentration versus time curve from time Day 3 to t days after the Risperidone Implant for subjects who do not complete the implantation period; calculated using the linear trapezoid rule.
C_{avg}	Average steady-state concentration Oral tablet: measured as $AUC_{0\text{-}24\ hr}$ on Day -1 divided by 24 Risperidone Implant: measured as $AUC_{3\text{-}t}$ divided by t-3; t=days Risperidone Implant remained in situ.
C_{max}	Observed maximum plasma concentration; the highest concentration observed after the oral dose and after implantation with Risperidone Implant.
C_{trough}	The concentration at 24 hours following an oral dose of risperidone.
T_{max}	The time that C_{max} was observed.

11.6.2 Analysis of Pharmacokinetic Data

All PK data (concentration and pharmacokinetic variables) will be summarized using appropriate descriptive statistics. The ratios of Risperidone Implant C_{avg} over oral $C_{max,}$ over oral C_{avg} and over oral C_{trough} will be analyzed based on log-transformed scales using an ANOVA model with treatment effects. The two sided 95% confidence intervals will be presented. Inferiority is defined as the lower bound of 95% confidence interval of the ratio is <0.8.

The active moiety will be considered the primary interest. To control for Type I error rate, active moiety will be analyzed first, followed by the analysis for risperidone.

The concentrations of risperidone, 9-OH risperidone and active moiety on Days 1 to 3 will be summarized to characterize the pharmacokinetics of risperidone when changing the oral tablet to implant.

The study is designed to evaluate the PK profiles of the 900 mg implant arm. PK profile for 600 mg arm is exploratory.

11.7 Handling of Missing Values

Plasma concentrations below the limit of quantification (BLQ) will be set to half of BLQ value in the computation of mean concentration values; however, BLQ concentrations between 2 non-BLQ concentrations will be set to missing. For the computation of PK variables, the BLQ

concentrations prior to the first measurable concentration will be set to half of the BLQ value; other BLQ concentrations will be set to missing.

No imputation will be performed for demographic and safety data.

11.8 Safety Analysis

The safety analysis will be based on all subjects who received any study medication. The frequency of AEs will be tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term (PT), and treatment for each cohort. The maximum intensity and frequency of AEs will be summarized by treatment and cohort.

Vital sign, clinical laboratory, EPS assessments and ECG measurements will be summarized by treatment and study day (visit) using descriptive statistics or frequency distribution, as appropriate.

11.9 Protocol Deviations

A list of subjects with protocol deviations will be compiled. Prior to database lock, an evaluation of subjects with significant protocol deviations will be performed to assess the appropriateness of their inclusion into the PK analysis.

12 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1 Study Monitoring

The monitoring of the study will be performed in accordance with the principles of Good Clinical Practice (GCP) as described in the International Conference on Harmonization (ICH) E6 titled "Good Clinical Practice." Monitoring including source data verification should be routinely performed prior to the transfer of data to Data Management.

It is a prerequisite of this study that the study monitor has direct access to source data for data verification. This will be done by comparing data from the CRFs with those in the subject's medical notes (permission from the subject will be sought as part of the consent process). Such verification is an essential element of quality control, as it allows the rectification of transcription errors and omissions.

The Sponsor expects that, during monitoring visits, the study coordinator and Investigator will be available, the source documentation will be available, and a suitable environment will be provided for review of study related documents.

12.2 Audits and Inspections

Authorized representatives from the Sponsor, a regulatory authority or an IRB/independent ethics committee (IEC) may request access to all study records, including direct access to source data/documents, for inspection, audit and/or copying, in keeping with applicable regulations. The Investigator will permit study related monitoring, audits, IRB/IEC review, and regulatory inspections, providing direct access to source data/ documents. The Investigator should immediately notify the Sponsor of an upcoming regulatory authority inspection.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate clinical research facilities, review of protocol procedures with the Principal Investigator and associated personnel prior to start of the study, and periodic monitoring visits by the Sponsor or Sponsor representative.

Additional steps will include the design of suitable source documents by the Investigator with appropriate instructions for use; the monitoring of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability. Written instructions will be provided for collection, preparation, and shipment of blood and plasma samples. The Sponsor or Sponsor representative will review source documents for accuracy and completeness; any discrepancies will be resolved with the Investigator or designee, as appropriate. The data will be entered into the clinical study database and verified for accuracy, using the study specific data management plan.

14 ETHICS

14.1 Ethics Review

The Principal Investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, informed consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The Principal Investigator should also provide the IRB/IEC with a copy of the Investigator's Brochure or product labeling, information to be provided to subjects and any updates.

The Principal Investigator will provide the IRB/IEC with reports, updates, and other information (e.g., Safety Updates, Amendments) according to local regulations and guidelines.

Copies of all IRB/IEC approvals must be provided to the Sponsor prior to the start of the study and throughout the study as applicable.

14.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice and ICH guidelines and other applicable regulatory requirements.

14.3 Written Informed Consent

The Principal Investigator will ensure that each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

Each subject, or subject's authorized legal representative, must voluntarily sign and date the informed consent form (and other locally required documents) prior to the performance of any study-related activity. The consent form must be approved by both the reviewing IRB/IEC and by the Sponsor prior to use.

The consent form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorize the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The consent form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. For data verification purposes, authorized representatives of the Sponsor, a regulatory authority or an IRB/IEC may require direct access to source data relevant to the study, including the subjects' medical history.

15 DATA HANDLING AND RECORDKEEPING

15.1 Source Data Capture

Source worksheets will be used to record data at the clinical research facility. Data on the source worksheets will be transferred to the eCRF. All information requested on the source worksheet should be completed legibly. If the data are not available, the source worksheet and CRF should be documented as such.

15.2 Case Report Forms

Data collected will be entered at the clinical research facility into electronic case report forms (eCRFs). The eCRFs will be available through the electronic data capturing (EDC) system provided by the Sponsor. As the data are entered, they will be subjected to range checks and other edits to ensure accuracy. Electronic CRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. Electronic CRFs should be completed according to the instructions provided by the Sponsor. The Principal Investigator is responsible for maintaining accurate, complete and up-to-date records for each subject and for authenticating the data recorded in the eCRF.

15.3 Data Recording and Handling

Data collection and handling will involve the use of the Sponsor's EDC system to which only authorized personnel will have access. In addition to periodic monitoring occurring within the system by the Sponsor monitor, programmatic edit checks will be used to review the data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these edit checks, queries may be issued electronically to the clinical study site and closed electronically by the monitor, Sponsor's data management staff or authorized study site staff. The identifying information (assigned username, date, and time) for both the originator of the data change (if applicable), as well as the Investigator's approval of all changes performed on the subjects' data, will be recorded in various features of the EDC system.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee subject confidentiality in accordance with the legal stipulations applying to confidentiality of subject data. Study records (i.e., copies of eCRF, regulatory documents) will be retained at the study site, along with adequate source documentation in accordance with GCP and ICH guidelines. All study records will be available for inspection by the Sponsor, their authorized representatives, or regulatory agencies. At the completion of the study, the Sponsor or its representatives will supply the site with a copy of all data captured in the EDC system.

15.4 Inspection of Records

Periodically the Sponsor or Sponsor representative will review study documents to verify compliance with the protocol and accuracy of the data. All corrections or changes made to study data (e.g., source worksheet, CRF) must be appropriately documented (e.g., initialed and dated, audit trail) as per GCP/ICH guidelines.

15.5 Retention of Records

All regulatory documents (i.e., investigator study file), CRFs and all source documents (i.e., informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnoses and dates of therapy prior to and during this study, drug dispensing and disposition records) that support CRFs must be retained by the responsible Principal Investigator for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or 2 years after the last approval of a marketing application in an ICH region.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility and the Sponsor must be notified.

16 PROTOCOL MODIFICATIONS

Neither the Investigator nor the Sponsor will modify this protocol without obtaining the concurrence of the other. All protocol amendments must be signed and dated by the Investigator, and submitted and approved by the IRB/IEC prior to implementation of the amendment, unless it is administrative in nature or to protect the immediate well-being of study subjects. The Sponsor will submit protocol modifications to the appropriate regulatory authority as called for under applicable regulations.

If a protocol amendment requires a change to the informed consent form, then the Sponsor and the IRB/IEC must be notified. Approval of the revised informed consent form by the Sponsor and IRB/IEC is required before the revised form may be used. All ongoing subjects should be advised of any changes and they should be documented appropriately.

In situations requiring a departure from the protocol, the Investigator or other physician in attendance will contact the medical monitor by fax or telephone. If possible, this contact will be made before implementing any departure from protocol. In all cases, contact with the medical monitor must be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. The CRF and source document will reflect any departure from the protocol procedures and the circumstances requiring it. All departures will be a deviation; no waivers will be granted.

17 REFERENCES

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17.1 INVESTIGATOR AGREEMENT

RISPERIDONE IMPLANT Protocol Version 7: A PHASE II, OPEN-LABEL PHARMACOKINETIC STUDY IN SCHIZOPHRENIC PATIENTS ON A STABLE DOSE OF 4 MG ORAL RISPERIDONE TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF RISPERIDONE AND 9-HYDROXY (OH)- RISPERIDONE WHEN RISPERIDONE IS ADMINISTERED WITH A SIX MONTH IMPLANT

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.

Signature of Investigator	Date
Typed or Printed Name of Investigator	Site Number