CLINICAL STUDY PROTOCOL

Title: An Open-Label, Relative Bioavailability Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Ropinirole Implants in Patients with Parkinson's Disease Switched from Oral Immediate-Release Ropinirole While on L-Dopa

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Investigational Drug: Ropinirole Implant

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SUMMARY OF CHANGES

Amendment 1, Description of changes:

1. Section 2.2: Addition of secondary objectives related to analyses of ropinirole metabolites
2. Section 2.3: Addition of exploratory objectives related to Ropinirole Implant Applicator.
3. Figure 1: Updated study schematic and language throughout to change "Group" to "Cohort".
4. Sections 3.1 and 14.4: Revisions to dose escalation committee review requirements, including addition of pharmacokinetic (PK) profile data review for Cohorts 1and 2, and extending the period for safety and PK data from 4 weeks to 12-weeks for Cohort 1.
5. Sections 3.1.1, 5.2.1, and Table 2: Adjustment in screening period to 2-4 weeks. Overall duration of the subject participation revised to up to 17.5-19.5 weeks.
6. Section 3.1.2 – Clarification that enrolled subjects who withdraw early will not be replaced.
7. Sections 3.1.3.1: Clarification regarding L-Dopa dosing
8. Sections 3.1.3.1, 5.2.2.3, and Table 3: Clarification that on Day -1, immediate release ropinirole must be administered 8 hours apart.
9. Sections 3.1.3.3 and 5.2.4: Clarification that subjects should not transition back to oral ropinirole until after the 18-hour PK sample has been collected.
10. Section 3.1.3.5: Addition of section on investigator training.
11. Section 3.2.1: Clarification of safety assessments for AEs and SAEs, and addition of the Scales for Outcomes in Parkinson's disease–Psychiatric Complications (SCOPA-PC) as a safety assessment.
12. Sections 3.2.5, 3.2.6, 5.2.3.1, 5.2.4, 5.2.5.2, 6.9.1, 6.9.2, 6.10, and Table 2 Addition of assessments, including implant depth ultrasound, implant palpability, implant applicator complaints, failures, and malfunctions, and Implanting Physician and patient satisfaction surveys.
13. Section 4.1, Inclusion Criteria:
    - Clarification that age of eligible subjects is 30 to 80, inclusive, and that this should be assessed at time of informed consent.
    - Clarification on the timeframe for practicing acceptable methods of contraception (females of childbearing potential).
    - Clarification of the requirement for subjects with clinically stable Parkinson's Disease (PD).
14. Section 4.2, Exclusion Criteria:
    - Clarification of the location for prohibited scarring or tattoos.
    - Addition of exclusion criterion for BMI ≤19 and skin to fascia depth ≤3 mm at the bicipital groove of the brachium.

- Clarification of eligibility of subjects with Parkinson's disease-related psychosis.
- Revision to exclude subjects with current impulse control disorder or symptoms.
- Revision to exclude subjects using nicotine replacement products.
- Addition of prilocaine, chlorhexidine, and adhesive dressing to exclusion criterion regarding hypersensitivity.

15. Sections 4.2, 4.3, 5.2.1, 6.7.2, and Table 2: Clarification that urine drug screens are for drugs of abuse, and positive drug screens cannot be repeated. Positive alcohol breath tests can only be repeated during the screening period.
16. Section 4.3: Correction to implantation criterion 3 (change OR to AND)
17. Section 4.4: Addition of abuse of non-study assigned ropinirole as a subject withdrawal criterion. Clarification language added for recording reasons for discontinuation/removal.
18. Section 5.2.1: Clarification that screening assessments may be conducted across more than one visit during the screening period.
19. Sections 5.2 (Screening Period, Visit P1, Visit Day-2, Day 3 Visit, Day 4 Visit, and Weeks 1 through 14), 6.4.8, and Table 2: Addition of SCOPA-PC
20. Sections 5.2, 6.4.4, and Table 2: Height and weight separated from vital signs in Schedule of Events and in visit descriptions.
21. Section 5.2.1 and Table 2: Addition of Hauser Diary concordance training.
22. Section 5.2.2.2 (Visit Day -2): Correction of serum to urine pregnancy test.
23. Section 5.2.2.3 and Table 3: Addition of low fat meal requirement and recommended windows for PK sample collection.
24. Section 5.2.3.1 and Table 2: Respiratory rate and oral body temperature added to vital signs assessments.
25. Sections 5.2.4, 6.9.2, and Table 2: Addition of ultrasound prior to implant removal at Week 12 Visit.
26. Table 3: Addition of rows to clarify the required PK timepoints on Day -1. Removal of a redundant footnote.
27. Sections 7.1 and 7.2: Update of implant drug content range per Investigator's Brochure.
28. Section 7.2: Update of safety margin calculation and total drug content
29. Section 7.3: Change in Investigational Product packaging configuration
30. Section 8.1: Addition of language prohibiting use of marijuana.
31. Section 9.1.1.2: Clarification of SAE definition as related to unplanned hospitalizations related to implant placement or removal.
32. Section 9.1.3, Table 4: Addition of category for "Possibly Related" and revision of existing definition of "Related" to adverse event attribution table

33. Section 9.1.5.1: Addition of SAE reporting element for relationship to insertion/removal procedure. Addition of pharmacovigilance contact information.
34. Section 9.1.5.5: Collection and reporting of male subject partner pregnancies removed.
35. Section 9.1.5.6: Addition of section for reporting of implant applicator malfunction or failure
36. Section 10.2: Revision of definition of efficacy evaluable population.
37. Section 10.3.2.1: Addition of pharmacokinetic analyses for N-despropyl ropinirole and 7-hydroxy ropinirole.
38. Section 10.3.3: Clarification of planned AE listings.
39. Section 15.2: Clarifications for record retention requirements following study closure.
40. Administrative and grammatical edits were made throughout the protocol

INVESTIGATOR'S SIGNATURE

I have received and read the investigator's brochure for Ropinirole implants. I have read protocol ROP-001 Amendment 1 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Title of Investigator

_____

Signature of Investigator

_____

Date

SPONSOR'S SIGNATURE

Approved by:

[redacted] 6/9/2017

Executive Vice President, Chief Development Officer
Titan Pharmaceuticals, Inc.

Date

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LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Abbreviation or specialist term	Explanation
AE	adverse event
AR	adverse reaction
AUC_{0-t}	area under the plasma concentration versus time curve from time 0 to time of last measureable concentration
AUC_{0-24}	area under the plasma concentration versus time curve from time 0 to 24 hours
BLOQ	below the limit of quantitation
BP	blood pressure
CDS	continuous dopaminergic stimulation
CFR	Code of Federal Regulations
C_{max}	maximum measured plasma concentration
C_{min}	minimum measured plasma concentration
CRU	Clinical Research Unit
CS	clinically significant
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DBP	diastolic blood pressure
DEC	dose escalation committee
ECG	electrocardiogram
eCRF	electronic case report form
EE	efficacy evaluable
EOT	end of treatment
ESS	Epworth Sleepiness Scale
EVA	ethylene vinyl acetate
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation

IR	immediate-release
IRB	institutional review board
λz	first-order terminal elimination rate constant
L-Dopa	levodopa
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
MMSE	Mini-Mental State Examination
MOP	Manual of Procedures
NCS	not clinically significant
PD	Parkinson's disease
PDSS-2	Parkinson's Disease Sleep Scale
PK	pharmacokinetic(s)
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale
Ropinirole	ropinirole hydrochloride
SAE	serious adverse event
SAR	suspected adverse reaction
SBP	systolic blood pressure
SCOPA-PC	Scale for Outcomes of Parkinson's disease – Psychiatric Complications
SOP	standard operating procedure
$t_{½}$	terminal elimination half-life
t.i.d.	3 times daily
T_{max}	time to maximum plasma concentration
UAR	unexpected adverse reaction
WHO	World Health Organization

1. INTRODUCTION

Parkinson's disease (PD) is a progressively debilitating neurological disorder affecting around 1 million or more people in the United States and about 5 million people worldwide. This disease of the central nervous system is marked by various motor impairments including tremor, muscular rigidity, slowness of movement, decreased dexterity, and imbalance. Chiefly affecting middle-aged and elderly people, it is associated with degeneration of the basal ganglia of the brain and a regional deficiency of the neurotransmitter dopamine.

Treatment for PD is primarily based on a dopamine replacement strategy. While dopaminergic drugs are highly beneficial in the early stages of treatment, benefits are limited by the development of motor complications and other problems not related to dopamine deficiency, such as non-motor features. Higher doses of dopaminergic medication are often associated with an increased risk of motor fluctuations and dyskinesia as well as sedation and hallucinations (Olanow et al., 2013).

Ropinirole hydrochloride (ropinirole) is a dopamine agonist that provides anti-parkinsonian benefits similar to those of levodopa but with a lower risk of inducing motor complications (Rascol et al., 2000). It is currently marketed in immediate-release and extended-release (once-daily) formulations. Oral dosing with ropinirole typically provides an initial peak blood level of the drug, which declines relatively rapidly, reaching subtherapeutic trough levels after several hours, thus necessitating repeat dosing for maintenance of therapeutic effect. High maximum serum concentration levels in the initial period following dosing may contribute to side effects experienced with ropinirole in over one-third of PD patients; these include nausea, dizziness, hypotension, dyskinesias, and drowsiness

Titan Pharmaceuticals, Inc. (Titan) has developed an implant to provide sustained-release of ropinirole following subdermal insertion. Titan plans to develop this implant as a potential therapy for the signs and symptoms of idiopathic Parkinson's disease. This implant is based on the ProNeura™ technology utilized in Probuphine®, a buprenorphine hydrochloride implant. Pharmacokinetic (PK) studies of Probuphine demonstrated an early, brief pulse of buprenorphine release followed by sustained low plasma levels for 6 months. The ProNeura implant technology may offer a far more consistent and durable sustained-release profile as compared to biodegradable polymer formulations and there is no risk of unintended release that can sometimes occur with reservoir-based implants. When implanted subdermally, a ropinirole implant allows for the drug substance to be slowly and continuously released through the process of dissolution-controlled diffusion, resulting in sustained release of ropinirole over a 3-month period. Continuous dopaminergic stimulation (CDS) is a major aim for pharmacotherapy in PD, as there is strong evidence that it can provide substantial improvement for long-term outcomes (Fernandez et al., 2015 and Zulli et al., 2016). One important goal that CDS may provide is delay in the onset of levodopa-induced dyskinesias as well as their duration and severity if they do develop. Continuous dopaminergic stimulation via the ProNeura subdermal drug delivery system could mitigate the problems of pulsatile delivery of oral dopamine-replacement therapy, while simultaneously avoiding technical and tolerability problems associated with infusion pumps (currently used for apomorphine and carbidopa-levodopa gel suspension). Data from non-human primate models of PD using dopaminergic agonist-containing implants using the ProNeura platform have shown management of parkinsonian signs without skin irritation and inflammation, and with improvements in motor function, and attenuation of levodopa-induced dyskinesias (Bibbiani et al., 2005; Sreedharan et al., 2015).

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

2.1. Primary Objectives

- To assess the relative bioavailability of ropinirole implants versus oral immediate-release (IR) ropinirole as determined by plasma ropinirole AUC_{0-24} in subjects with PD.
- To assess the safety and tolerability of ropinirole implants over a 3-month course of treatment.

2.2. Secondary Objective

- To assess the efficacy of ropinirole implants in controlling motor fluctuations and drug-induced dyskinesias.
- To assess plasma pharmacokinetics for major metabolites of ropinirole, N-despropyl ropinirole and 7-hydroxyl ropinirole, for ropinirole implants versus oral IR ropinirole.

2.3. Exploratory Objectives

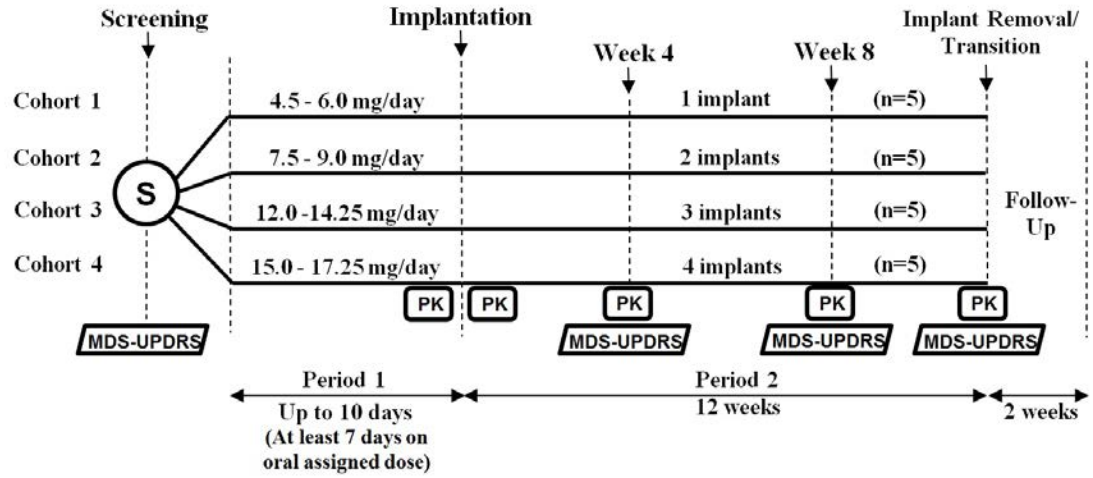
- To assess the efficacy of ropinirole implants on clinical features of PD.
- To assess the safety and effectiveness of the Ropinirole Implant Applicator for the subdermal placement of ropinirole implants.
- To assess Implanting Physician satisfaction with the design and functionality of the Ropinirole Implant Applicator for the subdermal placement of ropinirole implants.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This study is a phase 1/2 open-label relative bioavailability study evaluating the safety, tolerability, and PK of 4 dose levels of ropinirole implants. The doses will be administered sequentially in patients with PD. The study design schematic is shown in Figure 1; the study consists of 4 parts: Screening, Period 1, Period 2, and Follow-Up.

Figure 1: ROP-001 Study Design Schematic



IR = immediate release; PK = blood draw for pharmacokinetic assessments; S = screening; MDS-UPDRS = Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
Cohort 1: 4.5 – 6.0 mg/day, IR; 1 ropinirole implant
Cohort 2: 7.5- 9.0 mg/day, IR; 2 ropinirole implants
Cohort 3: 12.0 – 14.25 mg/day, IR; 3 ropinirole implants
Cohort 4: 15.0 – 17.25 mg/day, IR; 4 ropinirole implants

The study will enroll approximately 20 subjects across 1-3 sites in the U.S in 4 cohorts based on the fixed dose of IR ropinirole that the subject is currently taking, or if the subject is taking the extended-release product, they must convert to the IR formulation as shown in Table 1.

- Cohort 1: Subjects on a fixed dose in the range of 4.5 to 6.0 mg/day of IR ropinirole;
- Cohort 2: Subjects on a fixed dose in the range of 7.5 to 9.0 mg/day IR ropinirole;
- Cohort 3: Subjects on a fixed dose in the range of 12.0 to 14.25 mg/day IR ropinirole; and
- Cohort 4: Subjects on a fixed dose in the range of 15.0 to 17.25 mg/day IR ropinirole.

Enrollment will initially be restricted to Cohort 1 until the determination is made to open enrollment to Cohort 2 based on an evaluation of safety and characterization of the PK profile of approximately 5 subjects over the full 12-week period for Cohort 1 by both an independent data safety monitoring board (DSMB) and Titan, which make up the dose escalation committee (DEC). Prior to commencement of

enrollment for Cohort 3, review of Cohort 2 safety and PK data through the Week 4 Visit will be required, in addition to ongoing safety review of currently enrolled subjects. Prior to commencement of enrollment for Cohort 4, review of Cohort 3 safety data through the Week 4 Visit will be required, in addition to ongoing safety review of currently enrolled subjects.

Subjects who have provided written informed consent will undergo initial screening to determine eligibility. Screening data from each subject will be reviewed, and a determination on the suitability of the subject for the study will be made by the investigator prior to initiation of IR ropinirole or ropinirole implant study drug.

3.1.1. Study Duration

Subjects will be seen for approximately 18 visits over a period of up to 17.5-19.5 weeks (Table 2): Screening, P1, Day -2, Day -1, Implant (Day 1), Post-implant Day 2, Day 3, Day 4, Treatment (Weeks 1, 2, 3, 4, 6, 8, and 10), End of Treatment (EOT) (Week 12), and 2 Follow-up (Weeks 13 and 14). Additional visits may be necessary for unscheduled assessments due to adverse events (AEs).

3.1.2. Subject Participation

This study will enroll approximately 20 subjects (5 per cohort) meeting diagnostic criteria for idiopathic PD and the United Kingdom (UK) Brain Bank Diagnostic Criteria, aged 30 to 80 years, clinically stable on levodopa (L-Dopa) and ropinirole. Enrolled subjects who withdrawal early [prior to 12 weeks on implant(s)] will not be replaced.

3.1.3. Methodology and Dosing

3.1.3.1. Period 1

Subjects will enter screening having been on a fixed dose of 4.5 to 17.25 mg/day IR ropinirole and remain on their maintenance dose until implantation of ropinirole implants.

If subjects enter screening taking the extended-release formulation of ropinirole, their medication will be switched to the IR formulation, to be administered 3 times daily (t.i.d.) until implantation of ropinirole implants, as shown in Table 1. Period 1 will last up to 10 days, the last 7 consecutive days of which will be at a fixed dose. Tablet counts will be done at every visit and subjects will complete diary cards to log their awake "On and Off" periods and track medication compliance.

Table 1: Period 1 Dosing Schedule and Conversion from Ropinirole Extended-Release Formulation

Cohort	Ropinirole XL (once daily)	Total Daily Dose IR Ropinirole
1	4 mg	4.5 mg
2	8 mg	7.5 mg
3	12 mg	12 mg
4	16 mg	15 mg

IR = immediate-release; XL = extended-release;

Two days prior to the Implantation Visit (Day -2), subjects will be admitted to the Clinical Research Unit (CRU) in preparation for the first inpatient PK sampling visit. Pharmacokinetic samples will be taken the day prior to implantation (Day -1), at the Implantation Visit (Day 1), and at the Post-implant Visit (Day 2). The subjects will then be discharged on Day 2. An additional inpatient PK visit will occur at the EOT Visit.

On Day -1, each dose of IR ropinirole should be administered 8 hours apart. Dosing times may vary in the preceding days, however doses must be taken t.i.d.

Subjects will continue their L-Dopa medication as prescribed throughout the entire study.

3.1.3.2. Ropinirole Implant Insertion and Period 2 (Maintenance Phase)

Subjects meeting Implantation Criteria (Section 4.3) will undergo an in-office procedure to insert the ropinirole implant(s) at the start of Period 2. Subjects completing Period 1 in the 4.5 to 6.0 mg/day IR ropinirole dose range will have 1 implant inserted, subjects at an IR ropinirole dose of 7.5 to 9.0 mg/day will receive 2 implants, subjects at a dose of 12.0 to 14.25 mg/day will receive 3 implants, and subjects at a dose of 15.0 to 17.25 mg/day will receive 4 implants. Following implantation, subjects will be followed on treatment for 12 weeks (Period 2).

[redacted] The Ropinirole Implant Applicator is similar in design to the commercially approved applicators currently used for the insertion of Probuphine® and other implantable drugs, such as Implanon® (please see the study Manual of Procedures [MOP] for details regarding the insertion procedure). Subjects will be monitored closely for AEs and vital signs for at least 30 minutes following insertion by medically qualified study staff.

Subjects will return intermittently for assessments of safety, PK sampling, and/or motor symptoms (Table 2).

3.1.3.3. Ropinirole Implant Removal and Follow-up

Ropinirole implants will be removed at the Week 12 EOT Visit in an in-office procedure. See the Study MOP for Insertion/Removal Instructions and additional details regarding the removal procedure. Subjects will be admitted to the CRU the day prior in preparation for inpatient PK sampling. Following removal of the implant(s) and PK sampling, subjects will be transition to their pre-study treatment and will be followed for 2 weeks. The transition back to oral ropinirole may be initiated after the 18-hour PK sample has been collected at the EOT Visit. Subjects who are discontinued early from the study will attend the EOT Visit and the Follow-up Visits.

3.1.3.4. Ropinirole Implant Insertion and Removal Procedures

[redacted]

Implants are removed through a skin incision under local anesthesia using sterile technique. Detailed insertion and removal procedures are described in the MOP provided to the investigator.

3.1.3.5. Investigator Training

All study investigators and appropriate clinical staff will be trained prior to study start, including training in the correct ultrasound technique for the localization of the implants. The sponsor has developed an

extensive hands-on training program for Implanting Physicians that will include training on implant insertion and removal techniques.

3.2. Study Endpoints

3.2.1. Safety and Tolerability Assessments

Safety assessments will include:

- Adverse events (AEs) and serious adverse events (SAEs) related to the study drug
- AEs and SAEs related to the insertion/removal procedure
- Physical and neurological examinations
- Vital signs including positional blood pressure measurements
- 12-lead electrocardiograms (ECGs)
- Clinical laboratory tests (hematology, chemistry, coagulation, and urinalysis)
- Implant site examinations/treatment compliance
- Change from Baseline in the Columbia Suicide Severity Rating Scale (C-SSRS)
- Change from Baseline in the Scales for Outcomes in Parkinson's disease–Psychiatric Complications (SCOPA-PC)

3.2.2. Pharmacokinetic Assessments

The following noncompartmental PK parameters will be derived from ropinirole, N-despropyl ropinirole, and 7-hydroxy ropinirole plasma concentration versus time curves as appropriate:

- Maximum measured plasma concentration (C_{max})
- Minimum measured plasma concentration (C_{min})
- Time to maximum plasma concentration (T_{max})
- Area under the plasma concentration versus time curve from time 0 to time of last measureable concentration (AUC_{0-t})
- Area under the plasma concentration versus time curve from time 0 to 24 hours after dosing (AUC_{0-24})
- First-order terminal elimination rate constant (λz)
- Terminal elimination half-life ($t_{½}$)

Additional PK parameters may be calculated if deemed appropriate.

3.2.3. Efficacy Assessments

The following endpoints will be used to evaluate the efficacy of ropinirole implants in controlling motor fluctuations and drug-induced dyskinesias:

- Change from baseline in the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score

- Change from baseline in hours of awake "On and Off" time

3.2.4. Exploratory Assessments

The following assessments will be used to evaluate the efficacy of ropinirole implants on clinical features of PD:

- Change from baseline in Parkinson's Disease Sleep Scale (PDSS-2) total score
- Change from baseline in Epworth Sleepiness Scale (ESS) score
- Change from baseline in Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) total score

3.2.5. Other Assessments

- Depth of the implant(s) measured by ultrasound
- Palpability of the implant(s)
- Any Applicator complaints, failures and malfunctions during a procedure (whether or not associated with an AE)

3.2.6. Satisfaction Surveys

- Implanting Physician Satisfaction Survey to assess satisfaction with the design and functionality of the Ropinirole Implant Applicator
- Patient Satisfaction Survey to assess satisfaction with the study treatment and insertion and removal procedures

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1. Inclusion Criteria

A subject must meet all of the following inclusion criteria at Screening (i.e., the answer to all of these questions must be "YES") to be eligible to enroll in the study:

1. Has the subject voluntarily provided written informed consent prior to the conduct of any study-related procedures?
2. Is the subject 30 to 80 years (inclusive) of age at the time of informed consent?
3. If female of child-bearing potential, does the subject agree to practice a clinically accepted method of contraception from time of informed consent to the last Follow-up Visit (as defined in Section 6.2)?
4. Has the subject been on a fixed dose of L-Dopa and a fixed dose of ropinirole immediate release 4.5 to 17.25 mg/day (or ropinirole extended-release 4 to 16 mg/day) for at least 30 days, and have their PD deemed clinically stable and at baseline, in the opinion of the investigator, for at least 2 weeks immediately prior to the Screening Visit?
5. If the subject is taking a COMT inhibitor, MAO-B inhibitor, or amantadine medication, have they been on a fixed dose for at least 1 month prior to screening and are willing to remain at that dose for the duration of the study?
6. Does the subject meet diagnostic criteria for idiopathic PD and the UK Brain Bank Criteria?
7. Does the subject score ≥26 on the Mini-Mental State Examination (MMSE) at the Screening Visit?
8. Is the subject willing and able to comply with all study requirements (protocol, clinic visits, procedures, diaries, and medication administration), and is the subject sufficiently proficient in English to understand and complete study instruments?
9. If the subject is, or was, on hormone replacement therapy or therapy with any drug known to substantially inhibit cytochrome P450 (CYP) 1A2 (e.g., ciprofloxacin, fluvoxamine, cimetidine, ethinyl estradiol) or induce CYP1A2 (e.g., nicotine, omeprazole):
    a. Did the subject remain on a stable dose (i.e., did not withdraw, introduce, or change doses) in the 14 days prior to the Screening Visit?, and
    b. Is the subject willing to remain on a stable dose from the Screening Visit through the Follow-up Visit?

4.2. Exclusion Criteria

Subjects are not eligible for the study if any of the following criteria are met at screening (i.e., the answer to all of the following questions must be "NO"):

1. If the subject is female, is the subject pregnant, breastfeeding, or planning to become pregnant during the study or within 1 month after completion of the study?

2. Does the subject have a systolic blood pressure (SBP) ≥180 mmHg or ≤90 mmHg OR diastolic blood pressure (DBP) ≥110 mmHg or ≤50 mmHg at the Screening Visit (either supine or erect)?
3. Has the subject had any episodes of moderate to severe dizziness or syncope within the last 6 months, or does the subject exhibit orthostatic hypotension, defined as a fall in blood pressure (BP) after rising from the supine to standing posture of >20 mmHg for systolic pressure and >10 mmHg for diastolic pressure during the screening assessments?
4. Is the subject taking any dopamine agonists other than L-Dopa or ropinirole?
5. Has the subject undergone electroconvulsive therapy in the 90 days prior to the Screening Visit?
6. Does the subject have scarring or tattoos on his/her inner upper arms within 6 months prior to the Screening Visit or a history of keloidal scarring?
7. Does the subject have a BMI of ≤19, and if so, do they have a skin to fascia depth of ≤3 mm at the bicipital groove of the brachium on ultrasound?
8. Has the subject donated or lost greater than 400 mL of blood within 1 month prior to the Screening Visit?
9. Does the subject have a lifetime history of any suicide attempt (including an active attempt, interrupted attempt, or aborted attempt) or have had suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS at screening?
10. Does the subject have active epilepsy (i.e., occurrence of a seizure) within the past year prior to the Screening Visit?
11. Does the subject have a history of or any current non-Parkinson's-related psychosis?
12. If the subject has Parkinson's disease related psychosis, in the opinion of the investigator, are they likely to alter the risk-benefit of study participation or to interfere with study conduct or interpretation of results?
13. Does the subject have a history of or any current impulse control disorder or symptoms thereof?
14. Does the subject have severe clinical dementia, e.g., scoring 4 on MDS-UPDRS item 1.1 [Cognitive Impairment]?
15. Does the subject have cognitive impairment in the judgment of the investigator that excludes him/her from understanding consent or participating in the study?
16. Has the subject undergone deep brain stimulation or have a history of brain surgery or serious brain injury?
17. Does the subject have a history of any melanoma?
18. Does the subject have a history of alcohol or substance use disorder within the prior 12 months, according to investigator judgment?
19. Does the subject have a positive urine drug screen for drugs of abuse or breath alcohol test at the Screening Visit? Positive urine drug screens may not be repeated.

20. Does the subject use tobacco or nicotine replacement products, or have a positive urine cotinine test at the Screening Visit?
21. Does the subject have a definite or suspected personal history of clinically significant adverse reactions or hypersensitivity to ropinirole (or to drugs with a similar chemical structure) or ethylene vinyl acetate (EVA) that would preclude implantation with ropinirole/EVA?
22. Does the subject have a hypersensitivity to lidocaine , prilocaine, chlorhexidine, epinephrine, or adhesive dressing?
23. Does the subject have a history of wound healing problems?
24. Does the subject have a history of coagulopathy within the past 90 days; current anti-coagulant therapy, such as warfarin or any non-over the counter anti-coagulant; or any other medications or condition that in the opinion of the investigator would pose an increased risk of bleeding during a surgical procedure?
25. In the investigator's opinion, is the subject at risk of prolonged bleeding times based on history, prothrombin time, partial thromboplastin time, or platelet count?
26. Does the subject have an atypical parkinsonian syndrome or secondary parkinsonism (e.g., due to drugs, metabolic disorders, encephalitis, cerebrovascular disease, or degenerative disease) or has the subject used medications within 6 months prior to the Screening Visit that may cause secondary parkinsonism, including but not limited to: dopamine antagonists (other than quetiapine [up to 100 mg/day] or pimavanserin [at doses labelled for treatment of PD]), antipsychotic or neuroleptic medications, metoclopramide, alpha-methyldopa, flunarizine, cinnarizine, reserpine, or stimulant medications such as methylphenidate or amphetamine?
27. Does the subject have a history of neuroleptic malignant syndrome?
28. Has the subject used any other investigational drug within 60 days or 5 half-lives (whichever is longer) prior to the Screening Visit, or have plans to take such a drug any time during the study (through the end of the Follow-up period)?
29. Does the subject have a positive test for human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) at screening?
30. Does the subject have aspartate aminotransferase (AST) levels >2X the upper limit of normal (ULN), alanine aminotransferase (ALT) >2X ULN, total bilirubin >1.5X ULN (unless only from Gilbert's syndrome), or serum creatinine >1.5X ULN, or other significant abnormalities in laboratory or ECG tests at screening that in the investigator's opinion unfavorably alters the risk-benefit of study participation?
31. Does the subject have any clinically significant medical, surgical, psychiatric, or social condition(s) other than PD, or is taking a concomitant medication that, in the opinion of the investigator, unfavorably alters the risk-benefit of study participation or is likely to interfere with study participation or accurate data collection?

4.3. Implantation Criteria

Prior to implantation at the Implant Visit, subjects must meet the following criteria (i.e., the answer to all of these questions must be "YES"):

1. Does the subject continue to satisfy all inclusion and exclusion criteria?
2. Does the subject have a negative urine drug screen for drugs of abuse, cotinine and breath alcohol test at the Day -2 Visit? Positive urine drug and breath alcohol screens may not be repeated. Subjects should be informed that no alcohol should be consumed within 24 hours of any visit.
3. Does the subject have a supine or erect SBP of <180 mmHg or >90 mmHg AND DBP <110 mmHg or >50 mmHg at the Implant Visit?
4. Has the subject been compliant in taking his/her assigned IR ropinirole study medication?
5. Did the subject complete Period 1 with at least 7 consecutive days at the assigned fixed treatment dose of oral ropinirole tablets just prior to implantation?

4.4. Subject Withdrawal Criteria

Every subject has the right to refuse participation in treatment or the study at any time and without providing reasons. A subject's participation must be terminated immediately upon his/her request and reason(s) for discontinuation documented accordingly in the corresponding eCRF.

Any subject who meets one or more of the following criteria will be removed from study drug treatment without prejudice:

- Subject request
- Subject noncompliance, defined as refusal or inability to adhere to the study protocol or any other instances determined by the investigator
- Subject refusal to receive implants
- Evidence of implant removal or attempted removal of the implant
- A medically significant infection or other medically significant AE at the implant site
- Unacceptable or intolerable treatment-related AE
- Pregnancy
- Use of or abuse of non-study assigned ropinirole
- Use of dopamine antagonists other than quetiapine (up to 100 mg/day) or pimavanserin (at doses labelled for treatment of PD)
- Deep brain stimulation
- Use of any investigational treatment
- Intercurrent illness or circumstances that would, in the judgment of the investigator, affect assessments of clinical status to a significant extent, require discontinuation of drug, or both

- At request of Titan, regulatory agencies, or an institutional review board (IRB) of record
- Lost to follow-up

Any subject who meets the above criteria should be seen for an EOT Visit during which implant(s) will be removed. The reason for discontinuation/removal shall be documented. The implant(s) will not be replaced, and follow-up clinical evaluations will be performed as outlined in Section 5.2.5, where possible.

Titan retains the right to end the study at any time. In case of premature termination or suspension of the study, Titan will promptly inform the investigator/institutions and regulatory authorities, of the termination or suspension and the reason for termination/suspension.

4.5. Clinical Management

Based on preclinical data, a temporary increase in ropinirole plasma concentrations is expected to occur following insertion of the ropinirole implant and to last approximately 8-12 hours. Maximum measured plasma concentration (C_{max}) during this period may briefly reach a level corresponding to approximately two times the C_{max} following the subject's baseline oral dose. During this period, subjects may experience symptoms similar to those associated with mild ropinirole overdose. Such symptoms reported during clinical trials with ropinirole included vomiting, increased coughing, fatigue, syncope, vasovagal syncope, dyskinesia, agitation, chest pain, orthostatic hypotension, somnolence, and confusional state (Requip Label). These symptoms will be managed at the investigator's discretion.

5. STUDY SCHEDULE AND PROCEDURES

5.1. Study Schedule

The study schedule can be found in Table 2, and the PK blood sample collection schedule can be found in Table 3. Detailed information on study assessments is provided in Section 6.

5.2. Study Visits

5.2.1. Screening Period / Visit S1 (2 - 4 Weeks)

Screening (Visit S1) will begin within 4 weeks prior to the start of Period 1. Written informed consent must be obtained before any study-specific procedure is performed. Subjects must meet all eligibility criteria before being enrolled in the study (see Section 4). Screening assessments may be conducted across more than one visit during the screening period.

The following information will be collected and procedures performed:

- Obtain written informed consent
- Eligibility criteria review
- Demographics
- Obtain medical and medications history (including history of PD and PD medications)
- Urine drug and cotinine screen and alcohol breath test (to be performed prior to cognitive and motor assessments). Subjects with a positive alcohol breath test at the S1 Visit should be rescheduled to return to complete the remaining procedures along with another alcohol breath test. During the S1 Visit, and onward, subjects should be instructed not to consume alcohol within 24 hours of any subsequent visit.
- Clinical chemistry, hematology, coagulation profile, urinalysis
- Neurological examination
- UK Brain Bank Diagnostic Criteria
- MMSE
- Hoehn and Yahr scale
- MDS-UPDRS
- C-SSRS
- SCOPA-PC
- QUIP-RS
- Serum pregnancy test (females of childbearing potential only)
- Standard 12-lead ECG
- Height

- Weight
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
    - Two sets of measurements of supine/erect BP should be obtained at least 15 minutes apart. These measurements will be recorded in the eCRF. Subjects with any readings that are exclusionary will not be eligible for the study.
- Physical examination
- Virus serology: HBV, HCV, HIV (Ensure that the subject has been properly consented and was counseled prior to drawing blood for testing; HBV, HCV, and HIV testing is required unless a site's IRB or country-specific laws/regulations prohibit such testing.)
- Dispense subject diary cards
- Hauser Diary concordance training

5.2.2. Period 1 (Pre-Implantation Baseline)

5.2.2.1. Period 1 / Visit P1

The Period 1 (P1) Visit should occur as soon as all eligibility criteria have been satisfied following Visit S1. Period 1 will last up to 10 days, the last 7 consecutive days of which will be at a fixed dose of oral ropinirole. Refer to Section 3.1.3.1 for additional details on dosing during Period 1.

The following information will be collected and procedures performed:

- C-SSRS
- SCOPA-PC
- Weight
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
- Dispense and collect subject diary cards
- Dispense oral ropinirole tablets
- Record AEs
- Review concomitant medications

5.2.2.2. Period 1 / Visit Day -2

Two days prior to the Implantation Visit (Day -2), subjects will be admitted to the CRU in preparation for the first inpatient PK sampling visit beginning the following morning. Subjects will be confined to the CRU from the time of check-in on Day -2 until discharge following all scheduled procedures on Day 2. Subjects should be reminded to bring their unused study drug or empty packaging to this visit, and also that no alcohol is allowed within 24 hours of any study visit.

The following information will be collected and procedures performed:

- C-SSRS

- SCOPA-PC
- PDSS-2
- ESS
- Urine pregnancy test (females of childbearing potential only)
- Standard 12-lead ECG
- Weight
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
- Clinical chemistry, hematology, coagulation profile, urinalysis
- Urine drug and cotinine screen and alcohol breath test
- Collect subject diary cards
- Treatment compliance (tablet counts)
- Record AEs
- Review concomitant medications

5.2.2.3. Period 1 / Visit Day -1

On Day -1, the following information will be collected and procedures performed:

- Low fat meals should be provided to each subject at mealtime on this day. Low fat meals are meals where ≤30% of calories are from fat.
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
- PK blood sample collection:
    - Each dose of ropinirole should be administered with 8 ounces of water, dosing should be observed, a hand/mouth check should be performed, and the time of dosing should be recorded. On Day -1, each dose of IR ropinirole should be administered 8 hours apart. Dosing times may vary in the preceding days, however doses must be taken t.i.d. The second and third doses of ropinirole are to be taken immediately following the 8-hour and 16-hour PK draws, respectively.
    - PK sampling will be done predose (0 hours), and postdose at 0.5 hours, 1 hour, 1.5 hours, 2 hours, 4 hours, 8 hours,8.5 hours, 9 hours, 9.5 hours, 10 hours, 12 hours, 16 hours, 16.5 hours, 17 hours, 17.5 hours, 18 hours, 20 hours, and 24 hours as specified in Table 3.
    - Sites are encouraged to collect the inpatient PK samples within a ±2 minute window. Collections falling outside this window, unless the difference in time is inordinately large, will not be considered a protocol deviation.
    - The nondominant arm will be selected for blood draws, and implantation, so that the opposite arm will be available for BP readings and activities such as eating.

- Treatment compliance (tablet counts)
- Record AEs
- Review concomitant medications

5.2.3. Period 2 (Post-Implantation)

5.2.3.1. Period 2 / Implant Visit (Day 1)

Following the completion of the PK sample collection occurring on Day -1, the following baseline procedures will be performed on Day 1, prior to implantation. The subject will be served breakfast at least 1 hour prior to implantation.

Prior to Implantation:

- Eligibility criteria review, including Implantation Criteria in Section 4.3
- Neurological examination
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
    - Subjects with any BP readings that do not meet Implantation Criteria will not be implanted and will be withdrawn from study.
- Abbreviated review of systems
- Urine drug and cotinine screen and alcohol breath test
- Implant site examination/treatment compliance (tablet counts)
- PK blood sample collection (0 hour time point)

Implant Insertion:

- Insertion of ropinirole implant(s)
- Palpation of implant(s) as detailed in the MOP
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
    - Orthostatic hypotension measures (supine and standing BP and 60 second pulse rate) will be taken at the following post-implantation time points: 0.5 hours, 1 hour, 2 hours, and 4 hours.
    - Respiratory rate and body temperature will be collected at 15 minutes and 30 minutes following implant insertion.
- PK blood sample collection at 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, and 20 hours postimplantation as specified in Table 3
- Standard 12-lead ECG at 3 hours [±15 minutes]
- Dispense treatment identification card
- Provide wound care information sheet

- Record AEs (monitor AEs for at least 30 minutes after removal)
- Review concomitant medications
- Insertion Procedure Assessment Form
- Implanting Physician Satisfaction Survey

5.2.3.2. Period 2 / Day 2 Visit

This visit will occur the day after the Implant Visit, while the subject is still an inpatient. The following assessments and evaluations will occur at this visit:

- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
- Dispense subject diary cards
- Implant site examination/treatment compliance
- Record AEs
- Review concomitant medications
- PK blood sample collection at 24 hours and 36 hours post-implantation, as specified in Table 3
- Following collection of the, 36-hour PK sample on Day 2, subjects will be discharged from the CRU and instructed to return for Day 3

5.2.3.3. Period 2 / Day 3 Visit

The following assessments and evaluations will occur at this visit:

- C-SSRS
- SCOPA-PC
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
- Implant site examination/treatment compliance
- Record AEs
- Review concomitant medications
- PK blood sample collection at 0 hours (collected at the same time of day relative to the time of implantation)

5.2.3.4. Period 2 / Day 4 Visit

The following assessments and evaluations will occur at this visit:

- C-SSRS
- SCOPA-PC
- Weight

- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
- Implant site examination/treatment compliance
- Record AEs
- Review concomitant medications
- PK blood sample collection at 0 hours (collected at the same time of day relative to the time of implantation)

5.2.3.5. Period 2 / Weeks 1 – 10

Weeks 1-10 Visits should occur ±1 day relative to the projected time point as measured from the Implant Visit. All visits are outpatient. The following information will be collected and procedures performed at visits during Period 2.

5.2.3.6. Weeks 1, 2 and 3

- C-SSRS
- SCOPA-PC
- Weight
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
- Dispense and collect subject diary cards
- Implant site examination/treatment compliance
- Record AEs
- Review concomitant medications
- PK blood sample collection at 0 hours (collected at the same time of day relative to the time of implantation)

5.2.3.7. Week 4

- MDS-UPDRS
- C-SSRS
- SCOPA-PC
- PDSS-2
- ESS
- QUIP-RS
- Urine pregnancy test (females of childbearing potential only)
- Standard 12-lead ECG
- Weight

- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
- Abbreviated review of systems
- Clinical chemistry, hematology, coagulation profile, urinalysis
- Urine drug and cotinine screen and alcohol breath test
- Dispense and collect subject diary cards
- Implant site examination/treatment compliance
- Record AEs
- Review concomitant medications
- PK sampling will be done at the following time points: 0 hours (collected at the same time of day relative to the time of implantation), 12 hours, and 24 hours as specified in Table 3

5.2.3.8. Week 6

- C-SSRS
- SCOPA-PC
- Weight
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
- Dispense and collect subject diary cards
- Implant site examination/treatment compliance
- Record AEs
- Review concomitant medications
- PK blood sample collection at 0 hours (collected at the same time of day relative to the time of implantation)

5.2.3.9. Week 8

- MDS-UPDRS
- C-SSRS
- SCOPA-PC
- PDSS-2
- ESS
- QUIP-RS
- Urine pregnancy test (females of childbearing potential only)
- Weight

- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
- Abbreviated review of systems
- Dispense and collect subject diary cards
- Implant site examination/treatment compliance
- Record AEs
- Review concomitant medications
- PK blood sample collection at 0 hours (collected at the same time of day relative to the time of implantation), 12 hours, and 24 hours as specified in Table 3

5.2.3.10. Week 10

- C-SSRS
- SCOPA-PC
- Weight
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
- Dispense and collect subject diary cards
- Implant site examination/treatment compliance
- Record AEs
- Review concomitant medications
- PK blood sample collection at 0 hours (collected at the same time of day relative to the time of implantation)

5.2.4. End of Treatment / Week 12 or Early Withdrawal Visit

The EOT Visit should occur no less than 12 weeks from the Implant Visit, except in cases of early withdrawal. Subjects will report to the CRU for admission during the evening of the day prior to the Week 12 Visit or early termination, in preparation for implant removal and PK sampling beginning the following morning. Subjects should be reminded that no alcohol is allowed within 24 hours of any study visit. The subject will be served breakfast at least 1 hour prior to removal of the implant(s). The morning of the Week 12 Visit, prior to the implant removal procedure, the following procedures are performed.

Prior to Implant Removal:

- Palpation of implant(s) as detailed in the MOP
- Ultrasound
- Neurological examination
- MDS-UPDRS
- C-SSRS

- SCOPA-PC
- PDSS-2
- ESS
- QUIP-RS
- Standard 12-lead ECG
- Weight
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate)
- Abbreviated review of systems
- Clinical chemistry, hematology, coagulation profile, urinalysis
- Implant site examination/treatment compliance
- Collect subject diary cards
- PK blood sample collection (0 hour time point)

Implant Removal:

- Removal of ropinirole implant(s)
- Serum pregnancy test (females of childbearing potential only)
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
    - Orthostatic hypotension measures (supine and standing BP and 60-second pulse rate) will be taken at the following time points post implantation removal: 0.5 hours, 1 hour, 2 hours, and 4 hours
- Urine drug and cotinine screen and alcohol breath test
- Record AEs (monitor for AEs in the clinic for at least 30 minutes after removal)
- Review concomitant medications
- Provide wound care information
- Removal Procedure Assessment Form
- PK sampling will be done at the following time points relative to implant removal: 6 hours, 12 hours, and 18 hours. Any transition back to oral ropinirole should not occur until after the last PK sample has been collected.
- Subjects will be discharged from the CRU following collection of the 18 hour PK sample

5.2.5. Follow-up Period

5.2.5.1. Follow-up Period / Week 13

The following assessments and evaluations will occur at this visit:

- C-SSRS

- SCOPA-PC
- Weight
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
- Implant site examination
- Record AEs
- Review concomitant medications

5.2.5.2. Follow-Up Period / Week 14

The following assessments and evaluations will occur at this visit:

- C-SSRS
- SCOPA-PC
- Urine pregnancy test (females of childbearing potential only)
- Weight
- Vital signs (supine and standing BP [orthostatic measurements], pulse rate, respiratory rate, and oral body temperature)
- Implant site examination
- Patient Satisfaction Survey
- Record AEs
- Review concomitant medications

5.2.6. Unscheduled Visits

Subjects may experience AEs that necessitate an unscheduled visit. There may also be situations in which the investigator asks a subject to report for an unscheduled visit following the report of an AE or SAE. Should emergency removal of the implants be necessary during the study, subjects should be instructed to contact the 24-hour emergency contact number for the investigator, as listed on the treatment identification card (Section 8.4). All assessments, AEs, or SAEs associated with the unscheduled emergency visit will be recorded in the eCRF. If the subject is unable to see the investigator or seeks care elsewhere in a situation that requires emergency removal of the implants, the subject should present their treatment identification card to the health care provider, indicating that they are receiving ropinirole as part of the study. Follow-up care will be provided by the investigator, and the subject should complete an Early Withdrawal visit and Follow-Up Visits, where possible. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of subjects during the study. Electronic case report forms should be completed for each unscheduled visit.

Table 2: Study Schedule of Events

Event	**Screening** (up to 4 weeks)	**Period 1** (up to 10 days)			**Period 2**											**EOT or EWD**	**Follow-up**	
Visits[1]	S1	P1	Day -2	Day -1	Implant Visit (Day 1)	Day 2	Day 3	Day 4	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12	Week 13	Week 14
Written Informed Consent	X																	
Eligibility Criteria Review	X				X[2]													
Demographics	X																	
Medical and Medications History	X																	
Neurological Examination	X				X[2]											X[3]		
UK Brain Bank Diagnostic Criteria	X																	
MMSE	X																	
Hoehn and Yahr	X																	
MDS-UPDRS	X											X		X		X[3]		
C-SSRS	X	X	X				X	X	X	X	X	X	X	X	X	X[3]	X	X
SCOPA-PC	X	X	X				X	X	X	X	X	X	X	X	X	X[3]	X	X
PDSS-2			X									X		X		X[3]		
ESS			X									X		X		X[3]		
QUIP-RS	X											X		X		X[3]		
Pregnancy Test[4]	X		X									X		X		X		X
12-Lead ECG	X		X		X[5]							X				X[3]		
Implantation Criteria					X[2]													

Event	**Screening** (up to 4 weeks)	**Period 1** (up to 10 days)			**Period 2**											**EOT or EWD**	**Follow-up**	
Visits[1]	S1	P1	Day -2	Day -1	Implant Visit (Day 1)	Day 2	Day 3	Day 4	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12	Week 13	Week 14
Height	X																	
Weight	X	X	X					X	X	X	X	X	X	X	X	X	X	X
Vital Signs[6]	X[7]	X	X	X	X[8, 9]	X	X	X	X	X	X	X	X	X	X	X[8]	X	X
Physical Examination	X																	
Abbreviated Review of Systems					X[2]							X		X		X[3]		
Chemistry, Hematology, Coagulation Profile, Urinalysis	X		X									X				X[3]		
Urine Drug and Cotinine Screen and Breath Alcohol Test[10]	X		X		X[2]							X				X		
HBV, HCV, HIV	X[11]																	
Hauser Diary concordance training	X																	
Dispense Subject Diary Cards[12]	X	X				X			X	X	X	X	X	X	X			
Collect Subject Diary Cards[12]		X	X						X	X	X	X	X	X	X	X[3]		
Insertion Procedure					X[13]													
Palpation of Implant(s)[14]					X											X		
Ultrasound																X[3]		
Dispense Oral Study Medication		X																
PK Blood Sample Collection				X	X	X	X	X	X	X	X	X	X	X	X	X		
Implant Site Examination / Treatment Compliance[15]			X	X	X[2]	X	X	X	X	X	X	X	X	X	X	X[3]	X	X

Event	**Screening** (up to 4 weeks)	**Period 1** (up to 10 days)			**Period 2**											**EOT or EWD**	**Follow-up**	
Visits[1]	S1	P1	Day -2	Day -1	Implant Visit (Day 1)	Day 2	Day 3	Day 4	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12	Week 13	Week 14
Dispense Treatment Identification Card					X													
Removal Procedure																X		
Wound Care Information Sheet					X											X		
Patient Satisfaction Survey																		X
Implanting Physician Satisfaction Survey					X													
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications / Procedures		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BP = blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale; DBP = diastolic blood pressure; ECG = electrocardiogram; eCRF = electronic case report form; EOT = End of Treatment; ESS = Epworth Sleepiness Scale; EWD = early withdrawal; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IRB = Institutional Review Board; MDS-UPDRS = Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MMSE = Mini Mental State Examination; P = period; PD = Parkinson's disease; PDSS-2 = Parkinson's Disease Sleep Scale; PK = pharmacokinetic(s); QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; S = screening; SBP = systolic blood pressure; SCOPA-PC = Scale for Outcomes of Parkinson's disease–Psychiatric Complications

[1] Visit windows: The P1 Visit should occur once all screening assessments and eligibility criteria are met. Weeks 1-10 Visits should occur ±1 day relative to the projected time point as measured from the Implant Visit. The EOT Visit should occur no less than 12 weeks from the Implant Visit, except in cases of early withdrawal. The Week 13 Follow-up Visit should occur 1 week ±2 days from EOT visit. The Week 14 Follow-up Visit should occur 2 weeks ±2 days from last implant removed.

[2] To be performed prior to implantation.

[3] Measures to be completed prior to implant removal.

[4] For females of child-bearing potential, a serum pregnancy test will be performed at the Screening Visit and the EOT Visit (Week 12 or early withdrawal). An "in-office" urine pregnancy test will be required at Day -2, Week 4, Week 8, and Week 14 Follow-up Visit.

[5] Implant Visit ECG to be completed 3 hours (±15 minutes) following implant insertion.

[6] Vital signs include supine BP and standing BP, pulse rate, respiratory rate, and oral body temperature. Measurements for orthostatic hypotension will be taken at every study visit. Orthostatic measurements (supine and standing BP and 60 seconds of pulse rate) can be measured manually or using an automated BP machine; the same method of measurement should, however, be used throughout the study for a particular subject. The subject's BP and pulse rate will be

measured after the subject has been supine for approximately 5 minutes. The subject will be instructed to rise to a standing position, and a BP measurement will be taken after the subject has been standing for 1 minute. Orthostatic hypotension is defined as a reduction of SBP of >20 mmHg or DBP >10 mmHg within 3 minutes of quiet standing.

[7] At screening, two sets of measurements of supine/erect BP should be obtained at least 15 minutes apart. These measurements will be recorded in the eCRF. Subjects with any exclusionary readings will not be eligible for the study.

[8] Measures for orthostatic hypotension will be taken for: Implant Visit at 0 (prior to implantation), 0.5, 1, 2, and 4 hours postimplantation; EOT Visit at 0 (pre-implant removal), 0.5, 1, 2, and 4 hours post-implantation removal.

[9] Respiration rate and body temperature will be collected prior to implantation, and at 15 and 30 minutes following implant insertion.

[10] Subjects will also provide 3 random urines (to test for drugs of abuse and cotinine) and breath alcohol tests to be collected at any 3 non-PK inpatient stay study visits, with at least 2 collected during Period 2.

[11] It is the investigator's responsibility to understand and comply with all laws and regulations that apply to HIV, HBV, and HCV testing of blood. HIV, HBV, and HCV testing is required unless a site's IRB prohibits such testing.

[12] Awake “On and Off” time diaries will be completed for 2 consecutive days prior to Visit P1 and Day -2, and 2 consecutive days prior to each visit for Weeks 1 through 12.

[13] Prior to implant insertion, the Implantation Criteria must be met.

[14] As specified in the Manual of Procedures (MOP).

[15] The implant site will be visually inspected. If there is any evidence of removal or attempted removal of the implants, the subject will be withdrawn from the study and all implants will be removed. Tablet counts will be conducted to track compliance.

Table 3: Schedule of PK Blood Sample Collection

	Inpatient[1]			Outpatient[4]		Outpatient[4]				Inpatient[1]
Hour	**Day -1[2, 3]**	**Implant Visit (D1)**	**Day 2 (D2)**	**Days 3, 4 (D3, D4)**	**Weeks 1, 2, 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**EOT / Week 12 (or EWD)**
0[4]	X[5]	X[6]	X[7]	X	X	X	X	X	X	X[5, 6]
0.5	X									
1	X	X								
1.5	X									
2	X	X								
4	X	X								
6										X
8	X	X								
8.5	X									
9	X									
9.5	X									
10	X									
12	X	X	X[7]			X		X		X
16	X									
16.5	X									
17	X									
17.5	X									
18	X									X
20	X	X								
24	X					X		X		

CRU = clinical research unit; D = day; EOT = End of Treatment; EWD = early withdrawal; PK = pharmacokinetic(s)

[1] Sites are encouraged to collect their inpatient PK samples within a ±2 minute window. Collections falling outside this window, unless the difference in time is inordinately large, will not be considered a protocol deviation.

[2] Each dose of oral ropinirole should be administered with 8 ounces of water, dosing should be observed, a hand/mouth check should be performed, and the time of dosing should be recorded. . Each dose of IR ropinirole should be administered 8 hours apart on Day -1. The second and third doses of ropinirole are to be taken immediately following the 8-hour and 16-hour PK draws, respectively..

[3] The nondominant arm will be selected for blood draws and implantation, so that the opposite arm will be available for blood pressure readings and activities such as eating.

[4] Zero hour PK sampling time points are collected prior to each dosing on Day -1, on the Implant Visit prior to implantation, and at EOT Visit prior to implant removal. For all other days, it should be collected at the same time of day relative to the time of implantation ±3 hours.

[5] Subjects will check-in to the CRU the day prior to begin their inpatient stay.

[6] Breakfast will be served at least 1 hour prior to implantation and prior to removal of the implant(s).

[7] Zero-hour and 12-hour collections on Day 2 correspond to the 24-hour and 36-hour sample collections post-implantation

6. ASSESSMENTS

6.1. Informed Consent

Subjects must voluntarily provide written informed consent before any study-related procedure or assessment is performed (see Section 13.3 for additional details).

6.2. Eligibility Review

Prior to initiating dosing with study drug at Visit P1, subjects must meet all eligibility criteria as outlined in Sections 4.1 and 4.2.

To satisfy inclusion criterion 3, a clinically accepted method of contraception for females of childbearing potential includes being surgically sterile via bilateral tubal ligation or hysterectomy, has a male partner who is surgically sterilized, use of oral contraceptive (combined or progesterone only), use of any intrauterine device with published data showing that the lowest expected failure rate is less than 1% per year, use of a double-barrier method (any combination of physical and chemical barriers), use of implants of levonorgestrel, and use of any other methods with published data showing that the lowest expected failure rate for that method is less than 1% per year.

Prior to implant insertion, subjects must meet the criteria outlined in Section 4.3.

6.2.1. United Kingdom Brain Bank Diagnostic Criteria

Potential subjects will be evaluated against the UK Brain Bank diagnostic criteria for PD at the Screening Visit to determine eligibility (Hughes et al., 1992).

6.2.2. Mini Mental State Examination (MMSE)

The MMSE will be performed at screening to assess eligibility (Folstein et al., 1975). The subject must have a score ≥26 on the MMSE at the Screening Visit to be eligible for the study.

6.3. Demographics and Medical and Medications History

Information relating to the subject's sex, age, race, height, and weight will be recorded at screening on the appropriate eCRF page. A complete medical history and history of prior medications (including PD history and PD medication history) each subject will be collected at the Screening Visit and recorded on the appropriate eCRF page. The Hoehn and Yahr scale will also be used at the Screening Visit to assess PD severity (Hoehn and Yahr, 1967). The medical history will include any significant, previously diagnosed acute or chronic medical conditions, including any surgeries. The medication history will capture medications taken up to 30 days prior to signing informed consent. This history will also include any abnormalities found during the physical examination conducted at the Screening Visit.

6.4. Safety and Tolerability Assessments

6.4.1. Adverse Events

All AEs that occur between the time the subject signs the ICF and 30 days after study drug treatment has been discontinued must be documented in the eCRF. Adverse events that have been designated by the

investigator as related to study drug, and all serious AEs, will be followed until resolution or stabilization. Adverse events that are reported by the subject at times other than specified in the Schedule of Events (Table 2) should also be recorded. Details regarding AE definitions, collection, recording, and reporting are found in Section 9.

6.4.2. Physical and Neurological Examination and Abbreviated Review of Systems

A complete physical examination of all major body systems (excluding genitourinary exam) will be performed at the Screening Visit. At the Implant Visit and EOT Visit, an abbreviated review of systems will be performed to capture changes since screening. Additionally, a neurological exam will be performed at the Screening Visit, Day 1, and Week 12.

6.4.3. Implant Site Examination/Treatment Compliance

The implant site will be visually inspected for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing, and any other abnormalities. If there is any evidence of removal and the subject confirms the removal of some or all of the implants, the subject will be withdrawn from study and all implants will be removed.

6.4.4. Height and Weight

Height will be recorded at the Screening Visit only. Weight will be recorded at the visits listed in Table 2.

6.4.5. Vital Signs

Vital signs include supine BP and standing BP, pulse rate, respiratory rate, and oral body temperature. Measurements for orthostatic hypotension will be taken at every study visit and at specific time points as described in Table 2.

Orthostatic measurements (supine and standing BP and 60 seconds of pulse rate) can be measured manually or using an automated BP machine; the same method of measurement should, however, be used throughout the study for a particular subject. The subject's BP and pulse rate will be measured after the subject has been supine for approximately 5 minutes. The subject will be instructed to rise to a standing position, and a BP measurement will be taken after the subject has been standing for 1 minute

At the Screening Visit, two sets of measurements of supine/erect BP should be obtained at least 15 minutes apart. These measurements will be recorded in the eCRF. Subjects with any readings that are exclusionary per section 4.2 are not eligible for the study.

Orthostatic hypotension is defined as a reduction of SBP of >20 mmHg or DBP >10 mmHg within 3 minutes of quiet standing.

6.4.6. Electrocardiography (ECG)

A 12-lead ECG will be recorded and assessed at the Screening Visit, Day -2 Visit, Implant Visit, Week 4 Visit, and EOT Visit by the investigator or other designated, qualified individual from the study research team. At the Implant Visit, the ECG will be conducted 3 hours (±15 minutes) following implantation. The ECG will be signed and dated by a medically qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant. In general, abnormal, clinically significant ECGs are expected to be associated with an item recorded in medical history or with an AE.

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

The C-SSRS Baseline/Screening version will be used to assess suicidality of the subject at the Screening Visit; the "Since Last Visit" version will subsequently be completed at Visit P1, Visit Day -2, Post-implant Visit Day 3, Post-implant Visit Day 4, and at Weeks 1 through 14 (Posner et al., 2008) .

6.4.8. Scale for Outcomes of Parkinson's Disease-Psychiatric Complications (SCOPA-PC)

The SCOPA-PC is a semistructured questionnaire that has been validated to assess both psychotic and compulsive complications of therapy in PD (Visser et al., 2007). The SCOPA-PC assesses the severity of each of the 7 items on a scale from 0 (no symptoms) to 3 (severe symptoms). The SCOPA-PC will be completed at the Screening Visit; Visit P1, Visit Day -2, Post-implant Visit Day 3, Post-implant Visit Day 4, and at Weeks 1 through 14.

6.5. Efficacy Assessments

6.5.1. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS is a 4-part rating scale used to evaluate non-motor experiences of daily living (Part I), motor experiences of daily living (Part II), motor examination (Part III), and motor complications (Part IV) (Goetz et al., 2008). The MDS-UPDRS assessment will be performed at the Screening Visit, and Weeks 4, 8, and 12. The MDS-UPDRS must take place prior to implant removal at the Week 12 Visit.

6.5.2. Parkinson's Disease Sleep Scale (PDSS-2)

The PDSS-2 is used to quantify the quality of sleep and level of sleep disruption experienced by the subject in the past week (Trenkwalder et al., 2011). Subjects will complete this assessment on Day -2, and Weeks 4, 8, and 12.

6.5.3. Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire used to evaluate daytime sleepiness (Johns, 1991). In reference to the prior month, the subject will be asked to rate on a scale of 0 to 3 the chance of dozing in 8 situations of daily life. Subjects will complete this assessment on Day -2, and Weeks 4, 8, and 12.

6.5.4. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS)

The QUIP is a self-rated screening instrument developed and validated for the detection of impulse control disorders and related behaviors in PD. The QUIP-RS assesses the severity of the same behaviors with a Likert scale (Weintraub et al., 2012). Subjects will complete this assessment at the Screening Visit, and Weeks 4, 8, and 12.

6.5.5. Awake "On and Off" Time Diary (Hauser Diary)

In order to evaluate patterns in motor function, awake "On" and "Off" time will be assessed using a subject diary (Hauser et al., 2000). The diary will be used to record motor state in half-hour intervals over a 24-hour period (during waking hours) for 2 consecutive days prior to Visit P1, Day -2, and Weeks 1

through 12. Subjects will receive training on diary completion and rater concordance by the investigator or designee during the Screening Visit.

6.6. Concomitant Medications/Therapies

All concomitant medications/therapies collected throughout the study must be recorded on the Concomitant Medication eCRF. The prohibited concomitant medications/therapies for the study are discussed in Section 8.1.

6.7. Laboratory Assessments

6.7.1. Serum Chemistry, Hematology, Coagulation Profile, Urinalysis, and Virus Serology

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

Please refer to the appropriate central laboratory instruction manuals provided for information on the collection and shipment of study samples.

The following blood and urine samples will be collected during the specified clinic visits in Table 2:

Hematology	Hematocrit, hemoglobin, red blood cells (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC morphology, white blood cells (WBC) with differential, and platelet count
Chemistry (including liver profile)	Blood urea nitrogen, calcium, bicarbonate, chloride, creatinine, glucose, potassium, sodium, albumin, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total cholesterol, total protein
Coagulation Profile	Prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT)
Urinalysis	Routine urinalysis
Other	Plasma ropinirole levels, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV)

It is the investigator's responsibility to understand and comply with all laws and regulations that apply to the testing of blood for HIV, HBV, and HCV. These laws and regulations may include state laws related to written consent, separate from the ROP-001 ICF, and pre- and post-test counseling.

6.7.2. Urine Drug and Cotinine Screen and Breath Alcohol Test

A routine urine drug screen (for drugs of abuse), cotinine screen, and breath alcohol test will be conducted at screening, Day -2, Implant Visit (preimplantation), Week 4 Visit, and the EOT Visit. Subjects will also provide 3 random urines (to test for drugs of abuse and cotinine) and breath alcohol tests to be collected at any 3 non-PK inpatient stay study visits, with at least 2 collected during Period 2.

6.8. Pharmacokinetic Assessments

Plasma for ropinirole quantification will be collected on the days and time points presented in Table 3. Following implantation, venous blood samples should be drawn from the nondominant arm. Instructions for processing, storage, and shipping of PK samples will be provided to each site.

6.9. Other Assessments

6.9.1. Palpation of Implant(s)

Palpation will be performed and recorded on the eCRF to confirm the presence of each of the implant(s) at the Implant Visit immediately after insertion and at the EOT Visit prior to implant removal, in accordance with the detailed instructions in the MOP.

6.9.2. Ultrasound for Depth of Implant(s)

At the EOT Visit prior to implant removal, an ultrasound will be performed to measure placement depth of the implant(s). Evaluation of the depth of the implant to be conducted prior to removal by measuring and recording, in millimeters, the depth of each implant , using ultrasound with high frequency linear array transducer (10MHz or greater). These measurements will be reviewed by a centralized reader. Additional ultrasounds, at other visits, may be performed if imaging is necessary to localize the implant(s).

6.10. Satisfaction Surveys

An Implanting Physician satisfaction questionnaire related to functionality, design, technical aspects and safety of the Applicator will be completed after the insertion procedure with questions specific to the Ropinirole Applicator as used in the insertion procedure.

A Patient Satisfaction Survey will be administered at the Week 14 Visit. Each subject will rate their satisfaction with treatment across multiple domains including the implant insertion/removal procedures. In instances where the survey was not completed at the Week 14 Visit, a post visit phone contact may be conducted to obtain responses.

7. INVESTIGATIONAL DRUG INFORMATION AND MANAGEMENT

7.1. Investigational Drug Dose Regimen

Below is a brief description of the products and treatments to be used for this study. Please refer to the Requip Label for more information regarding IR ropinirole.

Ropinirole implants are designed to deliver a sustained dose of ropinirole for 3 months after subdermal implantation for the treatment of the signs and symptoms of PD. This formulation of the ropinirole implant is based on ProNeura technology, which is an EVA-based non-biodegradable solid matrix subdermal implant. The ropinirole implant is 3.5 mm in diameter and 60 mm in length, and contains 60% ropinirole HCl/40% EVA in the core and 3% ropinirole HCl/97% EVA in the shell. Each washed and terminally sterilized implant contains a nominal 200 mg ± 10% of ropinirole.

7.2. Dose Rationale

The dose selection for the ropinirole implant is based on the approved dose range of IR ropinirole described in the Prescribing Information for the RLD (Requip Label). [redacted]

7.3. Investigational Drug Packaging and Labeling

The IR ropinirole to be used in this study will be obtained from a commercial source.

Ropinirole implants are individually packaged in a foil-laminate, heat-sealed pouch. Pouches are then sterilized using radiation. Ropinirole implants will be packaged into bulk cartons, each containing 1 sterile pouched implant. A label will be applied to each implant pouch as well as the bulk carton. The bulk cartons will not be subject specific.

All investigational products used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures (SOPs) of the manufacturers, Good Manufacturing Practice guidelines, International Conference on Harmonisation (ICH) guidelines for GCP, and applicable regulations.

7.4. Investigational Drug Storage

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

Oral IR ropinirole should be stored at controlled room temperature (20° to 25°C / 68° to 77°F) and protected from light and moisture (Requip Label).

7.5. Investigational Drug Administration

An applicator consisting of a thin-walled cannula and obturator will be supplied for use in the subdermal insertion of the ropinirole implant(s). Each applicator is intended for a single insertion procedure of the implant(s) into a single subject and must be disposed after use.

Applicators will be provided sterile in a Tyvek pouch, with one Applicator per carton. Both the Applicator pouch and carton will be labeled.

Additional details on investigational product administration are provided in the Investigator Brochure and study MOP.

7.6. Investigational Drug Accountability

Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed, the running inventory, and the unused quantities returned to Titan's drug supply vendor at the end of the study. Please refer to the study MOP for more information.

Following implant removal, all removed implants should be packaged and shipped to appropriate laboratory vendor, as outlined in the MOP.

8. TREATMENT OF SUBJECTS

8.1. Concomitant Medication

Prohibited medications for this study include medications that may cause secondary parkinsonism, including but not limited to dopamine antagonists (other than quetiapine [up to 100 mg/day] or pimavanserin [at doses labelled for treatment of PD]), antipsychotic or neuroleptic medications, metoclopramide, alpha-methyldopa, flunarizine, cinnarizine, and reserpine; stimulant medications such as methylphenidate or amphetamine; anti-coagulant therapies (such as warfarin and platelet inhibitors), aspirin (greater than 162 mg/day); and any investigational drugs. Use of marijuana, including medical marijuana, and other compounds that interfere with study participation or accurate data collection are also prohibited.

8.2. Other Restrictions

No alcohol should be consumed within 24 hours of any visit post-screening and subjects should be reminded of this restriction prior to all alcohol testing.

8.3. Treatment Compliance

The implant site will be visually inspected by the investigator. If there is any evidence of removal (or attempted removal), subjects will be withdrawn from study and have implants removed (if applicable).

Treatment compliance with oral dosing of ropinirole will be evaluated by tablet counts.

8.4. Treatment Identification Card

Subjects will receive a wallet card indicating that they are receiving ropinirole as part of the study. This card should be presented to health care providers by the subject in the event of an emergency. Sample wallet cards will be provided for IRB submission.

8.5. Wound Care Information Sheet

Subjects will receive written instructions that explain how to care for the surgical site after implant insertion and removal.

9. ADVERSE EVENTS

9.1. Adverse and Serious Adverse Events

This section defines the types of AEs and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Information in this section complies with 21 Code of Federal Regulations (CFR) 312, *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting,* and *ICH Guideline E-6: Guidelines for Good Clinical Practice*.

The investigator is responsible for the detection and documentation of AEs regardless of treatment group or suspected causal relationship to the investigational product. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as an SAE or AE of special interest requiring immediate notification to Titan or its designated representative.

9.1.1. Definitions of Adverse Events

9.1.1.1. Adverse Event (AE)

An AE is defined as any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (ICH E6 Guidelines for GCP). Any medical condition that is present at the time that the subject is screened will be considered as medical history and not recorded as an AE; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

9.1.1.2. Serious Adverse Event (SAE)

An AE is considered "serious" if, in the view of either the investigator or Titan, it results in any of the following outcomes (21 CFR 312.32(a)):

- Death: A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to Titan whether it is considered treatment related or not.
- A life-threatening event: An AE or suspected adverse reaction (SAR) is considered "life-threatening" if, in the view of either the investigator or Titan, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such 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 investigational product dependency or abuse.

- Congenital anomaly or birth defect.

If an event meets any of the above definitions, regardless of the severity or relationship of the event to the study product, the event must be reported to Titan as described in Section 9.1.5.

Adverse events reported from clinical studies associated with hospitalization or prolongation of hospitalization are considered serious. Any hospital admission to an inpatient unit (excludes strictly observational admissions of less than 24 hours) meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the medical floor to the intensive care unit).

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities, or respite care (e.g., caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency room visits
- Same day surgeries (as outpatient/same day/ambulatory procedures)

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition that did not worsen
- Protocol-specified admission (e.g., for a procedure required by the study protocol), unless it is an unplanned hospitalization related to implant insertion or removal AE
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the individual subject
- Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE.

9.1.1.3. Adverse Reaction (AR) and Suspected Adverse Reaction (SAR)

An adverse reaction (AR) means any AE caused by a drug.

Suspected AR means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected AR implies a lesser degree of certainty about causality than an AR (21 CFR 312.32(a)).

9.1.1.4. Unexpected Adverse Reaction (UAR)

Titan is responsible for assessing AEs for expectedness. With regards to reporting to the Health Authority, an AE is considered "unexpected" when its nature (specificity), severity, or rate of occurrence

is not consistent with applicable product information as described in the safety information provided in the protocol/package insert/investigator's brochure/prescribing information for the study drugs. "Unexpected" as used in this definition, also refers to AEs or SARs that are mentioned in the investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a)).

For IR ropinirole, the expectedness of an AE will be determined by whether or not it is listed in the Requip Prescribing Information.

9.1.2. Severity of AEs/SAEs

The study site will grade the severity of AEs experienced by study participants using the categories noted below. This assessment is subjective and the investigator should use medical judgment to compare the reported AE to similar events observed in clinical practice.

- Grade 1 = mild; usually transient; requires no special treatment and does not interfere with the subject's daily activities
- Grade 2 = moderate; produces a low level of inconvenience to the subject and may interfere with daily activities. These events are usually ameliorated by simple therapeutic measures.
- Grade 3 = severe; interrupts daily activity and requires systemic drug therapy or other medical treatment.
- Grade 4 = life-threatening consequences; urgent intervention indicated.
- Grade 5 = death related to AE.

Note: The terms serious and severe are not synonymous. Serious criteria as defined in Section 9.1.1.2 above serve as a guide for defining regulatory reporting obligations. The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe headache); the event itself, however, may be of relatively minor medical significance. This is not the same as serious, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Therefore, an AE of severe headache might not be considered serious, but a moderate infection for which a subject is hospitalized should be reported as an SAE.

9.1.3. Relationship to Investigational Product

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product (drug, procedure) caused or contributed to an AE and must be provided for all AEs (serious and non-serious).

Titan's determination of attribution will be used for reporting to the appropriate health authorities. The relation of an AE to study participation will be determined using the descriptors and definitions provided in Table 4.

Table 4: Attribution of Adverse Events

Not Related	The AE is clearly or most probably caused by other etiologies such as participant's underlying condition, illness or injury or identifiable cause, or therapeutic intervention or concomitant therapy; or the delay between administration and the onset of the AE is incompatible with a causal relation; or the AE started before administration (screening phase). Therefore, there is not a reasonable possibility that the AE was caused by the investigational drug, or procedure.
Possibly Related	An adverse event that follows a reasonable temporal sequence from administration of the investigational product or procedure, follows a known or expected response pattern to the suspected investigational product or procedure, but that could readily have been produced by a number of other factors.
Related	The adverse event is clearly related to the investigational product or procedure – i.e. an event that follows a reasonable temporal sequence from administration of the investigational product or procedure, follows a known or expected response pattern to the suspected investigational product or procedure, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state

The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. Any AE that is suspected to be related to the investigational product will be classified as an AR.

9.1.4. Collecting and Recording Adverse Events

9.1.4.1. Period of Collection

All AEs will be documented and followed from the time the subject has signed the ICF until 30 days after study drug treatment has been discontinued. Serious AEs and AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization. All AEs and SAEs should be treated as medically appropriate.

9.1.4.2. Methods of Collection

Adverse events may be collected as follows:

- Observing the participant
- Questioning the participant in an unbiased and non-leading manner
- Receiving an unsolicited complaint from the participant

An abnormal value or result from a clinical or laboratory evaluation or an ECG can also indicate an AE if it is determined by the investigator to be clinically significant. If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the participant's safety is not at risk.

9.1.4.3. Recording Method

9.1.4.3.1. Adverse Events

All AEs occurring during this clinical study will be recorded by the investigator on the appropriate eCRF in precise medical terms, along with the date and time of onset and the date and time of resolution. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the Investigator should combine signs and symptoms into a single term that constitutes a single diagnosis. Each AE is to be evaluated for duration, severity, seriousness, and relatedness to study drug or procedure. The severity of the AE and its relationship to the study drug or procedure will be assessed by the investigator.

The investigator will treat participants experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes. If any medication is administered in response to the AE, this medication should be noted on the concomitant medication eCRF as a concomitant medication administered. The action taken and the outcome must also be recorded. Adverse events will be followed until resolution or until 30 days after a participant terminates from the study, whichever comes first. The terms of AE resolution (i.e., resolved, resolved with sequelae, improved, worsened, lost to follow-up) should also be recorded.

9.1.4.3.2. Serious Adverse Events

Serious adverse events will be recorded on the AE eCRF and on the SAE eCRF, and health authorities will be notified as outlined in Section 9.1.5.2.

9.1.5. Reporting Adverse Events or Ropinirole Implant Applicator Incidents

9.1.5.1. Reporting SAEs to Titan

The following process for reporting an SAE ensures compliance with 21 CFR 312 and ICH guidelines. After learning that a participant has experienced an SAE, the investigator or designee is responsible for reporting the SAE, regardless of relationship or expectedness, within 24 hours of becoming aware of the event. The initial SAE report should include as much information as possible, but at a minimum must include the following:

- Reporter
- Subject ID
- Study product or intervention
- Serious AE term
- Relationship to study medication(s)
- Relationship to insertion/removal procedure
- Reason why the event is serious

Supplemental eCRF pages should be current at the time of SAE reporting: medical history, concomitant medications, demographics, study drug administration, and death as applicable.

Unavailable details of the event should not delay submission of the known information. As additional details become available, the SAE eCRF should be updated and re-submitted via the electronic data

capture system. Every time the SAE eCRF is submitted, it should be signed by the investigator or subinvestigator.

For additional information regarding SAE reporting, contact:

9.1.5.2. Reporting SAEs to Health Authorities

Titan will report Investigational New Drug (IND) Safety Reports to the FDA and investigators in accordance with the FDA regulations detailed in 21 CFR 312.32.

Final study report

A complete summary of safety information is included in the final study report submitted at the closure of the protocol. This option applies if the AE is classified as one of the following:

- Serious, SAR
- Serious and not an SAR

9.1.5.3. Reporting SAEs to IRB(s)

It is the responsibility of the investigators to promptly notify their respective IRB(s) of IND Safety Reports or other matters involving risk to subjects as mandated by the IRBs.

9.1.5.4. Reporting SAEs to the DSMB

All SAEs will be reported to the DSMB as described in the DSMB charter.

9.1.5.5. Reporting Pregnancy

During the study, all subjects should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, the subject will be withdrawn from the study and followed until the pregnancy comes to term.

The investigator is responsible for reporting all available pregnancy information on the pregnancy eCRF within 24 hours of becoming aware of the event, although pregnancy itself if not considered an AE. The investigator should counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until the conclusion of the pregnancy. Follow-up information detailing the outcome of the pregnancy should be reported as it becomes available.

Any pregnancy complication or premature terminations including miscarriage, spontaneous abortion or elective termination of a pregnancy for medical reasons will be reported as an SAE, as described in Section 9.1.5. Should the pregnancy result in a congenital abnormality or birth defect, a separate SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality. In addition, any infant death that occurs after the

30-day reporting period that the investigator suspects is related to the in-utero exposure to the study treatment should also be reported.

9.1.5.6. Ropinirole Implant Applicator Malfunction or Failure and Reporting

Applicator complaint, malfunction, or failure and/or requests to the Sponsor for replacement Applicators due to mechanical problems during a procedure will be recorded (including all relevant applicator information) by the investigational site on the Implant Insertion Procedure Assessment Form and forwarded within 24 hours to the Sponsor for evaluation, regardless of whether or not a medical/adverse event was associated with the applicator malfunction or failure.

The details of the malfunction and medical circumstances will be captured on the Implant Insertion Procedure Assessment Form and in the eCRF by the investigator. Failed applicators will be inventoried and returned to the sponsor for investigation. The final determination of reportability for applicator malfunctions is made by the sponsor and the investigational site based on the medical circumstances surrounding the event.

10. STATISTICS

10.1. Power and Sample Size Determination

The sample size for this study is not based on a formal power calculation as the study is not intended to demonstrate bioequivalence, but has been determined to be adequate to meet the PK and safety objectives of the study.

10.2. Analysis Populations

The analysis populations are defined as follows:

- The safety population is defined as all subjects who receive at least 1 ropinirole implant. The safety analyses will be performed on the safety population.
- The PK population is defined as all subjects who received at least 1 ropinirole implant and for whom at least 1 PK parameter of interest can be calculated. In general, on a parameter-by-parameter basis, an individual subject's data may be excluded from analysis if insufficient data are available for that subject to calculate the specific parameter in question.
- The Efficacy Evaluable (EE) population will include all subjects who receive at least 1 ropinirole implant and complete at least 1 post-implantation efficacy assessment.

10.3. Pharmacokinetics and Safety Analyses

10.3.1. Background and Demographic Characteristics

Demographic and baseline characteristics (i.e., age, sex, race, and body mass index) will be analyzed using the safety population. Summary statistics (i.e., n, mean, median, standard deviation, standard error of the mean, coefficient of variation, minimum, and maximum) will be reported for each demographic and baseline characteristic.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Analyses and Presentations

The PK analyses will be performed using the PK population. The following PK noncompartmental parameters will be determined (as appropriate) from the plasma ropinirole concentration-time data collected on Day -1, Day 1, Day 2, Week 4, Week 8, and Week 12 (EOT):

C_{max}	Maximum measured drug concentration.
C_{min}	Minimum measured drug concentration.
T_{max}	Observed time of the maximum drug concentration (obtained without interpolation).
λz	Apparent terminal elimination rate constant calculated as the negative of the slope of the linear regression of the natural logarithm of concentration versus time for at least 3 data points that are decreasing in the terminal phase.

$t_{½}$	Apparent elimination half-life calculated as ln (2)/ λz.
AUC_{0-t}	Area under the drug concentration-time curve calculated using log/linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration.
AUC_{0-24}	Area under the drug concentration-time curve calculated using log/linear trapezoidal summation from time zero to 24 hours

Plasma AUC_{0-24} and AUC_{0-t} will be calculated using the log/linear trapezoidal rule. Plasma concentrations below the limit of quantitation (BLOQ) prior to the first quantifiable concentration will be set at BLOQ and not used in the calculation of the pharmacokinetic parameters. Plasma concentrations BLOQ after the first quantifiable concentration will be set at the lower limit of quantitation/2 for purposes of parameter estimation.

Additionally, plasma concentrations at steady state, and peak and total exposure to ropinirole will be compared between Week 4, Week 8, and Day -1 using descriptive statistics. No formal hypothesis testing or inferential statistical analyses will be performed.

Descriptive statistics including arithmetic and geometric mean, standard deviation, coefficient of variation, standard error of the mean, median, minimum, and maximum will be calculated for all PK parameters. Geometric means will only be calculated for sampling times with at least 80% of the concentrations not missing. Additionally, for AUC_{0-t}, AUC_{0-24}, and C_{max}, geometric mean ratios and 90% confidence intervals will be calculated. Actual sampling times, rather than scheduled sampling times, will be used in all plasma PK parameter computations involving sampling times. For ease of presentation, scheduled sampling times will be used to present results in tables and figures. Additional analyses of N-despropyl ropinirole and 7-hydroxy ropinirole metabolites will be specified.

10.3.3. Safety Analyses

Safety analyses will be performed using the safety population. Adverse events will be coded for preferred term and system organ class using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

A by-subject AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided for treatment-emergent AEs, drug-related and insertion/removal procedure-related AEs, SAEs, and premature discontinuations due to AEs.. Additionally, treatment-emergent AEs (i.e., any AEs recorded during or following implantation) will be summarized by treatment group and categorized by severity and relationship to the study procedures and to the investigational product.

If a subject has more than 1 occurrence of the same AE, he/she will be counted only once within that preferred term in the summary tables. The most severe occurrence of an AE, as well as the most extreme relationship of the AE to the study procedures and study drug, will be indicated in cases of multiple occurrences of the same AE. Serious AEs and AEs of special interest also will be summarized separately. All AEs will be presented in a listing. Additionally, listings of SAEs and AEs leading to discontinuation will be generated. All SAEs will be evaluated to determine whether they are UARs.

Vital signs, ECGs, and clinical laboratory values will be summarized by time of collection. The C-SSRS and SCOPA-PC will be summarized by visit. Summary statistics (n, mean, median, standard deviation,

minimum, and maximum) will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. In addition, mean change from baseline data will be included for vital signs and clinical laboratory results and a shift table that describes out of normal range shifts will be provided for clinical laboratory results.

Changes in physical and neurological examinations will be described in the text of the final study report.

10.3.4. Prior and Concomitant Medications; Concomitant Therapies

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary, and will be summarized by drug class and preferred name, and listed by subject.

Concomitant therapies will be coded using the WHO Drug Dictionary, and will be summarized by therapeutic intervention and listed by subject.

10.4. Efficacy and Exploratory Analyses

The EE population will be used for all efficacy and exploratory analyses. Descriptive statistical summaries (n, mean, median, standard deviation, minimum, and maximum) for quantitative data and frequency counts for qualitative data, will presented for the following efficacy endpoints:

- Change from baseline in MDS-UPDRS total score
- Change from baseline in PDSS-2 total score
- Change from baseline in ESS score
- Change from baseline in QUIP-RS total score
- Change from baseline in hours of awake “On and Off” time

10.5. Other Statistical Considerations

10.5.1. Missing Data

Adverse events with missing start dates will be considered treatment emergent. Adverse events with missing relationship or severity grades will be considered related and severe as applicable. Missing PK concentration data will not be imputed.

10.5.2. Visit Windows

All data collected during the study up will be displayed and analyzed according to the actual visit data in the eCRF. Assessments should be performed on the day when they are scheduled. Weeks 1-10: Visits should occur ±1 day relative to the projected time point as measured from the Implant Visit. The Week 13 Follow-up Visit should occur 1 week ±2 days from EOT Visit. The Week 14 Follow-up Visit should occur 2 weeks ±2 days from last implant removed.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1. Study Monitoring

According to ICH GCP guidelines, the sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. The sponsor is responsible for assigning the study monitor(s) to this study. The study monitor's duties are to aid the investigator and Titan (or designee) in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the investigator of the regulatory necessity for study-related monitoring, audits, IRB(s) or Ethics Committee(s) reviews, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the investigator all regulations applicable to the clinical evaluation of an investigational product as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the eCRFs and source documentation throughout the study to protect the rights of the subjects; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the study monitoring plan.

11.2. Source Documents

Titan requires that the investigator prepare and maintain adequate and accurate records for each subject treated with the investigational product. Source documents such as any hospital, clinic, or office charts and the signed informed consent forms are to be included in the investigator's files with the subject's study records.

Study data will be captured electronically. Study site personnel will record eCRF data from source documents. If any data are first recorded onto documents such as laboratory reports, these documents will be considered source.

11.3. Data Collection and Management

This study will be conducted in compliance with the ICH document "Guidance for Industry-E6 Good Clinical Practice: Consolidated Guidance," dated April 1996. This study will also be conducted in accordance with the Declaration of Helsinki (2013).

This study will use electronic data collection (techniques to collect data directly from the investigational site using eCRFs). The data will be stored centrally in a fully validated clinical database. The investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform 100% source document verification to ensure there are no inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP and the study monitoring plan.

Data management will be coordinated by the data managers of Titan (or designee) in accordance with their SOPs for data management and a formal study data management plan.

12. QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A quality assurance representative from Titan (or designee), who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include on-site inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

13. ETHICS

13.1. Ethics Review

The investigator will not start this study, nor will investigational drugs be shipped to the investigator's site, before providing Titan with evidence of IRB approval. The investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to subjects. The investigator will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the subjects. The investigator will provide progress reports to the IRB as required by the IRB. The investigator will provide a final report to the IRB after completion of participation in the study.

13.2. Ethical Conduct of the Study

The investigator should conduct the study in accordance with this protocol, the Declaration of Helsinki, and ICH GCP guidelines. The investigator and Titan (or designee) will sign the protocol and study contract to confirm agreement. The investigator will not implement any amendment (deviation or changes of the protocol) without agreement by Titan and the IRB approval/information, except where necessary to eliminate immediate hazards to study subjects or when changes involve only logistical or administrative aspects of the study.

13.3. Written Informed Consent

13.3.1. Subject Information and Informed Consent

The informed consent document will be approved by the IRB that is appropriate for each study site. The investigator is responsible for ensuring that the subject fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible. No subject should be obliged to participate in the study. Subjects must be given ample opportunity to inquire about details of the study. The information must make clear that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the subject's subsequent care. Subjects must be allowed sufficient time to decide whether they wish to participate.

The subject must be made aware of and give consent to direct access to his/her source medical records by study monitors, auditors, the IRB(s), and regulatory authorities. The subject should be informed that such access will not violate subject confidentiality or any applicable regulations. The subject should also be informed that he/she is authorizing such access by signing the informed consent form.

Each subject will be given a signed copy of the informed consent form to keep for his/her records.

13.3.2. Provision of New and Important Information Influencing Subject's Consent and Revision of the Written Information

When any new and important information that may be relevant to the subject's consent is obtained, the investigator and Titan (or designee) will consult with each other on how to deal with the information. When Titan (or designee) and a responsible investigator judge it necessary, the investigator must immediately provide the subjects with such information, revise the written information and other explanatory documents based on the new information, and obtain approval from the IRB. In this instance,

the investigator should also immediately inform subjects currently participating in the clinical study of such information, confirm their intention to continue participation, re-explain the study to them using the revised written information and other explanatory documents, and obtain written consent to continue participation based on their voluntary decision.

13.4. Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being. Each subject will be asked to complete a form allowing the investigator to notify the subject's primary health care provider of his/her participation in this study.

14. ADMINISTRATIVE PROCEDURES

14.1. Publications of the Clinical Study

The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c). The results of and data from this study belong to Titan Pharmaceuticals, Inc.

14.2. Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the investigator or Titan after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator and Titan. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and Titan. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s) will be promptly notified.

No deviation from the protocol or investigational plan will be made except to protect the life or physical well-being of a subject in an emergency. Except in such emergencies, prior approval of Titan, and the regulatory authorities (e.g., FDA) or the IRB if applicable, is required before deviations from the planned protocol. All protocol deviations that occur during the study will be documented and reported to Titan (or designee) and to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

14.3. Data and Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be established to safeguard the interests and safety of the study participants. A DSMB charter will be prepared by Titan, defining the primary responsibilities, membership, purpose, and operations of the DSMB. The charter also provides the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DSMB, and an outline of the content of the reports that will be provided to the DSMB. Any decision to interrupt or stop the study will be made by Titan based on recommendations of the independent DSMB.

14.4. Dose Escalation Committee (DEC)

The DSMB members and 2 representatives from Titan will comprise the DEC. Enrollment will initially be restricted to Cohort 1 until evaluation of safety and characterization of the PK profile over the full 12-week period for Cohort 1 is completed by the DEC and the determination is made to open enrollment to Cohort 2. Prior to commencement of enrollment for Cohort 3, review of Cohort 2 safety and PK data through the Week 4 Visit will be required, in addition to ongoing safety review of currently enrolled subjects. Prior to commencement of enrollment for Cohort 4, review of Cohort 3 safety data through the Week 4 Visit will be required, in addition to ongoing safety review of currently enrolled subjects..

Dose escalation policies and procedures will be described in the DSMB charter.

15. DATA HANDLING AND RECORD KEEPING

15.1. Inspection of Records

Titan, their designee(s), the IRB(s), or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The investigator agrees to allow Titan, their designee(s), the IRB(s), or regulatory authorities to inspect the investigational product storage area, investigational product stocks, investigational product records, subject charts and study source documents, and other records relative to study conduct.

15.2. Retention of Records

The principal investigator should retain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years. Following study closure, the Investigator must inform Titan if the location for study records storage is changed (e.g. the Investigator leaves the institution where the study was conducted). In order to ensure that documents are not inadvertently destroyed prematurely, please contact Titan prior to the destruction of any study-related documents.

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