STATISTICAL ANALYSIS PLAN

Study 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

PROTOCOL NUMBER: ROP-001

NCT03250117

SPONSORED BY

Titan Pharmaceuticals, Inc.
400 Oyster Point Blvd., Suite 505
South San Francisco, CA 94080

PREPARED BY

[redacted]

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This document has been reviewed and accepted by: Date:

[redacted]

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EVP and Chief Scientific Officer
Titan Pharmaceuticals, Inc.

This document has been prepared by:

[redacted] Date:

5/11/18

Senior Biostatistician
[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
BP	Blood Pressure
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DEC	Dose Escalation Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EE	Efficacy Evaluable
EOT	End of Treatment
ESS	Epworth Sleepiness Scale
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
IR	Immediate Release
IRB	Institutional Review Board
L-Dopa	Levodopa
MDS-UPDRS	Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
PD	Parkinson's Disease
PDSS-2	Parkinson's Disease Sleep Scale
PK	Pharmacokinetic
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorder in Parkinson' Disease Rating Scale
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCOPA-PC	Scales for Outcomes in Parkinson's Disease – Psychiatric Complications
TEAE	Treatment-Emergent Adverse Event
WHODrug	World Health Organization Drug Dictionary

1. PURPOSE OF THE ANALYSES

The statistical analysis plan (SAP) is being developed for Study ROP-001 protocol Amendment 1, dated 07Jun2017. The SAP is to be developed in two stages. The purpose of the initial SAP is to allow [redacted] to start programming earlier in the process for the interim analysis. Versions of the SAP up to initial Titan approval will be known as SAP 1.0. Changes following approval of SAP 1.0 will be tracked in the SAP Change Log and a last version of the SAP, known as SAP 2.0, will be issued for Titan approval prior to database lock.

The purpose of the analyses is to evaluate the safety, tolerability, and pharmacokinetics (PK) of ropinirole implants in patients with Parkinson's disease (PD). The bioanalytical analysis of the concentrations of ropinirole, 7-hydroxy ropinirole, and N-despropyl ropinirole in human plasma is outlined in a separate document.

The SAP contains detailed information to aid in the implementation of the statistical analysis and reporting of the study data for use in the clinical study report (CSR). This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials, and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the analysis sets that will be analyzed, the subject characteristics parameters, the efficacy parameters, and the safety parameters. The details of the specific statistical methods that will be used will be provided. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the CSR. Table, figure, and listing specifications are provided in separate documents.

2. PROTOCOL SUMMARY

2.1 Study Objectives

Primary Objectives

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

Secondary Objectives

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

Exploratory Objectives

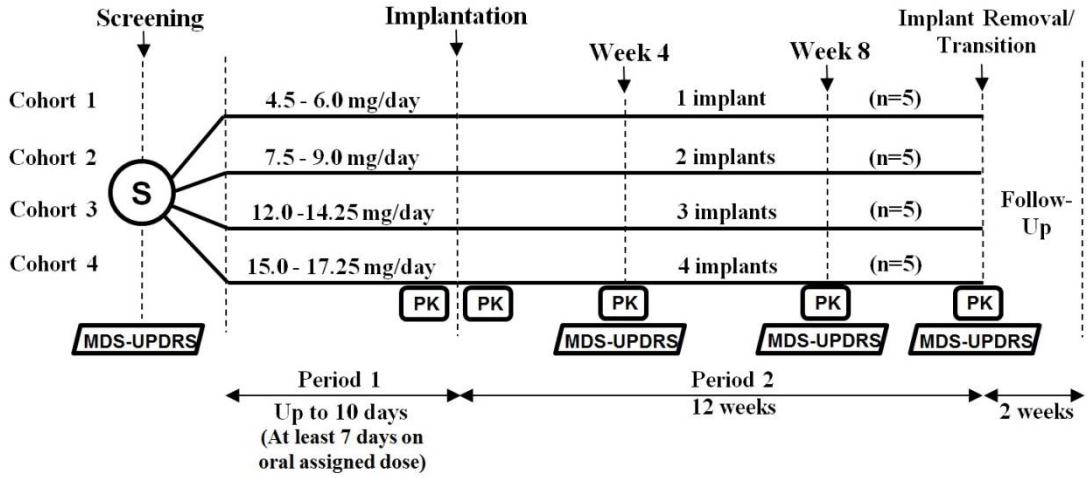
- To assess the efficacy of ropinirole implants on clinical features of PD.
- To assess the safety and effectiveness of the Ropinirole Implant Applicator for the subdermal placement of ropinirole implants.
- To assess Implanting Physician satisfaction with the design and functionality of the Ropinirole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

Plasma samples will be collected in order to assess ropinirole, 7-hydroxy ropinirole, and N-despropyl ropinirole concentrations. Pharmacokinetic collection times for each patient will be summarized by cohort and overall and presented in a listing. The analysis of these data is outside of the scope of this analysis plan and will be addressed in a separate document.

2.2 Overall Study Design and Plan

This study is a phase 1/2, open-label, relative bioavailability study evaluating the safety, tolerability, and PK in patients implanted with 1 of 4 dose levels of ropinirole implants. The study compares the oral dose period to the implant period that follows. The doses will be administered sequentially by cohort 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; MDS-UPDRS = Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PK = blood draw for pharmacokinetic assessments; S = screening
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 to 3 sites in the United States in 4 cohorts based on the fixed dose of IR ropinirole that the subject is currently taking; if the subject is taking the extended-release product, they must convert to the IR formulation as shown in Table 1 of the protocol.

- 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;
- 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 3 to 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.

2.3 Study Population

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 withdraw early (prior to 12 weeks on implant[s]) will not be replaced. The full list of inclusion and exclusion criteria can be found in the protocol.

2.4 Treatment Regimens

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 through Period 1 until implantation of ropinirole implants.

Subjects meeting implantation criteria, as specified in the protocol, 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 (Cohort 1), subjects at an IR ropinirole dose of 7.5 to 9.0 mg/day will receive 2 implants (Cohort 2), subjects at a dose of 12.0 to 14.25 mg/day will receive 3 implants (Cohort 3), and subjects at a dose of 15.0 to 17.25 mg/day will receive 4 implants (Cohort 4). Following implantation, subjects will be followed on treatment for 12 weeks (Period 2).

Ropinirole implants will be removed at the Week 12 End of Treatment (EOT) Visit in an in-office procedure.

2.5 Treatment Group Assignments or Randomization

There is no randomization for this open-label study. Enrollment is carried out sequentially by cohort, starting with Cohort 1. There will be no crossover of subjects between cohorts. Corresponding safety and PK data reviews for each applicable cohort will be performed prior to commencement of enrollment into the next cohort as detailed in Section 3.1 of the protocol and DSMB related documentation.

2.6 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.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

This SAP documents the planned analyses described in the Statistics section of the protocol (Amendment 1 [07 June 2017]) for study ROP-001 with the exception of the pharmacokinetic analyses section. The analysis of PK data is outside of the scope of this analysis plan and will be addressed in a separate document.

By-patient data listings will be prepared for all data collected in the electronic case report form (eCRF). All tables and listings will be produced as rich text format (RTF) files. Individual files will be created for each table and each listing output.

All tables, listings, and graphs will have a header and footer showing the sponsor company name, protocol number, DSMB database cut date, file name, run date/time, and page number.

Summary tables and data listings:

- Data in summary tables will be presented by cohort:
  - 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
- A Cohort column will be empty until data are available for at least one patient in that group.
- Categorical variables will be summarized using count and percentage and will be presented in the format ‘nn (pp.p%)’. All percentages will be based on the population count unless otherwise specified.
- Continuous variables will be summarized using number of observations (n), mean, standard error, 95% confidence interval (CI) of the mean, median, minimum, and maximum.
- Minimum and maximum will be reported to the same level of precision as the original data. Mean and median will be reported to 1 more significant digit than the original data. Standard error will be reported to 2 more significant digits than the original data.
- Only nominal/scheduled visit data will be reported in the tables. All visits, including unscheduled, will be presented in the listings.
- Data listings will be sorted in order of cohort, patient ID, and time of assessment, if applicable. Dates will be presented in YYYY-MM-DD format. If applicable, times will be presented in ISO format.

3.1 Software

All statistical programing will be performed using SAS version 9.4 or later.

All statistical deliverables will be produced, validated, and reviewed for accuracy/ consistency in accordance with [redacted] standard operating procedures and the processes described in the Statistical Validation and Quality Control Plan.

3.2 Definition of Baseline

Unless otherwise stated, the last observed measurement on Day 1 / Implant Visit, conducted prior to implantation, will be considered the baseline measurement.

4. 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 efficacy evaluable (EE) population will include all subjects who receive at least 1 ropinirole implant and complete at least 1 post-baseline efficacy assessment. The efficacy analyses will be performed on the EE population.

5. STUDY PATIENTS

5.1 Disposition of Patients

Disposition will be presented for all subjects who enter the study, and will include date and name of last visit, date of disposition, weeks implanted, completion status, and primary reason for early withdrawal (if applicable). The number and percentage of subjects in each study population as well as the number and percentage of subjects who discontinued the study and the reason for discontinuation will be summarized by cohort. Discontinuation reasons include: subject request, subject noncompliance, subject refusal to receive implants, evidence of implant removal or attempted removal, medically significant infection or other medically significant adverse event (AE) at the implant site, unacceptable or intolerable treatment-related AE, pregnancy, use or abuse of nonstudy-assigned ropinirole, use of dopamine antagonists other than quetiapine (up to 100 mg/day) or pimavanserin (at doses labeled for treatment of PD), deep brain stimulation, use of any investigational treatment, intercurrent illness or circumstances, request of Titan, regulatory agencies, or an institutional review board (IRB), lost to follow-up, or other. All disposition data will be presented in subject listings.

A screen failure will be defined as any subject who does not receive an implant. The number of screen failures occurring in Screening, during Period 1/prior to implant, and overall will be summarized. Failed criteria will also be summarized.

A study completer will be defined as any subject completing the 12-Week study visit schedule on their assigned treatment, with removal of implants at EOT /Week 12 Visit.

5.2 Protocol Deviations

All protocol deviations will be recorded. Major protocol violations will be identified prior to database lock, and reported in the listings by cohort.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be analyzed using the safety population. Demographic variables to be summarized include age, gender, race, body mass index at baseline, ethnicity, and baseline clinical characteristics. Summary statistics (i.e., n, mean, median, standard error of the mean, coefficient of variation, minimum, and maximum) will be reported for each demographic and baseline characteristic.

Age will be calculated based on the following conditional algorithm:

- Has the patient had their birthday that year?
    - Yes, then AGE = (year of informed consent) – (year of birth).
    - No, then AGE = (year of informed consent) – (year of birth) – 1.

Baseline clinical characteristics will include dose of levodopa/carbidopa, prestudy dose of oral ropinirole, percentage of subjects who entered on Requip XL formulation, age at PD onset, duration of PD (years), age (years) at PD diagnosis, duration of current L-dopa therapy, baseline Mini Mental State Evaluation (MMSE) score, and Hoehn and Yahr stage at screening.

An identical summary will be created for subjects who were screen failures.

6.2 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. It will be presented by system organ class and preferred term. A medical history listing will be presented.

7. EFFICACY EVALUATION

7.1 Overview of Efficacy Analysis Issues

7.1.1 Handling of Dropouts or Missing Data

All available data will be used. No imputations will be made for missing data unless otherwise specified. Calculation of rating scale data, as well as handling of missing rating scale data, will follow instructions received from the scale authors and/or their relevant publications.

7.1.2 Multicenter Studies

Subjects will be enrolled at approximately 1 to 3 sites. No adjustments will be made for multiple centers.

7.1.3 Assessment Time Windows

All data collected during the study 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 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 the EOT Visit. The Week 14 Follow-up Visit should occur 2 weeks ±2 days from removal of the last implant.

7.2 Efficacy Variables

Efficacy and exploratory endpoints consist of the following:

- Change from baseline in 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 (Hauser Diary)
- 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 Disorder in Parkinson's Disease-Rating Scale (QUIP-RS) total score

7.2.1 MDS-UPDRS

The MDS-UPDRS is a 4-part rating scale used to evaluate non-motor experiences of daily living (NM-EDL) (Part I), motor experiences of daily living (M-EDL) (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 at Weeks 4, 8, and 12. The MDS-UPDRS must take place prior to implant removal at the Week 12

Visit. The change from baseline in Part I score, , Part II score, Part III score, Part IV score, MDS-UPDRS total score, and Part II plus Part III score will be summarized by cohort and visit. Information on how to calculate the MDS-UPDRS score is presented in Appendix 17.2.

7.2.2 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 at Weeks 4, 8, and 12. The total score will be calculated by adding all the individual items in the scale. If one or two items are missing, then the item(s) will be imputed by averaging all the non-missing items. If more than two items are missing, the non-missing items will be summarized, but a total score will not be calculated. The PDSS-2 will be summarized by cohort and visit.

7.2.3 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. The total score is calculated by summing the scores for each of the eight responses, with a possible range of 0 to 24. If one or more item-scores are missing, then the total score will not be computed. Subjects will complete this assessment on Day -2, and at Weeks 4, 8, and 12. The ESS score will be summarized by cohort and visit.

7.2.4 QUIP-RS

The QUIP-RS 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 these behaviors with a 5-point Likert scale (Weintraub et al., 2012). Individual responses, the total International Classification of Diseases (ICD) score (gambling, sex, buying, eating), and total QUIP-RS score will be recorded on the eCRF. The total ICD score can have values from 0 through 64. The total QUIP-RS score can have values from 0 through 112. Subjects will complete this assessment at the Screening Visit, and at Weeks 4, 8, and 12. The QUIP-RS total score will be summarized by cohort and visit.

7.2.5 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. If more than 4 half-hour segments are missing, then the data from that 24-hour period will not be used. Daily totals for waking hours will be normalized to a 16 hour waking day and averaged across the 2 consecutive days prior to each visit. Awake time “on” without troublesome dyskinesia is comprised of “on without dyskinesia” and “on with non-troublesome

dyskinesia. The data from the Hauser Diary will be summarized by cohort and visit for the variables below:

Variable	Units
Awake time "on"	Number of hours per 24-hour period
Awake time "on"	% of hours per 24-hour period
Awake time without troublesome dyskinesia	Number of hours per 24-hour period
Awake time without troublesome dyskinesia	% of hours per 24-hour period
Awake time "off"	Number of hours per 24-hour period
Awake time "off"	% of hours per 24-hour period

7.3 Analysis Methods

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

7.3.1 Primary Efficacy Analyses

The primary endpoints for this study are PK and safety. There are no primary efficacy endpoints.

7.3.2 Efficacy Analyses

The efficacy endpoints for this study are change from baseline in MDS-UPDRS total score and change from baseline in hours of awake time spent "on" and "off." Descriptive statistics will be provided by cohort and visit. Figures of mean MDS-UPDRS total score, percentage awake time spent "on", percentage awake time without troublesome dyskinesia, and percentage awake time "off" will be presented by cohort and visit. All data will be presented in subject listings.

7.3.3 Exploratory Efficacy Analyses

The exploratory endpoints include change from baseline in PDSS-2 total score, change from baseline in ESS score, and change from baseline in QUIP-RS total score. Descriptive statistics will be provided by cohort and visit. All data will be presented in subject listings.

7.4 Examination of Subgroups

There will be no subgroup analysis.

8. SAFETY EVALUATION

8.1 Overview of Safety Analysis Methods

Safety analyses will be performed using the safety population. Descriptive statistical summaries (mean, standard error, 95% CI of the mean, median, minimum, and maximum) will be presented for quantitative data, and frequency counts will be presented for qualitative data.

8.2 Measurements of Treatment Compliance and exposure

For Period 1 (oral dose), the time on dose, total dose, percentage of expected doses taken, and the dose at Day -1 will be summarized by cohort. For Period 2 (implantation), the total dose will be summarized by cohort. Throughout the study, sites will be checking to determine whether subjects have removed or attempted to remove the implant. The number and percentage of subjects who removed or attempted to remove the implant at any time during the study will be summarized. The number of days between implantation and implant removal will be summarized.

8.3 Adverse Events

Adverse events will be coded for preferred term and system organ class using the most recent version of the MedDRA.

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. Handling of missing or partial dates is presented in Appendix 17.1.

Treatment-emergent AEs (TEAEs) will be defined as any AE occurring during or following implantation or an AE that worsens after implantation. Implant site and non-implant site TEAEs will be summarized by cohort. Tables categorizing by severity and relationship to the insertion or removal procedures and to the investigational product will also be created.

In order to separate reactions specific to the insertion or removal of ropinirole implants from those specific to the drug substance and excipient, TEAEs will be categorized as either implant site related or non-implant site related. Implant site TEAEs are defined as TEAEs associated with the implant site (either spatially or temporally, according to the investigator). In contrast, non-implant site TEAEs are TEAEs not associated with the implant site.

Non-treatment-emergent adverse events will be summarized by cohort.

A by-subject AE data listing including onset and resolution dates, verbatim term, system organ class, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided for all TEAEs; drug-related, insertion procedure-related, and removal procedure-related AEs; serious adverse events (SAEs); and premature discontinuations due to AEs.

If a subject has multiple occurrences of the same AE, he/she will be counted only once within that system organ class and 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.

Additionally, a listing of AEs leading to study discontinuation will be generated.

8.4 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Deaths or hospitalizations, SAEs, and AEs of special interest (AESI) will be summarized separately. The AESI for this study include somnolence, sleep attacks, narcolepsy, syncope, hypotension, orthostatic hypotension, hallucinations, psychotic-like behavior, impulse control/compulsive disorder, cardiac events, and protrusion/extrusion or expulsion of the implant. Reported preferred terms and system organ class will be examined for terms related to the AESI and will be finalized prior to database lock. In addition, orthostatic hypotension will defined as a reduction of systolic blood pressure (BP) of >20 mmHg or diastolic BP >10 mmHg within 3 minutes of quiet standing as collected in the vital signs data.

All deaths, SAEs, and AESI will be presented in subject listings. All SAEs will be evaluated to determine whether they are unexpected adverse reactions (UARs).

8.5 Clinical Laboratory Evaluation

The clinical laboratories to be collected are presented below.

Hematology	Hematocrit, hemoglobin, red blood cells, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell morphology, white blood cells with differential, and platelet count
Chemistry (including liver profile)	Blood urea nitrogen, calcium, bicarbonate, chloride, creatinine, glucose, potassium, sodium, albumin, alkaline phosphatase, aspartate transaminase, alanine transaminase, total bilirubin, total cholesterol, total protein
Coagulation Profile	Prothrombin time, international normalized ratio, partial thromboplastin time
Urinalysis	Routine urinalysis (color, nitrite, leukocyte esterase, clarity, specific gravity, pH, blood, protein, glucose, urobilinogen, ketones, microscopic and bilirubin)

Clinical laboratory values will be summarized by time of collection. Summary statistics (n, mean, median, standard error, minimum, and maximum) will be calculated for quantitative laboratory data and frequency counts will be compiled for classification of qualitative laboratory data (urinalysis). Summary statistics will be presented by cohort. In addition, mean change from baseline value will be included for clinical laboratory

results and a shift table that describes out-of-normal range shifts will be provided. Listings of all laboratory data will be provided.

8.6 Vital Signs, Physical Findings, and Other Observations Related to Safety

8.6.1 Vital Signs

Vital signs include supine 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 the schedule of events.

Vital signs values will be summarized by time of collection. Summary statistics (n, mean, median, standard error, minimum, and maximum) for mean change from baseline will be presented by cohort. In addition, summaries of the number and percentage of abnormal clinically significant vital sign values by cohort and visit will be provided. All vital sign data will be reported in listings.

8.6.2 Physical Examinations

Abnormal values for neurological examination data will be summarized by cohort and visit. Listings will be provided for all physical and neurological examination data.

8.6.3 Electrocardiograms

Electrocardiogram (ECG) values will be summarized by time of collection. Summary statistics (n, mean, median, standard error, minimum, and maximum) for mean change from baseline will be presented by cohort and visit. In addition, summaries of the number and percentage of abnormal clinically significant ECG values cohort and visit will be provided. All ECG data will be reported in listings.

8.6.4 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, Day -2, Day 3, Day 4, and at Weeks 1 through 14 (Posner et al., 2008). The C-SSRS will be summarized by cohort and visit. All C-SSRS data will be presented in subject listings.

8.6.5 Scales for Outcomes in Parkinson's Disease – Psychiatric Complications

The Scales for Outcomes in Parkinson's Disease – Psychiatric Complications (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) through 3 (severe symptoms). The change from baseline in SCOPA-PC will be summarized by cohort and visit. SCOPA-PC data will be presented in subject listings.

8.6.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug), version 2017, Q1 version, and will be summarized by drug class and preferred name, and listed by subject.

Prior medications are defined as medications with stop dates occurring before the date of first administration of any study treatment

Concomitant medications/therapies are defined as medications/therapies with start dates occurring on or after the date of first administration of any study treatment and no more than 30 days after the last administration of any study treatment. Medications with start and stop dates that bracket the date of first administration of any study treatment component will be summarized as both prior and concomitant medications.

Concomitant therapies will be coded using WHODrug, and will be summarized by therapeutic intervention and listed by subject.

Medications with missing dates will be considered concomitant. Handling of partial and missing dates is presented in Appendix 17.1.

9. PHARMACOKINETIC EVALUATION

The analysis of PK data is outside of the scope of this analysis plan and will be addressed in a separate document.

10. ROPINIROLE IMPLANT PROCEDURES AND ROPINIROLE IMPLANT APPLICATOR

Data on functioning of the Ropinirole Implant Applicator prior to the insertion procedure and the presence of failure or malfunction during the insertion procedure will be presented.

Data from the insertion procedure will be summarized by cohort, including length of procedure, length of incision, number of palpable implants after insertion, whether an additional implant was used due to damage, whether an additional implant was used due to contamination, cannula and obturator correct function, total volume of anesthetic used, applicator failure or malfunction and whether the subject experienced insertion procedure-related AEs.

Data from the removal procedure will be summarized by cohort, including whether it was the first attempt to remove the implant(s), number of fractured implants, length of procedure, percentage of procedures that used [redacted], percentage of implants completely removed, and whether the subject experienced removal procedure-related AEs.

Central ultrasound reader evaluation of the depth of the implant by ultrasound will be summarized, including skin-to-fascia and skin-to-implant measurements. When values from the central ultrasound reader are not available for a given measure, the site's value will be used.

11. INTERIM ANALYSES AND DATA MONITORING

An independent 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 DSMB.

In addition to the DSMB, there will be a dose escalation committee (DEC). The DEC comprises the DSMB members and 2 representatives from Titan. 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.

Planned displays for the DSMB and the DEC are noted in Sections 14, 15, and 16.

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

There are no changes to the analyses planned in the protocol.

13. REFERENCES

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14. LIST OF PLANNED TABLES

[redacted] Table Identifier	Table No.	Title
DS-T01	14.x	Summary of Subject Disposition by Cohort
DS-T02	14.x	Summary of Screen Failures
DM-T01	14.x	Summary of Demographic and Baseline Characteristics by Cohort
DM_T02	14.x	Summary of Demographic and Baseline Characteristics for Screen Failures
MH-T01	14.x	Summary of Medical History by Cohort
CM-T01	14.x	Summary of Prior Medications by Cohort
CM-T02	14.x	Summary of Concomitant Medications and Therapies by Cohort
EX-T01	14.x	Summary of Study Drug Exposure and Compliance by Cohort
EX-T02	14.x	Summary of Insertion Procedure and Ropinirole Implant Applicator
EX-T03	14.x	Summary of Removal Procedure
EF-T01	14.x	Summary of Mean and Mean Change from Baseline MDS-UPDRS by Cohort and Visit
EF-T02	14.x	Summary of Mean and Mean Change from Baseline PDSS-2 by Cohort and Visit
EF-T03	14.x	Summary of Mean and Mean Change from Baseline ESS by Cohort and Visit
EF-T04	14.x	Summary of Mean and Mean Change from Baseline QUIP-RS Total Score by Cohort and Visit
EF-T05	14.x	Summary of Awake Time Spent “On” by Cohort and Visit
EF-T06	14.x	Summary of Awake Time Without Troublesome Dyskinesia by Cohort and Visit
EF-T07	14.x	Summary of Awake Time Spent “Off” by Cohort and Visit
AE-T01	14.x	Summary of All Treatment-Emergent Adverse Events by Cohort
AE-T02	14.x	Summary of All Non-Treatment-Emergent Adverse Events by Cohort, System Organ Class, and Preferred Term

AE-T03	14.x	Summary of All Treatment-Emergent Adverse Events by Cohort, System Organ Class, and Preferred Term
AE-T04	14.x	Summary of Treatment-Emergent Implant Site Adverse Events by Cohort, System Organ Class, and Preferred Term
AE-T16	14.x	Summary of Treatment-Emergent Non-Implant Site Adverse Events by Cohort, System Organ Class, and Preferred Term
AE-T05	14.x	Summary of All Treatment-Emergent Adverse Events Related to Study Drug by Cohort, System Organ Class, and Preferred Term
AE-T06	14.x	Summary of All Treatment Emergent Adverse Events Related to Insertion or Removal Procedure by Cohort, System Organ Class, and Preferred Term
AE-T07	14.x	Summary of All Treatment-Emergent Adverse Events Leading to Study Discontinuation by Cohort, System Organ Class, and Preferred Term
AE-T08	14.x	Summary of All Treatment-Emergent Adverse Events by Cohort, System Organ Class, Preferred Term and Intensity
AE-T09	14.x	Summary of Treatment-Emergent Implant Site Adverse Events by Cohort, System Organ Class, Preferred Term and Intensity
AE-T10	14.x	Summary of Treatment-Emergent Non-Implant Site Adverse Events by Cohort, System Organ Class, Preferred Term and Intensity
AE-T11	14.x	Summary of All Treatment-Emergent Serious Adverse Events by Cohort, System Organ Class, and Preferred Term
AE-T12	14.x	Summary of Treatment-Emergent Serious Implant Site Adverse Events by Cohort, System Organ Class, and Preferred Term
AE-T13	14.x	Summary of Treatment-Emergent Serious Non-Implant Site Adverse Events by Cohort, System Organ Class, and Preferred Term
AE-T14	14.x	Summary of All Treatment-Emergent Adverse Events Leading to Death or Hospitalization by Cohort, System Organ Class, and Preferred Term
AE-T15	14.x	Summary of Treatment-Emergent Adverse Events of Special Interest by Cohort, System Organ Class, and Preferred Term

LB-T01	14.x	Summary of Mean and Mean Change from Baseline in Hematology Values by Cohort and Visit
LB-T02	14.x	Shift from Baseline in Laboratory Test: Hematology by Cohort and Visit
LB-T03	14.x	Summary of Mean and Mean Change from Baseline in Serum Chemistry Values by Cohort and Visit
LB-T04	14.x	Shift from Baseline in Laboratory Test: Serum Chemistry Results by Cohort and Visit
LB-T05	14.x	Summary of Mean and Mean Change from Baseline in Coagulation Values by Cohort and Visit
LB-T06	14.x	Shift from Baseline in Laboratory Test: Coagulation Results by Cohort and Visit
LB-T07	14.x	Summary of Urinalysis Values by Cohort and Visit
SC-T01	14.x	Summary of Mean and Mean Change from Baseline SCOPA-PC Total Score by Cohort and Visit
ECG-T01	14.x	Summary of Mean and Mean Change from Baseline in ECG Values by Cohort and Visit
ECG-T02	14.x	Summary of 12-Lead ECG Conclusions
VS-T01	14.x	Summary of Mean and Mean Change from Baseline in Vital Sign Values by Cohort and Visit
VS-T02	14.x	Potential Orthostatic Hypotension by Cohort and Visit
CS-T01	14.x	Summary of C-SSRS by Cohort and Visit
UL-T01	14.x	Summary of Ultrasound

15. LIST OF PLANNED FIGURES

[redacted] Figure Identifier	Figure No.	Title
EF-T01		Mean Change from Baseline in Awake Time Spent "On" by Cohort and Visit
EF-T02		Mean Change from Baseline in Awake Time Without Troublesome dyskinesia by Cohort and Visit
EF-T03		Mean Change from Baseline Awake Time Spent "Off" by Cohort and Visit
EF-T04		Mean Change from Baseline in MDS-UPDRS Total Score by Cohort and Visit
EF-T05		Mean Change from Baseline in ESS Total Score by Cohort and Visit
EF-T06		Mean Change from Baseline in Total QUIP-RS Score by Cohort and Visit

16. LIST OF PLANNED DATA LISTINGS

[redacted]Listing Identifier	Listing No.	Title
DS-L01	16.x	Listing of Subject Disposition
DS-L02	16.x	Listing of Subject Eligibility
DS-L03	16.x	Listing of UK Brain Bank Diagnostic Criteria
DM-L01	16.x	Listing of Subject Demographic and Baseline Characteristics
MH-L01	16.x	Listing of Medical History
CM-L01	16.x	Listing of Prior Medications
CM-L02	16.x	Listing of Concomitant Medications and Therapies
EX-L05	16.x	Listing of Oral Ropinirole Dosing Log
EX-L03	16.x	Listing of Implantation Eligibility
EX-L01	16.x	Listing of Implant Site Examination
EX-L02	16.x	Listing of Implantation Procedure
EX-L04	16.x	Listing of Implant Removal
EF-L01	16.x	Listing of MDS-UPDRS Individual Items
EF-L06	16.x	Listing of MDS-UPDRS Sub-scores and Total Score
EF-L02	16.x	Listing of PDSS-2
EF-L03	16.x	Listing of ESS
EF-L04	16.x	Listing of QUIP-RS
EF-L05	16.x	Listing of Hauser Diary Data
AE-L01	16.x	Listing of All Adverse Events
AE-L02	16.x	Listing of All Treatment-Emergent Serious Adverse Events
AE-L03	16.x	Listing of All Treatment-Emergent Adverse Events Leading to Death or Hospitalization
AE-L04	16.x	Listing of All Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation
AE-L05	16.x	Listing of Preferred Terms Included in Adverse Events of Special Interest
LB-L01	16.x	Listing of Hematology Results
LB-L02	16.x	Listing of Serum Chemistry Results
LB-L03	16.x	Listing of Coagulation Results
LB-L04	16.x	Listing of Urinalysis Results
LB-L05	16.x	Listing of Urine Drug and Cotinine, and Breathalyzer Results

LB-L06	16.x	Listing of Pregnancy Results
LB-L07	16.x	Listing of Virus Serology
EG-L01	16.x	Listing of Electrocardiogram Values
VS-L01	16.x	Listing of Vital Signs
QS-L01	16.x	Listing of C-SSRS
QS-L02	16.x	Listing of SCOPA-PC
QS-L03	16.x	Listing of Mini Mental State Examination
PE-L02	16.x	Listing of Neurological Examination Results
PE-L01	16.x	Listing of Physical Examination Results
UT-L01	16.x	Listing of Ultrasound Results
PD-L01	16.x	Listing of Protocol Deviations

17. APPENDICES

17.1 Imputation Algorithm for Partial and Missing Dates

Adverse Events
Note that if any of the imputations below result in an onset date that is after AE end date, then onset date will be set to AE end date.
If onset date is completely missing, onset date is set to date of first dose.
If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of first dose, then set month and day to month and day of first dose
- If year < year of first dose, then set month and day to December 31.
- If year > year of first dose, then set month and day to January 1.

If month and year are present and day is missing:

- If year=year of first dose and
  - If month = month of first dose then set day to day of first dose
  - If month < month of first dose then set day to last day of month
  - If month > month of first dose then set day to first day of month
- If year < year of first dose then set day to last day of month
- If year > year of first dose then set day to first day of month

For all other cases, set onset date to date of first dose

Concomitant Medications
Start Date:
If start date is completely missing and end date is not prior to first dose, then the medication will be classified as concomitant. If start date is completely missing and end date is prior to first dose, then the medication will be classified as prior.
If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to January 1.
If year and month are present and day is missing then set day to first day of month.

End Date:
If end date is completely missing then the medication will be classified as concomitant.
If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to December 31.
If year and month are present and day is missing then set day to last day of the month.
Note that if both start and end dates are missing then the medication will be classified as concomitant.

17.2 MDS-UPDRS Scoring

Subscores
Part I – All 13 items with scores (excludes 1.A Source of Information, 1.6A Who is filling out questionnaire)
Part II – All 13 items

Part III – All 33 items with scores (excludes 3a, 3b, 3c, 3.C1, Were dyskinesias present, Did these movements interfere with ratings, Hoehn and Yahr Stage)
Part IV – All 6 items
Total Score = Sum of All Scores

Missing Data Rules

Part I subscore – 13 items with scores

- If missing > 1, then subscore = missing
- If missing <= 1, sum of the non-missing items X (total number of items)/ (number of items non-missing)

Part II subscore – 13 items with scores

- If missing > 2, then subscore = missing
- If missing <= 2, sum of the non-missing items X (total number of items)/ (number of items non-missing)

Part III subscore – 33 items with scores

- If missing > 7, then subscore = missing
- If missing <= 7, sum of the non-missing items X (total number of items)/ (number of items non-missing)

Part IV subscore – 6 items with scores

- If missing > 0, then subscore = missing

17.3 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

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
12-Lead ECG	X		X		X[5]							X				X[3]		
Implantation Criteria					X[2]													
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		

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
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
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 post-implantation; 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.