STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, double-blind, randomized, placebo-controlled crossover study evaluating the effect of RVT-101 on gait and balance in subjects with Alzheimer's Disease, Dementia with Lewy Bodies, or Parkinson's Disease Dementia
Protocol Number:	RVT-101-2003
Development Phase:	Phase 2
Investigational Product:	RVT-101 (Intepirdine)
Indications:	Alzheimer's Disease, Dementia with Lewy Bodies, Parkinson's Disease Dementia
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Version:	Final v1.0
Based on Protocol Version:	v3.0 – 07FEB2017

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FINAL STATISTICAL ANALYSIS PLAN APPROVAL

A Phase 2, double-blind, randomized, placebo-controlled crossover study evaluating the effect of RVT-101 on gait and balance in subjects with Alzheimer's Disease, Dementia with Lewy Bodies, or Parkinson's Disease Dementia

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DOCUMENT HISTORY

Draft Version	Date	Comments and Changes
v1.0	16 Oct 2017	Circulate for core team review
v1.1	10 Nov 2017	Circulate for extended team review
v1.2	21 Nov 2017	Update MDS-UPDRS, baseline per team comments
v1.2	28 Nov 2017	Add sensitivity analyses

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ABBREVIATIONS

Abbreviation	Term
AD	Alzheimer's Disease
AE	Adverse Event
ATC	Anatomic Therapeutic Chemical
CRF	Case Report Form
CS	Population of those who Completed the Study
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DLB	Dementia with Lewy Bodies
DOB	Date of Birth
FOG	Freezing of Gait
ECG	Electrocardiograms
ITT	Intent-to-Treat Population
LBD	Lewy Body Dementia
MedDRA	Medical Dictionary for Regulatory Activities Terminology
Mini-BESTest	Mini Balance Evaluation Systems Test
MMSE	Mini Mental State Examination
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
N	Total Sample Size
OC	Observed Cases
TEAE	Treatment-Emergent AE
PCS	Potential Clinical Significance
PDD	Parkinson's Disease Dementia
PGS	Primary Gait Screen assessment
PIGD	Postural Instability and Gait Difficulty
PP	Per-Protocol Population
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
ULN	Upper Limit of Normal
UPSIT	University of Pennsylvania Smell Identification Test
WHO-DD	World Health Organization's Drug Dictionary

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the detailed methodology for summary and statistical analyses to be performed following the completion of Study RVT-101-2003, a Phase 2, double-blind, randomized, placebo-controlled crossover study evaluating the effect of RVT-101 on gait and balance in subjects with Alzheimer's Disease, Dementia with Lewy Bodies, or Parkinson's Disease Dementia.

Study measurements and assessments, planned statistical methods, and derived variables are summarized in this plan. Planned tables, figures, and listings are specified in a separate spreadsheet. All decisions regarding final analyses, as defined in this SAP document, have been made prior to locking the database.

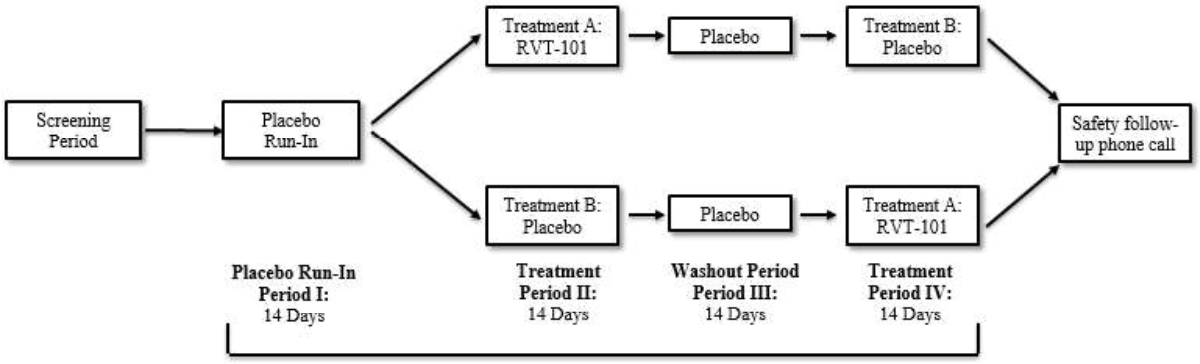
1.1 Study Design

This is a multi-center, double-blind, randomized, placebo-controlled, crossover study in dementia subjects with gait impairment. The primary objective of the study will be to evaluate the effect of intepirdine on gait speed. The secondary objective is to assess the safety and tolerability of intepirdine. Exploratory objectives of the study include the evaluation of the effects of RVT-101 on other quantitative and qualitative measures of gait and balance.

Following an initial screening period, eligible subjects will enter a two-week single-blind placebo run-in period (Period I). At the end of this period, all subjects who continue to meet the eligibility criteria will enter the first two-week double-blind treatment period (Period II). Following the completion of Period II, subjects will undergo a washout period (Period III) of two weeks during which subjects will receive placebo. After the two-week washout, subjects will enter the second two-week double-blind treatment period (Period IV). A safety follow-up telephone call will be conducted approximately 2 weeks after completion of Period IV.

Figure 1 provides a study scheme demonstrating the key design elements and scheduled study visits.

Figure 1. Study Design



1.2 Study Objectives

1.2.1 Primary Objective

The primary objective of this study is to assess the effect of intepirdine versus placebo on gait speed, a quantitative measure of functional mobility, on an electronic walkway system after 2 weeks of treatment.

1.2.2 Secondary Objective

Secondary objective is to assess the safety and tolerability of intepirdine.

1.2.3 Exploratory Objectives

Exploratory objectives of this study are:

- To assess the effect of intepirdine versus placebo on gait variability on an electronic walkway system after 2 weeks of treatment
- To assess the effect of intepirdine versus placebo on gait and balance, as measured by the Mini Balance Evaluation Systems Test (mini-BESTest) battery total score and individual subscores, after 2 weeks of treatment
- To assess the effect of intepirdine versus placebo on gait and balance, as measured by individual item scores calculated by Opal APDM sensors during performance of the mini-BESTest battery, after 2 weeks of treatment at sites where the technology and capability is available
- To assess the effect of intepirdine versus placebo on freezing of gait (FOG), as measured by clinical and quantitative scores, after 2 weeks of treatment
- To assess the effect of intepirdine versus placebo on movement and balance, as measured by the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts II and III, Postural Instability and Gait Difficulty (PIGD), and MDS-UPDRS 7-Item subscore, after 2 weeks of treatment
- To assess the effect of intepirdine versus placebo on smell, a proxy for cholinergic function, as measured by the University of Pennsylvania Smell Identification Test (UPSIT), after 2 weeks of treatment

1.3 Sample Size Considerations

The primary comparison of interest is to compare the efficacy of intepirdine to placebo after a two-week treatment period in subjects with Alzheimer's Disease (AD) or Lewy body dementia (LBD). LBD is an umbrella term that includes both Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD). A sample size of approximately 30-40 subjects (comprised of approximately 15-20 AD subjects and approximately 15-20 LBD subjects) will be included in this study. No formal power calculations were performed.

1.4 Randomization and Stratification

Each subject will be randomized 1:1 to one of the following sequences:

- Sequence 1: AB = Intepirdine in Period II and Placebo in Period IV
- Sequence 2: BA = Placebo in Period II and Intepirdine in Period IV

Randomization will be stratified according to Mini Mental State Examination (MMSE) score in the groups of 14-19 points and 20-26 points. Randomization will also be stratified according to whether subjects have AD or LBD.

1.5 Nomenclature

For purposes of this SAP, as well as in the analysis tables, figures, and listings, the study drug is referred to as "intepirdine". The study drug is also referred to (eg, in the protocol) as RVT-101.

2 STUDY ENDPOINTS

2.1 Co-Primary Endpoints

The co-primary endpoints in this study are:

- Change from baseline in gait speed measured on an electronic walkway system under single task trial condition at the end of each two-week treatment period
- Change from baseline in gait speed measured on an electronic walkway system under dual task trial condition at the end of each two-week treatment period

2.2 Secondary Endpoints

Secondary endpoints include occurrence of adverse events (AEs) and changes in physical examinations, vital signs measurements, electrocardiograms (ECGs), routine laboratory assessments, and Columbia Suicide Severity Rating Scale (C-SSRS).

Secondary endpoints are discussed in the Safety Analysis section of this SAP.

2.3 Exploratory Endpoints

The exploratory endpoints in this study are:

- Change from baseline in step time variability and step length variability measured on an electronic walkway system at the end of each treatment period
- Change from baseline in the mini-BESTest total score and individual subscores at the end of each treatment period
- Change from baseline in individual item scores calculated by Opal APDM sensors during performance of the mini-BESTest battery at the end of each treatment period

- Change from baseline in the FOG score and freezing ratio, incorporating input from Opal APDM sensors during turning conditions, at the end of each treatment period
- Change from baseline in MDS-UPDRS Parts II and III subscores, PIGD, and MDS-UPDRS 7-Item subscore at the end of each treatment period
- Change from baseline in UPSIT score at the end of each treatment period

2.4 Description of Efficacy Endpoints

2.4.1 Gait Speed

Electronic walkway systems, such as the GAITRite and Zeno Walkway system, are computerized assessment tools that utilize an electronic mat consisting of pressure-sensitive pads that can calculate spatiotemporal gait parameters which include gait speed (Buesing et al., 2015) as the primary efficacy endpoint.

Subjects will undergo the gait assessments under single and dual task conditions, each with 3 trials, at all study visits. All assessments will be done on the Zero Walkway system. The PKMAS software will be utilized to capture and process gait data in the study. The average of the 3 measurements will be used in the statistical analysis.

Each co-primary outcome measures (ie, gait speed assessed under single and dual task conditions) in this study will be tested at two-sided 5% level of significance.

2.4.2 Step Time and Length Variability

Step time variability and step length variability, similarly to gait speed are calculated during the electronic walkway system assessment. The calculated endpoints will be directly obtained from the electronic walkway system and will be utilized in statistical analysis separately by single and dual task conditions.

- Change in step time variability as measured on an electronic walkway system from the start to the end of each treatment period with intepirdine
- Change in step length variability as measured on an electronic walkway system from the start to the end of each treatment period with intepirdine

2.4.3 Mini Balance Evaluation Systems Test (Mini-BESTest)

The Mini-BESTest is a short, validated 14-item assessment of dynamic balance, specifically anticipatory postural transitions, postural responses, and dynamic gait (King et al., 2012). Each item is scored from 0-2 with a score of 2 being normal. The total score is out of 28. The analysis will be performed on the total score and individual subscores. The subscales are:

- Anticipatory: the total subscore is out of 6
- Reactive postural control: the total subscore is out of 6
- Sensory orientation: the total subscore is out of 6

- Dynamic gait: the total subscore is out of 10

2.4.4 Mini Balance Evaluation Systems Test (Mini-BESTest) Analyzed by OPAL Sensors

The Mini-BESTest assessment will be performed with subjects wearing the Opal APDM sensors if available at the site, which will collect quantitative measures of dynamic gait and balance as captured by the Mobility Lab Software. The following measurements calculated by Opal APDM sensors during performance of the mini-BESTest battery will be utilized in statistical analysis.

- MiniBest Item 1: Sit to stand
- MiniBest Item 3: Stand on one leg
- MiniBest Item 7: Stance (feet together)
- MiniBest Item 8: Stance (feet apart on foam surface)
- MiniBest Item 9: Stance (feet apart on firm surface)

2.4.5 Freezing of Gait (FOG) Assessment

FOG is a symptom where subjects experience a paroxysmal inability to either continue or initiate gait (Shine et al., 2011). FOG is an independent risk factor for future falls in PD (Latt et al., 2009).

- In this study, freezing of gait will be assessed while subjects perform a procedure involving multiple turns. Subjects will wear Opal APDM sensors while performing this procedure, which will provide quantitative data related to freezing of gait. The calculated FOG ratio is evaluable only if duration of turn is at least 50 seconds (Martina Mancini, personal communication, November 21, 2017).
- Additionally, the freezing of gait assessment will be done by a rater. This freezing severity will be on a 0 to 4 scale: 0, Absent (no freezing episodes); 1, Mild (hesitation or episodic slowing); 2, Moderate (at least arrest); 3, Severe (multiple arrests); 4, Unable (required assistance).

2.4.6 Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts II and III

The MDS-UPDRS is considered the 'gold standard' clinical scale for PD (Song et al., 2009). The MDS-UPDRS is a revision of the original UPDRS (Goetz et al., 2008) made by the Movement Disorder Society. Part II of the MDS-UPDRS is a questionnaire that focuses on motor aspects of experiences of daily living (13 items, score range: 0 to 52) and Part III (18 items, 33 ratings, score range: 0 to 132) is a motor examination. Each item on the MDS-UPDRS is rated on a 0 to 4 scale, where 4 represents the worst disability and 0 represents no disability. Part II and Part III totals will be analyzed separately and then combined.

The PIGD 4-item subscale of MDS-UPDRS Part III (ie, posture, gait, postural stability, arising from chair) focuses on items related to postural instability and gait difficulty which are highly correlated with fall risk (Rudzinska et al., 2007) and deficits of executive function (Xu et al., 2014). The scale measurement range is 0 to 16.

The MDS-UPDRS 7-item subscale of MDS-UPDRS Part III (ie, facial expression, rigidity, global spontaneity of movement, postural tremor of hands [right, left], kinetic tremor of hands [right, left], rest tremor amplitude, constancy of rest tremor) was found to have high specificity and sensitivity for cognitively impaired patients with extrapyramidal features (Ballard et al., 1997) and can be computed as the sum of numeric responses to MDS-UPDRS Part III items 2, 3 (5 ratings), 14, 15 (2 ratings), 16 (2 ratings), 17 (5 ratings) and 18, with subscale scores ranging from 0 to 68 (inclusive).

2.4.7 University of Pennsylvania Smell Identification Test (UPSIT)

Approximately 90% of subjects with early stage PD have olfactory dysfunction, and olfactory dysfunction correlates with loss of cholinergic neurons in structures such as the nucleus basalis of Meynert (nBM) (Doty, 2012; Mancini and Horak, 2010). The UPSIT is a 40-item 'scratch-and-sniff' test that takes about 15 minutes to administer and is a reliable measure of olfactory function. The result of the test is the number of items correctly identified.

3 ANALYSIS POPULATIONS

It is intended that a complete accounting of subjects for the analysis populations will be provided, from the Screened Population through the Completers Population.

3.1.1 Screened Population

All subjects who have signed an informed consent and completed the screening phase will be included in the Screened Population.

3.1.2 Run-In Population

All subjects entering the Placebo Run-in will be included in the Run-In population. This population will be used to provide an accounting of the disposition of subjects during this phase of the study.

3.1.3 Randomized Population

The Randomized Population will include all subjects who are randomized.

3.1.4 Safety Population

The Safety Population will consist of all subjects who were randomized and took at least one dose of double-blind investigational product.

3.1.5 ITT Population

The Intent-to-Treat (ITT) Population will consist of all subjects randomized to treatment who have taken at least one dose of double-blind investigational product and have an evaluable baseline assessment and a valid post baseline primary efficacy assessment during double-blind treatment period. This will be the primary population used for the efficacy analysis.

3.1.6 Per-Protocol (PP) Population

The Per-Protocol (PP) Population will be defined on the sponsor's protocol deviation guidance. The PP Population will consist of those members of the ITT Population who have no major protocol violations deemed to have a potential impact on the primary efficacy analysis.

3.1.7 Completers (CS) Population

The Study Completers (CS) Population will consist of those members of the ITT Population who have completed the entire sequence (Period II and Period IV). This population will be used for supportive analysis of the primary efficacy variable and other efficacy endpoints.

4 GENERAL CONSIDERATIONS AND HANDLING OF MISSING DATA

4.1 Definitions

4.1.1 Study Drugs

There are two study drugs being given:

- Intepirdine 35mg (Test therapy)
- Placebo (Reference)

4.1.2 Baseline

For both safety and efficacy evaluations, baseline for Period II is the pre-dose assessment at Visit 3 and baseline for Period IV is the pre-dose assessment at Visit 5.

4.1.3 Age

Age in years will be determined using the date of informed consent as recorded in the Case Report Form (CRF).

Some birth dates may be incomplete. If the month and the day are missing, we will impute January 1; if the day is missing, we will impute the 1st of the month.

4.1.4 Study Day

Study day will be calculated separately for Period II and Period IV. Day on Treatment will be calculated as the first dose date during Period II and Period IV, respectively.

- If the assessment date of interest is on or after the first dose date of Period II or Period IV, but before or on the last day of Period II or Period IV:
  Day on Treatment = assessment date – first dose of Period II (or Period IV) + 1
- If Day of Assessment falls in the washout or follow-up periods, the day from the beginning of the previous period (Period II for the washout and Period IV for the follow up) will be calculated and appropriately flagged to differentiate it from Day on Treatment
- If Day of Assessment falls in the run-in or screening:
  Day on Treatment = assessment date – first dose of Period II

The study day will be displayed in all relevant data listings.

4.1.5 Visits and Periods

There are 5 study periods during this study:

- The Screening Period is defined as the period of time prior to the subject receiving the first dose of single-blind placebo run-in medication.
- The Single-Blind Placebo Run-In Period (Period I) is defined as the period from the first dose of single-blind run-in medication and ends on the last dose date of single-blind run-in medication. The assessments taken on the date of the first dose of randomized double-blind investigational product will be assumed to have been completed before the first dose of double-blind investigational product and will be slotted to this period.
- The First Two-Week Double-Blind Treatment Period (Period II) starts on the date of first dose of double-blind investigational product and ends on the last dose date. If the first dose of randomized investigational product is taken on the same day as Visit 3 assessments, it will be assumed that the assessments were completed before the first dose of double-blind investigational product has been taken.
- The Single-Blind Placebo Washout Period (Period III) starts one day after the last dose of the double-blind medication has been taken in Period II and lasts until the first dose of the double-blind investigational product in Period IV. The assessments taken on the date of the first dose of randomized double-blind investigational product will be assumed to have been completed before the first dose of double-blind investigational product and will be slotted to this period.
- The Second Two-Week Double-Blind Treatment Period (Period IV) starts on the date of the first dose of double-blind investigational product and ends on the last dose date. If the first dose of randomized investigational product is taken on the same day as Visit 5 assessments, it will be assumed that the assessments were completed before the first dose of double-blind investigational product has been taken.

A safety follow-up telephone call will be conducted approximately 2 weeks after completion of Period IV.

Study visits will be determined from the scheduled times as reported on the CRF. As indicated in Table 1, Schedule of Assessments visit windows of +/- 3 days are allowed for scheduling purposes. For analysis purposes in this crossover study, no visit reassignment will be used even if a visit falls before or after the scheduling window.

Table 1: Schedule of Events

Visit Description	Screening	Beginning of Period I	Randomization / Beginning of period II	Beginning of Period III	Beginning of Period IV	End of Study	Follow-up Visit	ET[1]
Study Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**n/a**
Study Week	**W (-6)**	**W (-2)**	**W0**	**W2**	**W4**	**W6**	**W8**	**n/a**
Study Day[2]	**Up to 28 + 14 days before V2**	**14 +3 days before V3**	**0**	**14 ± 3**	**28 ± 3**	**42 ± 3**	**56 + 5**	**n/a**
Informed consent	X							
Inclusion/Exclusion criteria	X	X	X					
Demography	X							
Medical History	X							
Concomitant medications	X	X	X	X	X	X		X
Blood alcohol and urine drug screen	X		X					
C-SSRS, Screening version	X							
C-SSRS, Since Last Visit version		X	X	X	X	X		X
Randomization			X					
Dispense IP		X	X	X	X			
Assess IP compliance			X	X	X	X		X
Physical exam	X[3]	X[4]	X[4]	X[4]	X[4]	X[3]		X[3]
Complete neurological exam[5]	X	X	X	X	X	X		X
MRI or CT[6]	X							
12-Lead ECG	X	X	X	X	X	X		X
Vital signs[7]	X	X	X	X	X	X		X
Review Adverse Events	X	X	X	X	X	X	X	X
Serum OR urine pregnancy test[8]	X		X					X
Urine pregnancy test[8]						X		
Hep B and Hep C screen[9]	X							
TSH, vitamin B_{12}, syphilis serology[10]	X							
Serum chemistry	X	X	X	X	X	X		X
Hematology	X	X	X	X	X	X		X
Urinalysis	X	X	X	X	X	X		X
MMSE	X							
UPSIT	X		X	X	X	X		
Primary Gait Screen: assessment of gait speed	X	X	X					
Single and dual task gait assessments	X	X	X	X	X	X		
Mini BESTest assessment		X	X	X	X	X		
Freezing of gait evaluation		X	X	X	X	X		
MDS-UPDRS Parts II and III		X	X	X	X	X		

Visit Description	Screening	Beginning of Period I	Randomization / Beginning of period II	Beginning of Period III	Beginning of Period IV	End of Study	Follow-up Visit	ET[1]
Study Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**n/a**
Study Week	**W (-6)**	**W (-2)**	**W0**	**W2**	**W4**	**W6**	**W8**	**n/a**
Study Day[2]	**Up to 28 + 14 days before V2**	**14 +3 days before V3**	**0**	**14 ± 3**	**28 ± 3**	**42 ± 3**	**56 + 5**	**n/a**
Caregiver-adapted Falls Efficacy Scale - International	X							
Handgrip strength evaluation	X							
Hachinski Ischemia Scale	X							

Abbreviations: ECG = electrocardiogram; Hep = hepatitis; IP = investigational product; mini-BESTest = mini Balance Evaluation Systems Test; MMSE = mini-mental state examination; TSH = thyroid stimulating hormone; MDS-UPDRS = Movement Disorder Society - Unified Parkinson's Disease Rating Scale; UPSIT = University of Pennsylvania Smell Identification Test

1. Early Termination visit should be performed within 7 days of stopping study drug if permanently discontinued between scheduled clinic visits.
2. If the visit window is used, the subsequent visit should be scheduled according to the date when the prior study visit actually took place and not according to the original visit schedule (ie, the subsequent visit date should be re-calculated from the date of the previous visit).
3. Full physical exam will be performed at Screening, V6, and ET; abbreviated physical exam will be performed at V2, V3, V4, and V5.
4. Brief, symptoms-directed physical examination will be performed at V2, V3, V4, and V5.
5. Neurological examinations will include assessment of gait, balance, coordination, cranial nerves, and motor and sensory systems, including assessment of peripheral neuropathy.
6. MRI or CT will be performed between V1 and V2 if no CT or MRI scan has been performed within the previous five years since diagnosis. These scan findings must be consistent with the diagnosis of AD, DLB, or PDD without any other clinically significant pathologies.
7. Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature and body weight at each visit and height at screening. Postural changes in blood pressure and heart rate will also be assessed at every visit.
8. Required only for women of childbearing potential. Either a serum or urine pregnancy test is to be performed at V1, V3, and Early Termination. A urine pregnancy test is to be performed at Visit 6. If a urine pregnancy test result is positive, an unscheduled serum pregnancy test must be performed to confirm the results.
9. If these tests were performed within 3 months prior to the planned first dose of investigational product, testing is not required. Records must be present in the subject's source documents.
10. If these tests were performed within 12 months prior to the planned first dose of investigational product, testing is not required. Records must be present in the subject's source documents.

4.2 Standard Reporting Conventions

Tables, listings, and figures will be prepared in accordance with the current International Conference on Harmonization Guidelines. The information and explanatory notes in the "footer" or bottom of each table and listing will include the following information:

- Date of output generation
- SAS® program name, including the path that generates the output
- Any other output specific details that require further elaboration

All hypothesis tests and confidence intervals will be two-sided at an alpha level of 5%.

Version 9.1 or higher of the SAS system will be used to analyze the data, as well as to generate tables, figures, and listings.

In general, tables will be formatted with a column displaying findings for all subjects combined. The summary tables will clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.

The treatment groups will be referred to in the tables, listings, and figures with the following conventions:

- Intepirdine 35 mg
- Placebo

Data analyses will be performed by, or under the direct supervision of, Axovant Sciences.

Efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, SDs, medians, maximum, minimum, and number of subjects. Categorical data will be summarized by counts and percentages.

Data collected in the CRF, as well as laboratory data, will be provided in data listings, sorted (in general) by sequence, subject, period, and date. For date fields, Day on Treatment will be calculated and presented in these listings.

Deviations from the analyses as described in this SAP will be identified in the final Clinical Study Report. When differences exist between the protocol-described analysis and the SAP, the SAP will take precedence.

4.3 Handling of Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

Where necessary for the calculation of derived variables, partial dates will be completed using the earliest calendar date based on the partial date provided. This rule is valid for all partial dates with the exception of the following:

- Start and stop dates of adverse events
- Start and stop dates of concomitant medication

Completely missing dates will not be replaced and the corresponding derived variables will be set to missing.

4.3.1 Incomplete Dates for Concomitant Medication and Adverse Events

For analyses of AEs and concomitant medication usage, a complete date must be established in order to correctly identify the AE or medication as occurring during treatment or not. For purposes of imputing missing components of partially-reported start and stop dates for AEs and for medication use, the algorithms listed below will be followed. Start and stop dates of AEs or concomitant medication will be displayed as reported in the subject data listings (ie, no imputed values will be displayed in data listings).

Missing start day, but month and year present:

- If the occurrence of the AE/concomitant medication is in the same month and year as is the date of first dose of investigational product in Period II (which is the first Two-Week Double-Blind Treatment Period), then the start day of the event/concomitant medication will be assigned to the day of the first dose of investigational product taken in Period II.
- If the occurrence of the AE/concomitant medication is in the same month and year as is the date of the first dose of investigational product in period IV (which is the second Two-Week Double-Blind Treatment Period), then the start day of the event/concomitant medication will be assigned to the day of the first dose of investigational product taken in Period IV.
- If the dates of first dose of investigational product for Period II and for Period IV fall in the same month, then the start date day of the event/concomitant medication will be assigned to the day of the first dose of investigational product taken in Period II.
- Otherwise, the start day will be set to the 1st day of the month.

Missing start day and month, but year present:

- If the occurrence of the AE/concomitant medication is in the same year as is the date of first dose of investigational product in Period II (which is the first Two-Week Double-Blind Treatment Period), then the start day of the event/concomitant medication will be assigned to the day of the first dose of investigational product taken in Period II.
- If the occurrence of the AE/concomitant medication is in the same year as is the date of the first dose of investigational product in period IV (which is the second Two-Week

Double-Blind Treatment Period), then the start day of the event/concomitant medication will be assigned to the day of the first dose of investigational product taken in Period IV.

- If the dates of first dose of investigational product for Period II and for Period IV fall in the same year, then the start date day of the event/concomitant medication will be assigned to the day of the first dose of investigational product taken in Period II.
- Otherwise the start day and month will be set to January 1st.

Missing end day, but month and year present:

- The end day will be set to the last day of the month.

Missing end day and month, but year present:

- The end day and month will be set to the maximum of the date of study termination or the date equivalent to 30 days after the last dose of the double-blinded medication.
- However, if the study termination year and year for the date of the last dose of the double-blinded medication +30 days are greater than the event/concomitant medication year, the day and month are to be set to December 31st.

4.3.2 Missing Walkway Data

No values will be imputed for missing data. If one of the triplicate measurements for a Gait parameter are missed, the average of the remaining two measurements can be used in the analyses. If two of or all the triplicate measurements are missing at a timepoint for a Gait parameter, no values will be imputed or calculated for this timepoint.

4.3.3 Missing MDS-UPDRS Data

MDS-UPDRS items with missing responses will be recoded with imputed values. The imputation approach used for each missing item within a scale will be mean item substitution, such that the missing item response will be recoded as the mean of the subjects' numeric responses to all non-missing items on the same scale (ie, Part II or Part III) at the same assessment.

According to a recent report by Goetz et al. (2015), values for missing items within a scale will only be imputed at assessments for which the number of missing items on the scale comprise ≤ 2 items for Part II, and ≤ 7 items for Part III. If a value for a missing item cannot be computed, then no scale or composite score which includes that item can be calculated.

No separate imputations for missing values will be conducted for items specific to the PIGD 4-item and MDS-UPDRS 7-item subscales. These subscales will be scored only if values are available for all the corresponding Part III items.

4.3.4 Missing Baseline Data

For efficacy evaluations, the baseline is considered invalid and will be excluded from the analysis if an assessment being analyzed is completed after the first dose of double-blind investigational product has been taken.

To assess sensitivity to missing data assumptions, the primary analysis of gait speed will be repeated with above invalid baseline included or substituting them with the respective non-missing assessment at Visit 2.

4.4 Subgroups

The efficacy and safety analyses will also be presented by the following subgroups:

- Dementia type (AD, LBD)
- Baseline MMSE (14-19, 20-26)
- Sex (Male, Female) [Note: efficacy analysis only]

5 BASELINE AND OTHER SUMMARIES AND ANALYSES

5.1 Subjects Disposition

The total number of subjects that participated in the study will be summarized, including whether they were randomized or not. A tabulation will be provided for the number of subjects screened and screen-failed prior to the Placebo Run-in period. The denominator for those outcomes for this analysis will be based on the number of screened subjects.

The number of subjects entering the Placebo Run-in and the number of subjects not completing the Placebo Run-in (and reasons for not completing) will be presented, using the subjects entering the Placebo Run-in as the denominator.

The number of subjects randomized, as well as the number of subjects in the analysis populations (Safety, ITT, Per Protocol, Completers populations), will be presented for the Randomized Population. This will be summarized by sequence.

An overall summary of the number and percentage of subjects who completed or withdrew prematurely from the study will be displayed by sequence, for the overall population as well as by dementia type (AD versus LBD [DLB and PDD]) strata. Reasons for premature withdrawal will be presented in the order they are displayed in the CRF. Subjects who withdrew prematurely from the study will be listed by treatment group and subject.

5.2 Screen Failures

Screen failure data will be tabulated by reason subjects were found to not be eligible for the study.

5.3 Protocol Deviations

Protocol deviations will be identified prior to the database lock and unblinding, and the Per-Protocol Population will be determined based on a review of those deviations. Protocol deviations will be tabulated and listed, indicating major/minor. In addition, a listing of subjects for whom the treatment blind was broken during the study will also be provided, if appropriate.

5.4 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the Safety Population.

- The variables to be included in the summary are age, sex, race, ethnicity, baseline body weight, height, body mass index (BMI), history of smoking, baseline MMSE, dementia type, fall history, and caregiver-adapted Falls Efficacy Scale – International.
- Details of the primary caregiver (relationship to subject, live with the subject) will be included in a tabulation.
- All demographic data will be tabulated overall and then by sequence.
- Other characteristics collected on the CRF will be listed as appropriate.

5.5 Subject Inclusion and Exclusion Criteria

Subjects not meeting specific eligibility criteria questions will be listed.

5.6 Medical History and Medical Conditions Present at Entry

Past and current medical conditions will be collected and coded using the Medical Dictionary for Regulatory Activities (MedDRA), using Axovant Sciences coding conventions.

A tabulation displaying medical history will be provided by system organ class (SOC) and preferred term for the safety population.

5.7 Prior and Concomitant Medications

Prior and concomitant medication verbatim text will be coded using the World Health Organization's Drug Dictionary (WHO-DD), and will be classified according to the default Anatomical Therapeutic Chemical (ATC) classification system code, WHO-DD Drug Name, and preferred term.

Medications will be tabulated as:

- Prior medications
- Concomitant medications
  - Single-blind run-in and washout periods
  - Double-blind periods

Medications received prior to the date of first dose of single-blind investigational product are considered as prior medications. Medications will be considered as concomitant if the start date of the medication is on or after the date of first intake of investigational product or if the start date is prior to the first date of investigational product, but the medication is ongoing during the treatment period in the study.

Concomitant medications will be further split by concomitant medications taken during the Single-Blind Placebo Run-In Periods and concomitant medications taken during the Double-Blind Treatment Periods. Those will be presented by treatment group. It should be noted that a concomitant medication can be counted in more than one period.

Use of non-investigational products will be summarized (number and percentage of subjects) by treatment, the highest ATC class level, and preferred term for the safety population.

A listing of non-medication therapy will be provided.

5.8 Extent of Treatment Exposure

Duration of exposure for the Double-Blind Treatment Period (Period II and Period IV) will be calculated by treatment group as follows:

- Duration of exposure in days = (Double-Blind Treatment Period stop date – Double-Blind Treatment Period start date) + 1

Duration of exposure will be tabulated descriptively and categorized as:

- 0 to 1 week
- >1 to 2 weeks
- >2 weeks

Note: Duration of exposure will exclude any dates with documented dose interruptions.

5.9 Treatment Compliance

Compliance with study drug will be assessed during the run-in and over the Double-Blind Treatment Periods (Period II and Period IV) using drug dispensing records. Treatment compliance during the double-blind period will be computed by determining the number of tablets taken relative to the number of tablets expected. Subjects are expected to take one tablet per day of each.

Treatment compliance based on the drug accountability per subject/period will be calculated as follows:

- Compliance (%) = (number of tablets taken in the period)/(number of tablets expected)*100

- Number of tablets taken = the number of tablets dispensed in the period – the number of tablets returned
- Number of tablets expected = (date of the last dose-date of the first dose+1 in the period)

Summary of treatment compliance will be presented by treatment group. The number and percentage for compliance expressed as a categorical variable (<80%, ≥80% to ≤120%, and >120%) will also be presented by treatment group.

5.10 Overdose

Any occurrence of overdose will be provided in the data listing in the same section of dose administration record.

6 EFFICACY SUMMARIES AND ANALYSES

6.1 General Considerations

Tabulation of the primary and exploratory endpoints will generally be presented for the ITT, Per-Protocol, Completers Population (as described in Section 3), and subgroups (as identified in Section 4.4). The primary efficacy assessments will be performed on the ITT dataset. Sensitivity analysis will be performed on CS dataset. The per-protocol analysis (on the PP population) will also be conducted. If deemed necessary

6.2 Statement of the Null and Alternate Hypothesis

This study will examine the following primary hypothesis:

- H_o: There is *NO* difference between treatment with intepirdine and treatment with placebo with respect to changes from baseline in gait speed (under single and dual task conditions) at the end of two-week double-blind treatment periods (Period II and Period IV).
- H_a: There *IS* a difference between treatment with intepirdine and treatment with placebo with respect to changes from baseline in gait speed (under single and dual task conditions) at the end of two-week double-blind treatment periods (Period II and Period IV).

The primary comparison of interest will be performed at the 5% level of significance. All hypothesis tests will be two-sided. The primary objective of the study will be considered met only if the primary analyses of both endpoints indicate statistical significance in favor of Intepirdine. No correction for multiplicity will be taken.

6.3 Analyses of the Primary Efficacy Endpoints

6.3.1 Co-Primary Endpoints

The co-primary endpoints in this study are change from baseline in gait speed observed at the end of the two-week double-blind treatment period (Period II and Period IV) under either single or dual task condition.

6.3.2 Primary Efficacy Analyses

Separately by each trial condition, treatment comparisons between intepirdine and placebo in change from baseline in gait speed at the end of the two-week double-blind treatment period (Period II and Period IV) will be analyzed for the ITT Population using a mixed model for crossover design with restricted maximum likelihood estimation and an unstructured covariance matrix. Degrees of freedom will be calculated using Satterthwaite's method.

- This model corrects for dropouts and missing values replacement is not necessary.
- Therefore, no imputation of the missing values will be made or required and the data used in the analysis will be the actual observed responses.
- The statistical model will be fitted initially with sequence, treatment, period, baseline value, both stratification factors (ie, MMSE and dementia type), sex, dementia type by treatment interaction as fixed effects and with subject within sequence as a random effect.
  - If the effects of sex and/or dementia type by treatment interaction are not statistically significant ($p > 0.10$), they will be removed from the final analysis model.
  - If the sequence effect is statistically significant ($p \leq 0.05$) in the model described above, subjects within a sequence will be fitted separately in the model with treatment, baseline value, and both stratification factors (ie, MMSE and dementia type).

The estimated treatment difference for "intepirdine – Placebo" will be displayed together with the 95% confidence interval and the associated p-value.

Least Squares Means will also be presented with the standard error and the number of subjects contributing to the Least Squares Means.

The model will be fitted using SAS PROC MIXED procedure with restricted maximum likelihood estimation and an unstructured covariance matrix. The unstructured covariance is the least restrictive and generally performs well with limited number of repeated measures per subject and puts no parameters on the data with respect to the covariance structure assumptions.

Only in the unlikely circumstance that there are convergence problems with the analysis will other covariance structures be examined to resolve the convergence issue (ie, we would evaluate other additional variance-covariance structures, including compound symmetry (CS), heterogeneous compound symmetry (CSH), and auto-regressive [AR(1)]). In this

eventuality, the Akaike's Information Criterion (AIC) will be used to determine the optimal variance-covariance structure matrix for the primary comparisons.

6.4 Analysis of the Exploratory Efficacy Endpoints

Continuous and ordinal variables will be analyzed in a fashion similar to that of the primary endpoints, using the mixed model for crossover design on the ITT dataset.

6.4.1 Exploratory Endpoints

The exploratory endpoints in this study will be analyzed using the same mixed model as for the primary endpoints. The exploratory endpoints in this study are:

- Change from baseline in step time variability and step length variability measured on an electronic walkway system at the end of each treatment period
- Change from baseline in the mini-BESTest total score and subscores at the end of each treatment period
- Change from baseline in quantitative gait and balance measurements calculated by Opal APDM sensors during performance of the mini-BESTest battery at the end of each treatment period
- Change from baseline in the FOG score and freezing ratio, incorporating input from Opal APDM sensors during turning conditions, at the end of each treatment period
- Change from baseline in the FOG assessment by the rater on 0 to 4 ordinal scale can range from -4 to 4 and will also be analyzed using the same mixed model as for the primary endpoints
- Change from baseline in MDS-UPDRS Parts II and III subscores, PIGD and MDS-UPDRS 7-Item subscores at the end of each treatment period
- Change from baseline in UPSIT score at the end of each treatment period

6.4.2 Responder Analyses

The percentage of subjects with a 1-point, 3-point, and 5-point reduction in the MDS-UPDRS will be presented graphically overall by treatment, and then by subgroups of dementia type, baseline MMSE, and sex. No inferential statistics will be calculated to compare differences in proportion of subjects meeting each of these 3 thresholds after 2-week double-blind treatment period between treatment groups.

6.4.3 Other Analyses

If deemed appropriate, additional sensitivity analyses of the data not specified in the SAP may be undertaken and will be described in the clinical study report.

7 SAFETY SUMMARIES AND ANALYSES

The safety analysis will be descriptive in nature, and will be presented for the Safety Population. All safety data collected and captured in the CRF will be included in data listings sorted by domain, sequence, subject, and time point, or as appropriate. Mean changes from pre-treatment to on-treatment (Periods II and IV together) will be tabulated by treatment, while the number of subjects with potentially clinically significant values at pre-treatment and at the end of each double-blind two-week treatment period (Period II and Period IV) will be presented.

Generally, safety data will be presented for the Placebo Run-In Period, for the Double-Blind Treatment Period by treatment group (Period II and Period IV plus 7 days after the end of these periods, for the Washout Period starting at day 8 of the Washout Period, and for the post-treatment Follow-up Period starting at day 8 of the Follow-up Period.

All safety data will be summarized overall and then by stratified subgroup: dementia type (AD, LBD) and baseline MMSE (14-19 and 20-26).

7.1 Adverse Events

Adverse events will be classified using the MedDRA version 18.1 coding dictionary. Tabulations will include an overall incidence of at least one adverse event, incidence within system organ class (SOC), and incidence by preferred term. Each subject may only contribute once per treatment group, that is by first occurrence to each of the incidence rates, regardless of the number of occurrences, as follows:

- Adverse events occurring prior to the first dose of double-blind investigational product will be referred to as Treatment-Emergent AEs (TEAEs) and presented as Placebo Run-In events.
- Adverse events occurring on or after the first dose of each double-blind two-week treatment period (Period II and period IV), and within 7 days of the last dose of double-blind investigational product, will be referred to as TEAEs and presented by treatment group.
- Events occurring 7 days after the last dose of Period II and Period IV and for the post-treatment Follow-up Period starting at day 8 (up to 14 days post-last-dose) will be presented as Post-Treatment Period. These events will only be included in a data listing.

Tabulations of the incidence of AEs will be presented as follows:

- Overview of TEAE
- TEAE by SOC and preferred term
- TEAE by preferred term
- TEAE by SOC, preferred term, and relationship to study drug
- TEAE by SOC, preferred term, and maximum severity (mild, moderate, and severe)

All AEs will be listed with its relationship to study drug and severity, flagging those which are not events during treatment-emergent period.

A listing of all deaths and serious AEs will be provided. Any TEAE leading to study drug temporary and permanent discontinuation will also be listed.

7.2 Clinical Laboratory

Clinical laboratory parameters will be presented using three methods:

1. Tabulations of observed values for the double-blind two-week periods pre-and post-treatment (Period II: Visit 3 and Visit 4; Period IV: Visit 5 and Visit 6) by treatment group.
2. Tabulations of the incidence of potentially clinically significant (PCS) values by treatment group. A focus will be on new-onset PCS values (ie, subjects with pre-existing PCS values at pre-treatment will not be considered to have new-onset values on-treatment). For purposes of this analysis, the most extreme (highest and lowest) value AT ANY TIME during Period II plus 7 days and Period IV plus 7 days for a parameter (for a given subject) will be used. Thus, a subject may contribute to both a low PCS value for a parameter as well as a high PCS value for that same parameter. PCS laboratory values are presented for serum chemistry in Table 2 and for hematology in Table 3.
3. Shifts from baseline to on-treatment, where values are categorized as low, normal, or high according to the lab normal values by treatment group. For purposes of this analysis, the most extreme on-treatment values will be used (most extreme low and most extreme high). On-Treatment values are considered values during Period II plus 7 days and during Period IV plus 7 days. Shifts from baseline will be based on laboratory normal ranges as provided by the central laboratory.

In addition, the incidence of TEAEs relating to hematology and serum chemistry laboratory parameters during Period II plus 7 days and Period IV plus 7 days will be presented by treatment group. These laboratory AEs will be identified from a review of the adverse events and select SOC and preferred terms will be included.

Table 2: Serum Chemistry Potentially Clinically Significant Criteria

Parameter	Gender	Low PCS	High PCS
Alanine aminotransferase (U/L)	Male	NA	133
	Female	NA	100
Albumin (g/L)	Male/Female	29	NA
Alkaline phosphatase (U/L)	Male	NA	323
	Female	NA	246
Aspartate aminotransferase (U/L)	Male	NA	118

	Female	NA	103
Direct bilirubin (umol/L)	Male/Female	NA	7.7
Total bilirubin (umol/L)	Male/Female	NA	30.8
Calcium (mmol/L)	Male/Female	1.99	2.91
Creatinine (umol/L)	Male	NA	174
	Female	NA	147
GGT (U/L)	Male	NA	136
	Female	NA	93
Creatinine clearance (mL/min)	Male/Female	59	NA
Random glucose (mmol/L)	Male/Female	2.9	NA
Potassium (mmol/L)	Male/Female	3.4	5.6
Sodium (mmol/L)	Male/Female	129	151

Table 3: Hematology and Differentials Potentially Clinically Significant Criteria

Parameter	Gender	Low PCS	High PCS
WBC (10^9/L)	Male/Female	2.9	100.1
Hemoglobin (g/L)	Male	99	196
	Female	99	181
Platelets (10^9/L)	Male/Female	74	NA
Absolute neutrophil count (10^9/L)	Male/Female	1.4	NA
Calculated absolute neutrophil count (10^9/L)	Male/Female	1.4	NA
Absolute lymphocyte count (10^9/L)	Male/Female	0.7	5.1
Calculated absolute lymphocyte count (10^9/L)	Male/Female	0.7	4.1

7.3 Vital Signs

Vital sign data (blood pressure [BP], pulse, and weight) will be summarized by treatment, and listed by subject and sequence.

Change from baseline will also be summarized by treatment group using data from Periods II and IV. The incidence of PCS values will be presented, with a focus on new-onset PCS values.

PCS ranges for these parameters are provided in Table 4.

Table 4: List of Potentially Clinically Significant Ranges for Vital Sign Parameters

Systolic blood pressure:
Low: < 90 and decrease ≥30 mm Hg
High: >140

Diastolic blood pressure:
Low: < 50 and decrease ≥20 mm Hg
High: >90 and increase ≥20 mm Hg
Pulse
Low: <50 bpm and Decrease ≥30 bpm
High: >100 and Increase ≥30 bpm
Weight
≥ 10% increase from baseline
≥ 10% decrease from baseline

7.4 ECGs

ECG data will be listed by sequence, subject, and time point. Change from baseline will be summarized by treatment group using data collected during the double-blind treatment periods plus 7 days.

The ECG analysis will include a careful review of QTcF values. As part of this review, a summary of the number (percent) of subjects with QTcF values in the following ranges will be provided: ≤450 msec, >450 to ≤480 msec, >480 to ≤500 msec, and >500 msec. This will be performed at ANY time during the double-blind treatment periods plus 7 days (where the highest QTcF value will be used for that assessment) and presented by treatment group.

The overall Investigator interpretation of ECG by treatment (shifts from baseline) will be tabulated. The incidence of PCS values will be presented, with a focus on new-onset PCS values in Table 5.

Table 5: List of Potentially Clinically Significant Ranges for ECG Parameters

QTcF Interval:
High: ≥500 msec only
High: Increase ≥ 60 msec only
High: ≥500 and Increase ≥60

7.5 Physical Examination

Physical examination data will be summarized by treatment group and listed by sequence, subject, and time point.

7.6 Suicidality

The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definitions of the composite and comparative endpoints, and to enable clarity in the presentation of the results.

- Category 1 – Wish to be Dead
- Category 2 – Non-specific Active Suicidal Thoughts
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Category 6 – Preparatory Acts or Behavior
- Category 7 – Aborted Attempt
- Category 8 – Interrupted Attempt
- Category 9 – Actual Attempt (non-fatal)
- Category 10 – Completed Suicide
- Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no)

Endpoints based on the above categories are defined below.

- Suicidal ideation: A "yes" answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS
- Suicidal behavior: A "yes" answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS
- Suicidal ideation or behavior: A "yes" answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS
- Self-injurious behavior without suicidal intent: a binary response (yes/no)

The number and percentage of subjects with any occurring suicidal events (ideation or behavior) will be presented by treatment group and time point.

A listing of all C-SSRS data will be provided, while a listing of subjects who demonstrated a worsening on any one of the four endpoints will also be provided for pre-and post-treatment (V3 vs V4 and V5 vs V6) including the Day on Treatment the C-SSRS was collected.

7.7 Pregnancy

If any female subjects or female partners of male subjects become pregnant during the study, a listing will be provided.

8 INTERIM AND FINAL ANALYSES

No unblinded interim efficacy or safety analyses are planned for this study. This final analysis will be performed upon completion of the following items:

- The database has been locked according to the Study Data Management Plan
- The list of subjects excluded from Per-Protocol Population has been identified

9 CHANGES FROM THE PROTOCOL TO THIS SAP

There are no meaningful changes from the protocol to this SAP. Additional details and specifications have been included in this SAP to allow for better understanding of the intended procedures.

10 REFERENCES

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