Official Title: A Randomized, Double-Blind, Placebo-Controlled, 52-Week Phase II Study to Evaluate the Efficacy of Intravenous RO7046015/Prasinezumab (PRX002) in Participants With Early Parkinson's Disease With a 6-Year All-Participants-on-Treatment Extension (Pasadena)

NCT Number: NCT03100149

Document Date: Protocol Version 6: 20-March-2020

PROTOCOL

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 52-WEEK PHASE II STUDY TO EVALUATE THE EFFICACY OF INTRAVENOUS RO7046015/*PRASINEZUMAB* (PRX002) IN PARTICIPANTS WITH EARLY PARKINSON'S DISEASE WITH A *6-YEAR ALL-PARTICIPANTS-ON-TREATMENT* EXTENSION (PASADENA)**
PROTOCOL NUMBER:	BP39529
VERSION:	6
EUDRACT NUMBER:	2017-000087-15
IND NUMBER:	119602
TEST PRODUCT:	RO7046015
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 01 March 2017
DATE AMENDED:	Version 2: 13 November 2017 Version 3: 27 June 2018 Version 4: 23 October 2019 Version 5: 6 March 2020 Version 6: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
20-Mar-2020 11:44:09	Company Signatory	[redacted]

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 52-WEEK PHASE II STUDY TO EVALUATE THE EFFICACY OF INTRAVENOUS RO7046015/*PRASINEZUMAB* (PRX002) IN PARTICIPANTS WITH EARLY PARKINSON'S DISEASE WITH A *6-YEAR ALL-PARTICIPANTS-ON-TREATMENT* EXTENSION (PASADENA)**
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SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your study files, and return a copy to your local Study Monitor.

PROTOCOL AMENDMENT, VERSIONS 5 AND 6: RATIONALE

Note: Protocol BP39529 Version 5 has not been submitted to health authorities and this rationale presents the changes included in both Version 5 and 6, respectively.

Protocol BP39529 Version 5 has been amended to incorporate the following changes:

- Addition of Part 3: A 5-year all participants on treatment extension. BP39529 has been amended to allow the patients who completed Part 2 and who completed the 12-week treatment free follow up visit to enroll in Part 3. Part 3 is a 5-year all participants on treatment extension aiming to assess long-term safety and efficacy effects of RO7046015. Part 3 will start with the doses of RO7046015 tested in Part 2, patients will remain blinded to the dose they are receiving, and they were previously assigned too. When the dose used in the coming Phase III study will be known, patients will be switched to that dose. Details on this procedure and the schedule of activities have been added. (New sections: Section 3.1.1.3; Section 3.2.6; Appendix 3; updated sections: Section 1.3.1, Section 2.2, Section 2.3, Section 3.1.1, Figure 1, Section 3.1.1.4, Section 3.1.3, Section 3.2, Section 3.3.4, Section 4.2.2, Section 4.4.4, Section 6.6, Section 6.9; minor updates to other sections throughout protocol to include reference to Part 3).
- Section 1 (Background and Rationale) has been updated to include details on the most recent clinical study data. As such, Section 1.2 has been updated to include details on an additional Phase I study that has been performed. Section 1.3 has been updated to reflect the most recent safety data as presented in the latest Investigator Brochure.
- Section 2.3 and Section 3.3.4 have been updated to align and clarify the study objectives with the listed outcome measures and vice versa.

Protocol BP39529 Version 6 has been amended to incorporate the following changes:

- Two additional MRI sequences (iron and neuromelanin-sensitive imaging) have been added to the MRI battery. Sections 2.3, Section 3.2.7.2, Section 3.3.4, Section 4.6.1.9 and Appendix 2 & 3 have been updated to reflect these changes.

Additional minor corrections and changes have been made to improve clarity and consistency. Substantial new information (for Version 5 and Version 6) appears in *book antiqua italics*. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 52-WEEK PHASE II STUDY TO EVALUATE THE EFFICACY OF INTRAVENOUS RO7046015/*PRASINEZUMAB* (PRX002) IN PARTICIPANTS WITH EARLY PARKINSON'S DISEASE WITH A *6-YEAR ALL-PARTICIPANTS-ON-TREATMENT* EXTENSION (PASADENA)**
PROTOCOL NUMBER:	BP39529
VERSION:	6
EUDRACT NUMBER:	2017-000087-15
IND NUMBER:	119602
TEST PRODUCT:	RO7046015
PHASE:	II
INDICATION:	Parkinson's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES

Primary Objectives

The primary objective of this study is:

- To evaluate the efficacy of RO7046015 versus placebo at Week 52 in participants with early Parkinson's disease (PD) (Hoehn & Yahr [H&Y] Stages I-II) who are untreated or treated with monoamine oxidase B (MAO-B) inhibitors since baseline, as measured by change from baseline on the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Total Score (sum of Parts I, II and III).

Secondary Objectives

The secondary objectives of this study are:

- To evaluate the effects of RO7046015 versus placebo at Week 52, in participants with early PD (H&Y Stages I-II) who are untreated or treated with MAO-B inhibitors since baseline, on the following:
  - MDS-UPDRS Part IA, Part IB, Part I total, Part II total, Part III total and Part III subscores
  - Dopamine transporter imaging with single photon emission computed tomography (DaT-SPECT) in the ipsilateral (to the clinically dominant side) putamen.
  - Montreal Cognition Assessment (MoCA) total score
  - Clinical Global Impression of Improvement (CGI-I)
  - Patient Global Impression of Change (PGIC)
  - Schwab and England Activity of Daily Living (SE-ADL) score
  - Time to worsening in motor or non-motor symptoms
  - Time to start of dopaminergic PD treatment (levodopa or dopamine agonists)
  - Safety and tolerability of RO7046015.
- To evaluate the safety and tolerability of treatment with RO7046015 for up to 104 weeks

(Part 2) and up to Part 3 Week 260, with or without concomitant dopaminergic treatment.

- To evaluate the immunogenicity of RO7046015.
- To describe the pharmacokinetics (PK) of RO7046015 using population PK modelling.

Exploratory Objectives

The exploratory objectives of this study are:

- To compare consistency and accuracy in MDS-UPDRS Part III total, Part III subscores centrally rated by video-tapes vs locally rated by the site *(in Part 1 and Part 2 only)*
- Time to worsening in motor or non-motor symptoms or starting dopaminergic PD treatment (levodopa or dopamine agonist)
- To evaluate the effect of RO7046015 versus placebo over 52 weeks, on change from baseline in:
  - Modified Hoehn and Yahr, Hospital Anxiety and Depression Scale (HADS), Patient Assessment of Constipation Symptoms (PAC-SYM), Scales for outcomes in Parkinson's disease autonomic dysfunction (SCOPA-AUT), Parkinson's Disease Sleep Scale Revised Version 2 (PDSS-2), 39-item Parkinson's Disease Questionnaire (PDQ-39), European Quality of Life Questionnaire 5-level version [EQ-5D-5L] and Smartphone and wrist-worn wearable assessments.
  - Serum, *plasma,* cerebrospinal fluid (CSF), skin, and imaging biomarkers related to Parkinson's disease.
- To evaluate clinical and biomarker outcomes (as outlined above) over a period of up to 104 weeks including data from the one-year extension (Part 2) *(*all-participants-on-treatment*,* blinded to dose) with or without concomitant dopaminergic treatment.
- *To evaluate clinical and biomarker outcomes (as outlined above) in the five-year extension (Part 3) (all-participants-on-treatment, blinded to dose until Phase III study dose has been identified) with or without concomitant dopaminergic treatment.*
- To evaluate the dose-exposure-response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship for MDS-UPDRS, DaT-SPECT and other functional, biomarker and safety parameters.
- To evaluate an immunohistochemical assay for α-synuclein pathology in peripheral nerves (skin biopsy samples from randomized participants and DaT-SPECT screen failures).
- *To assess time to start or change of co-medication for non-motor symptoms that may be related to PD (cognition, constipation, depression, anxiety, excessive daytime sleep, nocturnal sleep, urogenital symptoms/sexual dysfunction).*
- *To assess start or change of co-medication for non-motor symptoms that may be related to imaging biomarkers (DAT Scan and ASL).*
- *To assess Parkinson-related effects on the loss of autonomic tone as measured by heart rate variability.*
- *To evaluate motor progression as assessed by a composite score of MDS-UPDRS Part II (patient reported motor experiences of daily living) and MDS-UPDRS Part III (clinician rated motor signs of PD) sub-items*
- *To assess motor complications as assessed by MDS-UPDRS Part IV at Week 52, at Week 104 and Part 3 Week 260 in participants who started dopaminergic treatment (levodopa or dopamine agonist).*

STUDY DESIGN

Description of Study

This is a multicenter, Phase II study to evaluate the effect of IV administration of RO7046015 in participants with early stage (H&Y Stages I-II) PD. Participants will be eligible if they have idiopathic PD with bradykinesia plus one of the other cardinal signs of PD (resting tremor, rigidity) being present, without any other known or suspected cause of PD (adapted from the

MDS Clinical Diagnostic Criteria for Parkinson's Disease) and are either untreated or treated only with MAO-B inhibitor.

The study will consist of *three* parts: a 52-week, double-blind, placebo-controlled treatment period (Part 1) after which eligible participants will continue into an all-participants-on-treatment (RO7046015) blinded to dose extension for an additional 52 weeks (Part 2). *Participants who complete Part 2 (including the 12-week treatment free follow up visit assessing long term safety and efficacy of RO7046015) will be offered participation in Part 3 (all-participants-on-treatment (RO7046015) blinded to dose until Phase III study dose has been identified) for an additional 260 weeks.*

Part 1

During Part 1 of the study, participants will receive IV infusions of RO7046015 or placebo once every four weeks (Q4W) over a period of 52 weeks.

Participants will be randomized with a 1:1:1 allocation ratio to placebo, or one of the two active treatment doses: high dose (4500 mg for body weight $\geq$65 kg; 3500 mg for body weight $<$65 kg), low dose (1500 mg; for all body weights).

Randomization will be stratified by sex, age group and existence or lack of prior background therapy (untreated or treated with stable MAO-B inhibitor therapy at baseline).

To enhance the tolerability of RO7046015 infusions, a dose titration regimen that may reduce the risk of IRRs will be implemented for the high dose, as follows: 2000 mg will be infused on Day 1 followed by an up-titration to the full dose of 4500 mg ($\geq$65 kg body weight) or 3500 mg ($<$65 kg body weight) on the second infusion (Day 28) during Part 1.

Participants are expected not to start dopaminergic therapy (levodopa or dopamine agonist) or other symptomatic PD therapy during the 52-week double-blind placebo-controlled period. Some participants may experience worsening of their symptoms to an extent that they are unable to tolerate in their personal or professional life. These participants may start dopaminergic or symptomatic PD treatment according to local guidelines after completing the assessments at the "prior to start of dopaminergic or symptomatic PD treatment" visit according to the schedule of assessments and the Investigator must record the reasons and the type and dose of dopaminergic or symptomatic PD treatment started.

For the main analysis of the primary endpoint and other efficacy endpoints that are sensitive to dopaminergic treatment (such as MDS-UPDRS part III, PGIC, CGI-I), only data up to the last measurement before start of symptomatic PD treatment will be used. Data after start of symptomatic PD treatment will be included in safety, sensitivity, exploratory and biomarker evaluations as appropriate.

All participants, including those that have started symptomatic PD treatment, will be eligible to participate in Part 2 if they have completed Part 1 with the predefined minimum of infusions and assessments as defined below.

Part 2

Part 2 is a one-year all-participants-on-treatment, blinded to dose extension.

Participants must meet the following criteria to enter Part 2: DaT-SPECT and magnetic resonance imaging (MRI) scans completed at Screening and Week 52 and received at least 10 doses of study treatment (RO7046015 or Placebo) during Part 1 of the study. Participants may initiate or change symptomatic PD treatment (including dopaminergic treatment) as per standard of care (SOC) during Part 2.

For Part 2, participants who complete the initial placebo-controlled part and fulfil the criteria mentioned above will switch into the extension:

- Participants initially randomized to placebo will be re-randomized to one of the two active doses using a 1:1 allocation ratio.

  Randomization will be stratified by: dopaminergic therapy since start of the study (Yes versus No), age group ($<$60 versus $\geq$60) and prior background therapy with MAO-B inhibitor (Yes versus No). Note that for age group and prior background therapy with MAO-B inhibitor the values collected for Part 1 will be used.

Participants receiving placebo during Part 1 and randomized to the high dose at the start of Part 2 (extension) will receive 2000 mg IV on Week 56 followed by an up-titration to the full dose of 4500 mg (≥ 65 kg body weight) or 3500 mg (< 65 kg body weight) on the second infusion (Week 60).

- Participants initially randomized to the active dose will remain on their dose.

Part 3

Part 3 is a 5-year extension in which all participants will be on treatment. Participants will be blinded to dose until the Phase III study dose is identified (Note: this dose will not exceed the high dose tested in the present BP39529 study). Once the Phase III study dose is identified, participants will be switched to that dose (if applicable).

Participants must meet the following criteria to enter Part 3:

- *Having completed Part 2 (i.e., completed Week 104 visit) as well as the 12-week treatment free follow up visit. Participants may initiate or change symptomatic PD treatment (including dopaminergic treatment) as per standard of care during Part 3.*
- *Not having received another investigational medication during the treatment free period (i.e., between Week 104 visit and Part 3 Week 1 visit).*
- *Participation in Part 3 not deemed inappropriate by the Investigator (e.g., patient with serious medical condition or other concerns that preclude their safe participation in Part 3 or their ability to comply with the required procedures should not be enrolled).*

NUMBER OF PARTICIPANTS

Approximately 300 participants are planned to be enrolled which could be increased to a maximum of 360 depending on the outcome of the independent Data Monitoring Committee (iDMC) safety review. The sample size may also be adjusted to up to 360 participants if assumptions (e.g., drop-out rate) used for sample size calculation need to be adapted.

TARGET POPULATION

Men and women, aged 40 to 80 years inclusive, with early PD (H&Y Stage I or II), who were recently (≤ 2 years) diagnosed, and either de novo (untreated) or treated with a MAO-B inhibitor.

Only early stage PD patients with a clinical condition not requiring dopaminergic PD medication at baseline and not expected to require dopaminergic treatment within 12 months from baseline will be eligible to participate in the study. Patients with a history of stable parkinsonian symptoms who are on a stable dose of MAO-B inhibitor (rasagiline or selegiline) for at least 90 days prior to baseline may also be included.

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria:

Participants must meet the following criteria for study entry:

1. Idiopathic PD with bradykinesia plus one of the other cardinal signs of PD (resting tremor, rigidity) being present, without any other known or suspected cause of PD untreated or treated with MAO-B inhibitor.
2. Male or female, 40 to 80 years of age, body weight range of ≥ 45 kg/99 lbs to ≤ 110 kg/242 lbs and a body mass index (BMI) of 18 to 34 kg/m2.
3. A diagnosis of PD for 2 years or less at screening.
4. H&Y Stage I or II.
5. A screening brain DaT-SPECT consistent with PD (central reading).
6. Clinical status does not require dopaminergic PD medication and is not expected to require dopaminergic treatment within 52 weeks from baseline.
7. If presently being treated for PD, a stable dose of MAO-B inhibitor (rasagiline or selegiline) for

at least 90 days prior to baseline and not expected to change within 52 weeks.

8. Able and willing to provide written informed consent and to comply with the study protocol according to ICH and local regulations.
9. For women of childbearing potential: use of highly effective contraceptive methods (that result in a failure rate of < 1% per year) during the treatment period and for at least 30 days (or longer if required by local regulations) after the last dose of study drug.

   A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

   Examples of highly effective contraceptive methods (with a failure rate of < 1% per year) include bilateral tubal ligation, vasectomized partner, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

   The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
10. For men: use of contraceptive measures as defined below:

    With female partners of childbearing potential or pregnant female partners, men must use a condom during the treatment period and for at least 30 days (or longer if required by local regulations) after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period. The female partners should use a contraception method with a failure rate of < 1% per year during the treatment period and for at least 30 days (or longer if required by local regulations) after the last dose of study drug.

    The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria:

Participants who meet any of the following criteria will be excluded from study entry:

Current or Past Medical History

1. Medical history indicating a Parkinson syndrome other than idiopathic PD, including but not limited to, progressive supranuclear gaze palsy, multiple system atrophy, drug-induced parkinsonism, essential tremor, primary dystonia.
2. Known carriers of certain familial PD genes (Parkin, PINK1, DJ1). Note: GBA, synuclein, LRRK2 mutation carriers are allowed.
3. History of PD-related freezing episodes or falls.
4. A diagnosis of a significant CNS disease other than Parkinson's disease (including but not limited to Huntington's disease, normal pressure hydrocephalus, cerebrovascular disease including stroke, fronto-temporal dementia, Alzheimer's disease); history of repeated head injury; history of epilepsy or seizure disorder other than febrile seizures as a child.
5. Mini Mental State Examination (MMSE) ≤ 25.
6. Reside in a nursing home or assisted care facility.
7. History of or screening brain MRI scan indicative of clinically significant abnormality including, but not limited to, prior hemorrhage or infarct > 1 cm3, > 3 lacunar infarcts.
8. Concomitant disease or condition within six months of screening, or as specified below, that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study or interfere with the participant's ability to comply with study procedures or abide by

study restrictions, or with the ability to interpret safety data, including, but not limited to:

a. Autoimmune disease (however, well controlled conditions such as, but not limited to, quiescent rheumatoid arthritis [RAS], controlled type I diabetes, or mild-to-moderate psoriasis not requiring systemic medications may be acceptable after discussion with Sponsor/Medical monitors).

b. A history of cancer within 5 years of baseline with the exception of fully excised non-melanoma skin cancers or non-metastatic prostate cancer that has been stable for at least 6 months.

c. Any active infectious disease at baseline.

d. Current or history of, alcohol or drug abuse or other dependence (except nicotine dependence) within two years before screening.

e. Any febrile illness within one week prior to first dose administration.

f. Any current psychiatric diagnosis according to Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5), International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) or equivalent, that may interfere with the participant's ability to perform the study and all assessments (e.g., major depression, mental retardation, schizophrenia, bipolar disorder, etc.). Note: Mild depression, depressive mood or mild anxiety arising in the context of PD, are not exclusionary.

9. The following cardiovascular conditions:

a. Myocardial infarction within 12 months of baseline.

b. Known history or documentation of uncontrolled hypotension or bradycardia on more than one occasion within 3 months prior to baseline.

c. Known history or documentation of uncontrolled hypertension on more than one occasion within three months prior to baseline.

d. Resting pulse rate (PR) greater than 100 or less than 45 bpm.

e. Clinically significant cardiovascular disease including any of the following: unstable angina, decompensated congestive heart failure, clinically significant arrhythmias or symptomatic orthostatic hypotension.

f. A corrected QT (QTcF) interval measurement $>$ 450 ms for males or $>$ 470 ms for females at screening, or a family history of long QT syndrome.

g. Intermittent second or third degree atrioventricular (AV) heart block or AV dissociation is excluded (asymptomatic first degree AV block may be included).

10. Clinically significant abnormalities in laboratory test results at the Screening visit, including hepatic and renal panels, complete blood count, chemistry panel and urinalysis, including:

a. Total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>$ 2 times the upper limit of normal (ULN).

b. Serum creatinine $>$ 1.5 times the ULN.

c. Hematocrit (Hct) less than 35% for males and less than 32% for females, or absolute neutrophil cell count of $<$ 1500/µL (with the exception of a documented history of a chronic benign neutropenia), or platelet cell count of $<$ 120,000/µL; international normalized ratio (INR) $>$ 1.4 (in patients not on anticoagulants) or other coagulopathy.

d. A clinically significant abnormal thyroid-stimulating hormone (TSH) test.

e. A positive urine drug screen for a drug of abuse.

- For participants treated with selegiline, the amphetamine drug abuse test should be based on the results from a urine assay by liquid chromatography-mass spectrometry which is able to differentiate "false positive methamphetamine" from "true positive methamphetamine".

- For participants treated with benzodiazepines: a positive urine drug screen for benzodiazepines is allowed, provided that the prescription has been stable for 90 days prior to baseline (please also refer to exclusion criterion 15).

f. Positive result for acute or chronic infectious hepatitis B (HBV; [i.e., HBsAg positive test]), for hepatitis C (HCV), or HIV 1 or 2. Successfully treated HCV patients (undetectable HCV RNA) are eligible for enrollment. Participants who are immune due to HBV natural infection or HBV vaccination are eligible.

g. For women of childbearing potential, a positive urine or blood pregnancy test.

11. Lactating women.

Medications and treatments

12. Prior treatment with dopaminergic medication (e.g., levodopa or a dopaminergic agonist) with no clinical treatment response or a clinical treatment response inconsistent with PD (e.g., absence of observable response to a sufficiently high dose of levodopa [i.e., $\geq$ 600 mg/day]).
13. Use of any of the following: catechol-O-methyl transferase (COMT) inhibitors (entacapone, tolcapone), amantadine or anticholinergics, or dopaminergic medication (levodopa and both ergot and non-ergot [pramipexole, ropinirole, rotigotine] dopamine agonists) for more than a total of 60 days or within 60 days of baseline.
14. Anti-epileptic medication for non-seizure-related treatment which has not remained stable for at least 60 days prior to baseline.
15. Anti-depressant or anxiolytic use that has not remained stable for at least 90 days prior to baseline. The use of fluoxetine and fluvoxamine is not permitted. For patients treated with an MAO-B inhibitor and an antidepressant (except fluoxetine and fluvoxamine), a 6-month period of stable and tolerated dosing before baseline is required.
16. Use of any of the following within 90 days prior to baseline; antipsychotics (including clozapine and olanzapine), metoclopramide, alpha methyldopa, flunarizine, amoxapine, amphetamine derivatives, reserpine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norephedrine, phentermine, phenylpropanolamine, and modafinil.
17. Participated in an investigational drug, device, surgical or stem cell study in PD.
18. Any prior treatment with an investigational PD-related vaccine (including active immunization or passive immunotherapy with monoclonal antibodies).
19. Prior participation in any RO7046015 or PRX002 study.
20. Receipt of any non-PD investigational product or device, or participation in a non-PD drug research study within a period of 30 days (or 5 half-lives of the drug, whichever is longer) before baseline.
21. Receipt of any monoclonal antibody or investigational immunomodulator within 180 days (or 5 half-lives, whichever is longer) before baseline (e.g., monoclonal antibodies, intravenous immunoglobulin [IVIG], interleukin 2 [IL-2], interleukin 12 [IL-12], interferon or immunosuppressive drugs).
22. Immunomodulating drugs within 30 days prior to baseline.
23. Allergy to any of the components of RO7046015 such as citrate, trehalose and polysorbate (Tween) 20 or a known hypersensitivity or an infusion-related reaction (IRR) to the administration of any other monoclonal antibody.

Procedural

24. Any contraindications to obtaining a brain MRI (e.g., claustrophobia unresponsive to reassurance or low dose of an anxiolytic agent, tooth implants) and any contraindications to obtain a DaT-SPECT (i.e., known hypersensitivity to the active substance or to any of the excipients). Patients with a hypersensitivity to iodine may receive an alternative thyroid blocking agent (e.g., potassium perchlorate or sodium perchlorate).
25. For participants consenting to provide optional CSF samples by lumbar puncture (LP): LP will

only be performed if the participant does not have any contraindication to undergoing an LP including, but not limited to: INR > 1.4 or other coagulopathy, platelet cell count of < 120,000/μL, infection at the desired LP site, taking anti-coagulant medication within 90 days of baseline (Note: low dose aspirin (acetylsalicylic acid [ASA] is permitted), severe degenerative arthritis of the lumbar spine, suspected non-communicating hydrocephalus or intracranial mass, prior history of spinal mass or trauma is/are identified. Participants failing to meet these criteria can still participate in the study and all other study assessments (with the exception of LP) as appropriate. Participants could be excluded from the study if the CSF has more than 5 WBCs/mm3 (according to local laboratory assessment). This should be discussed with the Medical Monitor (e.g., if there is evidence that the spinal tap was traumatic, the participant may still be considered for study eligibility).

26. For skin biopsy at the cervical paravertebral region:

    Condition that either precludes the safe performance of the skin punch biopsy or may interfere with obtaining evaluable skin tissue biopsies, including any previous or active significant dermatological disease (e.g., previous biopsy with any of the following findings: inflammatory disease, scar tissue, psoriasis, keloid formation, skin cancer).

    Participants failing to meet these criteria can still participate in the study and all other study assessments (with the exception of skin biopsy) as appropriate.

27. Donation of blood over 500 mL within three months prior to screening.

LENGTH OF STUDY

The study for each patient will be divided as follows:

- Screening: Up to 8 weeks
- Treatment period: *364* weeks (52 weeks in Part 1, 52 weeks in Part 2 *and 260 weeks in Part 3*)
- Safety Follow-up: up to 12 weeks after cessation of *double-blind* treatment (regardless of whether cessation of treatment occurs at the end of or during Part 1 or Part 2).
- *Part 3 Safety Follow-up: 12 weeks after cessation of treatment (regardless of whether cessation of treatment occurs at the end of or during Part 3).*

END OF STUDY

The end of the study is defined as the date when the last participant last observation (LPLO) occurs at the follow-up visit. LPLO is expected to occur *approximately 388* weeks after the last participant is enrolled, or earlier in the case that the study is discontinued following any of the planned interim analyses.

OUTCOME MEASURES

SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

- Changes in safety laboratory tests (hematology, chemistry and coagulation) from baseline over time.
- Incidence of treatment-emergent abnormal laboratory values and abnormal laboratory values reported as adverse events (AEs).
- Incidence and severity of AEs.
- Incidence of anti-drug antibodies (ADAs)
- Changes in electrocardiogram (ECG) assessments from baseline over time; incidence of abnormal ECG assessments.
- Change in blood pressure (BP [systolic and diastolic], heart rate, and orthostatic measurement from baseline over time, incidence of abnormal blood pressure [systolic and

diastolic], heart rate, and orthostatic changes).

- Incidence of exacerbation of motor and psychiatric side-effects (including C-SSRS).
- Incidence of MRI abnormalities.

PHARMACOKINETIC OUTCOME MEASURES

The PK outcome measures for this study are as follows:

- Population and individual primary PK parameter estimations (e.g., clearance and volume of distribution) and the influence of various covariates on these parameters.
- Secondary PK parameters (e.g., AUC, C_{trough}) derived from the individual post-hoc predictions.

EFFICACY OUTCOME MEASURES

The primary efficacy outcome measure for this study is as follows:

- Change in total MDS-UPDRS score (sum of Parts I, II and III) from baseline at Week 52.

The secondary efficacy outcome measures for this study (after 52 weeks of treatment with RO7046015 or placebo) are as follows:

- Change from baseline in MDS-UPDRS Part IA, Part IB, Part I total, Part II total, Part III total and Part III subscores
- Change from baseline in DaT-SPECT in ipsilateral (to the clinically dominant side) putamen binding ratio values.
- Change from baseline in MoCA total score
- Change from baseline in Clinical Global Impression (CGI-I).
- Change from baseline in Patient Global Impression of change (PGIC).
- Change from baseline in Schwab and England Activities of Daily Living (SE-ADL)
- Time to worsening of motor or non-motor symptoms as measured by MDS-UPDRS
- Time to start of dopaminergic PD treatment (levodopa or dopamine-agonists)

EXPLORATORY OUTCOME MEASURES

The exploratory outcome measures for this study are change from baseline *to Week* 52*, to Week* 104 *and to Part 3 Week 260* in:

- MDS-UPDRS Part III total and Part III subscores central vs local ratings for consistency and accuracy
- Time to worsening of motor or non-motor symptoms as measured by MDS-UPDRS or starting dopaminergic treatment (levodopa or dopamine agonist)
- Modified Hoehn & Yahr (mH&Y).
- PDSS-2 total score and sub-scales.
- SCOPA-AUT total score and subdomain scores.
- PDQ-39 total score and sub-scales
- Digital Biomarkers and patient-reported outcomes (Smartphone and wrist-worn wearable assessments):
- Diary questions (patient-reported outcome [PRO])
- PAC-SYM questionnaire (PRO)
- Hospital Anxiety and Depression Scale (HADS), anxiety (HADS-A), and depression (HADS-D) sub-scales (PRO)
- EQ-5D-5L questionnaire (PRO)
- Sensor data collected during “Active Tests”, assessing motor symptoms (upper and lower

body movement, upper limb dexterity, voice/speech) and non-motor symptoms (including an electronic version of the Symbol Digital Modalities Test (eSDMT) to measure attention and executive function).

- Sensor data collected during "Passive Monitoring" assessing activity, movement and motor symptoms associated with routine daily living.
- Sensor data collected during "In-Clinic Assessments", including the Timed Up and Go Test and selected items from the Berg Balance Scale.
- Serum*, plasma,* and CSF biomarkers related to PD.
- α-synuclein pathology in peripheral nerves (skin biopsies in eligible participants).
- DaT-SPECT binding ratio values for: striatum, caudate and putamen (average, ipsilateral and contralateral)
- Diffusion tensor imaging (DTI) MRI for mean diffusivity and fractional anisotropy
- Resting state functional magnetic resonance imaging (rs-fMRI) for functional brain connectivity
- Arterial spin labelling (ASL) MRI for cerebral blood flow.
- *NM-MRI for substantia nigra integrity.*
- *Iron imaging for brain iron accumulation.*
- Time to start or change of co-medication for non-motor symptoms that may be related to PD (cognition, constipation, depression, anxiety, excessive daytime sleep, nocturnal sleep, urogenital symptoms/sexual dysfunction).
- Start or change of co-medication for non-motor symptoms that may be related to imaging biomarkers (DAT Scan and ASL).
- Parkinson-related effects on the loss of autonomic tone as measured by heart rate variability.
- Composite score of MDS-UPDRS Part II (patient reported motor experiences of daily living) and MDS-UPDRS Part III (clinician rated motor signs of PD) sub-items
- MDS-UPDRS Part IV at Week 52*, at Week 104 and Part 3 Week 260* in participants who started dopaminergic treatment (levodopa or dopamine agonist).

INVESTIGATIONAL MEDICINAL PRODUCT(S)

Test Product

The investigational medicinal product (IMP) in this study is RO7046015 for IV infusion, supplied as a concentrate for solution for infusion of 500 mg. Participants will receive IV infusions of RO7046015 high dose (4500 mg for BW $\geq$ 65 kg; 3500 mg for BW $<$ 65 kg), low dose (1500 mg; for all BW), or placebo, Q4W.

Study drug should be given as IV infusion over 2 hours for the first three doses and if well tolerated, the infusion time can be reduced to one hour in subsequent doses.

To enhance the tolerability of RO7046015 infusions, a dose titration regimen that may reduce the risk of IRRs will be implemented for the high dose, as follows: 2000 mg will be infused on Day 1 followed by an up-titration to the full dose of 4500 mg ($\geq$ 65 kg body weight) or 3500 mg ($<$ 65 kg body weight) on the second infusion (Day 28) during Part 1. Participants receiving placebo during Part 1 and randomized to the high dose at the start of Part 2 (extension) will receive 2000 mg IV on Week 56 followed by an up-titration to the full dose of 4500 mg ($\geq$ 65 kg body weight) or 3500 mg ($<$ 65 kg body weight) on the second infusion (Week 60).

Placebo

Placebo formulation will not be provided. Participants randomized to placebo will receive an IV infusion of normal saline.

Other

Symptomatic/dopaminergic PD medication and premedication before infusion are considered non-investigational medicinal products (NIMPs).

PROCEDURES

All assessments must be performed according to the Schedule of Assessments (SoA).

The sequence of study assessments at each visit must be carried out according to the Sequence of Study Assessments.

STATISTICAL METHODS

PRIMARY EFFICACY ANALYSIS

The primary efficacy endpoint is the change in total MDS-UPDRS (sum of Parts I, II and III) from baseline to Week 52 (end of Part 1 of the study). It will be analyzed using a mixed-effect model for repeated measures (MMRM) with treatment (placebo and each active dose), background therapy (with or without MAO-B inhibitor treatment), age group (< 60 years vs $\geq$ 60 years), sex, DaT binding ratio at baseline and visit (seven levels) as fixed effects, treatment-by-visit interaction term, and the baseline value for total MDS-UPDRS (sum of Parts I, II and III) as a covariate; an interaction term between baseline MDS-UPDRS by visit will also be included. Within each participant, the model will incorporate an unstructured variance-covariance matrix for the random error terms. Observations from different participants are considered independent. For each active dose arm tested at the final analysis, this model will be used to test the null hypothesis of no treatment difference between the placebo arm and each active arm at a two-sided α-level of 20%, which corresponds to a one-sided α-level of 10%.

Starting symptomatic PD treatment for the statistical analysis is defined as starting COMT inhibitors (entacapone, tolcapone), amantadine, anticholinergics, levodopa, dopamine agonists, or MAOB inhibitors and - for patients already on MAO-B inhibitors at baseline - also increases in dose or regimen of the MAOB inhibitor. Assessments performed after starting symptomatic PD treatment will not be included in the primary analysis.

Missing values will be handled via the MMRM methodology.

The primary endpoint will also be summarized using descriptive statistics.

SECONDARY EFFICACY ANALYSES

For the endpoints of MDS-UPDRS Part IA, Part IB, Part I total, Part II total, Part III total, and Part III subscores, CGI-I, and PGI-C the information collected after symptomatic PD treatment or after an increase in MAO-B inhibitor therapy will be handled as in the primary analysis. The analysis of all other secondary endpoints will include all the information available regardless of start of symptomatic PD treatment.

An important biomarker secondary endpoint is the change (between baseline and the Week 52 visit) in DaT-SPECT uptake values in the ipsilateral putamen, which will be analyzed via an analysis of covariance (ANCOVA), regardless of intake of symptomatic PD therapy during the first 52 weeks. The model will include the baseline value of the respective DaT binding ratio as a covariate and age group, sex, treatment, background therapy as main effects. There will be no imputation for missing values.

Other secondary endpoints, which will also be analyzed at the end of Part 1 (after 52 weeks of treatment with either placebo or active treatment) include:

- Change in MDS-UPDRS sub-scores from baseline to Week 52 for Part IA, Part IB, Part I total, Part II total, Part III total, and Part III subscores (bradykinesia, resting tremor and axial symptoms) analyzed with exactly the same MMRM approach as for the primary endpoint.
- Change in MoCA total score from baseline to Week 52 analyzed with an analysis of covariance (ANCOVA).
- CGI-I will be analyzed using a logistic regression model, including the covariates described for the primary efficacy analysis

- PGI-C will be analyzed using a logistic regression model, including the covariates described for the primary efficacy analysis.
- Change in Schwab and England Activities of Daily Living (SE-ADL) from baseline to Week 52 will be analyzed with ANCOVA.
- Time to first occurrence of either of the following: $\geq$ 3 points change from baseline in MDS-UPDRS Part I, or $\geq$ 3 points change from baseline in MDS-UPDRS Part II will be analyzed with a Cox proportional hazards model including the covariates described for the primary efficacy analysis along with a Kaplan-Meier Plot.
- Time to start dopaminergic treatment (levodopa or dopamine agonists) will be analyzed with a Cox proportional hazards model including the covariates described for the primary efficacy analysis, along with a Kaplan-Meier plot. Events in this analysis will only consider the start of levodopa or dopamine agonist.

All secondary endpoints will be summarized using descriptive statistics.

SAFETY ANALYSES

All randomized participants receiving at least one dose of study drug will be included in the safety analysis.

As appropriate, listings, summary tables and graphs will be provided for safety and tolerability assessments.

Safety data will be summarized using descriptive statistics.

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Non-linear mixed effects modelling (with software NONMEM) will be used to analyze the sparse sampling dose-concentration-time data of RO7046015. Population and individual pharmacokinetic parameters (e.g., CL and central volume) will be estimated and the influence of various covariates (such as age, sex and body weight) on these parameters will be investigated. The data collected during the study will be pooled with data collected in the previous Phase I studies conducted in healthy volunteers and patients with PD. Secondary PK parameters such as AUC, C_{max} and C_{trough} at steady-state will be derived from the individual post-hoc predictions.

Interim Analyses

An interim analysis for efficacy may be conducted. If so, the efficacy interim analysis will be reviewed by the iDMC based on predefined criteria outlined in a statistical analysis plan.

In addition to the primary analysis performed at Week 52, the Sponsor may choose to conduct additional interim efficacy analyses during Part 2 and/or Part 3 of the trial. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

SAMPLE SIZE JUSTIFICATION

A sample size of 100 randomized participants per group (300 participants for the three groups) has been chosen to obtain a power of approximately 80% at two-sided α-level of 20%, which corresponds to a one-sided α-level of 10%, for the pairwise comparison of each active dose arm to placebo. The power calculation was based on simulations of the mixed-effect model repeated measures (MMRM) analysis planned for the primary efficacy variable. Assessments performed while on any symptomatic treatment started after randomization will not be included in the analysis. The following assumptions were made for simulating the data:

- Seven post-baseline assessment visits
- An overall rate of missing values (due to participants starting symptomatic therapy or prematurely withdrawing from study medication during the 52-week placebo-controlled treatment period) of 25% in the placebo group and 20% in each dose group at Week 52, with incremental rates over the 52-week placebo-controlled period
- A linear mean increase of the primary endpoint (natural progression) of eight points/year for the placebo arm, with a linearly increasing common standard deviation reaching nine points at Week 52.
- An effect size of 0.33 (difference = 3 points, relative reduction of progression = 37.5%) for one dose group versus placebo at Week 52 with increasing magnitude of treatment difference over the placebo-controlled period.
- A compound symmetry correlation structure assuming a correlation coefficient of 0.55 between different visits.

These assumptions were derived from analyses based on the Parkinson's Progression Markers Initiative (PPMI) database and various sources of information from the literature.

The sample size of 100 patients per arm provides also 76% power (α = 20%, two-sided or α = 10%, one-sided) to demonstrate a 37.5% reduction (effect size = 0.318 based on assumption of decline over 52 weeks and standard deviation of 0.185 derived from the PPMI database) for the key secondary endpoint, the DaT-SPECT signal loss at Week 52, for the pairwise comparison of each active dose arm to placebo.

No adjustments for multiple comparisons were incorporated into the analyses.

The sample size may be adjusted depending on the outcome of the iDMC safety review performed during the study or if assumptions (e.g., drop-out rate) used for sample size calculation need to be adapted.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse events
ADA	Anti-drug antibody
ALT	Alanine aminotransferase
ANS	Autonomic nervous system
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
ASL	Arterial spin labelling
AST	Aspartate aminotransferase
AUC	Area under the curve
BA	Bioavailability
BP	Blood pressure
CBF	Cerebral blood flow
CGI-I	Clinical Global Impression of Improvement
CL	Systemic clearance
C_{max}	Peak serum concentration
C_{trough}	Trough serum concentration
CNS	Central nervous system
CRO	Contract research organization
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common technical document
DaT-SPECT	Dopamine transporter imaging with single photon emission computed tomography
DNA	Deoxyribonucleic acid
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
EC	*Ethics Committee*
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EEA	European Economic Area
ePRO	Electronic patient-reported outcome
EQ-5D-5L	European Quality of Life Questionnaire 5-level version
ESF	Eligibility Screening Form

Abbreviation	Definition
eSDMT	Electronic Symbol Digit Modalities Test
EU	European Union
FDA	Food and Drug Administration
FDG-PET	2-deoxy-2-(^{18}F) fluoro-D-glucose positron emission tomography
FLAIR	Fluid-attenuated inversion recovery
FSH	Follicle-stimulating hormone
GRE	Gradiant echo
HADS	Hospital Depression and Anxiety Scale
HBsAG	Hepatitis B surface antigen
HbcAb	Total hepatitis B core antibody
HCV	Hepatitis C
HDL	High density lipoproteins
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
H&Y	Hoehn and Yahr
ICH	International Conference on Harmonisation
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IP	Intraperitoneal
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reaction
IRT	Item Response Theory
IUD	Intrauterine device
IV	Intravenous
IxRS	Interactive (voice/web) response system
LDH	Lactate dehydrogenase
LDL	Low density lipoproteins
LH	Luteinizing hormone
LPLV	Last patient, last visit
LPLO	Last participant, last observation
mAb	Monoclonal antibody
MAD	Multiple ascending doses

Abbreviation	Definition
MAO-B	Monoamine oxidase B
MD	Multiple doses
MDS-UPDRS	Movement Disorder Society - Unified Parkinson's Disease Rating Scale
mITT	Modified intent-to-treat
MMRM	Mixed-effect model for repeated measures
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MTD	Maximal tolerated dose
NM	*Neuromelanin*
NOAEL	No-observed-adverse-effect level
OTC	Over-the-counter
PAC-SYM	Patient Assessment of Constipation Symptoms
PD	Parkinson's disease
PDSS-2	Parkinson's Disease Sleep Scale Revised Version 2
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
PPMI	Parkinson's Progression Markers Initiative
PRO	Patient-reported outcome
PT	Prothrombin time
Q4W	Once every 4 weeks
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia formula
RBC	Red blood cell
RBD	Rapid eye movement sleep behavior disorder
RBR	Research Biosample Repository
REM	Rapid eye movement
RNA	Ribonucleic acid
RR	RR interval
rs-fMRI	Resting state *functional* magnetic resonance imaging
SAD	Single ascending dose
SAE	Serious adverse event
SCOPA-AUT	Scales for outcomes in Parkinson's disease autonomic dysfunction
SD	Single dose

Abbreviation	Definition
SE-ADL	Schwab and England Activities of Daily Living
SNc	Substantia nigra pars compacta
SoA	Schedule of assessments
SmPC	Summary of Product Characteristics
sMRI	Structural MRI
SNRI	Serotonin and norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
V	Volume of distribution
VAS	Visual analogue scale
WBC	White blood cell
WGS	Whole genome sequencing

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND ON DISEASE

Parkinson's disease (PD) is a progressive and chronic neurodegenerative disease estimated to affect between 7-10 million people worldwide (Parkinson's Disease Foundation). In the United States (US), an estimated 725,000 people are affected (extrapolated from Kowal et al 2013) and over 50,000 new cases are reported every year (National Institute of Neurological Disorders and Stroke). Although 5 to 10 percent of patients are diagnosed before age 50, it is generally considered a disease that targets older adults, affecting one out of every 100 people over the age of 60 and it is more common in men than women (National Institute of Neurological Disorders and Stroke).

PD is pathologically characterized by the presence of Lewy bodies, composed of aggregated and phosphorylated α-synuclein, in the subcortical regions of the brain (Spillantini et al 1997). While the presence of Lewy bodies in the substantia nigra pars compacta (SNc) is a pathologically-defining feature of PD, it is now well appreciated that α-synuclein pathology can be present in other brain regions (e.g., olfactory bulb, medulla oblongata, midbrain, basal forebrain, neocortex, etc.) and is not restricted to the central nervous system (CNS) as it is also abundantly present in the peripheral nervous system. Extra-nigral α-synuclein pathology appears to precede the pathology in the SNc (Braak et al 2003) and presence of α-synuclein pathology has been visualized in the peripheral nervous system using ante-mortem biopsy and post-mortem autopsy specimens from various regions of the body, such as colon, salivary glands and skin (for review see Malek et al 2014).

While the exact cause of the disease is unknown, there is a strong correlation between motor symptoms and the loss of the dopaminergic neurons in the substantia nigra and the presence of α-synuclein containing Lewy bodies and Lewy neurites in both central and peripheral nervous systems (Beach et al 2009). Moreover, genetic evidence indicates that both missense mutations (Kay et al 2008) and increased production of α-synuclein due to genomic duplication or triplication of the α-synuclein gene (SNCA) (Singleton et al 2003, Ibanez et al 2004) can cause early onset autosomal dominant Parkinson's disease.

At the time of diagnosis, patients may present with prominent motor and non-motor symptoms. Motor symptoms often include resting tremor, limb stiffness or rigidity, slowness of movement (i.e., bradykinesia), and gait or balance problems (i.e., postural instability). Non-motor symptoms, present in most patients, can often dominate the clinical presentation and may include cognitive decline, depression, constipation, anosmia, pain, and sleep disorders. A diagnosis of PD is typically supported by asymmetric onset of motor symptoms and by a substantial and sustained response to levodopa or dopaminergic agents (Gibb and Lees 1988; Gelb et al 1999; Bhidayasiri and Reichmann 2013). As the disease slowly progresses, there is ongoing decline and debilitation. Patients are at high risk for the development of psychiatric illness and

dementia with disease-related complications that can reduce life-expectancy (de Lau et al 2005; Weintraub and Burn 2011).

Current treatments for PD manage the early motor symptoms of the disease, mainly through the use of dopamine replacement therapy and dopamine receptor agonists. Treatment with levodopa and other dopaminergic agents temporarily addresses the motor symptoms and is used extensively. However, this does not reverse, slow or halt pathological processes related to the disease. As the disease progresses and dopamine neurons continue to be lost, these drugs become less effective at controlling the symptoms.

Patients who take these medications often develop side-effects such as motor complications (e.g., response oscillations, wearing off phenomena and drug-induced dyskinesias), as well as nausea, daytime somnolence, sleep attacks, orthostatic hypotension or impulse control disorders (Sprenger and Poewe 2013). Symptomatic treatment of non-motor symptoms of PD, e.g., sleep disturbances, anxiety and depression, are also available. To date, there are no approved treatments that have demonstrated protection of neurons or modification of the disease course.

1.2 BACKGROUND ON RO7046015

RO7046015 (PRX002) is an immunoglobulin class G1 (IgG1) humanized monoclonal antibody (mAb) directed against an epitope in the C-terminus of human α-synuclein. The molecule is composed of two heterodimers. Each of the heterodimers is composed of a heavy polypeptide chain of ~48 kDa (446 amino acids) and a kappa light polypeptide chain of ~24 kDa (220 amino acids). The antibody protein has a humanized amino acid sequence with a total molecular mass of approximately 147 kDa. There are two binding sites for the α-synuclein epitope per antibody molecule.

Note: RO7046015 is also known as prasinezumab but in this document, RO7046015 will be used.

For details on non-clinical and clinical studies, see the RO7046015 Investigator's Brochure.

1.2.1 Previous Non-Clinical Studies

Non-clinical studies showed that RO7046015 and/or its murine form, 9E4, bind to monomeric human α-synuclein with nanomolar affinity (K_D approximately 20-35 nM) and high specificity for α-synuclein over other members of the synuclein family (β- and γ-synuclein). RO7046015 binding affinity was comparable between human and cynomolgus monkey α-synuclein but was not measurable against murine α-synuclein, nor was binding to rat or rabbit α-synuclein *detected*. The epitope for RO7046015/9E4 binding is included in amino acids 118-126 of human α-synuclein. RO7046015 and 9E4 bind to fibrillar α-synuclein, which is evident by their capacity to immunostain thioflavin-positive Lewy bodies and Lewy neurites in PD brain samples. Furthermore, the apparent

affinity/avidity of those antibodies *to the pathological aggregated forms of α-synuclein* was demonstrated to be substantially higher *compared to affinity/avidity to* monomers. An in vitro model of cell-to-cell transmission of α-synuclein was established and used to demonstrate that 9E4 blocks the intercellular transmission of α-synuclein. In vivo efficacy was evaluated in two transgenic mouse models of α-synucleinopathy, the Line D and Line 61 models, using 9E4 to ensure efficient engagement of Ig receptor function by utilizing a mouse-in-mouse system. In both transgenic models, weekly intraperitoneal (IP) administration of 9E4 over 5-6 months reduced brain pathology manifested as α-synuclein deposits in cortical and subcortical regions, protected against synaptic loss, and prevented the decline in cognitive and motor behavior.

In a 26-week cynomolgus monkey study, there were no specific effects of intravenous (IV) infusion of RO7046015 on any safety pharmacology endpoints, including the cardiovascular system, at dose levels up to 300 mg/kg/week (the maximum dose studied). There were also no effects on the respiratory system up to 100 mg/kg/week (maximum dose studied) for 13 weeks. In GLP toxicology studies, RO7046015 was well tolerated and no target organ toxicity has been described in the monkey up to 300 mg/kg/week for 26 weeks. At the end of the 26-week GLP toxicology study, the average serum $AUC_{0\text{-}28d}$ and C_{max} 300 mg/kg/week IV were 894,000 μg • h/mL (average $AUC_{0\text{-}7d}$ of 223,500 μg • h/mL × 4 weeks) and 7030 μg/mL, respectively. Toxicokinetic parameters were generally similar after first and last administrations and there was a tendency for higher systemic exposure in males compared to females. Following repeated IV administration (100 mg/kg IV infusion once weekly for 13 weeks) in cynomolgus monkey, RO7046015 was demonstrated to reach the cerebrospinal fluid (CSF) (0.1-0.4% CSF/serum AUC ratio).

1.2.2 Previous Clinical Studies

RO7046015 or placebo has been administered as an IV infusion in *three* Phase I clinical studies. *A total of 64 healthy subjects and 80 participants with PD have taken part in these studies, of whom 48 healthy subjects and 55 participants with PD have received prasinezumab as an IV infusion.*

Study PRX002-CL001 (BP29477; single-ascending dose *[*SAD*] in healthy subjects in the United States [US])* was a randomized, double-blind, placebo-controlled study which assessed the safety and PK of RO7046015 administered to 40 healthy participants in 5 ascending-dose cohorts in which participants were randomly assigned to receive a single IV infusion of study drug (0.3, 1, 3, 10 or 30 mg/kg; n = 6/cohort) or placebo (n = 2/cohort). Serum RO7046015 exposure parameters increased proportionally with the dose of RO7046015 over the dose range of 0.3 mg/kg to 30 mg/kg and resulted in dose- and time-dependent reductions in mean serum free α-synuclein levels (unbound) and increases in mean serum total α-synuclein levels (bound plus free). RO7046015 demonstrated favorable safety, tolerability, and pharmacokinetic profiles at all doses

tested, with no immunogenicity. No serious adverse events, discontinuations as a result of adverse events, or dose-limiting toxicities were reported (Schenk et al 2016).

Study JP40211 (SAD study in healthy male Japanese subjects) was a randomized, double-blind, placebo-controlled study *SAD study which assessed the safety and tolerability of RO7046015 and evaluated PK of RO7046015 in 24 healthy Japanese male participants in three ascending-dose cohorts in which participants were randomly assigned to receive a single IV infusion of study drug (10, 30 or 60mg/kg; n =6/cohort) or placebo (n =2/cohort). Across the dose range of 10 mg/kg to 60 mg/kg, the PK of RO7046015* in healthy Japanese subjects were similar *to that of healthy subjects in the US* in the PRX002-CL001 SAD study. In addition, RO7046015 demonstrated favorable safety, tolerability, and pharmacokinetic profiles comparable to the healthy subjects in the US, with no immunogenicity. No serious adverse events, discontinuations because of adverse events, or dose-limiting toxicities were reported.

Study PRX002-CL002 (multiple-ascending dose (MAD) study *in participants with mild-to-moderate PD)* (Jankovic et al 2018) was a randomized, double-blind, placebo-controlled study which assessed the safety, PK and pharmacodynamics of RO7046015 administered to 80 participants with mild to moderate PD (Hoehn and Yahr [H&Y] Stages I-III), in six ascending-dose cohorts in which patients were randomly assigned to receive study drug (0.3, 1, 3, 10 mg/kg, n=8/cohort or 30, 60 mg/kg, n=12/cohort) or placebo (n=4/cohort) for three IV infusions administered every 28 days. The PK in patients was similar to that in healthy volunteers. Exposure increased approximately proportional*ly* with increasing dose. The highest mean exposure (at 60 mg/kg dose) in terms of C_{max} and AUC_{tau} after the third dose was 1160 μg/mL and 168000 μg • h/mL, respectively, and well below the no-observed-adverse-effect level (NOAEL) exposure in cynomolgus monkey. A population PK model described the pharmacokinetics very well, estimating clearance as 2.5-3-fold higher than for a typical IgG1 and the effective half-life as 13-15 days (see RO7046015 Investigator's Brochure). The reduction in free serum α-synuclein levels were comparable to those seen in healthy subjects after the first dose, and more pronounced after the third dose.

RO7046015 was well tolerated without any reports of treatment-emergent serious adverse events (SAEs). The most frequently reported mild to moderate treatment-emergent adverse events (TEAEs) in the MAD study in PD patients (PRX002-CL002, see RO7046015 Investigator's Brochure) included constipation (9.1%), infusion-related reactions (IRRs) (7.3%), diarrhea (5.5%), peripheral edema (5.5%) and post-lumbar puncture syndrome (5.5%). Mild to moderate IRRs, that all resolved were limited to the 60 mg/kg dose cohort and were observed in 4 of *the* 12 treated patients. One patient had a confirmed anti-drug antibody (ADA) titer to RO7046015; however, this patient received placebo indicating that the finding was a false positive. No clinically relevant trends in clinical laboratory data, physical examination, vital sign, or electrocardiogram (ECG) parameters were observed after dosing, and no TEAE trends related to these evaluations were reported.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study Rationale

Current treatments for PD manage the early motor symptoms of the disease, mainly through the use of dopamine replacement therapy and dopamine receptor agonists. However, these treatments do not reverse, slow or halt the pathological processes related to the disease. As the disease progresses and dopamine neurons continue to be lost, symptomatic treatments become less effective and patients develop side-effects such as motor complications including response oscillations, wearing-off phenomena and drug-induced dyskinesias (Sprenger and Poewe 2013). To date, there are no approved treatments which have demonstrated protection of neurons or modification of the disease course.

Clinical and non-clinical evidence suggest that aggregated forms of α-synuclein self-propagate and spread between interconnected nervous system regions, contributing to the progression of PD. Strong non-clinical evidence suggests that RO7046015, a monoclonal antibody designed to preferentially target aggregated forms of α-synuclein, has the potential to slow or halt the progression of PD by preventing cell-to-cell spreading of α-synuclein pathology (Section 1.2.1 and RO7046015 Investigator's Brochure).

Disease-modifying (neuroprotective) treatment is expected to be most effective in early PD patients who still have a substantial number of vulnerable neurons which could be protected. The most suitable population in which to test the hypothesis that treatment with RO7046015 will slow or halt the progression of PD is in patients with early-stage clinical PD, DaT-SPECT-confirmed dopaminergic deficit and rapid disease progression that is not yet modified by symptomatic treatment with levodopa or dopaminergic agonists.

Proof-of-concept (POC) will be demonstrated by a reduction in clinical progression of PD symptoms measured using a well-characterized scale, the Movement Disorder Society (MDS)-sponsored revision of the Unified Parkinson's Disease Rating Scale (UPDRS). The UPDRS is a well-validated scale that has been used for many pivotal studies for the symptomatic treatment of PD. In order for a Phase II POC study to assess the disease-modifying potential of study treatment, it is essential to define a population that optimizes the rate of progression of the placebo population when using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Based on analysis of data from the Parkinson's Progression Markers Initiative (PPMI) study (Marek et al 2011, Simuni et al 2015), a 52-week treatment duration is expected to be sufficient to demonstrate relevant between-group differences due to the effects of a disease-modifying treatment that changes the rate of progression in early stage PD patients without dopaminergic treatment.

Participants completing Part 1 of the study (52-week placebo-controlled period) with a pre-defined minimum of infusions and assessments will be offered the option to continue with Part 2 (52-week all-on-active-treatment extension) and receive RO7046015 infusions Q4W (blinded to dose) until Week 104 to further study the long-term safety and clinical effects of RO7046015 and to offer potential benefits of treatment with RO7046015 to all participants *(see Section 3.1.1 for further details)*.

Participants completing Part 2 of the study (52-week all-active-treatment extension) and completing the 12 weeks treatment free follow-up will be offered the option to participate in Part 3 (260 weeks all-on-active-treatment extension followed by 12 weeks treatment free follow-up). In Part 3 participants will be administered RO7046015 infusions Q4W (blinded to dose until Phase III study dose has been identified) until Part 3 Week 260 to further study the long-term safety and clinical effects of RO7046015 and to continue to offer potential benefits of treatment with RO7046015 to all participants. When the Phase III study dose is identified, based on Part 1 data analysis, all participants will receive the Phase III dose for the remaining duration of this study.

1.3.2 Benefit-Risk Assessment

RO7046015 and its murine form, 9E4, bind to monomeric human (and cynomolgus monkey) α-synuclein with nanomolar affinity and with substantially higher apparent affinity/avidity to the pathological aggregated forms of α-synuclein. In vitro data show that 9E4 can block cell-to-cell transmission of α-synuclein. In two transgenic mouse models of α-synucleinopathy, weekly intraperitoneal (IP) administration of 9E4 over 5-6 months reduced brain pathology (α-synuclein deposits) in cortical and subcortical regions, protected against synaptic loss, and prevented the decline in cognitive and motor behavior. Reduction of brain pathology and improvement of cognition was observed after 1 mg/kg weekly IP, and additional beneficial effects on other behavioral endpoints were observed after 10 mg/kg weekly IP. For further details, see the RO7046015 Investigator's Brochure.

To date, no treatments have been identified that change the neuropathological progression of PD. Consequently, there are no predictive biomarkers and the translatability of available PD animal models to man is not known. Furthermore, there are no biomarkers to measure target engagement (aggregated α-synuclein) in the CNS in humans. Therefore, a fixed (flat) high dose IV (4500 mg for BW ≥ 65 kg; 3500 mg for BW < 65 kg), corresponding to the maximum dose tested in Phase I clinical studies (60 mg/kg IV) will be tested in the Phase II study. This dose achieves average trough serum concentrations in the range of those observed after 10 mg/kg weekly IP dose in the transgenic mouse model (approximately 70 μg/mL). In addition, a second fixed (flat) dose of 1500 mg IV (for all BW), that achieves serum trough concentration levels above those noted with 1 mg/kg in the mouse efficacy model (approximately 17 μg/mL, which is achieved with a human Q4W dose of 800 mg) will be tested as a potential low

efficacious dose with sufficient separation from the maximum dose to allow exposure-response analyses (see Section 3.2.3).

In a 26-week cynomolgus monkey study, there were no specific effects of IV infusion of RO7046015 on any safety pharmacology endpoints, including the cardiovascular system, at dose levels up to 300 mg/kg/week (the maximum dose studied). RO7046015 was well tolerated and no target organ toxicity has been described up to 300 mg/kg/week for 26 weeks. The average $AUC_{0\text{-}28d}$ and C_{max} values at 300 mg/kg/week were 894,000 μg • h/mL and 7030 μg/mL, respectively.

In clinical studies conducted with RO7046015, the highest mean exposure (after three infusions with a 60 mg/kg dose) in terms of C_{max} and AUC_{tau} after the third dose was 1160 μg/mL and 168000 μg • h/mL, respectively, and well below the no-observed-adverse-effect level (NOAEL) exposure in cynomolgus monkey (C_{max} six times and AUC five times).

In the clinical studies with healthy volunteers or PD patients, no treatment-emergent SAEs were reported (Section 1.2.2). No studies were terminated prematurely. Mild to moderate IRRs were observed in 4 of 12 treated patients in the 60 mg/kg dose cohort in the MAD study (PRX002-CL002, see RO7046015 Investigator's Brochure). IRRs have been reported with the use of many antibodies and other biologic therapies, usually with the first or second infusion of a therapeutic monoclonal antibody and they tend to be dose-related. In order to reduce the occurrence and potential impact of IRRs, several measures have been included in the current protocol, such as dose titration, two different flat doses (based on body weight) for the high dose group, slower infusion time and premedication for the first three infusions, as well as implementation of an independent data monitoring committee that will monitor IRRs and other adverse event (AE) reports and may reduce the highest dose level if necessary (see Section 4.4.2 and Section 5.2.1). *As of 29 November 2019, 84 participants out of 316 participating in the currently ongoing BP39529 Phase II study and receiving either prasinezumab or placebo had at least one IRR: 50 participants experienced IRR at the highest grade 1; 32 experienced IRR at the highest Grade 2 and 2 pts experienced IRR at the highest of Grade 3 (see RO7046015 Investigator's Brochure). Review of blinded data from the 316 safety evaluable participants in the ongoing study (BP39529) shows a safety profile that is consistent with that observed in the Phase I study (PRX002-CL002).*

A benefit of RO7046015 in patients has not yet been demonstrated and the study described in this protocol is designed to assess this. Based on the evidence *collected to date* supporting a potential beneficial effect, the high unmet medical need for therapies which may modify the course of disease progression in PD, and the observed safety profile to date, further clinical development of RO7046015 is supported.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is:

- To evaluate the efficacy of RO7046015 versus placebo at Week 52 in participants with early PD (H&Y Stages I-II) who are untreated or treated with monoamine oxidase B (MAO-B) inhibitors since baseline, as measured by change from baseline on the MDS-UPDRS Total Score (sum of Parts I, II and III).

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To evaluate the effects of RO7046015 versus placebo at Week 52, in participants with early PD (H&Y Stages I-II) who are untreated or treated with MAO-B inhibitors since baseline, on the following:
  - MDS-UPDRS Part IA, Part IB, Part I total, Part II total, Part III total and Part III subscores
  - Dopamine transporter imaging with single photon emission computed tomography (DaT-SPECT) in the ipsilateral (to the clinically dominant side) putamen
  - Montreal Cognition Assessment (MoCA) total score
  - Clinical Global Impression of Improvement (CGI-I)
  - Patient Global Impression of Change (PGIC)
  - Schwab and England Activity of Daily Living (SE-ADL) score
  - Time to worsening in motor or non-motor symptoms
  - Time to start of dopaminergic PD treatment (levodopa or dopamine agonists)
  - Safety and tolerability of RO7046015.
- To evaluate the safety and tolerability of treatment with RO7046015 for up to 104 weeks *(Part 2) and up to Part 3 Week 260*, with or without concomitant dopaminergic treatment.
- To evaluate the immunogenicity of RO7046015.
- To describe the PK of RO7046015 using population PK modelling.

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are:

- To compare consistency and accuracy in MDS-UPDRS Part III total, Part III subscores centrally rated by video-tapes vs locally rated by the site *(in Part 1 and Part 2 only)*

- Time to worsening in motor or non-motor symptoms or starting dopaminergic PD treatment (levodopa or dopamine agonist)
- To evaluate the effect of RO7046015 versus placebo over 52 weeks, on change from baseline in:
  - Modified Hoehn and Yahr, Hospital Anxiety and Depression Scale (HADS), Patient Assessment of Constipation Symptoms (PAC-SYM), scales for outcomes in Parkinson's disease autonomic dysfunction (SCOPA-AUT), Parkinson's Disease Sleep Scale Revised Version 2 (PDSS-2), 39-item Parkinson's Disease Questionnaire (PDQ-39), European Quality of Life Questionnaire 5-level version [EQ-5D-5L] and Smartphone and wrist-worn wearable assessments.
  - Serum, *plasma,* CSF, skin and imaging biomarkers related to PD.
- To evaluate clinical and biomarker outcomes (as outlined above) over a period of up to 104 weeks including data from the one-year extension (Part 2) *(*all-participants-on-treatment*,* blinded to dose) with or without concomitant dopaminergic treatment.
- *To evaluate clinical and biomarker outcomes (as outlined above) in the five-year extension (Part 3) (all-participants-on-treatment, blinded to dose until Phase III study dose has been identified) with or without concomitant dopaminergic treatment.*
- To evaluate the dose-exposure-response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship for MDS-UPDRS, DaT-SPECT and other functional, biomarker and safety parameters.
- To evaluate an immunohistochemical assay for α-synuclein pathology in peripheral nerves (skin biopsy samples from randomized participants and DaT-SPECT screen failures).
- *To assess time to start or change of co-medication for non-motor symptoms that may be related to PD (cognition, constipation, depression, anxiety, excessive daytime sleep, nocturnal sleep, urogenital symptoms/sexual dysfunction).*
- *To assess start or change of co-medication for non-motor symptoms that may be related to imaging biomarkers (DAT Scan and ASL).*
- *To assess Parkinson-related effects on the loss of autonomic tone as measured by heart rate variability.*
- *To evaluate motor progression as assessed by a composite score of MDS-UPDRS Part II (patient reported motor experiences of daily living) and MDS-UPDRS Part III (clinician rated motor signs of PD) sub-items*
- *To assess motor complications as assessed by MDS-UPDRS Part IV at Week 52, at Week 104 and Part 3 Week 260 in participants who started dopaminergic treatment (levodopa or dopamine agonist).*

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a multicenter, Phase II study to evaluate the effect of IV administration of RO7046015 in participants with early stage (H&Y Stages I-II) PD. Participants will be eligible if they have idiopathic PD with bradykinesia plus one of the other cardinal signs of PD (resting tremor, rigidity) being present, without any other known or suspected cause of PD (adapted from the MDS Clinical Diagnostic Criteria for Parkinson's Disease, see Postuma et al 2015) and are either untreated or treated only with MAO-B inhibitor.

The study will consist of *three* parts: a 52-week, double-blind, placebo-controlled treatment period (Part 1) after which eligible participants will continue into an all-participants-on-treatment (RO7046015) blinded to dose extension for an additional 52 weeks (Part 2). *Participants who complete Part 2 (including the 12-week treatment free follow up visit assessing long term safety and efficacy of RO7046015) will be offered participation in Part 3 (all-participants-on-treatment (RO7046015) blinded to dose until Phase III study dose has been identified) for an additional 260 weeks (see Section 3.1.1.3 for further details on Part 3).*

An overview of the study design is provided in Figure 1.

3.1.1.1 Part 1

During Part 1 of the study, participants will receive IV infusions of RO7046015 or placebo Q4W over a period of 52 weeks.

Approximately 300 participants will be randomized with a 1:1:1 allocation ratio to placebo, or one of the two active treatment doses: high dose (4500 mg for body weight ≥ 65 kg; 3500 mg for body weight < 65 kg), low dose (1500 mg; for all body weights). The number of randomized participants could be increased to a maximum of 360 depending on the outcome of the safety review by the independent Data Monitoring Committee (iDMC; Section 3.1.2.1). The sample size may also be adjusted if the initial assumptions on dropout rate and likelihood to start dopaminergic therapy as described in Table 4 are different from the actual values observed. If that is the case, the Sponsor may increase enrolment up to 20% of the total sample size. The aim of this increase in sample size is to ensure that the pairwise comparison of each active dose arm to placebo remains adequately powered (see Section 6.1).

Randomization will be stratified by sex, age group (< 60 years vs ≥ 60 years), and prior background therapy with MAO-B inhibitor at randomization (Yes vs No).

To enhance the tolerability of RO7046015 infusions, a dose titration regimen that may reduce the risk of IRRs (Gazyvaro SmPC) will be implemented for the high dose, as follows: 2000 mg will be infused on Day 1 followed by an up-titration to the full dose of

4500 mg (≥65 kg body weight) or 3500 mg (<65 kg body weight) on the second infusion (Day 28) during Part 1.

Only early stage PD patients with a clinical condition not requiring dopaminergic PD medication at baseline and not expected to require dopaminergic treatment within 12 months from baseline will be eligible to participate in the study. Patients with a history of stable parkinsonian symptoms who are on a stable dose of MAO-B inhibitor (rasagiline or selegiline) for at least 90 days prior to baseline may also be included (see Section 4.5.1).

Participants are expected to not start dopaminergic (levodopa or dopamine agonist) or other symptomatic PD therapy (as defined in Section 4.5.3) during Part 1. Some participants may experience worsening of their symptoms to an extent that they are unable to tolerate it in their personal or professional life. These participants may start dopaminergic or symptomatic PD treatment according to local guidelines after completing the assessments at the "prior to start of dopaminergic treatment" visit according to the schedule of assessments (SoA; Appendix 1) and the Investigator must record the reasons and the type and dose of dopaminergic or symptomatic PD treatment started. Participants who have started dopaminergic or symptomatic PD treatment will then continue in the study, as per their regular scheduled study visits.

For the main analysis of the primary endpoint and other efficacy endpoints that are sensitive to symptomatic PD treatment (such as MDS-UPDRS part III, PGIC, CGI-I), only data up to the last measurement before start of dopaminergic treatment will be used. Data after start of symptomatic PD treatment will be included in safety, sensitivity, exploratory and biomarker evaluations as appropriate.

All participants, including those that have started symptomatic PD treatment, will be eligible to participate in Part 2 if they have completed Part 1 with the predefined minimum of infusions and assessments as defined in Section 3.1.1.2.

3.1.1.2 Part 2

Part 2 is a one-year all-participants-on-treatment, blinded to dose extension.

Participants must meet the following criteria to enter Part 2: DaT-SPECT and magnetic resonance imaging (MRI) scans completed at Screening and Week 52 and have received at least 10 doses of study treatment (RO7046015 or Placebo) during the first 52 weeks of the study (Part 1). Participants may initiate or change symptomatic PD treatment (including dopaminergic treatment) as per standard of care during Part 2 (see Section 4.5.3).

For Part 2, participants who complete the initial placebo-controlled part and fulfil the criteria mentioned above will switch into the extension as follows:

- Participants initially randomized to placebo will be re-randomized to one of the two active doses using a 1:1 allocation ratio.

  Randomization will be stratified by: dopaminergic therapy since start of the study (Yes versus No), age group (<60 versus ≥60) and prior background therapy with MAO-B inhibitor (Yes versus No). For age group and prior background therapy with MAO-B inhibitor, the values collected for Part 1 will be used.

  Participants receiving placebo during Part 1 and randomized to the high dose at the start of Part 2 (extension) will receive 2000 mg IV on Week 56 followed by an up-titration to the full dose of 4500 mg (≥ 65 kg body weight) or 3500 mg (< 65 kg body weight) on the second infusion (Week 60).
- Participants initially randomized to the active dose will remain on their dose.

3.1.1.3 *Part 3*

Part 3 is a 5-year extension in which all participants will be on treatment. Participants will be blinded to dose until the Phase III study dose is identified (Note: this dose will not exceed the high dose tested in the present BP39529 study). Once the Phase III study dose is identified, participants will be switched to that dose (if applicable).

Participants must meet the following criteria to enter Part 3:

- *Having completed Part 2 (i.e., completed Week 104 visit) as well as the 12-week treatment free follow up visit. Participants may initiate or change symptomatic PD treatment (including dopaminergic treatment) as per standard of care during Part 3 (see Section 4.5.3).*
- *Not having received another investigational medication during the treatment free period (i.e., between Week 104 visit and Part 3 Week 1 visit).*
- *Participation in Part 3 not deemed inappropriate by the investigator (e.g., patient with serious medical condition or other concerns that preclude their safe participation in Part 3 or their ability to comply with the required procedures should not be enrolled)*

Note: At the time Part 3 will be initiated and locally approved, the participants can be in one of the 3 following situations:

- *Situation #1: Participants have completed Part 2 and the 12-week free of treatment follow up (including the follow up visit)*
- *Situation #2: Participants have completed Part 2 but are still in the 12-week free of treatment follow up (follow up visit not done yet)*
- *Situation #3: Participants have not yet completed Part 2*

In any case, the time window between the date the protocol has been initiated and approved as per local regulation and the date of Part 3 Week 1 visit should not exceed 2 months.

If eligible, all these patients will be offered the possibility to participate in Part 3. The section below details how eligible participants will enter Part 3 according to their status in the study at the time Part 3 is initiated and approved as per local regulation.

- *Situation #1: Participants having already completed Part 2 and are free of treatment for more than 12-weeks at the time Part 3 is initiated and locally approved:*

  As long as the Phase III study dose is not identified, patients will take the same dose they received in Part 2. Dosing will be restarted as an IV infusion at the same infusion rate used in Part 2. In case of occurrence of IRR, instructions provided in Section 5.2.1 will be followed. Once the Phase III study dose is identified, and if applicable, participants will be switched to this dose as soon as possible.

- *Situation #2: Participants having completed Part 2 (i.e., Week 104 visit completed) and being in the 12-week treatment free follow up period at the time Part 3 is initiated and locally approved:*

  Patients will be asked to complete the 12-week treatment free period as well as the 12-week treatment free follow-up visit as per protocol. Within four weeks after the follow-up visit, they will be asked to start Part 3 (Note: Part 3 Week 1 visit cannot take place the same day as the 12-week treatment free follow-up visit).

  - If the Phase III study dose is not identified at that time, patients will take the same dose they received in Part 2. Dosing will be restarted as an IV infusion at the same infusion rate used in Part 2. In case of occurrence of IRR, instructions provided in Section 5.2.1 will be followed. Once the Phase III study dose is identified, and if applicable, participants will be switched to this dose as soon as possible.

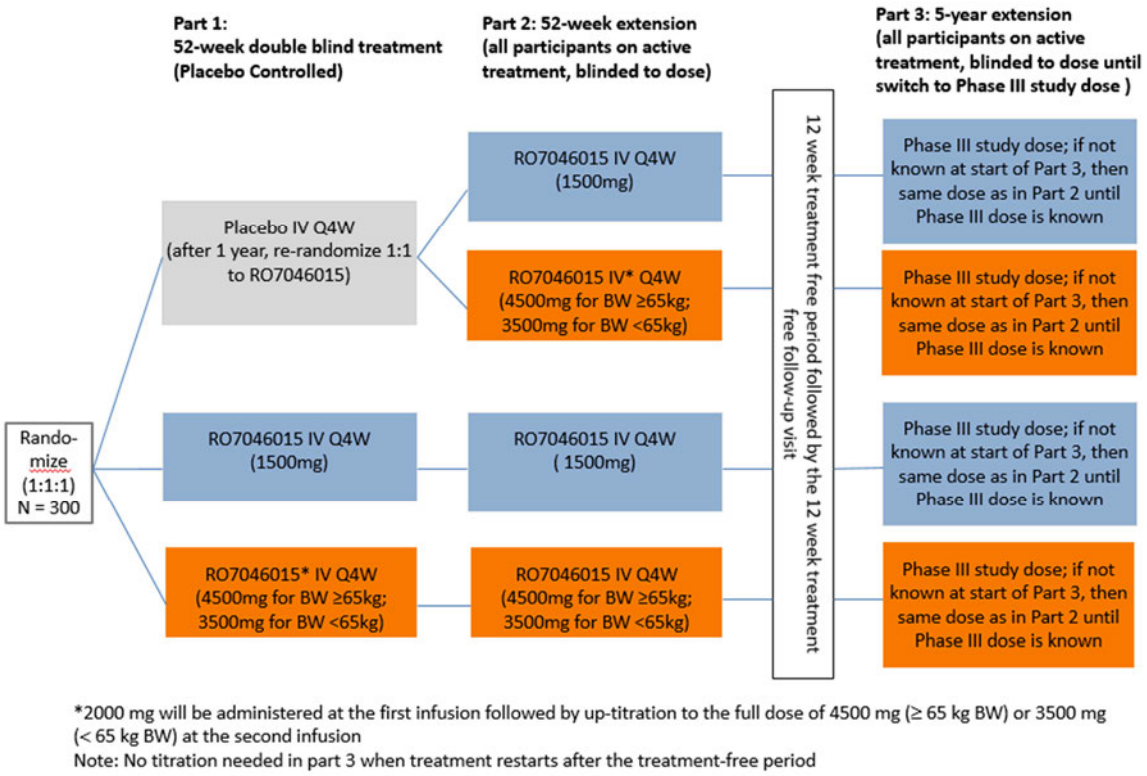
  - If the Phase III study dose is already identified at that time, dosing will be restarted with Phase III study dose as an IV infusion at the same infusion rate used in Part 2. In case of occurrence of IRR, instructions provided in Section 5.2.1 will be followed.

- *Situation #3: Participants not having completed Part 2 at the time Part 3 is launched and locally approved:*

  As per inclusion criteria, all participants have to have completed Part 2 to be eligible to Part 3, thus these participants will be asked to complete Part 2 (i.e., completed Week 104 visit and the 12-week treatment free follow-up visit). Within four weeks after 12-week treatment free follow up visit has been completed (but not on the same day this visit has been completed), dosing will be restarted with Phase III study dose as IV infusion at the same infusion rate

used in Part 2. In case of occurrence of IRR, instructions provided in Section 5.2.1 will be followed.

Figure 1 Study Design



*2000 mg will be administered at the first infusion followed by up-titration to the full dose of 4500 mg (≥ 65 kg BW) or 3500 mg (< 65 kg BW) at the second infusion
Note: No titration needed in part 3 when treatment restarts after the treatment-free period

3.1.1.4 Duration of Study

The study for each patient will be divided as follows:

- Screening: Up to 8 weeks
- Treatment period: *364* weeks (52 weeks in Part 1*,* 52 weeks in Part 2 *and 260 weeks in Part 3*)
- Safety Follow-up: up to 12 weeks after cessation of *double-blind* treatment (regardless of whether cessation of treatment occurs at the end of or during Part 1 or Part 2).
- *Part 3 Safety Follow-up: 12 weeks after cessation of treatment (regardless of whether cessation of treatment occurs at the end of or during Part 3).*

Day 1 will be designated as the first day the study drug (RO7046015 or placebo) is administered.

3.1.2 Independent Data Monitoring Committee

This study will utilize an independent Data Monitoring Committee (iDMC), which will monitor safety and may also conduct an efficacy interim analysis review, if deemed necessary by the Sponsor. The interim analyses will be conducted by an external statistical group and other external specialists, as appropriate, and reviewed by the iDMC. Interactions between the iDMC and the Sponsor will be carried out as specified in the iDMC Charter. Sponsor personnel will not have access to the results of these data analyses.

The iDMC will be composed of:

- Three to four independent clinical experts in the field of Parkinson's disease (external to Roche)
- An independent statistician (external to Roche)

3.1.2.1 Review of Safety Data by the Independent Data Monitoring Committee

An iDMC will be used during the study to monitor and ensure the participants' safety. The iDMC will be unblinded at the aggregate and individual level to review and evaluate safety data including AEs/SAEs, ECGs, and vital signs. No sponsor personnel will have access to the data displays reviewed by the iDMC. The iDMC will make recommendations to the Sponsor on the conduct of the clinical trial in accordance with the remit of the iDMC documented in the iDMC charter. In particular, the iDMC may recommend stopping enrollment in the highest dose cohort and introducing a new mid-dose cohort (3000 mg). In this case, participants already enrolled at a higher dose will continue in the study with the new mid-dose of 3000 mg (see Section 3.2.3).

The first and second iDMC meetings for review of safety data will take place after approximately 30 participants (approximately 10 participants per arm) and 60 participants (approximately 20 participants per arm), respectively, have received their first three infusions. The iDMC may be convened at an earlier or at additional time-points if warranted by safety considerations or for other reasons (for further details see the separate iDMC Charter).

Note that if the high-dose is discontinued, the sponsor may increase the sample size (by a maximum of 20%) and/or change the allocation ratio to ensure that the number of participants required to have approximately 80% power for the comparison between the new mid-dose and placebo is maintained (see Section 6.1).

3.1.2.2 Review of Efficacy Data by the Independent Data Monitoring Committee

The decision to conduct an optional interim analysis for efficacy, along with the rationale, timing, and statistical details for the analysis, will be documented in a Statistical Analysis Plan (SAP).

3.1.3 End of Study

The end of the study is defined as the date when the last participant last observation (LPLO) occurs at the follow-up visit. LPLO is expected to occur *approximately 388* weeks after the last participant is enrolled, or earlier in the case that the study is discontinued following any of the planned interim analyses.

The primary analysis will be performed after all active participants have completed the Week 52 visit (placebo-controlled, double-blind treatment period) or withdrew from the study prior to Week 52.

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Study Population

The clinical hypothesis is most efficiently tested in early PD patients (H&Y Stage I or II), that are recently ($\leq$ 2 years) diagnosed, and either de novo (untreated) or treated with a MAO-B inhibitor. Data from several previous treatment studies and longitudinal observational studies (Parkinson Study Group 2002, Parkinson Study Group PRECEPT Investigators 2007, Rascol et al 2011, NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators 2015, Simuni et al 2015) demonstrate that the progression rate in early PD patients measured using UPDRS or MDS-UPDRS is greater shortly after diagnosis and before the start of dopaminergic therapy (approximately 6 – 12 MDS-UPDRS total points/year without dopaminergic medication). The progression rate depends on baseline severity, study length, co-medication, and other factors. Several studies (both treatment and observational studies) have shown that it is feasible to enroll this early PD patient population in large, multicenter trials. The specificity of the diagnosis of Parkinson's disease based on established clinical diagnostic criteria by trained movement disorder specialists will be further enhanced by including only patients with a dopaminergic deficit confirmed using DaT-SPECT.

The likelihood of starting dopaminergic treatment within one year after diagnosis in such a population is highly variable and *a range* between 14 and 50% of enrolled patients *has* been reported (Parkinson Study Group 2002, Parkinson Study Group PRECEPT Investigators 2007, Rascol et al 2011, NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators 2015, Simuni et al 2015), depending on factors such as baseline severity, background therapy, study length and historical context. MAO-B inhibitor pre-treated patients have a reduced likelihood of starting dopaminergic therapy during the course of 12 months, while maintaining a relatively high progression rate (Parkinson Study Group 2002, Rascol et al 2011, NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators 2015).

After start of dopaminergic treatment (with *continuous* increases in levodopa doses and combination therapy with dopaminergic agonists), apparent progression rate is reduced to a value corresponding to an MDS-UPDRS total change of 2 – 4 points/year (e.g., Parkinson Study Group 2004, NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators 2015), while variability (due to individual progression rate and patient response to dopaminergic treatment) remains high. Both rate of clinical progression and progression to variability ratio is best in an early patient population before start of dopaminergic treatment (6-12 MDS-UPDRS total points/year) (Parkinson Study Group 2002, Parkinson Study Group PRECEPT Investigators 2007, Rascol et al 2011, NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators 2015, Simuni et al 2015).

Participants who initiate dopaminergic treatment in Part 1*,* Part 2 *or Part 3* (levodopa or dopamine agonist) will continue in the study, as per their regular scheduled study visits and will continue to receive study drug. Initiation of dopaminergic treatment should take place during a regular scheduled study visit. Before initiation of dopaminergic treatment, patients are requested to perform all assessments of the “prior to start of dopaminergic treatment” visit as per SoA (Appendix 1). For participants who have started dopaminergic treatment (levodopa or dopamine agonist), the MDS-UPDRS and Digital Biomarker in-clinic assessments at subsequent visits will be performed in a practically-defined “Off” state – no levodopa or dopamine agonist medication since the prior evening, including Part IV (motor assessment while on dopaminergic treatment), and the MDS-UPDRS Part III (motor assessment) will be repeated at least one hour after receiving their dopaminergic medication in the clinic (“On” state), along with Digital Biomarker in-clinic assessments.

The effect on clinical progression rate determined using the MDS-UPDRS will be supported with a panel of exploratory biomarkers to assess the potential reduction of pathological changes and/or reduction of neuronal damage (e.g., reduction of loss of dopaminergic terminals measured using DaT-SPECT). In these early PD participants (within two years of diagnosis), there is already measurable loss of dopaminergic synaptic terminals in the striatum as documented using DaT-SPECT(de la Fuente-Fernandez et al 2011, Nandhagopal et al 2011, Schwarz et al 2004). There is a high plausibility that disease progression can be slowed at this stage, while sufficient numbers of dopaminergic neurons and synapses (and other neuronal populations vulnerable to toxic α-synuclein aggregates) are still present and available to be rescued by a disease-modifying treatment. Regardless of dopaminergic treatment, early PD patients show the fastest decrease of DaT-SPECT signal (i.e., loss of dopaminergic terminals) resulting in an inverse exponential decline in striatal DaT-SPECT uptake values (Nandhagopal et al 2011, Schwarz et al 2004).

An empirical disease progression model based on data from the PPMI observational study (NCT01141023) was developed for patients not treated with symptomatic PD medication and patients on MAO-B inhibitors. The model was used to run clinical trial simulations that confirmed that the use of a mixed population (drug-naïve and on MAO-B inhibitor) is feasible and that more frequent assessments during the trial conduct may allow the detection of a disease-modifying effect.

3.2.2 Rationale for Control Group

This is the first POC study of RO7046015 in patients with PD, and information from other treatment and longitudinal studies (Parkinson Study Group 2002, Parkinson Study Group PRECEPT Investigators 2007, Rascol et al 2011, NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators 2015, Simuni et al 2015) was used to guide the current study design. In these studies, there was a high variability in the rate of disease progression depending upon factors such as population and study design, supporting the need for a placebo group in the current study.

As the MDS-UPDRS primary endpoint is planned for after 52 weeks, the duration of the placebo treatment is limited to Part 1 (52 weeks), with the option to enroll participants already on stable MAO-B inhibitor at baseline and expected to receive stable MAO-B inhibitor throughout the study. In Part 2 *and in Part 3*, dopaminergic treatment may be initiated according to standard of care. Both PPMI (Marek et al 2011, Simuni et al 2015) and FS-Zone (NCT01280123; NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators 2015) studies, which included de novo and MAO-B inhibitor-treated early PD populations, effectively managed early PD for 6 months to a year, without requiring dopaminergic treatment.

3.2.3 Rationale for Dosage Selection

Currently, there is no biomarker available to measure target engagement in the CNS, either directly or indirectly, in humans. As anticipated from non-clinical data, there were no effects on free α-synuclein in the CSF at IV doses administered up to 60 mg/kg in patients (MAD study, PRX002-CL002), while a dose-dependent reduction of free α-synuclein in serum of up to 97% was observed. Based on monkey PK/PD studies and modelling work that took into consideration the estimated brain penetration of RO7046015 and the binding of the antibody to monomeric α-synuclein (the predominant form in CSF), it was expected that there would be no effect on free α-synuclein in CSF measurable at the doses investigated in the SAD and MAD studies (PRX002-CL001 and PRX002-CL002, see RO7046015 Investigator's Brochure). Therefore, human PK/PD information obtained from the SAD and MAD studies cannot be used to guide efficacy dose selection in patients.

The dose-selection is guided by the in vivo animal pharmacology studies. In the dose-response study in the transgenic mouse model Line 61, effects on histopathological endpoints were seen at weekly IP doses of 1 mg/kg and higher. Effects on functional endpoints were seen at 1 mg/kg (spatial learning assessment) or at higher doses of at least 10 mg/kg (restoration of gait/balance impairment). A dose of 60 mg/kg every 4 weeks in patients with PD in the MAD study (PRX002-CL002) achieved average trough serum concentrations in the range of those observed after 10 mg/kg weekly IP dose in the transgenic mouse model (approximately 70 μg/mL) while the dose of 10 mg/kg Q4W in patients achieved mean trough concentrations above those observed after 1 mg/kg in mice (approximately 17 μg/mL).

RO7046015 was well tolerated without any reports of treatment-emergent SAEs. The most frequently reported mild to moderate treatment-emergent adverse events (TEAEs) in the MAD study in PD patients (PRX002-CL002) included constipation (9.1%), infusion-related reactions (IRRs) (7.3%), diarrhea (5.5%), peripheral edema (5.5%) and post-lumbar puncture syndrome (5.5%). Mild to moderate IRRs, that all resolved were limited to the 60 mg/kg dose cohort and were observed in 4 of 12 treated patients. Based on previous experience with other mAbs, it is expected that participants can safely be treated with such high doses provided certain measures are taken to minimize the risk for IRRs (see Section 4.4.2).

The exposure at the NOAEL in cynomolgus monkey was 6 times (C_{max}) and 5 times (AUC over 4 weeks) higher than the exposure achieved with 60 mg/kg in the MAD study, which is considered an acceptable safety window.

Since there is uncertainty around translatability of animal to man in this disease, it is recommended to use the maximal tolerable and/or achievable dose (e.g., 60 mg/kg) and a second dose that produces exposure levels that are well separated from the high dose while achieving trough levels at least as high as those *observed in the mouse model at* 1 mg/kg. Therefore, a second dose in patients equal to or greater than 10 mg/kg is appropriate as low dose.

The PK in humans is well described by a population PK model in the dose range of 0.3-60 mg/kg for single and multiple IV dosing from the SAD and MAD studies (PRX002-CL001 and PRX002-CL002). The PK is similar in healthy subjects and patients and exposure increases dose-proportionally (see RO7046015 Investigator's Brochure).

Body weight has an effect on clearance (and volume of distribution) such that exposure increases in patients with lower body weight. A switch to more convenient flat dosing is possible to achieve similar exposures across a large range of body weight provided the use of an approximately 25% lower dose in participants with lower body weight (<65 kg) is implemented at high doses where there is an increased risk for IRRs.

Therefore, two doses were selected to match approximately the exposure achieved with 60 mg/kg and a lower dose that achieves exposures at least as high as with 10 mg/kg and which leads to approximately 30% overlap of trough levels. The high-dose is 4500 mg for participants with body weight equal or higher than 65 kg or 3500 mg for participants with body weight lower than 65 kg), and the low-dose is 1500 mg (independent of the participant's body weight), given IV (Q4W). Additional information can be found the RO7046015 Investigator's Brochure. As described in Section 3.1.2.1, results of pre-specified safety interim analyses may lead to a stop of enrollment to the highest dose cohort and introduction of a new mid-dose cohort of 3000 mg (corresponding to a median AUC of approx. 112800 μg • h/mL and a median C_{max} of approx. 700 μg/mL, close to the values observed with the 30 mg/kg dose in the MAD study PRX002-CL002).

Part 1 results may guide Phase III study dose selection. Once identified (and if applicable), participants will be switched to this dose in Part 3 (see Section 3.1.1.3 for further details). This dose will not exceed the high dose tested in the present BP 39529 study.

3.2.4 Rationale for Duration of Treatment

Based on data from observational cohorts such as the PPMI study and previous placebo-controlled treatment trials (see Section 3.2.1), a 52-week treatment duration is expected to be sufficient to demonstrate between group differences due to the effects of a disease-modifying treatment that changes the rate of progression in early stage PD patients without dopaminergic treatment. See Section 3.2.5 for the rationale for the one-year extension *and Section 3.2.6 for the rationale for the five-year extension*.

3.2.5 Rationale for One-Year Extension (Part 2)

Participants who complete the double-blind, placebo-controlled treatment period (Part 1) will continue in an all-participants-on-treatment (RO7046015), blinded to dose extension for an additional 52 weeks (Part 2). See Section 3.1.1.2 for further information. This will allow collection of safety information on long-term exposure with RO7046015, as well as concomitant dopaminergic treatment.

The clinical and biomarker outcomes described in Sections 2.2 and 3.3.4 will also be evaluated over a period of up to 104 weeks (Part 1 and Part 2) using a disease progression model that will consider start of RO7046015 treatment, start of dopaminergic treatment and baseline severity to assess the effects of RO7046015 beyond one year of treatment and to identify potential parameters that are sensitive to RO7046015 treatment after start of dopaminergic treatment (see Section 6.7 and 6.8).

The doses of RO7046015 in Part 2 (52-week extension) will be the same as in Part 1. Participants randomized to RO7046015 in Part 1 will remain on the same dose, while participants randomized to placebo will be re-randomized at the start of Part 2 to one of the two active doses of RO7046015 with a 1:1 allocation ratio.

3.2.6 *Rationale for Five-Year Extension (Part 3)*

Participants who complete the blinded to dose extension (Part 2) will be offered participation in an all-participants-on-treatment extension (RO7046015) for an additional five years (Part 3), see Section 3.1.1.3 for further information. This will allow collection of safety and efficacy information on long-term exposure to RO7046015, as well as concomitant dopaminergic treatment.

Until the Phase III study dose is identified, participants will remain on the same dose they were assigned to in Part 2. Once identified (and if applicable), participants will be switched to the Phase III study dose as described in Section 3.1.1.3.

3.2.7 Rationale for Biomarkers and Digital Assessments

3.2.7.1 DaT-SPECT

A striatal dopamine transporter deficit on dopamine transporter imaging by DaT-SPECT currently represents the most established imaging marker in de novo PD, reflecting neurodegeneration in key brain regions affected by α-synuclein pathology. Indeed, longitudinal studies in PD patients have established an inverse exponential decline in striatal DaT-SPECT uptake values over time, i.e., with disease progression (Nandhagopal et al 2011, Schwarz et al 2004). Therefore, in PD, DaT-SPECT will be used as a secondary outcome measure to determine whether RO7046015 has *an effect on the underlying pathology of PD*.

3.2.7.2 Magnetic Resonance Imaging

Three different types of MRI will be explored in this study, in order to assess different aspects of brain function and integrity that have been proposed to be impacted by PD pathology (grey and white matter integrity, functional interaction between different brain regions and metabolic cost associated with brain function). *At the end of Part 2 (if applicable) and in Part 3, iron and neuromelanin-sensitive (NM) imaging will be added to the MRI battery.* Please note that *the MRI* sequences will only be acquired if the investigative sites have the required scanner software/sequences capabilities.

Diffusion Tensor Imaging

DTI is an MRI sequence which can be used to assess grey and white matter integrity in the brain. In-house analyses of the PPMI whole-brain DTI data *(Taylor et al, 2018)*, as well as a published report (Zhang et al 2016), demonstrated significant annual reductions in DTI-based measures of white matter integrity in PD compared to healthy control participants. Importantly, these changes significantly correlated with declining CSF α-synuclein levels (Zhang et al 2016), supporting the use of DTI as a downstream measure of progressive α-synuclein pathology (Burke and O'Malley 2013).

Resting State *Functional MRI*

*Rs-f*MRI provides a measure of functional brain network integrity, i.e., the ability of brain regions to interact with one another to enable thinking (Prodoehl et al 2014). R*esting state* functional connectivity analyses demonstrated that functional connectivity declines significantly over time in PD, independent of age effects (Olde Dubbelink et al 2014). Moreover, the magnitude of *resting state* functional connectivity over one year correlated significantly with decline in motor performance as measured by the MDS-UPDRS Part III motor scale (*Dukart et al 2017*, Manza et al 2016). The present study will therefore acquire *rs-fMRI* to perform striatal functional connectivity analyses testing for effects of RO7046015 treatment.

Arterial Spin Labeling

2-deoxy-2-[^{18}F] fluoro-D-glucose positron emission tomography (FDG-PET) has traditionally been used to assess metabolic cost associated with brain function, but it is an expensive and invasive procedure. Cerebral blood flow (CBF) provides another good approximation of metabolic cost associated with brain function. MRI ASL is a less expensive and non-invasive method to estimate CBF than FDG-PET (Teune et al 2014), and has recently reached a high level of multi-site standardization (Alsop et al 2015, Mutsaerts et al 2015). Whole-brain CBF patterns are disturbed in PD, and the degree of disturbance increases with time (e.g., Wu et al 2013). Therefore, the present study will examine participants with MRI ASL to compare changes in CBF patterns between the treatment groups.

Neuromelanin-sensitive MRI

NM sequesters metal ions are a product of dopamine metabolism. NM is enriched in the substantia nigra and considered a marker of nigral integrity in PD patients. In NM-MRI of Parkinson's patients, a loss of pigments has been repeatedly observed. Sensitivity and specificity for PD diagnosis was confirmed in a meta-analysis (Wang et al 2019). Further studies have demonstrated longitudinal decline in substantia nigra pars compacta contrast ratio (Matsuura et al 2016) and substantia nigra volume (Gaurav et al 2018). The present study will therefore examine treatment-specific slowing of substantia nigra NM loss in Parkinson's Disease patients.

Iron imaging

Iron accumulation in the brain leads to toxic reactive oxygen species and can trigger the aggregation of alpha synuclein (Wan et al 2017). In Parkinson's Disease, iron has consistently been shown to be increased relative to healthy controls, based on pathological and MRI studies (Wang et al 2016). In addition, longitudinal studies have shown a PD-specific increase in substantia nigra brain iron (Du et al 2018) which was correlated to clinical changes during the same time frame (Ulla et al 2013). The present study will therefore examine treatment-specific slowing of iron accumulation in the brain MRI in Parkinson's Disease patients.

3.2.7.3 Digital Biomarkers

Smartphones and wrist-worn wearables have high quality sensors that enable the remote, non-invasive, frequent and precise measurement of motor and non-motor symptoms (Maetzler et al 2013, Ossig et al 2016). These digital biomarkers may therefore provide more sensitive assessments of symptom progression and fluctuation over time than established clinical rating scales. Smartphone sensor data, including motion and location, were collected during the previous RO7046015 MAD study (PRX002-CL002), where patients completed daily "active tests" and then carried the phone with them throughout the day ("Passive Monitoring"), revealing very high acceptance and adherence and excellent correspondence with clinical measures of motor symptom severity (i.e., MDS-UPDRS III) (Lipsmeier et al 2018), similar to previous reports (e.g., Tsanas et al 2010, Kostikis et al 2014, Patel et al 2011, Kassavetis et al 2016). This digital biomarker approach will therefore be implemented in the current study to maximize the probability of detecting a potential therapeutic effect of RO7046015 and to potentially provide new insights into subject functioning and behavior.

3.2.7.4 Clinical Genotyping

Dissection of the genetic architecture of a complex disorder such as PD is important to understand its biological basis, assess the individual predisposition of disease, and evaluate the capacity of therapeutic interventions.

3.2.7.5 Cerebrospinal Fluid Biomarkers

Molecular changes that take place in the CNS can be mirrored in CSF as an accessible source of brain-derived proteins. Efforts together with Public Private Partnerships (e.g., the Michael J Fox Foundation) are ongoing to identify and validate CSF biomarkers that reflect disease severity, its progression and/or to serve as downstream markers of α-synuclein pathology. CSF biomarkers will be measured in patients who consent to an optional lumbar puncture. A matching serum sample will be collected *in Part 1 and Part 2, matching serum and plasma samples will be collected in Part 3*. See SoA (Appendix 1, Appendix 2 *and Appendix 3*) for the timing of CSF sampling.

3.2.7.6 Skin Biopsy and Collection of Screen Failure Data and Samples

No biomarker tools currently exist to detect and monitor aggregated α-synuclein in brain in vivo, and the definitive diagnosis can only be made post-mortem through neuropathology (Dickson et al 2009). However, Donadio et al (2014) recently reported that pathological forms of α-synuclein were detectable in the accessible peripheral neurons of skin biopsy samples obtained from PD patients, and a cross-sectional study indicated that the degree of peripheral nerve pathology was associated with disease severity (Wang et al 2013). Longitudinal skin biopsy sampling will therefore be implemented for the direct and in vivo assessment of α-synuclein pathology and its progression and response to therapy. Clinical data and samples, including skin biopsies, will be collected from DaT-SPECT negative screen failure participants to determine

whether the detection of α-synuclein skin pathology may be used as a sensitive and specific, less invasive, tool to diagnose PD.

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Changes in safety laboratory tests (hematology, chemistry and coagulation) from baseline over time.
- Incidence of treatment-emergent abnormal laboratory values and abnormal laboratory values reported as AEs.
- Incidence and severity of AEs.
- Incidence of ADAs.
- Changes in ECG assessments from baseline over time; incidence of abnormal ECG assessments.
- Change in blood pressure (BP [systolic and diastolic], heart rate, and orthostatic measurement from baseline over time, incidence of abnormal blood pressure [systolic and diastolic], heart rate, and orthostatic changes).
- Incidence of exacerbation of motor and psychiatric side-effects (including C-SSRS).
- Incidence of MRI abnormalities.

3.3.2 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Population and individual primary PK parameter estimations (e.g., clearance and volume of distribution) and the influence of various covariates on these parameters.
- Secondary PK parameters (e.g., AUC, C_{trough}) derived from the individual post-hoc predictions.

3.3.3 Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

- Change in total MDS-UPDRS score (sum of Parts I, II and III) from baseline at Week 52.

The secondary efficacy outcome measures for this study (after 52 weeks of treatment with RO7046015 or placebo) are as follows:

- Change from baseline in MDS-UPDRS Part IA, Part IB, Part I total, Part II total, Part III total and Part III subscores
- Change from baseline in DaT-SPECT in ipsilateral (to the clinically dominant side) putamen binding ratio values
- Change from baseline in MoCA total score

- Change from baseline in Clinical Global Impression of Improvement (CGI-I)
- Change from baseline in Patient Global Impression of Change (PGIC)
- Change from baseline in Schwab and England Activities of Daily Living (SE-ADL)
- Time to worsening of motor or non-motor symptoms as measured by MDS-UPDRS
- Time to start of dopaminergic PD treatment (levodopa or dopamine agonists)

3.3.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are change from baseline *to Week* 52*, to Week* 104 *and to Part 3 Week 260* in:

- MDS-UPDRS Part III total and Part III subscores central vs local ratings for consistency and accuracy
- Time to worsening of moto*r* or non-motor symptoms as measured by MDS-UPDRS or starting dopaminergic treatment (levodopa or dopamine agonist)
- Modified Hoehn & Yahr (mH&Y).
- PDSS-2 total score and sub-scales.
- SCOPA-AUT total score and subdomain scores.
- PDQ-39 total score and sub-scales
- Digital Biomarkers and patient-reported outcomes (Smartphone and wrist-worn wearable assessments):
  - Diary questions (patient reported outcome [PRO]).
  - PAC-SYM questionnaire (PRO).
  - Hospital Anxiety and Depression Scale (HADS) total score and sub-scales: anxiety (HADS-A), and depression (HADS-D) (PRO).
  - EQ-5D-5L questionnaire (PRO).
  - Sensor data collected during “Active Tests”, assessing motor symptoms (upper and lower body movement, upper limb dexterity, voice/speech) and non-motor symptoms - including an electronic Symbol Digital Modalities Test (eSDMT) to measure attention and executive function.
  - Sensor data collected during “Passive Monitoring” assessing activity, movement and motor symptoms associated with routine daily living.
  - Sensor data collected during “In-Clinic Assessments”, including the Timed Up and Go Test and selected items from the Berg Balance Scale.
- Serum*, plasma,* and CSF biomarkers related to Parkinson’s disease (CSF in consented patients only).
- α-synuclein pathology in peripheral nerves (skin biopsies in eligible participants; see exclusion criteria in Section 4.2.3).
- DaT-SPECT binding ratio values for: striatum, caudate and putamen (average ipsilateral and contralateral)

- DTI MRI for mean diffusivity and fractional anisotropy.
- *rs-fMRI for functional brain connectivity.*
- ASL MRI for cerebral blood flow.
- *NM-MRI for substantia nigra integrity.*
- *Iron imaging for brain iron accumulation.*
- Time to start or change of co-medication for non-motor symptoms that may be related to PD (cognition, constipation, depression, anxiety, excessive daytime sleep, nocturnal sleep, urogenital symptoms/sexual dysfunction).
- Start or change of co-medication for non-motor symptoms that may be related to imaging biomarkers (DAT Scan and ASL).
- Parkinson-related effects on the loss of autonomic tone as measured by heart rate variability.
- Composite score of *MDS-UPDRS* Part *II (patient reported motor experiences of daily living) and MDS-UPDRS Part III (clinician rated motor signs of PD) sub-items.*
- MDS-UPDRS Part IV at Week 52*, at Week 104 and Part 3 Week 260* in participants who started dopaminergic treatment (levodopa or dopamine agonist).

4. MATERIALS AND METHODS

4.1 CENTER

This is a multicenter study (approximately 60 centers) to be conducted in multiple countries worldwide. Additional site(s) may be included for back-up purposes and may be activated if needed.

4.2 STUDY POPULATION

4.2.1 Recruitment Procedures

Participants will be identified for potential recruitment per site-specific recruitment plans prior to consenting to take part in this study. Any recruitment materials for participants will receive Institutional Review Board or Ethics Committee (IRB/EC) approval prior to use.

4.2.2 Inclusion Criteria

Participants must meet the following criteria for study entry:

1. Idiopathic PD with bradykinesia plus one of the other cardinal signs of PD (resting tremor, rigidity) being present, without any other known or suspected cause of PD untreated or treated with MAO-B inhibitor.
2. Male or female, 40 to 80 years of age, body weight range of $\geq$ 45 kg/99 lbs to $\leq$ 110 kg/242 lbs and a body mass index (BMI) of 18 to 34 kg/m^2.
3. A diagnosis of PD for 2 years or less at screening.
4. H&Y Stage I or II.

5. A screening brain DaT-SPECT consistent with PD (central reading).
6. Clinical status does not require dopaminergic PD medication and is not expected to require dopaminergic treatment within 52 weeks from baseline.
7. If presently being treated for PD, a stable dose of MAO-B inhibitor (rasagiline or selegiline) for at least 90 days prior to baseline and not expected to change within 52 weeks.
8. Able and willing to provide written informed consent and to comply with the study protocol according to ICH and local regulations.
9. For women of childbearing potential: use of highly effective contraceptive methods (that result in a failure rate of $<1\%$ per year) during the treatment period and for at least 30 days (or longer if required by local regulations) after the last dose of study drug.

   A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

   Examples of highly effective contraceptive methods (with a failure rate of $<$ 1% per year) include bilateral tubal ligation, vasectomized partner, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

   The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
10. For men: use of contraceptive measures as defined below:

    With female partners of childbearing potential or pregnant female partners, men must use a condom during the treatment period and for at least 30 days (or longer if required by local regulations) after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period. The female partners should use a contraception method with a failure rate of $<1\%$ per year during the treatment period and for at least 30 days (or longer if required by local regulations) after the last dose of study drug.

    The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.2.3 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from study entry:

Current or Past Medical History

1. Medical history indicating a Parkinson syndrome other than idiopathic PD, including but not limited to, progressive supranuclear gaze palsy, multiple system atrophy, drug-induced parkinsonism, essential tremor, primary dystonia.
2. Known carriers of certain familial PD genes (Parkin, PINK1, DJ1). Note*:* GBA, synuclein, LRRK2 mutation carriers are allowed.
3. History of PD-related freezing episodes or falls.
4. A diagnosis of a significant CNS disease other than Parkinson's disease (including but not limited to Huntington's disease, normal pressure hydrocephalus, cerebrovascular disease including stroke, fronto-temporal dementia, Alzheimer's disease); history of repeated head injury; history of epilepsy or seizure disorder other than febrile seizures as a child.
5. Mini Mental State Examination (MMSE) $\leq$ 25.
6. Reside in a nursing home or assisted care facility.
7. History of or screening brain MRI scan indicative of clinically significant abnormality including, but not limited to, prior hemorrhage or infarct $>$ 1 cm3, $>$ 3 lacunar infarcts.
8. Concomitant disease or condition within six months of screening, or as specified below, that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study or interfere with the participant's ability to comply with study procedures or abide by study restrictions, or with the ability to interpret safety data, including, but not limited to:
    a. Autoimmune disease (however, well controlled conditions such as, but not limited to, quiescent rheumatoid arthritis (RAS), controlled type I diabetes, or mild-to-moderate psoriasis not requiring systemic medications may be acceptable after discussion with Sponsor/Medical monitors).
    b. A history of cancer within 5 years of baseline with the exception of fully excised non-melanoma skin cancers or non-metastatic prostate cancer that has been stable for at least 6 months.
    c. Any active infectious disease at baseline.
    d. Current, or history of, alcohol or drug abuse or other dependence (except nicotine dependence) within two years before screening.
    e. Any febrile illness within one week prior to first dose administration.
    f. Any current psychiatric diagnosis according to Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5), International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) or equivalent, that may interfere with the participant's ability to perform the

study and all assessments (e.g., major depression, mental retardation, schizophrenia, bipolar disorder, etc.). Note: Mild depression, depressive mood or mild anxiety arising in the context of PD, are not exclusionary.

9. The following cardiovascular conditions:
    a. Myocardial infarction within 12 months of baseline.
    b. Known history or documentation of uncontrolled hypotension or bradycardia on more than one occasion within three months prior to baseline.
    c. Known history or documentation of uncontrolled hypertension on more than one occasion within three months prior to baseline.
    d. Resting pulse rate (PR) greater than 100 or less than 45 bpm.
    e. Clinically significant cardiovascular disease including any of the following: unstable angina, decompensated congestive heart failure, clinically significant arrhythmias or symptomatic orthostatic hypotension.
    f. A corrected QT (QTcF) interval measurement $>$ 450 ms for males or $>$ 470ms for females at screening, or a family history of long QT syndrome
    g. Intermittent second or third degree atrioventricular (AV) heart block or AV dissociation is excluded (asymptomatic patients with first degree AV block may be included).
10. Clinically significant abnormalities in laboratory test results at the Screening visit, including hepatic and renal panels, complete blood count, chemistry panel and urinalysis, including:
    a. Total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>$ 2 times the upper limit of normal (ULN).
    b. Serum creatinine > 1.5 times the ULN.
    c. Hematocrit (Hct) less than 35% for males and less than 32% for females, or absolute neutrophil cell count of $<$ 1500/μL (with the exception of a documented history of a chronic benign neutropenia), or platelet cell count of $<$ 120,000/μL; international normalized ratio (INR) $>$ 1.4 (in patients not on anticoagulants) or other coagulopathy.
    d. A clinically significant abnormal thyroid-stimulating hormone (TSH) test.
    e. A positive urine drug screen for a drug of abuse.
        - For participants treated with selegiline, the amphetamine drug abuse test should be based on the results from a urine assay by liquid chromatography-mass spectrometry which is able to differentiate “false positive methamphetamine” from “true positive methamphetamine”.
        - For participants treated with benzodiazepines: a positive urine drug screen for benzodiazepines is allowed, provided that the prescription has been stable for 90 days prior to baseline (refer to exclusion criterion 15).
    f. Positive result for acute or chronic infectious hepatitis B (HBV; [i.e., HBsAg positive test]), for hepatitis C (HCV), or HIV 1 or 2. Successfully treated HCV patients (undetectable HCV RNA) are eligible for enrollment. Participants who are immune due to HBV natural infection or HBV vaccination are eligible.
    g. For women of childbearing potential, a positive urine or blood pregnancy test.

11. Lactating women.

Medications and treatments

12. Prior treatment with dopaminergic medication (e.g., levodopa or a dopaminergic agonist) with no clinical treatment response or a clinical treatment response inconsistent with PD (e.g., absence of observable response to a sufficiently high-dose of levodopa [i.e., ≥ 600 mg/day]).
13. Use of any of the following: catechol-O-methyl transferase (COMT) inhibitors (entacapone, tolcapone), amantadine or anticholinergics, or dopaminergic medication (levodopa and both ergot and non-ergot [pramipexole, ropinirole, rotigotine] dopamine agonists) for more than a total of 60 days or within 60 days of baseline.
14. Anti-epileptic medication for non-seizure-related treatment which has not remained stable for at least 60 days prior to baseline.
15. Anti-depressant or anxiolytic use that has not remained stable for at least 90 days prior to baseline. The use of fluoxetine and fluvoxamine is not permitted. For patients treated with an MAO-B inhibitor and an antidepressant (except fluoxetine and fluvoxamine), a 6-month period of stable and tolerated dosing before baseline is required.
16. Use of any of the following medications within 90 days prior to baseline; antipsychotics (including clozapine and olanzapine), metoclopramide, alpha methyldopa, flunarizine, amoxapine, amphetamine derivatives, reserpine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norephedrine, phentermine, phenylpropanolamine, and modafinil.
17. Participated in an investigational drug, device, surgical, or stem cell study in PD.
18. Any prior treatment with an investigational PD-related vaccine (including active immunization or passive immunotherapy with monoclonal antibodies).
19. Prior participation in any RO7046015 or PRX002 study.
20. Receipt of any non-PD investigational product or device, or participation in a non-PD drug research study within a period of 30 days (or 5 half-lives of the drug, whichever is longer) before baseline.
21. Receipt of any monoclonal antibody or investigational immunomodulator within 180 days (or 5 half-lives, whichever is longer) before baseline (e.g., monoclonal antibodies, intravenous immunoglobulin [IVIG], interleukin 2 [IL-2], interleukin 12 [IL-12], interferon or immunosuppressive drugs).
22. Immunomodulating drugs within 30 days prior to baseline.
23. Allergy to any of the components of RO7046015 such as citrate, trehalose and polysorbate (Tween) 20 or a known hypersensitivity or an IRR to the administration of any other monoclonal antibody.

Procedural

24. Any contraindications to obtaining a brain MRI (e.g., claustrophobia unresponsive to reassurance or low dose of an anxiolytic agent, tooth implants) and any contraindications to obtain a DaT-SPECT (i.e., known hypersensitivity to the active substance or to any of the excipients). Patients with a hypersensitivity to iodine may receive an alternative thyroid blocking agent (e.g., potassium perchlorate or sodium perchlorate).
25. For participants consenting to provide optional CSF samples by lumbar puncture (LP): LP will only be performed if the participant does not have any contraindication to undergoing an LP including, but not limited to: INR $>$ 1.4 or other coagulopathy, platelet cell count of $<$ 120,000/μL, infection at the desired LP site, taking anti-coagulant medication within 90 days of baseline (Note: low dose aspirin (acetylsalicylic acid [ASA] is permitted), severe degenerative arthritis of the lumbar spine, suspected non-communicating hydrocephalus or intracranial mass, prior history of spinal mass or trauma is/are identified. Participants failing to meet these criteria can still participate in the study and all other study assessments (with the exception of LP) as appropriate. Participants could be excluded from the study if the CSF has more than 5 WBCs/mm^3 (according to local laboratory assessment). This should be discussed with the Medical Monitor (e.g., if there is evidence that the spinal tap was traumatic, the participant may still be considered for study eligibility).
26. For skin biopsy at the cervical paravertebral region:

    Condition that either precludes the safe performance of the skin punch biopsy or may interfere with obtaining evaluable skin tissue biopsies, including any previous or active significant dermatological disease (e.g., previous biopsy with any of the following findings: inflammatory disease, scar tissue, psoriasis, keloid formation, skin cancer).

    Participants failing to meet these criteria can still participate in the study and all other study assessments (with the exception of skin biopsy) as appropriate.
27. Donation of blood over 500 mL within three months prior to screening.

4.3 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization will be done via an Interactive Web Response System (IWRS) or an equivalent method (IxRS). Patients can only be randomized once all screening assessments have been completed and eligibility confirmed.

In Part 1, participants will be randomized to placebo, or one of the two active treatment doses: 4500 mg (3500 mg in participants with body weight lower than 65 kg) and 1500 mg with a 1:1:1 allocation ratio, see Section 3.1.1.1.

For Part 2, participants who complete the initial placebo-controlled part will switch into the extension, in which case, a re-randomization will take place using the rules described in Section 3.1.1.2. Although only placebo patients will be re-randomized at the start of Part 2, all patients will be registered in IxRS at the start of Part 2 to ensure the blind is maintained.

For Part 3, participants will remain at the same dose they received in Part 2 until the Phase III study dose is identified. Once identified and if applicable, participants will be switched to the Phase III study dose as described in Section 3.1.1.3. All patients will be registered in IxRS at the start of Part 3 to keep track of the study period. Also the IxRS will record the date in which the patients switched to the Phase III dose.

The randomization list will be generated by the IxRS provider. The list will be provided to statisticians, and/or programmers, and/or other specialists external to Roche as needed to create unblinded data displays for the iDMC reviews (see Section 3.1.2). Members of the iDMC will be fully unblinded; no Roche personnel will have access to the unblinded data displays reviewed by the iDMC.

Treatment assignment for Part 1 will only be made available to the Sponsor personnel analyzing and interpreting the data from the placebo-controlled period (after completion of Part 1 of the study). However, site personnel and participants will remain blinded throughout the study, including Part 2 *and Part 3. Once Phase III study dose is identified, site personnel and participants will be informed of that dose.*

The randomization list will also be made available to the pharmacist preparing the study treatment (for the corresponding study center only) to the individuals responsible for PK and ADA sample bioanalysis and to other study personnel as described in a separate document (List of Unblinded Site Members and Unblinded Non-Site Members).

If unblinding is necessary for patient management (in the case of a serious adverse event), the Investigator and the Sponsor will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If possible, the responsible Scientific Leader/Medical Monitor should be contacted before the code is broken.

If the Investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor. The Investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

As per Health Authority reporting requirements, the Sponsor will break the treatment code for all unexpected serious adverse events (see Section 5.1) that are considered by the Investigator to be related to study drug. All such occurrences must be documented in the study file.

Whenever disclosure of the identity of the test medication is necessary, adequate procedures will be in place to ensure integrity of the data. Any unblinding at the investigating site will be documented in the study report with date, reason for identifying the drug and the name of all the person(s) who requested the unblinding.

4.4 STUDY TREATMENT

4.4.1 Formulation, Packaging, and Handling of RO7046015

The investigational medicinal product (IMP) in this study is RO7046015 for IV infusion, which needs to be prepared locally. Placebo formulation will not be provided; patients randomized to placebo will receive an IV infusion of normal saline (provided by the sites).

Symptomatic/dopaminergic PD medication and premedication before infusion are considered non-investigational medicinal products (NIMPs).

RO7046015 drug product is supplied as a concentrate for solution for infusion of 500 mg in a 10-mL glass vial with elastomeric stopper and aluminum seal.

Prior to use, the appropriate volume of RO7046015 solution for infusion should then be added to normal saline (after removal of the same amount of saline from the bag) by the unblinded study pharmacist who is uninvolved in any other aspects of the study, for IV administration to participants in the clinical study. Placebo will be prepared using the same type of infusion bag and tubing that will be used for the active RO7046015. All infusion kits will be blinded to other site staff, as described in the Pharmacy Manual.

Study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and strength.

The packaging and labeling of the study medication will be in accordance with Roche standard and local regulations.

RO7046015 vials should be stored at 2–8°C until use. For further details, see the RO7046015 Investigator's Brochure.

4.4.2 Dosage, Administration and Compliance

RO7046015 study drug product 50 mg/mL (supply vials 500 mg/10 mL) will be administered IV after dilution in 250 mL 0.9% NaCl bags. The qualified individual (unblinded study pharmacist) responsible for dispensing the study drug at the site will prepare the correct dose according to the randomization schedule. This individual will write the date dispensed and participant's number on the study drug box label and on the Drug Inventory/Dispensing Log. This individual will also record the study drug (e.g., batch number) received by each patient during the study.

Premedication ***in Part 1 and Part 2***

In vitro studies have characterized RO7046015 as having a low potential for induction of cytokine release (RO7046015 Investigator Brochure). A premedication regimen will be administered 30-60 min prior to infusion for the first three doses in Part 1 and first three doses in Part 2 of the study. The premedication regimen will consist of the following:

- Loratadine 10 mg by mouth (PO). In countries or sites where loratadine is not readily available, the following alternatives are acceptable in the preferred order:
  - Desloratadine 5 mg PO
  - Cetirizine 10 mg PO
  - Other alternatives may be considered acceptable upon consultation with the Sponsor/Medical Monitor.

AND

- acetaminophen 650 mg PO (or minimum recommended adult dose of paracetamol as per local regulation).

Premedication in Part 3

In Part 3, no systematic premedication is required for the three first doses; premedication is based on signs and symptoms at previous infusion. Thus, participants who experienced a Grade 2 or higher IRR on a previous infusion should be pre-medicated for subsequent infusion with:

- *an antihistamine (H1-receptor antagonist), anti-pyretics (acetaminophen 500-1000 mg PO/IV or alternatively ibuprofen 400-600 mg or other NSAIDs per institutional standard if acetaminophen cannot be tolerated).*

If a participant experienced a Grade 3 IRR, the same as above should apply and 200 mg hydrocortisone IV (or equivalent dose of another corticosteroid) is recommended to be added.

Premedication regimens for subsequent cycles may be reduced or omitted in case of ≤ Grade 1 events in the previous cycle.

Premedication in case of IRR recurrence in Part 3

In case of recurrent IRRs (irrespective of grading) the premedication regimen will consist of the following:

- *a dose of an antihistamine (H1-receptor antagonist, as per local practice) is taken the night before the administration*

AND

- *the same dose of the same antihistamine (H1-receptor antagonist), with an anti-pyretics (acetaminophen 500-1000 mg PO/IV or alternatively ibuprofen 400-600 mg or other NSAIDs per institutional standard if acetaminophen cannot be tolerated) are taken 1-2 hours before infusion.*
- *Addition of steroids may be considered in case of previous Gr 3 IRR.*

Study Drug Administration

Study drug must be administered in a setting where full emergency resuscitation capabilities/facilities are immediately available and participants are under close supervision of the Investigator at all times. For all infusions, vital signs must be monitored pre-infusion, every 15 minutes until the end of infusion, and thereafter, every 30 minutes until the infusion line is removed *(see* Appendix 1, Appendix 2 *and* Appendix 3 *for further details*).

Study drug should be given as IV infusion over 2 hours for the first three doses and if well tolerated, the infusion time can be reduced to one hour in subsequent doses. Date, start and end time of infusions should be recorded on the eCRF. The study drug should be administered through a dedicated line with an inline filter. Intravenous infusion pumps should be used to control the infusion rate of study drug. Study drug should not be administered as an IV push or bolus. After the end of infusion, the IV line should remain in place for a minimum of 1 hour for all infusions. If no infusion-related symptoms occur within 1 hour post-infusion, the infusion line may be removed.

If an IRR develops, the infusion should be temporarily interrupted. The participant should be monitored until complete resolution of the symptoms and treated as clinically indicated. Upon resolution of symptoms, the infusion may be resumed at 50% of the previous infusion rate. For the management of IRRs and hypersensitivity reactions, see Section 5.2.1 and Table 1.

In Part 3, if a patient had experienced an IRR at previous visit, the rate of infusion should be reduced at the subsequent visit and 2 hours duration of infusion should be considered. Rate of infusion may be increased again in case of ≤ Grade 1 events in the previous cycle.

To reduce the risk of IRRs, 2000 mg will be infused on Day 1 followed by an up-titration to the full dose of 4500 mg (≥65 kg body weight) / 3500 mg (<65 kg body weight) on the second infusion (Day 28) during Part 1. Participants receiving placebo during Part 1 and randomized to the high dose at the start of Part 2 (extension) will receive 2000 mg IV on Week 56 followed by an up-titration to the full dose of 4500 mg (≥ 65 kg body weight) or 3500 mg (< 65 kg body weight) on the second infusion (Week 60).

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.2.1.

Cases of accidental overdose or medication error along with any associated AEs, should be reported as described in Section 5.3.5.11.

4.4.3 Investigational Medicinal Product Accountability

All IMPs (RO7046015) required for completion of this study will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs via IxRS, to confirm the shipment condition and content. Any damaged shipments will be replaced. Temperature excursion will be evaluated by the Sponsor/CRO.

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Inventory/Dispensing Log) of the study drug must be maintained. The Drug Inventory/Dispensing Log must be kept current and should contain the following information:

- The identification of the patient to whom the study drug was dispensed (for example patient date of birth).
- All records and drug supplies must be available for inspection by an unblinded Monitor [at every monitoring visit].

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor/CRO. Local or institutional regulations may require immediate destruction of used investigational medicinal product for safety reasons. In these cases, it may be acceptable for investigational study site staff to destroy dispensed investigational product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, destroyed and provided that adequate storage and integrity of drug has been confirmed.

The site must obtain written authorization from the Sponsor/CRO before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Written documentation of destruction must contain the following:

- Identity [batch number] of investigational product[s] destroyed
- Quantity of investigational product[s] destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person [or company] who destroyed investigational product[s].

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory/Dispensing Log.

4.4.4 Post-trial Access to RO7046015

The Sponsor will offer continued access to study drug (RO7046015) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug (RO7046015) after completing the study if all of the following conditions are met:

- *The patient has a life-threatening or severe medical condition and requires continued Sponsor study drug treatment for his or her well-being*
- *There are no appropriate alternative treatments available to the patient*
- *The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them*

A patient will not be eligible to receive study drug (RO7046015) after completing the study if any of the following conditions are met:

- *The Sponsor study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)*
- *The Sponsor has discontinued development of the drug or data suggest that the drug is not effective for PD*
- *The Sponsor has reasonable safety concerns regarding the drug as treatment for PD*
- *Provision of the drug is not permitted under the laws and regulations of the patient's country*
- *Patient is eligible to enroll in an ongoing RO7046015 open-label study*

4.5 CONCOMITANT THERAPY

Concomitant therapy includes any medication, e.g., prescription drugs, over-the-counter drugs, approved dietary and herbal supplements, nutritional supplements and any non-medication interventions (e.g., individual psychotherapy, cognitive behavioral therapy,

smoking cessation therapy, and rehabilitative therapy) used by a patient from at least 90 days prior to screening until the follow-up visit. All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

All medication administered to manage adverse events should also be recorded on the Adverse Event eCRF.

4.5.1 Permitted Therapy

4.5.1.1 For Participants on MAO-B Inhibitor Therapy

Participants who are currently under treatment for PD with a MAO-B inhibitor (rasagiline or selegiline), should be on a stable dose for at least 90 days prior to baseline and during the first year of the study (prior to extension). These patients will be treated with stable daily doses as recommended by the USPI or SmPC for rasagiline monotherapy and selegiline monotherapy and should not increase doses or switch between different MAO-B inhibitors during the study. Furthermore, if a participant is on a stable and well tolerated treatment regimen of a combination of a selective MAO-B inhibitor (rasagiline or selegiline) and an antidepressant for a period of at least 6 months prior to baseline, he/she may, at the discretion of the treating physician and in accordance with the local standard of care, continue on this therapy (without increasing the dosage) for the duration of their participation in the study.

Participants that are untreated at baseline should not start MAO-B inhibitor treatment during the 52-week placebo controlled period (Part 1). If participants do start MAO-B inhibitor treatment at any time during the study, they will also complete the assessments described in the SoA under “prior to start of dopaminergic/symptomatic PD treatment”. Likewise, any changes of MAO-B inhibitor treatment and the reasons will be recorded.

4.5.1.2 Other Permitted Therapy

Participants who are currently being treated with antidepressants or anxiolytics should remain on a stable dose for at least 90 days prior to baseline and, barring any unforeseen circumstances, remain on that dose for the duration of the study.

Participants who are receiving anti-epileptic medication for non-seizure related treatment should remain on a stable dose for at least 60 days prior to baseline.

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

All preventive/routine immunizations (e.g., tetanus/diphtheria booster, herpes zoster, pneumococcal pneumonia, influenza) should be administered at least 30 days prior to baseline. In the event that an immunization is needed during the study, it should be administered between the third and 12th infusion in Part 1 or Part 2. The timing of the vaccination should be around mid-cycle (between 2 infusions).

Use of anti-platelet medications such as low dose ASA, clopidogrel, prasugrel, or ticagrelor prescribed for the prevention of cardiovascular events are permitted.

4.5.2 Prohibited Therapy

4.5.2.1 MAO-B Inhibitor Therapy

Participants on MAO-B inhibitor therapy for PD must not receive fluoxetine, fluvoxamine, meperidine, tramadol, methadone, propoxyphene and MAO inhibitors (MAOIs), including other selective MAO-B inhibitors, because of the risk of serotonin syndrome. At least 14 days should elapse between discontinuation of the selective MAO-B inhibitor and initiation of treatment with these medications. Concomitant use of St. John's wort, cyclobenzaprine and dextromethorphan is also prohibited (see MAO-B inhibitor prescribing information).

Due to the potential risk of serotonin syndrome, starting a new treatment with any antidepressant in a participant already on a stable course of MAO-B inhibitor treatment will be decided on a case-by-case basis after a discussion between the Investigator and the Sponsor.

Participants that are untreated at baseline should not start MAO-B inhibitor treatment during the 52-week placebo-controlled period (Part 1). If participants do start MAO-B inhibitor treatment at any time during the study, they will also complete the assessments described in the SoA under "prior to start of dopaminergic/symptomatic PD treatment". Likewise, any changes of MAO-B inhibitor treatment and the reasons will be recorded.

4.5.2.2 Other Prohibited Therapy

Other prohibited therapy includes:

- Antipsychotics (including clozapine and olanzapine), metoclopramide, alpha methyldopa, flunarizine, amoxapine, amphetamine derivatives, reserpine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norephedrine, phentermine, phenylpropanolamine and modafinil within 90 days prior to baseline and over the study period.
- Immunomodulating drugs within 30 days prior to baseline and over the study period.
- For participants undergoing Lumbar Puncture, oral anticoagulants (Direct Factor Xa Inhibitors and Direct Thrombin Inhibitors), low-molecular-weight heparin (LMWH), warfarin (Coumadin) acenocoumarol and phenprocoumon are prohibited.

4.5.3 Other Symptomatic PD Therapy

During Part 1 (52-week double blind placebo-controlled period), participants should not start symptomatic treatment for PD, including COMT inhibitors (entacapone, tolcapone), amantadine or anticholinergics, dopaminergic medication (levodopa), both ergot and non-ergot (pramipexole, ropinirole, rotigotine) dopamine agonists, and MAO-B inhibitors (see Section 4.5.2.1). Some participants may experience worsening of their PD symptoms to an extent that they cannot tolerate in their personal or professional life. These patients may start symptomatic treatment according to local guidelines during a regular study visit after completing the assessments described in the SoA under visit "prior to start of dopaminergic/symptomatic PD treatment". Investigators will record the reasons and the type and dose of symptomatic treatment started. These participants will continue in the study as per their regular scheduled study visits.

During the extensions (Part 2 *and Part 3*), symptomatic treatment for PD including *but not limited to* COMT inhibitors (entacapone, tolcapone), amantadine or anticholinergics, dopaminergic medication (levodopa), both ergot and non-ergot (pramipexole, ropinirole, rotigotine) dopamine agonists may be prescribed.

4.5.4 Dietary Restrictions

Foods with a high tyramine content should be avoided by participants on selegiline or rasagiline due to the potential for a hypertensive reaction (see local label).

4.6 STUDY ASSESSMENTS

4.6.1 Description of Study Assessments

All examinations listed below will be performed according to the Schedule of Assessments (SoA) outlined in Appendix 1, Appendix 2 *and Appendix 3*. A recommended sequence of assessments to be carried out at each visit is outlined in Appendix 4.

Note that in those patients that start dopaminergic treatment during the course of the study, the majority of functional assessments (including MDS-UPDRS Part I + II + III) are to be performed prior to administration of dopaminergic treatment on that day. Only selected functional assessments such as MDS-UPDRS Parts III + IV will be performed at least 1 hour after dopaminergic treatment.

4.6.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, use of alcohol and drugs of abuse and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 90 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity, where applicable. The patient's number of years of education will also be recorded.

4.6.1.2 Physical and Neurological Examinations

A complete physical examination will be performed at the time-points specified in the SoA (see Appendix 1*,* Appendix 2 *and Appendix 3*). The examination should include an evaluation of the head, eyes, ears, nose and throat (HEENT), neck and lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

The physical exam will NOT include pelvic, rectal or breast exams.

An abbreviated physical examination will be performed at all other study visits *in Part 1 and 2*. It will include HEENT, heart & lung exams and any assessment based on the complaints expressed by the patient at visit. *In Part 3, abbreviated physical examination will be performed as indicated in the SoA (see Appendix 3) and may be performed outside of SoA at any visit if deemed necessary by the investigator or if the patient expresses any complaints / presents any symptoms at an in-clinic visit.*

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Changes from baseline abnormalities should be recorded in participant's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Height will only be recorded at screening. Weight will be recorded at time-points for complete Physical Examination as specified in the SoA (Appendix 1*,* Appendix 2 *and Appendix 3*).

A neurological exam will also be conducted at screening, baseline and every six months, and at the last completed visit. *A neurological exam may be performed at any visit if deemed necessary by the investigator (e.g., in case of an adverse event).*

4.6.1.3 Vital Signs

Vital signs will include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a semi-supine position (upper body is not completely horizontal but rather tilted at an angle of about 45°) after the patient has been resting for approximately 5 minutes at each visit. Additionally, a single BP and pulse will be obtained after 2 minutes of standing for orthostatic vital signs at the time-points specified in the SoA (Appendix 1*,* Appendix 2 *and Appendix 3*). When possible, the same arm should be used for all blood pressure measurements.

*In Part 1 and 2, b*lood pressure (BP), pulse rate, respiratory rate and body temperature will be recorded at the time-points specified in the SoA (Appendix 1 and Appendix 2). *In Part 3, blood pressure (BP), pulse rate and respiratory rate will be recorded at the time-points specified in the SoA; body temperature may be taken at any visit if deemed necessary by the Investigator but is no longer mandatory at each visit (Appendix 3).*

Any clinically significant abnormal vital sign value should be repeated to ensure accuracy. If the abnormality persists upon repeat measurement, the patient should be assessed by the Investigator.

Blood pressure, pulse rate and respiratory rate should be obtained in a quiet room at a comfortable temperature, with the participant's arm unconstrained by clothing or other material. All measurements will be obtained from the same arm and, with the same cuff size, using a well-calibrated automatic instrument with a digital readout, throughout the study (the "ideal" cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference [a length-to-width ratio of 2:1]). The automatic cuff should be placed on the designated arm prior to dosing. The participant should be asked to remove all clothing that covers the location of cuff placement. The individual should be comfortably seated, with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum). After the patient has been resting in a semi-supine position for at least 5 minutes, blood pressure, pulse rate and respiratory rate will be obtained.

4.6.1.4 Electrocardiograms

Triplicate ECG recordings (i.e., three useful ECGs without artifacts) will be obtained within approximately 2-5 minutes at each specified time-point. The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT). *In Part 3, triplicate ECG recordings or single ECG recordings will be obtained as detailed in the SoA (Appendix 3).* Whenever possible, the same brand/model of a standard high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements should be used for each participant. The conditions should be as close as possible to pre−dose time-points; this includes but is not limited to food intake, activity level, stressors and room temperature.

To minimize variability, it is important that participants be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements, blood draws and study drug infusion. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the participant's permanent study file at the site. ECGs will be analyzed at a central laboratory.

Digital ECG recordings will be analyzed and read by a central reader and available on the vendor's ECG portal. The ECG data from the central reader will include heart rate, QRS duration, and PR, QT intervals, QTcF (Fridericia's correction), RR, T-wave and

U-wave morphology and overall ECG interpretation. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

4.6.1.5 Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. Laboratory safety tests shall be collected at time-points specified in the SoA (Appendix 1, Appendix 2 *and Appendix 3*).

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor participant safety. Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated once per discretion of the Investigator before randomization to confirm eligibility. If there is an alternative explanation for a positive urine or blood test for drugs of abuse, e.g., previous occasional intake of a medication or food containing for example codeine, benzodiazepines or opiates, the test could be repeated to confirm washout.

After randomization, in the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. Results from local or central clinical laboratory testing will be either recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the central laboratory and loaded on the eCRF.

Blood and urine samples will be collected for the following clinical laboratory tests at the time-points indicated in the SoAs (Appendix 1, Appendix 2 *and Appendix 3*).

- Hematology (leukocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells]).
- Serum chemistry (sodium, potassium, chloride, bicarbonate, glucose (fasting for screening visit), urea, creatinine, protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, LDH).
- Coagulation (INR, aPTT, PT)
- Viral serology:
  - HIV (specific tests HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody)
  - Hepatitis B surface antigen (HBsAg)
  - Total hepatitis B core antibody (HBcAb)
  - Hepatitis C virus (HCV) antibody
  - HCV RNA test for successfully treated HCV patients
- Urinalysis: A midstream, clean-catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, leucocytes, nitrites and pH. If there is a clinically

significant positive result (i.e., confirmed by a positive repeated dipstick sample), urine will be sent to the local laboratory for microscopy and/or culture. If there is an explanation for the positive dipstick result, e.g., menses, it should be recorded, and there is no need to send for additional testing.

- Urine drug screen: This should at a minimum include: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines (for further details regarding the type of urine drug screen and the handling of a positive urine drug screen for benzodiazepines, see Section 4.2.3, exclusion criterion 10 e).
- Lipids (cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)
- Thyroid hormones (free T4 and TSH)
- Other hormones (estradiol, follicle stimulating hormone [FSH], luteinizing hormone [LH] in females).
- All women who are not post-menopausal or surgically sterile will have a serum pregnancy test at screening. Urine pregnancy tests will be performed prior to dosing and all DaT-SPECT scans based on patient age/menopausal status. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.
- CSF: erythrocyte and leukocyte cell counts, protein and glucose.

4.6.1.6 Pharmacokinetic Assessments

Serum samples for population PK analysis will be collected in all randomized participants in this study. These samples will be collected at the time-points specified in the SoA (Appendix 1, Appendix 2 *and Appendix 3*). On each of the specified visits *in Parts 1 and 2, and in the first year of Part 3*, one sample pre-dose and one sample post-dose at the end of the infusion will be collected. *In Years 2 to 5 of Part 3, one sample predose will be collected at the specified visits in the SoA.* In addition, a sample will be collected at any time on Days 7 and 14 *(of Part 1)* for the first 90 participants enrolled in the US. The date and time of each sample will be recorded in the eCRF.

RO7046015 levels will be analyzed by using validated assays. Samples from participants randomized to placebo will not be analyzed in the first instance, but will be retained for subsequent analysis if appropriate.

Remaining PK volume may also be used for additional validation experiments after the mentioned intended uses.

Details on sampling procedures, sample storage and shipment are given in the laboratory manual.

4.6.1.7 Immunogenicity Assessments

Although RO7046015 is a humanized antibody, there is a risk that ADA against RO7046015 could develop, potentially reducing its efficacy and/or potentially resulting in symptomatic hypersensitivity reaction, in particular immune-complex reactions.

Blood samples for anti-drug antibodies (ADA) will be taken as described in the SoA (Appendix 1, Appendix 2 *and Appendix 3*). Additional ADA samples will be drawn at the time of treatment discontinuation or at the safety follow-up visit and in participants who experience a Grade ≥2 IRR and in participants with clinical signs of hypersensitivity reaction, in particular immune-complex reaction. In any case, for each collected ADA sample, a corresponding PK sample will be collected at the same time-point for the determination of the RO7046015 concentration. The date and time of each sample will be recorded in the eCRF.

Validated screening, confirmatory, and titer assays will be employed to detect ADAs against RO7046015.

Samples from participants randomized to placebo will not be analyzed in the first instance, but will be retained for subsequent analysis if appropriate.

If required, remaining ADA samples may also be used for additional assay development/validation experiments.

Details on sampling procedures, sample storage and shipment are given in the laboratory manual.

4.6.1.8 Biomarker Samples

The following samples will be collected to analyze biomarkers associated with PD:

- Serum *and plasma* biomarker sample
- Whole blood for clinical genotyping
- Lumbar puncture for CSF (optional)

  Lumbar puncture will be performed on consenting participants only. Note: baseline LP should be performed during the screening period prior to Day -4 to allow recovery before dosing. The LP should be performed in the morning (between 08:00 and 12:00 hours) to minimize potential diurnal variation of CSF parameters. Any participants with a headache due to the LP should not be dosed until it has resolved. Participants taking low-dose aspirin (ASA) may be at a higher risk of LP complications. At the discretion of the Investigator, if not contraindicated, low dose ASA may be discontinued for a period of time prior to performing the LP; stop and start dates must be documented on the appropriate Concomitant Medication eCRF. An aliquot of the CSF samples will be used for local laboratory analysis (erythrocyte and leukocyte cell counts, protein, and glucose) to test for signs of infection or inflammation while the remainder of the sample will be sent for central biomarker assessment.

- Punch biopsies to collect skin tissue from the cervical paravertebral region will be performed under local anesthesia (lidocaine). If skin biopsies are collected at visits with study drug administration, they should be collected pre-dose.

- All biomarker samples, including samples from screen failures, will be destroyed within 5 years after the date of final clinical study report. Other residual material (may include blood, serum specimens, extracts, tissue, on-study blocks, slides, etc.) will be destroyed within 5 years after the final clinical study report unless the patient gives specific consent for the remainder of the sample(s) to be used for optional exploratory research within the Research Biosample Repository (RBR). If the patient provides consent for optional exploratory research, the samples will be stored until no longer needed or used up.

For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual.

Based on continuous analysis of the data in this study and other studies, any sample type not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

Data arising from all biosamples including samples for analyses of inherited DNA will be subject to the confidentiality standards described in Section 8.4.

The sample collected for DNA extraction may be used for whole genome sequencing (WGS) and other genetic analysis and may be sent to one or more laboratories for analysis.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

4.6.1.9 Disease-Specific Assessments

Movement Disorder Society-Unified Parkinson's Disease Rating Scale (In-clinic)

The MDS-UPDRS is a multimodal scale assessing both impairment and disability and is separated into four subscales (Parts I-IV). The MDS-UPDRS includes components assessed by the rater as well as sections completed by the participant. The MDS-UPDRS rater will be a trained, experienced movement disorder specialist who should not be involved in the clinical assessments at dosing days as described in Appendix 4 (specifically AE reporting, concomitant medication, physical or neurological exams). To reduce variability, every effort should be made to have the same rater perform the ratings for an individual participant throughout the course of the study. The MDS-UPDRS rater should also rate the Modified Hoehn and Yahr Stage and the CGI-I.

- Part I assesses non-motor experiences of daily living and is comprised of two components:
  - Part IA contains 6 questions that are assessed by the rater.
  - Part IB contains 7 questions that are part of the Patient Questionnaire completed by the participant.
- Part II assesses motor experiences of daily living. There are an additional 13 questions that are also part of the Patient Questionnaire completed by the participant.
- Part III assesses the motor signs of PD and is administered by the rater. Part III contains 33 scores based on 18 items, several with right, left or other body distribution scores.
- Part IV assesses motor complications, dyskinesias and motor fluctuations using historical and objective information. The Investigator will complete this assessment once a participant has started dopaminergic treatment.

For each question a numeric score is assigned between 0-4, where 0=Normal, 1=Slight, 2=Mild, 3=Moderate, 4=Severe. Composite scores (for each Part and total) are determined by summing the numeric values of each question.

In participants that do not receive any dopaminergic (levodopa or dopamine agonist) PD treatment, only MDS-UPDRS Parts I, II and III will be assessed and total MDS-UPDRS score in this population is the sum of Parts I, II and III (primary outcome measure).

Participants who have started dopaminergic treatment (levodopa or dopamine agonist) during the course of the study will continue in the study, as per their regular scheduled study visits. For these participants, the MDS-UPDRS (Parts I, II, III and IV) and Digital Biomarker in-clinic assessments (Section 4.6.1.9) will be performed in a practically defined “Off” state – no levodopa or dopamine agonist medication since the prior evening, and Part III (motor assessment) will be repeated at least one hour after receiving medication in clinic (“On” state). These participants will need to be reminded **not** to take dopaminergic treatment prior to their study visit in which MDS-UPDRS is administered, but to bring their dopaminergic medication to the study visit, to take their regular dopaminergic treatment dose at least one hour prior to the “On” state assessments.

In Part 1 and Part 2, MDS-UPDRS Part III administration to participants is videotaped at each administration of MDS-UPDRS scale, and videotapes are transferred to a central vendor. In parallel to the MDS-UPDRS ratings from trained site raters, central vendor will centrally score MDS-UPDRS Part III from videotapes to address consistency and accuracy.

Hoehn and Yahr Stages (In-clinic)

The H&Y provides a global assessment of the severity of Parkinson's disease based on clinical findings and functional disability. The scale allocates stages from 0 to 5 to indicate the relative level of motor disability and is a commonly used system for describing how the symptoms of PD progress. This scale is included within the MDS-UPDRS and will be completed for all participants.

- Stage 0: No symptoms.
- Stage 1: Symptoms on one side of the body only.
- Stage 2: Symptoms on both sides of the body. No impairment of balance.
- Stage 3: Balance impairment. Mild to moderate disease. Physically independent.
- Stage 4: Severe disability, but still able to walk or stand unassisted.
- Stage 5: Wheelchair-bound or bedridden unless assisted.

Modified Hoehn and Yahr Stages (In-clinic)

The mH&Y staging is an adaptation of the H&Y (see above) which includes two additional stages (1.5 and 2.5) to account for the intermediate course of Parkinson disease, mH&Y will be measured across this study as an exploratory endpoint to better understand changes in motor symptoms across the study. The mH&Y stage should be assessed by the same rater as the MDS-UPDRS.

- Stage 0: No symptoms.
- Stage 1: Symptoms on one side of the body only.
- Stage 1.5: Symptoms on one side of the body and axial involvement
- Stage 2: Symptoms on both sides of the body. No impairment of balance.
- Stage 2.5: Mild symptoms on both sides of the body with recovery on pull test.
- Stage 3: Balance impairment. Mild to moderate disease. Physically independent.
- Stage 4: Severe disability, but still able to walk or stand unassisted.
- Stage 5: Wheelchair-bound or bedridden unless assisted.

REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) (In-clinic)

The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) is a 10-item self-rated questionnaire to assess sleep-wake disturbances. Patients with clinical characterizations of sleep behavior disorder may represent early manifestations of progressive neurodegenerative disorders, including Parkinson's disease, thus making this an important tool for early diagnosis and stratification in longitudinal prospective studies.

DaT-SPECT

DaT-SPECT (DaT (^{123}I-FP-CIT) SPECT) assessments will be performed at Screening as part of the eligibility criteria and for consideration as a baseline scan for statistical

analyses. Further DaT-SPECT scans will be acquired after 52 weeks*,* 104 weeks, *Part 3 Week 104 and Part 3 Week 208* or upon early termination. The technical details and communication lines will be outlined in a separate DaT-SPECT technical operations manual. Scans will be reviewed and managed by a central reader DaT-SPECT Core Lab and it will be the assessment of this central reader that will be used for eligibility decision and for efficacy analyses.

Imaging Procedure: Women of childbearing potential must have a confirmed negative urine pregnancy test just prior to injection of DaTSCAN™. Before the DaTSCAN™ injection, participants will be pre-treated with stable iodine (e.g., 10 drops of a saturated solution of potassium iodide or other liquid formulation or tablets, as per local standard practice) to reduce the uptake of DaTSCAN™ by the thyroid. Patients with a hypersensitivity to iodine may receive an alternative thyroid blocking agent (e.g., potassium perchlorate or sodium perchlorate). Participants will then be injected with 3-5 mCi of tracer. About 4 hours (±30 minutes) following the injection, participants will undergo SPECT imaging on the camera. The data and quality assurance procedures to be employed in this study, as well as technical details on DaT-SPECT acquisition will be provided in a separate DaT-SPECT technical operations manual.

Magnetic Resonance Imaging (MRI)

The MRI should be performed using a 3-Tesla (3T) magnet. If a 3T magnet is not available in reasonable proximity to the study center, a 1.5T magnet may be used. All technical details and communication lines will be outlined in a separate MRI manual. Qualifying MRI scans will be performed on healthy volunteers having provided informed consent at each MRI center as part of the certification process with the MRI service provider. All MRI scans will be managed by a central MRI Core Lab monitoring and ensuring the integrity and quality of the acquired data.

Eligibility and safety MRI assessments (fluid-attenuated inversion recovery [FLAIR], diffusion-weighted imaging [DWI], gradiant echo [GRE], structural MRI [sMRI]) will be performed at screening as part of the eligibility criteria. Further safety MRI scans will be acquired at the time-points specified in the SoA (Appendix 1*,* Appendix 2 *and Appendix 3*), upon early termination and prior to start of DT. For assessing MRI-related study eligibility criteria at screening and for safety monitoring, the assessment by the local neuroradiologists will be used.

Exploratory efficacy MRI assessments (including DTI, ASL, *rs-fMRI, NM-MRI, iron imaging*) as described in Section 3.2.7.2 will be performed at Screening for consideration as a baseline scan, after 52 and 104 weeks of treatment*, at Part 3 Week 1, after Part 3 Week 104 and Part 3 Week 208*, and upon early termination/withdrawal from the study.

Participants who have started dopaminergic treatment (levodopa or dopamine agonist) will have the MRI assessment in a practically defined ‘Off’ state. These participants will

need to be reminded **not** to take dopaminergic treatment on the day of each study visit in which MRI is acquired.

MRIs should not be performed unless at least 3 to 4 hours have passed since a lumbar puncture.

Clinical Global Impression of Severity and Improvement (CGI-S and CGI-I) (In-clinic)

The generic Global Impression is a measure commonly used in PD clinical trials to provide concise information on overall health state (Guy 1976). The CGI-I should be assessed by the same rater as the MDS-UPDRS.

The severity component (CGIS) is intended as a measure of disease severity.

1 = Normal, not at all ill; 2 = Borderline ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; 7 = Among the most extremely ill patients.

The improvement component (CGI-I) is intended as a measure of change in health state. A 7-point clinician-based (CGI-I) global impression of improvement will be employed:

1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; 7 = Very much worse

Mini Mental State Examination (MMSE) (In-clinic)

The Mini Mental State Examination (MMSE) consists of a set of standardized questions to assess a participant's mental status and identify the individual's general level of impairment. The questions target five areas; orientation, short term memory retention, attention, short term recall and language. This will be used as an inclusion criterion, to ensure that the patient is not cognitively impaired.

The Montreal Cognitive Assessment (MoCA) (In-clinic)

In early Parkinson's disease, patients usually perform in the normal range on the widely used MMSE. The Montreal Cognitive Assessment (MoCA) is a rapid screening instrument like the MMSE but was developed to be more sensitive to patients presenting with mild cognitive complaints. It briefly assesses short term and working memory, visuospatial abilities, executive function, attention, concentration, language and orientation (Nasreddine et al 2005).

Schwab and England Activities of Daily Living (SE-ADL) (In-clinic)

The SE-ADL is a single item scale assessing Activities of Daily Living on a scale ranging from 0% (bedridden) to 100% (completely independent), using 10% intervals (Schwab & England 1969).

Digital Biomarker Assessments (Smartphone & Wrist-Worn Wearable)

Each participant will receive a preconfigured smartphone and wrist-worn wearable with installed software for the digital biomarker assessments. They will use the devices and software to assess motor and non-motor symptoms, as well as activities associated with routine daily living. The smartphone will also be used to complete selected PROs (see Section 4.6.1.10).

Digital Biomarker Remote Monitoring

Participants will be provided and trained on the devices during screening. During the study, participants will be instructed to conduct an "Active Test" every day *in Part 1 and Part 2, and as per SoA in Part 3*, at approximately the same time (ideally in the morning, after breakfast). The "Active Test" consists of a short, preconfigured sequence of tasks that assess motor symptoms (upper and lower body movements, upper limb dexterity, voice/speech) and non-motor symptoms (including an eSDMT for cognition). For "Passive Monitoring", participants will be instructed to carry the smartphone and wear the wrist-worn wearable throughout the day as they go about their daily routine. Selected PROs will be administered on the smartphone to reduce the site visit burden.

Device sensor data will be recorded continuously, throughout the "Active Tests" and "Passive Monitoring". Sound will only be recorded during selected "Active Test" tasks. Data are encrypted and uploaded to secure servers whenever the phone is connected to WIFI.

Participants are asked to charge the devices overnight. If participants have a WIFI network at home, they are encouraged to connect their smartphone to enable data transfer. If no WIFI network is available, the sensor data will be transferred during site visits or after the devices have been returned.

Digital Biomarker In-Clinic Assessments

In Part 1 and Part 2, participants are instructed to bring the smartphone and wearable to every clinic visit to check adherence and technical status of the devices. *In Part 1 and Part 2, participants will receive replacement device sets if they are defective. In Part 3, device sets may not be replaced if they are defective. In Part 3, participants are instructed to bring the sets to the visits with in-clinic digital biomarker assessments once a quarter.*

*In Part 1 and Part 2, a*t selected clinic visits, participants will be asked to conduct the "Active Test" tasks and two additional in-clinic only assessments (selected items from the Berg Balance Scale and the Timed-Up and Go Test) under the supervision of a person trained on the digital biomarker approach. *In Part 3 participants will only perform the "Active Tests" at the specified in-clinic site visits.*

For participants who have started dopaminergic treatment (levodopa or dopamine agonist), the in-clinic assessments will be performed in a practically defined "Off" state

(i.e., no levodopa or dopamine agonist medication since the evening before). The in-clinic assessments will be repeated not earlier than one hour after receiving medication in clinic (“On” state).

The smartphone and wearable must be returned to the clinic in cases where the subject does not meet eligibility criteria, at the end of the study and upon early termination.

At the end of the study or at the time when the subject has completed the study, participants will be asked to complete a pen & paper satisfaction survey on how they experienced using the smartphone and wrist-based wearable during the study.

The full detailed digital biomarker is described in the ‘PD Digital Biomarker (Smartphone) Manual’.

Columbia−Suicide Severity Rating Scale (C-SSRS) (In-clinic)

The C-SSRS (Posner et al 2011) is an assessment tool used to assess the lifetime suicidality of a patient (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual/potential lethality. The “C-SSRS at Baseline” will be collected at baseline and the “C-SSRS since Last Visit” will be collected at subsequent visits.

The C-SSRS will be conducted at the time-points indicated in the SoA. The assessment will be completed by a certified C-SSRS rater after interviewing the participant at the visit.

4.6.1.10 Participant-Reported Outcomes

For a recommended order of assessments to be performed at each visit see Appendix 4.

PRO data will be elicited from the participant in this study to more fully characterize the clinical profile of the study drug. The PRO instruments, translated as required in the local language, will either be distributed by the Investigator staff and completed in their entirety by the participant at specified time‑points during the study (“In-clinic”), or participants will use an electronic device (“Smartphone”) to capture PRO questionnaire data.

To ensure instrument validity and that data standards meet Health Authority requirements, PRO questionnaires administered at the investigational site, should be self-administered prior to the administration of study treatment.

Entries should be reviewed for completeness by the site staff during the visit and the participant should be requested to complete any blank items. Changes to the form should not be made once the participant has left the site for that visit.

39-item Parkinson’s Disease Questionnaire (PDQ-39) (In-clinic)

The PDQ-39 is a 39-item, self-administered questionnaire with eight domains of: Mobility (10 items); Activities of daily living (ADL, 6 items); Emotional well-being (6 items); Stigma

(4 items); Social support (3 items); Cognitions (4 items); Communication (3 items); and Bodily discomfort (3 items) (Peto et al 1995). Questions ask about the frequency with which participants have experienced difficulties due to having PD “during the last month”. All items are scored from 0 (never) to 4 (always). Summary indices can be calculated for both the total scale and the subscales: the lower the index, the better the Health-Related Quality of Life. Each scale is transformed to have a range from 0 (best, i.e., no problem at all) through to 100 (worst, i.e., maximum level of problem) with each scale being calculated as follows: scale score = the total of the raw scores of each item in the scale divided by the maximum possible raw score of all the items in the scale multiplied by 100.

Patient Global Impression of Change (PGIC) (In-clinic)

The generic Global Impression is a measure commonly used in PD clinical trials to provide concise information on overall health state (Guy 1976). The change component is intended as a measure of change in health state and can be adapted for participant self-assessment (PGIC). A 7-point participant-based (PGIC) global impression of change will be employed.

PGIC: 1 = Very much improved; 2 = Much improved; 3 = Somewhat improved; 4 = No change; 5 = Somewhat worse; 6 = Much worse; 7 = Very much worse

Parkinson’s Disease Sleep Scale Revised Version (PDSS-2) (In-clinic)

The PDSS-2 is a 15-item, self-reported scale that asks about the frequency of various sleep and nocturnal disturbances, using a five-point response scale ranging from zero (never) to four (very frequent), with a total score ranging from zero (no disturbance) to 60 (maximum nocturnal disturbance) (Trenkwalder et al 2011). The scale can be divided into three different domains that reflect the complexity of sleep problems in PD:
1) nocturnal motor symptoms such as akinesia, early morning dystonia, tremor during waking period at night, periodic limb movements (PLM), restless behavior or immobility, and motor symptoms probably due to REM sleep behavior disorder (RBD);
2) PD-specific nocturnal symptoms like hallucinations, confusion states, pain, muscle cramps, difficulties in breathing with snoring, and immobility; and 3) sleep-specific disturbances like insomnia, sleep maintenance, unrestored sleep in the morning, getting up at night to pass urine, and the overall subjective quality of sleep.

Scales for Outcomes in Parkinson’s Disease Assessment of Autonomic Dysfunction (SCOPA-AUT) (In-clinic)

The Scales for Outcomes in Parkinson’s disease assessment of autonomic dysfunction (SCOPA-AUT) is a 25-item self-administered test developed to evaluate autonomic symptoms, such as gastrointestinal and urinary problems, in patients with PD (Visser et al 2004). Region scores of: gastrointestinal (seven items); urinary (six items); cardiovascular (three items); thermoregulatory (four items); pupillomotor (one item); and sexual (two items for men and two for women) problems can also be derived. Higher scores reflect worse autonomic functioning.

Hospital Anxiety and Depression Scale (HADS) (Smartphone)

The HADS is a 14-item self-rated scale yielding sub-scores for depression (7 items) and anxiety (7 items) (Snaith and Zigmond 2000).

Patient Assessment of Constipation Symptoms (PAC-SYM) Questionnaire (Smartphone)

The PAC-SYM is a 12-item self-report questionnaire subdivided in three symptom subscales (i.e., abdominal, stool, and rectal) (Frank et al 1999). The questionnaire asks about severity of symptoms in the past two weeks, using a five-point response scale from absent (0) to severe (4).

EuroQol EQ-5D-5L Questionnaire (Smartphone)

The EQ-5D-5L Questionnaire is a generic, preference-based health utility measure with questions about mobility, self‑care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the participant's health status. The EQ‑5D-5L Questionnaire will be utilized in this study for economic modelling.

Diary Questions (Smartphone)

A series of novel diary questions assessing aspects of insomnia, REM sleep behavior disorder, daytime somnolence, bowel movements, autonomic system functioning (i.e., swallowing, overproduction of saliva, urine retention, perspiration and sensitivity to heat). Patient Global Impression of Severity will also be assessed via the Smartphone. *Once available, participants will also be asked about reasons for not performing the active tests.*

4.6.1.11 Patient Engagement Application

The Smartphone Patient Engagement Application is an optional service that participants can opt-in to use to remind them of activities/tasks relevant to study compliance, e.g., attend study visits. The application also provides supportive guides to help participants to be aware of visit procedures, study information and instructions. Additional details are found in Appendix 5.

This application will no longer be used in Part 3.

4.6.1.12 Samples for Research Biosample Repository

Overview of the Research Biosample Repository

The Roche Research Biosample Repository (RBR) is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage and analysis of these specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future.

Specimens will be collected from participants who give specific consent to participate in this optional Research Biosample Repository. Collected specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site.

Sample Collection

The following samples will be collected for identification of dynamic (non-inherited) biomarkers:

- Residual CSF samples
- Plasma *and serum* samples
- Whole Blood for RNA extraction
- Residual Skin tissue material

The following samples will be collected for identification of genetic (inherited) biomarkers:

- Blood for DNA extraction
- The sample collected for DNA extraction may be used for whole genome sequencing (WGS) and other genetic analysis and may be sent to one or more laboratories for analysis.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For all samples, dates of consent and specimen collection should be recorded on the associated RBR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual.

RBR specimens will be stored and used until no longer needed or until they are exhausted. The Research Biosample Repository storage period will be in accordance with the IRB/EC‑approved Informed Consent Form and applicable laws (e.g., Health Authority requirements).

The repository specimens will be subject to the confidentiality standards (as described under Confidentiality and in Section 8.4.

Confidentiality

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local Health Authorities, and monitors, representatives, and collaborators, as appropriate.

Participant medical information associated with RBR specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data derived from RBR specimen analysis on individual participants will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Participants will not be identified by name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with investigators or participants unless required by law.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR specimen data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The Investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide optional RBR specimens. Participants who decline to participate will not provide a separate signature.

The Investigator should document whether or not the participant has given consent to participate by completing the RBR Sample Informed Consent eCRF.

In the event of death or loss of competence of a participant who is participating in the Research, the participant's specimens and data will continue to be used as part of the RBR.

Withdrawal from the Research Biosample Repository

Participants who give consent to provide specimens for the RBR have the right to withdraw their specimens at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her specimens, the Investigator must inform the Medical Monitor in writing of the participant's wishes using the RBR Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the Research Biosample Repository Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the trial is closed. A participant's withdrawal from Study BP39529 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a participant's withdrawal from the RBR does not constitute withdrawal from Study BP39529. Data already generated before time of withdrawal of consent to Research Biosample Repository will still be used.

Monitoring and Oversight

Specimens collected for the Research Biosample Repository will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Monitors and auditors will have direct access to appropriate parts of records relating to participant participation in Research Biosample Repository for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

4.6.2 Timing of Study Assessments

For a recommended sequence of assessments to be completed at each visit, see Appendix 4.

4.6.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study‑specific screening tests or evaluations. Informed Consent Forms for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site.

All screening and pre-treatment assessments must be completed and reviewed to confirm that participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

An Eligibility Screening Form (ESF) documenting the Investigator's assessment of each screened participant with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

Screening and pre-treatment assessments must be performed within up to 56 days prior to Baseline/Day 1. The screening period may be extended by a maximum of 14 days upon consultation with the Sponsor/Medical Monitor.

Participants may be allowed to be rescreened, once upon approval from the Sponsor, for the following reasons:

- In case of screen failure due to a transient abnormal laboratory or ECG result which is likely to normalize upon retesting or due to another reversible condition which does not compromise patient safety, screening can be repeated once with approval from the Sponsor.
- In case of screen failure due to a patient failed screening based on an inclusion/exclusion criterion which was updated in a protocol amendment, screening may be repeated if recruitment for the study is still ongoing.
- In case of screen failure due to logistical, personal, or technical reasons for participants otherwise eligible. These reasons may include but are not limited to temporary site closure, scheduling visit delays due to the participant's availability or delayed protocol-required central-read assessment results.

In case of rescreening, as a minimum, laboratory tests, physical examination and any screening tests which were not performed previously should be conducted. Repetition of other tests will require agreement between the Investigator and the Sponsor prior to rescreening. MRI, DaT-SPECT, skin biopsy and lumbar puncture will not be repeated.

4.6.2.2 Assessments during Treatment

Under no circumstances will participants who enroll in this study and have completed treatment as specified or withdraw from the study prematurely, be permitted to be allocated a new randomization number and re-enroll in the study.

All assessments must be performed as per SoA (see Appendix 1, Appendix 2 *and Appendix 3*). Assessments scheduled on the day of study treatment administration should be performed prior to the administration, unless otherwise noted in the SoA.

4.6.2.3 Assessments Prior to Start of Dopaminergic/Symptomatic PD Treatment

Participants who plan to start symptomatic treatment for PD (see Sections 4.5.2.1 and 4.5.3) should complete the "prior to start of dopaminergic treatment" visit assessments (see Appendix 1, Appendix 2 *and Appendix 3* for details), prior to the start of such treatment. Participants may continue in the study at their normal study visits.

4.6.2.4 Assessments at Study Completion/Early Termination Visit

Participants who complete the *first two parts of the* study (defined as completion of Week 104 visit) will be asked to return to the clinic 12 weeks ± 7 days after the last dose of study treatment for a follow-up visit.

Participants who complete the all-on-treatment 5-year extension (defined as completion of Part 3 Week 260 visit) will be asked to return to the clinic 12 weeks ± 7 days after the last dose of study treatment for the Part 3 follow-up visit.

Participants who discontinue from the study early should complete the Early Termination assessments and return to the clinic 12 weeks ± 7 days after the last dose of study treatment for the follow-up visit *if they discontinue from Part 1 or Part 2 or for Part 3 follow-up visit if they discontinue early from Part 3*.

12-Week Treatment-free Follow-Up Assessments

After the treatment period is completed or participant withdraws from the study, the 12-week treatment-free follow-up assessments provided in the SoA should be completed.

After the study completion/early termination visit, adverse events should be followed as outlined in Sections 5.5 and 5.6.

4.6.2.5 Assessments at Unscheduled Visits

Assessments at unscheduled visits are based on the medical need of the patient. Assessments that are conducted at regular scheduled visits can be conducted at unscheduled visits at the discretion of the Investigator.

4.7 PARTICIPANT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to close and replace (if required) a site at any time. Reasons may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice

4.7.2 Participant Discontinuation

The Investigator has the right to discontinue a participant from study treatment or withdraw a participant from the study at any time. In addition, participants have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason. Reasons for discontinuation of study treatment or withdrawal from the study may include, but are not limited to, the following*:*

- Participant withdrawal of consent at any time
- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the participant
- Participant non-compliance

4.7.2.1 Discontinuation from Study Treatment

Participant must discontinue study treatment if they experience any of the following:

- Pregnancy

Participants who discontinue study treatment prematurely will be asked to return to the clinic for an early termination visit (see Section 4.6.2.4) and may undergo follow-up assessments (Section 4.6.2.4). The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

4.7.2.2 Withdrawal from Study

Every effort should be made to obtain information on participants who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

Participants will not be followed for any reason after consent has been withdrawn.

When a participant voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless participant specifically requests for these to be discarded or local laws require their immediate destruction. A participant's withdrawal from Study BP39529 does not, by itself, constitute withdrawal of specimens donated to the Research Biosample Repository.

Participants who withdraw from the study for safety or for any other reason after receiving the first dose will not be replaced.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol‑specified safety laboratory assessments; measurement of protocol-specified vital signs, ECGs, MRIs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.1.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.8.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X‑ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

5.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death).
- Life-threatening (i.e., the adverse event, in the view of the Investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10).
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Significant medical event in the Investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a pre-defined grading criteria (e.g., NCI CTCAE criteria; see Table 2 and Table 3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.1.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6.

- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.1.4 Selected Adverse Events

Additional data will be collected for the following selected adverse events:

- Infusion-Related Reactions

  Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., “infusion-related reaction”) on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF.

5.2 SAFETY PLAN

5.2.1 Management of Specific Adverse Events

Infusion-related reactions (IRRs) have been reported with the use of biologic therapies, such as RO7046015. IRRs are usually reported with the first or second infusion of a therapeutic monoclonal antibody and tend to be dose-related. Such reactions typically occur during or shortly after an infusion or within 24 hours after study drug infusion. IRR symptoms may be indistinguishable from a Type 1 hypersensitivity reaction (i.e., flushing, rash, respiratory difficulty, hypotension, tachycardia); however, hypersensitivity reactions (IgE-mediated) generally do not occur with the first exposure to a biologic therapy.

Specific management steps for IRRs and hypersensitivity reactions of different severity are provided in Table 1. The participant should be monitored until complete resolution of the symptoms and treated as clinically indicated.

Table 1 Guidelines for Managing IRRs

Event	Action to Be Taken
Infusion-related reaction Grade 1	Stop or slow down study drug infusion to 50% of the initial rate. Assess vital signs. Clinical observation for improvement/resolution of symptoms. No treatment is needed. Participant may remain in the study.
Infusion-related reaction Grade 2	Stop study drug infusion. Perform serial vital signs assessment every 15 minutes, supportive therapy (fluids [Normal Saline or Lactated Ringers], supplemental oxygen, diphenhydramine 25 – 50mg PO or IV Q6h for rash, acetaminophen 650 mg PO [or minimum recommended adult dose of paracetamol]) Q6h. ADA and PK levels should be drawn if the event starts during the visit. If symptoms resolve completely during the visit, infusion may resume at 50% of the previous infusion rate. Participant may remain in the study and receive pre-medications of an antihistamine (loratadine 10 mg PO OR diphenhydramine 25 – 50 mg as well as acetaminophen 650 mg [or minimum recommended adult dose of paracetamol] PO 30 – 60 minutes prior to subsequent doses, as per Principal Investigator's [PI's] discretion).
Infusion-related reaction Grade 3	Stop study drug infusion. Perform serial vital signs assessment as dictated by the patient's clinical symptoms, supportive therapy (fluids [Normal Saline or Lactated Ringers], supplemental oxygen, diphenhydramine 25 – 50mg PO or IV for rash, acetaminophen 650 mg PO [or minimum recommended adult dose of paracetamol], methylprednisolone 125 mg IV). Labs: Tryptase, cytokine panel, C3a, C5a within 3 hours of the event and to be repeated in 48 – 72 hours post event. ADA and PK levels should be drawn if the event starts during the visit and/or patient is hospitalized. Overnight inpatient observation per discretion of the PI. Future dosing plans can only be determined after the PI has had a discussion with the participant and Sponsor.
Infusion-related reaction Grade 4	Stop study drug infusion. Perform serial vital signs assessment every 5 minutes, supportive therapy (fluids [Normal Saline or Lactated Ringers], supplemental oxygen/ intubation and ventilatory support, diphenhydramine 25 – 50 mg PO or IV for rash, acetaminophen 650 mg PO [or minimum recommended adult dose of paracetamol], methylprednisolone 125 mg IV). Labs: tryptase, cytokine panel, C3a, C5a within 3 hours of the event and to be repeated in 48 – 72 hours post event. ADA and PK levels should be drawn. Discontinue patient from the study. Hospitalization for further evaluation and treatment.

Table 1 Guidelines for Managing IRRs (cont.)

Event	Action to Be Taken
Anaphylaxis	Stop study drug infusion. Assess vital signs every 5 minutes. Administer IV fluids (Normal saline or Lactated Ringers), supplemental oxygen/ventilatory support, for systemic symptoms (angioedema, bronchospasm) epinephrine 1:1000, 0.3 mL subcutaneous (may be repeated in 20 minutes; in patients on beta blockers, glucagon administration may be needed), diphenhydramine 25 – 50 mg IV, methylprednisolone 125 mg IV). Labs: tryptase, cytokine panel, C3a, C5a within 3 hours of the event and to be repeated in 48 – 72 hours post-event. Discontinue patient from the study. ADA and PK levels should be drawn. Hospitalization for further observation and treatment. See Lieberman et al 2015 for anaphylaxis guidance.

Figure 2 describes the process for the overall evaluation of AEs to determine whether an AE is an IRR.

Figure 2 Evaluation and Reporting of Infusion Related Reactions (IRR)

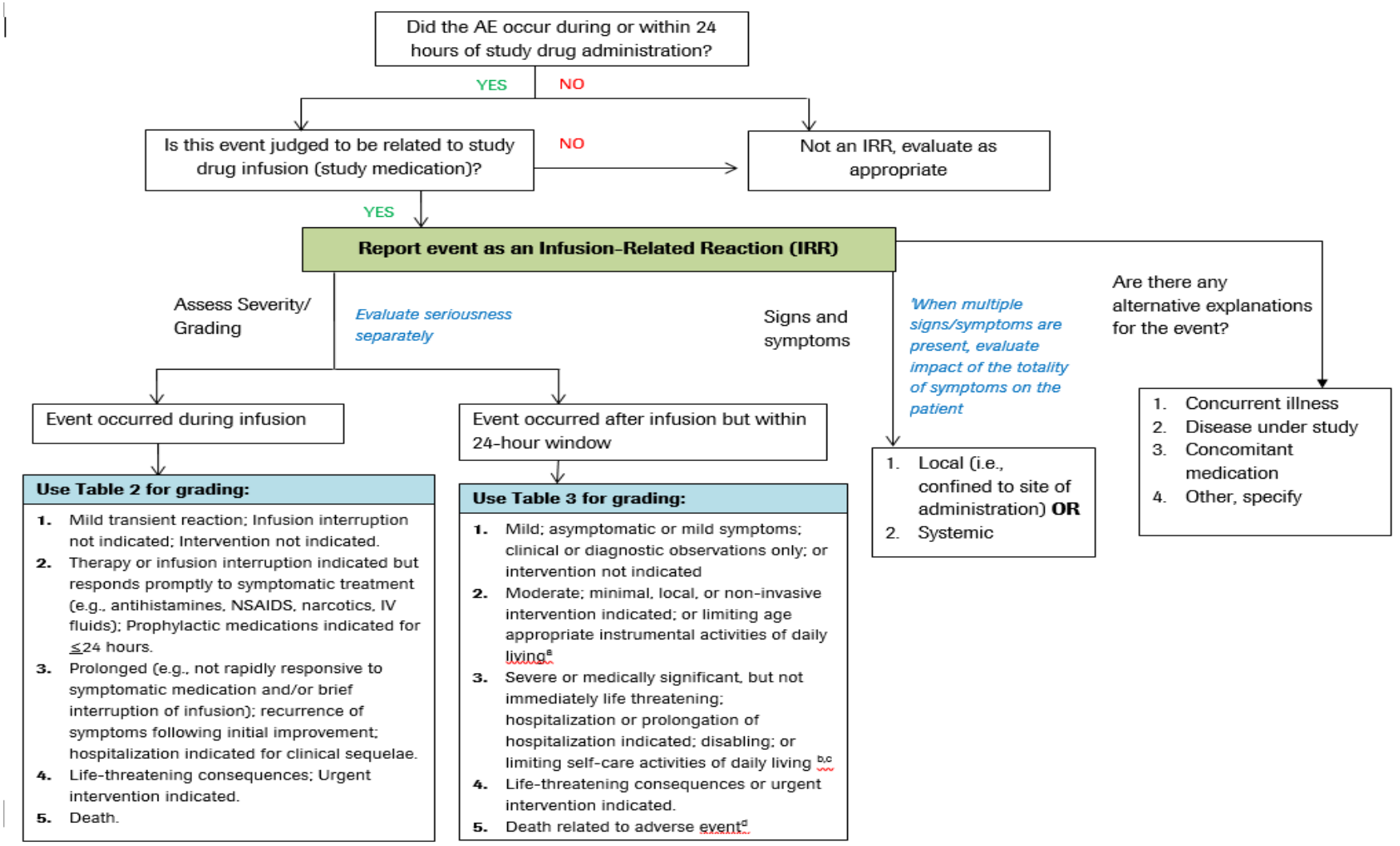


Figure 2 Evaluation and Reporting of Infusion Related Reactions (IRR) (cont.)

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v4.03), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

a Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

c If an event is assessed as a "significant medical event," it must be reported as a serious adverse event.

d Grade 4 and 5 events must be reported as serious adverse events.

The following guidelines are recommended for IRR grading:

- For IRRs with onset during the infusion, refer to Table 2 - Infusion Related Reaction Grading
- For IRRs with onset within 24-hours after the end of the infusion, refer to Table 3 - Adverse Event Severity Grading

Table 2 Infusion-Related Reaction Grading

Grade	Infusion-Related Reaction
1	Mild transient reaction; Infusion interruption not indicated; Intervention not indicated.
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); Prophylactic medications indicated for ≤24 hours.
3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.
4	Life-threatening consequences; Urgent intervention indicated.
5	Death.

Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v4.03), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all adverse events (see Section 5.1.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4-5.6.

For each adverse event recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the participant's medical record. Adverse events will then be reported on the Adverse Event eCRF as follows:

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies). Any other adverse event should not be reported.

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 12 weeks after the last dose of study drug.

After a period of 12 weeks from the last dose of study drug, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time-points. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 3 provides guidance for assessing adverse event severity.

Table 3 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the NCI CTCAE (v4.03), which can be found at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.1.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.1.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction or discontinuation of study drug
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions (IRRs)

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g. “infusion-related reaction”) on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated Infusion related-reaction eCRF.

Other Adverse Events

For adverse events other than IRRs (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time-points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation time-points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal (ULN) associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term “sudden death” should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.5.9 Lack of Efficacy or Worsening of Parkinson’s Disease

Medical occurrences or symptoms of deterioration that are anticipated as part of PD progression will generally be recorded by means of the efficacy assessment (MDS-UPDRS).

If judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature of PD at any time during the study, it would then be important to report an unanticipated worsening of PD as an Adverse Event eCRF and convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated PD”).

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.3.5.10), except as outlined below.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of a disease.
  - The participant has not suffered an adverse event

5.3.5.11 Overdoses and Medication Errors

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. Medication error is the accidental deviation in the administration of a drug. In some cases, a medication error may be intercepted prior to administration of the drug.

An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data. However, if any patient responses suggestive of a possible adverse event are identified during site review of the PRO questionnaires, site staff will alert the Investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment in the participant's medical record per site practice. If the event meets the criteria for an adverse event, it will be reported on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events
- Non-serious adverse events of special interest

- Pregnancies

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local Health Authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical monitors is available 24 hours a day 7 days a week. Medical monitors' contact details will be available on a separate list generated by the study management team.

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the SAE Responsible immediately (i.e., no more than 24 hours after learning of the event).

5.4.2.2 Events That Occur after Study Drug Initiation

For reports of serious adverse events and non-serious adverse events of special interest (see Sections 5.1.2 and 5.1.3) that occur after initiation of study treatment, investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Serious Adverse Event / Adverse Event of Special Interest eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the SAE Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Participants

Female participants of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 12 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Pregnancy should not be recorded on the Adverse Event eCRF. The Investigator should discontinue RO7046015 and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy.

5.4.3.2 Pregnancies in Female Partners of Male Participants

Male participants will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 12 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the Investigator will update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Any induced abortion due to maternal toxicity and/or embryo-fetal toxicity should also be classified as serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Elective abortion not associated with toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female participant or female partner of a male participant exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The Investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 5.4.2.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Investigator is not required to actively monitor participants for adverse events after the end of the adverse event reporting period (defined as 12 weeks after the last dose of study treatment).

If the Investigator becomes aware of any other serious adverse event occurring after the end of the adverse event reporting period, if the event is believed to be related to prior study treatment, the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- RO7046015 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

A sample size of 100 randomized participants per group (300 participants for the three groups) has been chosen to obtain a power of approximately 80% at two-sided α-level of 20% (which corresponds to a one-sided α-level of 10%) for the pairwise comparison of each active dose arm to placebo. The power calculation was based on simulations of the mixed-effect model repeated measures (MMRM) analysis planned for the primary efficacy variable. Assessments performed while on any symptomatic treatment started after randomization will not be included in the analysis. The following assumptions were made for simulating the data:

- Seven post-baseline assessment visits,
- An overall rate of missing values (due to participants starting symptomatic therapy or prematurely withdrawing from study medication during the 52-week placebo-controlled treatment period) of 25% in the placebo group and 20% in each dose group at Week 52, with incremental rates over the 52-week placebo-controlled period
- A linear mean increase of the primary endpoint (natural progression) of eight points/year for the placebo arm, with a linearly increasing common standard deviation reaching nine points at Week 52
- An effect size of 0.33 (difference = 3 points, relative reduction of progression = 37.5%) for one dose group versus placebo at Week 52 with increasing magnitude of treatment difference over the placebo-controlled period

- A compound symmetry correlation structure assuming a correlation coefficient of 0.55 between different visits.

Table 4 provides the additional information needed to perform the simulations.

Table 4 Assumptions Used for Simulations

Post-Baseline Visit (weeks)	8	16	24	32	40	48	52
Change from baseline in MDS-UPDRS total, placebo arm (points)	1.2	2.4	4	4.8	6	7.2	8
Change from baseline in MDS-UPDRS total, active treatment arm (points)	0.8	1.5	2.5	3.0	3.8	4.5	5
Common standard deviation for change from baseline in MDS UPDRS total (points)	6.75	7.25	7.75	8	8.5	8.75	9
Percentage of patients with non-evaluable data, placebo*	1%	3%	5%	7%	17%	22%	25%
Percentage of patients with non-evaluable data, treatment*	1%	3%	5%	7%	12%	17%	20%

*Includes data from patients that prematurely dropped out from the study and/or started symptomatic therapy after randomization.

The assumptions on progression, variability, dropout rate and likelihood to start symptomatic therapy within the first 52 weeks of treatment, with or without a MAO-B inhibitor as background therapy, were derived from analyses based on the PPMI database (Marek et al 2011, Simuni et al 2015) and various sources of information from the literature.

The sample size of 100 patients per arm also provides 76% power ($\alpha = 20\%$, two-sided or $\alpha = 10\%$, one-sided) to demonstrate a 37.5% reduction (effect size = 0.318 based on assumption of decline over 52 weeks of 0.157 for the placebo arm and standard deviation of 0.185 derived from the PPMI database) for the key secondary endpoint, the DaT-SPECT signal loss at Week 52, for the pairwise comparison of each active dose arm to placebo. The missing values assumption used was 15% and included participants who withdrew from study medication before Week 52 or who did not have a valid DaT-SPECT assessment at Week 52. Assessments performed while on any symptomatic treatment started after randomization will not be excluded from the analysis.

No adjustments for multiple comparisons were incorporated into the analyses.

The sample size may be adjusted depending on the outcome of the iDMC review performed during the study. If the enrollment to the high dose is stopped and a new dose is introduced as advised by the iDMC, the Sponsor may propose the enrolment of (up to) an additional 20% of patients, see Section 3.1.2.1. The aim of this increase in sample size would be to ensure a power of approximately 80% at two-sided α-level of 20% (corresponding to a one-sided α-level of 10%) for the pairwise comparison of the new dose arm to the placebo group consisting of participants randomized after the decision to include the new dose arm.

The sample size may also be adjusted if the initial assumptions on dropout rate and likelihood to start dopaminergic therapy as described in Table 4 are different from the actual values observed. If that is the case, the Sponsor may increase enrolment up to 20% of the total sample size. The aim of this increase in sample size is to ensure that the pairwise comparison of each active dose arm to placebo remains adequately powered.

6.2 SUMMARIES OF CONDUCT OF STUDY

To determine whether the integrity of the study was maintained, listings/summaries of data referring to the general conduct of the study (such as enrollment, protocol violations, use of prohibited co-medication, blinding details) will be generated.

6.3 ANALYSIS POPULATIONS

6.3.1 Safety Analysis Population

All randomized participants receiving any amount of the study drug will be included in the safety analysis. Patients who received any randomized treatment other than that to which they were randomized will be analyzed according to the treatment actually received.

6.3.2 Efficacy Analysis Populations

The modified intent-to-treat (mITT) population is defined as consisting of all participants randomized, who received any amount of the study treatment, participants will be grouped according to which treatment they were randomized.

6.3.3 Immunogenicity Analysis Population

Participants who had at least one pre-dose and one post-dose ADA assessment will be included and analyzed according to the RO7046015 dose they actually received. Only samples from RO7046015-treated participants will be analyzed (see Section 4.6.1.7).

6.3.4 Pharmacokinetic Analysis Population

All participants providing pharmacokinetic data will be included in the PK Analysis Population. Subjects may be excluded from the PK Analysis Population if, for example, data are unavailable or incomplete which may influence the pharmacokinetic analysis. This will be precisely defined in the statistical analysis plan. Excluded cases will be documented together with the reason for exclusion.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographics, baseline characteristics and all baseline laboratory values will be summarized descriptively by treatment using frequency tables and summary statistics as appropriate.

Baseline assessments will be defined in the Statistical Analysis Plan.

6.5 SAFETY ANALYSES

All safety analyses will be based on the safety analysis population, defined in Section 6.3.1.

As appropriate, listings, summary tables and graphs will be provided for safety and tolerability assessments, including:

- Incidence of AEs (overall, by intensity and by relationship to study medication).
- Incidence of SAEs.
- Incidence of laboratory abnormalities (including hematology, clinical chemistry, coagulation, and urinalysis parameters).
- Incidence of BP abnormalities.
- Incidence of ECG abnormalities (including changes from baseline).
- Incidence of MRI abnormalities (changes from baseline only).
- Incidence of ADAs.
- C-SSRS (per visit).

Further details on the safety parameters are given in Section 5.1. Safety data will be summarized using descriptive statistics.

6.5.1 Adverse Events

The original terms recorded on the eCRF by the Investigator for adverse events will be standardized by the Sponsor.

Adverse events will be summarized by mapped term and appropriate thesaurus level.

6.5.2 Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Participant listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing.

Laboratory test values will be presented by individual listings with flagging of values outside the normal ranges.

6.5.2.1 Standard Reference Ranges and Transformation of Data

Roche standard reference ranges, rather than the reference ranges of the investigator, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of investigator ranges, e.g., enzyme tests that include AST, ALT, and alkaline phosphatase and total bilirubin. Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

6.5.2.2 Definition of Laboratory Abnormalities

For all laboratory parameters included, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in patient listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for each laboratory parameter. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a patient, the midpoint of the standard reference range will be used as the Patient's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the patient listings as "HH" for very high or "LL" for very low.

6.5.3 Vital Signs

Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities (these will be precisely defined in the statistical analysis plan). In addition, tabular summaries will be used, as appropriate.

6.5.4 ECG Data Analysis

ECG data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities (these will be precisely defined in the statistical analysis plan). In addition, tabular summaries will be used, as appropriate.

The standard deviation of the RR interval for the individual participant may be assessed as an exploratory endpoint, as studies (unpublished data) have reported signs of autonomic dysfunction in patients with PD. This may be a potential prodromal marker or marker of a subtype of PD.

6.5.5 Concomitant Medications

The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by assigning preferred terms.

Concomitant medications will be presented in summary tables and listings.

6.6 EFFICACY ANALYSES

The primary analysis population for all efficacy analyses will be based on the modified ITT population, as defined in Section 6.3.2.

Analyses of efficacy endpoints (primary, secondary, and exploratory) will include the following covariates in the model:

- Treatment: placebo, RO7046015 high dose (4500 mg and 3500 mg) and RO7046015 low dose (1500 mg).
- Background therapy at baseline (MAO-B inhibitor treatment): Yes or No.
- Age group: < 60 years vs ≥ 60 years.
- Sex: male or female.
- DaT-SPECT ipsilateral (to the clinically dominant side) putamen binding ratio at baseline.

For each continuous endpoint the baseline of the endpoint will also be included in the model.

In addition to the analyses described in Sections 6.6.1 and 6.6.2, the following analyses will be performed for the primary efficacy endpoint and secondary efficacy endpoints, respectively. Additional details of these analyses will be described in the statistical analysis plan:

- Sensitivity analyses to evaluate the robustness of results to the primary analysis methods:
  - The analysis of the primary endpoint (change in MDS-UPDRS total score) and change in MoCA will be repeated including only patients who completed Part 1 without starting symptomatic PD treatment

- The analysis of the primary endpoint of MDS-UPDRS total score (sum of Parts I, II, and III) will also be repeated using a baseline value calculated for each patient as the average of pre-treatment values of the MDS-UPDRS total score (sum of Parts I, II, and III), as the average of screening and Day 1 values). (The primary endpoint and the MoCA will be re-analyzed by only including patients who completed Part 1 without starting symptomatic PD treatment; the primary endpoint of MDS-UPDRS total score (sum of Parts I, II, and III) will be re-analyzed by calculating for each patient the baseline value as the average of pre-treatment values of the MDS-UPDRS total score (sum of Parts I, II, and III), i.e. the average of screening and Day 1)

- Subgroup analyses to evaluate the consistency of results across pre-specified subgroups:
  - MAO-B Inhibitors at baseline (yes vs. no)
  - Hoehn &Yahr stage (1 vs. 2),
  - REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) (RBDSQ < 5 vs ≥ 5),
  - Alpha-synuclein pathology in peripheral nerves from skin biopsies (positive vs. negative)
  - DaT-SPECT (very abnormal vs. abnormal).
  - Data-driven sub-phenotypes (diffuse malignant vs. mild motor-predominant vs. intermediate)

    For the derivations of the data-driven sub-phenotypes, scales are classified into motor and non-motor. The motor scales are UPDRS-Part II (Motor symptoms) and UPDRS-Part III (Motor signs). The non-motor scales are SCOPA-AUT, RDBSQ and MOCA. After each one of the scales have been divided into percentiles, the data-driven sub-phenotypes are defined as follows:

    - Diffuse malignant: either motor score greater than the 75th percentile AND at least 1 non-motor score greater than the 75th percentile OR all 3 non-motor scores greater than the 75th percentile
    - Mild motor-predominant: Motor and all non-motor scores less than the 75th percentile
    - Intermediate: All those individuals not meeting criteria for other subtypes

The efficacy analyses will include all enrolled patients and will be presented separately for Part 1, Part 2, and Part 3 of the study. All additional statistical details for the efficacy analyses will be documented in the Statistical Analysis Plan (SAP).

6.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in total MDS-UPDRS (sum of Parts I, II and III) from baseline to Week 52 (end of Part 1 of the study).

The primary efficacy endpoint will be analyzed using a MMRM with the covariates described in Section 6.6 and visit (seven levels) as fixed effects, treatment-by-visit interaction term, and the baseline value for total MDS-UPDRS (sum of Parts I, II and III) as a covariate; an interaction term between baseline MDS-UPDRS by visit will also be included. Within each participant, the model will incorporate an unstructured variance-covariance matrix for the random error terms. Observations from different participants are considered independent. For each active dose arm tested at the final analysis, this model will be used to test the null hypothesis of no treatment difference between the placebo arm and each active arm at a two-sided α-level of 20%, which corresponds to a one-sided α-level of 10%.

Starting symptomatic PD treatment for the statistical analysis is defined as starting COMT inhibitors (entacapone, tolcapone), amantadine, anticholinergics, levodopa, dopamine agonists, or MAOB inhibitors and - for patients already on MAO-B inhibitors at baseline - also increases in dose or regimen of the MAOB inhibitor. Assessments performed after starting symptomatic PD treatment will not be included in the primary analysis.

Missing values will be handled via the MMRM methodology.

The primary endpoint will also be summarized using descriptive statistics.

6.6.2 Secondary Efficacy Endpoints

For the endpoints of MDS-UPDRS Part IA, Part IB, Part I total, Part II total, Part III total, and Part III subscores, CGI-I, and PGI-C the information collected after symptomatic PD treatment or after an increase in MAO-B inhibitor therapy will be handled as in the primary analysis. The analysis of all other secondary endpoints will include all the information available regardless of start of symptomatic PD treatment.

An important biomarker secondary endpoint is the change (between baseline and the Week 52 visit) in DaT-SPECT uptake values in the ipsilateral putamen, which will be analyzed via an analysis of covariance (ANCOVA), regardless of intake of symptomatic PD therapy during the first 52 weeks. The model will include the covariates described in Section 6.6 as main effects. There will be no imputation for missing values.

Other secondary endpoints, which will also be analyzed at the end of Part 1 (after 52 weeks of treatment with either placebo or active treatment) include:

- Change in MDS-UPDRS sub-scores from baseline to Week 52 for Part IA, Part IB, Part I total, Part II total, Part III total, and Part III subscores (bradykinesia, resting tremor and axial symptoms) analyzed with exactly the same MMRM approach as for the primary endpoint.
- Change in MoCA total score from baseline to Week 52 analyzed with an analysis of covariance (ANCOVA).

- CGI-I will be analyzed using a logistic regression model, including the covariates described in Section 6.6.
- PGI-C will be analyzed using a logistic regression model, including the covariates described in Section 6.6.
- Change in Schwab and England Activities of Daily Living (SE-ADL) from baseline to Week 52 will be analyzed with ANCOVA.
- Time to first occurrence of either of the following: $\geq$ 3 points change from baseline in MDS-UPDRS Part I, or $\geq$ 3 points change from baseline in MDS-UPDRS Part II will be analyzed with a Cox proportional hazards model including the covariates described in Section 6.6, along with a Kaplan-Meier plot.
- Time to start of dopaminergic (levodopa or dopamine agonists) treatment will be analyzed with a Cox proportional hazards model including the covariates described in Section 6.6, along with a Kaplan-Meier plot. Events in this analysis will only consider the start of levodopa or dopamine agonist.

All secondary endpoints will also be summarized using descriptive statistics.

6.7 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Non-linear mixed effects modelling (with software NONMEM [Beal and Sheiner 1998]) will be used to analyze the sparse sampling dose-concentration-time data of RO7046015. Population and individual pharmacokinetic parameters (e.g., CL and central volume) will be estimated and the influence of various covariates (such as age, sex and body weight) on these parameters will be investigated. The data collected during the study will be pooled with data collected in the previous Phase I studies conducted in healthy volunteers and patients with PD. Secondary PK parameters such as AUC, C_{max} and C_{trough} at steady state will be derived from the individual post-hoc predictions.

Graphical exploration of the relationship between RO7046015 concentrations and MDS-UPDRS Total Score (sum of Parts I, II and III), other selected clinical endpoints, biomarkers and safety endpoints will be performed. If indicated by such exploration, more formal analyses of the PK/PD relationship using non-linear mixed effects modelling method will be undertaken.

In-house analysis to build a disease progression model was performed using the PPMI MDS-UPDRS Total Score (sum of Parts I, II and III). This model will serve as the basis for the development of the disease progression model using placebo data. Potential disease-modifying effect of RO7046015 will be explored. For the investigation of the drug effect, classical hierarchical PK/PD models like linear, E_{max} or sigmoidal E_{max} models will be tested. The possibility of a delay between the time-course of exposure and effects will be investigated using indirect pharmacodynamic models or using an effect compartment.

Details of the modelling analyses will be described in a Modelling and Simulation Analysis Plan. The results will be reported in a document separate from the clinical study report.

6.8 EXPLORATORY ANALYSES

The exploratory analysis may be done for the outcome measures described in Section 3.3.4.

If applicable, exploratory endpoints may be analyzed with the following methods:

- Continuous endpoints via ANCOVA and/or MMRM.
- Time-to-event data via Kaplan-Meier Plot and Cox proportional hazards model.
- Ordered categorical data (e.g., individual MDS-UPDRS items) via Wilcoxon rank sum test.
- Binary data (such as responder analyses) via logistic regression.

In addition the following exploratory analysis may also be done:

- Slope analyses comparing treatment groups (e.g., placebo – high-dose vs high dose – high dose) within Part 2 in order to explore the disease-modifying effect of the drug.
- MDS-UPDRS total at Week 52 analyzed via a disease-modelling approach (e.g., Holford) with parametrization accounting for possible symptomatic and disease modifying effect of the drug.
- Pooled active treatment doses compared to placebo.
- Relation between alpha-synuclein pathology assessed by the skin biopsy results and DaT-SPECT (both randomized and screen failures).
- Random coefficients model for the analysis of dBM endpoints.

The exploration of a disease model analysis to identify a potential disease modifying effect is described in Section 6.7.

Item response theory (IRT) can permit a more precise analysis by integrating the whole available items information and increase the probability to detect changes due to a drug effect (Ueckert 2014). Therefore, IRT has the potential to increase the sensitivity for assessing effects using the composite endpoint MDS-UPDRS and to detect a drug effect acting on the disease progression.

A baseline IRT model was built to analyze the baseline data in de novo patients from the PPMI database (Buatois et al 2015, Buatois et al 2016). It will be combined with longitudinal models for placebo and drug effect for which parameters will be estimated using the RO7046015 data.

The results of the IRT analysis will be reported in a document separate from the clinical study report.

6.9 EFFICACY INTERIM ANALYSES

An efficacy interim analysis may be conducted as described in Section 3.1.2.2.

In addition to the primary analysis performed at Week 52, the Sponsor may choose to conduct additional interim efficacy analyses during Part 2 and/or Part 3 of the trial. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Sites will be responsible for data entry into the Electronic Data Capture (EDC) system.

A comprehensive validation check program will verify the data. Discrepancies will be generated automatically in the system at the point of entry or added manually for resolution by the investigator or the Monitors.

The Sponsor will produce a Data Handling Manual and Data Management Plan that describes the quality checking to be performed on the data. Central laboratory data and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

Data for this study will be captured via an on line EDC system. The data collected in the source documents is entered onto the study eCRF. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. For each participant screened and enrolled or not, an eCRF must be completed and electronically signed by the Principal Investigator or authorized delegate from the study staff. If a participant withdraws from the study, the reason must be noted on the eCRF. If a participant is withdrawn from the study because of a treatment‑limiting adverse event, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

At the end of the study, the Investigator will receive participant data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 DIGITAL BIOMARKER DATA

During “Active Tests” and “Passive Monitoring”, the phone and wrist-worn wearable record movement and location data. Data on the technical status of the devices is also recorded. Participants can choose to pause location data recording. No patient identifiable information is stored on the devices. For selected “Active Test” tasks, touch and sound is also recorded. Video is not recorded.

Digital Biomarker Data are encrypted and uploaded to secure servers whenever the phone is connected to WIFI. If participants have a WIFI network at home, they are encouraged to connect their smartphone to enable data transfer. If no WIFI network is available, the sensor data will be transferred during site visits or after the devices have been returned.

All Digital Biomarker data will be managed by the Sponsor who will monitor and ensure the integrity and quality of the acquired data. This includes but is not limited to the analysis of sensor data together with basic demographic data (such as sex, year of birth, weight, height) and MDS-UPDRS data.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with Health Authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local Health Authorities, whichever is longer. After that period of time, the documents may be destroyed, according to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Audio files collected as part of digital Biomarker assessments will be retained for the full retention period of at least 15 years.

Video files collected for MDS-UPDRS will also be retained for the full retention period of at least 15 years.

For countries where ethics committees or the Ministry of Health will not approve audio/video recording of participant interviews, review of the scale worksheets, submitted as part of the assessment source information, will be performed to verify accuracy of scoring and adherence to study conventions.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC‑approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to take part. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes.

Participants must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the participant or the participant's legally authorized representative. All signed and dated Consent Forms must remain in each participant's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include participant authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for participant authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the participant, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, Investigators must comply with requirements for reporting serious adverse events to the local Health Authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each participant enrolled in the study through assignment of a unique participant identification number. This means that participant names are not included in data sets that are transmitted to any Sponsor location.

Participant medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local Health Authorities, monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (i.e., Last Participant Last Follow-Up Visit).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the Investigator will receive the participant data, which includes an audit trail containing a complete record of all changes to data.

Roche shall also submit a Development Safety Update Report (DSUR) once a year to the IEC and Competent Authorities according to local regulatory requirements and timelines of each country participating in the study.

It is the understanding of the Sponsor that this protocol (and any modifications) as well as appropriate consent procedures and advertisements, will be reviewed and approved by an Institutional Review Board (IRB). This board must operate in accordance with the current Federal Regulations. The Sponsor will be sent a letter or certificate of approval prior to initiation of the study, and also whenever subsequent amendments/modifications are made to the protocol. Roche shall also submit an IND Annual Report to FDA according to local regulatory requirements and timelines.

9.2 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The Investigator will permit national and local Health Authorities, monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

The Sponsor of the trial is F. Hoffmann – La Roche Ltd. The Sponsor is responsible for the study management, data management, statistical analysis and medical writing for the clinical study report.

A Contract Research Organization (CRO) will be responsible for the feasibility activities, countries and site management as well of other operational activities as appropriate. Medical Monitoring activities may be split between the Sponsor and the CRO.

An IxRS will be used to register the screening/screening failures, enrolment, drug allocation, withdrawal, early discontinuation, study completion of the participants.

A central laboratory will be used to provide sample kits to all sites and collect samples for the assessments listed in Section 4.6.1.5.

Specific external laboratories will be used to analyze the CSF samples, skin biopsies, PK samples and optional blood samples.

A central ECG company will provide all sites with ECG equipment and will collect ECGs electronically or on paper where required. The ECGs will be reviewed for safety purposes by this company.

Central imaging companies will collect the MRI and DaT-SPECT scans and analyze them as per the study defined requirements (see Section 4.6.1.9).

An external company and external consultants will provide training to all site raters on the various scales and will provide all sites with the relevant record forms, instruction manuals and kits as appropriate.

All other training, data acquisition and handling will be conducted by the Sponsor.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any substantial protocol amendments will be prepared by the Sponsor. Substantial protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or any non-substantial changes, as defined by regulatory requirements.

10. REFERENCES

Alsop DC, Detre JA, Golay X, et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. MRI in Medicine. 2015;73:102–116.

Beach TG, Adler CH, Lue L, et al. Arizona Parkinson's Disease Consortium. Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. Acta Neuropathol. 2009;117:613-634.

Beal S, Sheiner L (Eds.). NONMEM Users Guides, NONMEM Project Group, University of California at San Francisco, San Francisco. 1998.

Bhidayasiri R, Reichmann H. Different diagnostic criteria for Parkinson disease: What are the pitfalls? J Neural Transm. 2013;120:619–625.

Braak H, Del Tredici K, Rüb U, et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24:197-211.

Buatois S, Retout S, Gieschke R, et al. Using Item response theory to yield information from the MDS-UPDRS items in Parkinson's disease clinical trials. Page Meeting 2015 Website: http://www.page-meeting.org/?abstract=3417.

Buatois S, Retout S, Frey N, et al. Utilizing the items from the MDS-UPDRS score to increase drug effect detection power in de novo idiopathic Parkinson's disease patients. Page Meeting 2016 Website: http://www.page-meeting.org/default.asp?abstract=5865.

Burke RE, O'Malley K. Axon degeneration in Parkinson's disease. Exp Neurol. 2013;246:72-83.

de la Fuente-Fernández R, Schulzer M, Kuramoto L, et al. Age-specific progression of nigrostriatal dysfunction in Parkinson's disease. Ann Neurol. 2011 May;69(5):803-810.

de Lau LM, Schipper CM, Hofman A, et al. Prognosis of Parkinson disease: risk of dementia and mortality: the Rotterdam Study. Arch Neurol. 2005;62:1265-1269.

Dickson DW, Braak H, Duda JE, et al. Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria. Lancet Neurol. 2009;8:1150-1157.

Donadio V, Incensi A, Leta V, et al. Skin nerve α-synuclein deposits: a biomarker for idiopathic Parkinson disease. Neurology. 2014;82:1362-1369.

Du G, Lewis M M, Sica C, et al. Distinct progression pattern of susceptibility MRI in the substantia nigra of Parkinson's patients. Mov Dis. 2018;33: 1423–1431.

Dukart J, Sambataro F, Bertolino A. Distinct Role of Striatal Functional Connectivity and Dopaminergic Loss in Parkinson's Symptoms. Frontiers in Aging Neuroscience 2017;9:151.

Frank L, Kleinman L, Farup C, et al. Psychometric validation of a constipation symptom assessment questionnaire. Scandinavian J Gastroenterol. 1999;348:70–77.

Gaurav R, Pyatigorskaya N, Ewenczyk C, et al. Longitudinal changes in Neuromelanin MRI Signal in Parkinson's Disease. Mov Disord. 2018;33: 641-642.

Gazyvaro Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002799/WC500171594.pdf. Accessed 13 February 2017.

Gelb DJ, Oliver E, Gilman S Diagnostic Criteria for Parkinson Disease. Arch Neurol. 1999;56:33-39.

Gibb WRG, Lees AJ. The relevance of Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psych. 1988;51:745-752.

Guy W. ECDEU assessment manual for psychopharmacology. U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs in Rockville, Md, 1976.

Hilli J, Korhonen T, Laine K. Lack of clinically significant interactions between concomitantly administered rasagiline and escitalopram. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:1526–32.

Hoehn M, Yahr M. Parkinsonism: Onset, progression and mortality. Neurology. 1967;17(5):427–442.

Huang C, Tang C, Feigin A, et al. Changes in network activity with the progression of Parkinson's disease. Brain. 2007;130:1834-1846.

Ibáñez P, Bonnet AM, Débarges B, et al. Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. Lancet. 2004;364(9440):1169-1171.

Jankovic J, Goodman I, Safirstein B et al. Safety and tolerability of multiple ascending doses of PRX002/RG7935, an anti-α-synuclein monoclonal antibody, in patients with Parkinson disease. A randomized Clinical trial. JAMA Neurol. 2018; doi:10.1001/jamaneurol.2018.1487.

Kassavetis P, Saifee TA, Roussos G, et al. Developing a Tool for Remote Digital Assessment of Parkinson's Disease. Mov Dis Clin Pract. 2016;3:59–64.

Kay DM, Factor SA, Samii A, et al. Genetic association between alpha-synuclein and idiopathic Parkinson's disease. Am J Med Genet B Neuropsychiatr Genet. 2008;147B(7):1222-1230.

Kostikis N, Hristu-Varsakelis D, Arnaoutoglou M, et al. Smartphone-based evaluation of parkinsonian hand tremor: quantitative measurements vs clinical assessment scores. Conf Proc IEEE Eng Med Biol Soc. 2014:906-909.

Kowal SL, Dall TM, Chakrabarti R, et al. The current and projected economic burden of Parkinson's disease in the United States. Mov Disord. 2013;28:311-318.

Lieberman P, Nicklas R, Randolph C et al. Anaphylaxis-a practice parameter update. Annals Allergy Asthma Immunol. 2015;115(5):341–384.

Lipsmeier F, Taylor KI, Kilchenmann T, et al. Evaluation of smartphone-based testing to generate exploratory outcome measures in a Phase I Parkinson's disease clinical trial. Mov Disord. 2018; doi: 10.1002/mds.27376.

Little MA, McSharry PE, Hunter EJ, et al. Suitability of dysphonia measurements for telemonitoring of Parkinson's disease, IEEE Transactions on Biomedical Engineering 2009;56(4):1015-1022.

Maetzler W, Domingos J, Srulijes K. Quantitative wearable sensors for objective assessment of Parkinson's disease. Mov Disord. 2013;28:1628–1637.

Malek N, Swallow D, Grosset KA, et al. Alpha-synuclein in peripheral tissues and body fluids as a biomarker for Parkinson's disease - a systematic review. Acta Neurol Scand. 2014;130:59-72.

Maetzler P, Zhang S, Li C-SR, et al. Resting-state functional connectivity of the striatum in early-stage Parkinson's disease: Cognitive decline and motor symptomatology. Human Brain Mapping. 2016;37:648–662.

Manza P, Zhang S, Li C-SR, et al. Resting-state functional connectivity of the striatum in early-stage Parkinson's disease: Cognitive decline and motor symptomatology. Human Brain Mapping. 2016;37:648–662.

Marek K, Jennings D, Lasch S, et al. The Parkinson Progression Marker Initiative (PPMI). Prog Neurobiol. 2011;95(4):629-635.

Matsuura K, Maeda M, Tabei K et al. A longitudinal study of neuromelanin-sensitive magnetic resonance imaging in Parkinson's disease. Neuroscience Letters. 2016;633, 112–117.

Montgomery EB, Panisset M. Retrospective analysis of the incidence of serotonin toxicity in patients taking rasagiline and antidepressants in clinical trials. Mov Disord. 2009;24:359 (abstract).

Mutsaerts HJ, van Osch MJ, Zelaya FO, et al. Multi-vendor reliability of arterial spin labeling perfusion MRI using a near-identical sequence: implications for multi-center studies. Neuroimage. 2015;113:143-152.

Nandhagopal R, Kuramoto L, Schulzer M, et al. Longitudinal evolution of compensatory changes in striatal dopamine processing in Parkinson's disease. Brain. 2011;134:3290-3298.

Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. J Americ Geriatrics Soc. 2005;53:695–699.

National Institute of Neurological Disorders and Stroke. http://www.ninds.nih.gov/disorders/parkinsons_disease/detail_parkinsons_disease.htm. Accessed 30 January 2017.

NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators. Pioglitazone in early Parkinson's disease: a phase 2, multicentre, double-blind, randomised trial. Lancet Neurol. 2015;14(8):795-803. Erratum in: Lancet Neurol. 2015; 14(10):979.

Olde Dubbelink KT, Schoonheim MM, Deijen JB, et al. Functional connectivity and cognitive decline over 3 years in Parkinson disease. Neurology. 2014;83:2046-2053.

Ossig C, Antonini A, Buhmann C, et al. Wearable sensor-based objective assessment of motor symptoms in Parkinson's disease. JNeural Transm. 2016;123:57–64.

Panisset M, Chen JJ, Rhyee SH, et al. Serotonin toxicity association with concomitant antidepressants and rasagiline treatment: retrospective study (STACCATO). Pharmacotherapy. 2014;34:1250-1258.

Parkinson's Disease Foundation. http://www.pdf.org/en/parkinson_statistics. Accessed 30 January 2017.

Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. Arch Neurol. 2002;59(12):1937-1943.

Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. Arch Neurol. 2004;61(7):1044-53.

Parkinson Study Group PRECEPT Investigators. Mixed lineage kinase inhibitor CEP-1347 fails to delay disability in early Parkinson disease. Neurology. 2007;69(15):1480-1490.

Patel S, Chen B, Mancinelli C, et al. Longitudinal Monitoring of Patients with Parkinson's Disease via Wearable Sensor Technology in the Home Setting. Conf Proc IEEE Eng Med Biol Soc. 2011:1552-1555.

Peto V, Jenkinson C, Fitzpatrick R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Quality of Life Res. 1995;4:241–248.

Posner K, Brown GK, Stanley B, et al., The Columbia-Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. Am J Psychiatry. 2011;168:1266-1277.

Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015 Oct;30(12):1591-601.

Prodoehl J, Burciu RG, Vaillancourt, DE. Resting state functional magnetic resonance imaging in Parkinson's Disease. Curr Neurol Neurosci Rep. 2014;14:448-455.

Rascol O, Fitzer-Attas CJ, Hauser R, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease (the ADAGIO study): prespecified and post-hoc analyses of the need for additional therapies, changes in UPDRS scores, and non-motor outcomes. Lancet Neurol. 2011;10(5):415-423.

Reijnders, J. A Systematic Review of Prevalence Studies of Depression in Parkinson's Disease. Mov.Disord. 2008;23:183–189.

RO7046015 Investigator's Brochure, Version *6*, February *2020*.

Schenk DB, Koller M, Ness DK, et al. First-in-Human Assessment of PRX002, an Anti–a-Synuclein Monoclonal Antibody, in Healthy Volunteers. Mov Disord. 2016 Nov 25. doi: 10.1002/mds.26878. [Epub ahead of print]

Schwab RS, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson IML, eds. Third Symposium on Parkinson's disease. Edinburgh: E & S Livingstone. 1969;152–157.

Schwarz J, Storch A, Koch W, et al. Loss of Dopamine Transporter Binding in Parkinson's Disease Follows a Single Exponential Rather Than Linear Decline. J Nucl Med. 2004;45:1694-1697.

Schwid SR, Parkinson Study Group. Safety of rasagiline in combination with serotonin reuptake inhibitors. Ann Neurol. 2005;58(suppl 9):56.

Simuni T, Caspell-Garcia C, Coffey C, et al. One year longitudinal change in the MDS‐UPDRS scores in de novo Parkinson's disease patients: Results from the PPMI study [abstract]. Mov Disord. 2015;30 Suppl 1 :319.

Singleton AB, Farrer M, Johnson J, et al. Alpha-Synuclein locus triplication causes Parkinson's disease. Science. 2003;302(5646):841.

Smith KM, Eyal E, Weintraub D, et al. Combined rasagiline and antidepressant use in Parkinson disease in the ADAGIO study: effects on nonmotor symptoms and tolerability. JAMA Neurol. 2015;72:88-95.

Snaith RP, Zigmond AS. Hospital Anxiety and Depression Scale (HADS). In: Rush AJ, editors. Handbook of psychiatric measures. Washington D.C.: Am Psychiatric Ass. 2000;547–548.

Spillantini MG, Schmidt ML, Lee VM, et al. Alphasynuclein in Lewy bodies. Nature. 1997;388:839-840.

Sprenger F, Poewe W. Management of Motor and Non-Motor Symptoms in Parkinson's Disease. CNS Drugs 2013;27:259–272.

Taylor KI, Sambataro F, Boess F, et al. Progressive Decline in Gray and White Matter Integrity in de novo Parkinson's Disease: An Analysis of Longitudinal Parkinson Progression Markers Initiative Diffusion Tensor Imaging Data. Frontiers in Aging Neuroscience 2018;10:318.

Teune LK, Renken RJ, de Jong BM, et al. Parkinson's disease-related perfusion and glucose metabolic brain patterns identified with PCASL-MRI and FDG-PET imaging. Neuroimage Clin. 2014;5:240-244.

Trenkwalder C, Kohnen R, Högl B. Parkinson's Disease Sleep Scale - Validation of the Revised Version PDSS-2. Mov Disord. 2011;26:644-652.

Tsanas A, Little MA, McSharry PE, et al. Accurate telemonitoring of Parkinson's disease progression by noninvasive speech tests. 2010. IEEE Trans Biomed Eng. 2010;57:884–893.

Ueckert S, Plan EL, Ito K, et al. AC. Improved Utilization of ADAS-Cog Assessment Data Through Item Response Theory Based Pharmacometric Modeling. Pharm Res. 2014;31(8):2152-2165.

Ulla M, Bonny J M, Ouchchane L, et al. Is R2 a New MRI Biomarker for the Progression of Parkinson's Disease? A Longitudinal Follow-Up. PLoS ONE. 2013;8(3), e57904.*

Visser M, Marinus J, Stiggelbout AM, et al. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. Mov Disord. 2004;19;1306-1312.

Wan W, Jin L, Wang Z, et al. Iron deposition leads to neuronal a-synuclein pathology by inducing autophagy dysfunction. Frontiers in Neurology. 2017;8:2–11.

Wang N, Gibbons CH, Lafo J, et al. α-Synuclein in cutaneous autonomic nerves. Neurology. 2013;81:1604-1610.

Wang J, Zhuang Q, Zhu L, et al. Meta-analysis of brain iron levels of Parkinson's disease patients determined by postmortem and MRI measurements. Scientific Reports. 2016; 6:1–13.

Wang X, Zhang Y, Zhu C, et al. The diagnostic value of SNpc using NM-MRI in Parkinson's disease: meta-analysis. Neurological Sciences. 2019;40:2479–2489.

Weintraub D, Burn DJ. Parkinson's Disease: The Quintessential Neuropsychiatric Disorder. Mov Disord. 2011;26:1022-1031.

Writing Group for the NINDS Exploratory Trials in Parkinson Disease (NET-PD) Investigators., Kieburtz K, Tilley BC, Elm JJ, et al. Effect of creatine monohydrate on clinical progression in patients with Parkinson disease: a randomized clinical trial. JAMA. 2015;313(6):584-93.

Wu P, Wang J, Peng S, et al. Metabolic brain network in the Chinese patients with Parkinson's disease based on 18F-FDG PET imaging. Parkinsonism & Related Disorders. 2013;19:622–627.

Zhang Y, Wu I-W, Tosun D, et al. Progression of regional microstructural degeneration in parkinson's disease: a multicenter diffusion tensor imaging study. PLOS one. 2016;11: e0165540.

Appendix 1
Schedule of Assessments (Part 1)

Week	Screening	Week 1			Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Prior to Start of Dopaminergic/Symptomatic PD Treatment (if occuring during Part 1)	Early Termination[1] (if occurring during Part 1)	12 Week Treatment Free FUP[1] (if treatment terminated in Part 1)
Day	D-56 to D-1	Baseline/ Day 1	Day 2	Day 7[21]	Day 14[21]	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252	Day 280	Day 308	Day 336	Day 364			
Visit Window				+/- 2 days	+/- 2 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days			+/- 7 days
Dose Number		1				2	3	4	5	6	7	8	9	10	11	12	13	14			
Assessments			Phone Call[14]	Phone Call[14]	Phone Call[14]																
Informed Consent	X																				
Inclusion/Exclusion	X																				
Demography (including years of education)	X																				
Medical History	X																				
Modified Hoehn & Yahr	X						X		X		X		X		X		X	X	X	X	X
MDS-UPDRS (Parts I, II, III, IV)[12]	X	X					X		X		X		X		X		X	X	X	X	X
Vital Signs[6]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic BP[6]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (Full)[7]	X	X																X	X	X	X
Physical Examination (Abbreviated)[15]				X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Neurological Examination	X	X									X							X	X	X	X
CGIS		X																			
CGII/PGIC											X							X	X	X	X
MMSE	X																				
MoCA	X	X									X							X	X	X	X
C-SSRS (At Baseline)	X	X																			
C-SSRS (Since Last Visit)						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PDQ-39	X									X							X		X	X	X
SCOPA-AUT	X								X			X			X			X	X	X	X
Schwab & England - ADL		X									X							X	X	X	
RBDSQ-Multi item	X																				
PDSS-2		X									X						X		X	X	X
Digital Biomarker Remote Monitoring (incl. diary questions, HADS, PAC-SYM, EQ-5D-5L)[18]	←		→																↔	↔	
Digital Biomarker In-Clinic Assessments[13]	X	X					X		X		X		X		X		X	X	X	X	X
Triplicate ECG-12 lead[5]	X	X				X				X				X				X	X	X	X
DaT-SPECT[16]	X																	X		X[10]	
MRI (Safety, DTI, RS, ASL)[16]	X[3]																	X		X[10]	

Appendix 1
Schedule of Assessments (Part 1) (cont.)

Week	Screening	Week 1			Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Prior to Start of Dopaminergic/Symptomatic PD Treatment (if occuring during Part 1)	Early Termination[1] (if occurring during Part 1)	12 Week Treatment Free FUP[1] (if treatment terminated in Part 1)
Day	D-56 to D-1	Baseline/ Day 1	Day 2	Day 7[21]	Day 14[21]	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252	Day 280	Day 308	Day 336	Day 364			
Visit Window				+/- 2 days	+/- 2 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days			+/- 7 days
Dose Number		1				2	3	4	5	6	7	8	9	10	11	12	13	14			
Assessments			Phone Call[14]	Phone Call[14]	Phone Call[14]																
Hematology	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Chemistry and Lipids	X[17]	X			X	X	X	X			X			X				X	X	X	X
Coagulation	X	X			X	X	X	X			X			X				X	X	X	X
TSH and T4	X																X			X[10]	
Urinalysis	X	X			X	X	X	X			X			X				X	X	X	X
Drug of abuse/Alcohol urine test	X																				
Serology (HBV, HCV, HIV 1 AND 2)	X																				
Pregnancy Test[2]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FSH, LH and estradiol (in post-menopausal women only)	X																				
Serum RO7046015 (PK sampling)[4]		X		X	X	X				X				X				X	X	X	X
Serum Biomarker[4]		X		X	X	X				X				X				X	X	X	X
Serum Anti-RO7046015 Antibody[8]		X				X				X				X				X	X	X	X
Optional CSF via Lumbar Puncture (matching serum sample)[9]		X																X	X	X	
PreMedication - Loratadine 10mg PO, Acetaminophen 650 mg PO[19]		X				X	X														
Administration of Study Medication		X[20]				X[20]	X[20]	X	X	X	X	X	X	X	X	X	X	X			
Skin Biopsy	X																	X[11]	X[11]	X	
Clinical Genotyping	X																				
RBR - Optional Whole Blood Sample (genetic)	X																				
RBR - Optional Whole Blood RNA	X																	X	X	X	X
RBR - Optional Whole Blood Plasma	X																	X	X	X	X
Adverse Events	X	X	X[14]	X[14]	X[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments	X	X	X[14]	X[14]	X[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix 1
Schedule of Assessments (Part 1) (cont.)

1 If participants discontinue or withdraw from the study treatment prematurely, they should complete all of the Early Termination assessments and attend the Follow-up visit normally done at the end of the study, 12 weeks after the last dose of study medication.

2 Screening serum pregnancy test for women who are not post-menopausal or surgically sterile. Urine pregnancy test for female participants (based on participant age/menopausal status) performed prior to dosing and all DaT-SPECT Scans.

3 Screening brain MRI should only be performed after all other inclusion and exclusion have been reviewed and none exclude the participant from the trial, except DaT-SPECT which should be the final assessment. Screening MRI to include Structural, *resting state functional MRI (rs-fMRI)*, Diffusion Tensor Imaging (DTI), Arterial Spin Labelling (ASL). Please note that *rs-fMRI*, DTI and ASL sequences will only be acquired if the investigative sites have the required scanner software/sequences capabilities.

4 Day 1 / Week 4 / 20 / 36 / 52: serum RO7046015 (PK Sampling) and serum biomarker samples will be collected just prior to dosing and at the end of the infusion. At Days 7 / 14 / early termination and FUP: anytime (all time points of collection to be recorded in CRF).

5 ECG (12-lead) will be obtained at pre-dose on Day 1 and again at the end of study drug infusion. For all the designated dosing visits the ECGs should be obtained at pre-dose only. For the Screening/early termination/FUP, the ECGs should be obtained early in the day to approximate the timing of the pre-dose ECGs during the study. All ECGs (12-lead) will be performed in triplicate, 1-2 minutes apart within 5 minutes.

6 Vital signs (including semi-supine blood pressure, respiratory rate, pulse rate and temperature) have to be monitored pre-infusion, every 15 minutes until the end of infusion, and thereafter, every 30 minutes until the infusion line is removed. In order to assess for orthostatic hypotension, BP and pulse rate will be evaluated after 2 minutes of standing still (after the semi-supine measurement) at screening and at pre-dose and 2 hours after completion of the first three infusions then 1 hour after end of infusion on subsequent dosing days. Note: any abnormal value in Vital Signs needs to be repeated for confirmation or intervention if needed.

7 Height and weight will be recorded at the screening visit only. Only weight will be measured at baseline, Weeks 52 and FUP.

8 On dosing days, serum anti-RO7046015 antibody samples will be collected prior to dosing as done for PK samples.

9 For consented participants only. Baseline lumbar puncture (LP) should be performed prior to Day -4 to allow recovery before first dosing. Then the ideal collection time is between 48-72 hours after the Week 52 infusions and early termination. LP should be performed in the morning (between 8:00 and 12:00 hours) to minimize potential diurnal variation of CSF parameters. Please refer to the protocol for handling of AEs related to LP and instructions on concomitant medication. An aliquot of the CSF samples will be sent for local laboratory analysis (erythrocyte and leukocyte cell counts, protein, and glucose) while the remainder of the sample will be sent for central biomarker assessment. Any remaining CSF aliquots will be stored for the Research Biosample Repository for patients participating in RBR.

Appendix 1
Schedule of Assessments (Part 1) (cont.)

10 MRI and DaT-SPECT scans should not be performed if already collected within 3 months of early termination. If a DaT-SPECT scan is required for early termination visit, TSH and T4 assessment must be performed prior to the scan.

11 Skin biopsy must be collected pre-dose if the sample is collected at visits with study drug administration.

12 At screening, Hoehn & Yahr staging will be assessed as part of the MDS-UPDRS Part III. MDS-UPDRS Part IV will be done for all participants on dopaminergic treatment (levodopa or dopamine agonist). For all participants that have started dopaminergic treatment, the MDS-UPDRS I-III, including Part IV and Digital Biomarker In-Clinic assessments will be assessed approximately 12 hours (e.g., overnight) after last dose of dopaminergic treatment. Only the MDS-UPDRS Part III and Digital Biomarker In-Clinic Assessments will then be repeated 1 hour after receiving dopaminergic treatment in the clinic.

13 The first Digital Biomarker In-Clinic Assessments should be done at least 7 days prior to Baseline. In Clinic Digital Biomarker Assessments include the Full Active Test, Short Berg Balance Test and Timed Up and Go.

14 Telephone interview on Day 2 and, for those subjects not participating in PK sampling, on Days 7 and 14 to assess for any clinically significant symptoms and/or new medication.

15 Abbreviated physical exam will include Head Ears Eyes Nose and Throat (HEENT), Heart & Lung exams and any complaints expressed by participant at visit.

16 MRIs should be performed with a time window of +/- 14 days from the study visit. DaT-SPECT should be performed within -14/-5 days if done prior to the visit clinic or within +14 days if done after the visit clinic. Refer to protocol Section 4.6.1.9 for procedure to follow in preparation of scans. In case participant takes dopaminergic treatment, MRI should be performed in a practically defined off state (no dopaminergic medication taken at the day of evaluation).

17 Fasting glucose will be analyzed at screening.

18 During screening, the Digital Biomarker Remote Monitoring should be started at least 7 days prior to Baseline. The PROs (patient reported outcome) are scheduled at regular intervals and administered on the digital biomarker smartphone. The PROs will typically be completed remotely since the scheduled days will often fall between clinic visit days.

19 Premedication is given 30-60 min prior to the first 3 infusions. Desloratadine 5 mg PO or other alternatives can be given in study centers where loratadine is not available.

20 Study drug should be given as IV infusion over 2 hours for the first three doses and if well tolerated can be reduced to 1 hour in subsequent doses.

21 Days 7 and 14 on-site visits will only be performed in the first 90 participants enrolled at sites in the USA. A telephone interview on Days 7 and 14 to assess clinically significant symptoms and/or new medications will be done for all other participants.

Appendix 2
Schedule of Assessments (Part 2)

Week	Week 56	Week 57	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96	Week 100	Week 104	Prior to Start of Dopaminergic/Symptomatic PD Treatment (if occuring during Part 2)	Early Termination[1] (if occuring during Part 2)	12 Week Treatment Free FUP[1] (at end of study or if treatment terminated in Part 2)
Day	Day 392	Day 393	Day 420	Day 448	Day 476	Day 504	Day 532	Day 560	Day 588	Day 616	Day 644	Day 672	Day 700	Day 728			
Visit Window	+/ 4 days		+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days			+/ 7 days
Dose Number	15		16	17	18	19	20	21	22	23	24	25	26	27			
Assessments		Phone Call[13]															
Eligibilty for Extension[15]	X																
Modified Hoehn & Yahr	X			X		X		X		X		X		X	X	X	X
MDS UPDRS (Parts I, II, III, IV)[10]	X			X		X		X		X		X		X	X	X	X
Vital Signs[5]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic BP[5]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (Full)	X													X	X	X	X[6]
Physical Examination (Abbreviated)[14]			X	X	X	X	X	X	X	X	X	X	X				
Neurological Examination	X							X						X	X	X	X
CGII/PGIC	X							X						X	X	X	X
MoCA	X							X						X	X	X	X
C SSRS (Since Last Visit)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PDQ 39	X													X	X	X	X
SCOPA AUT	X							X						X	X	X	X
Schwab & England ADL	X							X						X	X	X	
RBDSQ Multi item																	
PDSS 2	X							X					X		X	X	X
Digital Biomarker Remote Monitoring (incl. diary questions, HADS, PAC SYM, EQ 5D 5L)[17]	←													→	↔	↔	
Digital Biomarker In Clinic Assessments 12	X			X		X		X		X		X		X	X	X	X
Triplicate ECG 12 lead[4]	X		X					X						X	X	X	X
DaT SPECT[16]														X		X[9]	
MRI (safety & efficacy)[16]														X		X[9]	

Appendix 2
Schedule of Assessments (Part 2) (cont.)

Week	Week 56	Week 57	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96	Week 100	Week 104	Prior to Start of Dopaminergic/Symptomatic PD Treatment (if occuring during Part 2)	Early Termination[1] (if occuring during Part 2)	12 Week Treatment Free FUP[1] (at end of study or if treatment terminated in Part 2)
Day	Day 392	Day 393	Day 420	Day 448	Day 476	Day 504	Day 532	Day 560	Day 588	Day 616	Day 644	Day 672	Day 700	Day 728			
Visit Window	+/ 4 days		+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days	+/ 4 days			+/ 7 days
Dose Number	15		16	17	18	19	20	21	22	23	24	25	26	27			
Assessments		Phone Call[13]															
Hematology	X		X	X		X		X		X		X		X	X	X	X
Blood Chemistry and Lipids	X		X					X				X		X	X	X	X
Coagulation	X		X					X				X		X	X	X	X
TSH and T4													X			X[9]	
Urinalysis	X		X					X				X		X	X	X	X
Pregnancy Test[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum RO7046015 (PK sampling)[3]	X				X			X						X	X	X	X
Serum Biomarker[3]	X				X			X						X	X	X	X
Serum Anti RO7046015 Antibody[7]	X				X			X						X	X	X	X
Optional CSF via Lumbar Puncture (matching serum sample)[8]														X	X	X	
PreMedication Loratadine 10mg PO, Acetaminophen 650 mg PO[18]	X		X	X													
Administration of Study Medication	X[19]		X[19]	X[19]	X	X	X	X	X	X	X	X	X	X			
Skin Biopsy														X[11]	X[11]	X	
RBR Optional Whole Blood RNA														X	X	X	X
RBR Optional Whole Blood Plasma														X	X	X	X
Adverse Events	X	X[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments	X	X[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix 2
Schedule of Assessments (Part 2) (cont.)

1 If participant discontinues or withdraws from the study treatment prematurely, they should complete all of the Early Termination assessments and attend the Follow-up visit normally done at the end of the study, 12 weeks after the last dose of study medication.

2 Urine pregnancy test for female participants (based on participant age/menopausal status) performed prior to dosing and all DaT-SPECT Scans.

3 Week 56 / 68 / 80 / 104: serum RO7046015 (PK sampling) and serum biomarkers samples will be collected just prior to dosing and at the end of the infusion. At early termination and FUP: anytime (all time points of collection to be recorded in CRF).

4 On Week 56 ECG will be obtained pre-dose and at end of study drug infusion. For all the designated dosing visits the ECGs should be obtained at pre-dose only. For the early termination/FUP the ECG timing should be early in the visit to approximate the pre-dose measurements. All ECGs (12-lead) will be performed in triplicate, 1-2 minutes apart within 5 minutes.

5 Vital signs (including semi-supine blood pressure, respiratory rate, pulse rate and temperature) have to be monitored pre-infusion, every 15 minutes until the end of infusion, and thereafter, every 30 minutes until the infusion line is removed. In order to assess for orthostatic hypotension, BP and pulse rate will be evaluated after 2 minutes of standing still (after the semi-supine measurement) at pre-dose and 2 hours after completion of the first three infusions then 1 hour after end of infusion on subsequent dosing days. Note: any abnormal value in Vital Signs needs to be repeated for confirmation or intervention if needed.

6 Height will not be measured at FUP.

7 On dosing days, serum anti-RO7046015 antibody samples will be collected prior to dosing as done for PK samples.

8 For consented participants only. The ideal collection time to perform Lumbar Puncture (LP) is between 48-72 hours after the Week 104 infusion and early termination. LP should be performed in the morning (between 8:00 and 12:00 hours) to minimize potential diurnal variation of CSF parameters. An aliquot of the CSF samples will be sent for local laboratory analysis (erythrocyte and leukocyte cell counts, protein, and glucose) while the remainder of the sample will be sent for central biomarker assessment. Any remaining CSF aliquots will be stored for the Research Biosample Repository for patients participating in RBR.

9 MRI and DaT-SPECT scans should not be performed if already collected within 3 months of early termination. If a DaT-SPECT scan is required for early termination visit, TSH and T4 assessment must be performed prior to the scan.

10 MDS-UPDRS Part IV will be done for all participants on dopaminergic treatment (levodopa or dopamine agonist). For all participants that have started dopaminergic treatment, the MDS-UPDRS Parts I- III, including Part IV and Digital Biomarker In-Clinic assessments, will be assessed approximately 12 hours (e.g., overnight) after last dose of dopaminergic treatment. Only the MDS-UPDRS Part III and Digital Biomarker In-Clinic assessments will then be repeated 1 hour after receiving dopaminergic treatment in the clinic.

11 Skin biopsy must be collected pre-dose if the sample is collected at visits with study drug administration.

12 In Clinic Digital Biomarker Assessments include the Full Active Test, Short Berg Balance Test, and Timed Up and Go.

Appendix 2
Schedule of Assessments (Part 2) (cont.)

13 Telephone interview to assess for any clinically significant symptoms and/or new medication.

14 Abbreviated physical exam will include Head Ears Eyes Nose and Throat (HEENT), Heart & Lung exams and any complaints expressed by participant at visit.

15 The participants must meet the following criteria to enter the Part II: Dat-SPECT and MRI scans completed at screening and Week 52 and at least 10 doses of study treatment.

16 MRIs should be performed with a time window of +/- 14 days from the study visit. DaT-SPECT should be performed within -14/-5 days if done prior to the clinic visit or within +14 days if done after the visit clinic. Refer to protocol Section 4.6.1.9 for procedure to follow in preparation of scans. In case participant takes dopaminergic treatment, MRI should be performed in a practically defined off state (no dopaminergic medication taken at the day of evaluation).

17 The PROs (patient reported outcome) are scheduled at regular intervals and administered on the digital biomarker smartphone. The PROs will typically be completed remotely since the scheduled days will often fall between clinic visit days.

18 Premedication is given 30-60 min prior to the first 3 infusions.

19 Study drug should be given as IV infusion over 2 hours for the first three doses and if well tolerated can be reduced to 1 hour in subsequent doses.

Appendix 3
Schedule of Assessments (Part 3)

Part 3 is a 5-year extension. Please see separate SoA for each year as follows:

Schedule of Assessments Part 3 - Year 1

Schedule of Assessments Part 3 - Year 2

Schedule of Assessments Part 3 - Year 3

Schedule of Assessments Part 3 - Year 4

Schedule of Assessments Part 3 - Year 5

Schedule of Assessments Part 3 - Year 1

Treatment Week	Part 3 Week 1	Part 3 Week 4	Part 3 Week 8	Part 3 Week 12	Part 3 Week 16	Part 3 Week 20	Part 3 Week 24	Part 3 Week 28	Part 3 Week 32	Part 3 Week 36	Part 3 Week 40	Part 3 Week 44	Part 3 Week 48	Part 3 Week 52	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[18] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP[18] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 1	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252	Day 280	Day 308	Day 336	Day 364				
Visit Window		+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14				
Assessments																		
Eligibilty for Extension[1]	X																	
Modified Hoehn & Yahr	X			X			X			X				X	X	X	X	X
MDS-UPDRS (Parts I, II, III, IV)[3]	X			X			X			X				X	X	X	X	X
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic BP[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (Full)[5]	X[2]													X	X	X	X	X
Physical Examination (Abbreviated)[6]							X								X			
Neurological Examination	X[2]						X							X	X	X	X	X
CGII/PGIC	X[2]						X							X	X	X	X	X
MoCA	X[2]						X							X	X	X	X	X
C-SSRS (Since Last Visit)	X[2]						X							X	X	X	X	X
PDQ-39	X[2]						X							X	X	X	X	X
SCOPA-AUT	X[2]						X							X	X	X	X	X
Schwab & England - ADL	X[2]						X							X	X	X	X	X
PDSS-2	X[2]						X							X	X	X	X	X
Digital Biomarker Remote Monitoring (incl. diary questions, HADS, PAC-SYM, EQ-5D-5L)[7]	X[20]			X[20]			X[20]			X[20]				X[20]	X		X[21]	X[21]
Digital Biomarker In-Clinic Assessments[8]	X			X			X			X				X	X	X	X	X

Part 3 - Year 1 (cont.)

Treatment Week	Part 3 Week 1	Part 3 Week 4	Part 3 Week 8	Part 3 Week 12	Part 3 Week 16	Part 3 Week 20	Part 3 Week 24	Part 3 Week 28	Part 3 Week 32	Part 3 Week 36	Part 3 Week 40	Part 3 Week 44	Part 3 Week 48	Part 3 Week 52	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[18] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP [18] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 1	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252	Day 280	Day 308	Day 336	Day 364				
Visit Window		+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14				
Assessments																		
Triplicate ECG-12 lead[9]	X														X	X	X	X
Pre dose 12-Lead ECG							X							X	X			
DaT-SPECT[10]																	X[19]	
MRI (safety & efficacy)[10]	X[2]														X		X[19]	
Hematology	X[2]			X			X			X				X	X	X	X	X
Blood Chemistry and Lipids	X[2]						X							X	X	X	X	X
Coagulation	X[2]						X							X	X	X	X	X
TSH and T4														X	X		X[19]	
Urinalysis	X[2]						X							X	X	X	X	X
Pregnancy Test[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum RO7046015 (PK sampling)[12]	X						X							X	X		X	X
Serum and plasma Biomarker[12]	X						X							X	X	X	X	X
Serum Anti-RO7046015 Antibody[13]	X						X							X	X		X	X
Optional CSF via Lumbar Puncture (matching serum and plasma sample)[14]																X	X[19]	

Part 3 - Year 1 (cont.)

Treatment Week	Part 3 Week 1	Part 3 Week 4	Part 3 Week 8	Part 3 Week 12	Part 3 Week 16	Part 3 Week 20	Part 3 Week 24	Part 3 Week 28	Part 3 Week 32	Part 3 Week 36	Part 3 Week 40	Part 3 Week 44	Part 3 Week 48	Part 3 Week 52	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination [18] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP [18] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 1	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252	Day 280	Day 308	Day 336	Day 364				
Visit Window		+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14				
Assessments																		
PreMedication Loratadine 10mg PO, Acetaminophen 650 mg PO [15]															x			
Administration of Study Medication	x [16]	x	x	x	x	x	x	x	x	x	x	x	x	x				
Skin Biopsy																x[17]	x	
RBR - Optional Whole Blood RNA														x		x	x	x
RBR - Optional Whole Blood Plasma														x		x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Previous and Concomitant Treatments	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Part 3 - Year 1 (cont.)

1 The participants must meet the following criteria to enter the Part 3: Having completed Part 2 (i.e., completed Week 104 visit) and having completed the 12 week treatment free follow up visit.

2 Not needed for the participants who performed 12-week treatment free FUP visit less than 30 days from Part 3 Week 1 visit ago

3 Hoehn & Yahr staging will be assessed as part of the MDS-UPDRS Part III. MDS-UPDRS Part IV will be done for all participants on dopaminergic treatment. For all participants that have started dopaminergic treament MDS-UPDRS Part III and Part IV will be assessed approximately 12 hours (e.g., overnight) after last dose of dopaminergic treatment. MDS-UPDRS Part III will then be repeated at least 1 hour after dopaminergic treatment along with MDS-UPDRS Part IV and Digital Biomarker assessments.

4 Vital signs (including semi-supine blood pressure, respiratory rate and pulse rate) have to be monitored pre-infusion, every 15 minutes until the end of infusion, and thereafter, every 30 minutes until the infusion line is removed. In order to assess for orthostatic hypotension, BP and pulse rate will be evaluated after 2 minutes of standing still (after the semi-supine measurement) at pre-dose and 1 hour after end of infusion. Note: any abnormal value in Vital Signs needs to be repeated for confirmation or intervention if needed.

5 Including weight

6 Abbreviated physical exam will include Head Ears Eyes Nose and Throat (HEENT), Heart & Lung exams and any complaints expressed by participant at visit

7 The PROs (patient reported outcome) are scheduled at regular intervals and administered on the digital biomarker smartphone. The PROs will typically be completed remotely since the scheduled days will often fall between clinic visit days.

8 In Clinic Digital Biomarker Assessments only include the Full Active Test.

9 On Part 3 Week 1 ECG will be obtained pre-dose and at end of study drug infusion. For the Part 3 early termination/Part 3 FUP the ECG timing should be early in the visit to approximate the pre-dose measurements. For all the designated visits, ECGs (12-lead) will be performed in triplicate, 1-2 minutes apart within 5 minutes.

10 MRIs should be performed with a time window of +/- 14 days from the study visit. DaT-SPECT should be performed within -14/-5 days if done prior to the clinic visit or within +14 days if done after the visit clinic. Refer to protocol Section 4.6.1.9 for procedure to follow in preparation of scans. In case participant takes dopaminergic treatment, MRI should be performed in a practically defined off state (no dopaminergic medication taken at the day of evaluation).

11 Urine pregnancy test for female participants (based on participant age/menopausal status) performed prior to dosing and all DaT-SPECT Scans.

12 Serum RO7046015 (PK sampling) will be collected just prior to dosing and at the end of the infusion; serum and plasma biomarkers samples will be collected just prior to dosing . At Part 3 early termination and Part 3 FUP: Serum RO7046015 (PK sampling) and serum & plasma biomarkers sampling will be collected anytime (all time points of collection to be recorded in CRF).

13 On dosing days Serum anti-RO7046015 antibody samples will be collected prior to dosing.

14 For consented participants only. The ideal collection time to perform Lumbar Puncture (LP) is between 48-72 hours after early termination. LP should be performed in the morning (between 8:00 and 12:00 hours) to minimize potential diurnal variation of CSF parameters. An aliquot of the CSF samples will be sent for local laboratory analysis (erythrocyte and leukocyte cell counts, protein, and glucose) while the remainder of the sample will be sent for central biomarker assessment. Any remaining CSF aliquots will be stored for the Research Biosample Repository for patients participating in RBR.

15 Premedication guidance is given in Section 4.4.2.

16 Study drug should be given as IV infusion at the same infusion rate as the last infusion in Part 2.

17 Skin biopsy must be collected pre-dose if the sample is collected on visits with study drug administration.

18 If participant discontinues or withdraws from the study treatment prematurely, they should complete all of the Part 3 Early Termination assessments and attend the Part 3 Follow-up visit normally done at the end of the study, 12 weeks after the last dose of study medication.

19 Should not be performed if already collected within 3 months of Part 3 early termination. If a Dat-SPECT scan is required for Part 3 early termination, TSH and T4 assessment should be performed prior to the scan.

Part 3 - Year 1 (cont.)

20 While the patients can continue active and passive digital biomarker remote monitoring on a daily basis if they are willing, digital biomarker remote monitoring is mandatory only for 2 weeks every 3 months in Part 3. Active and passive digital biomarker remote monitoring is recommended to start the day after digital biomarker in-clinic assessments are scheduled (e.g. patient performs digital biomarker in-clinic assessments on Part 3 Day 1 and performs active and passive digital biomarker remote monitoring from Part 3 Day 2 to Part 3 Day 15).

21 In case of Part 3 early termination, active and passive digital biomarker remote monitoring in treatment free follow up should start the day after digital biomarker in-clinic Part 3 early termination assessments have been performed and should last for at least 14 days.

Schedule of Assessments Part 3 - Year 2

Treatment Week	Part 3 Week 56	Part 3 Week 60	Part 3 Week 64	Part 3 Week 68	Part 3 Week 72	Part 3 Week 76	Part 3 Week 80	Part 3 Week 84	Part 3 Week 88	Part 3 Week 92	Part 3 Week 96	Part 3 Week 100	Part 3 Week 104	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[14] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP[14] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 392	Day 420	Day 448	Day 476	Day 504	Day 532	Day 560	Day 588	Day 616	Day 644	Day 672	Day 700	Day 728				
Visit Window	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	15	16	17	18	19	20	21	22	23	24	25	26	27				
Assessments																	
Modified Hoehn & Yahr				X			X			X			X	X	X	X	X
MDS-UPDRS (Parts I, II, III, IV)[1]				X			X			X			X	X	X	X	X
Vital Signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic BP[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (Full)[3]													X	X	X	X	X
Physical Examination (Abbreviated)[4]							X							X			
Neurological Examination							X						X	X	X	X	X
CGII/PGIC							X						X	X	X	X	X
MoCA							X						X	X	X	X	X
C-SSRS (Since Last Visit)							X						X	X	X	X	X
PDQ-39							X						X	X	X	X	X
SCOPA-AUT							X						X	X	X	X	X
Schwab & England - ADL							X						X	X	X	X	X
PDSS-2							X						X	X	X	X	X
Digital Biomarker Remote Monitoring (incl. diary questions, HADS, PAC-SYM, EQ-5D-5L)[5]				X[16]			X[16]			X[16]			X[16]	X		X[17]	X[17]
Digital Biomarker In-Clinic Assessments[6]				X			X			X			X	X	X	X	X

Part 3 - Year 2 (cont.)

Treatment Week	Part 3 Week 56	Part 3 Week 60	Part 3 Week 64	Part 3 Week 68	Part 3 Week 72	Part 3 Week 76	Part 3 Week 80	Part 3 Week 84	Part 3 Week 88	Part 3 Week 92	Part 3 Week 96	Part 3 Week 100	Part 3 Week 104	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[14] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP [14] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 392	Day 420	Day 448	Day 476	Day 504	Day 532	Day 560	Day 588	Day 616	Day 644	Day 672	Day 700	Day 728				
Visit Window	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	15	16	17	18	19	20	21	22	23	24	25	26	27				
Assessments																	
Triplicate ECG-12 lead[7]														X	X	X	X
Pre dose 12-Lead ECG							X						X	X			
DaT-SPECT[8]													X			X[15]	
MRI (safety & efficacy)8													X	X		X[15]	
Hematology				X			X			X			X	X	X	X	X
Blood Chemistry and Lipids							X						X	X	X	X	X
Coagulation							X						X	X	X	X	X
TSH and T4													X	X		X[15]	
Urinalysis							X						X	X	X	X	X
Pregnancy Test[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum RO7046015 (PK sampling)[11]							X						X	X		X	X
Serum and plasma Biomarker[10]							X						X	X	X	X	X
Serum Anti-RO7046015 Antibody[11]							X						X	X		X	X
Optional CSF via Lumbar Puncture (matching serum and plasma sample)[12]													X		X	X[15]	

Part 3 - Year 2 (cont.)

Treatment Week	Part 3 Week 56	Part 3 Week 60	Part 3 Week 64	Part 3 Week 68	Part 3 Week 72	Part 3 Week 76	Part 3 Week 80	Part 3 Week 84	Part 3 Week 88	Part 3 Week 92	Part 3 Week 96	Part 3 Week 100	Part 3 Week 104	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[14] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP [14] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 392	Day 420	Day 448	Day 476	Day 504	Day 532	Day 560	Day 588	Day 616	Day 644	Day 672	Day 700	Day 728				
Visit Window	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	15	16	17	18	19	20	21	22	23	24	25	26	27				
Assessments																	
PreMedication - Loratadine 10mg PO, Acetaminophen 650 mg PO														x			
Administration of Study Medication	x	x	x	x	x	x	x	x	x	x	x	x	x				
Skin Biopsy													x[13]		x[13]	x	
RBR - Optional Whole Blood RNA													x		x	x	x
RBR - Optional Whole Blood Plasma													x		x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Previous and Concomitant Treatments	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Part 3 - Year 2 (cont.)

1 Hoehn & Yahr staging will be assessed as part of the MDS-UPDRS Part III. MDS-UPDRS Part IV will be done for all participants on dopaminergic treatment. For all participants that have started dopaminergic treament MDS-UPDRS Part III and Part IV will be assessed approximately 12 hours (e.g., overnight)after last dose of dopaminergic treatment. MDS-UPDRS Part III will then be repeated at least 1 hour after dopaminergic treatment along with MDS-UPDRS Part IV and Digital Biomarker assessments.

2 Vital signs (including semi-supine blood pressure, respiratory rate and pulse rate) have to be monitored pre-infusion, every 15 minutes until the end of infusion, and thereafter, every 30 minutes until the infusion line is removed. In order to assess for orthostatic hypotension, BP and pulse rate will be evaluated after 2 minutes of standing still (after the semi-supine measurement) at pre-dose and 1 hour after end of infusion on subsequent dosing days. Note: any abnormal value in Vital Signs needs to be repeated for confirmation or intervention if needed.

3 Including weight

4 Abbreviated physical exam will include Head Ears Eyes Nose and Throat (HEENT), Heart & Lung exams and any complaints expressed by participant at visit.

5 The PROs (patient reported outcome) are scheduled at regular intervals and administered on the digital biomarker smartphone. The PROs will typically be completed remotely since the scheduled days will often fall between clinic visit days.

6 In Clinic Digital Biomarker Assessments only include the Full Active Test.

7 For the Part 3 early termination/Part 3 FUP the ECG timing should be early in the visit to approximate the pre-dose measurements. For all the designated visits, ECGs (12-lead) will be performed in triplicate, 1-2 minutes apart within 5 minutes.

8 MRIs should be performed with a time window of +/- 14 days from the study visit. DaT-SPECT should be performed within -14/-5 days if done prior to the clinic visit or within +14 days if done after the visit clinic. Refer to protocol Section 4.6.1.9 for procedure to follow in preparation of scans. In case participant takes dopaminergic treatment, MRI should be performed in a practically defined off state (no dopaminergic medication taken at the day of evaluation).

9 Urine pregnancy test for female participants (based on participant age/menopausal status) performed prior to dosing and all DaT-SPECT Scans.

10 Serum and plasma biomarkers samples will be collected just prior to dosing. At Part 3 early termination and Part 3 FUP: anytime (all time points of collection to be recorded in CRF).

11 On dosing days Serum RO7046015 (PK sampling) and serum anti-RO7046015 antibody samples will be collected prior to dosing. At Part 3 early termination and Part 3 FUP: anytime (all time points of collection to be recorded in CRF).

12 For consented participants only. The ideal collection time to perform Lumbar Puncture (LP) is between 48-72 hours after the Part 3 Week 104 infusion and early termination. LP should be performed in the morning (between 8:00 and 12:00 hours) to minimize potential diurnal variation of CSF parameters. An aliquot of the CSF samples will be sent for local laboratory analysis (erythrocyte and leukocyte cell counts, protein, and glucose) while the remainder of the sample will be sent for central biomarker assessment. Any remaining CSF aliquots will be stored for the Research Biosample Repository for patients participating in RBR.

13 Skin biopsy must be collected pre-dose if the sample is collected on visits with study drug administration.

14 If participant discontinues or withdraws from the study treatment prematurely, they should complete all of the Part 3 Early Termination assessments and attend the Part 3 Follow-up visit normally done at the end of the study, 12 weeks after the last dose of study medication.

15 Should not be performed if already collected within 3 months of Part 3 early termination. If a Dat-SPECT scan is required for Part 3 early termination, TSH and T4 assessment should be performed prior to the scan.

16 While the patients can continue active and passive digital biomarker remote monitoring on a daily basis if they are willing, digital biomarker remote monitoring is mandatory only for 2 weeks every 3 months in Part 3. Active and passive digital biomarker remote monitoring is recommended to start the day after digital biomarker in-clinic assessments are scheduled.

17 In case of Part 3 early termination, active and passive digital biomarker remote monitoring in treatment free follow up should start the day after digital biomarker in-clinic Part 3 early termination assessments have been performed and should last for at least 14 days.

Schedule of Assessments Part 3 - Year 3

Treatment Week	Part 3 Week 108	Part 3 Week 112	Part 3 Week 116	Part 3 Week 120	Part 3 Week 124	Part 3 Week 128	Part 3 Week 132	Part 3 Week 136	Part 3 Week 140	Part 3 Week 144	Part 3 Week 148	Part 3 Week 152	Part 3 Week 156	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[14] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP[14] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 756	Day 784	Day 812	Day 840	Day 868	Day 896	Day 924	Day 952	Day 980	Day 1008	Day 1036	Day 1064	Day 1092				
Visit Window	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	28	29	30	31	32	33	34	35	36	37	38	39	40				
Assessments																	
Modified Hoehn & Yahr				X			X			X			X	X	X	X	X
MDS-UPDRS (Parts I, II, III, IV)[1]				X			X			X			X	X	X	X	X
Vital Signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic BP[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (Full)[3]													X	X	X	X	X
Physical Examination (Abbreviated)[4]							X							X			
Neurological Examination							X						X	X	X	X	X
CGII/PGIC							X						X	X	X	X	X
MoCA							X						X	X	X	X	X
C-SSRS (Since Last Visit)							X						X	X	X	X	X
PDQ-39							X						X	X	X	X	X
SCOPA-AUT							X						X	X	X	X	X
Schwab & England - ADL							X						X	X	X	X	X
PDSS-2							X						X	X	X	X	X
Digital Biomarker Remote Monitoring (incl. diary questions, HADS, PAC-SYM, EQ-5D-5L)[5]				X[16]			X[16]			X[16]			X[16]	X		X[17]	X[17]
Digital Biomarker In-Clinic Assessments[6]				X			X			X			X	X	X	X	X

Part 3 - Year 3 (cont.)

Treatment Week	Part 3 Week 108	Part 3 Week 112	Part 3 Week 116	Part 3 Week 120	Part 3 Week 124	Part 3 Week 128	Part 3 Week 132	Part 3 Week 136	Part 3 Week 140	Part 3 Week 144	Part 3 Week 148	Part 3 Week 152	Part 3 Week 156	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[14] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP[14] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 756	Day 784	Day 812	Day 840	Day 868	Day 896	Day 924	Day 952	Day 980	Day 1008	Day 1036	Day 1064	Day 1092				
Visit Window	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	28	29	30	31	32	33	34	35	36	37	38	39	40				
Assessments																	
Triplicate ECG-12 lead[7]														X	X	X	X
Pre dose 12-Lead ECG							X						X	X			
DaT-SPECT[8]																X[15]	
MRI (safety & efficacy)8														X		X[15]	
Hematology				X			X			X			X	X	X	X	X
Blood Chemistry and Lipids							X						X	X	X	X	X
Coagulation							X						X	X	X	X	X
TSH and T4													X	X		X[15]	
Urinalysis							X						X	X	X	X	X
Pregnancy Test[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum RO7046015 (PK sampling)[10]							X						X	X		X	X
Serum and plasma Biomarker[10]							X						X	X	X	X	X
Serum Anti-RO7046015 Antibody[11]							X						X	X		X	X
Optional CSF via Lumbar Puncture (matching serum and plasma sample)[12]															X	X[15]	

Part 3 - Year 3 (cont.)

Treatment Week	Part 3 Week 108	Part 3 Week 112	Part 3 Week 116	Part 3 Week 120	Part 3 Week 124	Part 3 Week 128	Part 3 Week 132	Part 3 Week 136	Part 3 Week 140	Part 3 Week 144	Part 3 Week 148	Part 3 Week 152	Part 3 Week 156	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[14] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP [14] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 756	Day 784	Day 812	Day 840	Day 868	Day 896	Day 924	Day 952	Day 980	Day 1008	Day 1036	Day 1064	Day 1092				
Visit Window	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	28	29	30	31	32	33	34	35	36	37	38	39	40				
Assessments																	
PreMedication - Loratadine 10mg PO, Acetaminophen 650 mg PO														x			
Administration of Study Medication	x	x	x	x	x	x	x	x	x	x	x	x	x				
Skin Biopsy															x[13]	x	
RBR - Optional Whole Blood RNA													x		x	x	x
RBR - Optional Whole Blood Plasma													x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Previous and Concomitant Treatments	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Part 3 - Year 3 (cont.)

1 Hoehn & Yahr staging will be assessed as part of the MDS-UPDRS Part III. MDS-UPDRS Part IV will be done for all participants on dopaminergic treatment. For all participants that have started dopaminergic treament MDS-UPDRS Part III and Part IV will be assessed approximately 12 hours (e.g. overnight) after last dose of dopaminergic treatment. MDS-UPDRS Part III will then be repeated at least 1 hour after dopaminergic treatment along with MDS-UPDRS Part IV and Digital Biomarker assessments.

2 Vital signs (including semi-supine blood pressure, respiratory rate and pulse rate) have to be monitored pre-infusion, every 15 minutes until the end of infusion, and thereafter, every 30 minutes until the infusion line is removed. In order to assess for orthostatic hypotension, BP and pulse rate will be evaluated after 2 minutes of standing still (after the semi-supine measurement) at pre-dose and 1 hour after end of infusion on subsequent dosing days. Note: any abnormal value in Vital Signs needs to be repeated for confirmation or intervention if needed.

3 Including weight

4 Abbreviated physical exam will include Head Ears Eyes Nose and Throat (HEENT), Heart & Lung exams and any complaints expressed by participant at visit

5 The PROs (patient reported outcome) are scheduled at regular intervals and administered on the digital biomarker smartphone. The PROs will typically be completed remotely since the scheduled days will often fall between clinic visit days,

6 In Clinic Digital Biomarker Assessments only include the Full Active Test.

7 For the Part 3 early termination/Part 3 FUP the ECG timing should be early in the visit to approximate the pre-dose measurements. For all the designated visits, ECGs (12-lead) will be performed in triplicate, 1-2 minutes apart within 5 minutes.

8 MRIs should be performed with a time window of +/- 14 days from the study visit. DaT-SPECT should be performed within -14/-5 days if done prior to the clinic visit or within +14 days if done after the visit clinic. Refer to protocol Section 4.6.1.9 for procedure to follow in preparation of scans. In case participant takes dopaminergic treatment, MRI should be performed in a practically defined off state (no dopaminergic medication taken at the day of evaluation).

9 Urine pregnancy test for female participants (based on participant age/menopausal status) performed prior to dosing and all DaT-SPECT Scans.

10 Serum and plasma biomarkers samples will be collected just prior to dosing. At Part 3 early termination and Part 3 FUP: anytime (all time points of collection to be recorded in CRF).

11 On dosing days Serum RO7046015 (PK sampling) and serum anti-RO7046015 antibody samples will be collected prior to dosing. At Part 3 early termination and Part 3 FUP: anytime (all time points of collection to be recorded in CRF).

12 For consented participants. The ideal collection time to perform Lumbar Puncture (LP) is between 48-72 hours after early termination. LP should be performed in the morning (between 8:00 and 12:00 hours) to minimize potential diurnal variation of CSF parameters. An aliquot of the CSF samples will be sent for local laboratory analysis (erythrocyte and leukocyte cell counts, protein, and glucose) while the remainder of the sample will be sent for central biomarker assessment. Any remaining CSF aliquots will be stored for the Research Biosample Repository for patients participating in RBR.

13 Skin biopsy must be collected pre-dose if the sample is collected on visits with study drug administration

14 If participant discontinues or withdraws from the study treatment prematurely, they should complete all of the Part 3 Early Termination assessments and attend the Part 3 Follow-up visit normally done at the end of the study, 12 weeks after the last dose of study medication.

15 Should not be performed if already collected within 3 months of early termination. If a Dat-SPECT scan is required for early termination, TSH and T4 assessment should be performed prior to the scan.

16 While the patients can continue active and passive digital biomarker remote monitoring on a daily basis if they are willing, digital biomarker remote monitoring is mandatory only for 2 weeks every 3 months in Part 3. Active and passive digital biomarker remote monitoring is recommended to start the day after digital biomarker in-clinic assessments are scheduled.

17 In case of Part 3 early termination, active and passive digital biomarker remote monitoring in treatment free follow up should start the day after digital biomarker in-clinic Part 3 early termination assessments have been performed and should last for at least 14 days.

Schedule of Assessments Part 3 - Year 4

Treatment Week	Part 3 Week 160	Part 3 Week 164	Part 3 Week 168	Part 3 Week 172	Part 3 Week 176	Part 3 Week 180	Part 3 Week 184	Part 3 Week 188	Part 3 Week 192	Part 3 Week 196	Part 3 Week 200	Part 3 Week 204	Part 3 Week 208	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[14] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP[14] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 1120	Day 1148	Day 1176	Day 1204	Day 1232	Day 1260	Day 1288	Day 1316	Day 1344	Day 1372	Day 1400	Day 1428	Day 1456				
Visit Window	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	41	42	43	44	45	46	47	48	49	50	51	52	53				
Assessments																	
Modified Hoehn & Yahr				X			X			X			X	X	X	X	X
MDS-UPDRS (Parts I, II, III, IV)[1]				X			X			X			X	X	X	X	X
Vital Signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic BP[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (Full)[3]													X	X	X	X	X
Physical Examination (Abbreviated)[4]							X							X			
Neurological Examination							X						X	X	X	X	X
CGII/PGIC							X						X	X	X	X	X
MoCA							X						X	X	X	X	X
C-SSRS (Since Last Visit)							X						X	X	X	X	X
PDQ-39							X						X	X	X	X	X
SCOPA-AUT							X						X	X	X	X	X
Schwab & England - ADL							X						X	X	X	X	X
PDSS-2							X						X	X	X	X	X
Digital Biomarker Remote Monitoring (incl. diary questions, HADS, PAC-SYM, EQ-5D-5L)[5]				X[16]			X[16]			X[16]			X[16]	X		X[17]	X[17]
Digital Biomarker In-Clinic Assessments[6]				X			X			X			X	X	X	X	X

Part 3 - Year 4 (cont.)

Treatment Week	Part 3 Week 160	Part 3 Week 164	Part 3 Week 168	Part 3 Week 172	Part 3 Week 176	Part 3 Week 180	Part 3 Week 184	Part 3 Week 188	Part 3 Week 192	Part 3 Week 196	Part 3 Week 200	Part 3 Week 204	Part 3 Week 208	Unscheluded	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[14] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP[14] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 1120	Day 1148	Day 1176	Day 1204	Day 1232	Day 1260	Day 1288	Day 1316	Day 1344	Day 1372	Day 1400	Day 1428	Day 1456				
Visit Window	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	41	42	43	44	45	46	47	48	49	50	51	52	53				
Assessments																	
Triplicate ECG-12 lead[7]														X	X	X	X
Pre dose 12-Lead ECG							X						X	X			
DaT-SPECT[8]													X			X[15]	
MRI (safety & efficacy)8													X	X		X[15]	
Hematology				X			X			X			X	X	X	X	X
Blood Chemistry and Lipids							X						X	X	X	X	X
Coagulation							X						X	X	X	X	X
TSH and T4													X	X		X[15]	
Urinalysis							X						X	X	X	X	X
Pregnancy Test[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum RO7046015 (PK sampling)[10]							X						X	X		X	X
Serum and plasma Biomarker[10]							X						X	X	X	X	X
Serum Anti-RO7046015 Antibody[11]							X						X	X		X	X
Optional CSF via Lumbar Puncture (matching serum and plasma sample)[12]													X		X	X[15]	

Part 3 - Year 4 (cont.)

Treatment Week	Part 3 Week 160	Part 3 Week 164	Part 3 Week 168	Part 3 Week 172	Part 3 Week 176	Part 3 Week 180	Part 3 Week 184	Part 3 Week 188	Part 3 Week 192	Part 3 Week 196	Part 3 Week 200	Part 3 Week 204	Part 3 Week 208	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[14] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP[14] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 1120	Day 1148	Day 1176	Day 1204	Day 1232	Day 1260	Day 1288	Day 1316	Day 1344	Day 1372	Day 1400	Day 1428	Day 1456				
Visit Window	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	41	42	43	44	45	46	47	48	49	50	51	52	53				
Assessments																	
PreMedication - Loratadine 10mg PO, Acetaminophen 650 mg PO														X			
Administration of Study Medication	X	X	X	X	X	X	X	X	X	X	X	X	X				
Skin Biopsy													X[13]		X[13]	X	
RBR - Optional Whole Blood RNA													X		X	X	X
RBR - Optional Whole Blood Plasma													X		X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Part 3 - Year 4 (cont.)

1 Hoehn & Yahr staging will be assessed as part of the MDS-UPDRS Part III. MDS-UPDRS Part IV will be done for all participants on dopaminergic treatment. For all participants that have started dopaminergic treatment MDS-UPDRS Part III and Part IV will be assessed approximately 12 hours (e.g., overnight)after last dose of dopaminergic treatment. MDS-UPDRS Part III will then be repeated at least 1 hour after dopaminergic treatment along with MDS-UPDRS Part IV and Digital Biomarker assessments.

2 Vital signs (including semi-supine blood pressure, respiratory rate and pulse rate) have to be monitored pre-infusion, every 15 minutes until the end of infusion, and thereafter, every 30 minutes until the infusion line is removed. In order to assess for orthostatic hypotension, BP and pulse rate will be evaluated after 2 minutes of standing still (after the semi-supine measurement) at pre-dose and 1 hour after end of infusion on subsequent dosing days. Note: any abnormal value in Vital Signs needs to be repeated for confirmation or intervention if needed.

3 Including weight

4 Abbreviated physical exam will include Head Ears Eyes Nose and Throat (HEENT), Heart & Lung exams and any complaints expressed by participant at visit

5 The PROs (patient reported outcome) are scheduled at regular intervals and administered on the digital biomarker smartphone. The PROs will typically be completed remotely since the scheduled days will often fall between clinic visit days.

6 In Clinic Digital Biomarker Assessments only include the Full Active Test.

7 For the Part 3 early termination/Part 3 FUP the ECG timing should be early in the visit to approximate the pre-dose measurements. For all the designated visits, ECGs (12-lead) will be performed in triplicate, 1-2 minutes apart within 5 minutes.

8 MRIs should be performed with a time window of +/- 14 days from the study visit. DaT-SPECT should be performed within -14/-5 days if done prior to the clinic visit or within +14 days if done after the visit clinic. Refer to protocol Section 4.6.1.9 for procedure to follow in preparation of scans. In case participant takes dopaminergic treatment, MRI should be performed in a practically defined off state (no dopaminergic medication taken at the day of evaluation).

9 Urine pregnancy test for female participants (based on participant age/menopausal status) performed prior to dosing and all DaT-SPECT Scans.

10 Serum and plasma biomarkers samples will be collected just prior to dosing. At Part 3 early termination and Part 3 FUP: anytime (all time points of collection to be recorded in CRF).

11 On dosing days Serum RO7046015 (PK sampling) and serum anti-RO7046015 antibody samples will be collected prior to dosing. At Part 3 early termination and Part 3 FUP: anytime (all time points of collection to be recorded in CRF).

12 For consented participants only. The ideal collection time to perform Lumbar Puncture (LP) is between 48-72 hours after the Week 312 infusion and early termination. LP should be performed in the morning (between 8:00 and 12:00 hours) to minimize potential diurnal variation of CSF parameters. An aliquot of the CSF samples will be sent for local laboratory analysis (erythrocyte and leukocyte cell counts, protein, and glucose) while the remainder of the sample will be sent for central biomarker assessment. Any remaining CSF aliquots will be stored for the Research Biosample Repository for patients participating in RBR.

13 Skin biopsy must be collected pre-dose if the sample is collected on visits with study drug administration

14 If participant discontinues or withdraws from the study treatment prematurely, they should complete all of the Part 3 Early Termination assessments and attend the Part 3 Follow-up visit normally done at the end of the study, 12 weeks after the last dose of study medication.

15 Should not be performed if already collected within 3 months of Part 3 early termination. If a Dat-SPECT scan is required for Part 3 early termination, TSH and T4 assessment should be performed prior to the scan.

16 While the patients can continue active and passive digital biomarker remote monitoring on a daily basis if they are willing, digital biomarker remote monitoring is mandatory only for 2 weeks every 3 months in Part 3. Active and passive digital biomarker remote monitoring is recommended to start the day after digital biomarker in-clinic assessments are scheduled

17 In case of Part 3 early termination, active and passive digital biomarker remote monitoring in treatment free follow up should start the day after digital biomarker in-clinic Part 3 early termination assessments have been performed and should last for at least 14 days.

Schedule of Assessments Part 3 - Year 5

Treatment Week	Part 3 Week 212	Part 3 Week 216	Part 3 Week 220	Part 3 Week 224	Part 3 Week 228	Part 3 Week 232	Part 3 Week 236	Part 3 Week 240	Part 3 Week 244	Part 3 Week 248	Part 3 Week 252	Part 3 Week 256	Part 3 Week 260	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[14] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP[14] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 1484	Day 1512	Day 1540	Day 1568	Day 1596	Day 1624	Day 1652	Day 1680	Day 1708	Day 1736	Day 1764	Day 1792	Day 1820				
Visit Window	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	54	55	56	57	58	59	60	61	62	63	64	65	66				
Assessments																	
Modified Hoehn & Yahr				X			X			X			X	X	X	X	X
MDS-UPDRS (Parts I, II, III, IV)[1]				X			X			X			X	X	X	X	X
Vital Signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Orthostatic BP[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (Full)[3]													X	X	X	X	X
Physical Examination (Abbreviated)[4]							X							X			
Neurological Examination							X						X	X	X	X	X
CGII/PGIC							X						X	X	X	X	X
MoCA							X						X	X	X	X	X
C-SSRS (Since Last Visit)							X						X	X	X	X	X
PDQ-39							X						X	X	X	X	X
SCOPA-AUT							X						X	X	X	X	X
Schwab & England - ADL							X						X	X	X	X	X
PDSS-2							X						X	X	X	X	X
Digital Biomarker Remote Monitoring (incl. diary questions, HADS, PAC-SYM, EQ-5D-5L)[5]				X[16]			X[16]			X[16]			X[17]	X		X[17]	X[17]
Digital Biomarker In-Clinic Assessments[6]				X			X			X			X	X	X	X	X

Part 3 - Year 5 (cont.)

Treatment Week	Part 3 Week 212	Part 3 Week 216	Part 3 Week 220	Part 3 Week 224	Part 3 Week 228	Part 3 Week 232	Part 3 Week 236	Part 3 Week 240	Part 3 Week 244	Part 3 Week 248	Part 3 Week 252	Part 3 Week 256	Part 3 Week 260	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[14] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP [14] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 1484	Day 1512	Day 1540	Day 1568	Day 1596	Day 1624	Day 1652	Day 1680	Day 1708	Day 1736	Day 1764	Day 1792	Day 1820				
Visit Window	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	54	55	56	57	58	59	60	61	62	63	64	65	66				
Assessments																	
Triplicate ECG-12 lead[7]													X	X	X	X	X
Pre dose 12-Lead ECG							X							X			
DaT-SPECT[8]																X[15]	
MRI (safety & efficacy)8														X		X[15]	
Hematology				X			X			X			X	X	X	X	X
Blood Chemistry and Lipids							X						X	X	X	X	X
Coagulation							X						X	X	X	X	X
TSH and T4													X	X		X[15]	
Urinalysis							X						X	X	X	X	X
Pregnancy Test[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum RO7046015 (PK sampling)[10]							X						X	X		X	X
Serum and plasma Biomarker[10]							X						X	X	X	X	X
Serum Anti-RO7046015 Antibody[11]							X						X	X		X	X
Optional CSF via Lumbar Puncture (matching serum and plasma sample)[12]															X	X[15]	

Part 3 - Year 5 (cont.)

Treatment Week	Part 3 Week 212	Part 3 Week 216	Part 3 Week 220	Part 3 Week 224	Part 3 Week 228	Part 3 Week 232	Part 3 Week 236	Part 3 Week 240	Part 3 Week 244	Part 3 Week 248	Part 3 Week 252	Part 3 Week 256	Part 3 Week 260	Unscheduled	Prior to Start of Dopaminergic/ Symptomatic PD Treatment (if occuring during Part 3)	Part 3 Early Termination[14] (if occuring during Part 3)	Part 3 12 Week Treatment Free FUP[14] (at end of study or if treatment terminated early in Part 3)
Treatment Day	Day 1484	Day 1512	Day 1540	Day 1568	Day 1596	Day 1624	Day 1652	Day 1680	Day 1708	Day 1736	Day 1764	Day 1792	Day 1820				
Visit Window	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days	+/- 4 days				+/- 7 days
Dose Number	54	55	56	57	58	59	60	61	62	63	64	65	66				
Assessments																	
PreMedication Loratadine 10mg PO, Acetaminophen 650 mg PO														X			
Administration of Study Medication	X	X	X	X	X	X	X	X	X	X	X	X	X				
Skin Biopsy															X[13]	X	
RBR - Optional Whole Blood RNA													X		X	X	X
RBR - Optional Whole Blood Plasma													X		X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Part 3 - Year 5 (cont.)

1 Hoehn & Yahr staging will be assessed as part of the MDS-UPDRS Part III. MDS-UPDRS Part IV will be done for all participants on dopaminergic treatment. For all participants that have started dopaminergic treament MDS-UPDRS Part III and Part IV will be assessed approximately 12 hours (e.g., overnight)after last dose of dopaminergic treatment. MDS-UPDRS Part III will then be repeated at least 1 hour after dopaminergic treatment along with MDS-UPDRS Part IV and Digital Biomarker assessments.

2 Vital signs (including semi-supine blood pressure, respiratory rate and pulse rate) have to be monitored pre-infusion, every 15 minutes until the end of infusion, and thereafter, every 30 minutes until the infusion line is removed. In order to assess for orthostatic hypotension, BP and pulse rate will be evaluated after 2 minutes of standing still (after the semi-supine measurement) at pre-dose and 1 hour after end of infusion on subsequent dosing days. Note: any abnormal value in Vital Signs needs to be repeated for confirmation or intervention if needed.

3 Including weight

4 Abbreviated physical exam will include Head Ears Eyes Nose and Throat (HEENT), Heart & Lung exams and any complaints expressed by participant at visit.

5 The PROs (patient reported outcome) are scheduled at regular intervals and administered on the digital biomarker smartphone. The PROs will typically be completed remotely since the scheduled days will often fall between clinic visit days.

6 In Clinic Digital Biomarker Assessments only include the Full Active Test.

7 For the Part 3 early termination/Part 3 FUP the ECG timing should be early in the visit to approximate the pre-dose measurements. For all the designated visits, ECGs (12-lead) will be performed in triplicate, 1-2 minutes apart within 5 minutes.

8 MRIs should be performed with a time window of +/- 14 days from the study visit. DaT-SPECT should be performed within -14/-5 days if done prior to the clinic visit or within +14 days if done after the visit clinic. Refer to protocol Section 4.6.1.9 for procedure to follow in preparation of scans. In case participant takes dopaminergic treatment, MRI should be performed in a practically defined off state (no dopaminergic medication taken at the day of evaluation).

9 Urine pregnancy test for female participants (based on participant age/menopausal status) performed prior to dosing and all DaT-SPECT Scans.

10 Serum and plasma biomarkers samples will be collected just prior to dosing. At Part 3 early termination and Part 3 FUP: anytime (all time points of collection to be recorded in CRF).

11 On dosing days Serum RO7046015 (PK sampling) and serum anti-RO7046015 antibody samples will be collected prior to dosing. At Part 3 early termination and Part 3 FUP: anytime (all time points of collection to be recorded in CRF).

12 For consented participants only. The ideal collection time to perform Lumbar Puncture (LP) is between 48-72 hours after early termination. LP should be performed in the morning (between 8:00 and 12:00 hours) to minimize potential diurnal variation of CSF parameters. An aliquot of the CSF samples will be sent for local laboratory analysis (erythrocyte and leukocyte cell counts, protein, and glucose) while the remainder of the sample will be sent for central biomarker assessment. Any remaining CSF aliquots will be stored for the Research Biosample Repository for patients participating in RBR.

13 Skin biopsy must be collected pre-dose if the sample is collected on visits with study drug administration.

14 If participant discontinues or withdraws from the study treatment prematurely, they should complete all of the Part 3 Early Termination assessments and attend the Part 3 Follow-up visit normally done at the end of the study, 12 weeks after the last dose of study medication.

15 Should not be performed if already collected within 3 months of Part 3 early termination. If a Dat-SPECT scan is required for Part 3 early termination, TSH and T4 assessment should be performed prior to the scan.

16 While the patients can continue active and passive digital biomarker remote monitoring on a daily basis if they are willing, digital biomarker remote monitoring is mandatory only for 2 weeks every 3 months in Part 3. Active and passive digital biomarker remote monitoring is recommended to start the day after digital biomarker in-clinic assessments are scheduled.

17 At Part 3 Week 260 or in case of Part 3 early termination, active and passive digital biomarker remote monitoring in treatment free follow up should start the day after digital biomarker in-clinic Part 3 Week 260 or Part 3 early termination assessments have been performed and should last for at least 14 days.

Appendix 4
Recommended Sequence of Study Assessments

A. Screening

Written informed consent must be obtained before performing any study-specific screening tests or evaluation and maintained at the study site.

The assessments required during screening can be performed throughout several visits to allow flexibility to the participants (3 in-clinic visits are acceptable). The following evaluations and procedures will be performed within 56 days prior to the first study drug administration (Baseline / Day 1):

Recommended sequence of assessments:

Screening Visit 1:

- Signed Informed Consent
- Demography
- Medical history including diagnosis and duration of PD
- Modified H&Y (Note: original H&Y stage is used for eligibility determination)
- Vital signs including temperature, pulse rate, respiratory rate, and BP
- Orthostatic Blood Pressure
- Physical examination (full)
- Neurological examination
- ECG
- Blood tests
    - Hematology, chemistry (including **fasting** glucose), lipids, coagulation, TSH, T4, serology, serum pregnancy test (pre-menopausal), FSH/LH/estradiol (post-menopausal)
    - Clinical genotyping
    - Optional whole blood sample (genetic), optional whole blood RNA, optional whole blood plasma
- Urine tests (urinalysis, drugs of abuse/alcohol)
- Adverse events
- Previous and concomitant medication
- MDS-UPDRS (Part I, II, III) (at least 7 days prior to Baseline visit) including H&Y staging
- Review of Inclusion/Exclusion criteria (should be assessed throughout the visit and further assessments stopped if criteria not met)

Appendix 4
Recommended Sequence of Study Assessments (cont.)

Screening Visit 2 can be scheduled and take place immediately after (or on the same day as) Screening Visit 1, and before central reading results for safety labs and ECG are available, if no relevant eligibility concern arose at the end of Screening Visit 1 (e.g., no complex medical history requiring laboratory or ECG confirmatory results).

If the patient had normal MRI result within 6 months of the screening visit, the study MRI and Dat-SPECT can be scheduled on the same day at investigator's discretion.

Screening Visit 2:

- C-SSRS
- SCOPA-AUT
- PDQ-39
- RBDSQ
- MMSE
- MoCA
- Provision of smartphone and wrist-worn wearable and training of participants for remote Digital Biomarker Remote Monitoring
- Digital Biomarker In-Clinic Assessments including Active Test, selected items from the Berg Balance Scale and the Timed Up and Go test (at least 7 days prior to Baseline visit)
- Adverse events
- Review of Inclusion/Exclusion criteria (should be assessed throughout the visit and further assessments stopped if criteria not met)
- Skin punch biopsy
- Brain MRI (should only be performed after all other inclusion and exclusion have been reviewed and none exclude the participant from the trial, except DaT-SPECT which should be the final assessment)

Screening Visit 3:

- DaT-SPECT (Note: it should be the last screening assessment)

Remote visit (phone call), after all Screening data available:

- Adverse events
- Final review of Review of Inclusion/Exclusion criteria (once DaT-SPECT results are received) and confirmation of eligibility or non-eligibility to the participant
- Note: The smartphone and wrist-worn wearable must be returned to the clinic if the participant does not meet eligibility criteria

Appendix 4
Recommended Sequence of Study Assessments (cont.)

Baseline Lumbar Puncture assessment:

- The lumbar puncture can be performed anytime during screening including at a planned screening visit and does not require a separate visit as long as it is done at least 4 days before Baseline/Day 1 visit and, if performed after the DAT-SPECT, must be at least 5 days after the scan.

B. Dosing Days

At Dosing Visits, **the sequence of assessments described below is recommended for the assessments applicable to the specific study days**:

Breaks and Lunch should be planned as well throughout the visits whenever deemed necessary or requested by the participants.

- *Prior to in-clinic visits with digital biomarker in-clinic assessments:* Patients should be reminded by a phone call prior to *the* in-clinic visit to bring their Smartphone to the next in-clinic visit.
- If on dopaminergic treatment, they should also be reminded to refrain from taking their medication at home on specific clinic days when MDS-UPDRS will be performed, and bring their medication to the next in-clinic visit.
- Patient Global Impression of Change (PGIC)
- Modified H&Y (should be performed by the same rater as MDS-UPDRS)
- MDS-UPDRS (I, II, III, IV). should be performed at approximately the same time at each relevant visit
    - Part IV is only performed with participants who have started dopaminergic treatment (levodopa or dopamine agonists)
- Clinical Global Impression - Severity (CGI-S) (should be performed by the same rater as MDS-UPDRS, only at baseline)
- Clinical Global Impression - Improvement (CGI-I) (should be performed by the same rater as MDS-UPDRS)
- C-SSRS

Appendix 4
Recommended Sequence of Study Assessments (cont.)

- Patient-reported outcomes / Neuropsychological tests
    - SCOPA-AUT
    - PDSS-2
    - PDQ-39
    - SE-ADL
    - MoCA
    - Digital Biomarker In-Clinic Assessments including Active Tests, selected items from the Berg Balance Scale and the Timed Up and Go test
- Dopaminergic treatment administration for participants who have started dopaminergic treatment
- Clinical assessments
    - Concomitant medications
    - Neurological / physical examinations
    - Vital signs pre-dose
    - Urinalysis, Pregnancy test
    - Adverse Events
    - Skin Punch Biopsy (pre-dose)
    - ECG pre-dose
    - Blood draws (PK sampling pre-dose, serum anti-RO7046015 antibody, safety samples)
    - Pre-medication - required 30-60 minutes prior to first 3 infusions in Part 1 and Part 2;
    - **Drug infusion** (2 hours for first 3 infusions); vital signs to be measured during infusion
    - Blood draw (PK sampling post dosing using a cannula different from the infusion cannula)
    - Vital signs post-dose
    - ECG post-dose
    - MDS-UPDRS Parts III and Digital Biomarker In-Clinic Assessments including Active Tests, selected items from the Berg Balance Scale and the Timed Up and Go test – for participants receiving dopaminergic treatment, at least 1 hour after receiving dopaminergic treatment, as described in Section 4.6.1.9

Appendix 4
Recommended Sequence of Study Assessments (cont.)

Notes regarding MRI, DaT-SPECT, Lumbar Puncture, Skin Punch Biopsy:

- A urine pregnancy test must be performed in women of childbearing potential prior to the DaT-SPECT scan
- All biosamples (serum, *plasma,* CSF, skin) should not be collected within 5 days after a DaT-SPECT. If serum, CSF or skin collection are planned on the same day, they must be performed prior to the DaT-SPECT
- If MRI and DaT-SPECT scans are performed on the same day, MRI must be performed first
- MRI and DaT-SPECT may be performed on a different day than the regular dosing visit (within the time windows allowed in the Schedule of Assessments) to minimize the visit duration, as follows:
    - MRI may be performed within ±14 days of the clinic visit specified in the SoA
    - DaT-SPECT should be performed within -14/-5 days if done prior to the visit clinic or within +14 days if done after the visit clinic
- For participants receiving dopaminergic treatment, MRI should be done 'Off-state' (no dopaminergic treatment taken on the day of MRI)
- For participants consenting to CSF sampling:
    - Baseline lumbar puncture (LP) should be performed prior to Day -4 to allow recovery before first dosing.
    - The post-baseline LP must be done 48 – 72 hours after the drug infusion and can be done on the same day as MRI or DaT-SPECT (but this is not mandatory). In this case, the LP must be performed at least 3-4 hours prior to the scans. During these 3-4 hours, if the scan facility is located at the site, the cognitive assessments may be completed.

Appendix 5
Patient Engagement Application

The Patient Engagement Application is a Smartphone system, referred to as an “app” that can be used by a patient or the legally authorized representative of a patient in the BP39529 study.

The app is an optional service that patients can opt-in to use to remind them of activities/task relevant to study compliances like when to take their study medication, attend site visit, track goals. The app also provides supportive guides to help volunteers be aware of visit procedures, study information and instructions.

The app’s interactive features are intended to be a companion to the user during the course of a trial and include the following modules:

- Study Information: targeted study information throughout the duration of the study.
- Visit Schedule: site visit reminder based on predefined Schedule of Assessments
- Goals: ability to implement study defined or personal goal targets (e.g., weight, exercise, sleep, etc.).
- Reminders: reminders for activities/task relevant to study compliances.
- Site Information: module where patients can enter their site contacts details.

The app is available for download to smartphone devices that support iOS or Android. The app will contain study-specific information only once activated by a patient. The study coordinator will provide the patient with a secure activation code, which they can use to activate the app upon their first use.

The app does not collect any participant-identified information or clinical data. It cannot be installed on the phone provided by the Sponsor for conducting the digital biomarker assessments. This app is intended for informational purposes only. It is not a substitute for professional medical advice. Participants should contact the study site investigator or coordinator with any medical questions or concerns.