Official Title: A Phase IIb, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Intravenous Prasinezumab in Participants with Early Parkinson's Disease

NCT Number: NCT04777331

Document Date: Protocol Version 5: 15-April-2025

PROTOCOL

TITLE:	**A PHASE IIb, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF INTRAVENOUS PRASINEZUMAB IN PARTICIPANTS WITH EARLY PARKINSON'S DISEASE**
PROTOCOL NUMBER:	BN42358
STUDY NAME:	PADOVA
VERSION NUMBER:	5
TEST PRODUCT:	Prasinezumab (RO7046015)
STUDY PHASE:	Phase IIb
REGULATORY AGENCY IDENTIFIERS:	IND Number: 119602 EU CT Number: 2023-507132-21-00 NCT Number: NCT04777331
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
5	*See electronic date stamp on the final page of this document.*
4	*30 October 2023*
3	4 November 2022
2	30 May 2022
1	29 October 2020

PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Protocol BN42358 has been amended to make the protocol CTR compliant.

Changes to the protocol, along with a rationale for each change, are summarized below:

- Reference to the Prasinezumab Investigator's Brochure for expected benefits and risks of prasinezumab have been added, as clarification to ensure the reader has access to the most recent prasinezumab data (Section 1.3.2).
- "Early termination" text has been added when referring to the open-label extension end-of-study visit to clarify that during the open-label extension period, the early termination visit and end-of-study visit are one single visit (Section 3.1.4 and Appendix 1, Table 2).
- Clarification has been provided regarding the pharmacist role during the double-blind period and open-label extension, because the strictness of the pharmacist's role depends on whether the pharmacist prepared double-blind period IMP or only open label extension IMP (Section 4.3.1.1).
- Section 4.5.5 has been updated to clarify that [redacted] During the open-label extension period this restriction does not apply.
- Text related to Sponsor-provided pregnancy testing and urinalysis have been updated to clarify that only Sponsor-provided tests should be used (Section 4.5.6.1).
- A window for scale completion during the OLE has been added because the previous standard window for visits was deemed unnecessarily strict during OLE, given that the scale completion frequency has been reduced from monthly to every 3 months (Appendix 1, Table 2).
- An appendix for investigational and auxiliary and non-investigational/medicinal product designations in the EEA and UK was added to the protocol to make it CTR compliant (Appendix 4).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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TEST PRODUCT:	Prasinezumab (RO7046015)
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 retain the signed original of this form for your study files. Please return a copy of the signed form to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IIB, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF INTRAVENOUS PRASINEZUMAB IN PARTICIPANTS WITH EARLY PARKINSON'S DISEASE**
REGULATORY AGENCY IDENTIFIER NUMBERS:	*IND Number: 119602* *EU CT Number: 2023-507132-21-00* *NCT Number: NCT04777331*

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of prasinezumab compared with placebo in patients with early Parkinson's disease (PD). Specific objectives and corresponding endpoints for the study are outlined below.

PRIMARY EFFICACY OBJECTIVE

The primary efficacy objective for this study is to evaluate the efficacy of prasinezumab compared with placebo on the basis of the following endpoint:

- Time to confirmed motor progression event

SECONDARY EFFICACY OBJECTIVE

The secondary efficacy objective for this study is to evaluate the efficacy of prasinezumab compared with placebo on the basis of the following endpoints:

- Time to worsening of patient's motor function as reported by the patient (≥3 points increase in MDS-UPDRS Part II score from baseline) in the presence of a confirmed motor progression event (as defined in Section 2.1.1).
- Time to meaningful worsening (defined as a rating of "very much worse," "much worse," or "minimally worse" reported to be important to the patient) in Patient Global Impression of Change (PGI-C, Overall Disease Subscale)
- Time to meaningful worsening (defined as a rating of "very much worse," "much worse," or "minimally worse" reported to be clinically meaningful) in Clinician Global Impression of Change (CGI-C, Overall Disease Subscale)
- Change in motor function from baseline to Week 76, as measured by the MDS-UPDRS Part III score (assessed in "OFF" medication state)
- Change in bradykinesia and rigidity from baseline to Week 76, as measured by the MDS-UPDRS Part III bradykinesia and rigidity subscore (assessed in "OFF" medication state)
- Time to onset of motor complications as assessed through MDS-UPDRS Part IV

EXPLORATORY EFFICACY OBJECTIVE

The exploratory efficacy objective for this study is to evaluate the efficacy of prasinezumab compared with placebo on the basis of the following endpoints:

- [redacted]
-
-

- [redacted]

SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of prasinezumab compared with placebo on the basis of the following endpoints:

- Nature, incidence, seriousness, and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Incidence of adverse events of special interest
- Incidence of treatment discontinuation due to adverse events
- Nature, incidence, seriousness, severity, and timing of infusion-related reactions (IRRs)
- Mean change in vital signs from baseline over time and incidence of abnormal vital sign measurements
- Changes in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Change from baseline and incidence of laboratory abnormalities (including hematology, clinical chemistry, coagulation, and urinalysis parameters)
- Incidence of physical and neurologic examination abnormalities
- Change from baseline in suicidal ideation, as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS)

PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to characterize the prasinezumab PK profile on the basis of the following endpoint:

- Serum concentration of prasinezumab at specified timepoints or PK parameters of prasinezumab

The exploratory PK objective for this study is to evaluate potential relationships between drug exposure and the efficacy and safety of prasinezumab on the basis of the following endpoints:

- Relationship between serum concentration or secondary PK parameters of prasinezumab and efficacy endpoints
- Relationship between serum concentration or secondary PK parameters of prasinezumab and biomarker endpoints
- Relationship between serum concentration or secondary PK parameters of prasinezumab and safety endpoints

IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to prasinezumab on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

BIOMARKER OBJECTIVES

[redacted]

HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with prasinezumab on the basis of the following endpoint:

- Change from baseline EQ5D5L indexbased and Visual Analog Scale (VAS) scores at Week 76

OPEN-LABEL EXTENSION OBJECTIVES

The main objective for the open label extension (OLE) period of the study is to evaluate long-term safety and tolerability of prasinezumab in patients with early PD that have completed the double-blind treatment period of the PADOVA study on the basis of the following endpoints:

- Nature, incidence, seriousness and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Incidence of adverse events of special interest
- Incidence of treatment discontinuation due to adverse events
- Nature, incidence, seriousness, severity, and timing of IRRs
- Mean change in vital signs from baseline over time and incidence of abnormal vital sign measurements
- Changes in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Change from baseline and incidence of laboratory abnormalities (including hematology, clinical chemistry, coagulation, and urinalysis parameters)
- Incidence of physical and neurologic examination abnormalities
- Change from baseline in suicidal ideation, as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS)

In addition, exploratory objectives of this OLE are to evaluate long-term clinical and biomarker efficacy of prasinezumab in patients with early PD on the basis of similar endpoints to those of double-blind period. The OLE will also help to further assess potential relationships between drug exposure and the efficacy and safety of prasinezumab. [redacted]

STUDY DESIGN

DESCRIPTION OF STUDY

Study BN42358 is a Phase IIb, randomized, double-blind, placebo-controlled, parallel group, multicenter study to evaluate efficacy and safety of prasinezumab, administered as a 1500 mg IV infusion every 4 weeks (Q4W), to patients with early PD on stable symptomatic monotherapy with either monoamine oxidase B (MAO-B) inhibitors or levodopa (L-Dopa). This study will consist of the following phases: screening, double-blind treatment, and safety follow-up.

Patients providing informed consent will undergo screening prior to study drug administration. Eligible patients will be randomly assigned (in a [redacted] ratio) in a blinded fashion to receive either placebo or prasinezumab. To maintain a balanced number of patients in each treatment arm and to ensure the arms are comparable, randomization will be stratified by use of PD medication (MAO-B inhibitors vs. L-Dopa). Randomization will be performed through an interactive voice or web-based response system.

The expected sample size will be approximately 575 patients. Patients will be recruited globally. Approximately 125 sites in approximately nine countries in North America and Europe will participate in this study. Patients who prematurely discontinue from the double-blind period of the study treatment will be asked to continue the visits as per the schedule of activities until the primary analysis, and will not be replaced.

[redacted] All study participants will continue to receive double-blind study treatment until both of these conditions are fulfilled [redacted] Once the double-blind treatment period of the study is completed, participants who consent and are eligible will enter the OLE portion of the trial and will receive prasinezumab for approximately 2 years.

Participants and sites will remain blinded to prior randomization assignment until the end of the OLE period.

An independent Data Monitoring Committee (iDMC) will be employed to monitor and evaluate patient safety throughout the double-blind period of the study, until the primary analysis is performed. Monitoring details will be described in the iDMC charter.

SCREENING

The screening phase will last up to 12 weeks. Patients who are candidates for enrollment in the study will be evaluated by the investigator to ensure that all eligibility criteria are met. All patients must have signed the Informed Consent Form prior to screening and prior to any changes to their existing medication for the purposes of enrollment in the study.

It is recommended that MRI, DaT-SPECT imaging, and optional CSF collection (for patients consenting to this procedure) are performed last, after all other screening requirements have been satisfactorily completed, to ensure that these procedures are only performed for patients otherwise deemed eligible for the trial. During the screening phase, patients will also be asked to begin performing digital assessments. Note that due to the length of time required to complete digital assessments, the screening period will last for a minimum of 28 days (up to a maximum of 12 weeks).

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion after at least 3 months have elapsed from screening failure, with the exception of screen failure for imaging not consistent with PD, in which case rescreening is not permitted. Patients must re-sign the consent form prior to re-screening. The investigator will record reasons for screen failure in the screening log. In case of re-screening, all screening assessments must be repeated with the exception of: lumbar puncture (LP; for patients having previously consented to this procedure), MRI, and DaT-SPECT imaging if previous results were within eligible ranges and conducted no earlier than 6 months prior to the baseline visit.

For patients that are re-screened, because of the potentially long screening phase (up to 12 weeks), the investigator is required to verify that the patient still meets eligibility criteria prior to randomization. All patients must be on stable regimen of the symptomatic monotherapy (MAO-B inhibitors or L-Dopa) for at least 3 months prior to randomization, with no plan to change treatment or dosage for the duration of the study.

In rare cases where an unexpected delay occurs due to logistical or technical reasons, the screening period may be extended by a few days. Extending the screening period beyond 12 weeks must be approved by the Medical Monitor and should be reserved for exceptional circumstances only; careful scheduling should remain a priority.

No patient may begin treatment prior to randomization and assignment of a patient identification number. Under no circumstances are patients who are randomized in the study, and who complete treatment as specified or who are prematurely discontinued from the study, permitted to be re-randomized in this study.

DOUBLE-BLIND TREATMENT

[redacted]

All study participants will continue to receive double-blind study treatment until both of these conditions are fulfilled [redacted]

Study assessments should be performed as described in the schedule of activities. Randomization will only occur after the patient has met all inclusion and exclusion criteria. Patients will be randomly assigned to receive either prasinezumab or placebo.

Study drug (prasinezumab or placebo) will be administered in this study Q4W. The three first doses will be given as an IV infusion over 2 hours; if well tolerated, the infusion time may be reduced to 1 hour for subsequent doses. All patients will receive mandatory premedication prior to the three first infusions. Dosing should take place as specified in the schedule of activities.

The first drug infusion should occur within 24–48 hours of randomization. If the baseline visit is split over two consecutive days, the investigator must ensure that all inclusion and exclusion criteria are still met on the day of the first study treatment infusion.

Patients who prematurely discontinue study treatment during the double-blind treatment period will remain blinded to treatment, and will be asked to continue the visits for safety and efficacy as per the schedule of activities, regardless of whether they change symptomatic treatment type or dosage, until the primary analysis has been completed. These patients will also be asked to participate in end-of-study and safety follow-up visits.

OPEN-LABEL EXTENSION

The OLE is a 2-year extension in which all participants will receive treatment. Participants and sites will remain blinded to prior treatment assignment until the end of the OLE period.

Prior to the double-blind treatment end-of-study visit, participants will be asked about their interest in joining the OLE. In order to join the OLE, participants must have completed the double-blind treatment period, must be deemed eligible and must have consented to participate in the OLE. Should the participants meet these requirements, and once all the double-blind treatment end-of-study visit assessments have been completed, the participants will be given the first dose of prasinezumab in the OLE period. Participants will continue with Q4W dosing of prasinezumab for 104 weeks.

ASSESSMENTS AT END-OF-STUDY VISIT OR EARLY TERMINATION VISIT

At the end of the double-blind period, all patients will be asked to return to the clinic to complete final efficacy and safety assessments 28 days (±7 days) following their final double-blind study treatment dose (end-of-study visit). Participants joining the OLE will be asked to return for an OLE end-of-study visit and for a safety follow-up visit 10 weeks (70 [± 7] days) after their last OLE dose. The participants who do not enter the OLE will be asked to return for a safety follow-up visit 10 weeks (70 [± 7] days) after their last dose of prasinezumab during the double-blind treatment period. The study will be closed after all participants who entered the OLE have completed 104 weeks of treatment and the safety follow-up visit.

All patients who discontinue treatment or withdraw from the study early (during the double-blind treatment period) will be asked to return approximately 28 days (±7 days) after the final dose of study drug in order to complete the early termination visit.

In addition, patients who discontinue treatment during the double-blind period of the study will be asked to return for collection of safety and efficacy data according to the schedule of activities until the end of the double-blind treatment period (including end-of-study and safety follow-up visits). Participants who withdraw from treatment during the OLE will be asked to return for the safety follow-up visit 70 days (±7 days) after last dose.

Autopsy reports, including cause of death, for all patients who die during the study (i.e., prior to the safety follow-up visit) should be requested.

See the schedule of activities for information about the assessments that should be performed upon study completion at the end-of-study or early termination visit.

SAFETY FOLLOW-UP

All participants will be asked to come back for a safety follow-up visit after the end of the double-blind treatment period (for patients not enrolling in the OLE), or at the end of OLE (for participants enrolling in the OLE). When patients complete the end-of-study visit or the early termination visit, every effort should be made to ensure that the safety follow-up visit and all related assessments are completed. After the end-of-study visit or early termination visit, adverse events should be recorded.

NUMBER OF PATIENTS

Approximately 575 patients will be enrolled in this study.

TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 50–85 years at time of signing the Informed Consent Form

- Ability to comply with the study protocol
- Body weight ranging from 45–110 kg (99–242 lbs.) and a body mass index of 18–34 kg/m^2
- Diagnosis of idiopathic PD based on MDS criteria, with bradykinesia plus one of the other cardinal signs of PD (resting tremor, rigidity), without any other known or suspected cause of parkinsonism
- Monotherapy treatment with MAO-B inhibitors (up to 1 mg rasagiline per day, or up to 10 mg selegiline per day) or up to 450 mg L-Dopa per day, with stable doses for at least 3 months prior to baseline
  - Monotherapy treatment implies that the patient has been treated with the same, unique treatment (MAO-B inhibitors only or L-Dopa only) for 3 months prior to baseline.
  - Stable doses for 3 months prior to baseline implies that the daily dose and the daily frequency of dosing was stable for 3 months prior to baseline.
  - For patients on carbidopa and levodopa extended-release capsules (Rytary®), the equivalent dose of immediate release L-Dopa needs to be calculated, and this value needs to be ≤450 mg/day, with stable doses for 3 months prior to baseline.
- A diagnosis of PD for at least 3 months to maximum 3 years at screening
- MDS-UPDRS Part IV score = 0 at screening and prior to randomization MDS-UPDRS Part IV is not administered to a patient on MAO-B inhibitors)
- Hoehn and Yahr Stage I or II in OFF medication state at screening and prior to randomization
- DaT–SPECT imaging consistent with dopamine transporter deficit, as assessed by the central reader (note: ^{123}Iloflupane [DaTSCAN™] tracer is used for dopamine imaging)
- No anticipated changes in PD medication from baseline throughout the study duration based on clinical status during screening
- Willingness and ability to use a smartphone application to measure PD-related symptoms for the duration of the study
- Willingness and ability to wear a smartwatch to measure PD-related motor signs
- Fluency in the language of the outcome measures at the site
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 70 days after the final dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, 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 participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

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

Current or Past Medical History

- Medical history indicating a Parkinsonian syndrome other than idiopathic PD, including but not limited to, progressive supranuclear palsy, multiple system atrophy, drug-induced parkinsonism, essential tremor, vascular parkinsonism, primary dystonia.
- Known carriers of PD gene mutations (*PRKN, PINK1,* or DJ1).
  - Note: Carriers of *GBA*, synuclein, or *LRRK2* mutations are allowed.
- History of MDS-UPDRS Part IV > 0 and/or of PD-related motor complications (e.g., dyskinesias and motor fluctuations)
- History of PD-related freezing episodes or falls
- History of brain surgery for PD
- Diagnosis of PD dementia
- Diagnosis of a significant neurological disease other than PD (including but not limited to Huntington's disease, normal pressure hydrocephalus, cerebrovascular disease including stroke, frontotemporal dementia, Alzheimer's disease, dementia with Lewy bodies, multiple sclerosis, brain tumor); history of repeated head injury; history of epilepsy or seizure disorder other than febrile seizures as a child
- History of chronic pain that could interfere with the assessment of the motor aspects of the disease
- History of, or screening brain MRI scan indicative of, clinically significant abnormality including but not limited to prior hemorrhage or infarct >1 cm^3 or >3 lacunar infarcts
- History of clinical psychiatric symptoms (e.g., confusion, hallucination, delusion, excitation, delirium, abnormal behavior) or any clinically significant psychiatric disease other than mild depression, depressive mood, or mild anxiety arising in the context of PD
- History of malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, non-metastatic prostate cancer, or Stage I uterine cancer
- Within the last year, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction)
  - Heart failure classified as New York Heart Association Class I or II cardiac disease is allowed if not associated with hospitalization within the previous 12 months
- Uncontrolled hypertension (e.g., blood pressure [BP] generally 160 mmHg systolic or 95 mmHg diastolic)
- Drug and/or alcohol abuse within 12 months prior to screening, in the investigator's judgment
  - Nicotine is allowed
  - Marijuana use is not allowed (this includes all forms of cannabidiol and tetrahydrocannabinol even if given for therapeutic use).
- Resident of a nursing home or assisted care facility
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 70 days after the final dose of study drug
  - Women of childbearing potential must have a negative serum pregnancy test result during screening prior to initiation of study drug.
- Clinically significant abnormalities in laboratory test results at the screening visit, including hepatic and renal panels, complete blood count, chemistry panel and urinalysis, including:
  - Total bilirubin, ALT or AST $>2\times$ the upper limit of normal (ULN)
  - Serum creatinine $>1.5\times$ the ULN

- Hematocrit less than 35% for males and less than 32% for females, or ANC count of < 1500/μL (with the exception of a documented history of a chronic benign neutropenia), or platelet cell count of < 120,000/μL; INR > 1.4 (in patients not treated with anticoagulants) or other coagulopathy.
- A clinically significant abnormal TSH test.
- 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 positives from true positives for 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.
- Positive result for acute or chronic infectious hepatitis B virus (HBV; [i.e., hepatitis B surface antigen (HBsAg positive test)]), for hepatitis C virus (HCV), or HIV 1 or 2. Successfully treated patients with HCV (undetectable HCV RNA) are eligible for enrollment. Participants who are immune due to HBV natural infection or HBV vaccination are eligible.

- Concomitant disease or unstable medical condition within 6 months of screening, or as specified below, that could interfere with, or treatment that might interfere with, the conduct of the study, or that would, in the opinion of the investigator or Sponsor, 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:
  - Autoimmune disease. However, well controlled conditions such as, but not limited to, quiescent rheumatoid arthritis, controlled type I diabetes, or mild-to-moderate psoriasis not requiring immunomodulating medications may be acceptable.
  - Any active infectious disease at baseline. Participants with active or uncontrolled infection including participants exhibiting symptoms consistent with SARS-CoV-2 infection coronavirus disease 2019 (COVID-19) should not be randomized until complete resolution of signs and symptoms. Participants who have tested positive for SARS-CoV-2 in the past, but without any current COVID-19-related symptoms, should be carefully and comprehensively evaluated as per usual medical practice and institutional guidance before enrollment. The investigator should assess the benefit/risk ratio for each participant with a history of SARS-CoV-2 infection; enrollment has to be discussed with the participant.
- Any febrile illness within 1 week prior to first dose administration.

<u>Medications and Treatments</u>

- Any previous administration of prasinezumab or other compound targeting α–synuclein.
- Enrollment in another investigational study.
  - Enrollment in a non-interventional study may be allowed but it is recommended to discuss with the Medical Monitor to ensure all potential contraindications have been assessed.
- Treatment with any monoclonal antibody or investigational immunomodulator within 180 days (or 5 half-lives, whichever is longer) before baseline (e.g., monoclonal antibodies, intravenous immunoglobulin, interleukin-2 [IL-2], interleukin-12 [IL-12], interferon or immunosuppressive drugs).
- Treatment with any other investigational therapy within 5 drug elimination half-lives or 90 days (whichever is longer) prior to initiation of study treatment or during study treatment.
- Allergy to any of the components of prasinezumab, a known hypersensitivity, or a previous IRR following administration of any other monoclonal antibody.

- Use of any treatment given to target PD motor symptoms and signs other than L-Dopa and MAO-B inhibitors, including, but not limited to, levodopa-carbidopa intestinal gel, dopamine agonists, COMT inhibitors (entacapone, opicapone, tolcapone), amantadine, adenosine A_{2a} antagonists or anticholinergics, for more than a total of 60 days or within 3 months from baseline
- Treatment with safinamide for more than a total of 60 days or within 60 days of baseline
- Anti-epileptic medication for non-seizure-related treatment, which has not remained stable for at least 60 days prior to baseline.
- 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.
- 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.
- Treatment with 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.
- Immunomodulating drugs including oral corticosteroids within 30 days prior to baseline.
  - Note: Nasal, inhaled, and topical corticosteroids are allowed.

Procedural

- Any contraindications to obtaining a brain MRI (e.g., claustrophobia unresponsive to reassurance or low dose of an anxiolytic agent, tooth implants).
- Any contraindications to DaT-SPECT imaging (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).
- Donation of blood over 500 mL within 3 months prior to screening
- Poor peripheral venous access
- For participants consenting to provide optional CSF samples by LP, the procedure 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
  - History of spinal mass or trauma
  - Participants failing to meet these criteria can still participate in the study and all other study assessments (with the exception of LP) as appropriate

Eligibility for Open-Label Extension

Participants who have been randomized and who have completed the double-blind treatment period will be eligible to participate in the OLE; however, participants who meet any of the following criteria will be excluded from entry in the OLE:

- Discontinued from study treatment during the double-blind treatment period

- Received any other investigational medication during the double-blind treatment period or after the end of double-blind treatment
- Participation in the OLE deemed inappropriate by the investigator (e.g., any serious medical condition or other concerns that preclude the participant's safe participation in the OLE or ability to comply with the required procedures)

Note: Participants may initiate or change symptomatic PD treatment as per standard of care during the OLE. This includes treatments given for advanced PD (including, but not limited to, deep brain stimulations, continuous levodopa-carbidopa intestinal gel).

END OF STUDY AND LENGTH OF STUDY

[redacted]

It is anticipated that the study will take approximatively 95 weeks to reach full enrollment. All patients will receive the study treatment for at least 76 weeks (this can be longer depending on when the required number of confirmed motor progression events is achieved). All patients will be asked to return to the clinic for an end-of-study visit 28 days (±7 days) after their final double-blind study treatment dose. If participants are eligible to join the OLE, they will receive prasinezumab for 104 weeks and will be asked to return for an OLE end-of-study visit and for a safety follow-up visit 10 weeks (70 [±7] days) after their final OLE dose. The participants who do not enter the OLE will be asked to return for a safety follow-up visit 10 weeks (70 [±7] days) after their final dose of prasinezumab during the double-blind treatment period. The study will be closed after all participants who have entered the OLE have completed 104 weeks of treatment and the safety follow-up visit.

Due to the longer than anticipated time to reach full enrollment, the Sponsor may take the decision to advance the clinical cut-off of the study and end the double-blind treatment period slightly earlier than completing 76 weeks treatment for all participants, provided that the observed number of events would be adequate to evaluate the primary outcome.

In addition, the Sponsor may decide to terminate the study at any time.

INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal product for this study is prasinezumab.

TEST PRODUCT (INVESTIGATIONAL DRUG)

The dose of prasinezumab administered in this study will be 1500 mg, given as an IV infusion Q4W.

COMPARATOR

The comparator for this study will be placebo, given as an IV infusion Q4W.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

Symptomatic PD medication (MAO-B inhibitors or L-Dopa), ^{123}I-Ioflupane (DaTSCAN™) tracer, and premedication given before infusion are considered non-investigational medicinal products.

STATISTICAL METHODS

PRIMARY ANALYSIS

The purpose of this study is to investigate the treatment effect of prasinezumab relative to placebo. The primary efficacy analysis will be based on an intent-to-treat (ITT) population that includes all randomized patients, with patients grouped according to their randomly assigned treatment.

All randomized patients receiving any amount of the study drug will be included in the safety analysis. Patients who are administered with study treatment other than the treatment they were randomly assigned to receive will be analyzed according to the treatment they actually received.

Primary Efficacy Analyses

The primary efficacy objective for this study is to evaluate the efficacy of prasinezumab compared with placebo on the basis of time to disease progression as assessed a confirmed motor progression event .

Confirmed motor progression is defined as a worsening event sustained over two consecutive assessments. The worsening event is defined either by :

- A≥5 points increase in MDS-UPDRS Part III score (assessed in "OFF" medication state) from baseline sustained over two consecutive assessments OR
- A change in medication after the first occurrence of a≥5-points increase in MDS-UPDRS Part III score (assessed in "OFF" medication state) from baseline and before the follow-up assessment

The primary efficacy analysis (ITT) population will consist of all randomized participants, with participants grouped according to their assigned treatment.

The primary estimand is the hazard ratio of a confirmed motor progression between prasinezumab and placebo in participants with PD.

For the analysis of the primary estimand, there are two intercurrent events that may occur before a participant can experience a confirmed event. The first is starting or changing symptomatic therapy, which will be handled using a treatment-policy strategy. The second is death, which will be considered a progression event at the time of death.

Details concerning the estimand strategy and different sensitivity analysis will be defined in the Statistical Analysis Plan (SAP).

A formal treatment comparison will be made using a [redacted] The same stratification factors used for randomization (type of symptomatic medication: MAO-B inhibitors vs. L-Dopa) will be used for this comparison. Disease progression curves in each treatment arm will be estimated using Kaplan–Meier estimates. The Kaplan–Meier estimates will provide a visual description of the disease progression curves and the difference across treatment arms. The treatment effect will be quantified via a hazard ratio, computed from a stratified Cox proportional-hazards regression, including a 95% CI. The effect of prognostic and predictive factors on disease progression will be assessed in an exploratory analysis using Cox multivariate regression.

[redacted]

Secondary Efficacy Analyses

The following secondary endpoints will be tested for the ITT population with participants grouped according to their assigned treatment.

- Time to worsening of patient's motor function as reported by the patient (≥3 points increase in MDS-UPDRS Part II total score from baseline) in the presence of a confirmed motor progression event (as defined in Section 6.4.1)
- Time to meaningful worsening (defined as a rating of "very much worse", "much worse" or "minimally worse" reported to be important to the patient) in Patient Global Impression of Change (PGI-C, Overall Disease Subscale)
- Time to meaningful worsening (defined as a rating of "very much worse", "much worse" or "minimally worse" reported to be clinically meaningful) in Clinician Global Impression of Change (CGI-C, Overall Disease Subscale)
- Change in motor function from baseline to Week 76, as measured by the MDS-UPDRS Part III total score (assessed in "OFF" medication state)
- Change in bradykinesia and rigidity from baseline to Week 76, as measured by the MDS-UPDRS Part III bradykinesia and rigidity subscore (assessed in "OFF" medication state)
- Time to onset of motor complications as assessed through MDS-UPDRS Part IV

A hierarchical testing procedure will be applied to adjust for multiple statistical testing of the confirmatory secondary endpoints. The overall type I error rate will thereby be controlled. Details about order of the hierarchical testing procedure will be given in the SAP.

Exploratory Efficacy Analyses

The following exploratory endpoints will be analyzed for the ITT population, as described in the Statistical Analysis Plan:

- [redacted]

In addition, summary descriptive statistics will be provided for all data acquired after Week 76 (including end-of-study visit) and further related data analyses may be detailed in the SAP.

Safety Analyses

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

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

- Nature, incidence, seriousness and severity of adverse events, with severity determined according to NCI CTCAE v5.0
- Incidence of adverse events of special interest
- Incidence of treatment discontinuations due to adverse events
- Nature, incidence, seriousness, severity, and timing of IRRs
- Mean change in vital signs from baseline over time and incidence of abnormal vital sign measurements

- Changes in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Change from baseline and incidence of laboratory abnormalities (including hematology, clinical chemistry, coagulation, and urinalysis parameters)
- Incidence of physical and neurologic examination abnormalities
- Change from baseline in suicidal ideation, as measured by C-SSRS

Pharmacokinetic Analyses

Patient data will be included in the PK analysis if there is sufficient dosing information and at least one adequately documented and quantifiable prasinezumab concentration per patient.

The previous population PK model (Report 1081130) that was developed using the Phase I data of prasinezumab and updated with PK data from Study BP39529 (PASADENA), will be used to analyze the sparse sampling dose-concentration-time data of prasinezumab collected during this study. Non-linear mixed effects modeling (with software NONMEM) will be used. Structural model refinement will be driven by the data and will be based on various goodness of fit indicators. The model may be revised if necessary.

Population and individual PK parameters (e.g., clearance 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. Secondary PK parameters such as area under the concentration-time curve (AUC), maximum concentration (C_{max}), and trough concentration (C_{trough}) at steady state will be derived from the individual post-hoc predictions. Additional PK analyses will be conducted as appropriate.

Graphical exploration of the relationship between prasinezumab exposure and disease progression (assessed as a ≥ 5 point worsening in MDS-UPDRS Part III) will be performed. If indicated by such exploration, more formal analyses of the PK/pharmacodynamic relationship using non-linear mixed effects modeling method will be conducted.

Further modeling analyses may be performed and will be documented in the SAP.

Exploratory analyses will also be performed in order to explore:

- The relationship between serum concentration or secondary PK parameters of prasinezumab and biomarker endpoints
- The relationship between serum concentration or secondary PK parameters of prasinezumab and safety endpoints.

Immunogenicity Analyses

As ADA samples from patients assigned to the placebo group will not be analyzed for prasinezumab PK concentration in the first instance, except by request, only the treated group will undergo statistical analysis in the first instance. The immunogenicity analysis population will consist of all patients on active treatment with at least one ADA assessment.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 4-fold greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported using descriptive statistics.

Biomarker Analyses

[redacted]

Health Status Utility Analyses

Change from baseline in EQ-5D-5L health utility index-based and VAS scores will be calculated at specified timepoints.

Open-Label Extension Period Analysis

Descriptive statistics will be used to summarize the OLE. Statistical methods similar (but not limited) to the double-blind period will be used to analyze the data and will further be described in the SAP.

The analyses will be performed at the end of the OLE. In case the Sponsor chooses to conduct additional analyses prior to end of OLE, this will be prospectively defined in the SAP.

DETERMINATION OF SAMPLE SIZE

The purpose of this study is to investigate the effect of prasinezumab on time to clinical disease progression, defined as a confirmed motor progression on MDS-UPDRS Part III score. Point and interval estimates of the true underlying hazard ratio will be obtained. A total of approximately 575 participants will be randomized in this study, with an assumed dropout rate of [redacted] annually.

[redacted]

INTERIM ANALYSES

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct an interim efficacy analysis. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP which will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analysis, and the iDMC Charter will also be made available to relevant health authorities.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
3T	3-Tesla
ADA	anti-drug antibody
ASA	acetylsalicylic acid
[redacted]	[redacted]
AUC	area under the concentration-time curve
BP	blood pressure
BW	body weight
CGI-C	Clinician Global Impression of Change
CGI-S	Clinician Global Impression, Severity
ClinRO	clinician-reported outcome
C_{max}	maximum concentration observed
COMT	catechol-O-methyl transferase
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DaT-SPECT	dopamine transporter imaging with single photon emission computed tomography
[redacted]	[redacted]
EC	Ethics Committee
eCOA	electronic clinical outcome assessment
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	Food and Drug Administration
FDG-PET	2-deoxy-2-[18F] fluoro-D-glucose positron emission tomography
GLP	Good Laboratory Practice
[redacted]	[redacted]
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
H&Y	Hoehn and Yahr
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee

Abbreviation	Definition
IgG1	Immunoglobulin class G1
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IP	intraperitoneal
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent-to-treat
IxRS	interactive voice or web-based response system
L-Dopa	levodopa
LP	lumbar puncture
mAb	monoclonal antibody
MAD	multiple ascending doses
MAO-B	monoamine oxidase B
MDS-UPDRS	Movement Disorder Society - Unified Parkinson's Disease Rating Scale
MN	mobile nursing
[redacted]	[redacted]
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NIMP	non-investigational medicinal product
NM	neuromelanin
[redacted]	[redacted]
NSAID	non-steroidal anti-inflammatory drug
OLE	open-label extension
PD	Parkinson's disease
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic
PPMI	Parkinson's Progression Markers Initiative
PRO	patient-reported outcome
Q4W	every 4 weeks
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
[redacted]	[redacted]
SAD	single ascending dose

Abbreviation	Definition
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SmPC	Summary of Product Characteristics
[redacted]	[redacted]
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
USPI	U.S. Package Insert
VAS	Visual Analog Scale

1. BACKGROUND

1.1 BACKGROUND ON PARKINSON'S DISEASE

Parkinson's disease (PD) is estimated to affect more than 10 million people worldwide (Parkinson's Disease Foundation 2020), making it the most common neurodegenerative movement disorder (de Rijk et al. 1997). PD is approximatively 1.5 times more common in men than in women (Parkinson's Disease Foundation 2020). PD is generally considered to be a disease of older adults, with the incidence increasing 5- to 10-fold from the sixth to the ninth decades of life (Simon et al. 2020). Based on current demographic trends, the number of patients with PD is expected to increase significantly over the next two decades (Dorsey et al. 2018).

PD is a progressive and chronic disorder of the central and peripheral nervous systems, presenting clinically with characteristic motor signs including bradykinesia, rigidity and resting tremor, postural instability and a plethora of debilitating non-motor symptoms. PD is defined by hallmark neuropathological features, most notably progressive loss of dopaminergic neurons in the substantia nigra pars compacta and their axonal fields in the striatum, and the presence of pathological α-synuclein aggregates that manifest as Lewy bodies in the neuronal cytoplasm and Lewy neurites in dendrites and axons (Spillantini et al. 1997; Poewe et al. 2017). Progressive loss of dopaminergic innervation of the striatum leads to reduced local dopamine release, which is associated with the onset and progression of motor signs (e.g., bradykinesia).

PD is clinically diagnosed by the presence of bradykinesia and at least one additional cardinal motor feature (rigidity, resting tremor), as well as supporting and exclusionary criteria (Postuma et al. 2015). Typically, the cardinal symptoms begin on one side of the body and affect the other side over time (Fahn 2008). Disease progression from early to advanced stage is marked by the appearance of motor complications and fluctuations (Luquin et al. 2017). Diagnosis is further supported by a substantial and sustained motor response to dopaminergic supplementation (Gibb and Lees 1988; Gelb et al. 1999; Bhidayasiri and Reichmann 2013).

In addition to the cardinal motor symptoms, many patients with PD also present with non-motor symptoms at the time of diagnosis. Some non-motor symptoms can precede the onset of classical motor symptoms by years or even decades (Poewe et al. 2017), and inevitably emerge with disease progression (Chaudhuri et al. 2006). Thus, non-motor symptom PD rating scales can help to detect early clinical disease. Non-motor symptoms include olfactory loss, constipation, rapid eye movement sleep behavior disorder (RBD), depression, anxiety, pain, and cognitive impairment (Martinez-Martin and Chaudhuri 2018). Non-motor symptoms have been associated with α-synuclein accumulation within the central and peripheral nervous system, which are affected before clinical diagnosis of PD (Del Tredici and Braak 2016). Non-motor symptoms become increasingly prevalent over the course of the disease and contribute

to severe disability, impaired quality of life, and shortened life expectancy (Chaudhuri et al. 2006).

Given that there is currently no objective clinical test that can support a definitive diagnosis (Postuma et al. 2016), misdiagnosis is common at the early stages of the disease (Poewe and Wenning 2002; Atik et al. 2016). Dopamine transporter imaging with single photon emission computed tomography (DaT-SPECT), which enables measurement of dopamine transporter proteins in dopaminergic neurons, can help improve the accuracy of PD diagnosis (Marek et al. 2014; Suwijn et al. 2015). A number of rating scales are used in PD to quantitatively assess motor function and other disease symptoms, and patient quality of life, in order to select appropriate treatment and disease management strategies (European Parkinson's Disease Association 2017).

Current treatments for PD mostly manage motor symptoms of the disease by boosting the function of remaining dopamine neurons using dopamine replacement therapy, dopamine receptor agonists, or inhibitors of the dopamine metabolizing enzyme monoamine oxidase B (MAO-B). However, these extensively used treatments do not modify the neuropathological processes that cause PD. These agents initially alleviate motor symptoms, but as dopaminergic and non-dopaminergic areas continue to degenerate, these drugs become less effective. Moreover, dopamine supplementation medications are associated with the onset of motor complications, nausea, daytime somnolence, sleep attacks, orthostatic hypotension, and impulse control disorders (Sprenger and Poewe 2013). Motor complications represent one of the most bothersome PD related symptoms in advanced PD (Politis et al. 2010). These include wearing off (the benefits of symptomatic medications begin to fade before it is time to take the next dose); "ON-OFF" phenomenon (cyclic alternation of good and bad symptom control, with "ON" periods where symptoms are relatively well managed, and "OFF" periods when symptom control is poor); delayed "ON" (after administration of symptomatic therapy, it takes longer for the symptoms to improve); partial "ON" (after administration of symptomatic therapy, the symptoms do not fully improve); dose failure (after administration of symptomatic therapy, the symptoms do not improve at all); freezing (incapacity to move the body, lasting from seconds to minutes); dystonia (muscles twisting without control, lasting from seconds to hours); and dyskinesias (uncontrolled involuntary movements that can affect one limb, such as an arm or leg, or the whole body). Treatments are also available to manage certain non-motor symptoms of PD (e.g., sleep disturbances, anxiety, and depression) that develop as neurodegeneration progresses beyond nigrostriatal dopaminergic areas.

PD is a progressive movement disorder that causes severe disability driven by increasing severity symptoms over time despite the use of symptomatic medications. Therapies that target the underlying neuropathological processes could slow, halt, or reverse the clinical progression and represent a clear unmet medical need for patients with PD.

1.2 BACKGROUND ON PRASINEZUMAB

Prasinezumab is an immunoglobulin class G1 (IgG1) humanized monoclonal antibody (mAb) directed against an epitope in the C-terminus of human α-synuclein.

In Phase I and Phase II studies, prasinezumab demonstrated favorable safety, tolerability, and pharmacokinetic (PK) profiles at all doses tested, with no immunogenicity concerns. The Phase II Study BP39529 (PASADENA) did not meet its primary endpoint (Movement Disorder Society – Unified Parkinson's Disease Rating Scale [MDS-UPDRS] total score including Parts I, II, and III); however, secondary endpoint analyses suggested a reduction in progression of the MDS-UPDRS Part III score, including bradykinesia and resting tremor. This finding was supported by the independent central rating of the motor score. Key prasinezumab nonclinical and clinical studies are summarized below.

1.2.1 Nonclinical Studies

[redacted]

[redacted]

1.2.2 Clinical Studies

The Phase I clinical development program for prasinezumab consisted of three clinical studies; Study PRX002-CL001 (BP29477; single ascending dose [SAD] study in healthy subjects in the United States; Schenk et al. 2017), Study JP40211 (SAD study in healthy male Japanese subjects), and Study PRX002-CL002 (BP29478; multiple ascending doses [MAD] study in participants with mild-to-moderate PD; Jankovic et al. 2018). All three studies have been completed and while their objectives were primarily safety and PK, the SAD studies (PRX002-CL001 and JP40211) included several serum biomarkers and the MAD study (PRX002-CL002) included several exploratory serum and CSF biomarker and clinical efficacy endpoints. 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 BP39529 (PASADENA) is an ongoing Phase II study in participants with early PD who are treatment naïve or taking MAO-B inhibitors. This study is exploring prasinezumab's safety, tolerability, efficacy, pharmacokinetics, and effects on biomarker levels.

Key findings from these studies are summarized below. Refer to the Prasinezumab Investigator's Brochure for further information.

1.2.2.1 Study BP29477

The first-in-human Study PRX002-CL001 (BP29477) assessed the safety, PK, and pharmacodynamics of prasinezumab in 40 healthy participants in five 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 per cohort) or placebo (n=2 per cohort). Serum prasinezumab exposure parameters increased proportionally with dose, resulting in dose- and time-dependent reductions in mean free serum α-synuclein levels (unbound), and increases in mean total serum α-synuclein levels (bound plus free). Prasinezumab demonstrated favorable safety, tolerability, and PK profiles at all doses tested, with no immunogenicity (Schenk et al. 2017).

1.2.2.2 Study JP40211

This randomized, double-blind, placebo-controlled SAD study assessed the safety, tolerability, pharmacokinetics, and pharmacodynamics of prasinezumab in 24 healthy Japanese participants at doses of 10, 30, or 60 mg/kg; (n=6 per cohort) or placebo (n=2 per cohort). Across the dose range of 10–60 mg/kg, the pharmacokinetics and pharmacodynamics (serum α–synuclein levels) of prasinezumab in healthy Japanese subjects were similar to previous observations in healthy non-Japanese subjects. In addition, prasinezumab demonstrated favorable safety and tolerability at all doses tested, with no immunogenicity.

1.2.2.3 Study PRX002-CL002

This randomized, double-blind, placebo-controlled MAD study assessed the safety, pharmacokinetics, and pharmacodynamics of prasinezumab in 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 prasinezumab (0.3, 1, 3, 10 mg/kg, n=8 per cohort; or 30, 60 mg/kg, n=12 per cohort) or placebo (n=4 per cohort) for three IV infusions administered every 28 days (Jankovic et al. 2018).

The highest mean exposure (at 60 mg/kg dose) in terms of C_{max} and the average area under the concentration-time curve (AUC) to the end of the dosing period (AUC_{tau}) after the third dose was 1160 μg/mL and 7000 μg • d/mL, respectively. These levels fall well below the no-observed-adverse-effect level (NOAEL) exposure in the cynomolgus monkey. CSF concentrations measured 1 week following the last dose were, on average, 0.3% (0.2–0.5%) of serum concentrations.

Treatment with prasinezumab resulted in a rapid and dose-dependent reduction in free serum α-synuclein (maximal decrease of 97%, 1 hour after 60 mg/kg infusion). The inhibition was long-lasting, starting 1 hour post-infusion and lasting for up to several weeks with increasing prasinezumab doses.

Prasinezumab was generally safe and well tolerated, with a trend for mild to moderate infusion-related reaction (IRRs; observed in 4 of 12 patients) at the highest dose tested (60 mg/kg). No patients developed anti-drug antibodies (ADAs) to prasinezumab during the study.

1.2.2.4 Study BP39529 (PASADENA)

Study BP39529 (PASADENA) is a fully enrolled ongoing study with 316 patients.

PASADENA is a Phase II, multicenter study to evaluate the effects of prasinezumab in patients with early PD (H&Y Stages I–II) who are either treatment naïve or treated with a MAO-B inhibitor. Participants were randomized in a 1:1:1 allocation ratio to placebo, or one of two prasinezumab doses: (1) high dose (4500 mg for body weight ≥ 65 kg; 3500 mg for body weight < 65 kg), or (2) low dose (1500 mg; for all body weights). This signal-detection study was designed to include 100 patients per arm, resulting in

80% power and two-sided alpha of 0.20, to detect a relative change in the efficacy of prasinezumab versus placebo, as measured by a change from baseline at Week 52 in the MDS-UPDRS total score (sum of Parts I, II, and III). The study consists of three parts: a 52-week, double-blind, placebo-controlled treatment period (Part 1) after which eligible participants continue into an all-participants-on-treatment, blinded-to-dose extension for 52 weeks (Part 2), followed by a 5-year open-label extension (OLE, Part 3).

The PASADENA Part 1 study did not meet its primary endpoint. However, prasinezumab was generally well tolerated with a favorable safety profile, no life-threatening adverse events, no adverse events related to study drug that resulted in withdrawal from treatment, and no immunogenicity concerns. Prasinezumab also showed signals of efficacy in secondary, exploratory and post-hoc analysis, including: a reduced decline in progression of MDS-UPDRS Part III score for both on-site and central ratings, and in MDS-UPDRS Part III bradykinesia subscore; a reduced risk on time to worsening of motor signs (+5 points on MDS-UPDRS Part III); a reduced decline in digital measures of motor function (digital biomarker motor score) with divergence of slopes. Prasinezumab did not show an effect on DaT-SPECT, MDS-UPDRS Part II, Part I, [redacted], or time to worsening for [redacted] motor aspects of daily living (+3 points on MDS-UPDRS Part I or II). These results were consistent in both the drug-naïve subgroup and patients treated with MAO-B inhibitors at baseline. Low and high doses showed a similar benefit-risk profile. PK analyses indicated that the exposure of prasinezumab in treated patients was consistent with expectations. These findings support the potential of prasinezumab to slow clinical decline in patients with PD. For further details, refer to Pagano et al. 2020.

Pre-specified exploratory analyses were conducted in PASADENA Part 2 to compare patients who received prasinezumab high dose or low dose for 104 weeks (early-start group) with patients who received placebo for the first 52 weeks (Part 1) and then prasinezumab high dose or low dose between Week 56 and 104 (Part 2) (delayed-start group). In line with the results of Part I, the exploratory analyses from baseline to Week 104 plus the 12-week treatment-free follow-up suggest a potential signal of efficacy on motor progression (MDS-UPDRS Part III score, MDS-UPDRS Part III bradykinesia subscore, and a reduced risk for time to meaningful progression of motor signs) in the early-start versus the delayed-start group. Refer to the Prasinezumab Investigator's Brochure for further information.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

To date, there are no approved treatments with demonstrated effects on underlying pathology capable of altering the disease course for patients with PD.
Current treatments for PD ameliorate the early motor symptoms of the disease, mainly

through the use of dopamine replacement therapy and dopamine receptor agonists. As the disease progresses and dopamine neurons continue to degenerate, symptomatic treatments become less effective and patients develop motor complications including response oscillations, wearing-off phenomena, and dyskinesias (Armstrong and Okun 2020).

Clinical and nonclinical evidence suggests that α-synuclein pathology may propagate in a directed fashion between anatomically connected brain regions. It is hypothesized that pathogenic aggregated forms of α-synuclein may be transmitted between neurons, thereby contributing to the progression of PD (Fields et al. 2019). Nonclinical evidence suggests that prasinezumab, a monoclonal antibody designed to preferentially bind to aggregated forms of α-synuclein, has the potential to slow or halt the progression of PD by preventing cell-to-cell transmission of pathogenic forms of α-synuclein (Section 1.2.1 and Prasinezumab Investigator's Brochure).

Signs of efficacy have been observed in the Phase II PASADENA study: patients treated with prasinezumab had a reduced rate of worsening of PD motor symptoms including bradykinesia, a cardinal feature of PD that contributes to disability. Based on its proposed mechanism of action, prasinezumab differs from any of the approved symptomatic therapies used in PD. Study BN42358 (PADOVA) is designed to assess the effect of prasinezumab on disease progression in patients with early PD who are receiving MAO-B inhibitors or levodopa (L-Dopa) to manage motor symptoms.

1.3.1.1 Rationale for Patient Population

In progressive neurodegenerative diseases such as PD, treatments targeting the underlying causes of the disease are expected to provide more benefit during the early stages, when further neuronal damage could still be prevented. While symptomatic treatments show short-term benefit by improving the symptoms of PD, they do not slow the progression of the underlying disease, providing an opportunity to explore the additional benefit of treatments with a different mechanism of action on disease progression. As symptomatic medications are expected to temporarily improve motor function, changes to these medications (dose or drug class) may confound the assessment of the treatment effect of prasinezumab. Thus, it is important for patients to be maintained on stable doses of their symptomatic treatment for as long as their symptom progression allows. Therefore, this study will enroll patients with early PD who are being treated with a stable dose of MAO-B inhibitors (selegiline up to 10 mg/day or rasagiline up to 1 mg/day) or L-Dopa (with a maximum dose of 450 mg/day). This study will not enroll treatment-naïve patients, who are expected to require symptomatic medication within a short time (Houghton et al. 2019). In addition, this study will not enroll patients taking dopamine agonists even if dosing is stable, because their side effect profile leads to frequent changes in dosage which may interfere with assessment of the primary outcome. For additional details about the requirements for maintaining patients on stable symptomatic treatment regimens for this study, see Section 3.4.2.

For additional details about permitted and prohibited symptomatic treatments, see Sections 4.4.1 and 4.4.4.

1.3.1.2 Rationale for Primary Endpoint

Treatments that address the underlying causes of neurodegeneration are expected to slow the clinical progression of the disease. However, in PD as in other neurodegenerative disorders, disease progression is generally slow. It typically starts with subtle motor changes that only gradually translate into functional impairment which negatively affects daily living. MDS-UPDRS is a well-validated scale that has been used in many pivotal studies for the symptomatic treatment of PD. It is composed of four parts: Part I assesses non-motor experiences of daily living; Part II assesses motor experiences of daily living; Part III assesses motor signs of PD, and Part IV assesses motor complications (see Section 4.5.5.1 for further details on this scale). An early PD cohort study (Parkinson's Progression Markers Initiative [PPMI]) demonstrated that MDS-UPDRS scores progress in a linear fashion over 5 years in PD study participants who were treatment naïve at enrollment (Holden et al. 2018). This study also demonstrated that progression was mainly driven by changes in the MDS-UPDRS Part III score, indicating the relative importance of motor signs over functional impairment in characterizing progression in the early stage of disease.

Based on this evidence, the primary endpoint for this study will be time to confirmed motor progression, defined as a worsening event sustained over two consecutive assessments. The worsening event is defined either by ≥ 5 points increase in MDS-UPDRS Part III (assessed in "OFF" medication state) sustained over two consecutive assessments or by a change in medication after the first occurrence of a ≥ 5 points increase in MDS-UPDRS Part III and before the follow-up assessment.

A time-to-event approach was selected in order to minimize the potential impact of changes in symptomatic therapy during the trial (effects of these changes are more pronounced when a continuous scale is used, i.e., when using the motor score itself), and to help ensure that any measured changes in MDS-UPDRS Part III score are clinically meaningful. Within-patient increase of ≥ 5 points on MDS-UPDRS Part III is considered meaningful progression in motor signs of PD. This threshold was selected based on an analysis conducted by Horváth et al. (2015), and verified by expert input to be clinically relevant. Horváth et al. (2015) assessed the mean change in MDS-UPDRS Part III score in patients classified as minimal worsening on the Clinical Global Impression of Change instrument. A mean value of +4.63 points [95% CI: 3.52 to 5.73] was identified using this approach. As this is a patient-level estimate and not a group-level comparison (i.e., it is not appropriate for use in comparing differences between groups, such as treatment arms), only integer values are possible. Thus, the score was rounded to 5 points.

A confirmation of the progression event at the subsequent assessment will be required to avoid interpreting transient worsening or fluctuations of motor signs as true events of

motor progression. In addition, a change in symptomatic PD medication could result in an improvement in motor signs potentially masking motor progression. Thus, a change in symptomatic PD medication after the first occurrence of the event and before the follow-up assessment will be considered as confirmation of motor progression.

1.3.1.3 Rationale for the Need to Maintain Stable Symptomatic Therapy

A key challenge for clinical trials in patients with PD who are taking medications to manage their symptoms is that disease progression may be masked by changes in symptomatic treatment (either type or dose), potentially reducing the ability to accurately assess treatment effects of therapies that target the underlying neuropathology. This is particularly relevant when using continuous endpoints. Time-to-event endpoints are only impacted if the change in medication occurs prior to the progression milestone.

An in-house analysis of PPMI data (PPMI 2020), based on data extracted on 27 January 2020, revealed similar rates of progression to a 5-point worsening on MDS-UPDRS Part III score for all participants, irrespective of the type of symptomatic treatment, or change in therapy. In this analysis, for treatment-naïve patients who started symptomatic therapy for the first time, an updated baseline value was taken at the time of the start of symptomatic therapy; data from these patients were not excluded from the analysis if their treatment was changed. Patients on MAO-B inhibitors or L-Dopa monotherapy progressed to the 5-point milestone at a similar rate, with a median time of 19 months (95% CI: 17 to 26 months and 16 to 23 months, respectively). This analysis indicates that for the patient population that will be enrolled in this study, the key event for the primary endpoint is likely to occur within the planned study timeframe. In the PASADENA study, approximately 75% of patients who required symptomatic treatment to be initiated or changed within the first 52 weeks from randomization reached the motor 5-point progression milestone before medication change was made. Medication changes were driven predominantly by worsening of PD symptoms linked to daily activities or employability. Thus, it is expected that most PD symptomatic medication changes in the present study would also occur after reaching the progression milestone. Nevertheless, changes in symptomatic therapy should be carefully managed to minimize the potential impact of these changes on the study endpoints. Patients will only be eligible to participate in the trial if their symptomatic therapy dose is stable prior to baseline, with no anticipated changes in PD medication throughout the study on the basis of their clinical status during screening (see Section 3.4.2 for additional details).

1.3.2 Benefit-Risk Assessment

To date, no treatments have been identified that alter the neuropathological progression of PD; thus the potential benefit of prasinezumab to patients with PD is promising and warrants its further exploration.

Clinical experience with prasinezumab to date (see Section 1.2.2) indicates that prasinezumab is well-tolerated with no significant safety concerns. No treatment-emergent serious adverse events were reported in healthy volunteers, and no studies were terminated prematurely. CNS penetration was demonstrated by a dose-dependent increase in prasinezumab levels in CSF, and a mean concentration of prasinezumab in CSF of 0.3% relative to serum across all dose levels. Additional results showed a rapid, dose- and time-dependent mean reduction of free serum α-synuclein levels of up to 97% after a single dose, which were statistically significant ($p < 0.0001$), and were maintained following two additional monthly doses. The study results supported advancing prasinezumab into the BP39529 (PASADENA) Phase II clinical study in patients with early PD.

Data from Part 1 of the PASADENA study provided information on 52 weeks of treatment with prasinezumab and suggested a reduction of progression of MDS-UPDRS Part III motor signs at both low and high doses based on scores reported by study sites; this finding was supported by independent central rating scores (see Section 1.2.2.4 for further details).

In Part 1, prasinezumab was safe and well tolerated. IRRs occurred with higher frequency and severity in the high-dose prasinezumab group than in the low-dose and placebo groups, while IRRs occurred with similar frequency and severity in the low-dose and placebo groups (34.0% in the high-dose group, 19.0% in the low dose group, and 16.2% in the placebo group). No IRRs led to study drug discontinuation.

The safety data from Part 2 of the PASADENA study on additional 48 weeks of treatment confirms the overall good tolerability of prasinezumab observed in Part 1; with 7.2% and 21.0% of IRRs in the low dose group and in the high-dose group respectively. Most of them occurred in participants who received placebo in Part 1 and then randomized to prasinezumab in Part 2. One IRR in the high dose group led to study discontinuation.

IRRs have been reported with the use of many antibodies and other biologic therapies. They are more likely to occur with the first or second infusion of a therapeutic monoclonal antibody, and the incidence and severity is related to dose and exposure (as observed in PASADENA). In order to reduce the occurrence and potential impact of IRRs, the mitigation measures employed in Part 1 and Part 2 of PASADENA study have been included in this protocol (i.e., prolonging infusion time to up to 2 hours and premedication for the first three infusions). In addition, an independent Data Monitoring Committee (iDMC) will monitor IRRs and other adverse event reports to ensure patient safety throughout the double-blind treatment period of the study (see Section 3.2 for further details).

Refer to Section 5.1 for information on anticipated risks for prasinezumab and risk mitigation measures, including guidelines for managing adverse events associated with prasinezumab.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of prasinezumab can be found in the Prasinezumab Investigator's Brochure.

The current study is designed to evaluate the effect of prasinezumab on slowing clinical progression, as measured by the time to confirmed motor progression in patients who are treated with standard-of-care symptomatic medication. Based on the evidence collected to date regarding prasinezumab potential clinical benefit, the high unmet medical need for therapies that can slow the disease progression in PD, and the observed safety profile to date, further clinical development of prasinezumab is warranted.

Benefit–Risk Assessment Specific to Concomitant Use of COVID-19 Vaccines in Participants Enrolled in Prasinezumab Clinical Trials

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, participants with PD are likely a more vulnerable population as COVID-19 appears to affect older adults more severely. On the basis of the current mode of action of prasinezumab, together with the clinical experience to date, there is no reason to believe that prasinezumab administration would cause participants to become immunocompromised or would increase susceptibility to infections. However, there is currently not enough clinical data available to definitively determine whether prasinezumab affects the risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

On the basis of mode of action of prasinezumab, together with clinical experience to date, there is no evidence to suggest that administration of prasinezumab would affect the efficacy of COVID-19 vaccinations, nor worsen the adverse events experienced in response to the vaccinations.

PD is a progressive and chronic disorder. In many countries (e.g., United Kingdom), patients with PD are considered clinically vulnerable and are a high priority patient group to receive COVID-19 vaccines. A group of PD experts has recently reviewed the benefit and risks of COVID-19 vaccines and recommended that patients with PD should receive COVID-19 vaccinations unless another health issue prevents this vaccination (Bloem et al. 2021). Per Concomitant Therapy section of this protocol, all preventive and routine immunizations are permitted (see Section 4.4.3). This permitted therapy would include all approved COVID-19 vaccines.

As with any other medication, COVID-19 vaccines should be reported as concomitant therapy by using the standard fields in the clinical database (see Section 4.4.3). Any adverse event due to the vaccination and any symptomatic treatment (e.g., with

analgesic and/or antipyretic medicinal products) should be adequately reported as adverse events.

In summary, based on no expected interaction with prasinezumab nor any impact of prasinezumab on vaccine efficacy, the currently effective protocol-mandated safety monitoring and risk mitigation measures are considered satisfactory in the context of conducting the study with the concomitant use of COVID-19 vaccines in participants enrolled in prasinezumab clinical trials.

2. OBJECTIVES AND ENDPOINTS

The PADOVA study will evaluate the efficacy, safety, and pharmacokinetics of prasinezumab compared with placebo in patients with early PD. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of prasinezumab compared with placebo on the basis of the following endpoint:

- Time to confirmed motor progression event

Details on the definition of confirmed motor progression event are provided in Section 1.3.1.2 and Section 6.4.1.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of prasinezumab compared with placebo on the basis of the following endpoints:

- Time to worsening of patient's motor function as reported by the patient (≥ 3 points increase in MDS-UPDRS Part II score from baseline) in the presence of a confirmed motor progression event (as defined in Section 2.1.1).
- Time to meaningful worsening (defined as a rating of "very much worse," "much worse," or "minimally worse") in Patient Global Impression of Change (PGI-C, Overall Disease Subscale)
- Time to meaningful worsening (defined as a rating of "very much worse," "much worse," or "minimally worse") in Clinician Global Impression of Change (CGI-C, Overall Disease Subscale)
- Change in motor function from baseline to Week 76, as measured by the MDS-UPDRS Part III score (assessed in "OFF" medication state)
- Change in bradykinesia and rigidity from baseline to Week 76, as measured by the MDS-UPDRS Part III bradykinesia and rigidity subscore (assessed in "OFF" medication state)
- Time to onset of motor complications as assessed through MDS-UPDRS Part IV

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of prasinezumab compared with placebo on the basis of the following endpoints:

- [redacted]

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of prasinezumab compared with placebo on the basis of the following endpoints:

- Nature, incidence, seriousness and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Incidence of adverse events of special interest
- Incidence of treatment discontinuation due to adverse events
- Nature, incidence, seriousness, severity, and timing of IRRs
- Mean change in vital signs from baseline over time and incidence of abnormal vital sign measurements
- Changes in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Change from baseline and incidence of laboratory abnormalities (including hematology, clinical chemistry, coagulation, and urinalysis parameters)
- Incidence of physical and neurologic examination abnormalities
- Change from baseline in suicidal ideation, as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS)

2.3 PHARMACOKINETIC OBJECTIVES

The PK objective for this study is to characterize the prasinezumab PK profile on the basis of the following endpoint:

- Serum concentration of prasinezumab at specified timepoints or PK parameters of prasinezumab

The exploratory PK objective for this study is to evaluate potential relationships between drug exposure and the efficacy and safety of prasinezumab on the basis of the following endpoints:

- Relationship between serum concentration or secondary PK parameters of prasinezumab and efficacy endpoints
- Relationship between serum concentration or secondary PK parameters of prasinezumab and biomarker endpoints
- Relationship between serum concentration or secondary PK parameters of prasinezumab and safety endpoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to prasinezumab on the basis of the following endpoint:

- Prevalence of ADAs at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

2.5 BIOMARKER OBJECTIVES

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with prasinezumab on the basis of the following endpoint:

- Change from baseline in EQ-5D-5L index-based and Visual Analog Scale (VAS) scores at Week 76

2.7 OPEN-LABEL EXTENSION (OLE): OBJECTIVES

The main objective for the OLE period of the study is to evaluate long-term safety and tolerability of prasinezumab in patients with early PD that have completed the double-blind treatment period of the PADOVA study on the basis of the following endpoints:

- Nature, incidence, seriousness and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Incidence of adverse events of special interest
- Incidence of treatment discontinuation due to adverse events
- Nature, incidence, seriousness, severity, and timing of IRRs
- Mean change in vital signs from baseline over time and incidence of abnormal vital sign measurements

- Changes in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Change from baseline and incidence of laboratory abnormalities (including hematology, clinical chemistry, coagulation, and urinalysis parameters)
- Incidence of physical and neurologic examination abnormalities
- Change from baseline in suicidal ideation, as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS)

In addition, exploratory objectives of this OLE are to evaluate long-term clinical and biomarker efficacy of prasinezumab in patients with early PD on the basis of similar endpoints to those of double-blind period. The OLE will also help to further assess potential relationships between drug exposure and the efficacy and safety of prasinezumab. [redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study BN42358 is a Phase IIb, randomized, double-blind, placebo-controlled, parallel group, multicenter study to evaluate efficacy and safety of prasinezumab, administered as a 1500 mg IV infusion every 4 weeks (Q4W), to patients with early PD on stable symptomatic monotherapy (MAO-B inhibitors or L-Dopa). This study will consist of the following periods: screening, double-blind treatment, OLE and safety follow-up. Participants who do not continue into the OLE will complete a safety follow-up after the double-blind treatment.

Patients providing informed consent will undergo screening prior to study drug administration. Eligible patients will be randomly assigned (in a [redacted] ratio) in a blinded fashion to receive either placebo or prasinezumab. To maintain a balanced number of patients in each treatment arm and to ensure the arms are comparable, randomization will be stratified by use of PD medication (MAO-B inhibitors vs. L-Dopa). Randomization will be performed through an interactive voice or web-based response system (IxRS).

The expected sample size will be approximately 575 patients. Patients will be recruited globally. Approximately 125 sites in approximately nine countries in North America and Europe will participate in this study. Patients who prematurely discontinue from the study treatment will be asked to continue the visits as per the schedule of activities until the primary analysis, and will not be replaced.

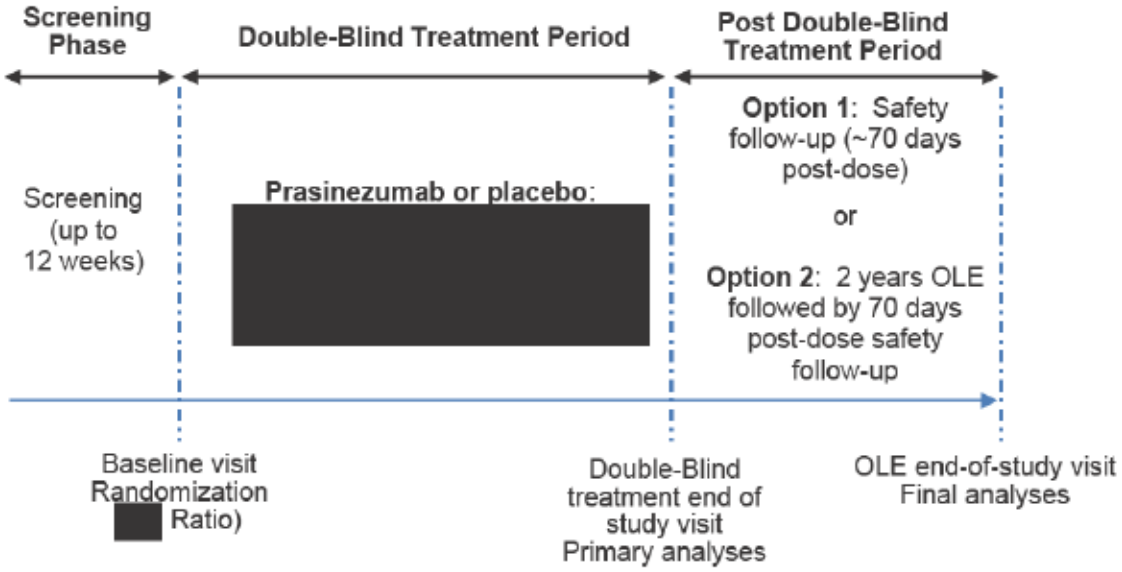
[redacted]

[redacted] All study participants will continue to receive double-blind study treatment until both of these conditions are fulfilled [redacted] Once the double-blind treatment period of the study is completed, participants who consent and are eligible will enter the OLE portion of the trial and will receive prasinezumab for approximately 2 years. Participants and sites will remain blinded to prior randomization assignment until the end of the OLE period.

An iDMC will be employed to monitor and evaluate patient safety throughout the double-blind treatment period, until the primary analysis is performed. Monitoring details will be described in the iDMC Charter.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



OLE=open-Label extension.

3.1.1 Screening

The screening phase will last up to 12 weeks. Patients who are candidates for enrollment in the study will be evaluated by the investigator to ensure that all eligibility criteria are met (see Sections 4.1.1 and 4.1.2). All patients must have signed the Informed Consent Form prior to screening and prior to any changes to their existing medication for the purposes of enrollment in the study.

Screening procedures are detailed in Appendix 1. It is recommended that MRI, DaT-SPECT imaging, and optional CSF collection (for patients consenting to this procedure) are performed last, after all other screening requirements have been satisfactorily completed, to ensure that these procedures are only performed for patients otherwise deemed eligible for the trial. During the screening phase, patients will also be asked to begin performing digital assessments (see Appendix 1 for further details on screening assessments). Note that due to the length of time required to complete digital assessments, the screening period will last for a minimum of 28 days (up to a maximum of 12 weeks). Careful scheduling of screening assessments is highly encouraged to ensure that patients can be randomized into the trial within the agreed screening period. It is recommended to perform all screening assessments within 6–8 weeks to allow for unforeseen issues that may delay the originally planned randomization dates.
Because of the potentially long screening phase (up to 12 weeks), the investigator is required to systematically verify that the patient still meets eligibility criteria prior to randomization. In order to be randomized and to receive double-blind treatment, patients must have no significant change in medical, psychiatric or neurological conditions or change in medication since screening.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion after at least 3 months have elapsed from screening failure, with the exception of screen failure for imaging not consistent with PD or for any condition indicating the patient is no longer at the early stage of PD (e.g., MDS-UPDRS Part IV score>0, H&Y stage>II), in which case rescreening is not permitted.
Patients must re-sign the consent form prior to re-screening. The investigator will record reasons for screen failure in the screening log. In case of re-screening, all screening assessments must be repeated with the exception of: lumbar puncture (for patients having previously consented to this procedure), MRI, and DaT-SPECT imaging if previous results were within eligible ranges and conducted no earlier than 6 months prior to the baseline visit.

For patients that are re-screened, because of the potentially long screening phase (up to 12 weeks), the investigator is required to verify that the patient still meets eligibility criteria prior to randomization. All patients must be on stable regimen of the symptomatic monotherapy (MAO-B inhibitors or L-Dopa) for at least 3 months prior to randomization, with no plan to change treatment or dosage for the duration of the study (see Section 3.4.2 for additional information).

In rare cases where an unexpected delay occurs due to logistical or technical reasons, the screening period may be extended by a few days. Extending the screening period beyond 12 weeks must be approved by the Medical Monitor and should be reserved for exceptional circumstances only; careful scheduling should remain a priority.

No patient may begin treatment prior to randomization and assignment of a patient identification number. Under no circumstances are patients who are randomized in the study, and who complete treatment as specified or who are prematurely discontinued from the study, permitted to be re-randomized in this study.

3.1.2 Double-Blind Treatment

[redacted] All study participants will continue to receive double-blind study treatment until both of these conditions are fulfilled [redacted].

Study assessments should be performed as described in the schedule of activities (see Appendix 1). Randomization will only occur after the patient has met all inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2). Patients will be randomly assigned to receive either prasinezumab or placebo.

Study drug (prasinezumab or matching placebo) will be administered in this study Q4W. The three first doses will be given as an IV infusion over approximately 2 hours; if well tolerated, the infusion time may be reduced to approximately 1 hour for subsequent doses. All patients will receive mandatory premedication prior to the three first infusions (see Section 4.3.3). Dosing should take place as specified in the schedule of activities (Appendix 1).

The first drug infusion should occur within 24–48 hours of randomization. If the baseline visit is split over two consecutive days, the investigator must ensure that all inclusion and exclusion criteria are still met on the day of the first study treatment infusion.

Patients who prematurely discontinue study treatment during the double-blind treatment period will remain blinded to treatment, and will be asked to continue the visits for safety and efficacy as per the schedule of activities (Appendix 1), regardless of whether they change symptomatic treatment type or dosage, until the primary analysis has been completed. These patients will also be asked to participate in end-of-study and safety follow-up visits.

3.1.3 Assessments at Double-Blind Treatment End-of-Study Visit or Double-Blind Treatment Early Termination Visit

At the end of the double-blind period, all patients will be asked to return to the clinic to complete final efficacy and safety assessments 28 days (±7 days) following their final dose (end-of-study visit).

All patients who discontinue treatment or withdraw from the study early (during the double-blind treatment period) will be asked to return approximately 28 days (±7 days) after the final dose of study drug in order to complete the early termination visit.

In addition, patients who discontinue treatment will be asked to return for collection of safety and efficacy data according to the schedule of activities (Appendix 1) until the end of the double-blind treatment period. These patients will also be asked to participate in end-of-study and safety follow-up visits.

Autopsy reports, including cause of death, for all patients who die during the study (i.e., prior to the safety follow-up visit) should be requested.

See the schedule of activities (Appendix 1) for information about the assessments that should be performed upon study completion at the end-of-study or early termination visit.

3.1.4 Open Label Extension

The OLE is a 2-year extension in which all participants will receive treatment. Participants and sites will remain blinded to prior treatment assignment until the end of the OLE period.

Prior to the double-blind treatment end-of-study visit, participants will be asked about their interest in joining the OLE. In order to join the OLE, participants must have completed the double-blind treatment period, must be deemed eligible and must have consented to participate in the OLE. Should the participants meet these requirements, and once all the double-blind treatment end-of-study visit assessments have been completed, the participants will be given the first dose of prasinezumab in the OLE period. Participants will continue with Q4W dosing of prasinezumab for 104 weeks.

The first three doses of prasinezumab during the OLE period will be given as an IV infusion over approximately 2 hours; if well tolerated, the infusion time may be reduced to approximately 1 hour for subsequent doses. All participants will receive mandatory premedication prior to the first three infusions (see Section 4.3.3). Dosing should take place as specified in the schedule of activities (Appendix 1).

Participants who prematurely discontinue study treatment during the OLE period will remain blinded to prior treatment assignment, and will be asked to complete the OLE *early termination*/end-of-study visit and OLE safety follow-up visit.

3.1.5 Safety Follow-Up

All participants will be asked to come back for a safety follow-up visit after the end of the double-blind treatment period (for participants not enrolling in the OLE), or at the end of the OLE (for participants enrolling in the OLE; see Appendix 1).

When patients complete the end-of-study visit or the early termination visit, every effort should be made to ensure that the safety follow-up visit and all related assessments are completed.

After the end-of-study visit or early termination visit, adverse events should be recorded as outlined in Sections 5.5 and 5.6.

See the schedule of activities (Appendix 1) for the list of assessments to be performed at the safety follow-up visit.

3.2 INDEPENDENT DATA MONITORING COMMITTEE

The iDMC will evaluate patient safety in this study, and if deemed necessary by the Sponsor and/or the iDMC, may review efficacy data. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, IRRs, ECGs, vital signs), the iDMC will review all necessary cumulative data at regular intervals during the study; efficacy, PK and ADA data may also be reviewed if deemed necessary. 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. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, the protocol should be amended, enrollment should be held pending further safety evaluations). The iDMC may also evaluate unplanned interim analyses for efficacy or futility (see Section 6.10).

The first iDMC meeting for review of safety data will occur after approximately 90 participants (approximately 45 participants per arm) have received their first three infusions. After that, regular iDMC meetings for review of safety data will be scheduled approximately every 6 months until the end of double-blind treatment period. The iDMC may be convened earlier, or at additional timepoints, if warranted by safety considerations or for other reasons as specified in the iDMC Charter.

3.3 END OF STUDY AND LENGTH OF STUDY

The double-blind treatment period will end when a [redacted].

It is anticipated that the study will take approximatively 95 weeks to reach full enrollment. All patients will receive the study treatment for at least 76 weeks (this can be longer depending on when the required number of confirmed motor progression events is achieved). All patients will be asked to return to the clinic for an end-of-study visit 28 days (±7 days) after their final double-blind study treatment dose. If participants are eligible to join the OLE, they will receive prasinezumab for 104 weeks and will be asked to return for an OLE end-of-study visit and for a safety follow-up visit 10 weeks (70 [±7] days) after their last OLE dose. The participants who do not enter the OLE will be asked to return for a safety follow-up visit 10 weeks (70 [± 7] days) after their last

dose of prasinezumab during the double-blind treatment period. The study will be closed after all participants who entered the OLE have completed 104 weeks of treatment and the safety follow-up visit.

Due to the longer than anticipated time to reach full enrollment, the Sponsor may take the decision to advance the clinical cut-off of the study and end the double-blind treatment period slightly earlier than completing 76 weeks treatment for all participants, provided that the observed number of events would be adequate to evaluate the primary outcome.

In addition, the Sponsor may decide to terminate the study at any time.

3.4 RATIONALE FOR STUDY DESIGN

Study BN42358 is a Phase IIb, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of prasinezumab in patients with early PD on stable treatment with symptomatic monotherapy (MAO-B inhibitors or L-Dopa).

3.4.1 Rationale for Prasinezumab Dose and Schedule

The dose of prasinezumab administered in this study will be 1500 mg, given as an IV infusion Q4W. Dose selection was guided by in vivo nonclinical pharmacological studies, as well as Part 1 results from PASADENA (BP39529), a Phase II study in patients with early PD who were treatment-naïve or were taking MAO-B inhibitors at the start of the trial (see Section 1.2.2.4).

In a dose-response study conducted in a transgenic mouse model of α-synucleinopathy, weekly intraperitoneal (IP) doses of 1 mg/kg and higher produced effects on neuropathological endpoints. 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 and/or balance impairment), suggesting that 1–10 mg/kg/week dosing in mice resulted in therapeutic drug exposure levels (for details, refer to the Prasinezumab Investigator's Brochure). [redacted]

In the PASADENA study (BP39529), low and high doses were selected to fall in the predicted therapeutic range identified in mouse efficacy models and minimize the risk of IRR. The low dose (1500 mg IV for all body weights [BW]) was predicted to achieve serum trough concentration levels above those attained with 1 mg/kg/week dosing in mice. The high dose (4500 mg IV for BW ≥65 kg; 3500 mg IV for BW <65 kg) was predicted to achieve serum trough concentrations comparable to 10 mg/kg/week dosing in mice. Further, this high dose was predicted to achieve serum maximum concentrations comparable to those with the maximum tolerable dose (60 mg/kg) in the

MAD study, where 4 of 12 patients experienced IRRs. The low and high doses were expected to be sufficiently separated to enable dose- and exposure-response analyses.

As described in Section 1.2.2.4, analyses of PASADENA Part 1 showed a reduction of progression of motor signs measured by MDS-UPDRS Part III, in particular bradykinesia and resting tremor. These data were confirmed by independent central rating scoring. Post-hoc analyses of PASADENA Part 1 also suggested a reduced risk for time to worsening of motor signs (≥5 points on MDS-UPDRS Part III). No clear dose response was observed, suggesting that the prasinezumab low and high doses chosen for PASADENA study have similar efficacy profiles. Exposure at steady-state in the low and high-dose groups reached target levels predicted from Phase I data using population PK modeling. Mean steady-state trough concentrations in the low-dose group were approximately 33 μg/mL, well above the mean concentration of 17 μg/mL achieved with 1 mg/kg/week dosing in mice. Mean trough concentrations in the high-dose group were approximately 97 μg/mL, above the mean concentration of 70 μg/mL achieved with 10 mg/kg/week dosing in mice. As with the dose-response analysis, no exposure-response relationship was identified, despite the dose-dependent increase in exposure between 1500 mg and 3500/4500 mg doses. Collectively, these results suggest that 1500 mg and 3500/4500 mg are similarly efficacious doses in humans.

In Part 1 of the PASADENA study, the majority of adverse events were Grade 1 or 2 in severity. The percentage of patients with adverse events in the prasinezumab groups was similar to the percentage of patients with adverse events in the placebo group (93.3% in the low dose [1500 mg] group, 91.5% in the high dose [3500/4500 mg] group, and 82.9% in the placebo group). IRRs in the 1500 mg dose group were reported with the similar frequency (19.0%) when compared with the placebo group (16.2%), and at higher frequency in the high-dose group (34.0%). Most IRR reported in the 1500 mg dose group were of Grade 1 and occurred on a single occasion. No IRR led to study discontinuation. No clinically relevant trends in clinical laboratory data, physical examination, vital sign, or ECG parameters were observed.

In Part 2 of the PASADENA study, the proportion of reported serious adverse events was 7.6% in the high-dose group compared to 4.6% in low-dose group In the low-dose group, the adverse event with the highest incidence (≥10%) was nasopharyngitis (15.1%), while in the high-dose group, adverse events with the highest incidence (≥10%) were IRRs (21.0%). Most of the IRRs reported in Part 2 occurred in patients who received placebo in Part 1 and who started prasinezumab in Part 2. One IRR led to study discontinuation.

Thus, in light of the favorable safety and tolerability profile at 1500 mg Q4W, and the similar efficacy profiles at 1500 mg Q4W and 3500/4500 mg Q4W, a dosing regimen of 1500 mg Q4W was chosen for this study.

3.4.2 Rationale for Patient Population

PD is a neurodegenerative disease, and mounting evidence suggests that the protein α-synuclein may be responsible for initiating and spreading neuropathological processes in PD (Fernandez-Valle et al. 2019; Balestrino and Schapira 2020; Simon et al. 2020). There are similarities between the α-synuclein hypothesis of PD and the hypothesized propagation of tau pathology in Alzheimer's disease (Goedert 2015; Visanji et al. 2019). It is well accepted in both the PD and Alzheimer's fields that the benefit of a treatment targeting underlying causes of neurodegeneration is likely to be greater if initiated early in the disease course. For this reason, the development of prasinezumab has focused on patients with early PD.

This study will evaluate the efficacy of prasinezumab, when compared with placebo, on slowing progression of motor signs of PD in patients who have been recently diagnosed with this disease and are receiving symptomatic treatment. More precisely, participants will be eligible if they have idiopathic PD with bradykinesia along with one of the other cardinal signs of PD (resting tremor, rigidity), without any other known or suspected cause of parkinsonism (adapted from the MDS Clinical Diagnostic Criteria for Parkinson's Disease, Postuma et al. 2015). All participants will be required to undergo DaT-SPECT imaging to evaluate dopamine transporter levels. The results from this scan must be consistent with neurodegenerative parkinsonism as determined by a central laboratory. Patients are also required to be receiving a stable regimen of symptomatic monotherapy for PD (MAO-B inhibitors or L-Dopa) for at least 3 months prior to randomization.

In this study, only MAO-B inhibitor or L-Dopa monotherapy is allowed. Patients on other therapies (including other monotherapies) will not be eligible. PD is a heterogeneous disease characterized by variable clinical phenotypes with distinct rates of disease progression (Erro et al. 2013; Greenland et al. 2019). Minimizing variability in the symptomatic treatments that patients receive during the trial will help to reduce sources of heterogeneity within the study population. MAO-B inhibitors, dopamine agonists, and L-Dopa are widely prescribed in early PD. Dopamine agonists were excluded due to their side effect profile leading to frequent changes in dosage, which could interfere with the primary outcome measurement in this study. Other treatments targeting PD (e.g., levodopa/carbidopa intestinal gel, catechol-O-methyl transferase [COMT] inhibitors, glutamate antagonists, adenosine A_{2a} antagonists, anticholinergics) are available but these are often prescribed later in the course of the disease, and/or in combination with other PD treatments; therefore these treatments will not be permitted symptomatic therapies for patients in this study.

At baseline, all study participants must have been on a stable regimen of symptomatic treatment for at least 3 months. Changes in symptomatic treatment (type or dosage) are discouraged while patients are participating in the double-blind part of the study. If a study participant experiences a marked and persistent change in their PD symptoms to

an extent that they cannot tolerate in their personal or professional life, changes to symptomatic therapy in accordance with local guidelines may be permitted. It is recommended to discuss such changes with the Medical Monitor if they occur during the double-blind part of the study. [redacted]

3.4.3 Rationale for Control Group in the Double-Blind Treatment Period

Information from other treatment and longitudinal studies (PPMI 2011; Kieburtz et al. 2015) was used to guide the current study design. In these studies, there was 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 this study.

Given that there are currently no approved compounds with a similar mechanism of action as prasinezumab that would be appropriate to include as an active control, patients will be randomly assigned to receive prasinezumab or placebo in addition to standard-of-care symptomatic therapies.

3.4.4 Rationale for a 2-Year Open-Label Extension

Participants who complete the double-blind treatment period will have the option to enroll in a 2-year OLE, see Section 3.1.4 for further information. The OLE will allow for the collection of safety and efficacy information on long-term exposure to prasinezumab.

3.4.5 Rationale for Biomarker Assessments

[redacted]

[redacted]

3.4.5.2 Digital Biomarkers

Smartphones and wrist-worn wearables have high-quality sensors that enable remote, non-invasive, frequent, and precise measurement of motor and non-motor symptoms (Maetzler et al. 2013; Ossig et al. 2016). Digital biomarkers may therefore provide more sensitive assessments of motor progression and fluctuation over time than established clinical rating scales. Smartphone sensor data, including motion and location, were collected during the previous RO7046015 MAD (PRX002-CL002) and PASADENA (BP39529) studies, where patients completed daily "active tests" and then carried the telephone with them throughout the day ("passive monitoring"). Analyses of these data revealed very high adherence and convergent validity with clinical measures of motor severity (i.e., MDS-UPDRS Part III score; Lipsmeier et al. 2018, 2019), similar to previous reports (e.g., Tsanas et al. 2010; Patel et al. 2011; Kostikis et al. 2014; Kassavetis et al. 2016). On the basis of this evidence, digital biomarkers will be collected in the current study to maximize the probability of detecting a potential therapeutic effect, and to potentially provide new insight into the nature of motor and non-motor deficits in PD, as well as their impact on daily living, by means of real-time data collection outside of the clinic setting.

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will randomize approximately 575 patients with DaT-SPECT imaging results consistent with a dopamine transporter deficit who have been diagnosed with PD for at least 3 months to maximum of 3 years at the time of screening. All patients enrolled in the study must have been on a stable regimen of monotherapy treatment with an MAO-B inhibitor or L-Dopa for at least 3 months, with no treatment or dosage changes expected for the duration of the study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥50–85 years at time of signing the Informed Consent Form
- Ability to comply with the study protocol
- Body weight ranging from 45–110 kg (99–242 lbs.) and a body mass index (BMI) of 18–34 kg/m^2
- Diagnosis of idiopathic PD based on MDS criteria (Postuma et al. 2015) with bradykinesia plus one of the other cardinal signs of PD (resting tremor, rigidity), without any other known or suspected cause of parkinsonism
- Monotherapy treatment with MAO-B inhibitors (up to 1 mg rasagiline per day, or up to 10 mg selegiline per day) or up to 450 mg L-Dopa per day with stable doses for at least 3 months prior to baseline

  'Monotherapy treatment' implies that the patient has been treated with the same unique treatment (MAO-B inhibitors only or L-Dopa only) for at least 3 months prior to baseline

  'Stable doses' for at least 3 months prior to baseline implies that the daily dose and the daily frequency of dosing was stable for at least 3 months prior to baseline

  For patients on carbidopa and levodopa extended-release capsules (Rytary®), the equivalent dose of immediate release L-Dopa needs to be calculated, and this value needs to be ≤450 mg/day, with stable doses for at least 3 months prior to baseline
- A diagnosis of PD for at least 3 months to maximum 3 years at screening
- An MDS-UPDRS Part IV score of 0 at screening and prior to randomization (Note: MDS-UPDRS Part IV is not administered to a patient on MAO-B inhibitors)
- H&Y Stage I or II in OFF medication state at screening and prior to randomization
- DaT–SPECT imaging consistent with dopamine transporter deficit, as assessed by the central reader (note: ^{123}I-Ioflupane (DaTSCAN™) tracer is used for dopamine imaging)
- No anticipated changes in PD medication from baseline throughout the study duration based on clinical status during screening
- Willingness and ability to use a smartphone application to measure PD-related symptoms for the duration of the study
- Willingness and ability to wear a smartwatch to measure PD-related motor signs
- Fluency in the language of the outcome measures at the site
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:

Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 70 days after the final dose of study drug.

A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, 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 participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

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

Current or Past Medical History

- Medical history indicating a Parkinsonian syndrome other than idiopathic PD, including but not limited to, progressive supranuclear palsy, multiple system atrophy, drug-induced parkinsonism, essential tremor, vascular parkinsonism, primary dystonia.
- Known carriers of PD gene mutations (*PRKN, PINK1,* or DJ1).

  Note: Carriers of *GBA*, synuclein, or *LRRK2* mutations are allowed.
- History of MDS-UPDRS Part IV > 0 and/or of PD-related motor complications (e.g., dyskinesias and motor fluctuations)
- History of PD-related freezing episodes or falls
- History of brain surgery for PD
- Diagnosis of PD dementia
- Diagnosis of a significant neurologic disease other than PD (including but not limited to Huntington's disease, normal pressure hydrocephalus, cerebrovascular disease including stroke, fronto-temporal dementia, Alzheimer's disease, dementia with Lewy bodies, multiple sclerosis, brain tumor); history of repeated head injury; history of epilepsy or seizure disorder other than febrile seizures as a child

- History of chronic pain that could interfere with the assessment of the motor aspects of the disease
- History of, or screening brain MRI scan indicative of, clinically significant abnormality including but not limited to prior hemorrhage or infarct > 1 cm^3 or > 3 lacunar infarcts
- History of clinically significant psychiatric symptoms (e.g., confusion, hallucination, delusion, excitation, delirium, abnormal behavior) or any clinically significant psychiatric disease other than mild depression or, depressive mood, or mild anxiety arising in the context of PD
- History of malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, non-metastatic prostate cancer, or Stage I uterine cancer
- Within the last year, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction)
  - Heart failure classified as New York Heart Association Class I or II cardiac disease is allowed if not associated with hospitalization within the previous 12 months
- Uncontrolled hypertension (e.g., blood pressure [BP] generally 160 mmHg systolic or 95 mmHg diastolic)
- Drug and/or alcohol abuse within 12 months prior to screening, in the investigator's judgment
  - Nicotine is allowed
  - Marijuana use is not allowed (this includes all forms of cannabidiol and tetrahydrocannabinol even if given for therapeutic use)
- Resident of a nursing home or assisted care facility
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 70 days after the final dose of study drug
  - Women of childbearing potential must have a negative serum pregnancy test result during screening prior to initiation of study drug.
- Clinically significant abnormalities in laboratory test results at the screening visit, including hepatic and renal panels, complete blood count, chemistry panel and urinalysis, including:
  - Total bilirubin, ALT or AST > 2 × the upper limit of normal (ULN)
  - Serum creatinine > 1.5 × the ULN
  - Hematocrit less than 35% for males and less than 32% for females, or ANC count of < 1500/μL (with the exception of a documented history of a chronic benign neutropenia), or platelet cell count of < 120,000/μL; INR > 1.4 (in patients not treated with anticoagulants) or other coagulopathy.
  - A clinically significant abnormal thyroid-stimulating hormone (TSH) test.
  - 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 positives from true positives for 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.
  - Positive result for acute or chronic infectious hepatitis B virus (HBV; [i.e., hepatitis B surface antigen (HBsAg positive test)]), for hepatitis C virus (HCV), or HIV 1 or 2. Successfully treated patients with HCV (undetectable HCV RNA) are eligible for enrollment. Participants who are immune due to HBV natural infection or HBV vaccination are eligible.
- Concomitant disease or unstable medical condition within 6 months of screening, or as specified below, that could interfere with, or treatment that might interfere with, the conduct of the study, or that would, in the opinion of the investigator or Sponsor, 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:
  - Autoimmune disease

    However, well controlled conditions such as, but not limited to, quiescent rheumatoid arthritis, controlled type I diabetes, or mild-to-moderate psoriasis not requiring immunomodulating medications may be acceptable.
  - Any active infectious disease at baseline

    Participants with active or uncontrolled infection including participants exhibiting symptoms consistent with SARS-CoV-2 infection should not be randomized until complete resolution of signs and symptoms. Participants who have tested positive for SARS-CoV-2 in the past, but without any current COVID-19-related symptoms, should be carefully and comprehensively evaluated as per usual medical practice and institutional guidance before enrollment. The investigator should assess the benefit/risk ratio for each participant with a history of SARS-CoV-2 infection; enrollment has to be discussed with the participant.
- Any febrile illness within 1 week prior to first dose administration

Medications and Treatments

- Any previous administration of prasinezumab or other compound targeting α-synuclein.
- Enrollment in another investigational study

  Enrollment in a non-interventional study may be allowed but it is recommended to discuss with the Medical Monitor to ensure all potential contraindications have been assessed.
- Treatment with any monoclonal antibody or investigational immunomodulator within 180 days (or 5 half-lives, whichever is longer) before baseline (e.g., monoclonal

antibodies, intravenous immunoglobulin, interleukin-2 [IL-2], interleukin-12 [IL-12], interferon or immunosuppressive drugs).

- Treatment with any other investigational therapy within 5 drug elimination half-lives or 90 days (whichever is longer) prior to initiation of study treatment or during study treatment
- Allergy to any of the components of prasinezumab, a known hypersensitivity, or a previous IRR following administration of any other monoclonal antibody.
- Use of any treatment given to target PD motor symptoms and signs other than L-Dopa and MAO-B inhibitors, including but not limited to levodopa-carbidopa intestinal gel, dopamine agonists, COMT inhibitors (entacapone, opicapone, tolcapone), amantadine, adenosine A_{2a} antagonists or anticholinergics, for more than a total of 60 days or within 3 months from baseline.
- Treatment with safinamide for more than a total of 60 days or within 60 days of baseline
- Anti-epileptic medication for non-seizure-related treatment, which has not remained stable for at least 60 days prior to baseline
- 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.
- 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.
- Treatment with 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.
- Immunomodulating drugs including oral corticosteroids within 30 days prior to baseline.

  Note: Nasal, inhaled, and topical corticosteroids are allowed.

Procedural

- Any contraindications to obtaining a brain MRI (e.g., claustrophobia unresponsive to reassurance or low dose of an anxiolytic agent, tooth implants)
- Any contraindications to DaT-SPECT imaging (i.e., known hypersensitivity to the active substance or to any of the excipients)

  Participants with a hypersensitivity to iodine may receive an alternative thyroid-blocking agent (e.g., potassium perchlorate or sodium perchlorate).
- Donation of blood over 500 mL within 3 months prior to screening
- Poor peripheral venous access

- 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,
  - History of spinal mass or trauma,

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

4.1.3 Eligibility for the Open-Label Extension

Participants who have been randomized and who have completed the double-blind treatment period (including the end-of-study visit) will be eligible to participate in the OLE; however, participants who meet any of the following criteria will be excluded from entry in the OLE:

- Discontinued from study treatment during the double-blind treatment period
- Received any other investigational medication during the double-blind treatment period or after the end of double-blind treatment
- Participation in the OLE deemed inappropriate by the investigator (e.g., any serious medical condition or other concerns that preclude the participant's safe participation in the OLE or ability to comply with the required procedures)

Note: Participants may initiate or change symptomatic PD treatment as per standard of care during the OLE (see Section 4.4.2). This includes treatments given for advanced PD (including but not limited to deep brain stimulation, continuous levodopa-carbidopa intestinal gel)

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an IxRS.

Patients will be randomly assigned to one of two treatment arms: prasinezumab or placebo. Randomization will occur in a [redacted] ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm.

Randomization will be stratified according to the following criterion: PD medication (MAO-B inhibitor vs. L-Dopa).

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include specialists external to Roche as needed to create unblinded data displays for the iDMC reviews (see Section 3.2). Members of the iDMC will be fully unblinded; no Roche personnel will have access to the unblinded data displays reviewed by the iDMC.

The randomization list will also be made available to the IxRS service provider, to the individuals responsible for PK and ADA sample bioanalysis.

While PK and immunogenicity samples must be collected from patients assigned to the placebo arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK and ADA samples from patients assigned to the placebo will not be analyzed for prasinezumab PK or ADA concentration except by request (e.g., to evaluate a possible error in dosing). Samples collected from patients on placebo will not be analyzed in the first instance, but retained for subsequent analysis if appropriate.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. However, the treatment code should not be broken except in emergency situations. The investigator should inform the Medical Monitor that the treatment code has been broken.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly.
The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and

personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is prasinezumab. Symptomatic PD medication (MAO-B inhibitors or L-Dopa), ^{123}I-Ioflupane (DaTSCAN) tracer and premedication given before infusion are considered non-investigational medicinal products (NIMPs). *Appendix 4 identifies all investigational, auxiliary, and non-investigational medicinal products for this study.*

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Prasinezumab and Placebo

Prasinezumab will be supplied by the Sponsor as a sterile concentrate for solution for infusion in a glass vial with elastomeric stopper and aluminum seal. Each vial contains 500 mg of prasinezumab. Placebo will be supplied by the Sponsor as a generic diluent in a glass vial. The infusion bag content must be prepared locally; normal saline bags will be provided by the sites.

Prior to use, the appropriate volume of concentrated prasinezumab solution or generic diluent should be added to normal saline by the study pharmacist. *The study pharmacist who is responsible for preparing the double-blind period study drug should not be involved* in any other aspects of the study *during the double-blind period and during the OLE period. A study pharmacist who is responsible for preparing the OLE-period study drug and never prepared double-blind period study drug, may be involved in other parts of the study* (see Pharmacy Manual for further details). 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.

IMP vials should be stored at 2–8°C until use.

For information on the prasinezumab formulation, see the Pharmacy Manual and Prasinezumab Investigator's Brochure.

4.3.1.2 Symptomatic PD Medication and Premedication

Symptomatic PD medications and premedications used to mitigate IRRs and hypersensitivity are considered NIMPs.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The dose of prasinezumab administered in this study will be 1500 mg, given as an IV infusion Q4W.

Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

At applicable sites, study treatment may be administered by a trained health care professional at the patient's home or another suitable location, if the patient has given written informed consent to participate in mobile nursing visits. Study visits eligible for mobile nursing (MN) are detailed in Appendix 1.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2.

4.3.2.1 Prasinezumab and Placebo

Prasinezumab or placebo will be administered by IV infusion to all participants during the double-blind treatment period. During the OLE period, all participants will receive prasinezumab IV infusions.

Prasinezumab drug product 180 mg/mL (supplied as 500 mg/ 2.78mL filled in 6 mL colorless glass vials) will be administered IV after dilution in 250 mL 0.9% sodium chloride bags. The qualified individual (unblinded study pharmacist or designee) responsible for dispensing the study drug at the site will prepare the correct dose according to the randomization schedule. This individual will record the date dispensed and participant's number on the study drug box label, and on the Drug Inventory and Dispensing Log. This individual will also record the study drug (e.g., batch number) received by each patient during the study.

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for mobile nursing visits. Patients will be alerted to watch for signs of anaphylactic and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted. Study drug must be administered by a health care professional and all patients will stay under close supervision of health care personal for at least one hour after each infusion. For the first three infusions during the double-blind treatment period and during the OLE period, vital signs must be monitored before each infusion, every 15 minutes during the infusion, and every 30 minutes after the infusion until the infusion line is removed. For subsequent treatment infusions, vital signs must be monitored before each infusion, every

30 minutes during the infusion, and every 30 minutes after the infusion until the infusion line is removed, unless safety considerations necessitate a different monitoring frequency.

During the double-blind treatment period and during the OLE period, study drug should be given as IV infusion over approximately 2 hours for the first three doses. If the first three infusions are well tolerated, infusion time can be reduced to approximately 1 hour for subsequent doses. The date of the infusion, as well as start and end times, should be recorded on the eCRF. The study drug should be administered through a dedicated line with an in-line filter. IV 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 *the entire duration of the post-dose observation period, which is* a minimum of 1 hour for all infusions. If no IRRs 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. For the management of IRRs and hypersensitivity reactions, see Section 5.1.1.1.

ADA samples should be collected for patients who experience a Grade 2 or higher IRR or show clinical signs of a hypersensitivity reaction, including an immune-complex reaction. For each ADA sample, a corresponding PK sample should be collected at the same time so that the prasinezumab concentration at the time of the IRR or hypersensitivity can be determined. The time and date for each sample should be recorded in the eCRF. In addition, if a patient experiences a Grade 2 or higher IRR, a blood sample should be taken to assess immunologic parameters (tryptase, cytokine panel, C3, C3a, C5a, and total IgE). A blood sample for immunologic parameters will be taken for all patients at baseline.

If a patient experienced a Grade 1 or higher IRR during a previous infusion, the rate of infusion should be reduced for all subsequent infusions. An infusion length of approximately 2 hours is recommended. If the patient experiences no further IRRs during the next infusion, the rate of infusion may once again be increased.

Guidelines for treatment interruption or discontinuation are provided in Section 5.1.2.1 Cases of accidental overdose or medication error, including a description of associated adverse events, should be reported as described in Section 5.3.5.12.

Prasinezumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Infusions of Prasinezumab

First Three Infusions	Subsequent Infusions
• Administer the infusion at a rate of 750 mg/hr • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines (see Section 4.3.3). If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).	• If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, begin the infusion at an initial rate of 750 mg/hr and follow instructions for the first three infusions. • If the patient tolerated the prior infusions well (no ≥ Grade 2 reactions) the infusion rate can be increased to 1500 mg/hr. • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines (see Section 4.3.3). If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).

4.3.3 Premedication

Prasinezumab has a low potential to induce cytokine release, as determined by in vitro studies (for additional details, refer to the Prasinezumab Investigator's Brochure). In the PASADENA (Study BP39529), premedication and a slow rate of infusion were mandatory for the first three study drug administrations. For subsequent doses, these measures could be applied at the investigator's discretion. Part 1 data from PASADENA showed that the incidence and severity of IRRs were comparable in the placebo and the low dose (1500 mg) prasinezumab group. The incidence of IRRs had the same rapid decline from the first to the third infusions in both treatment groups. Afterwards IRRs were rare in frequency and mild in severity. Therefore, the same premedication strategy used for PASADENA will be implemented in Study BN42358 in the double-blind treatment period and upon entry into the OLE period.

4.3.3.1 First Three Infusions of the Double-Blind Treatment Period and of the Open-Label Extension

A premedication regimen will be administered 30–60 minutes prior to infusion for the first three doses of the double-blind treatment period and first three doses of the OLE.
The premedication regimen will consist of the following:

- An antihistamine (H_1-receptor antagonist) **and** an anti-pyretic medication (acetaminophen 500–1000 mg PO or IV (or alternatively ibuprofen 400–600 mg or other non-steroidal anti-inflammatory drugs [NSAID] per institutional standard if acetaminophen cannot be tolerated).

4.3.3.2 Fourth and Subsequent Infusions of the Double-Blind Treatment Period and of the Open-Label Extension

No systematic premedication is required; the decision to use premedication should be based on signs and symptoms observed during previous infusions. Thus, participants who experienced a Grade 2 or higher IRR on a previous infusion should be treated with the following premedications:

- An antihistamine (H_1-receptor antagonist) **and** an anti-pyretic (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 experiences a Grade 3 IRR, in addition to the premedication specified above, 200 mg hydrocortisone IV (or equivalent dose of another corticosteroid) should be added to the list of premedication for subsequent infusions.

Premedication regimens for subsequent treatments may be reduced or omitted in case of Grade 1 events or no IRRs during the previous treatment.

4.3.3.3 Premedication in Case of Infusion-Related Reaction Recurrence

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

- A dose of antihistamine (H_1-receptor antagonist, as per local practice) is taken the night before the administration, and
- The same dose of the same antihistamine (H_1-receptor antagonist), with an anti-pyretic medication (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 the infusion.

The addition of steroids may be considered in case of previous Grade 3 or higher IRR.

4.3.4 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist or mobile nurse]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposal or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP.
The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received, and that any

discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients randomized in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the Pharmacy Manual and/or the Prasinezumab Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.5 Continued Access to Prasinezumab

Currently, the Sponsor does not have any plans to provide Roche IMP (prasinezumab) or any other study treatments to patients who have completed the double-blind treatment period of the study or the OLE. The Sponsor may evaluate whether to continue providing prasinezumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

https://assets.roche.com/f/176343/x/1b18e080e0/2025-revision-roche_global_policy_on_continued_access_to_investigational_interventions.pdf

4.4 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 90 days prior to screening to the follow-up visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy during the Double-Blind Treatment Period

4.4.1.1 MAO-B Inhibitor Monotherapy

Participants who are currently receiving treatment for PD with a MAO-B inhibitor (up to 1 mg/day of rasagiline or up to 10 mg/day of selegiline) should be on a stable dose for at least 3 months, prior to baseline. Patients will be treated with stable daily doses as recommended by the U.S. Package Insert (USPI) or Summary of Product Characteristics (SmPC) for rasagiline monotherapy or selegiline monotherapy and are

encouraged to maintain consistent treatment and dosing, and refrain from switching to other PD treatments during the study.

4.4.1.2 L-Dopa Monotherapy

Participants who are currently receiving treatment for PD with L-Dopa monotherapy (up to 450 mg/day) should be on a stable dose for at least 3 months, prior to baseline. Patients will be treated with stable daily doses as recommended by the USPI or SmPC and are encouraged to maintain consistent treatment and dosing, and refrain from switching to other PD treatments during the study.

For these participants, the MDS-UPDRS (Parts II, III, and IV) and digital biomarker in-clinic assessments will be performed in a practically defined "OFF" medication state: no L-Dopa medication since the prior evening (defined as ≥ 12 hours since the last dose of L-Dopa). Part III (motor assessment) and digital biomarker in-clinic assessments will be repeated at least one hour after receiving medication in-clinic ("ON" medication state) at pre-specified visits (see Appendix 1). These participants will need to be reminded not to take their L-Dopa treatment in advance of their study visit in which MDS-UPDRS is administered, and should be asked to bring their medication to the study visit so that they can take their regular L-Dopa dose. At visits including assessments in "ON" medication state, the regular L-Dopa dose should be taken at least 1 hour before the "ON" medication state assessments.

4.4.2 Permitted Therapy during the Open-Label Extension Period

During the OLE period, symptomatic treatment for PD including but not limited to MAO-B inhibitors, COMT inhibitors (entacapone, tolcapone), amantadine, anticholinergics, levodopa, both ergot and non-ergot (pramipexole, ropinirole, rotigotine) dopamine agonists may be prescribed. This also includes all treatments given for advanced PD (e.g., deep brain stimulation).

4.4.3 Other Permitted Therapy during the Double-Blind Treatment Period and during the Open-Label Extension Period

Participants who are currently being treated with antidepressants or anxiolytics should remain on a stable dose for at least 3 months 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 or routine immunizations (e.g., tetanus/diphtheria booster, herpes zoster, pneumococcal pneumonia, influenza, COVID-19) should be timed to coincide mid-cycle (halfway between two infusions).

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

Premedication with antihistamines, antipyretics, and/or NSAIDs may be administered at the discretion of the investigator based on guidance provided in Section 4.3.3.

Over-the-counter, herbal medications, food/nutritional supplements and/or homeopathic remedies are permitted.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated as detailed in Section 4.3.3.

4.4.4 Prohibited Therapy during the Double-Blind Treatment Period

During the study, it is discouraged to change the dosage of current PD therapy or to start a new symptomatic treatment for PD, including levodopa-carbidopa intestinal gel, COMT inhibitors (entacapone, opicapone, tolcapone), amantadine, adenosine A_{2a} antagonists or anticholinergics, both ergot and non-ergot (pramipexole, ropinirole, rotigotine) dopamine agonists and any other treatment given to target PD motor symptoms and signs.

If the study participant experiences a marked and persistent change in their PD symptoms to an extent that they cannot tolerate in their personal or professional life, changes to symptomatic treatment dosage or type that are in accordance with local guidelines may be permitted. It is recommended to discuss such changes with the Medical Monitor. [redacted]

4.4.5 Prohibited Therapy during the Double-Blind Treatment Period and during the Open-Label Extension Period

Other prohibited therapies include:

- Antipsychotic agents (including clozapine and olanzapine), metoclopramide, α-methyldopa, flunarizine, amoxapine, amphetamine derivatives, reserpine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norephedrine, phentermine, phenylpropanolamine and modafinil within 90 days prior to baseline and during the study
- Immunomodulating drugs within 30 days prior to baseline and during the study, except nasal, inhaled and topical corticosteroids

- For participants undergoing LP, oral anticoagulants (direct Factor Xa inhibitors and direct thrombin inhibitors), low-molecular-weight heparin, warfarin (Coumadin), acenocoumarol, and phenprocoumon
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 5 drug elimination half-lives or 90 days (whichever is longer) prior to initiation of study treatment and during study treatment

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

At applicable sites, certain study assessments may be performed by a health care professional at the patient's home or another suitable location, to improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for providing mobile nursing (MN) services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, trained, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient, and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the site. MN visits will be scheduled on specified visit days, to allow relevant assessments to be performed at the patient's home or another suitable location. For some sites, where possible, site staff may also conduct patient visits at home or at another suitable location, if applicable by law, with Sponsor's agreement, conditions permitting and provided that the patient has provided informed consent. The schedule of activities (see Appendix 1) specifies the visits that are eligible to be conducted at the patient's home or another suitable location. Further details are provided in the Mobile Nursing Manual.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for randomized patients and for patients who are not subsequently randomized will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking

history, and use of alcohol and drugs of abuse, will be recorded at screening. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient from 90 days prior to screening to the follow-up visit will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

As this study is being conducted in multiple geographic regions, it is likely that patients of different ethnic origins will be randomized in the study. Although there is currently no indication that prasinezumab is metabolized or eliminated differently or that the treatment effect would be different in patients of different ethnic origins, collecting this information is essential to adequately evaluate the results of this study (e.g., possible differences in PK exposure [concentration of the drug in the blood] or treatment effect).

4.5.3 Physical and Neurological Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated. A neurologic examination, performed at screening and other specified visits, should include an assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic BP 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 measurement will be obtained after 2 minutes of standing for orthostatic vital signs at the protocol-specified time-points. When possible, the same arm should be used for all blood pressure measurements.

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.

In the OLE, body temperature may be taken at any visit if deemed necessary by the Investigator, but is no longer mandatory at each visit.

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Disease-Specific Assessments

4.5.5.1 Movement Disorder Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

- 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. In this study, Part II–IV will be used. Part II assesses motor experiences of daily living. This subscale consists in 13 questions answered 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 of symptomatic treatment, dyskinesias, and motor fluctuations using historical and objective information. The rater will complete this assessment only for patients on L-Dopa treatment. [redacted]

For each question a numeric score is assigned between 0–4, where 0 = Normal, 1 = Slight, 2 = Mild, 3 = Moderate, 4 = Severe impairment. Composite scores (for each Part) are determined by summing the numeric values of each question. For Part II, score ranges from 0 to 52, Part III score ranges from 0 to 132 and Part IV score ranges from 0 to 24, with higher scores indicating greater impairment. For rigidity, subscore ranges from 0 to 20, bradykinesia subscore ranges from 0 to 52, with higher scores indicating greater impairment.

For participants taking L-Dopa, MDS-UPDRS Parts II, III, and IV should be assessed in the "OFF" medication state (defined as ≥ 12 hours since the last dose of L-Dopa). Following these assessments, the patient should take their delayed L-Dopa dose in the clinic. At pre-specified visits, the Part III (motor assessment) should be repeated ≥ 1 hour later in the "ON" medication state. Participants will need to be reminded not to take L-Dopa prior to study visits where MDS-UPDRS assessments will

be performed, and instead bring their missed L-Dopa dose to the clinic to be taken during the study visit.

The MDS-UPDRS Part III/IV rater will be [redacted] As per MDS guidelines, the rater should rate the performance of each task as the patient performs it at the time of the clinical assessment. [redacted]

[redacted]

Additional details are provided in the Project Plan Manual.

In the double-blind treatment period of the study, the MDS-UPDRS Part II will be clinician administered and will be assessed every 2 weeks from baseline until the double-blind treatment end-of-study visit. Assessments that coincide with in-clinic dosing visits should be performed at the clinic. The remaining assessments will be performed via telemedicine (i.e., the investigator or a designated representative will call the participant at their home and administer MDS-UPDRS Part II, PGI-C, and PGI-S over the phone starting at Week 2). Participants taking L-Dopa do not need to be in an "OFF" medication state for MDS-UPDRS Part II assessments performed via telemedicine. The rater who administers MDS-UPDRS Part II [redacted]

4.5.5.2 Hoehn and Yahr Stages (H&Y)

The H&Y assessment provides a global measure of the severity of PD based on clinical findings and functional disability. The scale allocates stages from 0 to 5 to indicate the relative level of motor disability; this is a commonly used system to quantify progression of PD symptoms. This scale is included within the MDS-UPDRS and will be completed for all participants. The stages are defined as follows:

- Stage 0: Asymptomatic.
- Stage 1: Unilateral involvement only.
- Stage 2: Bilateral involvement without impairment of balance.
- Stage 3: Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.
- Stage 4: Severe disability; still able to walk or stand unassisted.

- Stage 5: Wheelchair-bound or bedridden unless aided.

[redacted]

4.5.5.4 Digital Biomarkers Assessments

Each participant will receive a preconfigured smartphone and smartwatch with installed software for the digital biomarker assessments. The devices can only be used for the purpose of the study. Participants will use the devices and software to assess motor and non-motor symptoms. The smartphone will also be used to complete selected patient-reported outcomes (PROs; see Section 4.5.8).

Digital biomarker assessments will not be performed in the OLE.

Digital Biomarker Remote Monitoring

Participants will be provided with devices for digital biomarker collection and trained how to use them during a screening visit. During the study, including the screening period, participants will be instructed to conduct "active tests" every day, at approximately the same time (ideally in the morning, after breakfast). The "active tests" consist of a short, preconfigured sequence of tasks that assess motor symptoms (upper and lower body movements, upper limb dexterity, voice, and speech) and non-motor symptoms (including an electronic Trail Making Test and Information Processing Speed Test for cognition). For "passive monitoring," participants will be instructed to carry the smartphone and wear the smartwatch throughout the day as they go about their daily routine.

Data are encrypted and uploaded to secure servers whenever the phone is connected to Wi-Fi.

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

Digital Biomarker In-Clinic Assessments

Participants will be instructed to bring the smartphone and smartwatch to every clinic visit to check adherence and technical status of the devices. Participants will receive replacement device sets if they are defective.

At selected clinic visits, participants will be asked to conduct the full "active tests" under the supervision of a person trained on the digital biomarker approach.

For participants taking L-Dopa, the in-clinic assessments will be performed in the "OFF" medication state (defined as ≥ 12 hours since the last dose of L-Dopa). At pre-specified visits, the in-clinic assessments will be repeated ≥ 1 hour after the patient takes their L-Dopa dose in the clinic ("ON" medication state).

The smartphone and smartwatch must be returned to the clinic in cases where the subject does not meet eligibility criteria or at the end of the study.

Approximately 3–6 months prior to the end of the double-blind period or at the time when the patient discontinues the study during the double-blind period, participants will be asked to complete a satisfaction survey regarding their experience using the smartphone and smartwatch during the study.

Additional details about digital biomarker assessments are provided in the PD Digital Biomarker Manual.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

4.5.6.1 Standard Laboratory Samples

Samples for the following laboratory tests will be sent to a central laboratory for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

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. When the clinical significance of abnormal laboratory results is considered to be uncertain, screening laboratory 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 can 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.

- Hematology: WBC count, RBC count (including MCV and RBC morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard-of-care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and LDH
- Coagulation: INR, aPTT, and PT
- Thyroid function testing: TSH and free thyroxine (also known as T4)

- HIV serology: HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody
- HBV serology: HBsAg, total hepatitis B core antibody (HBcAb), and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- Lipids: cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.
- Other hormones: follicle stimulating hormone (FSH) in female participants to confirm postmenopausal status at screening only.
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed *locally at the site (using the test provided by the Sponsor)* at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Urinalysis*: A urine* dipstick *for* protein, blood, glucose, leucocytes, nitrites, pH, specific gravity and ketones *(using the dipsticks provided by the Sponsor) will be performed locally at the site*. Microscopic examination will be performed by the central laboratory if blood and/or protein results are positive (i.e., confirmed by a positive repeated dipstick sample).
- Urine drug screen: This should at a minimum include: amphetamines, barbiturates, cannabinoids, cocaine, opiates, 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 4.1.2).

For sampling procedures, storages conditions, and shipment instructions, refer to the Laboratory Manual.

4.5.6.2 Pharmacokinetic Samples

The following samples will be sent to a central laboratory for analysis:

- Serum samples for PK analysis

The samples for population PK analysis will be collected from all randomized participants in this study at pre-specified timepoints. For treatment visits where PK samples are required, samples will be collected before and after study drug infusion. Additional PK samples will be collected from the first 40 participants who are enrolled in the trial (see Appendix 1). The date and time of sample collection should be recorded on the eCRF.

Prasinezumab concentrations will be determined using validated assay. Samples from participants randomly assigned to receive placebo will not be analyzed by default, but

will be retained for subsequent analysis if appropriate. If required, remaining PK samples may also be used for additional validation experiments. Details on sampling procedures, storage, and shipment are provided in the Laboratory Manual.

4.5.6.3 Anti-Drug Antibodies Samples

The following samples will be sent to a central laboratory for analysis:

- Serum samples for immunogenicity analysis

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

Blood samples for ADA will be taken at pre-specified timepoints. ADA samples should also be collected for participants who experience a Grade 2 or higher IRR, and for participants with clinical signs of hypersensitivity reaction (in particular, immune-complex reactions).

For all ADA samples, a corresponding PK sample should be collected at the same time so that prasinezumab concentration can be determined. The date and time of sample collection should be recorded on the eCRF.

Validated screening, confirmatory, and titer assays will be employed to detect ADAs against prasinezumab. Samples from participants randomly assigned to receive placebo will not be analyzed by default, but will be retained for subsequent analysis if appropriate.

If required, remaining ADA samples may also be used for additional assay development or validation experiments. Details on sampling procedures, storage, and shipment are provided in the Laboratory Manual.

4.5.6.4 Biomarker Samples

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Serum and plasma biomarker samples.

[redacted] These samples may also be used for the development of disease-related tests or tools.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.6.5 Timeframe for Sample Storage and Testing

For sampling procedures, storage conditions, and shipment instructions, see the separate Laboratory Manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.15), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- All blood samples collected for biomarker research and assay development will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

4.5.7 Electrocardiograms

12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1). ECGs acquired on different days should be as closely time-matched as possible. During the double-blind study period, three interpretable ECG recordings (e.g., without artifacts) must be obtained at each timepoint (±5 minutes). The average of these three readings will be used to determine ECG intervals (e.g., PR, QRS, and QT). Single ECG recordings may be obtained at unscheduled timepoints as indicated. During the OLE, single ECG recordings must be obtained at each timepoint as specified in the Appendix 1 and single ECG recoding may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 2 hours

after a meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be collected by a central ECG vendor and made available on the vendor's ECG portal. The ECG data 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. Any morphologic waveform changes or other ECG abnormalities observed by the investigator must be documented on the eCRF.

4.5.8 Clinical Outcome Assessments

PRO and clinician-reported outcome (ClinRO) instruments will be used to assess the treatment benefit and more fully characterize the safety profile of prasinezumab. In addition, PRO instruments will enable the measurement of each patient's direct experience with prasinezumab.

PRO and ClinRO data will be collected through use of the electronic tablets and smartphones (see Appendix 3 for further details).

4.5.8.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered or interviewer-administered (as appropriate) at the clinic at specified timepoints during the study (see Appendix 1), and on a daily basis at home. At the clinic, PRO instruments will be administered prior to study drug infusions.

PRO instruments (translated into the local language as appropriate) will be completed via an electronic device provided by the Sponsor. The device will be pre-programmed to enable the instrument to be administered at specified timepoints. Site staff will provide electronic devices and instructions for completing PRO instruments. PRO data will be transmitted to a central database maintained by the electronic device vendor. The data will be made available to appropriate study personnel.

Patients should be given the following instructions for completing PRO instruments at home:

- [redacted]
- [redacted]
- [redacted]

During clinic visits and visits conducted by an MN professional, PRO instruments should be administered as outlined below:

- [redacted]

ClinRO instruments will be completed at the clinic at specified timepoints during the study (see Appendix 1). ClinRO instruments will be administered before study drug infusions. ClinRO instruments will be completed through use of electronic devices provided by the Sponsor. Clinicians must complete the official version of each ClinRO instrument, as provided by the Sponsor. The data will be transmitted to a central database maintained by the electronic device vendor and the Sponsor.

4.5.8.2 Description of Clinical Outcome Assessment Instruments

REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)

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

Daily Questions

Daily questions will be completed on the smartphone provided to the patient.
Daily questions include a PGI-S for motor PD symptoms, a medication tracker, and a questionnaire collecting the reasons for missed "active tests" digital biomarker assessments.

EQ-5D-5L

The EQ-5D-5L is a validated self-reported health status questionnaire that is used to calculate a health status utility score for use in health economic analyses

(EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state on a graduated (0–100) scale, with higher scores for higher health related quality of life. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete and will be used in this study for informing pharmacoeconomic evaluations. This assessment will be completed on the smartphone provided to the patient.

Patient Global Impression of Change and Severity (PGI-C and PGI-S)

The Patient Global Impression is a measure commonly used in PD clinical trials to provide a concise assessment of overall health state (Guy 1976). The change component (PGI-C) is intended to measure health state changes relative to the start of the study, and can be adapted for participant self-assessment. In this study, [redacted] The participant-reported PGI-C is rated on a 7-point scale: "Very much improved," "Much improved," "Minimally improved," "No change," "Minimally worse," "Much worse," and "Very much worse." [redacted]

The PGI-S is based on the same principle as the PGI-C and is intended to measure severity over the past 7 days. This scale has been adapted for participant self-assessment. In this study, symptom severity will be assessed in [redacted]. The participant-reported PGI-S uses a 5-point ordinal scale, ranging from "Not at all/very mildly" [redacted] or "Normal/very mild" (overall), to "Very severely" [redacted] or "Very severe" (overall).

Clinical Global Impression of Change and Severity (CGI-C and CGI-S)

The CGI is a measure commonly used in PD clinical trials to provide a concise assessment of overall health state (Guy 1976). [redacted] The CGI-C and CGI-S have been adapted for this study, and include items and response options analogous to those in the PGI-C and PGI-S (described above).

[redacted]

[redacted]

[redacted]

4.5.9 Patient Experience Questionnaire

Approximately 3–6 months prior to the end of the double-blind period, patients will be asked to complete a satisfaction survey regarding their experience participating in this trial.

4.5.10 Columbia-Suicide Severity Rating Scale (C-SSRS)

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 or 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 following the timing specified in the schedule of activities (Appendix 1). The assessment must be completed by a certified C-SSRS rater following an interview with the patient.

[redacted]

[redacted]

4.5.11.1 Healthy Volunteer Magnetic Resonance Imaging Scans for Site Qualification

As part of site qualification, one to two healthy volunteers at each site should be scanned using the machine and performing the sequences to be used for Study BN42358 before any patient is scanned in this study. The selection of healthy volunteers is at the discretion of the investigator and/or the imaging center, and the healthy volunteer must provide written consent. Healthy volunteers must not have any contraindications for MRI scanning (evaluation per local procedures at the imaging site), and they will not be enrolled in the study or undergo any other assessments as part of the trial. A central reader will review the healthy volunteer scans for suitable image quality. This procedure will help to ensure consistency in scanning quality across sites in the study. At the time of a major upgrade to the site's scanner, any other event deemed significant enough to affect image quality, or per central reader guidance, an additional scan (preferably on the same volunteer) may be needed, at which time a qualitative comparison may be performed. Additional instructions regarding the procedures for MRI facility qualification can be found in the MRI Manual.

4.5.11.2 Eligibility and Efficacy MRI Assessments

Eligibility MRI assessments [redacted] will be performed during screening as part of assessing eligibility criteria. MRI-related study eligibility criteria will be assessed at screening by the central MRI core laboratory.

[redacted]

For participants taking L-Dopa, all MRI assessments should be performed in the "OFF" medication state (defined as ≥12 hours since the last dose of L-Dopa).
These participants will need to be reminded <u>not</u> to take L-Dopa prior to study visits that include MRI assessments.

For postbaseline assessments in which the optional LP is performed prior the MRIs, the MRIs should be performed after at least 5 days has elapsed since the LP was performed.

4.5.12 <u>DaT-SPECT Imaging</u>

DaT-SPECT (DAT [^{123}I-FP-CIT] SPECT) assessments will be performed at screening. DaT-SPECT should be performed once all other eligibility screening results are available and the participant has been deemed eligible for the study on the basis of these results. This scan will serve as a baseline for statistical analyses. 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 laboratory, and this assessment will be used to determine eligibility.

Women of childbearing potential must have a confirmed negative urine pregnancy test immediately prior to injection of DaTSCAN. Before the DaTSCAN injection, participants will be pre-treated with stable iodine to reduce the uptake of DaTSCAN by the thyroid. Patients with a hypersensitivity to iodine may receive an alternative thyroid blocking agent. 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.

[redacted]

[redacted]

[redacted]

4.5.15 Optional Samples for Research Biosample Repository

4.5.15.1 Overview of the Research Biosample Repository

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

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- 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

4.5.15.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's 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 (Section 4.5.15) will not be applicable at that site.

4.5.15.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to prasinezumab or α-synuclein, diseases, or drug safety:

- Leftover blood, serum, plasma, and any derivatives thereof (e.g., DNA, proteins, peptides), and CSF (if applicable).

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing, whole exome sequencing, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole genome and whole exome sequencing provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.15.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

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

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

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

4.5.15.5 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 patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.15.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of their RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.15.7 Monitoring and Oversight

RBR samples 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 samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. 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 RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator determination that treatment discontinuation is in the best interest of the participant
- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

Participants will return to the clinic for an early (treatment) termination visit 28 days (±7 days) after the final dose of study drug (see Appendix 1 for additional details).

In addition, participants who withdraw from treatment during the double-blind treatment period will be asked to return for collection of safety and efficacy data according to the schedule of activities until the end of the double-blind treatment period (including end-of-study visit and safety follow-up visit). Participants who withdraw from treatment during the OLE will be asked to return for the safety follow-up visit 70 days (±7 days) after last dose.

4.6.2 Participant Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF.

All patients who withdraw from the study early will be asked to return to the clinic for an early termination visit 28 days (±7 days) after the final dose of study drug (see Appendix 1 for additional details) and for a safety follow-up visit 70 days (±7 days) after last dose).

Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.3 Study 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 patients
- Participant enrollment is unsatisfactory
- Sponsor determines it is in the best interest of the participant

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site 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 Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all participants have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Prasinezumab is not approved, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with prasinezumab in completed and ongoing studies. The anticipated important safety risks for prasinezumab are outlined below. Please refer to the Prasinezumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Prasinezumab

5.1.1.1 Infusion-Related Reactions

Hypersensitivity and/or IRR are potential adverse events associated with the use of therapeutic monoclonal antibodies. Therefore, rescue medication to treat anaphylaxis and anaphylactoid reactions must be available at the site or at location for mobile nursing visits and if needed must be administered by a trained health care professional. All participants should be closely monitored for possible infusion-associated adverse events and/or hypersensitivities associated with the study drug administration.

Detailed information on the characteristic signs and symptoms of IRRs (e.g., rash, urticaria, and pruritus) will be recorded on the dedicated eCRF page (see Section 5.3.5.1 and Figure 2 for details on reporting IRRs).

5.1.1.2 Immunogenicity

As with administration of any exogenous protein, there is the potential for the development of ADAs, which can be neutralizing and/or sensitizing, and which can potentially lead to febrile or allergic reactions including anaphylaxis.

Participants should be told how to recognize the signs and symptoms of hypersensitivity reactions and be monitored.

5.1.2 Management of Participants Who Experience Adverse Events

5.1.2.1 Management Guidelines of Infusion-Related Reactions

IRRs have been reported with the use of biologic therapies, such as prasinezumab. 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 2. The participant should be monitored until complete resolution of the symptoms and treated as clinically indicated.

Table 2 Infusion-Related Reaction Management Guidelines

Grade [a]	Action to Be Taken
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • Assess vital signs; clinical observation for improvement/resolution of symptoms. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt infusion. • Perform serial vital sign assessments every 15 minutes. Monitor participant until symptoms resolve completely. • IV fluids (e.g., normal saline) may be administered as clinically indicated. • Administer symptomatic treatment as needed: - Symptomatic treatment: acetaminophen/paracetamol and an antihistamine, such as diphenhydramine 25–50 mg PO or IV Q6H, if these medications have not been previously administered in the last 4 hours. - For bronchospasm, urticaria, or dyspnea: antihistamines, supplemental oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators may be administered per institutional practice. • Blood samples to determine tryptase, cytokine panel, C3, C3a, C5a, and total IgE should be drawn within 3 hours of the event and repeated within 48–72 hours after the event. • Paired blood samples to determine 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. • For subsequent infusions, administer premedication per guidelines in Section 4.3.3.

ADA = anti-drug antibody; C = complement component; IRR = infusion-related reaction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PK = pharmacokinetic; Q6H = every 6 hours.

[a] Refer to the NCI CTCAE, v5.0 for the grading of symptoms.

[b] See Lieberman et al. 2015 for anaphylaxis guidance.

Table 2 Infusion-Related Reaction Management Guidelines (cont.)

IRR Grade [a]	Action to Be Taken
IRR, Grade 3	• Interrupt infusion. • Perform serial vital signs assessment as dictated by the participant's clinical symptoms. • Monitor participant until symptoms resolve completely. • IV fluids (e.g., normal saline) may be administered as clinically indicated. • Administer symptomatic treatment as needed including corticosteroids: - Symptomatic treatment: acetaminophen/paracetamol 650 mg PO (or minimum recommended adult dose of paracetamol) and an antihistamine, such as diphenhydramine 25–50mg PO or IV Q6H, if these medications have not been previously administered in the last 4 hours. - For bronchospasm, urticaria, or dyspnea: antihistamines, supplemental oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators may be administered per institutional practice. • Blood samples to determine tryptase, cytokine panel, C3, C3a, C5a, and total IgE should be drawn within 3 hours of the event and repeated within 48–72 hours after the event. • Paired blood samples to determine ADA and PK levels should be drawn if the event starts during the visit and/or the participant is hospitalized. • If symptoms resolve completely during the visit, infusion may resume at 50% of the previous infusion rate. • Overnight inpatient observation per discretion of the investigator at the site. • Future dosing plans can only be determined after the investigator at the site has had a discussion with the participant and Sponsor. • For subsequent infusions, administer premedication per guidelines in Section 4.3.3.

ADA=anti-drug antibody; C=complement component; IRR=infusion-related reaction; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PK=pharmacokinetic; Q6H=every 6 hours.

[a] Refer to the NCI CTCAE, v5.0 for the grading of symptoms.

[b] See Lieberman et al. 2015 for anaphylaxis guidance.

Table 2 Infusion-Related Reaction Management Guidelines (cont.)

IRR Grade [a]	Action to Be Taken
IRR, Grade 4	• Permanently stop the infusion. • Perform serial vital signs assessment every 5 minutes. Monitor participant until symptoms resolve completely. • IV fluids (e.g., normal saline) may be administered as clinically indicated. • Administer symptomatic treatment as needed including corticosteroids: - Symptomatic treatment: acetaminophen/paracetamol 650 mg PO (or minimum recommended adult dose of paracetamol) and an antihistamine, such as diphenhydramine 25–50mg PO or IV Q6H, if these medications have not been previously administered in the last 4 hours. - For bronchospasm, urticaria, or dyspnea: supplemental oxygen or intubation and ventilatory support, antihistamines, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators may be administered per institutional practice. • Blood samples to determine tryptase, cytokine panel, C3, C3a, C5a, and total IgE should be drawn within 3 hours of the event and repeated within 48–72 hours after the event. • Paired blood samples to determine ADA and PK levels should be drawn. • Discontinue participant from the study treatment. • Hospitalization for further evaluation and treatment.
Anaphylaxis [b]	• Permanently stop the infusion. • Assess vital signs every 5 minutes. • IV fluids (e.g., normal saline) may be administered as clinically indicated. • Supplemental oxygen and ventilatory support. • For systemic symptoms (angioedema, bronchospasm) epinephrine 1:1000, 0.3 mL SC (may be repeated in 20 minutes; in participants on β-blockers, glucagon administration may be needed), diphenhydramine 25–50 mg IV, methylprednisolone 125 mg IV or equivalent). • Blood samples to determine tryptase, cytokine panel, C3, C3a, C5a, and total IgE should be drawn within 3 hours of the event and repeated within 48–72 hours after the event. • Paired blood samples to determine ADA and PK levels should be drawn. • Discontinue participant from the study treatment. • Hospitalization for further observation and treatment.

ADA=anti-drug antibody; C=complement component; IRR=infusion-related reaction; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PK=pharmacokinetic; Q6H=every 6 hours.

[a] Refer to the NCI CTCAE, v5.0 for the grading of symptoms.

[b] See Lieberman et al. 2015 for anaphylaxis guidance.

Figure 2 describes the process for the overall evaluation of adverse events to determine whether an adverse event should be considered to be an IRR.

The following guidelines are recommended for IRR grading:

- For IRRs with onset during the infusion, see Figure 2.
- For IRRs with onset ≤24 hours after the end of the infusion, see Table 3.

Figure 2 Guidelines for Evaluating and Reporting Infusion-Related Reactions

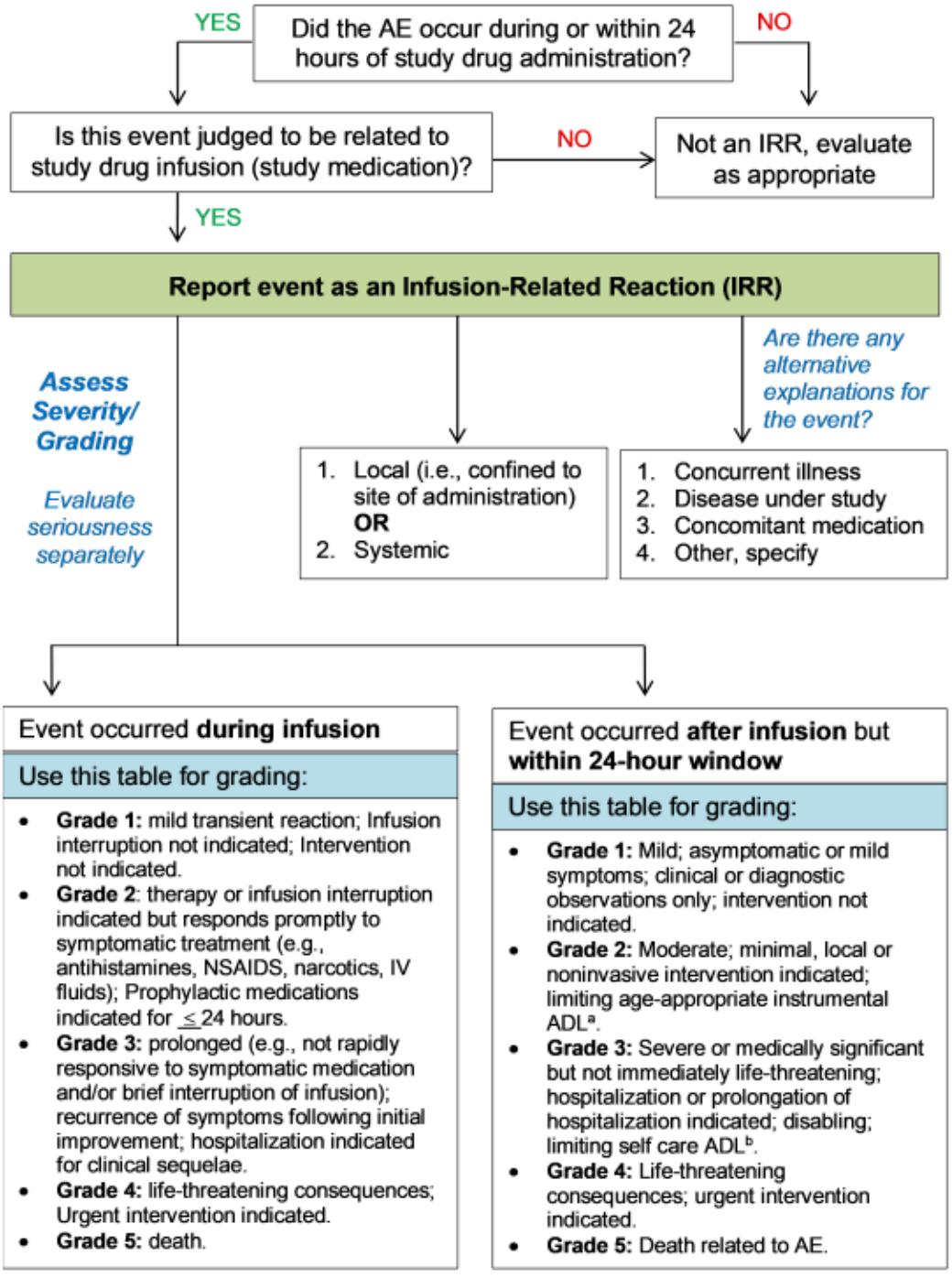


Figure 2 Guidelines for Evaluating and Reporting Infusion-Related Reactions (cont.)

ADL=activities of daily living; AE=adverse event; IRR=infusion-related reaction; NCI CTCAE= National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDS=nonsteroidal anti-inflammatory drugs.

Note: Based on the NCI CTCAE (v5), which can be found at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

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

[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, ECGs, and conducting 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.

5.2.1 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) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- 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 LP)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is 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 5.3.5.11)
- 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)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a 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 (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Table 2 and Table 3, see Section 5.3.3); 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).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

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 are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- 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.

5.2.4 Selected Adverse Events

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

- 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.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 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 5.2.2 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 patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as DaT-SPECT imaging or LP) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

In addition, after initiation of the DaT-SPECT tracer but prior to initiation of study drug, all serious adverse events occurring within 24 hours of DaT-SPECT tracer administration should be reported regardless of relatedness to the DaT-SPECT tracer (see Section 5.4.2). After this 24-hour timepoint, only serious adverse events considered related to the DaT-SPECT tracer should be reported.

After initiation of study drug, all adverse events will be reported until the participant's last visit (i.e. until the safety follow-up visit).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in 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 timepoints. 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

Guidelines for assessing the severity of adverse events are provided in Table 3.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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 most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[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 oneself, 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 5.2.2.

[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 5.2.2.

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 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, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- 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 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" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related (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.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are 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. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event 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 consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both 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.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

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

- Is 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 (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is 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 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) 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 whether 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 only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

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

- Is 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
- Is 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 only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST >3×ULN in combination with total bilirubin >2×ULN
- Treatment-emergent ALT or AST >3×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 5.3.5.2) 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 an adverse event of special interest (see Section 5.4.2).

5.3.5.8 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). This includes death attributed to progression of PD.

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. 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. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of PD, PD should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 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").

5.3.5.10 Lack of Efficacy or Worsening of Parkinson's Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- 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 the disease.

  The patient has not experienced an adverse event.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Accidental Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose

- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness 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).
For prasinezumab or matching placebo, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with prasinezumab or matching placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.

- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient -Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

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 drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information 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 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

5.4.2 Reporting Requirements for Serious Adverse Events and 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 drug, only serious adverse events caused by a protocol-mandated intervention should be reported as well as all serious adverse events that occur within 24 hours of DaT-SPECT tracer administration regardless of causality. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the participant's last visit (i.e. until the safety follow-up visit). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report

via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur until the participant's last visit (i.e., until the safety follow-up visit) are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 70 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.
Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), 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).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity 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). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient 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 PATIENTS 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 patient is lost to follow-up, or the patient 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 patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, 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 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as the participant's last visit [i.e., the safety follow-up visit]), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations 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 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.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authority (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the following reference safety information in the document listed below: Prasinezumab 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

The purpose of this study is to investigate the treatment effect of prasinezumab relative to placebo. The primary efficacy analysis will be based on an intent-to-treat (ITT) population that includes all randomized patients, with patients grouped according to their randomly assigned treatment.

All randomized patients receiving any amount of the study drug will be included in the safety analysis. Patients who are administered with study treatment other than the treatment they were randomly assigned to receive will be analyzed according to the treatment they actually received.

Approximately 575 patients will be randomized in the study.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is to investigate the effect of prasinezumab on time to clinical disease progression, defined as a confirmed motor progression on MDS-UPDRS Part III score (in "OFF" medication state for participants on L-Dopa background therapy). Point and interval estimates of the true underlying hazard ratio will be obtained. A total of approximately 575 participants will be randomized in this study, with an assumed dropout rate of [redacted] annually.

[redacted]

[redacted]

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized by treatment arm. Reasons for premature study discontinuation will be listed and summarized. Enrollment, major protocol deviations, and study drug administration will be summarized by treatment arm. Patient disposition will be summarized by treatment arm and will include whether treatment was completed or discontinued early, and the reason for early treatment discontinuation.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including age, sex, symptomatic treatment, disease duration, race and/or ethnicity, and H&Y stage) will be summarized descriptively for the ITT population, grouped according to the assigned treatment arm.

Descriptive summaries of continuous date will present the means, standard deviations, medians, and minimum and maximum. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of patients.

6.4 EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all randomized patients, with patients grouped according to their assigned treatment.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of prasinezumab compared with placebo on the basis of time to disease progression as assessed by a confirmed motor progression event.

Confirmed motor progression is defined as a worsening event sustained over two consecutive assessments. The worsening event is defined either by:

- A ≥ 5 points increase in MDS-UPDRS Part III score (assessed in "OFF" medication state) from baseline sustained over two consecutive assessments OR
- A change in medication after the first occurrence of a ≥ 5-points increase in MDS-UPDRS Part III score (assessed in "OFF" medication state) from baseline and before the follow-up assessment

The primary efficacy analysis (ITT) population will consist of all randomized participants, with participants grouped according to their assigned treatment.

The primary estimand is the hazard ratio of a confirmed motor progression between prasinezumab and placebo in participants with PD.

For the analysis of the primary estimand, there are two intercurrent events that may occur before a participant can experience a confirmed event. The first is starting or changing symptomatic therapy, which will be handled using a treatment-policy strategy (see ICH E9 [R1] 2020). The second is death, which will be considered a progression event (at the time of death).

Details concerning the estimand strategy and different sensitivity analysis will be defined in the SAP in accordance with ICH E9 (R1) 2020.

A formal treatment comparison will be made using a [redacted] The same stratification factors used for randomization (type of symptomatic medication: MAO-B inhibitors vs. L-Dopa) will be used for this comparison. Disease progression curves in each treatment arm will be estimated using Kaplan–Meier estimates. The Kaplan–Meier estimates will provide a visual description of the disease progression curves and the difference across treatment arms. The treatment effect will be quantified via a hazard ratio, computed from a stratified Cox proportional-hazards regression, including a 95% CI. The effect of prognostic and predictive factors on disease progression will be assessed in an exploratory analysis using Cox multivariate regression.

[redacted]

6.4.2 Secondary Efficacy Endpoints

The following secondary endpoints will be tested for the ITT population with participants grouped according to their assigned treatment.

- Time to worsening of patient's motor function as reported by the patient (≥3 points increase in MDS-UPDRS Part II total score from baseline) in the presence of a confirmed motor progression event (as defined in Section 6.4.1)
- Time to meaningful worsening (defined as a rating of "very much worse", "much worse" or "minimally worse" reported to be important to the patient) in PGI-C (Overall Disease Subscale)
- Time to meaningful worsening (defined as a rating of "very much worse", "much worse" or "minimally worse" reported to be clinically meaningful) in CGI-C (Overall Disease Subscale)
- Change in motor function from baseline to Week 76, as measured by the MDS-UPDRS Part III total score (assessed in "OFF" medication state)
- Change in bradykinesia and rigidity from baseline to Week 76, as measured by the MDS-UPDRS Part III bradykinesia and rigidity subscore (assessed in "OFF" medication state)
- Time to onset of motor complications as assessed through MDS-UPDRS Part IV

A hierarchical testing procedure will be applied to adjust for multiple statistical testing of the confirmatory secondary endpoints. The overall type I error rate will thereby be controlled. Details about order of the hierarchical testing procedure will be given in the SAP.

6.4.3 Exploratory Efficacy Endpoints

The following exploratory endpoints will be analyzed for the ITT population, as described in the Statistical Analysis Plan:

- [redacted]

- [redacted]

In addition, summary descriptive statistics will be provided for all data acquired after Week 76 (including end-of-study visit) and further related data analyses may be detailed in the SAP.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

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

- Nature, incidence, seriousness and severity of adverse events, with severity determined according to NCI CTCAE v5.0
- Incidence of adverse events of special interest
- Incidence of treatment discontinuations due to adverse events
- Nature, incidence, seriousness, severity, and timing of IRRs
- Mean change in vital signs from baseline over time and incidence of abnormal vital sign measurements
- Changes in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Change from baseline and incidence of laboratory abnormalities (including hematology, clinical chemistry, coagulation, and urinalysis parameters)

- Incidence of physical and neurologic examination abnormalities
- Change from baseline in suicidal ideation, as measured by C-SSRS

6.6 PHARMACOKINETIC ANALYSES

Patient data will be included in the PK analysis if there is sufficient dosing information and at least one adequately documented and quantifiable prasinezumab concentration per patient.

The previous population PK model (Report 1081130) that was developed using the Phase I data of prasinezumab and updated with PASADENA PK data, will be used to analyze the sparse sampling dose-concentration-time data of prasinezumab collected during this study. Non-linear mixed effects modeling (with software NONMEM [Beal and Sheiner 1998]) will be used. Structural model refinement will be driven by the data and will be based on various goodness of fit indicators. The model may be revised if necessary.

Population and individual PK parameters (e.g., clearance 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. Secondary PK parameters such as AUC, C_{max}, and C_{trough} at steady state will be derived from the individual post-hoc predictions. Additional PK analyses will be conducted as appropriate.

Graphical exploration of the relationship between prasinezumab exposure and disease progression (e.g., as assessed as a ≥ 5 point worsening in MDS-UPDRS Part III) will be performed. If indicated by such exploration, more formal analyses of the PK/pharmacodynamic relationship using non-linear mixed effects modeling method will be conducted.

Further modeling analyses may be performed and will be documented in the SAP.

Exploratory analyses will also be performed in order to explore:

- The relationship between serum concentration or secondary PK parameters of prasinezumab and biomarker endpoints
- The relationship between serum concentration or secondary PK parameters of prasinezumab and safety endpoints.

6.7 IMMUNOGENICITY ANALYSES

As ADA samples from patients assigned to the placebo group will not be analyzed for prasinezumab PK concentration in the first instance, except by request, only the treated group will undergo statistical analysis in the first instance. The immunogenicity analysis population will consist of all patients on active treatment with at least one ADA assessment.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 4-fold greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported using descriptive statistics.

6.8 BIOMARKER ANALYSES

6.9 HEALTH STATUS UTILITY ANALYSES

Change from baseline in EQ-5D-5L health utility index-based and VAS scores will be calculated at specified timepoints.

6.10 INTERIM ANALYSIS

6.10.1 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct an interim efficacy analysis. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC.

Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP which will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analysis, and the iDMC Charter will also be made available to relevant health authorities.

6.11 OPEN LABEL EXTENSION PERIOD ANALYSIS

Descriptive statistics will be used to summarize the OLE. Statistical methods similar (but not limited) to the double-blind period will be used to analyze the data and will further be described in the SAP. [redacted]

[redacted]

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. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and all electronic data from external vendors will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO and ClinRO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

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

7.3 ELECTRONIC PATIENT AND CLINICIAN REPORTED OUTCOME DATA

An electronic device will be used to capture electronic PRO and ClinRO data. [redacted] The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). Upon completion of electronic clinical outcomes assessment (eCOA) on an electronic tablet, the rater will submit a completed scale to secured web-based portal, while the tablet is online. In this way, the data will be transmitted to a centralized database maintained by the electronic device vendor.

The completed PDF renditions of eCOA will be viewable for authorized site users upon submission from a tablet, via a secured web-based portal. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived by the Sponsor. The investigator will receive patient data in form of PDF rendition of completed eCOA along with site-level audit trail reports that must be kept with the study records as source data. Acknowledgement of receipt of the data is required to be provided to the Sponsor. In addition, the Sponsor will receive all data in form of PDF rendition of completed eCOA along with study-level audit trail reports.

7.4 DIGITAL BIOMARKER DATA

During "Active Tests" and "Passive Monitoring," device sensor will continuously record data from the smartphone and wrist-worn wearable. Location data will be recorded but obfuscated; participants can also choose to pause location data recording. Data on the technical status of the devices is also recorded. No patient identifiable information is

stored on the devices. For selected "Active Test" tasks, touch and sound are also recorded. Video is not recorded.

Digital biomarker data are encrypted and uploaded to secure servers whenever the phone is connected to Wi-Fi. If participants have a Wi-Fi network at home, they are encouraged to connect their smartphone to enable data transfer. If no Wi-Fi 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 protocol-specified assessments.

7.5 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review 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, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

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 7.7.

To facilitate source data verification and review, 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 study site must also allow inspection by applicable health authorities.

7.6 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study 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.

7.7 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO and ClinRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, and images, must be retained by the Principal Investigator for 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, subject 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.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

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 applicable 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 European Union or European Economic Area will comply with the Clinical Trials Regulation (536/2014; EEA sites only) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) 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.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient 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 patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. 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 patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient'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 patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient 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 patient, 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 patient 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 9.6).

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request (see Section 9.6).

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 1 year after completion of the study (see definition of end-of-study in Section 3.3).

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 patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits are provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring. Roche will delegate site monitoring to a third party.

Approximately 125 sites globally will participate to enroll approximately 575 patients. Enrollment and study drug distribution will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., ECG, specified laboratory tests, biomarker and PK analyses, rating scales, MRI and DaT-SPECT imaging, as applicable), as specified in Section 4.5.

An iDMC will be employed to monitor and evaluate patient safety and efficacy as deemed appropriate throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation,

and will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. 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.

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.

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

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.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. 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 patients or changes that involve logistical or administrative aspects only.

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APPENDIX 1 SCHEDULE OF ACTIVITIES

TableA1 1 Double-Blind Period

	Screening[a]	Double-Blind Treatment Period																								DB Tx End-of-Study Visit[b,d]	Safety Follow-Up Visit[b]	Early Termination Visit[c,d]	Unscheduled Visit
Week	−12 to −1	BL[c,f]	1[g]	2[g,y]	4[c]	8[c]	12	16	20	24[c]	28	32	36	40	44	48	52[c]	56	60	64	68	72	76[c]	N Reg.[h] (Q4W)	N Saf.[h] (Q12W)				
Dose number		1			2	3	4	5[i]	6[i]	7	8[i]	9[i]	10	11[i]	12[i]	13[i]	14	15[i]	16[i]	17	18[i]	19[i]	20	n[i]	n				
Visit window (days)			±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		
Informed consent	x																												
Review of inclusion and exclusion criteria	x	x																											
Demographic data (including years of education)	x																												
Medical history	x																												
RBDSQ	x																												
Vital signs[j]	x	x	x[k]	x[k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height and weight	x																									x		x	x
Neurologic examination[l]	x	x								x							x						x		x	x	x	x	x

Appendix 1: Schedule of Activities

Table A1-1. Double-Blind Period

	Screening[a]	Double-Blind Treatment Period																								DB Tx End-of-Study Visit[b,c]	Safety Follow-Up Visit[b]	Early Termination Visit[c,d]	Unscheduled Visit
Week	−12 to −1	BL[c,f]	1[g]	2[g,y]	4[c]	8[c]	12	16	20	24[c]	28	32	36	40	44	48	52[c]	56	60	64	68	72	76[c]	N Reg.[h] (Q4W)	N Saf.[h] (Q12W)				
Dose number		1			2	3	4	5[i]	6[i]	7	8[i]	9[i]	10	11[i]	12[i]	13[i]	14	15[i]	16[i]	17	18[i]	19[i]	20	n[i]	n				
Visit window (days)			±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		
Complete physical examination[m]	x	x																					x			x	x	x	x
Limited physical examination[m]			x[k]	x[k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x				x
Triplicate ECG-12 lead[n]	x	x			x	x	x			x			x				x			x			x		x	x	x	x	x
Hematology[o]	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood chemistry and lipids[p]	x	x			x	x	x			x			x				x			x			x		x	x	x	x	x
Coagulation	x	x			x	x	x			x			x				x			x			x		x	x	x	x	x
Thyroid hormones	x																												
Drug of abuse/ alcohol urine test	x																												x
Serology (HBV, HCV, HIV 1 and 2)	x																												
Pregnancy test[q]	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1: Schedule of Activities

Table A1-1. Double-Blind Period

	Screening[a]	Double-Blind Treatment Period																								DB Tx End-of-Study Visit[b,c]	Safety Follow-Up Visit[b]	Early Termination Visit[c,d]	Unscheduled Visit
Week	−12 to −1	BL[c,f]	1[g]	2[g,y]	4[c]	8[c]	12	16	20	24[c]	28	32	36	40	44	48	52[c]	56	60	64	68	72	76[c]	N Reg.[h] (Q4W)	N Saf.[h] (Q12W)				
Dose number		1			2	3	4	5[i]	6[i]	7	8[i]	9[i]	10	11[i]	12[i]	13[i]	14	15[i]	16[i]	17	18[i]	19[i]	20	n[i]	n				
Visit window (days)			±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		
FSH (post-menopausal women only)	x																												
Urinalysis[r]	x	x			x	x	x			x			x				x			x			x		x	x	x	x	x
Immunologic sample[s]		x																											x
Serum PK sample[t,u]		x	x[k]	x[k]	x	x[k]	x			x			x				x			x			x		x	x	x	x	x
Serum ADA sample[u]		x			x	x[k]	x			x			x				x			x			x		x	x	x	x	x
Serum and plasma sample for biomarkers[t]		x																					x			x		x	x
Clinical genotyping[v]		x																											
Hoehn and Yahr[w]	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MDS-UPDRS Part II[x,y]	x	x[y]		x	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x	x	x	x
MDS-UPDRS Part III[x,z]	x	x[z]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[z]	x	x	x[z]	x	x[z]	x
MDS-UPDRS Part IV[x]	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1: Schedule of Activities

Table A1-1. Double-Blind Period

	Screening[a]	Double-Blind Treatment Period																								DB Tx End-of-Study Visit[b,c]	Safety Follow-Up Visit[b]	Early Termination Visit[c,d]	Unscheduled Visit
Week	−12 to −1	BL[c,f]	1[g]	2[g,y]	4[c]	8[c]	12	16	20	24[c]	28	32	36	40	44	48	52[c]	56	60	64	68	72	76[c]	N Reg.[h] (Q4W)	N Saf.[h] (Q12W)				
Dose number		1			2	3	4	5[i]	6[i]	7	8[i]	9[i]	10	11[i]	12[i]	13[i]	14	15[i]	16[i]	17	18[i]	19[i]	20	n[i]	n				
Visit window (days)			±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7			
[redacted]		x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CGI-C and CGI-S[ii]		x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PGI-C and PGI-S[y,ii]		x[y]		x	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x[y]	x	x	x	x
[redacted]		x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
[redacted]		x					x			x			x			x			x				x		x	x		x	x
[redacted]		x																					x			x			x
C-SSRS BL/SLV		x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Digital biomarker remote monitoring (incl. daily questions and EQ-5D-5L)[aa]	x[aa]	←																											
Digital biomarker in-clinic assessments[bb]	x	x[z]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[z]	x	x	x[z]	x	x	x
MRI[cc]	x																						x			x		x	x

Appendix 1: Schedule of Activities

Table A1-1. Double-Blind Period

	Screening[a]	Double-Blind Treatment Period																								DB Tx End-of-Study Visit[b,c]	Safety Follow-Up Visit[b]	Early Termination Visit[c,d]	Unscheduled Visit
Week	−12 to −1	BL[c,f]	1[g]	2[g,y]	4[c]	8[c]	12	16	20	24[c]	28	32	36	40	44	48	52[c]	56	60	64	68	72	76[c]	N Reg.[h] (Q4W)	N Saf.[h] (Q12W)				
Dose number		1			2	3	4	5[i]	6[i]	7	8[i]	9[i]	10	11[i]	12[i]	13[i]	14	15[i]	16[i]	17	18[i]	19[i]	20	n[i]	n				
Visit window (days)			±2	±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		
DaT-SPECT[dd]	x																												
Optional CSF sample[ee]	x																						x						
Optional CSF matching serum and plasma samples[ee]	x																						x						
Optional patient experience questionnaire																		To be complete 3–6 months prior to the end of the double-blind treatment period										
Premedication[ff]		x			x	x																							x
Concomitant medications	x	x	x[k]	x[k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	←																												→
Study drug administration[hh]		x[gg]			x[gg]	x[gg]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				

Appendix 1: Schedule of Activities

Table A1-1. Double-Blind Period

ADA=anti-drug antibody; ADL=activities of daily living; BL=baseline; BP=blood pressure; C=complement component; CGI-C=Clinician Global Impression, Change; CGI-S=Clinician Global Impression, Severity; CSF=cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; DaT-SPECT=dopamine transporter imaging with single proton emission computed tomography; DB =double-blind; eCRF= electronic Case Report Form; FSH=follicle-stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; IRR=infusion-related reaction; L-Dopa=levodopa; LP=lumbar puncture; MAO-B=monoamine oxidase B; [redacted] MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale; [redacted] MRI=magnetic resonance imaging; OLE=open-label extension; PGI-C=Patient Global Impression, Change; PGI-S=Patient Global Impression, Severity; PK=pharmacokinetic; PRO=patient-reported outcome; Q4W=every 4 weeks; Q12W=every 12 weeks; RBR=Research Biosample Repository; RDBSQ=REM Sleep Behavior Disorder Screening Questionnaire; Reg.=regular; Saf.=safety; [redacted] SLV=since last visit; Tx=treatment.

[a] The screening phase should last a minimum of 28 days (to allow sufficient time for digital biomarker assessments) and a maximum of 12 weeks. If a patient is re-screened, all screening assessments must be repeated except for LP, MRI, and DaT-SPECT, provided that these assessments were performed no earlier than 6 months prior to baseline and are within the eligible ranges.

[b] The double-blind treatment period will end when a [redacted] All participants will be asked to return to the clinic for an end-of-study visit 28 days (±7 days) after receiving the final dose and patients who are not enrolling in the OLE will be asked to return for a safety follow-up visit 70 days (±7 days) after receiving the final dose. For patients enrolling in the OLE, please refer to Appendix 1, Table 2.

[c] Visit may be split over 2 consecutive days. If so, all safety assessments should be performed the second day (i.e., prior to dosing unless specified). Scales and digital biomarkers ideally should all be done on the first day. If not possible, then MDS-UPDRS (all parts, in "OFF" and "ON" medication states), CGI-C, CGI-S, PGI-C, PGI-S, and digital biomarker in-clinic (in "OFF" and "ON" medication states) should be done on the first day. [redacted]

[d] Participants who discontinue study drug prematurely should return to the clinic for an early termination visit 28 days (±7 days) after their final dose, and will be asked to continue to follow the regular schedule of assessments for the remainder of the study.

[e] [redacted]

[f] The date of the first treatment (baseline) is considered to be Day 1 of the treatment period. If this visit is split over 2 consecutive days, then baseline is done on Day 1 and Day 0. All visit dates should be calculated relative to baseline (Day 1).

[g] The Week 1 visit should take place on Day 7 (±2 days) and the Week 2 visit should take place on Day 14 (±2 days).

[h] If the double-blind treatment period is extended beyond Week 76, regular dosing visits should be continued every 4 weeks (e.g., Week 80, 84, and so forth) until double-blind treatment is terminated. The assessments listed under "N Reg." should be performed at these visits. Additional safety and PK assessments should be performed every 12 weeks (e.g., Weeks 88, 100, 112, 124, and so forth). The assessments listed under "N Saf." should be performed at these visits. During this time if the study ends for any reason or if the patient must be withdrawn from treatment, an early termination visit should be performed.

[i] Visit suitable for home administration.

[j] Vital signs (including semi-supine systolic and diastolic blood pressure, respiratory rate, pulse rate, and temperature) must be monitored before the infusion and every 15 minutes during the infusion and every 30 minutes after the infusion until the infusion line is removed for the first three infusions. For subsequent infusions, vital signs should be monitored every 30 minutes until the infusion IV line is removed, unless safety considerations indicate that more frequent monitoring is warranted. In order to assess orthostatic hypotension during screening and treatment, BP and pulse rate should be evaluated after 2 minutes of standing still (after the semi-supine measurement). For the first three infusions, orthostatic hypotension measurements should be collected before and 2 hours after the end of the infusion. For subsequent infusions, measurements should be collected 1 hour after the end of the infusion. Abnormal values for vital signs should be repeated for confirmation or intervention if required.

[k] Only applicable for the first 40 patients randomized in the study.

[l] A neurologic examination should include an assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination.

[m] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated. Limited physical examinations should be symptom-directed or as clinically indicated.

[n] For all the designated dosing visits, the ECGs should be obtained pre- and post-dose. At dosing visits without PK sampling, the ECG can be done at any time post-dose. At visits with PK sampling, the ECG should be performed at the time of the PK sampling, ideally just before the PK sampling. For non-dosing visits, the ECGs should be obtained to approximate the timing of the pre-dose ECGs during the study. All ECGs will be performed in triplicate, spaced 1–2 minutes apart within 5 minutes.

[o] Hematology includes WBC count, RBC count (incl. MCV and RBC morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[p] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard-of-care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and LDH.

[q] 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 DaT-SPECT scan. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

Table A1-1. Double-Blind Period

[r] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood, leucocytes and nitrites); perform a microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) by central laboratory if blood and/or protein results are positive (i.e., confirmed by a positive repeated dipstick sample).

[s] This includes tryptase, cytokine panel, C3, C3a, C5a, and total IgE. In case of Grade ≥ 2 IRR, this sample should be drawn within 3 hours of the event and repeated within 48 to 72 hours post-event. Note that the baseline sample will only be analyzed if a postbaseline sample is collected (i.e., for participants who experience a Grade 2 or higher IRR).

[t] At dosing visits, serum PK and serum and plasma biomarker samples will be collected just prior to dosing; serum PK sample will also be collected at the end of the infusion. At non-dosing visits, sample collection can be performed at any time during the visit. In all cases, the time of sample collection should be recorded on the eCRF. Note: Serum and plasma biomarkers should be collected as two separate samples and not together.

[u] On dosing days, serum ADA samples will be collected prior to dosing. Additional ADA and PK samples should be collected in patients with signs and symptoms of infusion-related reactions and hypersensitivity reaction.

[v] If this sample is missed at baseline, it can be collected at any other scheduled visit. Not applicable for sites where genotyping is not approved.

[w] Hoehn and Yahr staging will be assessed as part of the MDS-UPDRS.

[x] MDS-UPDRS Part IV will only be assessed in patients taking L-Dopa. For these patients, MDS-UPDRS Part II, Part III and Part IV should be assessed approximately 12 hours (e.g., overnight) after the last dose of L-Dopa in the "OFF" medication state. Patients will need to be reminded not to take L-Dopa prior to study visits where MDS-UPDRS assessments will be performed, and instead bring their missed L-Dopa dose to the clinic to be taken during the study visit. MDS-UPDRS Part IV should also be administered whenever the participant starts to display motor complications such as dyskinesia's and/or motor fluctuations regardless of their background PD symptomatic treatment. MDS-UPDRS Part IV should also be administered at the [redacted]

[y] MDS-UPDRS Part II and PGI-C/PGI-S will be administered every two weeks. Assessments that coincide with in-clinic dosing visits should be performed at the clinic. The remaining assessments will be performed via telemedicine (i.e., the investigator or a designated representative will call the participant at their home and administer MDS-UPDRS Part II, PGI-C, and PGI-S over the telephone at Week 2, Week 6, and so on). Participants taking L-Dopa do not need to be in an "OFF" medication state for MDS-UPDRS Part II assessments performed via telemedicine.

[z] At baseline, Week 76, end-of-study, early termination, and [redacted] visits, MDS-UPDRS Part III and digital biomarker in-clinic tests should be repeated at least 1 hour after the missed L-Dopa dose is taken at the clinic, while the participant is in the "ON" medication state. At dosing days, the "ON" medication state assessments have to be performed predose.

[aa] During screening, the digital biomarker remote monitoring (incl. digital PROs) should be started at least 28 days prior to baseline. Digital PROs are scheduled at regular intervals and are administered on a smartphone provided to the patient for this purpose. The digital PROs will typically be completed remotely since the scheduled days will often fall between clinic visit days. Note that if a participant discontinues from study treatment, digital biomarker remote monitoring continue to be collected until the safety follow-up visit.

Table A1-1. Double-Blind Period

[bb] During screening, the first digital biomarker in–clinic assessments should be done at least 28 days prior to baseline; as the aim of this first in-clinic assessment is to introduce the digital tool to the patient, it is acceptable to perform this demonstration when the participant is in "ON" medication state. In–clinic digital biomarker assessments include the full active tests. For patients on L-Dopa treatment, in-clinic active tests will be assessed approximately [redacted] after the last dose of L-Dopa in the "OFF" medication state. These participants will need to be reminded not to take L-Dopa prior to study visits where digital biomarker in-clinic assessments will be performed, and instead bring their missed L-Dopa dose to the clinic to be taken during the study visit.

[cc] MRI(s) should be performed ± 14 days from the study visit except for the end-of-study visit MRI which can be performed up to 28 days prior the end-of-study visit (i.e., MRI cannot be scheduled after the end-of-study visit). No need to repeat the end-of-study visit MRI or the early termination MRI if the Week 76 MRI has been acquired in the previous 6 months. For all participants on L-Dopa treatment, MRI(s) should be performed when the patient is in an "OFF" medication state (i.e., no L-Dopa medication taken within 12 hours of the MRI). These participants will need to be reminded not to take L-Dopa prior to study visits where MRIs will be performed, and instead bring their missed L-Dopa dose to the clinic to be taken during the study visit. See Section 4.5.11.2 and the MRI Manual for further details on MRI sequences.

[dd] DaT-SPECT should be performed once all other screening assessments needed to assess eligibility have been performed, the results are available and the patient has been deemed eligible for the study on the basis of these results.

[ee] For participants who consent to the optional LP procedure, this procedure should be performed once all other screening results are available (including DaT-SPECT imaging) and the patient has been deemed eligible for the study on the basis of these results. The first LP should be performed more than 4 days before the first dose of study drug is administered in order to allow for full recovery. The second LP should ideally be performed 48–72 hours after the Week 76 infusion. LP should be performed in the morning (between 8:00 a.m. and 12:00 p.m.) to minimize potential diurnal variation of CSF parameters. Please refer to the protocol for managing adverse events related to LP, and for instructions regarding concomitant medication. The CSF and matching plasma and serum samples will be sent for central biomarker assessment. Any residual sample will be sent to the Research Biosample Repository for patients who have consented to participate in the RBR.

[ff] Premedication will be given 30–60 minutes prior to the first three infusions.

[gg] Study drug should be administered as an IV infusion over approximately 2 hours for the first three doses and the participant should stay under observation 2 hours post-infusion. If well–tolerated, infusion and observation times can be reduced to approximately 1 hour for subsequent doses.

[hh] Unless otherwise specified, all assessments should be done prior to dosing the participant.

[ii] At baseline only CGI-S and PGI-S are administered. CGI-C and PGI-C are administered from Week 4 and Week 2 on, respectively.

Appendix 1: Schedule of Activities

Table A1-2 Open-Label Extension

	OLE Treatment Period																											Early Termination visit [a, b] /OLE End of Study Visit [a]	Safety Follow-up [c]	Unscheduled Visit
Week	BL [a, d]	4 [a]	8 [a]	12	16	20	24 [a]	28	32	36	40	44	48	52 [a]	56	60	64	68	72	76 [a]	80	84	88	92	96	100	104 [a]			
Dose number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27			
Assessments																														
Informed consent	x																													
Eligibility for OLE	x																													
Vital signs [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Orthostatic blood pressure [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x
Neurologic examination [f]	(x) [g]						x							x						x								x	x	x
Complete physical examination [h]	(x) [g]													x														x	x	x
Limited physical examination [i]		x	x				x													x							x			x
Single ECG-12 lead [j]	x	x	x				x							x						x							x	x	x	x
Hematology [k]	(x) [g]	x	x				x							x						x							x	x	x	x
Blood chemistry & lipids [l]	(x) [g]	x	x				x							x						x							x	x	x	x
Coagulation	(x) [g]	x	x				x							x						x							x	x	x	x

Appendix 1: Schedule of Activities

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Week	BL [a, d]	4 [a]	8 [a]	12	16	20	24 [a]	28	32	36	40	44	48	52 [a]	56	60	64	68	72	76 [a]	80	84	88	92	96	100	104 [a]			
Dose number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27			
FSH (only woman who became postmenopausal during the DB treatment period)	x																													
Immunologic sample [m]	x																													x
Pregnancy test [n]	(x) [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis [o]	(x) [g]	x	x				x							x						x							x	x	x	x
Hoehn and Yahr [p]	(x) [g]			x			x			x				x			x			x			x				x	x	x	x
MDS-UPDRS Part II	(x) [g]			x			x			x				x			x			x			x				x	x	x	x
MDS-UPDRS Part III [p, q]	(x) [g]			x			x			x				x [q]			x			x			x				x	x [q]	x	x
MDS-UPDRS Part IV [p]	(x) [g]			x			x			x				x			x			x			x				x	x	x	x
[redacted]	(x) [g]			x			x			x				x			x			x			x				x	x	x	x
CGI-C and CGI-S	(x) [g]			x			x			x				x			x			x			x				x	x	x	x
PGI-C and PGI-S	(x) [g]			x			x			x				x			x			x			x				x	x	x	x
[redacted]	(x) [g]						x							x						x							x	x	x	x

Appendix 1: Schedule of Activities

Table A1-2. Open-Label Extension

	OLE Treatment Period																										Early Termination visit [a, b] /OLE End of Study Visit [a]	Safety Follow-up [c]	Unscheduled Visit
Week	BL [a, d]	4 [a]	8 [a]	12	16	20	24 [a]	28	32	36	40	44	48	52 [a]	56	60	64	68	72	76 [a]	80	84	88	92	96	100	104 [a]			
Dose number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27			
[redacted]	(x) [g]						x							x						x							x	x	x	x
[redacted]	(x) [g]						x							x						x							x	x	x	x
C-SSRS SLV	(x) [g]						x							x						x							x	x	x	x
MRI [r]	(x) [g]																										x	x [r]		
Serum PK sample [s]	x	x	x				x							x						x							x	x	x	x
Serum ADA sample [t]	(x) [g]	x	x				x							x						x							x	x	x	x
Serum and plasma sample for biomarkers [s]	(x) [g]																										x	x		x
Optional CSF [u]	x [v]																										x	x [u]		
Optional CSF matching serum sample [u]	x [v]																										x	x [u]		
Optional CSF matching plasma sample [u]	x [v]																										x	x [u]		
Premedication [w]	x	x	x																											x

Appendix 1: Schedule of Activities

Table A1-2. Open-Label Extension

	OLE Treatment Period																										Early Termination visit [a, b] /OLE End of Study Visit [a]	Safety Follow-up [c]	Unscheduled Visit
Week	BL [a, d]	4 [a]	8 [a]	12	16	20	24 [a]	28	32	36	40	44	48	52 [a]	56	60	64	68	72	76 [a]	80	84	88	92	96	100	104 [a]			
Dose number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27			
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	←																										→			
Study drug administration [x]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			

ADA=anti-drug antibody; ADL=activities of daily living; BL=baseline; BP=blood pressure; C=complement component; CGI-C=Clinician Global Impression, Change; CGI-S=Clinician Global Impression, Severity; CSF=cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; eCRF=electronic Case Report Form; FSH=follicle-stimulating hormone; IRR=infusion-related reaction; L-Dopa=levodopa; LP=lumbar puncture; [redacted] MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale; [redacted] MRI=magnetic resonance imaging; OLE=open-label extension; PGI-C=Patient Global Impression, on, Severity; PK=pharmacokinetic; RBR=Research Biosample Repository; [redacted] SLV=since last visit.

Note: The OLE baseline is expected to take place at the same day as the double-blind end-of-study visit (i.e. end-of-study visit 28 days (±7 days) after the final double-blind period dose); assessments specific to OLE BL cannot take place before the patient has consented to the OLE and before the double-blind end-of-study assessments have been completed. All subsequent OLE visit dates should be calculated relative to OLE baseline (OLE Day 1). The visit window for all OLE visits is ±7 days. *Whenever possible, scales should be performed at the visit timepoints indicated in the schedule of activities. However, in exceptional circumstances, if the primary rater or the participant cannot perform these assessments as per the schedule of activities, they may be performed up to 28 days out of window.*

[a] Visit may be split over 2 consecutive days. If so, all safety assessments should be performed the second day (i.e., prior to dosing unless specified). Scales ideally should all be done on the first day. If not possible, then MDS-UPDRS (all parts, in "OFF" and "ON" medication states), CGI-S and PGI-S should be done on the first day. [redacted]

[b] Participants who discontinue study drug prematurely should return to the clinic for an early termination/*end-of-study* visit 28 days (±7 days) after their final dose.

[c] The safety follow-up visit should take place 70 days (±7 days) after the final study dose (i.e., 70 days [+7 days] after OLE Week 104 or earlier for those participants who discontinue study drug prematurely).

[d] The date of the first OLE treatment (OLE baseline) is considered to be the OLE Day 1. If this visit is split over 2 consecutive days, then baseline is done on OLE Day 0 and on OLE Day 1. When the first OLE treatment is given the same day as the double-blind end-of-study visit, dosing should take place only after all double-blind end-of-study visit procedures are done and after the participant has consented for the OLE, eligibility for the OLE has been confirmed and all predose OLE safety assessments have been performed.

[e] Vital signs (including semi-supine systolic and diastolic blood pressure, respiratory rate and pulse rate) must be monitored before the infusion, every 15 minutes during the infusion and every 30 minutes after the infusion until the infusion line is removed for the first three infusions. For subsequent infusions, vital signs should be monitored every 30 minutes until the infusion IV line is removed, unless safety considerations indicate that more frequent monitoring is warranted. In order to assess orthostatic hypotension, BP and pulse rate should be evaluated after 2 minutes of standing still (after the semi-supine measurement). For the first three infusions, orthostatic hypotension measurements should be collected before and 2 hours after the end of the infusion. For subsequent infusions, measurements should be collected 1 hour after the end of the infusion. Abnormal values for vital signs should be repeated for confirmation or intervention if required.

[f] A neurologic examination should include an assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination.

[g] No need to repeat this assessment in the case it has already been assessed for the double-blind end-of-study visit.

[h] Complete physical examination includes weight and the evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.

[i] Limited physical examinations should be symptom-directed or as clinically indicated.

[j] For all the designated dosing visits, the ECGs should be obtained pre- and post-dose. At dosing visits without PK sampling, the ECG can be done at any time post-dose. At visits with PK sampling, the ECG should be performed at the time of the PK sampling, ideally just before the PK sampling. For non-dosing visits, the ECGs should be obtained to approximate the timing of the pre-dose ECGs during the study.

[k] Hematology includes WBC count, RBC count (including MCV and RBC morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[l] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard-of-care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and LDH.

[m] This includes tryptase, cytokine panel, C3, C3a, C5a, and total IgE. In case of Grade ≥2 IRR, this sample should be drawn within 3 hours of the event and repeated within 48 to 72 hours post-event. Note that the baseline sample will only be analyzed if a postbaseline sample is collected (i.e., for participants who experience a Grade 2 or higher IRR).

Table A1-2. Open-Label Extension

[n] Urine pregnancy test for female participants (based on participant age/menopausal status) performed prior to dosing. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[o] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood, leucocytes and nitrites); perform a microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) by central laboratory if blood and/or protein results are positive (i.e., confirmed by a positive repeated dipstick sample).

[p] Hoehn and 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. MDS-UPDRS Part IV should also be administered whenever the participant starts to display motor complications such as dyskinesia's and/or motor fluctuations regardless of his or her background PD symptomatic treatment. Note: For all participants that are on L-Dopa treatment MDS-UPDRS Part III and Part IV will be assessed approximately 12 hours (e.g., overnight) after the last dose of L-Dopa treatment. For deep brain stimulation device carriers, assessments will be carried out in the "ON" medication state only, no "OFF" medication state assessments are to be performed. Participants will need to be reminded not to take L-Dopa prior to study visits where MDS-UPDRS assessments will be performed, and instead bring their missed L-Dopa dose to the clinic to be taken during the study visit.

[q] At OLE Week 52, OLE end-of-study and early termination visits, MDS-UPDRS Part III should be repeated at least 1 hour after the missed L-Dopa dose is taken at the clinic, while the patient is in the "ON" medication state. At dosing days, the "ON" medication state assessments have to be performed predose.

[r] MRI should be performed ± 14 days from the study visit, except for the OLE end-of-study visit MRI which can be performed within 28 days prior the OLE end-of-study visit (i.e., MRI cannot be scheduled after the OLE end-of-study visit). For all participants on L-Dopa treatment, MRI should be performed when the participant is in an "OFF" medication state (i.e., no L-Dopa medication taken within 12 hours of the MRI). These participants will need to be reminded not to take L-Dopa prior to study visits where MRIs will be performed, and instead bring their missed L-Dopa dose to the clinic to be taken during the study visit. See Section 4.5.11.2 and the MRI Manual for further details on MRI sequences. MRI has to be done in case a participant is terminating early, but no need to repeat the early termination MRI if an MRI has been acquired in the previous 6 months. At the OLE end of the study if MRI has been done at Week 104 there is no need to repeat the examination at OLE end-of-study visit.

[s] At dosing visits, serum PK and serum and plasma biomarker samples will be collected just prior to dosing; serum PK sample will also be collected at the end of the infusion. At non-dosing visits, sample collection can be performed at any time during the visit. In all cases, the time of sample collection should be recorded on the eCRF. Note: Serum and plasma biomarkers should be collected as two separate samples and not together.

[t] On dosing days, serum ADA samples will be collected prior to dosing. Additional ADA and PK samples should be collected in participants with signs and symptoms of infusion-related reactions and hypersensitivity reaction.

[u] For participants who consent to the optional LP procedure, this procedure should be performed in the morning (between 8:00 a.m. and 12:00 p.m.) to minimize potential diurnal variation of CSF parameters. The ideal collection time to perform LP is between 48–72 hours after early termination. Optional LP has to be collected in case a patient is terminating early; at the OLE end of the study if optional LP has been collected at OLE Week 104 there is no need to repeat the exam at OLE end-of-study visit. Please refer to the protocol for managing adverse events related to LP, and for instructions regarding concomitant medication. The CSF and matching plasma and serum samples will be sent for central biomarker assessment. Any residual sample will be sent to the Research Biosample Repository for participants who have consented to participate in the RBR.

[v] No need to acquire a BL optional CSF sample and related matching plasma and serum samples if *the participant already participated in CSF collection during the double-blind period.*

[w] Premedication will be given 30-60 minutes prior to the first three infusions.

[x] Study drug should be administered as an IV infusion over approximately 2 hours for the first three doses and the participant should stay under observation 2 hours post-infusion. If well tolerated, infusion and observation times can be reduced to approximately 1 hour for subsequent doses. Unless otherwise specified, all assessments should be done prior to dosing the participant.

APPENDIX 2 ANAPHYLAXIS PRECAUTIONS

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

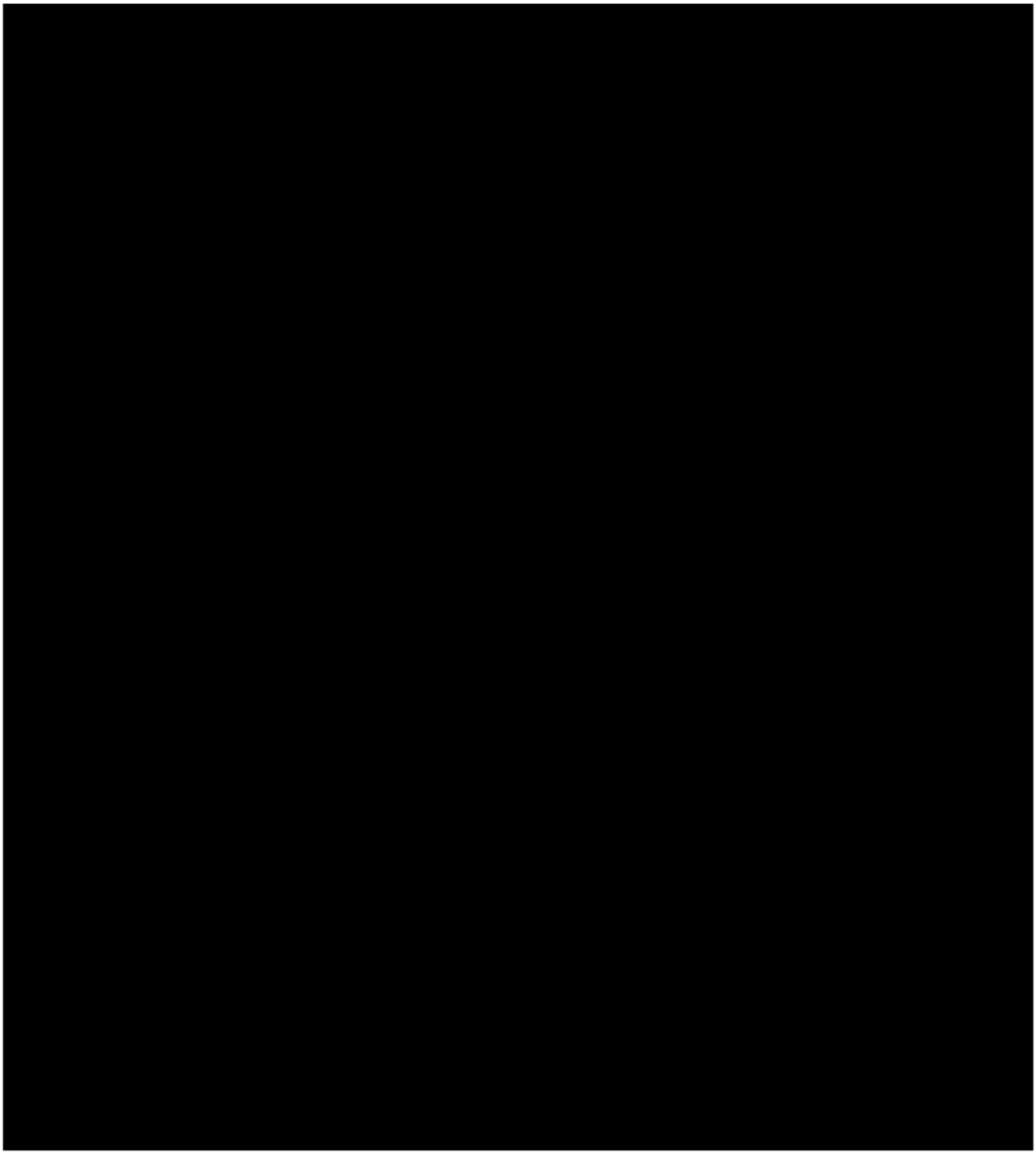
In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids, as required by patient status, and as directed by the physician in charge.
6. Continue to observe the patient and document observations.
7. Blood samples to determine tryptase, cytokine panel, C3, C3a, C5a, and total IgE should be drawn within 3 hours of the event and repeated within 48 to 72 hours post-event.
8. Paired blood samples to determine anti-drug antibody (ADA) and pharmacokinetic levels should be drawn.
9. Discontinue participant from the study treatment.

APPENDIX 3
CLINICIAN- AND PATIENT-REPORTED, AND PERFORMANCE OUTCOMES

Details regarding Clinician- and Patient-Reported, and Performance Outcome measures that will be collected during the study are provided in Table A3-1.

Table A3-1 Summary of Clinician- and Patient–Reported, and Performance Outcome Measures



APPENDIX 4
INVESTIGATIONAL AND AUXILIARY AND NON-INVESTIGATIONAL/MEDICINAL PRODUCT DESIGNATIONS (FOR USE IN EUROPEAN ECONOMIC AREA AND UNITED KINGDOM)

Table A4-1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	*IMP/AxMP Designation*	*Marketing Authorization Status in EEA*	*Used within Marketing Authorization*
Prasinezumab (RO7046015)	*IMP (test product)*	*Unauthorized*	*Not applicable*
Placebo (RO7046015)	*IMP (placebo)*	*Unauthorized*	*Not applicable*
Levodopa	*AxMP (background therapy)*	*Authorized*	*Yes*
Monoamine oxidase B inhibitor	*AxMP (background therapy)*	*Authorized*	*Yes*
Antihistamine (H1-receptor antagonist)	*AxMP (other) [a]*	*Authorized*	*Yes*
Acetaminophen/ paracetamol	*AxMP (other) [a]*	*Authorized*	*Yes*
NSAIDs	*AxMP (other) [a]*	*Authorized*	*Yes*
Corticosteroid	*AxMP (other) [b]*	*Authorized*	*Yes*
Ioflupane (^{123}I)	*AxMP (other) [c]*	*Authorized*	*Yes*

AxMP =auxiliary medicinal product; DaT-SPECT =dopamine transporter imaging with single-photon emission computed tomography; EEA =European Economic Area; IMP =investigational medicinal product; IRR =infusion-related reaction; NSAID =nonsteroidal anti-inflammatory drug.

[a] *All patients will receive mandatory premedication prior to the three first infusions and for subsequent infusions if an IRR Grade 2 or higher occurred on a previous infusion or in case of IRR recurrence. Premedication consists of an antihistamine (H1-receptor antagonist) and an antipyretic medication (acetaminophen or alternatively a NSAID if acetaminophen cannot be tolerated).*

[b] *If a patient experiences a IRR Grade 3 or higher, a corticosteroid should be added to the list of standard premedications.*

[c] *Ioflupane (^{123}I) will be used as a DaT-SPECT imaging tracer for screening purposes only.*

Table A4-2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in UK	Used within Marketing Authorization
Prasinezumab (RO7046015)	IMP (test product)	Unauthorized	Not applicable
Placebo (RO7046015)	IMP (placebo)	Unauthorized	Not applicable
Levodopa	NIMP (background therapy)	Authorized	Yes
Monoamine oxidase B inhibitor	NIMP (background therapy)	Authorized	Yes
Antihistamine (H1-receptor antagonist)	NIMP (other) [a]	Authorized	Yes
Acetaminophen/ paracetamol	NIMP (other) [a]	Authorized	Yes
NSAIDs	NIMP (other) [a]	Authorized	Yes
Corticosteroid	NIMP (other) [b]	Authorized	Yes
Ioflupane (^{123}I)	NIMP (other) [c]	Authorized	Yes

DaT-SPECT =dopamine transporter imaging with single photon emission computed tomography; IMP =investigational medicinal product; IRR =infusion-related reaction; NSAID =nonsteroidal anti-inflammatory drug; NIMP =non-investigational medicinal product; UK =United Kingdom.

[a] All patients will receive mandatory premedication prior to the three first infusions and for subsequent infusions if an IRR Grade 2 or higher occurred on a previous infusion or in case of IRR recurrence. Premedication consists of an antihistamine (H1-receptor antagonist) and an antipyretic medication (acetaminophen or alternatively a NSAID if acetaminophen cannot be tolerated).

[b] If a patient experiences a IRR Grade 3 or higher, a corticosteroid should be added to the list of standard premedications.

[c] Ioflupane (^{123}I) will be used as a DaT-SPECT imaging tracer for screening purposes only.

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