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

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STATISTICAL ANALYSIS PLAN

TITLE: **A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 52-WEEK PHASE II STUDY TO EVALUATE THE EFFICACY OF INTRAVENOUS RO7046015 (PRX002) IN PARTICIPANTS WITH EARLY PARKINSON'S DISEASE WITH A 52-WEEK BLINDED EXTENSION (PASADENA)**

PROTOCOL NUMBER: BP39529

STUDY DRUG: RO7046015

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PLAN PREPARED BY: [redacted]

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STATISTICAL ANALYSIS PLAN APPROVAL

.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
ADA	Anti-drug antibody
ANCOVA	Analysis of Covariance
AUC	Area Under the Curve
BP	Blood Pressure
CGI-I	Clinical Global Impression of Improvement
CSR	Clinical Study Report
DCC	Data Coordinating Center
eCRF	electronic Case Report Form
ECG	Electrocardiogram
eDiary	electronic diary
EDC	electronic data capture
ePRO	electronic patient-reported outcome
eTMF	Electronic Trial Master File
ICH	International Conference on Harmonization
iDMC	independent Data Monitoring Committee
IRR	Infusion-related reaction
MAO-B	Monoamine oxidase B
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
mITT	Modified-Intent-to-Treat
MMRM	Mixed-Effect Model Repeated Measures
MOCA	Montreal Cognitive Assessment score
MRI	Magnetic Resonance Imaging
PD	Parkinson's Disease
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
POC	Proof-of-concept
PPMI	Parkinson's Progression Markers Initiative
RBDSQ	REM Sleep Behavior Disorder Screening Questionnaire
SAP	Statistical Analysis Plan
SCOPA-AUT	Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire
SE-ADL	Schwab and England Activities of Daily Living score
SREP	Study Results Endorsement Plan

1. BACKGROUND

Current Parkinson's Disease (PD) treatments mainly consist of dopaminergic supplementation, which can control some symptoms of the disease for a limited period of time. Moreover, current treatments do not reverse, slow or halt the progressive development of disability or the pathological processes underlying the disease.

Although the etiology of PD is yet to be determined, experimental and human evidence suggests that aggregated forms of alpha-synuclein may spread between interconnected neurons and contribute to axonal and neuronal damage and thereby disease progression. For example, the pattern of Lewy pathology in patients with PD may be explained by a propagation over interconnected neuronal networks; embryonic mesencephalic neurons transplanted into PD patients develop Lewy pathology a decade after initial grafting; and intracerebral and intestinal injection of aggregated alpha-synuclein accelerates the onset of neurologic symptoms and death in transgenic mice expressing human alpha-synuclein. Altogether, these data support the therapeutic potential of agents that target aggregated forms of alpha-synuclein and block the spreading of extracellular alpha-synuclein in patients with PD.

RO7046015 (INN: prasinezumab, formerly RG7035 or PRX002) is an immunoglobulin class G1 (IgG1) humanized monoclonal antibody (mAb) directed against an epitope in the C-terminal of human alpha-synuclein, which binds preferentially to aggregated alpha-synuclein and has the potential of reducing neuronal toxicity, preventing the cell-to-cell transfer of pathological alpha-synuclein, and slowing disease progression.

Proof-of-concept (POC) will be demonstrated by a reduction in clinical progression of PD symptoms and/or reduction in DaT-SPECT signal decline.

The analyses specified in this SAP supersede the analysis plan described in the protocol. This SAP describes Part 1 analyses. Analyses for Part 2 will be described in a future version of the SAP or a separate SAP. The main body of this SAP includes all the analyses that will be created for the SREP, CSR and for informing decision making for the design of the Phase 3 trial. Exploratory analyses are listed in Appendix 1.

2. STUDY DESIGN

This is a multicenter, Phase II study to evaluate the effect of IV administration of prasinezumab in early PD patients (Hoehn & Yahr Stages I-II). Participants were eligible if they had idiopathic PD with bradykinesia plus one of the other cardinal signs of PD (resting tremor, rigidity) being present, without any other known or suspected cause of PD and are either untreated or treated with MAO-B inhibitors. All PD patients included also had a positive DaT-SPECT contralateral to the most clinical affected side, at the time of enrolment.

The study consists of two parts: a 52-week, randomized, double-blind, placebo-controlled treatment period (Part 1) after which eligible participants continue into an all-participants-on-treatment (prasinezumab) blinded to dose extension for an additional 52 weeks (Part 2).

2.1. PART 1

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

Protocol allowed approximately 300 participants to be randomized with a 1:1:1 allocation ratio to placebo, or one of the two active treatment doses: high dose (4500 mg for bodyweight $\geq$ 65 kg; 3500 mg for bodyweight $<$ 65 kg), low dose (1500 mg; for all bodyweights). The number of randomized participants could have been increased to a maximum of 360 depending on the outcome of the review by the safety Independent Data Monitoring Committee. (Safety iDMC; Section 3.2).

Randomization was stratified by sex, age group ($<$ 60 years vs $\geq$ 60 years), and prior background therapy with MAO-B inhibitor at randomization (Yes vs No).

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

Only early stage PD patients with a clinical condition not requiring symptomatic PD treatment (as defined in Section 4.3.1) at baseline and not expected to require dopaminergic treatment within 12 months from baseline were eligible to participate in the study. Patients with a history of stable parkinsonian symptoms who were on a stable dose of MAO-B inhibitor (rasagiline or selegiline) for at least 90 days prior to baseline may have also been included.

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

For the main analysis of the primary endpoint and other efficacy endpoints that are sensitive to symptomatic PD treatment, only data up to the last measurement before start of symptomatic PD treatment will be used (see analysis of each endpoint in

Section 4.7). Time to start of symptomatic PD treatment will be analysed as part of a exploratory time to event endpoint. Data after start of symptomatic PD treatment will be included in safety, sensitivity, exploratory and biomarker evaluations as appropriate. Time to start of dopaminergic PD treatment (levodopa and dopamine agonists) will be analysed as secondary time to event endpoint.

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

2.2. PART 2

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

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

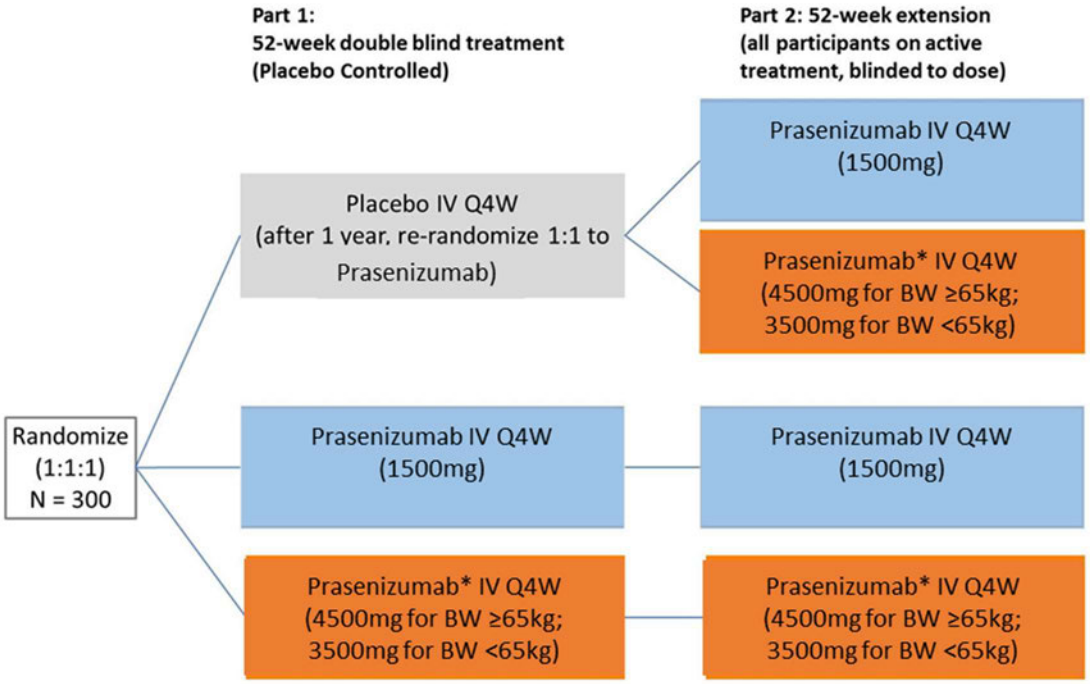
For Part 2, participants who complete the initial placebo-controlled part and fulfil the criteria mentioned above will switch into the extension as follows:

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

  Randomization is stratified by: symptomatic PD treatment since start of the study (Yes versus No), age group (<60 versus ≥ 60) and prior background therapy with MAO-B inhibitor (Yes versus No). Note that for age group and prior background therapy with MAO-B inhibitor, the values collected for randomization to Part 1 will be used.

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

Figure 1 Study Design



*2000 mg will be administered at the first infusion followed by up-titration to the full dose of 4500 mg (≥ 65 kg BW) or 3500 mg (< 65 kg BW) at the second infusion

2.3. OUTCOME MEASURES

2.3.1. Primary Efficacy Outcome Measures

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

2.3.2. Secondary Efficacy Outcome Measures

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

- Change from baseline in MDS-UPDRS Part IA, Part IB, Part I total, Part II total, Part III total and Part III subscores (rigidity, bradykinesia, resting tremor and axial symptoms)
- Change from baseline in DaT-SPECT in ipsilateral (to the clinically dominant side) putamen binding ratio values.
- Change from baseline in MoCA total score
- Change from baseline in Clinical Global Impression of Improvement (CGI-I)
- Change from baseline in Patient Global Impression of Change (PGIC)
- Change from baseline in Schwab and England Activities of Daily Living score (SE-ADL).

- Time to worsening of motor or non-motor symptoms as measured by MDS-UPDRS and defined as the first occurrence of either of the following:
    - ≥ 3 points change from Baseline in MDS-UPDRS Part I, or
    - ≥ 3 points change from Baseline in MDS-UPDRS Part II
- Time to start of dopaminergic PD treatment (levodopa or dopamine agonist)

2.3.3. Exploratory Efficacy Outcome Measures

For exploratory outcome measures see Appendix 1.

2.3.4. Pharmacokinetic Outcome Measures

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

2.3.5. Safety Outcome Measures

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

2.4. DETERMINATION OF SAMPLE SIZE

The sample size calculations were aimed to power the study for the primary endpoint of change in total MDS-UPDRS (sum of Parts I, II and III) at Week 52, see Section 4.7.2 for a full description of the endpoint.

A sample size of 100 randomized participants per group (300 participants for the three groups) was chosen to obtain a power of approximately 80% at two-sided α-level of 20% for the comparison of each active dose arm to placebo. The power calculation was based on simulations of the mixed-effect model repeated measures (MMRM) analysis

planned for the primary efficacy variable. Assessments performed while on any symptomatic treatment started after randomization will not be included in the analysis. The following assumptions were made for simulating the data:

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

Table 1 provides the additional information needed to perform the simulations.

Table 1. Assumptions Used for Simulations

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

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

The assumptions on progression, variability, dropout rate and likelihood to start symptomatic therapy within the first 52 weeks of treatment, with or without a MAO-B inhibitor as background therapy, were derived from analyses based on the Parkinson's Progression Markers Initiative (PPMI) database and various sources of information from the literature.

The sample size of 100 patients per arm also provides 76% power ($\alpha = 20\%$, two-sided) to reject the null hypothesis assuming a 37.5% reduction (or assuming an effect size $= 0.31$ based on assumption of decline over 52 weeks of 0.157 for the placebo arm and standard deviation of 0.185 derived from the PPMI database) for the key secondary endpoint, the DaT-SPECT signal loss at Week 52, for the pairwise comparison of each active dose arm to placebo. The missing values assumption used was 15% and included participants who withdrew from study medication before Week 52 or who did not have a valid DaT-SPECT assessment at Week 52. Assessments performed while on any symptomatic treatment started after randomization will not be excluded from the analysis.

No adjustments for multiple comparisons will be incorporated into the analyses.

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

The sample size could have been adjusted if the initial assumptions on dropout rate and likelihood to start symptomatic PD treatment as described in Table 4 were different from the actual values observed. If that was the case, the Sponsor could have increased enrolment up to 20% of the total sample size. The aim of this increase in sample size was to ensure that the pairwise comparison of each active dose arm to placebo remained adequately powered.

2.5. ANALYSIS TIMING

The following analyses were planned for this study

Table 2. Analyses Timings

Analysis	Timing of Analysis
First Safety interim	30 participants (approximately 10 participants per arm) have received three infusions
Second Safety interim	60 participants (approximately 20 participants per arm) have received three infusions
Part 1	all active participants have completed the Week 52 visit (Part 1: placebo-controlled, double-blind treatment period)
Part 2	all active participants have completed the follow-up visit, up to 12 weeks after cessation of treatment (regardless of whether cessation of treatment occurs at the end of or during Part 1 or Part 2)

2.6. DATA INCLUDED IN 52-WEEK DATA CUT (PART 1 ANALYSIS)

The analysis of Part 1 will take place once all the randomized patients in the study have reached the Week 52 visit or withdrawn from the study prior to Week 52; all data from the study are in the database, and the database is frozen. The patient data will be cut at the day prior to the Week 56 visit. All data prior to this cut-off will be cleaned and verified for completeness to the best extent possible.

The following data will be included in the 52-week data cut: all screening and post-baseline data with a clinical date (i.e., administration/assessment/onset/start date) the day before the date of re-randomization to Part 2 (Week 56) will be included.

The Part 1 data cut will include all data regardless of the type of study visit at which it was collected. This may include data collected at prior to start dopaminergic visits, unscheduled visits, dosing termination visits, early termination visits, or safety follow-up visits, if the visit date was before re-randomization to Part 2 (Week 56).

3. STUDY CONDUCT

3.1. RANDOMIZATION ISSUES

Randomization was done via an Interactive Voice/Web Response System (IxRS). Patients were randomized once all screening assessments had been completed and eligibility confirmed.

For Part 2, participants who complete the initial placebo-controlled part of the study (Part 1) and fulfil the criteria described in section 2.2 enter the extension part of the study (Part 2), in which case, a re-randomization will take place. Although only placebo patients will be re-randomized at the start of Part 2, see section 2.2, all patients will be registered in IxRS at the start of Part 2 to ensure the blind is maintained.

Both randomization lists were generated by the IxRS provider.

Note to file 29, found in eTMF system, was written to clarify when the correction of entry errors in IxRS for 'prior background therapy with MAO-B inhibitors' and/or 'Dopaminergic therapy since start of the study' is allowed. If an entry error in Part 1 is made regarding prior background therapy with MAO-B inhibitor, then the Sponsor will not allow a change in the IxRS as this variable is a stratification factor. If an entry error is made regarding the start of symptomatic PD therapy since the start of the study, the Sponsor will allow a change in IxRS since this item is not a stratification factor in Part 1; these changes are only allowed to be made before the patient is re-randomized at week 56.

The stratification factors to use in the analysis will be the ones obtained in the IxRS. A cross tabulation will be created to assess discrepancies between the IxRS stratification factors and the ones derived with the eCRF data.

3.2. DATA MONITORING

3.2.1. INDEPENDENT DATA MONITORING COMMITTEE

This study utilizes an independent Data Monitoring Committee (iDMC), which monitors safety of the study. There were two scheduled safety iDMC meetings: after approximately 30 participants (approximately 10 participants per arm) and 60 participants (approximately 20 participants per arm), respectively, received their first three infusions. The first meeting happened on 8th May 2018 and the second on 22nd June 2018. For both meetings the analyses of the safety data were conducted by an external statistical group and reviewed by the iDMC. The iDMC was unblinded at the aggregate and individual level to review and evaluate safety data. Interactions between the iDMC and the Sponsor were carried out as specified in the iDMC Charter. Sponsor personnel did not have access to the results of these data analyses.

The iDMC may be convened at additional time-points if warranted by safety considerations or for other reasons until the study is unblinded to the sponsor, end of Part 1 of the study (for further details see the separate iDMC Charter).

4. STATISTICAL METHODS

4.1. ANALYSIS POPULATIONS

4.1.1. Modified Intent-to-treat Population

The modified intent-to-treat (mITT) population will include all patients randomized in the study who received any amount of study drug treatment. Analyses based on the mITT population will be based on the treatment arm the patient was randomized.

4.1.2. Per Protocol Population

A Per Protocol (PP) population will not be defined.

4.1.3. Pharmacokinetic Analysis Population

Any subjects with at least one adequately documented PK measurement will be included in the PK Analysis Population. Any exclusion of such a subject will be documented together with the reason for exclusion.

4.1.4. Safety Analysis Population

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

4.1.5. Immunogenicity Analysis Population

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

4.1.6. Part 2 (Extension) Population

Participants who complete the double-blind, placebo-controlled treatment period (Part 1) will continue in an all-participants-on- prasinezumab treatment (high or low dose) for an additional 52 weeks (Part 2), but will be blinded to prasinezumab dose. This will allow collection of safety information on long-term exposure with prasinezumab, as well as concomitant dopaminergic treatment. Analyses for Part 2 will be described in a future version of the SAP.

4.2. DEFINITION OF BASELINE

Baseline for the MDS-UPDRS

Baseline for the MDS-UPDRS will be considered as the last time point before treatment when the three parts (I, II, and III) are non-missing following the rules stated in Section 4.7.2.1.

Definition of Baseline for Statistical Analyses

Baseline will be defined as last available pretreatment value taken on or before the day of first treatment dose and will be used in summaries of demographic characteristics as well as any change from baseline analyses of efficacy, and safety.

For endpoints defined in terms of change from baseline, patients who do not have a pretreatment value reported for a particular assessment (if any) will be excluded from the change from baseline analyses for that assessment.

4.3. CONCOMITANT EVENTS

It is expected that during the development of the study the events defined in this section will take place. The aim of this section is to define flags that will be created in the datasets and that will guide the analysis of the endpoints as defined in Section 4.7.

4.3.1. Start of symptomatic PD treatment

The start of symptomatic PD treatment visit will be derived according to the following algorithm:

1. For patients who are treatment naïve at baseline, symptomatic PD treatment includes the following medications: COMT inhibitors [entacapone, tolcapone], amantadine or anticholinergics, dopamine medication [levodopa], both ergot and non-ergot (pramipexole, ropinirole, rotigotine) treatments, MAOB inhibitors [rasagiline, selegine, safinamide], and dopamine agonists. These medications received by the patient during Part 1 will be extracted from the Concomitant Medications SDTMv domain (from Targeted ConMed eCRF page). The symptomatic PD treatments will be selected with the following criteria from the WHODrug dictionary: ATC Class Level 2 should be equal to "ANTI-PARKINSON DRUGS" (Class code N04).

   For patients on MAOB inhibitors at baseline, symptomatic PD treatment is defined as COMT inhibitors [entacapone, tolcapone], amantadine or anticholinergics, dopamine medication [levodopa], both ergot and non-ergot (pramipexole, ropinirole, rotigotine) treatments, and dopamine agonists received by the patient during Part 1. In addition, also an increase in dose or regimen of the MAO-B inhibitors compared to baseline is considered as “symptomatic PD treatment”. MAOB inhibitors will be selected from the concomitant medications at baseline when ATC Class Level 4 is equal to "MONOAMINE OXIDASE B INHIBITORS" and their dose/regimen increases when compared to baseline

2. The date when the first symptomatic PD treatment was received or an increase in dose/regimen in MAOB inhibitor from baseline happened (whichever is first) will be marked as the “first symptomatic PD treatment date”.

3. All visits with a date after the date of the first intake of symptomatic PD treatment will be flagged and considered as “after first symptomatic PD treatment”.

4.3.2. Start of dopaminergic treatment

The start of dopaminergic treatment visit will be derived according to the following algorithm:

1. All the dopaminergic treatments defined as dopamine medication [levodopa], both ergot and non-ergot (pramipexole, ropinirole, rotigotine) treatments and dopamine agonists received by the patient during Part 1 will be extracted from

the Concomitant Medications SDTMv domain (from Targeted ConMed eCRF page). The dopaminergic treatments will be selected with the following criteria from the WHODrug dictionary: ATC Class Level 4 should be equal to " DOPA AND DOPA DERIVATIVES or DOPAMINE AGONISTS".

2. The date when the first dopaminergic treatment was received will be marked as the "first dopaminergic treatment date".

3. All visits with a date after the date of the first intake of dopaminergic treatment will be flagged and considered as "after first dopaminergic treatment".

4.3.3. Defined symptomatic treatment start

The last visit whose date is before or the same date of the "first symptomatic PD treatment date" (as described in Section 4.3.1) will be flagged as the "Defined symptomatic treatment start".

4.3.4. Defined dopaminergic treatment start

The last visit whose date is before or the same date of the "first dopaminergic treatment date" (as described in Section 4.3.2) will be flagged as the "Defined dopaminergic treatment start".

4.3.5. Practically defined "Off" state

Participants who have started dopaminergic PD treatment (as per Section 4.3.2) during the course of the study will continue in the study, as per their regular scheduled study visits. For these participants, the MDS-UPDRS (Parts I, II, III and IV) will be performed in a practically defined "Off" state – no levodopa or dopamine agonist medication since the prior evening, and Part III (motor assessment) will be repeated at least one hour after receiving medication in clinic ("On" state).

For MDS-UPDRS Part III collected on the same visit day, the earliest date/time stamp will indicate that the measurement was undertaken during the OFF state. The second measurement will be flagged as the ON state.

For participants who have started symptomatic PD treatment different from dopa or dopamine agonists, the MDS-UPDRS Part III will not be repeated in ''OFF'' and ''ON'' state due to the long half-life of these compounds. If only one MDS-UPDRS Part III is collected on the visit date after starting symptomatic PD treatment different from dopa or dopamine agonists, this will be labelled as Practically defined "OFF" state. If two MDS-UPDRS Part III are collected on the same visit day, the earliest date/time stamp will be included as Practically defined "OFF" state.

4.4. ANALYSIS OF STUDY CONDUCT

4.4.1. Screening

The number of patients who were screened and the number and percentage of patients who were screen failures will be reported.

4.4.2. Study enrollment

The number of patients randomized will be summarized by treatment group, country, and study site.

4.4.3. Protocol Deviations

Protocol deviations will be reviewed and reported in accordance with the 'Global: Protocol Deviations' standard operating procedure (SOP-0105983). Major protocol deviations will be identified according to the Protocol Deviation Management System (PDMS) before data cut. The number and percentage of patients with major protocol deviation will be summarized by treatment group and protocol deviation category (inclusion criteria, exclusion criteria, procedures, or medication) and by inclusion/exclusion criteria not met.

4.4.4. Patient Disposition

Patient disposition (the number and percentage of patients randomized, receiving at least one dose of study drug during the treatment period, randomized but not receiving study drug, completed Part 1, discontinued from study, and time on study) will be summarized by treatment arm. Reasons for premature withdrawal from study will be summarized by treatment group.

The number and percentage of patients who started symptomatic PD treatment (as described in Sections 4.3.1) will be reported by treatment group, visit and country.

4.5. ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographics and baseline characteristics, including, but not limited to age, sex, race, ethnicity, weight, height, BMI, Hoehn & Yahr and modified Hoehn & Yahr (mH&Y) scale, MoCA, total (sum of Parts I, II, and III) and Part I, II and III of MDS-UPDRS, PDQ-39, SE-ADL, DaT-SPECT striatium, putamen and caudate (ipsilateral, contralateral and average) , MAOB inhibitor treatment (Yes/No), RBDSQ Multi Item (< 5, ≥ 5), MDS-UPDRS sub-scores: Parts IA, Part IB, Part I total and II, Parts III, and Part III subscores, PDSS-2, SCOPA-AUT, skin biopsy (positive or negative), mean diffusivity (MD) MRI, fractional anisotropy (FA) MRI, and cerebral blood flow (CBF) MRI striatium, putamen and caudate (ipsilateral, contralateral and average) will be summarized for the mITT population by treatment arm with the use of descriptive statistics.

4.6. TIME WINDOWS

The analysis of data will be undertaken using time windows. As all the endpoints in the study are collected at different time frequencies, three different set of time windows will be applied depending on the endpoint. The analysis of all the endpoints collected every four weeks will be undertaken using the time windows described in Table 3. For the scales and questionnaires collected every eight weeks or more, Modified Hoehn & Yahr, MDS-UPDRS, CGI-I, PGI-C, MoCA, PDQ-39, SCOPA-AUT, SE-ADL, and PDSS-2, the time windows that will be used in the analysis are described in Table 4. All the endpoints collected with the remote device will be analysed with the windows described in Table 5.

The reporting windows will be applied to every single data point obtained for analyses regardless of the visit label used to collect the data, i.e. scheduled, unscheduled, or prior to start symptomatic treatment visits. If there are two or more visits mapped to exactly the same reporting window, then the following rules will be used to apply the data analysis flag to the assessment, i.e. the data flag used for the by visits reported as described in this SAP:

1. If neither of the visits are labelled as “Prior to start dopaminergic treatment visit” (as per protocol), flag the data from the last available visit.

2. If any visit is labelled as “Prior to start dopaminergic treatment visit” (as per protocol), then flag the data from this visit in the analysis.

Table 3. Windows for assessments collected every four weeks (vitals, physical examination, C-SSRS, ECG, ADAs, hematology, etc).

	Scheduled Week	Scheduled Day	Reporting window		
Part 1	**1**	1	≤ 1		
	1	2	2	to	4
	1	7	5	to	10
	2	14	11	to	20
	4	28	21	to	41
	8	56	42	to	69
	12	84	70	to	97
	16	112	98	to	125
	20	140	126	to	153
	24	168	154	to	181
	28	196	182	to	209
	32	224	210	to	237
	36	252	238	to	265
	40	280	266	to	293
	44	308	294	to	321
	48	336	322	to	349
	52	364	350	to	Day before re-randomization to Part 2

Table 4. Windows for assessments collected every 8 weeks or more

	Scheduled Week	Scheduled Day	Reporting window		
Part 1	**1**	1	≤ 1		
	8	56	2	to	83
	16	112	84	to	139
	24	168	140	to	195
	32	224	196	to	251
	40	280	252	to	307
	48	336	308	to	349
	52	364	350	to	Day before re-randomization to Part 2

Table 5. Windows for assessments collected in the remote device

	Scheduled Week	Scheduled Day	Reporting window		
Part 1	1	1	≤ 1		
	2	14	2	to	20
	4	28	21	to	34
	6	42	35	to	48
	8	56	49	to	62
	10	70	63	to	76
	12	84	77	to	90
	14	98	91	to	104
	16	112	105	to	118
	18	126	119	to	132
	20	140	133	to	146
	22	154	147	to	160
	24	168	161	to	174
	26	182	175	to	188
	28	196	189	to	202
	30	210	203	to	216
	32	224	217	to	230
	34	238	231	to	244
	36	252	245	to	258
	38	266	259	to	272
	40	280	273	to	286
	42	294	287	to	300
	44	308	301	to	314
	46	322	315	to	328
	48	336	329	to	342
	50	350	343	to	356
	52	364	357	to	Day before re-randomization to Part 2

4.7. EFFICACY ANALYSIS

Efficacy summaries for the 52-week treatment period will include outcomes as described in Section 2.6. This includes data from patients collected at unscheduled visits, dosing termination visits, early termination visits, or safety follow-up visits, if the visit date was during the first 52 weeks of the study.

All efficacy endpoints will be plotted in dot plots or box plots.

4.7.1. Covariate Adjustment

Unless otherwise noted, analyses of efficacy endpoints (primary, secondary, and exploratory) will include the following covariates in the model:

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

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

4.7.2. Primary Efficacy Endpoint

The primary efficacy objective for Part 1 of the study is to evaluate the efficacy of prasinezumab compared with placebo on the basis of total MDS-UPDRS (sum of Parts I, II, and III).

Following the estimand framework outlined in draft the ICH E9 addendum (European Medicines Agency 2017), the attributes of the proposed primary estimand are defined as follows:

- The **population** is defined as the modified intent-to-treat population described in Section 4.1.1.
- The **variable** is absolute change from baseline in total MDS-UPDRS (sum of Parts I, II and III) at week 52 using measurements taken up to the start of symptomatic PD treatment.
- The **intercurrent event** of start of symptomatic PD treatment will be handled with a hypothetical strategy through the MMRM model, i.e. the model will estimate what would have happened to the patients if they had stayed in the trial and not started symptomatic PD treatment. Any other intercurrent event, for example study discontinuation or loss to follow up, that precludes the observation of the primary endpoint will also be handled with the hypothetical strategy.
- The **summary measure** is the difference in absolute change from baseline between each dose level and placebo

MDS-UPDRS

The MDS-UPDRS is a multimodal scale consisting of four subscales (Parts I-IV).

- Part I assesses non-motor experiences of daily living and is comprised of two components:
    - Part IA contains 6 questions focusing on complex behaviors (cognitive impairment, hallucinations and psychosis, depressed mood, anxious

mood, apathy, features of dopamine dysregulation syndrome) and it is assessed by the rater.

- Part IB contains 7 questions on non-motor experiences of daily living (sleep problems, daytime sleepiness, pain and other sensations, urinary problems, constipation problems, light headedness on standing, fatigue) that are part of the Patient Questionnaire completed by the participant.

- Part II assesses motor experiences of daily living. There are 13 questions (speech, saliva and drooling, chewing and swallowing, eating tasks, dressing, hygiene, handwriting, doing hobbies and other activities, turning in bed, tremor, getting out of bed, a car or a deep chair, walking and balance, freezing) that are also part of the Patient Questionnaire completed by the participant.

- Part III assesses the motor signs of PD and is administered by the rater. Part III contains 33 scores based on 18 items (speech, facial expression, rigidity, finger tapping, hand movements, pronation-supination movements of hands, toe tapping, leg agility, arising from chair, gait, freezing of gait, postural stability, posture, global spontaneity of movement (body bradykinesia), postural tremor of the hands, kinetic tremor of the hands, rest tremor amplitude, constancy of rest tremor) several with right, left or other body distribution scores. The rater also marks the patient's clinical state using the following definitions:

  - ON is the typical functional state when patients are receiving approved dopa or dopamine agonist treatment and have good response.
  - OFF is the typical functional state when patients have a poor response in spite of taking approved dopa or dopamine agonist treatment.

  Part III subscores are defined as:
  - *Bradykinesia*: sum of items 3.4 finger tapping, Items 3.5 hand movements, items 3.6 pronation-supination movements of hands, items 3.7 toe tapping, items 3.8 leg agility, items 3.9 arising from chair, item 3.13 posture and item 3.14 body bradykinesia.
  - *Rigidity*: sum of items 3.3. (Neck, Upper Limbs and Lower Limbs).
  - *Resting tremors*: sum of Items 3.17 rest tremor amplitude (Lip/Jaw, Upper Limbs and Lower Limbs) and Item 3.18 constancy of tremor.
  - *Axial symptoms*: sum of Item 3.10 gait, Item 3.11 freezing of gait and Item 3.12 postural stability.

- In Part IV the rater uses historical and objective information to assess two motor complications, dyskinesias (time spent with dyskinesias, functional impact on dyskinesias) and motor fluctuations (time spent in the OFF state, functional impact of fluctuations, complexity of motor fluctuations, painful OFF-state

dystonia). The Investigator will complete this assessment once a participant has started symptomatic PD treatment.

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

4.7.2.1. Missing Item Values

The number of missing values permissible to render valid scores for each MDS-UPDRS part is defined in accordance with (Goetz et al. 2015), see the table below.

Table 6. Maximal number of allowable missing items for MDS-UPDRS

MDS-UPDRS	Allowable Missing Items
Part I*, IA, or IB	1
Part II	1
Part III	3
Part IV	0

In the case that item 1.6 in Part I is missing, then it will not be considered as missing item towards the total of missing items for Part I. Missing items will not be allowed in Part IA or IB when they are being analysed individually.

Because the MDS-UPDRS has a consistent metric of 0 to 4 ratings across all items, the prorated method is proposed in (Goetz et al. 2015) to calculate a surrogate score for each Part if the number of missing items is below or equal to the maximum threshold defined in Table 6.

If the number of missing items is below or equal to the maximum threshold defined in Table 6, then a prorated score will be calculated as a surrogate score for Part *X* according to the following formula:

$$\frac{(\sum available\ scores)x\ (No.\ total\ items\ in\ the\ complete\ part\ of\ the\ MDS\ UPDRS\ Part\ X)}{No.\ of\ items\ with\ actual\ scores}$$

If the number of missing items for a given Part is above the maximum threshold defined in Table 6 then the value for that MDS-UPDRS Part will be set to missing.

If any of the MDS-UPDRS parts is missing, then the MDS-UPDRS Total will be considered missing.

4.7.2.2. Primary Analysis

The primary efficacy endpoint will be analyzed using a Mixed Model for Repeated Measures (MMRM) using the covariates described in Section 4.7.1 as fixed effects. The

model will also include week of treatment (as a categorical factor) and a treatment-by-visit interaction term, an interaction term between baseline MDS-UPDRS by visit will also be included. Within each participant, the model will incorporate an unstructured variance-covariance matrix for the random error terms. If the unstructured covariance matrix is non-estimable other covariance structures like heterogeneous autoregressive or compound symmetry would be used. Parameters will be estimated with the use of restricted maximum likelihood, and the Kenward-Roger method will be used for calculating the denominator degrees of freedom. Observations from different participants are considered independent. This model will be used to test the null hypothesis of no treatment difference at a two-sided α-level of 20% for the following comparisons:

- High dose vs placebo,
- Low dose vs placebo.

All the assessments that started after the "first symptomatic PD treatment date" (as defined in Section 4.3.1) will not be included in the analysis.

Missing scores (due to the assessments performed after the starting of symptomatic PD treatment or any other reason) for each of the individual parts of the MDS-UPDRS will not be imputed; they will be handled via the MMRM model. The MMRM assumes that missing data are missing at random (MAR). That is, MMRM assumes that given the statistical model and given the observed values of the endpoint, missing data are independent of the unobserved values (O'Kelly and Ratitch 2014). Correlation between successive observations on a subject allows data from subjects who dropped out to make a contribution to estimation of the effects at the final time point. The primary endpoint will also be summarized using descriptive statistics.

A cumulative distribution plot will be presented to show the proportion of responders when each possible cutoff point of the MDS-UPDRS total score (sum of Parts I, II, and III) is used as the definition of response. The proportion of patients in each treatment group with each unit of improvement or worsening will be presented in a cumulative plot. At a particular change from baseline MDS-UPDRS score x, the proportion of patients with a change of baseline value ≥ x will be presented in the cumulative plot. All the assessments flagged on and after the "first symptomatic PD treatment date" (as defined in Section 4.3.1) will not be included in the analysis.

4.7.3. Secondary Efficacy Endpoints

All secondary endpoints will also be summarized using descriptive statistics. For the endpoints of MDS-UPDRS Part IA, Part IB, Part I total, Part II total, Part III total, and Part III subscores, CGI-I, and PGI-C the information collected after symptomatic PD treatment will be handled as in the primary analysis. The analysis of all other endpoints will include all the information available regardless of start of symptomatic PD treatment.

Change from baseline in MDS-UPDRS sub-scores: Part IA, Part IB, Part I total, Part II total, Part III total, and Part III subscores.

Results from the MDS-UPDRS sub-scores Parts IA, Part IB, Part I total, Part II total, and Part III total will be analyzed using the same approach as for the primary endpoint (Section 4.7.2). Cumulative distribution plots will also be presented.

For participants that started symptomatic PD treatment (as described in Section 4.3) the analysis of Part III total will be performed in both the “On” and the practically defined “Off” state (as described in Section 4.3.5).

Change from baseline in DaT-SPECT in ipsilateral (to the clinically dominant side) putamen binding ratio values

DaT-SPECT is a dopamine transporter SPECT imaging that uses a radioactive agent called ^{123}I-ioflupane to show the distribution of the dopamine transporters in the striatum. Among other indications, ^{123}I-ioflupane imaging is used for assessment of disease severity and progression. The change (between baseline and Week 52) in DaT-SPECT uptake values in the ipsilateral putamen to the most clinical affected side, will be analyzed via an analysis of covariance (ANCOVA), regardless of intake of symptomatic PD therapy during the first 52 weeks. The model will include the baseline value of the respective DaT binding ratio as a covariate and the covariates described in Section 4.7.1 as main effects. All data, regardless of whether the participant has started symptomatic PD therapy will be included. There will be no imputation for missing values.

Change from baseline in Montreal Cognitive Assessment (MoCA) total score from baseline at week 24 and week 52.

The Montreal Cognitive Assessment (MoCA) was developed as a tool to screen patients who present with mild cognitive complaints and usually perform in the normal range on the MMSE. The change (between baseline and Week 52) in MoCA total score will be analyzed via an analysis of covariance (ANCOVA). The model will include the covariates described in Section 4.7.1 as main effects. All data, regardless of whether the participant has started PD symptomatic therapy will be included. The same model will be applied to the change from baseline at week 24.

Change from baseline Clinical Global Impression of Improvement Scales

The CGI-S is a measure of disease severity at baseline and is rated on a 7-point scale, with the severity (CGI-S) of illness scale using a range of responses from 1 (normal, not at all ill) through to 7 (amongst the most extremely ill patients). The CGI-S is only measured at baseline and will be described descriptively.

The CGI-I is intended as a measure of change in health status. CGI-I scores range from 1 (very much improved) through to 7 (very much worse).

For the CGI-I, patients will be divided into one of two groups:

- ‘Responders’: Score of 1-4 (i.e., rated as “no change”, “minimally improved”, “much improved” or “very much improved”).

- ‘Progressors’: Score of 5-7 (i.e., rated as “minimally worse”, “much worse” or “very much worse”).

The proportion of patients rated by CGI-I Scale grouping at week 24 and week 52 will be analyzed using a logistic regression model, including all appropriate covariates described in Section 4.7.1. The estimated odds ratio for ’responders’ and ‘progressors’ at week 24 and week 52 for treated patients compared to placebo will be presented with 80% CI.

Change from baseline in Patient Global Impression of Change (PGIC)

The Patient Global Impression of Change (PGIC) is intended as a measure of change in health state from the patient’s perspective. PGIC scores range from 1 (very much improved) through to 7 (very much worse). Analysis of the PGI-C will be follow the same methodology outlined for the CGI-I, above.

Change from baseline in Schwab and England Activities of Daily Living (SE-ADL) from baseline at week 52

The SE-ADL is a score when the participant selects the rating that most accurately describes their level of functional independence. The change (between baseline and Week 52) in SE-ADL score will be analyzed via an analysis of covariance (ANCOVA). The model will include the covariates described in Section 4.7.1 as main effects. All data, regardless of whether the patient has started PD symptomatic therapy will be included. The same model will be applied to the change from baseline at week 24.

Time to worsening of motor or non-motor symptoms as measured by MDS-UPDRS .

This endpoint is defined as the time to between first dose of study medication and the date when the patient increase in MDS-UPDRS Part I of 3 or more points, or in MDS-UPDRS Part II of 3 or more points, whatever come first.

The time to the composite event will be plotted using a Kaplan-Meier survival plot, and it will be analyzed via a Cox proportional hazards model to obtain a treatment difference between each of the prasinezumab dose levels against placebo; the covariates described in Section 4.7.1 will be included in the model. The time to the individual component of the composite event will be analyzed as indicated above by the composite event. If the assumption of proportional hazards is violated then a generalized Wilcoxon test will be undertaken to compare the survival curves. All data regardless of symptomatic PD treatment will be taken into consideration.

Time to start of dopaminergic (levodopa or dopamine agonist) treatment.

This endpoint is defined as the time to between first dose of study medication and the date when the patient starts dopaminergic treatment (as defined in Section 4.3.2). It will be plotted using a Kaplan-Meier survival plot, and will be analyzed via a Cox proportional

hazards. If the assumption of proportional hazards is violated then a generalized Wilcoxon test will be undertaken to compare the survival curves.

4.7.4. Sensitivity Analyses

The analysis for the primary efficacy endpoint will be repeated to also include data from assessments performed while on any symptomatic PD treatment started after randomization. These assessments will only be included in the analysis if performed in a practically defined OFF state, see section 4.3.5. A descriptive analysis of the OFF state data will also be reported using descriptive statistics.

The primary endpoint will be re-analysed by only including patients who completed Part 1 without starting symptomatic PD treatment.

The MoCA score will be analysed considering patients without symptomatic PD treatment.

The primary endpoint of MDS-UPDRS total score (sum of Parts I, II, and III) will be analysed by calculating for each patient the baseline value as the average of pre-treatment values of the MDS-UPDRS total score (sum of Parts I, II, and III), i.e. the average of screening and Day 1. The same MMRM model described in Section 4.7.2 will be used.

For the CGI-I and PGIC scores the analysis censors patients with symptomatic PD treatment prior to week 52. To enable use of all available data, two sensitivity analyses will be performed for each score:

- Patients who initiate symptomatic PD treatment prior to the analysis time point will be considered to be ‘progressors’ regardless of their CGI-I or PGIC score.

- Patients’ CGI-I or PGIC scores will be used to classify patients regardless of whether or not they initiated symptomatic PD treatment.

4.7.5. Subgroup Analyses

A subgroup analysis will be performed if there are at least 20% of patients from the mITT population in the subgroup at baseline. The model used for the main analysis of the endpoint will be run in each subgroup; the model will exclude the subgroup being analyzed if that was a covariate (e.g. MAO-B Inhibitors at baseline (yes vs. no)). The estimated treatment effects (prasinezumab vs. placebo) and corresponding 80% CIs from the models will be displayed graphically in a forest plot for each prasinezumab dose level and each level of the subgroups specified.

The following subgroup analyses will be undertaken for the primary endpoint, change from baseline in total MDS-UPDRS (sum of Parts I, II and III) at Week 52. The subgroup analyses will also be undertaken in the following endpoints: MDS-UPDRS Part II, MDS-

UPDRS Part III, Part III subscores, and MDS-UPDRS sums of Part II and III, DaT-SPECT, digital PASADENA motor score, MoCA score and the composite time to event:

- MAO-B Inhibitors at baseline (yes *vs.* no)
- Hoehn & Yahr stage at baseline (1 *vs.* 2)
- REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) at baseline (RBDSQ ≥5 *vs.* <5)
- Data-Driven sub-phenotypes (Diffuse malignant *vs.* mild motor-predominant *vs.* intermediate) at baseline
- Alpha-Synuclein Skin (positive *vs.* negative) (staining by immunohistochemistry on skin biopsy sections at baseline)
- DaT-SPECT ipsilateral putamen very abnormal vs. abnormal (defined on the baseline data with a validated cutoff of 0.6)

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

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

4.8. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Non-linear mixed effects modelling will be used to analyze the sparse sampling dose-concentration-time data of prasinezumab including investigation of the influence of potential covariates on pharmacokinetic parameters.

Graphical exploration of the relationship between prasinezumab concentrations and MDS-UPDRS Total Score (sum of Parts I, II and III), other selected clinical endpoints, biomarkers and safety endpoints will be performed. If indicated by such exploration, more formal analyses of the PK/PD relationship using non-linear mixed effects modelling method will be undertaken. A previously developed disease model of the PPMI MDS-UPDRS total Score (sum of Parts I, II, and III) may be used to explore potential disease-modifying effect of prasinezumab and investigate potential covariates.

For the investigation of the drug effect, classical hierarchical PK/PD models will be tested. The possibility of a delay between the time-course of exposure and effects will be investigated using indirect pharmacodynamic models or using an effect compartment.

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

4.9. SAFETY ANALYSES

All safety analyses will be based on the safety analysis population, defined in Section 4.1.4. Safety will be assessed through the summary of adverse events, laboratory test results (hematology and serum chemistry), ECG findings, and vital signs. Safety summaries for the 52-week period in Part 1 will include outcomes as described in Section 2.6.

The incidence of antibodies against prasinezumab (ADAs) will be summarized using the immunogenicity population (Section 4.1.5).

4.9.1. Exposure of Study Medication

The study drug product was provided in vials (500 mg/10 mL) and administered IV after dilution in 250 mL 0.9% NaCl bags. The qualified individual (unblinded study pharmacist) responsible for dispensing the study drug at the site prepared the correct dose according to the randomization schedule provided by IxRS. The actual number of vials used to prepare each infusion was entered in IxRS. For each infusion the following are defined:

- The actual prepared dose is equal to the actual number of vials times 500mg.
- The actual received dose is equal to:
    - The actual prepared dose, if the infusion was not modified (infusion modified is equal to “No”)
    - The actual prepared dose × min (sum of volume administered at the same visit (from eCRF), 250)/ 250, if the infusion has been modified (infusion modified is equal to “Yes”)

4.9.2. Adverse Events

Verbatim descriptions of treatment-emergent adverse events will be coded using the latest version of MedDRA in effect at the time of database freeze. A treatment-emergent adverse event is defined as any new adverse event or any worsening of an existing condition with an onset date on or after the first study drug administration date. Summaries of treatment-emergent events will be provided for each of the following categories:

- Incidence of adverse events
- Incidence of adverse events by intensity
- Incidence of adverse events by relationship to study medication
- Incidence of serious adverse events
- Incidence of adverse events leading to discontinuation of study treatment
- Incidence of adverse events of special interest
- Incidence of infusion related reactions

- C-SSR will be reported by visit

4.9.3. Laboratory Data

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

Descriptive summaries of laboratory test values will be presented by individual listings with flagging of values outside the normal ranges. Incidence of laboratory abnormalities (including hematology, clinical chemistry, coagulation, and urinalysis parameters) and incidence of BP abnormalities will be presented in summary tables by treatment arms.

Samples collected during Grade 3 and more severe IRRs will be analysed for tryptase, cytokine panel, C3a, C5a and their values will be presented by individual listings with flagging of values outside the normal ranges.

Standard Reference Ranges and Transformation of Data

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

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

Definition of Laboratory Abnormalities

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

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

4.9.4. Vital Signs

Vital signs data will be presented by individual listings with flagging of values outside the normal ranges (Table 7) and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate.

Orthostatic blood pressure and heart rate, together with its incidence of abnormal values will also be reported. Orthostatic hypotension is defined as a sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 min of standing (Freeman et al. 2011).

Postural orthostatic tachycardia is defined as a heart rate >120 beats/min (bpm) on standing or an increase in heart rate by > 30 bpm from a resting heart rate without clinically significant orthostatic hypotension (Argawal et al., 2007; Freeman et al., 2011).

Table 7. Vital sign normal ranges.

Parameters	Position	Low	High
Pulse Rate (bpm)	If supine is not available use semi-supine	50	99
SBP (mmHg)	If supine is not available use semi-supine	90	140
DBP (mmHg)	If supine is not available use semi-supine	60	90
Temperature (°C)		36.5	37.3
Respiration Rate (breaths per minute)	If supine is not available use semi-supine	12	25

Sitting values will be ignored.

4.9.5. ECG Data Analysis

ECG data will be presented by individual listings (each individual triplicate result will be listed) with flagging of values outside the normal ranges (Table 8) and flagging of marked abnormalities. If the overall interpretation for an ECG is normal, specific flagged abnormalities will not be listed. ECG results with a technical quality abnormal finding will be listed.

In addition, tabular summaries will be used, as appropriate. Incidence of ECG abnormalities (including changes from baseline) will be reported. The relationship between QTcF prolongation and the serum concentration of prasinezumab may be investigated in an exploratory manner. If positive dose-response trends are observed with prasinezumab in these analyses, concentration-QT modeling may be conducted with data pooled across studies PRX002-CL002 and BP39529.

The number and percentage of subjects falling into the clinical signal categories for QT/QTc ($\leqslant$ 450, 450 < and $\leqslant$ 480, 480 < and $\leqslant$ 500, 500 <) will be provided by treatment and time-point. Sex or age specific drug effects on QT are possible and will be investigated.

RR measurements on selected safety ECGs (i.e. Baseline/Day 1 (pre-dose), Week 52 and Week 104, or early termination), will be provided by Biotelemetry for an exploratory Heart Rate variability analysis. The standard deviation of the RR interval for the individual participant may be assessed as an exploratory endpoint.

Table 8. ECG normal ranges

Parameters	Method	Low	High
Heart Rate ECG (bpm)	12 LEAD TRIPLICATE	50	99
PQ(PR) (msec)	12 LEAD TRIPLICATE	110	200
QRS (msec)	12 LEAD TRIPLICATE	80	100
Mean RR interval (msec)	12 LEAD TRIPLICATE	926 (range 785-1160)	
SDNN (standard deviation of normal-to-normal intervals) (msec)	12 LEAD TRIPLICATE	50 (range 32-93)	

RR will be used for exploratory HR variability analysis

4.9.6. Immunogenicity Data Analysis

For the analysis, the following definitions based on Shankar et al. 2014 as well as a Sponsor's definition for ADA with neutralizing potential, will be used to describe prasinezumab patients' immunogenicity as follows:

ADA Negative Participants are defined as:

- Patients with ADA negative or missing data at baseline and all post-baseline samples are negative, OR

- Patients with ADA positive at baseline and no post baseline sample with a titre that it is at least ≥4 fold greater than the titre of the baseline sample (treatment unaffected).

ADA Positive Participants will be classified as:

- *Treatment induced*: patients with ADA negative or missing data at baseline, but develop an ADA response following study drug exposure. These patients will also be classified into:

    - *Persistent*: patients who have post-treatment ADA positive samples over 16 weeks or more or the last ADA timepoint is positive.

    - *Transient:* at least one post-treatment ADA positive sample AND has only one ADA positive sample or the time between the first and last ADA positive sample is less than 16 weeks AND the last ADA sample is negative

– *Treatment enhanced*: Patients with ADA positive at baseline and the titre of one or more post-baseline samples is at least ≥4 fold increase greater than the titre of the baseline sample.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) will be summarized by treatment group. For those who are ADA-positive, titers will be estimated as well as antibody subtype. In addition, the numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized for patients on active treatment only.

4.9.7. Concomitant Medications

The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor using the WHODrug dictionary.

Concomitant medications will be presented in summary tables and listings.

4.9.8. Other analyses

Incidence of MRI abnormalities (changes from baseline only) will be reported by visit. C-SSRS data will be reported in a shift analysis.

4.10. MISSING DATA

For the primary endpoint, the secondary endpoints of MDS-UPDRS Part III , CGI-I, and PGI-C, and all the exploratory PRO endpoints, assessments performed while on any symptomatic PD treatment started after randomization or after an increase in symptomatic PD treatment will not be included in the analysis. For the MDS-UPDRS missing values will be handled via the MMRM methodology. Missing items values for MDS-UPDRS are dealt with as described in section 4.7.2.1.

Data with missing visit and/or scheduled timepoint information (if relevant) will not be included in summary tables summarized by visit (and scheduled timepoint if relevant).

Missing data for PROs will be treated in line with license holder manuals

5. REFERENCES

Agarwal AK, Garg R, Ritch A, Sarkar P. Postural orthostatic tachycardia syndrome: Postgrad Med J. 2007;83:478–480.

Freeman R, Wieling W, Axelrod FB et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21(2):69-72.

Goetz CG, Luo S, Wang L, et al. Handling missing values in the MDS-UPDRS. Mov Disord. 2015 Oct; 30(12): 1632–1638.

Gottipati, G., Berges, A.C., Yang, S. et al. Pharm Res (2019) 36: 135. https://doi.org/10.1007/s11095-019-2668-6

O'Kelly M, Ratitch B. Clinical trials with missing data: a guide for practitioners. Chichester, UK: John Wiley & Sons: 2014.

Permutt T, Li F. Trimmed means for symptom trials with dropouts. Pharmaceutical Statistics (2017). 16 20-28.

Shankar G, Arkin S, Cocea L, Devanarayan V, Kirshner S, Kromminga A, Quarmby V, Richards S, Schneider CK, Subramanyam M, Swanson S, Verthelyi D, Yim S. Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations. The AAPS Journal, Vol. 16, No. 4, July 2014.

APPENDIX 1

The Appendix lists all the exploratory analyses that might not be included in the CSR.

Exploratory Efficacy Outcome Measures

Unless otherwise stated, the exploratory outcome measures for this study are absolute change from baseline at 52 weeks in:

- MDS-UPDRS Part III total and Part III subscores (bradykinesia, resting tremor and axial symptoms) central vs local ratings for consistency and accuracy
- Time to worsening of motor or non-motor symptoms as measured by MDS-UPDRS or starting dopaminergic treatment (levodopa or dopamine agonist) and defined as the first occurrence of either of the following:
    - $\geqslant$ 3 points from MDS-UPDRS (Part I), or
    - $\geqslant$ 3 points from MDS-UPDRS (Part II), or
    - Starting dopaminergic PD treatment (levodopa or dopamine agonist)
- Absolute change in digital PASADENA motor score - Remote Monitoring
- Percent change in digital PASADENA motor score - Remote Monitoring
- Modified Hoehn & Yahr (mH&Y).
- Parkinson's Disease Sleep Scale 2 (PDSS-2) total score and sub-scales evaluated at week 48.
- Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-AUT) total score and subdomain scores.
- Parkinson's Disease Questionnaire-39 (PDQ-39) total score and sub-scales evaluated at week 48.
- Digital Biomarkers and patient-reported outcomes (Smartphone and wrist-worn wearable assessments):
    - Diary questions (patient reported outcome [PRO]).
    - Patient Assessment of Constipation symptoms (PAC-SYM) questionnaire (PRO).
    - Hospital Anxiety and Depression Scale (HADS) total score and sub-scales: anxiety (HADS-A), and depression (HADS-D) (PRO).
    - EQ-5D-5L questionnaire (PRO).
    - Sensor data collected during "Active Tests", assessing motor symptoms (upper and lower body movement, upper limb dexterity, voice/speech) and non-motor symptoms - including an electronic Symbol Digital Modalities Test (eSDMT) to measure attention and executive function.
    - Sensor data collected during "Passive Monitoring" assessing activity, movement and motor symptoms associated with routine daily living.
    - Sensor data collected during "In-Clinic Assessments", including the Timed Up and Go Test and selected items from the Berg Balance Scale.

- Serum and CSF biomarkers related to Parkinson's disease (CSF in consented patients only) including (but not limited to) plasma levels of NFL and CSF levels of total alpha-synuclein, $ABeta_{1-40}$, $ABeta_{1-42}$, p-tau and total tau, soluble TREM2, YKL40, and IL-6..

- Change from baseline in α-synuclein pathology in peripheral nerves.
- Change from baseline in DaT-SPECT in binding ratio values for: striatum, caudate and putamen (average, ipsilateral and contralateral), except for ipsilateral putamen which is a secondary endpoint.
- DTI MRI for mean diffusivity and fractional anisotropy in striatum, caudate and putamen (ipsilateral, contralateral and average).
- ASL MRI for cerebral blood flow in striatum, caudate and putamen (ipsilateral, contralateral and average).
- Time to start or change of co-medication for non-motor symptoms that may be related to PD (cognition, constipation, depression, anxiety, excessive day time sleep, nocturnal sleep, urogenital symptoms/sexual dysfunction).
- Start or change of co-medication for non-motor symptoms that may be related to imaging biomarkers (DAT Scan and ASL).
- Parkinson-related effects on the loss of autonomic tone as measured by heart rate variability.
- Time to increase in symptomatic PD treatment dose.
- Time to decrease in symptomatic PD treatment dose.
- Composite of Part 2 and Part 3 sub-items (PCOR motor score) including all of MDS-UPDRS Part II items and the following four items from Part III: item 1: speech, item 9: arising from chair, item 10: gait, Item 11: freezing of gait.
- Composite of Part 2 and Part 3 sub-items (pREDi motor score) including the following MDS-UPDRS items: arising from chair, body bradykinesia, dressing, eating tasks, finger tapping dominant side, gait (Part 3), hand movements dominant side, hand movements non-dominant side, leg agility dominant side, leg agility non-dominant side, postural tremor dominant side, pronation supination movement of hand dominant side, pronation supination movement of hand non-dominant side, rest tremor amplitude upper extremity dominant side, rigidity upper extremity dominant side, speech (Part 2), speech problems (Part 3), toe tapping dominant side, turning in bed, walking and balance (Part 2); where dominant is the most affected side and non-dominant is the least affected side.
- MDS-UPDRS Part IV at week 52 only in participants who started dopaminergic treatment (levodopa or dopamine agonist).
- Time to the first occurrence of either of the following:
    - ≥ 2 points from MDS-UPDRS (Part I), or
    - ≥ 2 point from MDS-UPDRS (Part II), or

    - Start of dopaminergic PD treatment (levodopa or dopamine agonist)
- Time to the start symptomatic PD treatment
- Rank ANCOVA analysis for the absolute change from baseline in the following MDS-UPDRS endpoints: total score (sum of Parts I, II and III), Parts IA, Part IB, Part I total, Part II total, Part III total, and Part III subscores (rigidity, bradykinesia, resting tremor and axial symptoms).

Analysis of Exploratory Efficacy Endpoints

All exploratory endpoints described in Section 2.3.3 will be summarized using descriptive statistics. For PRO endpoints, assessment taken after the start of symptomatic PD treatment (as described in Section 4.3.1) will not be included in the analysis. If applicable, exploratory endpoints may be analyzed with the methods below and will include the covariates described in Section 4.7.1:

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

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

A baseline IRT model was built to analyze the baseline data in *de novo* patients from the PPMI database (Buatois et al 2015, Buatois et al 2016, Gottipatti 2019). It will be updated by including the Phase 2 data and extended to a longitudinal model that describes the time courses of the motor, non-motor and tremor disability in patient treated with placebo or with prasinezumab using non-linear mixed effects modelling (i.e. NONMEM). The results of the IRT analysis will be reported in a document separate from the clinical study report.

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

The analysis of the endpoints of time to increase or decrease in symptomatic PD treatment dose will only be undertaken if there are at least 20% of patients who had an increase or decrease in symptomatic PD treatment dose.

The primary endpoint of total MDS-UPDRS (sum of Parts I, II, and III) will be reanalysed by pooling the data from the two treatment arms and compare it to placebo.

Analysis of Endpoints from the Digital Biomarker Assessments (Smartphone & Wrist-Worn Wearable)

Each participant received a preconfigured smartphone and wrist-worn wearable with installed software for the digital biomarker assessments. The endpoints described in this section are derived from the results of the smartphone & wrist-worn wearable.

A separate document will describe how the model for the digital PASADENA motor score is being constructed.

Digital Biomarker (dBM) Single Features – Remote Monitoring

The following selected features from the digital biomarker remote monitoring will be analysed in the way described below:

Test Name	Feature Name
Draw a Shape	Trace Celerity for Spiral
Speeded Tapping Test 1F-2B	Uptime standard deviation
Hand Turning Test	Maximum Hand Turn Speed
Free Speech Test	Average difference of MFCC2 between voice segments
Sustained Phonation Test	Voice Jitter
Postural Tremor Test	Mean Squared Energy
Rest Tremor Test	Mean Squared Energy
Static Balance Test	Sway
Five U-turn Test	Median Turn Speed
Symbol Digit Modalities Functional Test	Total Score
Passive Monitoring – Turning	Median Turn Speed
Passive Monitoring – Gestures	Median Turn Speed

Each feature will be first normalised. Feature values will be aggregated by average over reported window (Table 5). Feature values will be considered missing if less than 3 feature values exist in this interval. The same random coefficients model used for primary analysis will be used for analysis of the dBM features. Assessment taken after the start of symptomatic PD treatment (described in Section 4.3.1) will not be included in the analysis.

Absolute change in digital PASADENA motor score – Remote Monitoring

The digital PASADENA motor score will be mapped according to the time windows described in Table 5. An average of the dBM score will be calculated for each visit using all the scores that are mapped within a single reporting window. Assessment taken after the start of symptomatic PD treatment (as described in Sections 4.3.1) will not be included in the analysis. A random coefficients model will be used for the analysis of the

dBM. The model involves a random intercept and a slope for each subject. Within each participant, the model will incorporate an unstructured variance-covariance matrix for the random error terms. If the unstructured covariance matrix is non-estimable other covariance structures like heterogeneous compound symmetry would be used. Parameters will be estimated with the use of restricted maximum likelihood, and the Kenward-Roger method will be used for calculating the denominator degrees of freedom.

Percent change in digital PASADENA motor score - Remote Monitoring

Percent change in digital PASADENA motor score will be analyzed in the same way as the absolute change in digital PASADENA motor as described above

Digital PASADENA motor Score – In Clinic Assessments

The digital PASADENA motor score derived from in clinic assessments will be analysed as the one obtained from remote monitoring, the only difference will be that the average of the dBM score will be over the time windows described in Table 4

Digital Biomarker Single Features – In Clinic Assessments

Selected features from the digital biomarker in clinic assessments will be analysed in the same way as the features from the remote monitoring.

dBM ePROs: PAC-SYM, Hospital Anxiety and Depression Scale (HADS), EQ-5D-5L will be analysed via ANCOVA and/or random coefficients model.

Diary Questions

The diary contained four questions related to symptoms with categorical responses ranging from 1 (no symptoms) to 6 (severe symptoms), three questions related to difficulty with sleeping with four categorical responses 1 (not at all) to 4 (a lot), two questions related to bowel movement with binary responses (Yes or No), and one question related to the number of nights with problems with sleep with categorical responses (Never, 1 night, 2-3 nights, 4-5 nights, 6-7 nights). The diary also contained a Health Survey with 5 questions capturing the number of days the patient had health related problems.

Each one of the responses from the diary questions will be mapped according to the windows described in Table 5. For questions with more than two categories, categorical responses will be treated as continuous and an average during the reporting window will be used for analysis; a random intercept model will be used for the analysis. For the questions with binary responses a logistic regression will be applied. Responses from the Health Survey will be analysed with a random coefficients model.

Exploratory subgroup analyses

The following subgroup analyses are exploratory and might not be reported in the clinical study report.

The following subgroup analyses will be undertaken for the primary endpoint, change from baseline in total MDS-UPDRS (sum of Parts I, II and III) at Week 52. The subgroup analyses will also be undertaken in the following endpoints: MDS-UPDRS Part II, MDS-UPDRS Part III, and MDS-UPDRS sums of Part II and III, DaT-SPECT, dBM score, MoCA score and the composite time to event. The subgroup analyses will be undertaken in the same way described for the subgroups analyses in Section 4.7.5:

- Age at baseline (< 60 years *vs.* >= 60)
- Gender (male *vs.* female)
- Disease duration (<12 months *vs.* >12 months)
- Age at diagnosis of Parkinson's disease (< 60 years *vs.* >= 60)
- Nucleus basalis of Meynert at baseline (atrophy *vs.* no atrophy)
- MoCA total score: lower (<22) *vs.* higher (>22)
- GBA Mutation (positive vs negative). This subgroup analysis will only be done if there are 15% of patients from the overall population.
- Motor sub-phenotypes:
    - tremor *vs.* akinetic-rigid *vs.* intermediate
    - tremor *vs.* postural instability gait dysfunction *vs.* indeterminate