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: Statistical Analysis Plan Version 2: 05-Aug-2024

STATISTICAL ANALYSIS PLAN

STUDY 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**
STUDY NUMBER:	BN42358
STUDY NAME:	PADOVA
VERSION NUMBER:	2
ROCHE COMPOUND:	Prasinezumab (RO7046015)
EUDRACT NUMBER:	2020-004997-23
IND NUMBER:	119602
NCT NUMBER:	NCT04777331
PLAN PREPARED BY:	[redacted], PhD

STATISTICAL ANALYSIS PLAN APPROVAL

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DATE FINAL:	See electronic date stamp on the last page of this document

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This statistical analysis plan (SAP) was developed based on Roche SAP model document Version (v)2.0.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	12th April 2024	v4.0, 30 October 2023
2	see electronic date stamp on the last page of this document	v4.0, 30 October 2023

STATISTICAL ANALYSIS PLAN AMENDMENT, VERSION 2: RATIONALE

The SAP of BN42358 has been amended to incorporate the FDA comments received in June 2024 on the SAP v1 submitted on the 19th of April 2024.

- Changes to the SAP, along with a rationale for each change, are summarized below: Section 4.6.4 from SAP version 1 was merged with Section 4.2.2. The new section has been renamed to change in symptomatic PD treatment.
- [redacted]
- [redacted]
- [redacted]

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

A2R	adenosine receptor subtype 2
ADA	anti-drug antibody
ADBL	analysis database lock
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
[redacted]	
ATC	anatomical therapeutic chemical
ATT	Average Treatment Effect in the Treated
AUC	area under curve
C-SSRS	Columbia-Suicide Severity Rating Scale
CCOD	clinical cutoff date
CGI-C	Clinician Global Impression of Change
CGI-S	Clinician Global Impression of Severity
CI	confidence interval
C_{max}	maximum concentration
C_{trough}	trough concentration
COMT	catechol-o-methyl-transferase
CSF	cerebrospinal fluid
CSR	Clinical Study Report
d-BAP	digital Biomarker Analysis Plan
DAP	Data Analysis Plan
DaT-SPECT	dopamine transporter with single photon emission computed tomography
[redacted]	
ECG	electrocardiogram
EQ-5D-5L	EuroQoL 5-Dimension 5-Level questionnaire
FAS	full analysis set
FDA	U.S. Food and Drug Administration
H&Y	Hoehn and Yahr
HR	hazard ratio
IAS	immunogenicity analysis set
[redacted]	
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IRR	infusion-related reaction

IV	intravenous
IxRs	interactive voice/web-based response system
L-Dopa	levodopa
LEDD	levodopa equivalent daily dose
LoPO	list of planned outputs
MAO-B	monoamine oxidase B
MAR	missing at random
MDD	minimum detectable difference
MDS-UPDRS	Movement Disorder Society - Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MIDD	Model Informed Drug Development
MMRM	mixed model for repeated measures
[redacted]	
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
[redacted]	
NONMEM	non-linear mixed effects modeling
OLE	open-label extension
PAS	pharmacokinetic analysis set
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
PS	propensity score
PSM	patient symptom measure
PT	preferred term
Q4W	every 4 weeks
REM	rapid eye movement
SAE	serious adverse events
SAP	Statistical Analysis Plan
SAS	safety analysis set
SMD	standardized mean differences
SOC	System Organ Class
SSS	simple sum score
SDTM	Study Data Tabulation Model
SDTMv	Study Data Tabulation Model view

TTE	time to event
V	version
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) covers the analyses planned for the randomized double-blind treatment period. Analyses will be listed directly in the corresponding list of planned outputs (LoPO). The description of layouts for the Clinical Study Report (CSR) outputs, the details about the underlying analysis datasets and programs, with the linking production outputs to sections in the CSR are not within the scope of this document and will be covered in separate documents, i.e., Data Analyses Plan (DAP) Modules 2 and 3. The analyses as part of the open-label extension (OLE) and the comparison of the OLE to an external comparator arm is also described in this updated version 2 of this SAP.

The analyses described in this SAP will further detail and supersede those specified in Protocol BN42358 (hereafter referred to as PADOVA) and will be reported in the primary CSR.

1.1 OBJECTIVES AND ENDPOINTS

Please see the study protocol (Section 2) for details on the study objectives and endpoints.

The Estimand definition for the primary objective is detailed in Table 1.

Table 1 Primary Objective and Estimand Definition

Primary Objective	Estimand Definition
To evaluate the efficacy of prasinezumab compared with placebo (in participants on stable symptomatic monotherapy with either MAO-B inhibitors or L-Dopa, irrespective of their increase in LEDD during the study, and study treatment discontinuation)	Population: Participants with early PD on stable symptomatic monotherapy with either MAO-B inhibitors or L-Dopa. Endpoint: Time to a confirmed motor progression event from the randomization date. Confirmed motor progression is defined as the first time point of a worsening event, 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 – LEDD increase (see Section 4.2.2), after the first occurrence of "a ≥ 5-points increase in MDS-UPDRS Part III score (assessed in "OFF" medication state) from baseline, and before any subsequent MDS-UPDRS Part III assessment. Treatment:

Primary Objective	Estimand Definition
	– Experimental arm: prasinezumab, administered as a 1500 mg IV infusion Q4W (in addition to the symptomatic monotherapy). – Control arm: placebo, administered as an IV infusion Q4W (in addition to the symptomatic monotherapy).
	[redacted]
	Population-level summary: hazard ratio of a confirmed motor progression event in MDS-UPDRS Part III score (“OFF” medication state) comparing the prasinezumab arm vs placebo.

IV = intravenous; L-Dopa = levodopa; LEDD = levodopa equivalent daily dose; MAO-B = monoamine oxidase B inhibitors; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PD = Parkinson’s disease; Q4W = every 4 weeks.

[redacted]

[redacted]

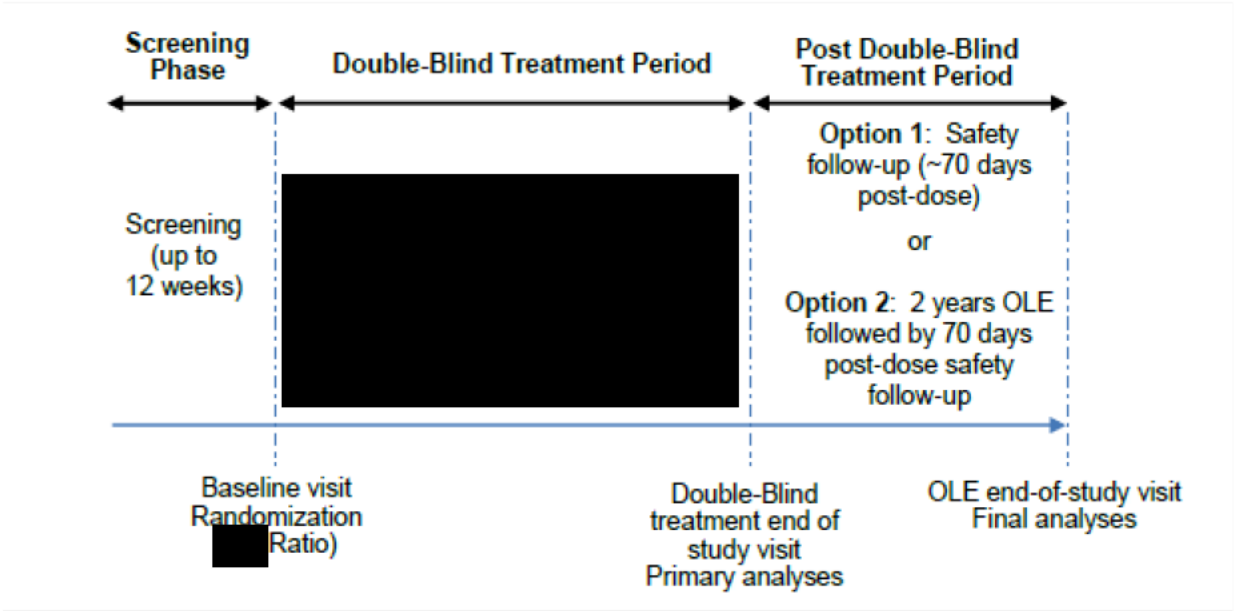
The secondary exploratory as well as pharmacokinetic (PK), immunogenicity, biomarker and safety objectives and endpoints are summarized in the study protocol. Their statistical analyses are further detailed in Section 4.3 , Section 4.4, Section 4.5 and Section 4.6.

1.2 STUDY DESIGN

PADOVA, is a randomized, double-blind, placebo-controlled, parallel group, multicenter study to evaluate efficacy and safety of prasinezumab, administered as 1500 mg intravenous (IV) infusion every 4 weeks (Q4W), to participants with early Parkinson's disease (PD) on stable symptomatic monotherapy (monoamine oxidase B [MAO-B] inhibitor or levodopa [L-Dopa]). See Figure 1 (study schema) for description of the study periods. [redacted] All study participants continue to receive double-blind study treatment until both of these conditions are fulfilled [redacted]
Please refer to Protocol Section 3 for further details regarding the study design.

Figure 1 presents an overview of the study design.

Figure 1 Study Schema



OLE = open-label extension.

1.2.1 Treatment Assignment

This is a randomized, double-blind study. After initial written informed consent was obtained, all screening procedures and assessments completed, and eligibility established (see Protocol Sections 4.1.1 and 4.1.2) for a participant, the study site received the participant's identification number and treatment assignment from an interactive voice/web-based response system (IxRS).

Participants were randomly assigned to one of two treatment arms: prasinezumab or placebo with study drug administered Q4W. Randomization occurs in a [redacted] ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization is stratified according to the following criterion: PD medication (MAO-B vs. L-Dopa).

1.2.2 Blinding

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.

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).

All participants 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, participants who prematurely discontinue from the study treatment 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. These participants will also be asked to participate in end-of-study and safety follow-up visits.

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

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

1.2.3 Data Monitoring

This study utilizes an independent Data Monitoring Committee (iDMC) to evaluate participant safety. Relevant efficacy data may be reviewed by the iDMC as part of risk/benefit assessments. More details on the role and process of the iDMC can be found in the iDMC charter.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

The hypotheses to be tested for the primary estimand are:

- [redacted].
- [redacted]

The null hypothesis will be tested at [redacted] (with the randomization stratification factor as defined in Section 4.2.5).

If the primary endpoint is met, the secondary endpoints will be tested confirmatory according to a [redacted] (see Section 4.3).

2.2 SAMPLE SIZE DETERMINATION

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 Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score (in “OFF” medication state for participants on L-Dopa background therapy).

[redacted]

A total of 575 participants were planned to be recruited into the study within 11 months and 586 participants were actually randomized in this study.

2.3 ANALYSIS TIMING

[redacted]

[redacted]

3. ANALYSIS SETS

The analysis population for the efficacy analyses is the full analysis set (FAS) consisting of all randomized participants, with participants grouped according to their randomized treatment.

The safety analysis set (SAS) consists of all randomized participants who received at least one dose of study drug, with participants grouped according to treatment received.

The analysis population for the pharmacokinetic analysis set (PAS) consists of all randomized participants exposed to study treatment with sufficient dosing information and at least one adequately documented and quantifiable prasinezumab concentration.

The immunogenicity analysis set (IAS) consists of all participants on active treatment with at least one anti-drug antibody (ADA) assessment.

The participant analysis sets are summarized in Table 3.

Table 3 Participant Analysis Sets

Participant Analysis Set	Description
FAS	All randomized participants according to the treatment they were randomized to.
SAS	All randomized participants exposed to study treatment according to the treatment received. Participants will be summarized in the active treatment arm if they received at least one dose of study drug.
PAS	All randomized participants exposed to study treatment with sufficient dosing information and at least one adequately documented and quantifiable prasinezumab concentration.
IAS	All participants on active treatment with at least one ADA assessment.

ADA = anti-drug antibody; FAS = full analysis set; IAS = immunogenicity analysis set; PAS = pharmacokinetic analysis set; SAS = safety analysis set.

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

All statistical tests will be conducted at a [redacted]

4.1.1 Definition of Baseline

For all efficacy analyses (including summaries of demographic characteristics as well as change from baseline), baseline will be defined as the assessment taken at the randomization date. [redacted]

For all safety analyses, the baseline will be defined as the last pre-dose assessment prior to the first drug intake. If this baseline assessment does not exist, an earlier assessment will be taken.

4.2 PRIMARY ANALYSIS

4.2.1 MDS-UPDRS Definition

The MDS-UPDRS is a multimodal scale consisting of four subscales (Parts I-IV), see Protocol Section 4.5.5.1.

4.2.2 Change in Symptomatic PD Treatment

It is expected that during the conduct of this trial, participants change their regimen of symptomatic PD treatment and it is considered as a concomitant event.

The dosage of all reported symptomatic PD treatments will be converted to a LEDD using the methods described in Tomlinson 2010 and Jost and Kaldenbach 2023.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

4.2.3 Primary Endpoint Analyses

The primary efficacy endpoint is time to a confirmed motor progression, defined as:

- A 5-points increase in MDS-UPDRS Part III score (assessed in "OFF" medication state) from baseline sustained over two consecutive assessments (regardless of the amount of time in between these two consecutive assessments),

OR

- LEDD increase (see Section 4.2.2), after the occurrence of a 5-points increase in MDS-UPDRS Part III score (assessed in "OFF" medication state) from baseline, and before any subsequent MDS-UPDRS Part III assessment (the first LEDD increase from the day of the occurrence of a 5-points progression and prior to the next assessment is considered to complete the event definition).

[redacted], see Section 4.2.6 for handling of the missing data.

Participants who had a confirmed motor progression event remain in the study and continue to receive double-blind study treatment without any changes in their schedule of assessments.

[redacted]

The population summary measure for the primary endpoint is the HR of a confirmed motor progression between prasinezumab and placebo as defined in Section 1.1 (see Table 1).

4.2.4 Main Analytical Approach for Primary Endpoint

[redacted]

Disease progression curves in each treatment arm will be estimated using Kaplan−Meier methodology. The treatment effect will be quantified via a HR, computed from a stratified Cox proportional-hazards regression model, including a 95% confidence interval (CI). [redacted]

A check of the proportional hazards assumption will be performed by plotting the log negative log of the estimated survivor function against log time.

Sensitivity analyses for the primary endpoint are described in Section 4.2.7.

4.2.5 Stratification and Covariates for Adjustment

For the primary analyses a stratified log-rank test and stratified Cox proportional hazards model will be conducted. [redacted]

[redacted]

In addition, the following covariates will be used in a supplementary analysis for the primary endpoint, as well as for secondary and exploratory endpoint analyses, further specified in Section 4.3 and Section 4.4:

1. [redacted]
2.
3.
4.
5.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.2.7 Sensitivity Analyses

The following sensitivity analysis will be performed in the FAS:

- The primary analysis will be repeated using an unstratified log-rank test.
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

4.3 STATISTICAL ANALYSES FOR SECONDARY ENDPOINTS

If the primary endpoint is met, secondary endpoints [redacted] If the statistical significance of the primary endpoint is not reached, p-values will be interpreted descriptively.

The secondary endpoints will be tested in the FAS in the following confirmatory order provided the null hypothesis of the primary endpoint is rejected:

1. Change in motor function from baseline to Week 76, as measured by the MDS-UPDRS Part III score (assessed in “OFF” medication state).
2. Change in bradykinesia and rigidity from baseline to Week 76, as measured by the MDS-UPDRS Part III bradykinesia and rigidity, sum of the two subscores (assessed in “OFF” medication state).
3. 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).
4. Time to onset ($\geq$ 1 point increase from baseline) of motor complications as assessed through MDS-UPDRS Part IV.

5. Time-to-worsening of participant's motor function as reported by the participant (≥ 3 points increase in MDS-UPDRS Part II score from baseline) in the presence of a confirmed motor progression event.
6. 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).

The change from baseline endpoints will be analyzed using a MMRM. [redacted]

Missing scores for the corresponding endpoint 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, the 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 the estimation of the effects at the final time point.

[redacted]

[redacted]

4.4 EXPLORATORY EFFICACY ANALYSES

The following TTE exploratory endpoints will be analyzed for the FAS using the same statistical methodology as defined for the primary endpoint (Section 4.2):

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

The following change from baseline exploratory endpoints will be analyzed in the FAS using the same statistical methodology as defined for the secondary endpoints using MMRM (see Section 4.3):

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

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

[redacted]

[redacted]

- [redacted]
- [redacted]

The following additional endpoints will be analyzed in the FAS using a MMRM with the model specifications as described in Section 4.3:

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

[redacted]

- [redacted]

4.4.1 Digital Biomarker Analysis Plan

The following exploratory endpoints will be analyzed:

- [redacted]
- [redacted]

A separate digital Biomarker Analysis Plan (d-BAP) will list and describe the motor and cognitive digital assessments performed using the Roche PD Mobile Application, v3.0, the single features to be extracted and analyzed, the patient-reported impression of motor symptom severity (smartphone PGI-S), along with the framework and methods used to build and analyze the simple sum score (SSS) and the patient symptom measure (PSM). The d-BAP will cover in detail the pre-processing steps that will be applied to digital sensor feature data, the analysis objectives, and the statistical methods used to analyze the single features, smartphone PGI-S and SSS.

The results from all the above-mentioned analyses will be reported separately and outside of the main study CSR.

4.4.2 EQ-5D-5L

The EuroQoL 5-Dimension 5-Level questionnaire (EQ-5D-5L) will be analyzed separately outside of SAP and will be reported outside of the CSR.

4.5 SAFETY ANALYSES

Descriptive statistics (including percentages and frequencies for categorical data, means and medians, standard deviations for continuous data) using the SAS will be used to analyze the safety data collected in the double-blind treatment period (Table 3).

The following safety and tolerability analyses will be conducted:

- Nature, incidence, seriousness and severity of AEs, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.
- Incidence of AEs of special interest.

- Incidence of treatment discontinuations due to AEs.
- 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 electrocardiogram (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).
- Shift tables of laboratory abnormalities (including hematology, clinical chemistry, coagulation, and urinalysis parameters).
- Change from baseline in suicidal ideation, as measured by Columbia-Suicide Severity Rating Scale (C-SSRS).

4.5.1 Extent of Exposure

Exposure to prasinezumab and placebo over the course of the study will be summarized using descriptive statistics for the safety population by treatment as follows:

- Treatment duration (weeks).
- Total number of administrations.
- Total cumulative dose (mg).
- Number of doses.
- Planned dose.
- Missed doses (by AE/other).

4.5.2 Adverse Events

Verbatim descriptions of treatment-emergent AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) in effect at the time of analysis database lock (ADBL). A treatment-emergent AE is defined as any new AE or any worsening of an existing condition with an onset date on or after the first study drug administration date.

Incidence in participant years and overview summaries of AEs, related AEs, serious adverse events (SAEs), AEs by greatest intensity/severity (NCI CTCAE) grade, AEs related to study drug, adverse event of special interest (AESI), ADA, risks and IRRs will be provided by System Organ Class (SOC) and preferred term (PT) where applicable.

[redacted]

4.5.4 Laboratory Data

Laboratory data will be summarized by treatment group for each assessment visit using descriptive statistics of absolute values, change from baseline values, and percentage change from baseline. In addition, incidence of laboratory abnormalities (including hematology, clinical chemistry, coagulation, and urinalysis parameters) will be summarized by treatment group, visit and baseline status. Shift tables for laboratory abnormalities will be provided.

4.5.5 Vital Signs and ECG

Absolute values and change from baseline values for vital signs and ECG will be summarized by descriptive statistics at each visit by treatment group. Incidence of abnormal vital signs and ECG measurements will be summarized descriptively by visit. Shift tables for vital signs and ECG will be provided too.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

The number of participants who enrolled, discontinued, or completed the study will be summarized by treatment arm. Reasons for premature study discontinuation will be listed and summarized. Enrollment, number of major protocol deviations (overall and by the standard four main categories: inclusion criteria, exclusion criteria, medication and procedural) and number of investigational medicinal product (IMP) administrations will be summarized by treatment arm. Participant disposition will be summarized by treatment arm and will include whether treatment was completed or discontinued early, and the reason for early treatment discontinuation.

4.6.2 Summaries of Treatment Group Comparability/Demographics and Baseline Characteristics

Demographic and baseline characteristics (including age, sex, symptomatic treatment, disease duration, number of years of education, race and/or ethnicity, and H&Y stage) will be summarized descriptively for the FAS (see Table 3).

Descriptive summaries of continuous data will present the means, standard deviations, medians, and minimum and maximum. Descriptive summaries of categorical data will include frequencies and percentages of participants.

4.6.3 Previous and Concomitant Medications

Previous medications recorded before screening until the start of treatment will be presented in summary tables as well as the concomitant medications.

The original terms recorded in the clinical database by the Investigator for concomitant medications will be standardized by the Sponsor using the WHO Drug dictionary.

4.6.4 Pharmacokinetic Analyses

Participants data (for the PAS, see Table 3) will be included in the PK analyses if there is sufficient dosing information and at least one adequately documented and quantifiable prasinezumab concentration per participant.

The population PK model (Report 1081130) initially developed with the Phase I data of prasinezumab and subsequently 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 different covariates [redacted] will be investigated. Secondary PK parameters such as area under 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 by a confirmed motor progression) will be performed. If indicated by such exploration, more formal analyses of the PK/pharmacodynamic relationship using non-linear mixed effects modeling methods will be conducted.

Exploratory analyses will also be performed in order to explore:

- The relationship between serum concentration or secondary PK parameters of prasinezumab and other efficacy endpoints.
- 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.

[redacted]

4.6.5 Immunogenicity Analyses

As ADA samples from participants 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 be conducted on IAS (see Table 3).

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

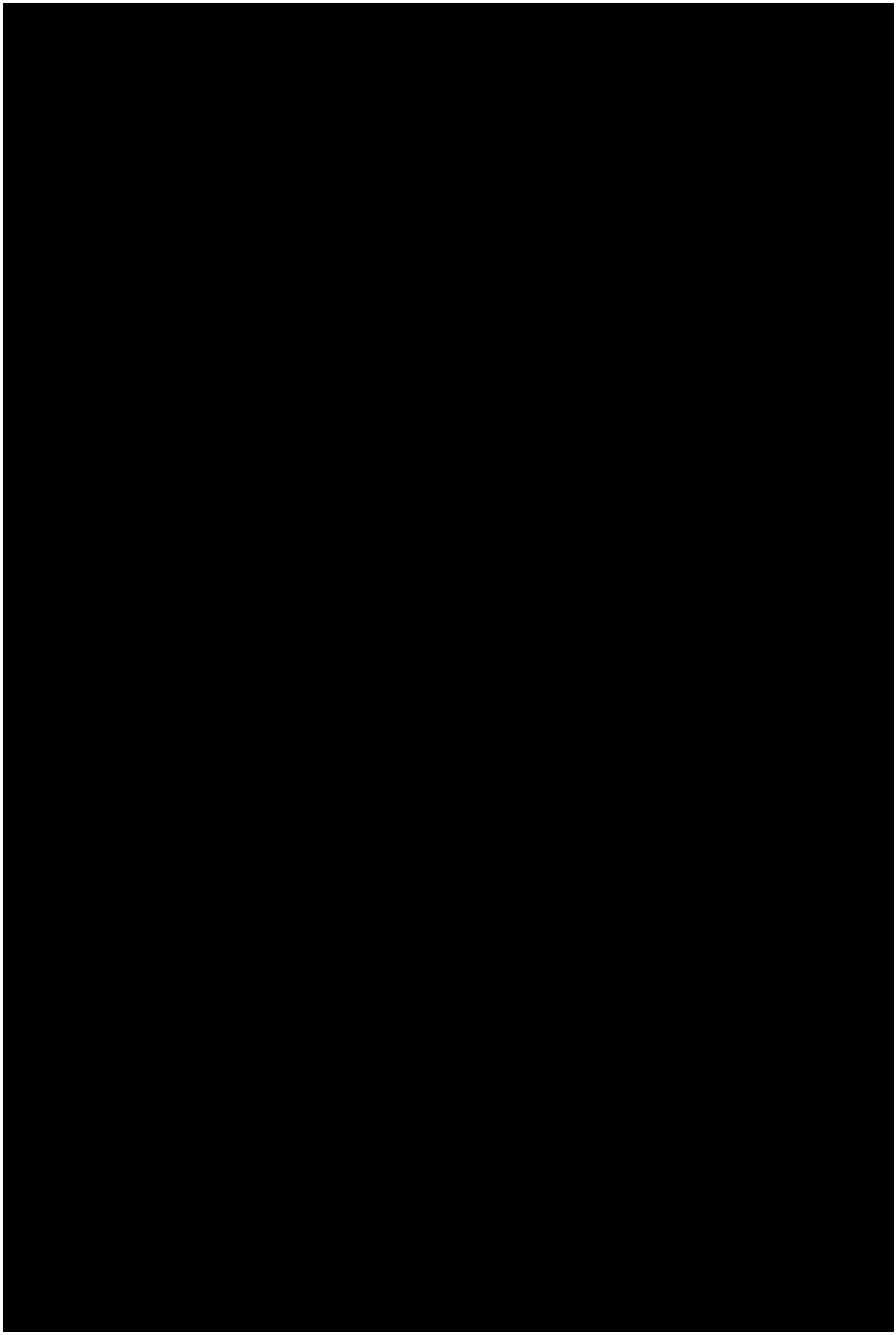
The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported using descriptive statistics.

4.6.6 Biomarker Analyses

Based on FAS (depending on availability of biomarker assessment for individual participants), ANCOVA analyses (with covariates and stratification factor as defined in Section 4.2.5) are planned for the following:

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

Further exploratory biomarker analyses may be conducted separately (e.g. on [redacted]) for which separate analysis plans will be used.



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- [redacted]

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[redacted]

[redacted]

- [redacted]

4.8 INTERIM ANALYSES

There is no plan to conduct any interim analysis.

4.9 CHANGES TO PROTOCOL- PLANNED ANALYSES

Not planned.

5. SUPPORTING DOCUMENTATION

This SAP is part of a broader DAP including DAP Module 2, and DAP Module 3. The LoPO will be described in the Roche DAP module 2.

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