STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase 1, Double-Blind, Placebo-Controlled, Single Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetics of PMN310 Infusions in Healthy Volunteers
Protocol Number:	PMN310-101
Phase:	Phase 1
Sponsor:	ProMIS Neurosciences, Inc. 1 Broadway Cambridge, MA 02142
SAP Version	SAP Final v1.0
SAP Date:	07MAR2024

[redacted]	AD ST-07 Statistical Analysis Plan Approval Form

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The statistical analysis plan has been reviewed and approved.

[redacted]

Signature Date

Sponsor: [redacted]

Author:

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2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the SAP are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

Abbreviation	Definition
ADA	antidrug antibody
ADaM	Analysis Data Model
AE	adverse event
ARIA	amyloid-related imaging abnormality
ATC	Anatomical Therapeutic Chemical
AUC_{0-t}	area under the curve from Time 0 to last sampling time
$AUC_{0-\infty}$	area under the curve from Time 0 to infinity
AUC_{extrap}	Area under the curve extrapolated from time t to infinity
AUC_{last}	area under the curve to the last timepoint
BLQ	Below the limit of quantification
BMI	body mass index
C	Celsius
CDISC	Clinical Data Interchange Standards Consortium
$C_{end\ of\ infusion}$	Concentration at the end of infusion
CL	clearance
C_{last}	Concentration corresponding to the time of last measurable concentration
C_{max}	maximum observed concentration
CRF	case report form
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
DBP	diastolic blood pressure
ECG	electrocardiogram
ET	early termination
FDA	Food and Drug Administration

Abbreviation	Definition
FIH	first in human
FSH	follicle-stimulating hormone
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
IV	intravenous
lambda_z (λ_Z)	Terminal elimination rate constant
LLOQ	Lower limit of quantification
LP	lumbar puncture
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCA	non-compartmental analysis
PK	pharmacokinetic
PT	preferred term
QTcF	QT interval corrected by Fridericia
SAE	serious adverse event
SAP	statistical analysis plan
SBP	Systolic blood pressure
SD	standard deviation
SDTM	Study Data Tabulation Model
SOC	System organ class
SOP	standard operating procedure
SRC	Safety Review Committee
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
t_{last}	Time of last measurable concentration
t_{max}	time to C_{max}
USA	United States of America
Vd	volume of distribution
WHO-DD	World Health Organization – Drug Dictionary

3 INTRODUCTION

3.1 Preface

This document presents the statistical analysis plan (SAP) for study PMN310-101 (A Phase 1, Double-Blind, Placebo-Controlled, Single Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetics of PMN310 Infusions in Healthy Volunteers).

Reference materials for this statistical plan include the PMN310-101 study protocol v2.0 (dated 22-September-2023), protocol clarification letter #1 (dated 09-October-2023), protocol clarification letter #2 (dated 26-October-2023), protocol clarification letter #3 (dated 16-November-2023), and Guidance for Industry: E9 Statistical Principles for Clinical Trials (1998).

The SAP described hereafter is an *a priori* plan. Any changes to this SAP will be finalized and approved prior to database lock. Statistical programming may occur as study data accumulate so that analysis programs are ready at study completion. Any future amendments made to the protocol will not necessitate amendments to the SAP unless changes in the protocol result in changes to key analyses.

3.2 Purpose of Analyses

The purposes of the planned analyses described in this SAP are to establish the safety, tolerability, and pharmacokinetics (PK) of a single intravenous (IV) infusion of PMN310. Results from the analyses completed will be included in the final clinical study report for Study PMN310-101 and may also be utilized for regulatory submissions, manuscripts, or other clinical development activities.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. Exploratory analyses will be clearly identified in the final clinical study report. Additional analyses not prospectively identified in this SAP may also be completed for publications or regulatory or funding inquiries. These analyses, if performed, may not be reported in the clinical study report but will be fully documented in the document containing the additional analyses.

3.3 Summary of Statistical Analysis Changes to the Protocol

The analyses described in this analysis plan are consistent with the analyses described in the study protocol and protocol clarification letters.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Study Objectives

4.1.1 Primary Objectives

- To assess safety and tolerability of escalating doses of PMN310 when administered as a single IV infusion in healthy volunteers

4.1.2 Secondary Objectives

- To assess the single dose PK of PMN310

4.1.3 Exploratory Objectives

- To assess the immunogenicity of PMN310 following single dose administration
- To assess biomarkers in healthy subjects

4.2 Study Endpoints

4.2.1 Primary Endpoints

- Adverse events (AEs), clinical laboratory tests (clinical chemistry, hematology, urinalysis), physical and neurological examinations, vital signs, and 12-lead electrocardiograms (ECGs)

4.2.2 Secondary Endpoints

- Serum PK: maximum observed concentration (C_{max}), time to C_{max} (t_{max}), area under the curve from Time 0 to last sampling time (AUC_{0-t}), area under the curve from Time 0 to infinity ($AUC_{0-\infty}$), terminal half-life ($t_{1/2}$), volume of distribution (Vd), clearance (CL)
- Cerebrospinal fluid (CSF) drug concentrations

4.2.3 Exploratory Endpoints

- Incidence and titers of antidrug antibodies (ADAs)
- Residual and unused serum and CSF samples will be stored for future use for the measurement of biomarkers

5 STUDY METHODS

5.1 General Study Design and Plan

This is a randomized, placebo-controlled, single ascending dose clinical study of PMN310 in healthy adult volunteers. The study aims to establish the safety, tolerability, and PK of a single IV infusion of PMN310.

Subjects who provide written informed consent and meet all eligibility criteria will be admitted to the study clinic on Day -1 (i.e., the day prior to dosing with PMN310 or placebo). Subjects will be domiciled for 4 nights with standardized meals provided during inpatient stay. On Day 1, subjects will be randomly assigned to receive either a single infusion of PMN310 or placebo (6:2 ratio). After randomization on Day 1, study drug will be administered followed by the collection of safety, tolerability, and PK data for 12 weeks postdose (outpatient follow-up period). Following completion of the postdose outpatient follow-up period, subjects may return for an optional follow-up visit to evaluate PK, ADA, and exploratory biomarkers, if warranted by previous data. The decision to recommend the optional follow-up visit will be made by the

Sponsor and communicated to the Investigator who will notify the subject about the timing of the optional visit.

All dose cohorts will have lumbar punctures (LPs) performed on Day 3 and Day 29. The timing of additional LPs will be based on available serum PK and CSF concentrations of PMN310 from prior cohorts. The timing of LPs will be communicated to the Investigator who will inform the subject. No subject will have more than 3 total LPs.

Coagulation assessments required within 2 days of lumbar puncture may be performed on Day 2 for results available prior to Day 3 lumbar puncture. For the remaining visits that require lumbar puncture, the Coagulation assessments can be performed the day prior to the lumbar puncture provided the assessment is performed within the visit window for that Study Day.

The study schema per cohort and schedule of assessments are shown in Figure 1 and Table 1, respectively.

Figure 1 Study Schema Per Cohort

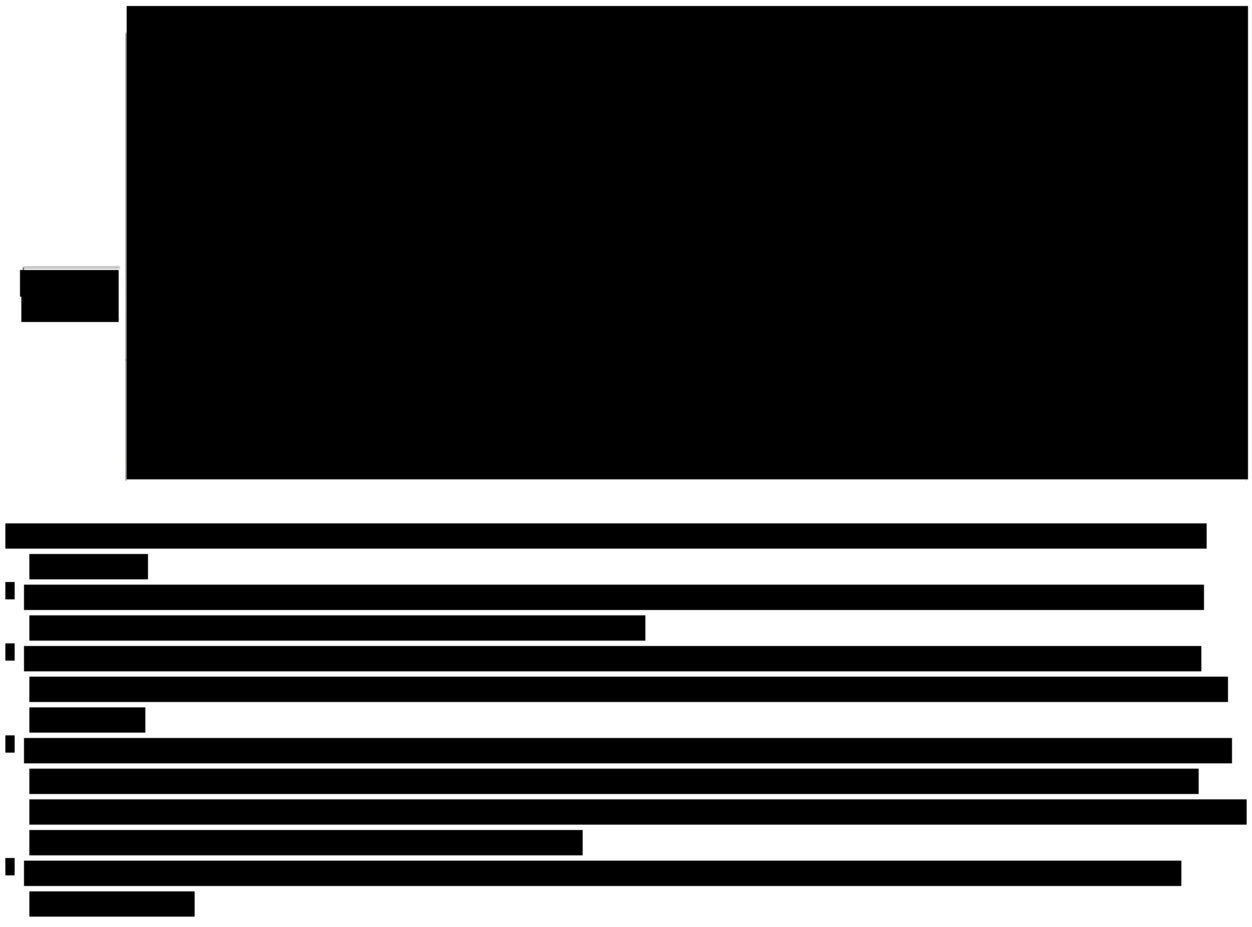

Table 1 Schedule of Assessments

Treatment Period	Screen	Inpatient						Outpatient Follow-Up						Optional Follow-Up[15]
Week	-4	0						1	2	4	6	8	12/ET	17
Day	-28 to -1	-1	1	2	3	4[1]	5	8	15	29	43	57	85	120
Window	na	na	na	na	na	na	na	± 1 day	± 1 day	± 3 days	± 3 days	± 3 days	± 4 days	± 7 days
Informed consent[2]	X													
Inclusion/exclusion criteria	X	X												
Lumbar x-rays (at investigator discretion)	X													
Admit to clinical research unit[3]		X												
Randomization prior to drug administration			X											
Study drug administration			X											
Meals and fluids[4]		X	X	X	X	X								
Discharge from clinical research unit						X								
Demography & medical history	X													
C-SSRS	X		X			X				X		X	X	
Height	X													
Physical & neurologic examination	X	X			X[5]					X[5]			X[5]	
Vital signs[6]	X	X	X	X	X	X		X	X	X	X	X	X	
Weight	X	X			X					X			X	
MRI	X										X[7]			
ECG[8]	X	X	X	X	X	X		X		X			X	
HBsAg and HCV tests	X													

Treatment Period	Screen	Inpatient						Outpatient Follow-Up						Optional Follow-Up[15]
Week	-4	0						1	2	4	6	8	12/ET	17
Day	-28 to -1	-1	1	2	3	4[1]	5	8	15	29	43	57	85	120
Window	na	na	na	na	na	na	na	± 1 day	± 1 day	± 3 days	± 3 days	± 3 days	± 4 days	± 7 days
FSH[9]	X													
Pregnancy test[10]	X	X						X					X	
Urine drug, urine cotinine, & serum alcohol screen	X	X						X					X	
Clinical laboratory tests	X	X			X			X	X	X	X	X	X	
Serum PK collection[11]			X	X	X	X	X	X	X	X	X	X	X	X
Serum ADA collection		X								X		X	X	X
Exploratory biomarkers[12]		X								X		X	X	X
Lumbar puncture[13]					X				(X)	X		(X)	(X)	
Concomitant medications	X	X	X	X	X	X		X	X	X	X	X	X	
Adverse events	X[14]	X[14]	X	X	X	X		X	X	X	X	X	X	

ADA = antidrug antibodies; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; MRI = magnetic resonance imaging; na = not applicable; PK = pharmacokinetics

[1] Date of discharge from the inpatient study clinic is at the discretion of the Investigator. It may be extended, if needed, and is dependent on the need for further observation and/or care.

[2] Informed consent must be documented before any study-specific screening procedures are performed.

[3] Admission to the study clinic should occur before 6 PM.

[4] Standardized breakfast, lunch, and dinner will be provided at fixed times on each inpatient study day. Meals are to be consumed within 45 minutes. Evening snacks will be provided at a consistent time each day. Fluids will be allowed liberally.

[5] Symptom directed physical examination and neurological examination will be performed at the indicated timepoints.

[6] Vital signs should always be collected up to 45 minutes before PK sampling (i.e., nominal time) unless otherwise indicated - before infusion, at the end of infusion (see protocol Section 5.2.1 for a definition for complete infusion), and at 0.5, 1, 2, 4, 8, and 12 hours after the end of infusion. Day 2 (24 and 36 hours), D3 (48 hours), and Day 4 (72 hours), Days 8, 15, 29, 43, 85. Subjects should be resting supine for at least 5 minutes before the vital sign assessment; the exact time of assessment is to be recorded.

[7] Only subjects ≥ 50 years of age will have MRI assessments at Day 43. If ARIA is detected, repeat MRIs will be performed every 3-4 weeks until ARIA is resolved.

[8] ECGs should always be performed up to 45 minutes before PK Sampling (i.e., nominal time) unless otherwise indicated - before infusion, at the end of infusion, and at 1, 2, 4, 8, and 12 hours after the end of infusion. Day 2 (24 and 36 hours), D3 (48 hours), and Day 4 (72 hours), , 8, 29, and 85.

[9] FSH will be evaluated for post-menopausal women only. Post-menopausal status will be confirmed through testing of FSH levels (≥ 40 IU/mL).

[10] Pregnancy test is not required for post-menopausal women. Serum human chorionic gonadotropin at Screening and urinary chorionic gonadotropin thereafter. If a urine pregnancy test is positive, a serum pregnancy test must be obtained. Additional details provided in protocol Section 7.1.9.

[11] Pharmacokinetic blood sampling for serum PMN310 concentrations should be performed as follows:

- Day 1: before infusion, at the end of infusion, and at 0.5, 1, 2, 4, 8, and 12 hours after the end of infusion
    - Acceptable windows for PK sampling are as follows (exact time of PK collection is to be recorded):
        - Pre-dose sample to be collected within 60 minutes prior to dosing
        - 0.5 to 4-hour post-dose samples to be collected ± 5 minutes
        - 8 to 12-hour post-dose samples to be collected ± 10 minutes
- Day 2 (24 and 36 hours)
    - Acceptable window for PK sampling is ± 30 minutes (exact time of PK collection is to be recorded)
- Day 3 (48 hours), Day 4 (72 hours) and Day 5 (96 hours)
    - Acceptable windows for PK sampling are ± 60 minutes (exact time of PK collection is to be recorded)
    - Day 5 (96) hours does not require inpatient collection
- Days 8, 15, 29, 43, 57, 85

[12] Note: Residual or unused serum and CSF samples will be stored for future use for the measurement of biomarkers. For Day 120, only serum will be stored for the measurement of biomarkers since CSF will not be collected at Day 120. Additional details are provided in protocol Section 7.1.12.

[13] CSF samples will be obtained via lumbar puncture (LP). All dose cohorts will have LPs on Day 3 and Day 29. The timing of additional LPs will be based on the available serum PK and CSF concentrations of PMN310 from prior cohorts, and may potentially include Day 15, Day 57, or Day 85 (shown in parentheses in the Schedule of Assessments). The timing of LPs will be communicated to the Investigator who will inform the subject. Coagulation results within 2 days prior to the LP must be confirmed and determined to be within normal range before LP. No subject will have more than 3 total LPs. Post LP, subjects will remain supine for a minimum of 4 hours, and may be kept longer for observation at the discretion of the Investigator. After the 4-hour observation period, safety and tolerability will be assessed and subjects will be discharged home.

[14] AE assessment of protocol-related procedures will be performed after informed consent is obtained.

[15] Following completion of the postdose outpatient follow-up period, subjects may return for an optional follow-up visit, if warranted by previous data. The decision to recommend the optional follow-up visit will be made by the Sponsor and communicated to the Investigator who will notify the subject about the timing of the optional visit. Additional details are provided in protocol Section 6.2.3.

5.2 Dose Levels

Table 2 summarizes the dose level cohorts that are planned to be evaluated.

Table 2 Planned Study Drug Dose Levels

Cohort	Expected Number of Evaluable Subjects	PMN310 Dose Level
1	6 PMN310, 2 placebo	175 mg (starting dose level)
2	6 PMN310, 2 placebo	350 mg
3	6 PMN310, 2 placebo	700 mg
4	6 PMN310, 2 placebo	1400 mg
5	6 PMN310, 2 placebo	2800 mg (optional cohort)

5.3 Dose Escalation/Stopping Rules

Each dose cohort will consist of 8 subjects (6:2; PMN310:placebo). To evaluate the short term safety and tolerability of PMN310, each cohort will enroll a sentinel group of 2 subjects (1:1, PMN310:placebo) who will be dosed prior to dosing the remaining 6 subjects in the cohort (5:1, PMN310:placebo). The Safety Review Committee (SRC) will review all safety data collected through 48 hours postdose from the 2 sentinel subjects to determine the acceptability of proceeding with dosing of the remaining 6 subjects in the cohort.

Dose escalation to the next cohort will only occur after approval by the SRC. The SRC will determine the acceptability of proceeding with enrollment of the next cohort based on review of safety and any available PK data at the time of review through 7 days postdose for a minimum of 6 of 8 subjects per cohort.

Dose escalation will be paused for review if any of the following occur,

- Two or more of the subjects in a cohort develop Grade ≥ 2 AEs **in the same category.**
- One or more subjects in a cohort develop Grade ≥ 3 AEs.
- It is determined that the limit of safety and/or tolerability has been reached as determined by the SRC.

The Sponsor or SRC may pause and then stop dosing within a cohort or decide to not dose escalate to a higher dose if it is determined that any AE is occurring that is intolerable or poses a medically unacceptable safety risk.

5.4 Subject Replacement Rules

Sentinel group subjects who discontinue before Day 7 will be replaced, unless they discontinued due to an SAE related to study drug.

Non-sentinel group subjects who discontinue before Day 7 may be replaced at the discretion of the Sponsor and the SRC.

5.5 End of Study Definition

The end of the study is defined as the date of the last scheduled procedure. If there is an unresolved AE or concomitant medication, or an assessment date that is after the end of study, the date of study completion will be inclusive of that resolution/assessment date.

A subject is considered to have completed the study if the subject did not discontinue or terminate the study early and has completed the last scheduled procedure as specified in the Schedule of Assessments.

5.6 Safety Review Committee

The SRC will be responsible for the review of safety and any available PK data at the time of review and making determinations regarding the acceptability of proceeding with dosing of the remaining 6 subjects in a cohort (based on review of sentinel subjects) and dose escalation to the next cohort. The SRC will be comprised of the Study Investigator, Medical Monitor, and Sponsor Medical Director. At a minimum, the SRC will review safety data assessments collected 48 hours after the sentinel subjects have been dosed in each cohort and ≥ 7 days postdose for a minimum of 6 of 8 subjects per cohort prior to each dose escalation. The SRC charter will specify operational details pertaining to roles and responsibilities, data to be reviewed, review frequency, and reporting for minutes and decisions.

5.7 Randomization and Blinding

5.7.1 Randomization and Blinding

Each subject will be assigned a unique identification number at the screening visit. Once an eligible subject is at the study site and prepared to receive the study drug, the subject will be assigned the treatment allocation according to the randomization sequence. The randomization sequence will be obtained by computer-generated random numbers and provided to unblinded study site staff members who will have primary responsibility for drug dispensing. Within each cohort, eligible subjects will be randomized to receive PMN310 (N = 6) or placebo (N = 2). The screening number and randomization number are different numbers.

Subjects and study personnel will be aware of the dosage level but will be blinded to the study drug administered (PMN310 or placebo). Only unblinded study site staff members assigned to prepare study drug will know whether a subject receives PMN310 or placebo. To maintain appropriate blinding, the unblinded pharmacist will consult the randomization sequence, prepare the PMN310 or placebo, and label the prepared study drug with the subject's study identifier and the phrase "PMN310 or placebo." The unblinded pharmacy staff will then provide prepared study drug in a blinded fashion to the Investigator (or designee) for infusion.

5.7.2 Unblinding for an Individual Subject

In case of an emergency, the Investigator has the sole responsibility of determining if unblinding of a subject' treatment is warranted. Blinding should only be broken in emergency situations when

knowledge of the treatment assignment is required for the assurance of the safety of the subject and the medical management of the subject. The Sponsor or representative should be contacted, when possible, before breaking the blind except in emergency circumstances when the Investigator has the sole responsibility for determining the need to unblind. Upon breaking the blind, the reason must be documented, and the Sponsor should be immediately notified. [redacted]

6 STATISTICAL CONSIDERATIONS

6.1 Sample Size

A total of 40 subjects will be enrolled across 5 dose cohorts. Cohort 5 is optional. Each dose cohort will consist of 8 subjects (6 PMN310, 2 placebo). The sample size of 8 subjects per cohort is based on feasibility and precedent for Phase 1 FIH studies. [redacted]

6.2 Analysis Populations

There will be four (4) analysis populations defined for this study. These analysis populations may be further refined, and additional analysis populations may be defined, for example, for the analysis of data for a specific assay, based on sample availability and suitability. Any changes will be summarized in the Clinical Study Report (CSR).

- The Safety population will include all subjects who receive study drug. Subjects will be analyzed as treated.
- The PK population will include all subjects who receive study drug and have at least 1 post-dose quantifiable concentration for PK analysis. The PK population will be used for the serum PMN310 concentration analyses. Subjects will be analyzed as treated.
- The Evaluable population will include all subjects who complete at least 1 post-dose lumbar puncture (LP). The Evaluable population will be used for the cerebrospinal fluid (CSF) PMN310 concentrations. Residual and unused CSF samples will be stored for future use for the measurement of exploratory CSF biomarker analyses. Subjects will be analyzed as treated.
- The Randomized population will include all subjects who were randomized. Subjects will be analyzed as randomized.

6.3 Covariates and Subgroups

Not applicable.

6.4 Management of Analysis Data

6.4.1 Baseline

Unless otherwise specified, baseline data is defined as the data most recently collected prior to the first dose.

Change from baseline is calculated as:

Change from baseline = post-baseline visit value – baseline value.

If either the baseline or visit value is missing, the change from baseline is set to "missing".

6.4.2 Data Handling

All assessments collected at scheduled and unscheduled days and time points will be included in the listings. For parameters that will be summarized by day and time point, the nominal day and time point as recorded in the CRF will be used. When the data from a scheduled assessment is not available, an unscheduled assessment within the assessment window defined in the Schedule of Assessments, if available, will be used to replace the scheduled assessment. If multiple unscheduled assessments are present in the assessment window, the unscheduled assessment closest to the nominal day and time point will be used. This algorithm will be implemented for chemistry, hematology, coagulation, and urinalysis labs, 12-lead ECG, vital signs, PK concentrations, ADA results, and exploratory biomarkers.

Note that blood draws for international normalized ratio/prothrombin time/partial thromboplastin time, and platelets may be drawn a day before a scheduled lumbar puncture to ensure results are available in time for the lumbar puncture procedure. The blood draw results that were obtained a day early will be analyzed with the scheduled blood draw results.

6.4.3 Missing Data

Unless otherwise specified, there will be no substitutions made to accommodate missing data points.

6.4.3.1 Handling of Missing Date Values

Partial or Missing Dates

The following conventions will be used to impute missing portions of dates for adverse events, medical history, and prior and concomitant medications, if warranted. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

A. Start Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
2) If the month is unknown, then:
   i) If the year matches the first dose date year, then impute the month and day of the first dose date.
   ii) Otherwise, assign 'January.'
3) If the day is unknown, then:
   i) If the month and year match the first dose date month and year, then impute the day of the first dose date.
   ii) Otherwise, assign the first day of the month.

B. Stop Dates
1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
2) If the month is unknown, then assign 'December.'
3) If the day is unknown, then assign the last day of the month.

6.4.3.2 Imputation Methods

Adverse Events

If the relationship of an AE is missing, it will be considered treatment related.

Missing AE severity grade will be coded as 3 (severe).

For the purpose of final analysis, any imputed AE relationship or severity grade will be highlighted with an asterisk (*) in listings.

PK Concentration and Parameter Estimation

The rules for imputing concentration data are detailed under Pharmacokinetics (Section 9).

6.4.4 Handling of Early Termination Visit Information

If a subject is terminated early from this study the early termination visit data will be analyzed at the closest scheduled visit. If the closest visit has valid data, the early termination data will be assigned to the next available visit.

6.4.5 Handling of Clinical Laboratory Results

Multiple laboratories will be utilized in the study. Prior to analysis, the clinical laboratory results and units will be standardized across both laboratories. Normal ranges and the identification of normal/abnormal not clinically significant/abnormal clinically significant/not evaluable results

will not be modified, the results from the original laboratory will be used. Full details will be provided in the ADaM Reviewer's Guide.

6.4.6 Coding Conventions for Events and Medications

All adverse events and medical history will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 26.1) system for reporting (preferred term and body system).

Prior and Concomitant medications will be coded using World Health Organization – Drug Dictionary (WHO-DD) (Version 01SEP2022_b3).

6.4.7 Analysis Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher) for Windows. PK parameter estimation will be performed using Phoenix® WinNonlin® Version 8.3 or higher. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

6.4.8 Study Data

All study data will be formulated into regulatory compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the CDISC Study Data Tabulation Model (SDTM Implementation Guide v3.3) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM Implementation Guide v1.1) architecture. All planned analyses will be performed using the ADaM data sets developed for this study. Controlled Terminology 31 March 2023 or later will be used.

6.5 Planned Study Analyses

6.5.1 Statistical Summaries: Descriptive and Inferential

Descriptive summaries of variables will be provided as appropriate. In general, for continuous variables, the number of non-missing values (n) and the mean, standard deviation (SD), median, interquartile range, minimum, and maximum will be tabulated. For PK analyses, coefficient of variation (CV%), geometric mean and geometric CV% will also be provided, where appropriate. For categorical variables, the count and proportion will be tabulated. Expansion of descriptive table categories within and/or across each treatment may occur.

In general, unless otherwise specified, summaries and analyses will be tabulated by PMN310 dose level within each cohort, placebo combined into a single group over all cohorts, and overall (ex., Cohort 1: 175 mg, Cohort 2: 350 mg, Cohort 3: 700 mg, Cohort 4: 1400 mg, Cohort 5: 2800 mg, All Placebo, Total).

All study related data collected, and all derived data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or figures but will be included in the data listings.

6.5.2 Interim Analyses and Data Monitoring

No formal interim analysis is planned for this study.

In order to evaluate accumulating safety information and to guide study conduct, a SRC will be regularly convened to inform dosing decisions. The SRC membership, responsibilities, operating procedures, frequency of meetings, data availability, reporting, and record keeping will be described in detail in a separate SRC Charter. Refer to SAP Section 5.6 for more details about the SRC.

6.6 Statistical Tests

While confidence intervals will be provided for select analyses, formal statistical hypothesis testing is not planned in this SAP.

6.7 Multiplicity

Not applicable.

7 SUMMARY OF STUDY DATA

7.1 Subject Disposition

A summary of the analysis sets includes the number and percentage of subjects in each treatment group for the following categories: subjects screened, subjects in the Randomized population, subjects in the Safety population, subjects in the PK population, and subjects in the Evaluable population. All percentages will be based on the number of subjects in the Safety population.

End of trial information will be summarized descriptively for categorical data, including the number of subjects completing the study and the number of subjects who prematurely discontinued the study with reasons for withdrawal. All percentages will be based on the number of subjects in the Safety population.

For randomized subjects, a listing of eligibility, including any criteria not met and protocol version under which each subject was enrolled will be generated.

Disposition data will be summarized by PMN310 dose level within each cohort, placebo over all cohorts, and overall.

Disposition data will be presented in a by-subject listing.

7.2 Protocol Deviations

The number of deviations and number and percentage of subjects with protocol deviations, by category, will be summarized descriptively for categorical data by PMN310 dose level within each cohort, placebo over all cohorts, and overall for the Safety population.

All protocol deviations will be presented in a by-subject listing.

7.3 Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be tabulated and summarized descriptively for continuous and categorical data by PMN310 dose level within each cohort, placebo over all cohorts, and overall for the Safety population. Data will include age in years, sex at birth, race, ethnicity, height, weight, BMI, and childbearing potential.

Individual subject demographics and baseline characteristics will be presented in by-subject listings.

7.4 Medical History

Medical History includes all relevant medical conditions, concomitant illness, surgeries within the 6 months before Screening. For female subjects, the last menstrual period should be recorded.

Medical history will be coded by system organ class (SOC) and preferred term (PT) and summarized descriptively for categorical data by PMN310 dose level within each cohort, placebo over all cohorts, and overall, for the Safety population.

Medical history data will be presented in a by-subject listing.

7.5 Prior and Concomitant Medications

All medications, including over-the-counter medications or herbal therapies, given during the study as well as any prior medications taken within 4 weeks prior to Screening are to be recorded.

Concomitant medications are defined as any medication taken on or after the day of first dose of study drug. Prior medications are defined as any medication that starts and ends prior to the day of first dose of study drug. If the start date of a medication is missing/incomplete and the end date is prior to the first dose of study drug, the medication will be assumed to be a prior medication. If the start date of a medication is missing/incomplete and the end date is on or after the first dose of study drug, the medication will be assumed to be a concomitant medication. If both the start date and end date are missing/incomplete, and it is not clear when the medication was taken, the medication will be considered concomitant.

The number and percentage of subjects with at least 1 concomitant medication will be summarized descriptively for categorical data by PMN310 dose level within each cohort,

placebo over all cohorts, and overall, Anatomical Therapeutic Chemical (ATC) level 4 and PT. If ATC level 4 is missing for a medication a higher (eg, ATC level 3) will be summarized for that medication. All summaries will be performed using the Safety population. Subjects will only be counted once within each category of medication taken.

The number and percentages of all prior medications will be summarized similarly to concomitant medications in a separate table.

Prior and concomitant medications data will be presented in a by-subject listing.

7.6 Treatment Compliance and Exposure

The volume of study drug infused (mL), volume of flush used (mL), and total volume infused (study drug + flush) (mL) will be summarized descriptively by PMN310 dose level within each cohort, placebo over all cohorts, and overall, for the Safety population.

All dosing information, including derived total exposure to PMN310, will be presented in a by-subject listing.

8 PRIMARY ENDPOINTS ANALYSES

The primary objective of this study is to assess the safety and tolerability of PMN310 of escalating doses of PMN310 when administered as a single IV infusion in healthy volunteers.

All safety summaries will be presented by PMN310 dose level within each cohort, placebo over all cohorts, and overall using the Safety population.

8.1 Adverse Events

In general, the number and percentage of subjects with treatment-emergent adverse events (TEAEs) will be summarized descriptively for categorical data by SOC and PT. At each level of summarization (SOC and PT) subjects are only counted once.

Only TEAEs will be tabulated, which are defined as any AEs with onset or worsening on or after the first dose of the study drug. In general, if a missing/incomplete start date is not clearly prior to initiation of treatment, then the AE will be considered a TEAE. If the AE end date is prior to the initiation of treatment, the AE will not be considered a TEAE.

An overall summary of TEAEs will be provided including the number and percentage of

- Subjects with at least one TEAE,
- Subjects with at least one study drug-related (possible or probably) TEAE,
- Subjects with at least one TEAE with severity Grade 3 (Severe),
- Subjects with at least one treatment-emergent serious adverse events (TESAE),
- Subjects with TEAE leading to treatment discontinuation.

The number and percentage of subjects with any TEAEs, and frequency of events, will be displayed by SOC and PT. Treatment related (probable or possible relationship to PMN310 treatment) will be summarized similarly. The number and percentage of subjects with any TEAEs, and frequency of events, will also be displayed by PT.

TEAEs will also be summarized by the greatest reported severity. Counts indicate subjects reporting one or more TEAEs that map to the severity grade classification for each PT. At each level of summarization (SOC or PT) subjects are only counted once and the worst severity case of repeated instances of the same TEAE will be used in tabulations. Missing severity will be considered as Grade 3 (Severe).

TEAEs will also be summarized by the strongest investigator assessment of relationship to study drug in a similar manner to the summary of TEAEs by severity. Missing relationship will be considered as probably related.

All AEs, including those that are not treatment-emergent, will be listed by subject.

8.2 Serious Adverse Events and Other Significant Adverse Events

8.2.1 Serious Adverse Events

The number and percentage of subjects with TESAEs, and frequency of events, will be displayed by SOC and PT, and relationship to study drug. Within each SOC and PT, subjects will be counted only once if they had more than one TESAE event reported.

All SAEs, including those that are not treatment-emergent, will be included in a by-subject listing.

8.2.2 Adverse Events Leading to Discontinuation of Study Drug

The number and percentage of subjects with TEAEs leading to discontinuation of study drug, and frequency of events, will be displayed by SOC and PT. Within each SOC and PT, subjects will be counted only once if they had more than one TEAE leading to discontinuation of study drug.

All TEAEs leading to discontinuation of study drug will be included in a by-subject listing.

8.3 Clinical Laboratory Evaluations

Chemistry, hematology, coagulation, and urine clinical laboratory results will be summarized descriptively for continuous and categorical lab results, as appropriate, by visit for the observed value as well as for the change from baseline value (continuous lab results only).

In addition, laboratory shift summary tables will be provided where normal/abnormal not clinically significant/abnormal clinically significant/not evaluable status is collected on the CRF.

For each of these lab tests, the shift table will tabulate the number and percentage of subjects that shifted from normal/abnormal not clinically significant/abnormal clinically significant/not evaluable at Baseline to normal/abnormal not clinically significant/abnormal clinically significant/not evaluable at each post-Baseline visit. Percentages will be based on the number of subjects with non-missing status at Baseline and each post-Baseline visit.

Individual laboratory parameters by visit with normal ranges, and abnormal laboratory assessments will be included in by-subject listings.

8.4 12-Lead Electrocardiogram (ECG)

Continuous ECG parameter data (heart rate (bpm), PR interval (msec), QRS interval (msec), QT interval (msec), and QTcF interval (msec)) will be summarized descriptively for continuous data for the observed value as well as for change from baseline value.

In addition, the number and percentage of subjects with ECG assessments, as reported on the CRF, of normal, abnormal not clinically significant, and abnormal clinically significant will be summarized categorically. Percentages will be based on the number of subjects with non-missing response at each visit and timepoint.

A categorical summary table describing the n (%) of subjects meeting the below thresholds at any post-baseline visit/time point will be generated.

QTcF Pre-Defined Thresholds

- QTcF > 450 msec
- QTcF > 480 msec
- QTcF > 500 msec
- QTcF increased by > 30 msec from baseline
- QTcF increased by > 60 msec from baseline

All ECG data will be presented in a by-subject listing. Subjects meeting pre-defined threshold values for QTcF will be flagged.

All abnormal ECG data (abnormal not clinically significant and abnormal clinically significant) will be presented in a by-subject listing. Subjects meeting pre-defined threshold values for QTcF will be flagged.

8.5 Physical and Neurological Examinations

All physical examination and neurological examination data will be presented in by-subject listings.

8.6 Vital Signs and Anthropometrics

Vital signs data collected include systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), pulse rate (bpm), respiratory rate (breaths/min), oral temperature (C), weight (kg), and BMI (kg/m^2) and will be summarized descriptively for continuous data by visit and timepoint for the observed value as well as for the change from baseline value, where available.

A categorical summary table describing the n (%) of subjects meeting the below thresholds at any post-baseline visit/timepoint will be generated.

Vital Sign Pre-Defined Thresholds

- SBP > 180 mmHg (High)
- SBP < 90 mmHg (Low)
- DBP > 110 mmHg (High)
- DBP < 50 mmHg (Low)
- SBP increased by ≥ 30 mmHg from baseline
- SBP decreased by ≥ 30 mmHg from baseline
- DBP increased by ≥ 20 mmHg from baseline
- DBP decreased by ≥ 20 mmHg from baseline

All vital signs data will be presented in a by-subject listing.

8.7 Magnetic Resonance Imaging (MRI)

MRI results for subjects where amyloid-related imaging abnormalities (ARIA) are detected will be presented in a by-subject listing.

All centrally read MRI data will be presented in a separate by-subject listing.

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

C-SSRS questions since last visit will be summarized descriptively.

All C-SSRS data will be presented in by-subject listings.

8.9 Other Measures

Urine drug, urine cotinine and alcohol screening; infectious disease tests; meal consumption data, and serum and urine pregnancy test data will be presented in by-subject listings.

If after the study results are reviewed, or Sponsor recommends additional safety parameters or analyses be completed, they will be fully described and documented in the final clinical study report. The SAP does not need to be amended to complete any other safety measures identified as post-hoc.

9 SECONDARY ENDPOINTS ANALYSES

9.1 Serum Pharmacokinetic Analyses

9.1.1 General Considerations

All PK analysis summaries will be presented using the PK Population. PMN310 serum concentration data will be listed by cohort, subject, and visit/sampling time point. Descriptive summary statistics will be provided by cohort and visit/sampling time point.

Any protocol deviations, concomitant medications, or adverse events which could impact PK concentration-data profiles and/or PK parameter estimates will be designated by the Sponsor to indicate whether these PK data should be excluded from analysis. All data that are excluded in this manner will be listed and the reason for exclusion clearly noted. This review will be done by blinded personnel prior to database lock.

Furthermore, subjects must not have quantifiable pre-dose (prior to the start of infusion) concentrations greater than 5% of the corresponding C_{max}. All PK data excluded in this manner will be evaluated on a case-by-case basis and agreed upon with the Sponsor *a priori*.

Serum concentrations of PMN310 will be measured by validated assays and PK parameters will be estimated using standard Phoenix® WinNonlin® (Version 8.3, Certara USA) non-compartmental analysis (NCA) methods and actual blood sampling times relative to dosing (i.e., relative to the end of infusion). If the actual collection time is unknown, the nominal collection time may be used for the purposes of PK parameter estimation.

For the calculation of summary statistics and graphical displays of serum concentrations (except for plots of geometric mean [geometric CV%]), concentrations that are below the limit of quantification (BLQ) will be set to zero (0) for all measurements. In addition, any quantifiable concentration observed after at least 2 consecutive BLQ values at the end of a profile will be evaluated on a case-by-case basis and may be set to missing along with the BLQ concentrations, if warranted. The number and percentage of values missing and the number and percentage of values BLQ will be presented with the other summary statistics. If >25% of values at a time point within a treatment level are missing or BLQ, no summary statistics will be presented.

Serum concentration data will be summarized descriptively for continuous data by PMN310 dose level and protocol-specified nominal timepoint. Summary statistics for concentration-time data will include: n, mean, standard deviation (SD), coefficient of variation (CV%), minimum, median, maximum, geometric mean, geometric CV%, and the number and percentage of samples that are BLQ and the number and percentage of samples that are missing. All concentration-time data and summary statistics will be reported to the same number of decimal places as displayed in the bioanalytical data, except for CV%, which will be reported to 1 decimal place.

Linear-linear and log-linear mean serum concentration-time vs nominal timepoint plots will also be presented by dose level, while linear-linear and log-linear individual concentration-time vs actual timepoint plots will be presented in a similar manner.

All serum concentration data (including actual blood sampling times) will be provided in a by subject-listing.

Serum concentration values that are BLQ will also be imputed as follows for the NCA:

1. BLQ values at time points prior to any measurable concentration or immediately prior to dosing (pre-dose [prior to the start of infusion]) are imputed as 0.
2. BLQ values between two measurable concentrations will be set to the LLOQ/2.
3. BLQ values after all measurable concentrations are set to missing.

Serum PK parameters will be summarized descriptively by PMN310 dose level. Summary statistics for the time-related serum PK parameters (t_{max}, t_{last} and $t_{1/2}$) will include: n, mean, SD, median, minimum, and maximum while summary statistics for AUC_{extrap} (%) will include n, number and percentage of subjects with AUC_{extrap}>20%, mean, SD, median, minimum, and maximum. $AUC_{0-\infty}$ values will be considered unreliable estimates if the AUC_{extrap} (%) is greater than 20% and will be excluded from summary statistics but will be listed.

Summary statistics for all other serum PK parameters include: n, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%.

Except for time-related PK parameters (t_{max}, t_{last}, and $t_{1/2}$), and reporting of CV%, all other PK parameters will be reported to 3 significant digits. For t_{max}, t_{last}, and $t_{1/2}$, round all statistics to two decimal places. CV% will be reported to 1 decimal place.

All PK parameter data will be presented in a by-subject listing.

9.1.2 Pharmacokinetic Endpoints

9.1.2.1 Serum Pharmacokinetic Parameters

PK parameters will be computed from the individual serum concentrations as data allow.

PK Parameter	Definition
Study Day 1	
AUC_{0-t} (AUC_{last})	Area under the serum concentration-time curve from time zero to the last measurable concentration
$AUC_{0-\infty}$ (AUC_{inf})	Area under the serum concentration-time curve from time zero extrapolated to infinity
AUC_{extrap}	Area under the serum concentration-time curve extrapolated from time t to infinity as a percentage of total area under the concentration-time curve
$C_{end\ of\ infusion}$	Concentration at the end of the intravenous infusion
C_{last}	Concentration corresponding to the time of last measurable concentration (t_{last})
C_{max}	Maximum observed serum concentration
t_{max}	Time to reach maximum serum concentration
t_{last}	Time of last measurable concentration
Span	Time interval used to determine λ_Z divided by the terminal elimination half-life ($t_{1/2}$)
Adjusted r^2	Coefficient of determination used as a criteria for the goodness-of-fit measurement of a regression analysis
$t_{1/2}$	Terminal elimination half-life
lambda_z (λ_Z)	Terminal elimination rate constant
CL	Total body clearance after intravenous infusion
Vd	Volume of distribution during the terminal phase

Additional PK parameters may be estimated as appropriate.

All AUCs including AUC_{0-t} and $AUC_{0-\infty}$ will be calculated using the linear-up/log-down trapezoidal method, using actual sampling times. Missing concentrations will be treated as missing and excluded from PK analysis except when they occur at pre-dose (prior to the start of infusion), where they will be set to 0.

$AUC_{0-\infty}$ will be calculated as outlined below:

$$AUC_{0-\infty} = AUC_{0-t} + (C_{last} / \text{lambda\_z } [\lambda_Z]),$$

where C_{last} (defined as the last measurable concentration) is the last temporal quantifiable serum concentration.

Maximum concentration (C_{max}), t_{max}, and t_{last} will be obtained directly from experimental observations. If multiple maxima occur at equal concentrations, the first temporal value will be taken.

The apparent terminal elimination half-life, $t_{1/2}$, where evaluable, will be calculated as the natural log of 2 divided by the terminal elimination rate constant, λ_z. The number of data points included in the regression will be determined by visual inspection, but a minimum of 3 data points in the terminal phase, excluding C_{max}, is required to estimate λ_z. In order for λ_z and λ_z derived

parameters ($AUC_{0-\infty}$, $t_{1/2}$, Vd, and CL) to be reported, the adjusted r^2 value reported in Phoenix® WinNonlin® must be ≥0.8. $t_{1/2}$ should be determined with a span ≥2. If this criterion is not met the data will be excluded from descriptive summaries but will be included in the listing of PK parameters and flagged.

Regression parameters for estimation of λ_z, including the number of time points used, time point range used for the regression (minimum time, maximum time), span, and adjusted r^2 will be listed.

9.1.2.2 Dose Proportionality

Dose proportionality will be analyzed using a power model. The natural log-transformed (ln) parameters (C_{max} and AUCs: AUC_{0-t} and $AUC_{0-\infty}$) will be fit to a linear model estimating the effect of ln(dose) (Gough 1995). The empirical relationship between a PK parameter and dose is in the following equation:

$$PK = e^{\alpha} * (dose)^{\beta}$$

Where PK represents the PK parameter AUCs and C_{max}. For analysis, this equation is natural log-transformed, obtaining the equation below:

$$InPK = \alpha + \beta * In(dose)$$

The slope β measures the dose-proportionality between dose and the PK parameter.

The confidence interval criteria for assessment of dose proportionality from Smith et al. (2000) will be used to test for dose proportionality. The *a priori* acceptance range for the slope, according to Smith, is given by:

$$1 + In(0.8)/In(r) < \beta < 1 + In(1.25)/In(r)$$

Where 1.25 and 0.8 are the critical *a priori* values suggested by regulatory authorities for any bioequivalence problem after a data log transformation, and r is the ratio of the largest dose to the smallest dose. Dose proportionality can be claimed if the 90% confidence interval for the slope is entirely contained within this *a priori* range.

Dose proportionality will also be explored graphically: regression/scatter plot in the In-In scale for the power analysis.

9.2 Cerebrospinal Fluid (CSF) Pharmacokinetic Analyses

All CSF analyses will be conducted using the Evaluable population.

Descriptive summaries of CSF concentration time data by nominal time point and cohort/dose level will be provided. Summary statistics for PMN310 concentration-time data will include the

following: n (number of participants with non-missing values), mean, SD, arithmetic coefficient of variation (CV (%)), median, minimum, maximum, geometric mean and 90% confidence interval (CI), geometric CV (%), and the number (percentage) of samples are BLQ. All concentration-time data and relevant summary statistics will be reported to the same number of significant figures as displayed in the bioanalytical data. For calculation of summary statistics, concentration values that are BLQ will be set to 0 for all BLQ concentrations. Nominal sampling time points relative to the start of dosing will be used for tabulation by time point for summaries of concentration-time data. If >25% of values at a time point within a treatment level are missing or BLQ, no summary statistics are presented.

No CSF parameters will be estimated apart from CSF:serum PMN310 ratio.

CSF PMN310 concentration data and serum PMN310 concentration data will be compared by cohort/dose level using summary statistics for nominal time points that have both data points available. Mean (±SD) values may also be plotted, as data permits.

All CSF data will be presented by timepoint in a by-subject listing.

10 EXPLORATORY ENDPOINT ANALYSES

10.1 Immunogenicity

All immunogenicity analyses will be conducted using the Safety population.

Immunogenicity results will be summarized descriptively by PMN310 dose level and visit for the number and percentage of subjects who develop detectable levels of anti-PMN310 antibodies (ADA). ADA status will be treated as categorical data (positive and negative) and summarized descriptively by visit. In addition, a subject will be considered positive for PMN310-induced immunogenicity if the subject has at least one confirmed positive ADA response after dosing in the study.

Titer data will also be summarized descriptively for continuous data (n, mean, standard deviation, median, minimum, maximum, geometric mean, and geometric CV%) by PMN310 dose level and visit for the observed value.

Individual serum and/or CSF concentrations of PMN310 and mean (±SD) PMN310 concentrations versus time may be presented separately in ADA positive and negative subjects. Possible correlation between PK concentrations and any post-dose ADA responses may be evaluated using graphical presentation to identify a potential impact of anti-PMN310 antibodies on drug exposure. The ADA status is considered in a cumulative manner at each time point (i.e., if a subject had a positive sample at any time point of assessment visit that subject would be counted as positive throughout the study).

All immunogenicity data will be presented by timepoint in a by-subject listing.

10.2 Biomarkers

Residual and unused serum and CSF samples will be stored for future use for the measurement of biomarkers.

11 REFERENCES

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