CLINICAL STUDY PROTOCOL

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
Protocol Date:	22 September 2023
Protocol Version:	2.0, Amendment 1
IND Number:	161194
Sponsor:	ProMIS Neurosciences, Inc. 1 Broadway Cambridge, MA 02142

PROTOCOL SIGNATURE PAGE

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
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Study Phase:	1
Sponsor:	ProMIS Neurosciences, Inc.

Sponsor Representatives

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

[redacted]

03-Oct-2023

Date

PROTOCOL SYNOPSIS

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
Investigational Agent:	PMN310
Phase:	1
Study Sites:	Up to 2 sites in the United States; if enrollment is challenging (e.g., enrollment is impacted by unexpected events, including but not limited to the COVID-19 pandemic) up to 2 additional sites may participate in this study
Indication:	PMN310 is being developed for the treatment of Alzheimer's disease (AD)
Study Objectives:	Primary • To assess safety and tolerability of escalating doses of PMN310 when administered as a single intravenous (IV) infusion in healthy volunteers
	Secondary • To assess the single dose pharmacokinetics (PK) of PMN310
	Exploratory • To assess the immunogenicity of PMN310 following single dose administration • To assess biomarkers in healthy subjects
Study Endpoints:	Primary • Adverse events (AEs), clinical laboratory tests (clinical chemistry, hematology, urinalysis), physical and neurological examinations, vital signs, and 12-lead electrocardiograms (ECGs)
	Secondary • 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
	Exploratory • 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
Study Design/Description:	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. <u>Dose Escalation Rules</u> 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. In the event that important safety concerns are observed at any time during the study, administration of study drug will be paused, subjects in the subsequent cohort(s) will not receive further study drug until further review of the safety data has occurred, and subsequent recommendations and approval have been provided by the SRC.
Study Population:	<u>Inclusion Criteria</u>: Subjects must meet all of the following inclusion criteria to be eligible for this study: 1. Male and females, 18 to 65 years of age, inclusive, at time of Screening. a. Female subjects of childbearing potential must not be breastfeeding and must have no plans to become pregnant during the course of the study through 120 days after infusion of study drug. Female subjects of childbearing potential who are heterosexual must agree to use 1 of the following methods of contraception considered to be highly effective (i.e., results in < 1% failure rate when used consistently and correctly) from Screening through 120 days after the last dose of study drug:

	• Intrauterine device or intrauterine system in place for at least 3 months prior to first dose. • Partner has had a vasectomy ≥ 4 months prior to participation. Vasectomy in the partner is considered to be highly effective only if the partner is the sole sexual partner of the female subject of child-bearing potential and the vasectomy (as communicated to the subject by the vasectomized partner) was medically assessed as surgically successful. • Stable hormonal contraception associated with inhibition of ovulation (including by not limited to approved oral, transdermal, or depot regimen) for at least 3 months prior to first dose. b. Female subjects of non-childbearing potential must have evidence from their medical history indicating that they are not of childbearing potential and must not currently be breastfeeding. Accepted evidence (self-reported medical history is acceptable) includes: • History of sterilization surgery, including tubal ligation, tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy. • Postmenopausal status (12 months with no menses and no alternative cause). Postmenopausal status will be confirmed with a follicle-stimulating hormone (FSH) test at Screening (FSH > 40 mIU/mL). If there is any doubt about a female subject's post-menopausal status the subject must use a form of highly effective birth control as noted in Inclusion Criterion 1a. 2. Any non-vasectomized male subjects must agree to use barrier contraceptives (male or female partner condom, diaphragm, cervical cap, sponges) plus spermicide for 200 days after dosing. No restrictions are required for a vasectomized male provided his vasectomy was performed 4 months or more prior to study start. A male who has been vasectomized less than 4 months prior to study start must follow the same restrictions as a non-vasectomized male. 3. Males must not donate sperm for at least 200 days after dosing. 4. Female subjects must agree not to donate or preserve eggs (ova) for 120 days after dosing. 5. Medically healthy with no clinically significant or relevant abnormalities in medical history, physical exam, vital signs, ECG, or laboratory evaluations (hematology, chemistry, and urinalysis) as assessed by the Investigator. At the Investigator's discretion, laboratory evaluations may be repeated at Screening or Baseline (pre-dose) to assess clinical significance of abnormalities prior to dosing. 6. Confirmed to have acceptable venous access for blood collections and IV dosing administration of study medication. 7. Has provided written informed consent. 8. Body mass index is between 18 and 32 kg/m^2 (inclusive).

	9. Screening magnetic resonance imaging (MRI) reveals normal appearance of the brain parenchyma, normal spacing of ventricular system and cisternal spaces and is without any significant abnormality, including, but not limited to evidence of prior microhemorrhages, lacunar infarcts, hemorrhage, or infarct > $1cm^3$, cerebral contusion, encephalomalacia, aneurysm, vascular malformation, subdural hematoma, hydrocephalus, space occupying lesion (e.g., abscess or brain tumor such as meningioma).
	Exclusion Criteria: Subjects having any of the following exclusion criteria are not eligible for this study: 1. Current or recurrent disease (e.g., cardiovascular, neurological, renal, liver, gastrointestinal, malignancy, autoimmune disease, or other condition) that could affect the action, absorption or disposition of the investigational product, or could affect clinical or laboratory assessments. 2. Clinically significant 12-lead ECG abnormality at Screening. QT interval corrected by Fridericia (QTcF) > 450 milliseconds. ECG may be repeated from the first one collected at Screening. If repeat ECG is ≤ 450 msec, the second ECG may be used to determine subject eligibility. However, if repeat ECG confirms QTcF > 450 msec, the subject is not eligible for this study. 3. Systolic blood pressure > 150 bpm or diastolic blood pressure > 90 bpm (measured in supine position after 5 minutes of rest) at Screening. Blood pressure may be repeated from the first assessment collected at Screening. If repeat systolic blood pressure ≤ 150 bpm or diastolic blood pressure ≤ 90 bpm, the second blood pressure may be used to determine subject eligibility. 4. Experienced a significant systemic illness, as judged by the Investigator, within 30 days of the first dose of study drug. 5. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures. 6. Currently using any medication (including over-the-counter or herbal, homeopathic preparations) except for acetaminophen as needed for miscellaneous aches and pains. 7. History of alcohol abuse and/or illicit drug use within 12 months prior dosing or a smoking history (use of tobacco products). 8. Unwilling to refrain from ingesting alcohol from Screening through Day 15 and unwilling to limit alcohol use to ≤ 7 drinks per week from Day 15 for the duration of the study; 1 drink is 5 ounces (150 mL) of wine, 12 ounces (360 mL) of beer, or 1.5 ounces (45 mL) of hard liquor. 9. Positive urine drug screen for drugs of abuse or cotinine, or positive serum alcohol at Screening or Day -1.

	10. Any significant concomitant disorder, including active bacterial, fungal, or viral infection, incompatible with participation in the study. 11. History of prior malignancy (except adequately treated non-melanoma skin cancer or carcinoma in-situ of the cervix). 12. Documented history of human immunodeficiency virus (HIV) antibody, or tested positive for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody at Screening. 13. Donated blood or blood products (e.g., plasma, platelets) within 28 days prior to first dose. 14. Received an investigational agent within the last 30 days or 5-half-lives (if known) prior to Screening, whichever is longer. 15. Contraindication to brain MRI. 16. Contraindication to undergoing LP including: sensitivity to local anesthetic, international normalized ratio (INR) > 1.4 or other coagulopathy, platelet cell count of < 120,000/μL, infection at the desired LP site, current use of anti-coagulant medication except for low dose aspirin, degenerative arthritis, spinal scoliosis, back surgery, suspected increased intracranial pressure on history or neurologic exam, non-communicating hydrocephalus or intracranial mass, or prior history of spinal mass or trauma and/or other known clinically significant spinal abnormalities. 17. Inability to undergo venipuncture or tolerate venous access. 18. Indication of potential suicidality risk as identified by the following: a. Lifetime history of recurrent serious or recurrent suicide behavior. b. History of suicide behavior in the past "5" years as indicated by a "yes" response to any suicide behavior question on the Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline – Screening version c. Suicidal ideation with intent or plan within the previous "12" months with a "yes" response to Item 4 or 5 on the C-SSRS Baseline – Screening version 19. Any of the following: clinically significant abnormalities on vital signs, physical exam, or laboratory testing at Screening and Baseline (pre-dose) per Investigator discretion.
Planned Sample Size:	40 subjects in 5 cohorts (8 subjects per cohort); Cohort 5 2800mg will be optional
Investigational Product, Dose, and Mode of Administration:	PMN310 will be administered as a single IV infusion over 60 minutes in 0.9% NaCl, adjusted to a total volume of 100 mL, followed by a 15 minute 0.9% NaCl flush. The following dose levels are planned to be evaluated: 175 mg (starting dose level), 350 mg, 700 mg, 1400 mg, and 2800 mg (optional cohort). Additional dose levels may be added to explore intermediate doses in lieu of the predefined doses. Any intermediate doses will be selected in accordance with the safety and tolerability data reviewed by the SRC, and will not exceed a single dose of 2800 mg.

Reference Therapy, Dose and Mode of Administration:	Placebo will consist of 100 mL 0.9% NaCl and will be administered as a matching single IV infusion over 60 minutes, followed by a 15 minute 0.9% NaCl flush.
Duration of Study:	Enrolled subjects are expected to be in the study for approximately 16 weeks including a screening period (up to 4 weeks), an inpatient single dose and observation period (5 days), and a postdose outpatient follow-up period (12 weeks). Subjects may return 5 weeks after completion of the postdose outpatient follow-up period for an optional follow-up visit.
Criteria for Evaluation:	<u>Safety:</u> • Vital signs • MRI evaluations will be performed at Screening for all subjects and at Day 43 for subjects ≥ 50 years of age to assess for amyloid-related imaging abnormalities (ARIA). If ARIA is detected, MRIs will be repeated every 3-4 weeks until there is resolution, regardless of whether or not the subject is symptomatic. MRIs will be read at an independent central reading laboratory after screening of the first two sentinel subjects for Cohort 1 (age < 50) who will have MRIs performed and read locally. • Sequences will include: ○ MRI T2-weighted fluid-attenuated inversion recovery (T2/FLAIR) sequence to detect amyloid-related imaging abnormalities characterized by vasogenic edema or sulcal effusions (ARIA-E) ○ MRI gradient recalled echo (GRE) sequence to detect amyloid-related imaging abnormalities characterized by parenchymal microhemorrhages or sulcal/leptomeningeal hemosiderin deposits (ARIA-H) ○ Diffusion weighted imaging (DWI) sequence can help differentiate ARIA-E from potential cytotoxic edema as may be noted with an incidental acute to subacute infarct • ECGs • Laboratory test results • Physical examinations • Neurologic examinations • AEs/serious adverse events (SAEs) • Serum ADA • C-SSRS
	<u>Pharmacokinetic:</u> • Serum PMN310 concentrations will be measured throughout the study to characterize standard PK parameters using non-compartmental methods (e.g., C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, Vd, and CL) • CSF will be collected for drug concentrations

	Biomarkers and ADAs • Serum and CSF samples will be obtained for measurement of biomarkers and serum samples for ADAs
	Exploratory • Incidence and titers of ADAs • Residual and unused serum and CSF samples will be stored for future use for the measurement of biomarkers
Statistical Methods:	Determination of Sample Size The sample size of this study is not based on statistical considerations; [redacted] Statistical Analyses A formal statistical analysis plan will be developed and finalized prior to unblinding the data. This plan will define the healthy population for analysis, outline all data handling conventions, and specify all statistical methods to be used for analysis of the data. Safety and tolerability results from this study will be assessed using summary statistics by cohort (e.g., n, mean, median, minimum, maximum, for continuous endpoints; n and % for binary and categorical endpoints). All placebo subjects from the different cohorts will be combined into a single group for summary purposes. PK parameters will be summarized by cohort using descriptive statistics (e.g., n, arithmetic means, geometric means, standard deviation, % coefficient of variation, median, minimum, and maximum). Figures will be created to display mean and individual subject PMN310 concentration time curves in serum on both a linear and logarithmic scale. Dose proportionality will be assessed using linear regression, or another acceptable approach. The outcomes of this first in human study will be used for dose selection and preliminary statistical power calculations for subsequent studies in patients with AD.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Aβ	amyloid-beta
AβO	Aβ oligomers
AD	Alzheimer's disease
ADA	antidrug antibody
AE	adverse event
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality-edema
ARIA-H	amyloid-related imaging abnormality-microhemorrhage
AUC	area under the curve
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_{last}	area under the curve to the last timepoint
CL	clearance
C_{max}	maximum observed concentration
CRF	case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
DWI	diffusion weighted imaging
ECG	electrocardiogram
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GRE	gradient recalled echo
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HED	human equivalent dose

Abbreviation	Definition
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference for Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
LP	lumbar puncture
MABEL	minimal anticipated biological effect level
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
PAD	pharmacologically active dose
PK	pharmacokinetic
PT	prothrombin time
PTT	partial thromboplastin time
QTcF	QT interval corrected by Fridericia
SAE	serious adverse event
SD	standard deviation
SPR	surface plasma resonance
SRC	Safety Review Committee
$t_{1/2}$	terminal half-life
T2/FLAIR	T2-weighted fluid-attenuated inversion recovery
T_{max}	time to C_{max}
Vd	volume of distribution

1. INTRODUCTION

1.1. Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease representing the most common cause of dementia, accounting for approximately 60% to 80% of all dementia cases (World Health Organization, 2023). Early AD includes a diverse set of signs and symptoms such as memory loss that may disrupt daily life, poor judgement, misplacing or losing things, mood or personality changes, increased anxiety or aggression, taking longer to complete daily tasks, etc. (Alzheimer's Association, 2020; National Institute on Aging, 2022). As the disease progresses inexorably, language deterioration, disorientation, poor judgment, confusion, and behavioral changes develop. Eventually AD destroys cognition, personality, and the ability to attend to activities of daily living. The early symptoms of AD, especially at the early stage of mild cognitive impairment, are often missed because they are frequently and mistakenly taken for 'natural signs of aging'.

There is no cure for AD and most approved therapies are aimed at treating symptoms and enhancing cognition. Current treatments largely comprise 2 major product categories, namely, acetyl cholinesterase inhibitors (donepezil, rivastigmine, galantamine), and an N-methyl-D-aspartate receptor antagonist (memantine). Two drugs with disease-modifying potential are currently approved, the monoclonal antibody Aduhelm® (aducanumab) (Aduhelm Prescribing Information, 2022) and Leqembi™ (lecanemab) (LEQEMBI™ Prescribing Information, 2023) were approved based on reduction in amyloid-beta (Aβ) plaques. There have been no antibodies approved that display selectivity for toxic amyloid-beta oligomers (AβO), while avoiding binding to either Aβ monomers or plaque.

1.1.1. Monoclonal Antibody Therapy in Alzheimer's Disease

Evidence from genetic and experimental studies supports a causative role for Aβ peptide in the pathogenesis of AD. Views on the nature of the Aβ species responsible for progressive neurodegeneration have evolved considerably along with a greater understanding of AD disease biology. While the presence of Aβ plaque is a hallmark of AD, it is increasingly recognized that the synaptic loss and neurodegenerative spread of AD is primarily mediated by soluble oligomers of misfolded Aβ rather than plaque (Cline et al., 2018). It is believed that a subset of misfolded AβO can propagate in a prion-like manner and form a seed or template capable of converting surrounding Aβ into the toxic oligomer form (Cline et al., 2018; Jucker & Walker, 2013). There is also evidence that toxic misfolded AβO can catalyze the misfolding of tau, another protein involved in the pathogenesis of AD (Jin et al., 2011). Targeting of AβO with selective antibodies, therefore, represents a strategy to inhibit progression of the neurodegenerative Aβ-tau cascade.

Targeting of AβO is supported by recent results of clinical trials with therapeutic monoclonal antibodies targeting AβO (van Dyck, 2023). Antibodies that bind Aβ monomers (e.g., solanezumab and crenezumab) showed a lack of efficacy (Cummings et al., 2018; Doody et al., 2014) suggesting that high selectivity for low abundance toxic AβO is desirable to prevent monoclonal antibodies from being consumed by unproductive binding to non-pathogenic, abundant monomers (target distraction). Other antibodies with reduced binding to monomers and greater selectivity for aggregated forms of Aβ produced more promising results:

aducanumab (Aduhelm) showed evidence of cognitive benefit in Phase 3 trials and received accelerated approval (Aduhelm Prescribing Information, 2022); lecanemab (Leqembi[redacted]) ([redacted] Prescribing Information, 2023) was approved based on reduction in [redacted] Donanemab also produced positive Phase 2 and 3 results [redacted] (Mintun et al., 2021; Swanson et al., 2021). While these antibodies partially [redacted] dose-limiting adverse events (AEs) of amyloid-related imaging abnormalities (ARIA) characterized by vasogenic edema or sulcal effusions (ARIA-E) and amyloid-related imaging abnormalities characterized by parenchymal microhemorrhages or sulcal/leptomeningeal hemosiderin deposits (ARIA-H) (Mintun et al., 2021; Swanson et al., 2021). Further [redacted]-selective antibodies capable of avoiding diversion by non-toxic monomers and avoiding binding to [redacted] educe the risk of ARIA. [redacted]-specific antibody has been described by Acumen, ACU193, a humanized immunoglobulin (Ig) G2 monoclonal antibody which initiated Phase 1 studies in June 2021 (ACU193 Overview Alzforum, 2022).

1.2. PMN310

[redacted]

1.2.1. Nonclinical Studies

[redacted]

[redacted]

[redacted] See the Investigator's Brochure for further details.

1.3. Study Rationale

[redacted] AβOs [redacted] Aβ [redacted]

This first-in-human (FIH) study aims to establish the safety, tolerability, pharmacokinetics (PK), and biomarkers of a single IV infusion of PMN310 in healthy volunteers.

1.4. Rationale for Dose Selection

[redacted]

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

[redacted]

[redacted] Planned doses include 175 mg, 350 mg, 700 mg, 1400 mg and 2800 mg (optional). Additional dose levels may be added to explore intermediate doses in lieu of the predefined doses. Any intermediate doses will be selected in accordance with the safety and tolerability data reviewed by the Safety Review Committee (SRC), and will not exceed a single dose of 2800 mg.

1.5. Benefit-Risk Assessment

PMN310 has not yet been evaluated in humans and the predicted safety and toxicology findings can only be garnered by the completed GLP-compliant toxicology studies in non-human primates. [redacted]

The safety of PMN310 will be assessed throughout the study by monitoring AEs, using criteria proposed by Sibille et al., 2010, clinical laboratory assessments, vital sign measurements, physical and neurological examinations, 12-lead ECG measurements, and magnetic resonance imaging (MRI) evaluations.

There are no expected direct health benefits to subjects in Study PMN310-101. The safety, tolerability, and PK data collected in Study PMN310-101 will provide initial data supporting the evaluation of PMN310 in patients with AD.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

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

2.1.2. Secondary Objectives

- To assess the single dose PK of PMN310

2.1.3. Exploratory Objectives

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

2.2. Study Endpoints

2.2.1. Primary Endpoints

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

2.2.2. 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

2.2.3. Exploratory Endpoints

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

3. STUDY DESIGN

3.1. Design Characteristics

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.

A detailed summary of the schedule of events is available in Appendix 1.

3.1.1. Dose Escalation Rules

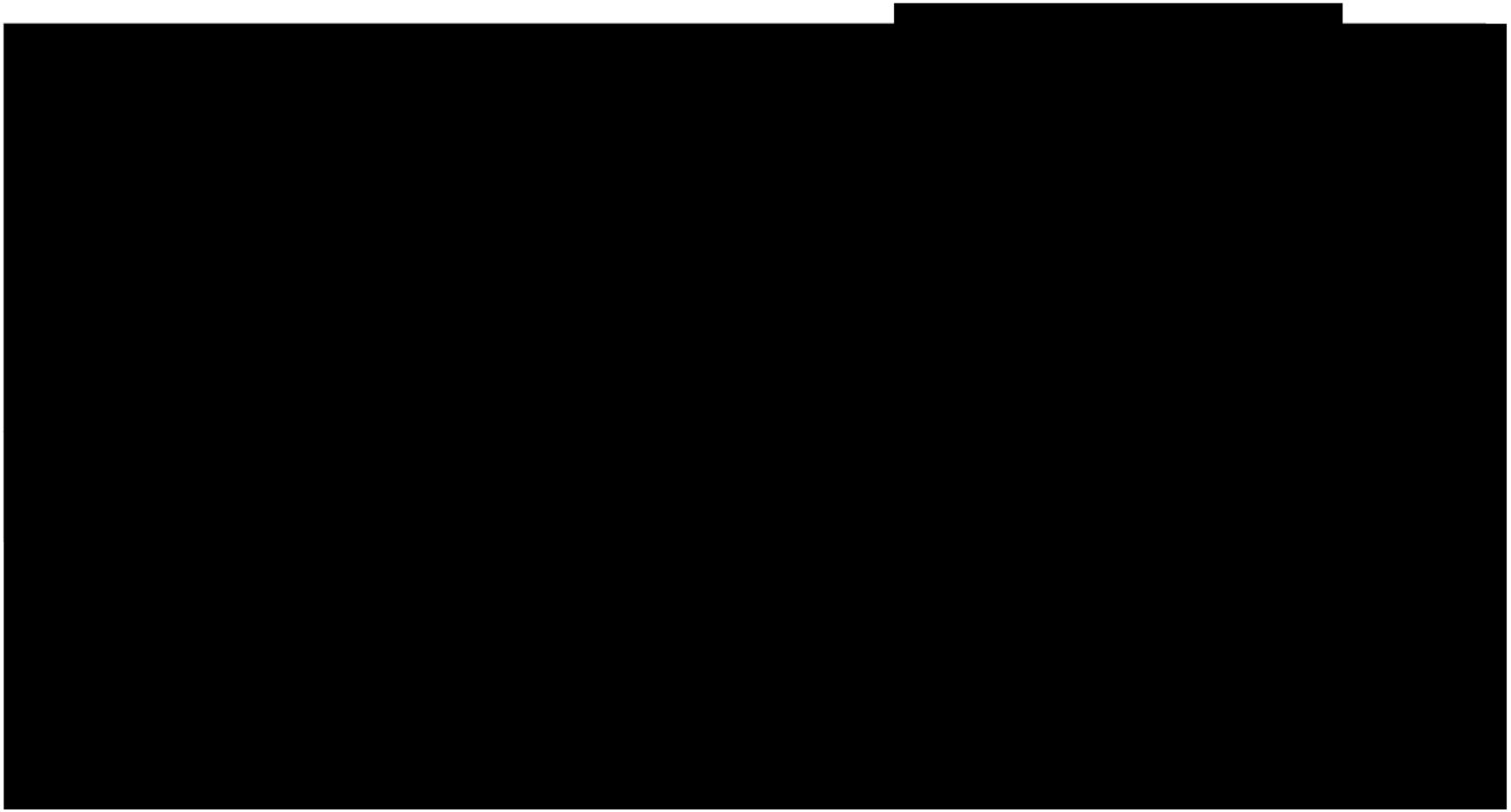
Each dose cohort will consist of 8 subjects (6:2; PMN310:placebo). To evaluate the short term safety and tolerability of PMN310, each cohort will enroll a sentinel group of 2 subjects (1:1, PMN310:placebo) who will be dosed prior to dosing the remaining 6 subjects in the cohort (5:1, PMN310:placebo). The first two sentinel subjects for Cohort 1 (age < 50) will have MRIs performed and read locally. The 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. Additional details on the SRC are provided in Section 3.1.2.

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. Doses to be evaluated are presented in Section 5.2.1.

In the event that important safety concerns are observed at any time during the study, administration of study drug will be paused, subjects in the subsequent cohort(s) will not receive further study drug until further review of the safety data has occurred, and subsequent recommendations and approval have been provided by the SRC. Dose escalation/stopping rules are detailed in Section 5.5.

A schematic illustrating the study design is provided in Figure 1.

Figure 1: PMN310-101 Study Schema Per Cohort



3.1.2. 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 post-dose 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.

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for this study:

1. Male and females, 18 to 65 years of age, inclusive, at time of Screening.
    a. Female subjects of childbearing potential must not be breastfeeding and must have no plans to become pregnant during the course of the study through 120 days after infusion of study drug. Female subjects of childbearing potential who are heterosexual must agree to use 1 of the following methods of contraception considered to be highly effective (i.e., results in < 1% failure rate when used consistently and correctly) from Screening through 120 days after the last dose of study drug:
        – Intrauterine device or intrauterine system in place for at least 3 months prior to first dose.
        – Partner has had a vasectomy ≥ 4 months prior to participation. Vasectomy in the partner is considered to be highly effective only if the partner is the sole sexual partner of the female subject of child-bearing potential and the vasectomy (as communicated to the subject by the vasectomized partner) was medically assessed as surgically successful.
        – Stable hormonal contraception associated with inhibition of ovulation (including by not limited to approved oral, transdermal, or depot regimen) for at least 3 months prior to first dose.
    b. Female subjects of non-childbearing potential must have evidence from their medical history indicating that they are not of childbearing potential and must not currently be breastfeeding. Accepted evidence (self-reported medical history is acceptable) includes:
        – History of sterilization surgery , including tubal ligation, tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy.
        – Postmenopausal status (12 months with no menses and no alternative cause). Postmenopausal status will be confirmed with a follicle-stimulating hormone (FSH) test at Screening (FSH > 40 mIU/mL). If there is any doubt about a female subject's post-menopausal status the subject must use a form of highly effective birth control as noted in Inclusion Criterion 1a.
2. Any non-vasectomized male subjects must agree to use barrier contraceptives (male or female partner condom, diaphragm, cervical cap, sponges) plus spermicide for 200 days after dosing. No restrictions are required for a vasectomized male provided his vasectomy was performed 4 months or more prior to study start. A male who has been vasectomized less than 4 months prior to study start must follow the same restrictions as a non-vasectomized male.
3. Males must not donate sperm for at least 200 days after dosing.

4. Female subjects must agree not to donate or preserve eggs (ova) for 120 days after dosing.
5. Medically healthy with no clinically significant or relevant abnormalities in medical history, physical exam, vital signs, ECG, or laboratory evaluations (hematology, chemistry, and urinalysis) as assessed by the Investigator. At the Investigator's discretion, laboratory evaluations may be repeated at Screening or Baseline (pre-dose) to assess clinical significance of abnormalities prior to dosing.
6. Confirmed to have acceptable venous access for blood collections and IV dosing administration of study medication.
7. Has provided written informed consent.
8. Body mass index is between 18 and 32 kg/m^2 (inclusive).
9. Screening MRI reveals normal appearance of the brain parenchyma, normal spacing of ventricular system and cisternal spaces and is without any significant abnormality, including, but not limited to evidence of prior microhemorrhages, lacunar infarcts, hemorrhage, or infarct > $1cm^3$, cerebral contusion, encephalomalacia, aneurysm, vascular malformation, subdural hematoma, hydrocephalus, space occupying lesion (e.g., abscess or brain tumor such as meningioma).

4.2. Exclusion Criteria

Subjects having any of the following exclusion criteria are not eligible for this study:

1. Current or recurrent disease (e.g., cardiovascular, neurological, renal, liver, gastrointestinal, malignancy, autoimmune disease, or other condition) that could affect the action, absorption or disposition of the investigational product, or could affect clinical or laboratory assessments.
2. Clinically significant 12-lead ECG abnormality at Screening. QT interval corrected by Fridericia (QTcF) > 450 milliseconds. ECG may be repeated from the first one collected at Screening. If repeat ECG is ≤ 450 msec, the second ECG may be used to determine subject eligibility. However, if repeat ECG confirms QTcF > 450 msec, the subject is not eligible for this study.
3. Systolic blood pressure > 150 bpm or diastolic blood pressure > 90 bpm (measured in supine position after 5 minutes of rest) at Screening. Blood pressure may be repeated from the first assessment collected at Screening. If repeat systolic blood pressure ≤ 150 bpm or diastolic blood pressure ≤ 90 bpm, the second blood pressure may be used to determine subject eligibility.
4. Experienced a significant systemic illness, as judged by the Investigator, within 30 days of the first dose of study drug.
5. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures.
6. Currently using any medication (including over-the-counter, herbal or homeopathic preparations) except for acetaminophen as needed for miscellaneous aches and pains.

7. History of alcohol abuse and/or illicit drug use within 12 months prior dosing or a smoking history (use of tobacco products).
8. Unwilling to refrain from ingesting alcohol from Screening through Day 15 and unwilling to limit alcohol use to ≤ 7 drinks per week from Day 15 for the duration of the study; 1 drink is 5 ounces (150 mL) of wine, 12 ounces (360 mL) of beer, or 1.5 ounces (45 mL) of hard liquor.
9. Positive urine drug screen for drugs of abuse or cotinine, or positive serum alcohol at Screening or Day -1.
10. Any significant concomitant disorder, including active bacterial, fungal, or viral infection, incompatible with participation in the study.
11. History of prior malignancy (except adequately treated non melanoma skin cancer or carcinoma in-situ of the cervix).
12. Documented history of human immunodeficiency virus (HIV) antibody, or tested positive for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody at Screening.
13. Donated blood or blood products (e.g., plasma, platelets) within 28 days prior to first dose.
14. Received an investigational agent within the last 30 days or 5 half-lives (if known) prior to Screening, whichever is longer.
15. Contraindication to brain MRI.
16. Contraindication to undergoing LP including: sensitivity to local anesthetic, international normalized ratio (INR) > 1.4 or other coagulopathy, platelet cell count of < 120,000/µL, infection at the desired LP site, current use of anti-coagulant medication except for low dose aspirin, degenerative arthritis, spinal scoliosis, back surgery, suspected increased intracranial pressure on history or neurologic exam, non-communicating hydrocephalus or intracranial mass, or prior history of spinal mass or trauma and/or other known clinically significant spinal abnormalities.
17. Inability to undergo venipuncture or tolerate venous access.
18. Indication of potential suicidality risk as identified by the following:
    a. Lifetime history of recurrent serious or recurrent suicide behavior.
    b. History of suicide behavior in the past “5” years as indicated by a “yes” response to any suicide behavior question on the Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline – Screening version.
    c. Suicidal ideation with intent or plan within the previous “12” months with a “yes” response to Item 4 or 5 on the C-SSRS Baseline – Screening version.
19. Any of the following: clinically significant abnormalities on vital signs, physical exam, or laboratory testing at Screening and Baseline (pre-dose) per Investigator discretion.

5. STUDY TREATMENTS

5.1. Identification and Description of Study Drug

5.1.1. PMN310

[redacted]

Additional information about PMN310 drug product is available in the Investigator's Brochure.

5.1.2. Placebo

Placebo will consist of 100 mL 0.9% NaCl.

5.2. Study Drug Preparation and Administration

5.2.1. PMN310

Study medication will be prepared at the study clinic by an unblinded pharmacist (or designee) based on an individual subject's randomization or assigned treatment. Once prepared, blinded IV drug for infusion will be dispensed to staff who will administer study drug. Specific instructions for preparation and administration of study medication will be provided in the Pharmacy Manual.

PMN310 will be administered as a single IV infusion over 60 minutes in 0.9% NaCl, adjusted to a total volume of 100 mL, followed by a 15 minute 0.9% NaCl flush. The complete infusion will consist of the IV infusion and the flush following the IV infusion.

The following dose level cohorts are planned to be evaluated: 175 mg (starting dose level), 350 mg, 700 mg, 1400 mg, and 2800 mg (optional cohort). The rationale for selecting these dose levels is provided in Section 1.4.

5.2.2. Placebo

Placebo will be administered as a matching single IV infusion over 60 minutes, followed by a 15 minute 0.9% NaCl flush. The complete infusion will consist of the IV infusion and the flush following the IV infusion.

5.3. Randomization and Blinding

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). 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.

5.4. 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. The applicable standard operating procedures (SOPs) will be followed for breaking the blind.

5.5. Dose Escalation/Stopping Rules

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.

5.6. Storage, Handling, and Accountability of Study Drug

PMN310 will be supplied directly to the study site. The study site will acknowledge receipt of the shipment and record inventory and usage of study drug on a drug disposition form. Upon arrival at the study site, vials will be stored frozen at -25ºC to -15ºC (-13°F to 5°F) inside the cartons to minimize exposure to light, with the cartons oriented such that the enclosed vials are in the upright position. An unblinded study monitor will perform reconciliation of the drug product.

Used vials will be destroyed according to the site's policy for investigational drug destruction. Unused vials will be either destroyed at the study site or returned to the Sponsor, as agreed between the site and Sponsor. Before disposal/destruction of unused vials, final drug accountability and reconciliation must be performed by the unblinded study monitor. Documentation of destruction of vials of PMN310 must be available for review by the study monitor.

5.7. Prior and Concomitant Therapy

5.7.1. Prohibited Medications

All medications, including over-the-counter, herbal, or homeopathic preparations (except for acetaminophen as needed for miscellaneous aches and pains), are prohibited during the study, unless required to be administered for the treatment of an AE. Subjects receiving a stable dose of medications for high blood pressure or high cholesterol may be included with Sponsor approval.

6. STUDY PROCEDURES BY PERIOD

The scheduled assessments for Screening, Inpatient, and Outpatient periods are summarized in Appendix 1.

For each study day described below, when multiple procedures are scheduled at the same nominal time relative to dosing, the following chronology of events should be adhered to, where possible:

- Vital signs and ECGs will be obtained as close as possible to the scheduled time (up to 45 minutes before PK sampling), but before blood specimen collection.
- Serum PK samples will be obtained at the scheduled time.
- After venipuncture, PK samples will be obtained first followed by clinical safety laboratory tests.

In the case of a clinical or laboratory abnormality, the Investigator may apply clinical judgement in repeating the measurement if the abnormality is believed likely to be an error.

6.1. Screening Period (Day -28 to Day -1)

Healthy volunteers will be recruited for this clinical study. Before initiation of screening assessments, the subject must be given a complete explanation of the purpose and procedures occurring during the study. Subsequently, the subject must sign and receive a copy of an Institutional Review Board (IRB)-approved informed consent form (ICF) (Section 11.4). Once informed consent has been obtained, screening assessments will be performed and eligibility of the subject will be determined based on the inclusion and exclusion criteria. Subjects who fail screening may be rescreened following Sponsor approval.

Study assessments are described in Section 7.

The following evaluations will be performed to assess the subject's eligibility for the study:

- Demography and medical history
- Suicidality evaluation: C-SSRS (Baseline - Screening version)
- Height
- Complete physical examination
- Neurologic examination
- Vital signs
- Weight
- MRI
- Lumbar x-rays (at investigator's discretion to rule out any contraindication to lumbar puncture)
- 12-lead ECG
- HBsAg and HCV tests

- FSH (post-menopausal women only)
- Pregnancy test (non-post-menopausal women only)
- Urine drug, urine cotinine, and serum alcohol screen
- Clinical laboratory tests:
  - Blood chemistry and hematology
  - Urinalysis
  - Coagulation
- Review of concomitant medications
- AE assessment of protocol related procedures only, to be performed after informed consent is obtained

The Investigator may use clinical judgment when determining the clinical significance of laboratory results throughout the study. The Medical Monitor may, depending on study criteria, be consulted before enrollment of a candidate with abnormal laboratory values.

6.2. Inpatient Period (Days -1, 1, 2, 3, and 4)

During the inpatient period, standardized breakfast, lunch, and dinner will be provided at fixed times. Meals are to be consumed within 45 minutes. Evening snacks will be provided at a consistent time each day. Fluids will be allowed liberally.

6.2.1.1. Day -1 (Day of Admission to the Study Clinic)

On Day –1 eligibility will be confirmed and eligible subjects will be admitted to the study clinic. Admission should occur before 6 PM.

The following assessments will be performed:

- Complete physical examination
- Neurologic examination
- Vital signs
- Weight
- 12-lead ECG
- Pregnancy test (non-post-menopausal women only)
- Urine drug, urine cotinine, and serum alcohol screen
- Clinical laboratory tests:
  - Blood chemistry and hematology
  - Urinalysis
  - Coagulation
- ADA serum sampling

- Residual and unused serum samples will be stored for future use for the measurement of biomarkers
- Review of concomitant medications
- AE assessment of protocol related procedures only

The subject will remain in the study clinic overnight.

6.2.1.2. Day 1 (Day of Study Drug Administration)

Subjects will be randomly assigned to study drug (PMN310 or placebo). After consumption of a standard breakfast, and pre-dosing assessments, study drug will be administered as an IV infusion as described in Section 5.2. After administration of study drug, inpatient follow-up data collection will include the following:

- C-SSRS (Since Last Visit version)
- Vital signs
- 12-lead ECG
- PK serum sampling: before infusion, at the end of infusion (see 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.
  - 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
- Review of concomitant medications
- AE assessment

The subject will remain in the study clinic overnight.

6.2.1.3. Day 2

On Day 2, subjects will undergo the following assessments:

- Vital signs
- 12-lead ECG
- PK serum sampling at 24 and 36 hours from end of Day 1 infusion
  - Acceptable windows for PK sampling are ± 30 minutes (exact time of PK collection is to be recorded)
- Review of concomitant medications
- AE assessment

The subject will remain in the study clinic overnight.

6.2.1.4. Day 3

On Day 3 subjects will undergo the following assessments:

- Symptom directed physical examination
- Neurologic examination
- Vital signs
- Weight
- 12-lead ECG
- Clinical laboratory tests:
  - Blood chemistry and hematology
  - Urinalysis
  - Coagulation
- PK serum sampling 72 hours from end of Day 1 infusion
  - Acceptable window for PK sampling is ± 60 minutes (exact time of PK collection is to be recorded)
- LP. INR/PT/partial thromboplastin time (PTT) and platelet results within 2 days prior to the LP must be confirmed and determined to be within normal range before LP.
- Review of concomitant medications
- AE assessment

The subject will remain in the study clinic overnight.

6.2.1.5. Day 4

On Day 4, subjects will undergo the following assessments:

- C-SSRS (Since Last Visit version)
- Vital signs
- PK serum sampling 96 hours from end of Day 1 infusion
  - Acceptable window for PK sampling is ± 60 minutes (exact time of PK collection is to be recorded)
- Review of concomitant medications
- AE assessment

Following the completion of assessments, unless the Investigator feels that a longer period of observation is warranted (e.g., due to side effects of the study drug or any study procedure), subjects will be discharged from the study clinic.

6.2.2. Outpatient Period (Days 8, 15, 29, 43, 57, and 85)

Subjects will return to the study site for follow-up outpatient visits on Days 8, 15, 29, 43, 57, and 85.

6.2.2.1. Day 8

On Day 8 (±1 day), subjects will undergo the following assessments:

- Vital signs
- 12-lead ECG
- Pregnancy test (non-post-menopausal women only)
- Urine drug, urine cotinine, and serum alcohol screen
- Clinical laboratory tests:
  - Blood chemistry and hematology
  - Urinalysis
  - Coagulation
- PK serum sampling
- Review of concomitant medications
- AE assessment

6.2.2.2. Day 15

On Day 15 (±1 day), subjects will undergo the following assessments:

- Vital signs
- Clinical laboratory tests:
  - Blood chemistry and hematology
  - Urinalysis
  - Coagulation
- PK serum sampling
- Possible LP. INR/ PT/PTT and platelet results within 2 days prior to the LP must be confirmed and determined to be within normal range before LP.
  - 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
- Review of concomitant medications
- AE assessment

6.2.2.3. Day 29

On Day 29 (±3 days), subjects will undergo the following assessments:

- C-SSRS (Since Last Visit version)
- Symptom directed physical examination
- Neurologic examination
- Vital signs
- Weight
- 12-lead ECG
- Clinical laboratory tests:
  - Blood chemistry and hematology
  - Urinalysis
  - Coagulation
- PK serum sampling
- ADA serum sampling
- Note: Residual and unused serum and CSF samples will be stored for future use for the measurement of biomarkers LP. INR/PT/PTT and platelet results within 2 days prior to the LP must be confirmed and determined to be within normal range before LP.
  - 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
- Review of concomitant medications
- AE assessment

6.2.2.4. Day 43

On Day 43 (±3 days), subjects will undergo the following assessments:

- Vital signs
- MRI (subjects > 50 years of age only). If ARIA is detected, subjects will return for additional MRI assessments every 3-4 weeks until the ARIA resolves.
- Clinical laboratory tests:
  - Blood chemistry and hematology
  - Urinalysis
  - Coagulation

- PK serum sampling
- Review of concomitant medications
- AE assessment

6.2.2.5. Day 57

On Day 57 (±3 days), subjects will undergo the following assessments:

- C-SSRS (Since Last Visit version)
- Vital signs
- Clinical laboratory tests:
  - Blood chemistry and hematology
  - Urinalysis
  - Coagulation
- PK serum sampling
- ADA serum sampling
- Note: Residual and unused serum and CSF (if applicable) samples will be stored for future use for the measurement of biomarkers Possible LP. INR/ PT/PTT and platelet results within 2 days prior to the LP must be confirmed and determined to be within normal range before LP.
  - 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
- Review of concomitant medications
- AE assessment

6.2.2.6. Day 85

On Day 85 (±4 days), subjects will undergo the following assessments:

- C-SSRS (Since Last Visit version)
- Symptom directed physical examination
- Neurologic examination
- Vital signs
- Weight
- 12-lead ECG
- Pregnancy test (non-post-menopausal women only)
- Urine drug, urine cotinine, and serum alcohol screen

- Clinical laboratory tests:
  - Blood chemistry and hematology
  - Urinalysis
  - Coagulation
- PK serum sampling
- ADA serum sampling
- Note: Residual and unused serum and CSF samples (if applicable) will be stored for future use for the measurement of biomarkers Possible LP. INR/ PT/PTT and platelet results within 2 days prior to the LP must be confirmed and determined to be within normal range before LP.
  - 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
- Review of concomitant medications
- AE assessment

6.2.3. Optional Follow-Up Visit – Day 120

The Day 120 visit (± 7 days) is optional. Subjects who elect to participate in the Day 120 visit will undergo the following assessments:

- PK serum sampling
- ADA serum sampling
- Note: Residual and unused serum samples will be stored for future use for the measurement of biomarkers

6.3. Early Termination

If a subject cannot complete the entire study, efforts will be made to collect all prespecified assessments for Day 85 (Appendix 1), if possible. If a subject withdraws consent before early termination no further procedures should be performed and no additional data should be collected. The Sponsor may retain and continue to use any data collected before the withdrawal of consent.

7. DESCRIPTION OF STUDY PROCEDURES

Study assessments and procedures are to be performed on the schedule outlined in Appendix 1 and listed by visit in Section 6.

Additional details for selected study procedures are provided in the sections below.

7.1.1. Demography and Medical History

Relevant medical conditions, concomitant illness, surgeries within the 6 months before Screening should be documented. For female subjects, the last menstrual period should be recorded.

7.1.2. Columbia-Suicide Severity Rating Scale

The C-SSRS is an interview with the subject that systematically evaluates suicidal ideation and behavior. The C-SSRS (Baseline - Screening and Since Last Visit versions) will be performed by a qualified trained rater.

At Screening, the C-SSRS will be used to exclude any candidate with a history of suicide behavior or ideation. If responses ("yes" answers to Item 4 or 5) indicate that the candidate may have experienced suicidal ideation associated with actual intent or plan within 12 months of Screening, may have had a history of suicidal behavior within the past 5 years, or had any lifetime history of recurrent suicidal behavior, the candidate will be excluded from participation in the study.

After Screening, the C-SSRS will be used to assess ideation and behavior at visits specified in Appendix 1. If there is a "yes" answer to Item 4 or 5, or to any behavioral question, a suicidal risk assessment must be performed as soon as possible by a qualified mental health practitioner (with expertise in evaluation of suicidality) to determine whether it is safe for the subject to continue participation in the study.

7.1.3. Physical Examination

A full physical examination in this study will include the following: skin, eyes, ears, nose, oral mucosa, and throat, cardiac, respiratory, abdomen, and extremities.

A symptom-directed physical examination will include both a full physical examination and a directed examination of the affected system related to any reported AE.

Clinically relevant findings on the physical examination performed at Screening will be recorded as medical history. Any clinically relevant treatment emergent new finding on examination will be documented as an AE.

7.1.4. Neurological Exam

Neurological examinations will include the following: mental status, level of consciousness, cranial nerve function, sensory function, motor function, and reflexes.

Clinically relevant findings from the neurological examination performed at Screening will be recorded as medical history. Any clinically relevant treatment-emergent new finding on examination will be documented as an AE.

7.1.5. Vital Signs

Vital signs will include heart rate, respirations, blood pressure, and temperature. All vital signs should be measured after the subject has rested for 5 minutes in a supine position. The same position should be used throughout a subject's participation in the study.

7.1.6. Body Measurements

Height (cm) will be measured without shoes at Screening.

Body weight (kg) will be measured without shoes, coats, or sweaters.

Body mass index will be calculated as follows:

$$\text{body weight (kg)} \div [\text{height (m)}]^2$$

7.1.7. Magnetic Resonance Imaging

MRI evaluations will be performed at Screening for all subjects and at Day 43 for subjects ≥ 50 years of age to assess for ARIA. If ARIA is detected, repeat MRIs will be performed every 3-4 weeks until the ARIA is resolved.

MRIs will be read at an independent central reading laboratory after screening of the first two sentinel subjects for Cohort 1 (age < 50) who will have MRIs performed and read locally.

Sequences will include the following:

- MRI T2-weighted fluid-attenuated inversion recovery (T2/FLAIR) sequence to detect ARIA-E
- MRI gradient recalled echo (GRE) sequence to detect ARIA-H
- Diffusion weighted imaging (DWI) sequence can help differentiate ARIA-E from potential cytotoxic edema as may be noted with an incidental acute to subacute infarct

7.1.8. Electrocardiogram

Throughout the study, subjects will be monitored for changes in cardiac conduction. Single 12-lead ECGs will be collected at designated visits after at least 5 minutes of quiet rest in a supine position.

7.1.9. Laboratory Assessments

All blood collections should be performed in non-fasting conditions.

Clinical laboratory tests include hematology, blood chemistry panel, urinalysis, and coagulation evaluations. The following assessments will be performed for the respective clinical laboratory tests:

- Hematology panel, including red blood cell count, erythrocyte mean corpuscular hemoglobin concentration, erythrocyte mean corpuscular volume, hematocrit, hemoglobin, leukocyte count, and absolute counts of lymphocytes, monocytes, neutrophils, basophils, eosinophils, and platelets.

- Blood chemistry panel, including blood glucose, calcium, albumin, total protein, sodium, potassium, bicarbonate, chloride, magnesium, blood urea nitrogen, creatinine, creatine kinase, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, bilirubin, lipase, lactate dehydrogenase, phosphorus, triglycerides, total cholesterol, high density lipoprotein cholesterol, and low-density lipoprotein cholesterol.
- Urinalysis, including osmolality, creatinine, calcium, sodium, turbidity, color, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite, leukocytes, and microscopic particles. Urine should not be first morning void. Microscopic examination will be performed if urinalysis results are abnormal for bacteria, casts, epithelial cells, erythrocytes or leukocytes. Urine should be collected within 1 hour of blood draws for hematology and chemistry panels. Trace protein will be considered positive.
- Coagulation panel, including (INR, PT, PTT and platelets); results within 2 days prior to the LP must be confirmed and determined to be within normal range before LP.

Other laboratory tests include the following:

- Viral serology, HBsAg and HCV tests
- FSH for post-menopausal women only. Post-menopausal status will be confirmed through testing of FSH levels (≥ 40 IU/mL).
- Pregnancy test for non-post-menopausal women only (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.
- Urine drug (amphetamines, methamphetamines, methadone, barbiturates, benzodiazepines, cocaine, opiates, methylenedioxymethamphetamine, phencyclidine, tetrahydrocannabinol), urine cotinine, and serum alcohol screen

7.1.10. Pharmacokinetic Sampling

Serum samples (approximately 5 mL) will be collected at the timepoints indicated in Appendix 1 to assess the serum PK profile of PMN310. On days when a PK sample is to be drawn and vital signs and/or an ECG are to be recorded, the PK sampling should be done shortly after completion of the vital signs and ECG. Details for collection, handling, and shipment of specimens are provided in the Laboratory Manual.

7.1.11. Antidrug Antibodies

Serum samples will be collected to evaluate the levels of ADAs to PMN310 per the schedule in Appendix 1. Details for collection, handling, and shipment of specimens are provided in the Laboratory Manual.

7.1.12. Exploratory Biomarkers

Residual and unused serum and CSF samples will be stored for the measurement of biomarkers at the timepoints outlined in Appendix 1. Retaining surplus samples from scheduled PMN310-101 study draws and lumbar punctures will be done for all subjects consenting to the study to

permit indefinite storage and subsequent use of those samples for biomarker analysis. Only serum and CSF samples may be saved. Samples retained will be coded or de-identified to permit retention of information at the cohort level. Access to the samples or data would be limited to the Sponsor, central laboratory, storage laboratory, and any third-party analysts. It is possible that data could be shared with future collaborators or published. In the event of publication, no data will be linked to specific subjects, all samples would be de-identified.

7.1.13. Lumbar Puncture

CSF samples to measure safety and concentrations of PMN310 will be collected via LP at times specified in Appendix 1. Up to 20 mL of CSF will be collected during each LP.

Details for collection, handling, and shipment of specimens are provided in the Laboratory Manual.

7.1.14. Concomitant Medication Use

All concomitant medications, including over-the-counter medications or herbal therapies taken within 4 weeks before Screening as well as all concomitant medications taken during the study, will be documented.

7.1.15. Adverse Events

All AEs and serious adverse events (SAEs) will be classified and graded as described below.
Definition of Adverse Event

Per the International Conference for Harmonization (ICH) E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A), and 21 CFR 312.32 IND Safety Reporting, an AE is defined as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events or Pre-existing Conditions case report form (CRF):

- From the time of informed consent through pre-dose on Day 1, only study protocol related AEs should be recorded. A protocol related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure. Otherwise, all other clinically significant medical conditions should be recorded in the medical history.
- All medical conditions present or ongoing prior to dosing on Day 1 should be recorded as medical history. Changes in medical conditions (including changes in severity, frequency, or character), during the safety reporting period should be recorded as AEs.
- All AEs reported during and postdose on Day 1 through the follow-up visit at Week 12 will be considered treatment-emergent adverse events.

- All AEs (regardless of relationship to study drug) should be recorded from the time of informed consent through the follow-up visit at Week 12 (see Section 7.1.15.6). Complications that occur in association with any procedure should be recorded as AEs with assessed severity whether or not the procedure was protocol mandated.
- In general, an abnormal diagnostic or laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms (i.e., assessed as clinically significant), requires an intervention, results in an SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a diagnostic or laboratory abnormality, the medical condition or diagnosis rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

7.1.15.1. Definition of a Serious Adverse Event

In this study, an SAE is defined as an AE that meets any of the following criteria:

- Results in death
- Is life-threatening: The term life-threatening in the definition of an SAE refers to an event in which the subject was at risk of death at the time of the event. The term life threatening does not refer to an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or a prolongation of an existing hospitalization: In general, hospitalization signifies that the subject has been detained at the hospital or emergency ward for observation or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs, but not necessarily SAEs. A medical occurrence or complication that prolongs hospitalization is an SAE. When there is doubt as to whether hospitalization occurred or was necessary, the AE should be considered an SAE. Hospitalization for elective treatments of a preexisting condition that did not worsen from its original baseline level is not considered an SAE.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions: This does not include AEs of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- A congenital anomaly or birth defect
- Other important medical event: Medical or scientific judgment should be exercised when deciding whether reporting is appropriate for other important medical events that may not result in death, be life-threatening, or require hospitalization but still may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed in this definition. These events should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or in the development of drug dependency or drug abuse.

An SAE requires additional detailed reports and follow-up (see Section 7.1.15.8). The content of these detailed reports must address the Investigator's estimate of causality. The Medical Monitor will review the SAE to determine if it is an expected SAE (i.e., whether or not the SAE is identified in nature, severity, and frequency in the Investigator Brochure).

7.1.15.2. Assessment of Adverse Event Severity

The Investigator will assess the intensity of each AE and SAE reported during the study on the basis of his or her clinical judgement.

The classifications in Table 1 should be used in assigning intensity of each AE recorded in the CRF.

Table 1: Classification of Adverse Events by Intensity

Intensity (Grade)	Definition
Mild AE (Grade 1)	An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate AE (Grade 2)	Some interference with activity not requiring medical intervention
Severe AE (Grade 3)	• Prevents daily activity and requires medical intervention • An event that, at the time of occurrence, put the subject at risk of death or resulted in a persistent or significant disability or incapacity. • An event that resulted in death..

AE = adverse event

Any AE that changes in intensity or grade during a single occurrence of an AE will be recorded in the CRF at the highest level experienced by the subject.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an AE (such as mild, moderate, or severe myocardial infarction). An AE, however, may be of relatively minor medical significance (e.g., a severe headache). Both AEs and SAEs can be assessed as severe. An AE is considered serious when it meets criteria for one of the predefined outcomes described in Section 7.1.15.1.

7.1.15.3. Assessment of Causality

The Investigator must estimate the relationship between study drug and the occurrence of each AE or SAE by using his or her best clinical judgment. Elements to consider for this estimate include the history of the underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to exposure to study drug. The Investigator must also consult the Investigator's Brochure in estimating causality.

Because of reporting timelines, the Investigator may have minimal information to include in the initial SAE report. The Investigator, however, must always assess causality for every SAE before transmitting the SAE report. The Investigator may change his or her opinion regarding

causality in light of follow-up information, with subsequent amendment of the SAE report. Causality assessment is 1 of the criteria used to determine regulatory reporting requirements, and should not be left blank on the CRF. The same applies to AEs that are to be processed as SAEs.

The causal relationship of the study drug to an AE will be rated according to the following 3-point scale:

- Unlikely: Does not follow a reasonable temporal sequence from study drug administration; may have been produced by the subject's clinical state or by environmental factors or other therapies administered
- Possible: Follows a reasonable temporal sequence from study drug administration; may have been produced by the subject's clinical state or by environmental factors or other therapies administered
- Probable: Clear temporal association with improvement on cessation of study drug. Reappears upon re-challenge or follows a known pattern of response to the study drug

For regulatory purposes, the following definitions will apply:

- Related Adverse Event: A related AE is an AE with a causality rating of "possible" or "probable"
- Unrelated Adverse Event: An unrelated AE is an AE with a causality rating of "unlikely"

7.1.15.4. Assessment of Expectedness

An unexpected adverse drug experience is defined as any adverse drug experience, that is not listed in the current Investigator Brochure. This includes events that may be symptomatically and pathophysiologically related to an event listed in the Investigator Brochure but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator Brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator Brochure only listed cerebral vascular accidents. The term unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the Investigator Brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the study drug.

7.1.15.5. Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during subject questioning, or discovered during physical examination, laboratory testing and/or other means and should be recorded on the CRF and/or SAE Report Form, as appropriate.

7.1.15.5.1. Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

7.1.15.5.2. Recording Adverse Events

The following information should be recorded on the Adverse Events CRF:

- Description of the event using accepted medical terminology
- Event onset and resolution dates
- Whether the AE met serious criteria
- Severity/grade
- Relationship to study treatment or other causality
- Outcome (final outcome)
- Action taken with study drug

7.1.15.5.3. Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms (e.g., Dyspnea is a symptom of Pneumonia, therefore, record the reached diagnosis of Pneumonia as the event term when determined). Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical practice. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

7.1.15.6. Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from the time of informed consent to the follow-up visit at Week 12. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the Investigator should also be reported to the Sponsor.

Serious adverse events must be followed until significant changes return to baseline levels, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the Investigator, or the subject dies or withdraws consent. All non-serious AEs will be followed through the follow-up visit at Week 12. Certain non-serious AEs of interest should be followed until resolution, changes return to baseline levels, or study closure.

7.1.15.7. Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and an SAE Report Form (paper or electronic). It should be noted that SAEs that occur prior to initiation of study drug (e.g., due to a study protocol procedure) will be entered into the clinical database, but not entered into the safety database.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE Report Form and CRF.
- For surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure

should be captured in the narrative as part of the action taken in response to the illness.

7.1.15.8. Reporting of Serious Adverse Events

Any SAE occurring after the subject signs the ICF must be reported to pharmacovigilance staff by phone, fax, or e-mail within 24 hours of the time the Investigator becomes aware of the SAE (Table 2). Any SAE reported by phone should be immediately followed up with the submission of the completed SAE Report Form (Table 2). Urgent reporting of SAEs is required for the following reasons:

1. To enable the Sponsor to fulfill the reporting requirements to the appropriate regulatory authority
2. To facilitate discussion between the Sponsor and the Investigator about appropriate follow-up measures (if necessary)
3. To facilitate the Sponsor's rapid dissemination of information about AEs to other Investigators or sites in a multicenter study
4. To facilitate reporting unanticipated problems involving risk to subjects to the IRB

Table 2: Timeline for Reporting Serious Adverse Events

Initial SAE Report		Follow-up SAE Report	
Time Frame	**Document**	**Time Frame**	**Document**
24 hours	SAE report	7 days	Updated SAE report

SAE = serious adverse event.

The SAE report will be completed as thoroughly as possible, including the following:

- Subject identification information
- Event term
- All available details about the SAE
- Causality of each SAE
- Signature of the Investigator

The SAE report will be forwarded to pharmacovigilance staff within designated time frames. If additional information to complete the SAE report is needed, the Investigator will not wait before notifying pharmacovigilance staff of the SAE. The SAE report will be updated by the Investigator when additional information is received.

7.1.15.9. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or female partner of a male subject are immediately reportable events.

In the event that a pregnancy or suspected pregnancy (including elevated beta-human chorionic gonadotropin or positive pregnancy test in a female subject) should occur while the subject is on study drug, or within 120 days of the subject's last dose of study drug, it will be considered an

immediately reportable event. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the study pharmacovigilance group immediately by email using the Pregnancy Reporting Form.

The female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy and must notify immediately about the outcome of the pregnancy (normal or abnormal outcome) by sending to the study pharmacovigilance group using the Pregnancy Follow-up Report Form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to the study pharmacovigilance group within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in-utero exposure to the study drug should also be reported to the study pharmacovigilance group within 24 hours of the Investigator's knowledge of the event.

Male subjects: If a female partner of a male subject receiving study drug becomes pregnant, the male subject taking study drug should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

8. STUDY TERMINATION AND SUBJECT DISCONTINUATION

8.1. Study Termination

If the Sponsor, Investigator, Medical Monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the site should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator, and Medical Monitor. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- A study conducted at a single site in a multicenter study also may warrant termination under the following conditions:
- Failure of the Investigator to enroll subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Submission of knowingly false information from the site to the Sponsor, Medical Monitor, or appropriate regulatory authority
- Insufficient adherence to protocol requirements

Study termination and follow-up will comply with conditions set forth in ICH E6, Guideline for Good Clinical Practice, Sections 4.12, 4.13, 5.20, and 5.21.

8.2. Removal or Early Withdrawal of Subjects from Therapy or Assessment

8.2.1. Removal of Subjects from Therapy or Assessment

Subjects are free to withdraw from the study at any time, without prejudice to their continued care.

The Sponsor or its designee must be notified if a subject is withdrawn from study treatment or from the study. The reason for withdrawal must be documented in the subject's medical records and CRF.

Subjects who withdraw from treatment prematurely should complete an Early Termination Visit (Section 6.3) as soon as possible.

8.2.1.1. Potential Criteria for Withdrawal from Study

Any of the following events are possible reasons for subject discontinuation from the study:

- Subject is noncompliant with the study procedures or medications.
- Subject takes prohibited concomitant medications as defined in this protocol.

- Subject has one or more clinically significant out-of-range laboratory values or clinically significant abnormal findings on physical examination.

The Investigator may contact the Medical Monitor to discuss a potential withdrawal of a subject from the study for one of these or other reason.

8.2.2. Definite Criteria for Withdrawal from Study

Subjects must be discontinued from the study if any of the following events occur:

- Adverse events (AEs) that are intolerable (as determined by the subject) or that put the subject at additional risk as judged by the Investigator
- Subject develops an illness that would interfere with his or her continued participation.
- Subject withdraws his or her consent.
- Confirmation of subject pregnancy during the study, as evidenced by a positive pregnancy test.
- The Sponsor/Sponsor's designee or a regulatory agency requests withdrawal of the subject.
- The Sponsor or a regulatory agency terminates the study.

8.3. Replacement of Study Subjects

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.

9. STATISTICAL ANALYSIS PLAN

9.1. General Overview

A formal statistical analysis plan will be developed and finalized prior to unblinding the data. This plan will define the healthy population for analysis, outline all data handling conventions, and specify all statistical methods to be used for analysis of the data.

9.2. Determination of 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. The sample size of this study is not based on statistical considerations; [redacted]

9.3. Analyzed Population Sets

- The safety population will include all subjects who receive study drug.
- The PK population will include all subjects who receive study drug and have at least 1 sample for PK analysis.
- The evaluable population will include all subjects who complete at least 1 postdose LP.

9.4. Statistical Analyses

9.4.1. Safety Analysis

Only subjects in the safety population will be included in the safety analysis. Safety and tolerability results including vital signs, MRI if/when indicated, ECGs, laboratory test results, physical and neurological examinations, AEs/SAEs, serum ADA, and C-SSRS from this study will be assessed using summary statistics by cohort (e.g., n, mean, median, minimum, maximum, for continuous endpoints; n and percentages for binary and categorical endpoints). All placebo subjects from the different cohorts will be combined into a single group for summary purposes.

9.4.2. Pharmacokinetic Analysis

The PK population will be used for the PK analysis. 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. Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV) (arithmetic and geometric), median, minimum, and maximum. Concentrations below lower limit of quantitation will be treated as zero in summary statistics.

On the basis of PMN310 concentration -time data, the following PK parameters will be estimated using standard noncompartmental methods using Phoenix® WinNonlin® Version 8.0 or higher:

- AUC_{0-t}, calculated by using the linear-log trapezoidal rule: linear trapezoidal rule up to maximum concentration, and then a log trapezoidal rule for the remainder of the curve, where t corresponds to the last measurable time point
- $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, where C_t is the last measurable serum PMN310 concentration and λ_z is the terminal elimination rate constant calculated by using log-linear regression of the terminal elimination phase of the serum concentration versus time curve
- C_{max} of PMN310 from the observed PMN310 concentration-time data
- T_{max} of PMN310 from the observed PMN310 concentration-time data
- $t_{1/2}$ calculated as follows: $\ln(2)/\lambda_z$
- Vd = volume of distribution during the terminal phase
- CL = total body clearance
- λz = terminal elimination rate constant

PK parameters will be summarized by cohort using descriptive statistics (e.g., n, arithmetic means, geometric means, SD, %CV, median, minimum, and maximum). Figures will be created to display mean and individual subject PMN310 concentration time curves in serum on both a linear and logarithmic scale.

Dose proportionality of PMN310 will be assessed using a power model. The PK parameters to be analyzed are C_{max} and AUC_{last}. A natural logarithmic transformation will be applied for the power model, which implies to a general linear model to the log transformed PK parameter with a fixed continuous log-dose effect (i.e. log (PK parameter) = $\log(\alpha) + \beta\log(\text{Dose}) + \varepsilon$). An assessment of the relationship between the doses of PMN310 and the PK parameters will be obtained from the estimate of the slope and the corresponding 90% confidence interval.

Cerebrospinal fluid (CSF) PMN310 concentrations will be listed by cohort, participant and summarized by cohort. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Training of site personnel on all protocol procedures during site initiation visits
- Routine study site monitoring
- CRF review against source documents
- Data management quality control checks

In addition, the Sponsor or designee may conduct periodic site audits.

10.1. Study Monitoring and Site Audits

Representatives designated by the Sponsor will monitor the clinical study in accordance with current FDA, ICH, national and local regulations and guidelines. During the clinical study, Clinical Monitors will visit the study site(s) on a regular basis to assess and assure satisfactory enrollment rates, data recording, maintenance of required regulatory documentation, and protocol compliance. The Investigator must ensure that all requested materials, including subject charts, CRFs, source documents, laboratory records, and study drug inventory records are available to the Clinical Monitor. The Investigator must also ensure that he/she and other qualified personnel are available at each study site visit to discuss and resolve any study-related issues.

As stipulated by 21 CFR 312.58 and ICH guidelines for Good Clinical Practice (GCP), representatives of the Sponsor, the FDA, or other regulatory agencies may conduct periodic study site audits. These representatives must have access to all requested materials, including subject charts, CRFs, source documents, laboratory records, and study drug inventory records.

10.2. Case Report Forms

Authorized site personnel will complete electronic CRFs designed for this study and provided by the CRO. The Investigator will ensure that the CRFs are accurate, complete, legible, and completed in a timely fashion. CRF completion guidelines and instructions for transmitting the CRFs to the Sponsor or designee will be provided.

10.3. Source Documentation

As stipulated by 21 CFR 312.57 and ICH guidelines for GCP, source documentation for this clinical study must be maintained to document the treatment and study course of subjects, and to substantiate the integrity of the clinical study data submitted for review to the regulatory agencies. Source documentation for clinical studies includes, but is not limited to, the following:

- Hospital, clinic, or office records documenting study visits, including treatments with PMN310 and other treatments or procedures
- Medical history and physical examination information
- Laboratory and special assessments results

- Medical consultations

The Investigator must ensure that source documents that are required to verify the validity and completeness of data transcribed on the CRFs are never obliterated or destroyed. Refer to Section 12.2 for record retention requirements.

The Investigator must ensure that source documentation is accessible to appropriate study personnel for purposes of study monitoring and site audits as described in Section 10.1.

10.4. Data Management

Data will be collected on CRFs as described in Section 10.2, entered into a clinical database, reviewed for data quality, completeness, timeliness of data entry, and protocol compliance, and analyzed by the Sponsor and its designated representatives.

11. ETHICAL CONSIDERATIONS

11.1. Institutional Review Board or Independent Ethics Committee

This protocol, the informed consent, Investigator Brochure, and any other relevant supporting information (e.g., all advertising materials) must be reviewed and approved by an appropriate IRB/Independent Ethics Committee (IEC) before study initiation. A letter confirming IRB/IEC approval of the protocol and informed consent, and a statement that the IRB/IEC is organized and operates according to GCP guidelines and the applicable laws and regulations, must be provided to Sponsor before screening subjects for the study. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, before the implementation of changes in this study (Section 11.3).

The Investigator is responsible for informing the IRB/IEC of the progress of the clinical study as appropriate and updating the IRB/IEC at least annually. Investigators are required to promptly submit Safety Reports or other updated safety information (e.g., amended Investigator Brochure) to the IRB/IEC.

The IRB/IEC may have other specific reporting requirements with which the Investigator is expected to comply.

11.2. Ethical Conduct of the Study

The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

11.3. Protocol Revisions and/or Deviations

Substantive changes in the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of subjects treated, or the subject-selection criteria. Such changes must be prepared as a protocol amendment by the Sponsor and implemented only upon joint approval of the Sponsor and the Investigator. A protocol amendment must receive IRB/IEC approval before implementation. In parallel with the IRB/IEC approval process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes in the ICF, the revised ICF prepared by the Investigator also must be approved by the Sponsor, Medical Monitor, and the IRB/IEC before implementation.

Departures from the protocol are allowed only in situations that eliminate an immediate risk to a subject and that are deemed crucial for the safety and wellbeing of that subject. The Investigator or the attending physician also will contact the Medical Monitor as soon as possible in the case of such a departure. These departures do not require preapproval by the IRB; however, the IRB and Medical Monitor must be notified in writing as soon as possible after the departure has been made. In addition, the Investigator (or designee) will document in the subject's CRF the reasons for the protocol deviation and the ensuing events.

11.4. Subject Information and Consent

The IRB/IEC-approved ICF and Subject Information Sheet, if required, must be provided by the Sponsor. The Investigator or designee must explain to the subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in 21CFR Part 50 and other applicable national and local regulations governing ICF.

Before the performance of any protocol-specific procedures that would not otherwise be done for a subject, a written and signed ICF must be obtained from the subject. The form must be signed and dated by the subject or by the subject's legally authorized representative if the subject is unable to sign. A copy of the ICF must be provided to the subject. If applicable, it can be provided in a certified translation into the local language. Signed ICFs must remain in each subject's study file and must be available for verification by the Medical Monitor or regulatory agencies at any time.

In the United States, subjects must also sign a Health Insurance Portability and Accountability Act (HIPAA)-compliant authorization containing the mandated core elements and requirements prior to participating in a clinical study.

11.5. Personal Data Protection

The subject's medical information obtained in this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. This information is protected as mandated by HIPAA (45 CFR Subpart E) for subjects in the United States. Further, each subject is assigned a unique identification number to correspond to data entered into computer databases and used in reports.

Because of the experimental nature of this treatment, the Investigator agrees to allow the IRB/IEC, representatives of the Sponsor, its designated agents and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. This includes providing de-identified copies of radiology or laboratory results when requested by the Sponsor. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

With the subject's permission, medical information may be given to the subject's personal physician or other appropriate medical personnel responsible for the subject's welfare.

12. STUDY ADMINISTRATION

12.1. Investigator Site File

The following documentation concerning the Investigator and study staff, the IRB/IEC, and the institution is required before site initiation:

- Signed protocol and protocol amendment(s) if applicable
- Signed statement of Investigator (if required by the regulatory agency)
- Institutional review board IRB/IEC composition
- Document indicating IRB/IEC approval of the final protocol and amendment(s) if applicable (to include name, address, and chairperson of the IRB/IEC)
- Document indicating IRB/IEC approval of the final and revised ICF if applicable (to include name, address, and chairperson of the IRB/IEC)
- Blank copy of the IRB/IEC-approved final and revised ICF
- Document indicating IRB/IEC approval of subject materials study advertisement, if applicable (to include name, address, and chairperson of the IRB/IEC)
- Signed Investigator's study agreement and confidentiality disclosure agreement
- Laboratory certification or accreditation and normal ranges for tests that are performed in the laboratory for study assessments
- Curricula vitae and if applicable, medical license for the Investigator and subinvestigator(s) listed on the Form FDA 1572 of the study
- Financial disclosure (as required) for the Investigator and subinvestigator(s) listed on the Form FDA 1572 of the study

Copies of these documents as well as supplemental information, such as the Investigator's obligations, the Investigator Brochure, the clinical study protocol and amendments, safety information, clinical study material, biological samples, laboratory, Pharmacy Manual, monitoring activities, Sponsor/Investigator/Medical Monitor correspondence, will be kept on-site in study site specific binders.

12.2. Retention of Study Records

According to ICH E6, Section 4.9, all CRFs, as well as supporting paper and electronic source documentation and administrative records, must be retained by the Investigator until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product in the United States. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Sponsor is responsible for informing the Investigator and institution as to when these documents no longer need to be retained. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the

study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another Investigator at the institution where the study was conducted.

Audit trails for electronic document must be retained for a period at least as long as the period required for the subject's electronic records to which they pertain. The Investigator must retain either the originals of the audit trails or a certified copy of the audit trails.

12.3. Publication and Disclosure Policy

Sponsor may use the results of this clinical study in registration documents for regulatory authorities in the United States or abroad. Publication of any study results in papers, abstracts, posters or other material presented at scientific meetings or published in professional journals must be approved by Sponsor.

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14. APPENDICES

APPENDIX 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]	8	15	29	43	57	85	120
Window	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	
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]	8	15	29	43	57	85	120
Window	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
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 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), Days 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 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) and Day 4 (72 hours)
  - Acceptable windows for PK sampling are ± 60 minutes (exact time of PK collection is to be recorded)
- 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 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 (INR/PT/PTT and platelet) 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 Section 6.2.3.