Sponsor	Supernus Pharmaceuticals, Inc., 9715 Key West Ave. Rockville, MD 20850, United States Phone: (301) 838-2500, Fax: (240) 403-0065
Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group Study to Evaluate the Efficacy and Safety of SPN-538 as a Therapy for the Prevention of Migraine in Subjects Ages 6-11 Years
Protocol Number:	538P401
Investigational Medicinal Product	SPN-538 (Topiramate extended-release capsule)
IND number	138,790
Phase	4
Protocol Version	4.0
Protocol Date:	14 December 2022
Statistical Analysis Plan Version:	Version 2.0
Statistical Analysis Plan Date:	06 January 2023

Summary of Changes from SAP version 1.0 dated 23 June 2022

Section, paragraph	Description of Change	Rationale
Cover page	Protocol version and date updated	Per the amended protocol
1	A sentence is added to clarify that the SAP does not include PK analyses. The sentence "The analysis methods presented in this SAP will supersede the statistical analysis methods described in the clinical protocol" is deleted.	Clarification Per FDA
2.2	Items 1 and 4 edited	Per the amended protocol
2.3	Primary Estimand section moved from Section 2.5 to 2.3	Administrative
2.4	Minor edits made to Items 1 and 4, Cognitive assessment added as a safety objective as item 5	Per the amended protocol
2.5	Section Title edited	Per the amended protocol
5.1	Math formula simplified with other minor editions	Administrative
5.2	Items 1 and 4 re-phrased Math formula simplified with other minor editions	Per the amended protocol Administrative
5.3	Minor edit made to item 4	Per the amended protocol
6.2	The last 2 bullet points re-phrased	Per the amended protocol

6.7.1, paragraph 1	The last sentence deleted	Administrative
6.10.1	The last 2 bullet points edited	Per the amended protocol
7.1, paragraphs 1 and 2	Editorial changes	Per the amended protocol
7.3	Editorial change	Per the amended protocol
10	Revised according to the amendment protocol	There is no change in any planned analyses per the amended protocol
11	First reference deleted	Administrative

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	adverse events of special interest
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CFB	change from baseline
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity of Illness
CI	confidence intervals
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	clinical study report
DBL	Double-blind
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition
ECG	electrocardiogram
EOS	end of study
ET	early termination
FAS	Full Analysis Set
HRQoL	Health-related quality of life
IC or ICF	informed consent or informed consent form
ICH	International Council for Harmonization
LS	least squares
MAR	missing at random
MedDRA	medical dictionary for regulatory activities
mg	milligram

MI	multiple imputation
MI	Metacognitive Index
MMRM	mixed model with repeated measures
MNAR	missing not at random
ms	millisecond
N	number
NA	not applicable
PP	per protocol
PT	preferred term
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SD	standard deviation
SM	study medication
SOC	system organ class
TEAE	treatment-emergent adverse event
TPM	Topiramate
WHO	World Health Organization
WHO-DDE	World Health Organization Drug Dictionary Enhanced

List of Tables and Figures

1. Introduction

This statistical analysis plan (SAP) describes the statistical analyses and data presentations to be performed on Study 538P401, protocol version 4.0, dated 14Dec2022.

The purpose of this SAP is to ensure the credibility of the study findings by specifying detailed statistical approaches to the analyses of the data prior to database lock. This SAP covers the planned analyses of all data collected on the eCRFs, headache and other diary pages including externally transferred laboratory data and will describe handling of data issues. It describes the efficacy and safety variables, anticipated data handling, and other details of the analyses not provided in the study protocol. The analysis of pharmacokinetics (PK) data and the population PK modelling are not covered in this SAP. Any deviations/changes from the planned analyses described in this SAP will be identified, with justification, in the appropriate section of the clinical study report.

2. Study Objectives

2.1. Primary Objective

The primary objective of this study is to evaluate the treatment effect of SPN-538 compared to placebo in reducing monthly migraine days in children 6 to 11 years old with migraine.

2.2. Secondary Objectives

The secondary objectives of this study are to assess the efficacy of SPN-538 treatment on the following:

1. Responder rate with a responder defined as a subject with at least a 50% reduction in monthly migraine days (MMDs).
2. Number of days per month requiring acute rescue medication.
3. Monthly rate of total headache days (migraine and non-migraine), duration and severity.
4. Onset of action, defined as the time to first statistically significant treatment effect observed and maintained until the end of the study (EOS).
5. Headache Disability Score as measured by the Pediatric Migraine Disability Assessment (PedMIDAS).
6. Health-related quality of life (HRQoL) as measured by the Pediatric Quality of Life Inventory, Version 4.0 (PedsQL 4.0), for the self-report and parent-report.

2.3. Primary Estimand

According to the ICH E9 Addendum, the attributes of the primary estimand (target of estimation) are provided below.

1. Treatment: To compare the treatment effect of SPN-538 vs Placebo.
2. Population: The population targeted for the scientific question is defined via the inclusion and exclusion criteria in children 6 to 11 years old (inclusive) with a history of migraine.

3. Variable: The primary efficacy endpoint is the change from baseline in the monthly (28-day) rate of migraine days during the last 4 weeks of the 20-week double-blind Treatment Phase relative to the Prospective Baseline Period based on the Full Analysis Set (FAS).
4. Intercurrent Events: For subjects discontinued due to adverse event (AE) or lack of efficacy, missing data will be imputed using multiple imputation under the Missing Not at Random (MNAR) assumption. For all other missing data due to Intercurrent events (ICE), missing data will not be imputed following the treatment policy strategy, which assumes that ICE did not occur.
5. Population level summary: The difference in the mean change from baseline in the monthly (28-day) rate of migraine days during the last 4 weeks of the Treatment Phase between the SPN-538 and placebo groups will be analyzed using a Mixed Model for Repeated Measures (MMRM).

2.4. Safety Objective

To evaluate the safety and tolerability of SPN-538 in children 6 to 11 years old as assessed by:

1. Incidence of AEs.
2. Clinical laboratory tests (blood chemistry and hematology, urinalysis).
3. Vital signs, physical and neurological examinations, and electrocardiograms (ECGs).
4. Columbia Suicide Severity Rating Scale (C-SSRS) Assessment.
5. Cognitive Assessment.

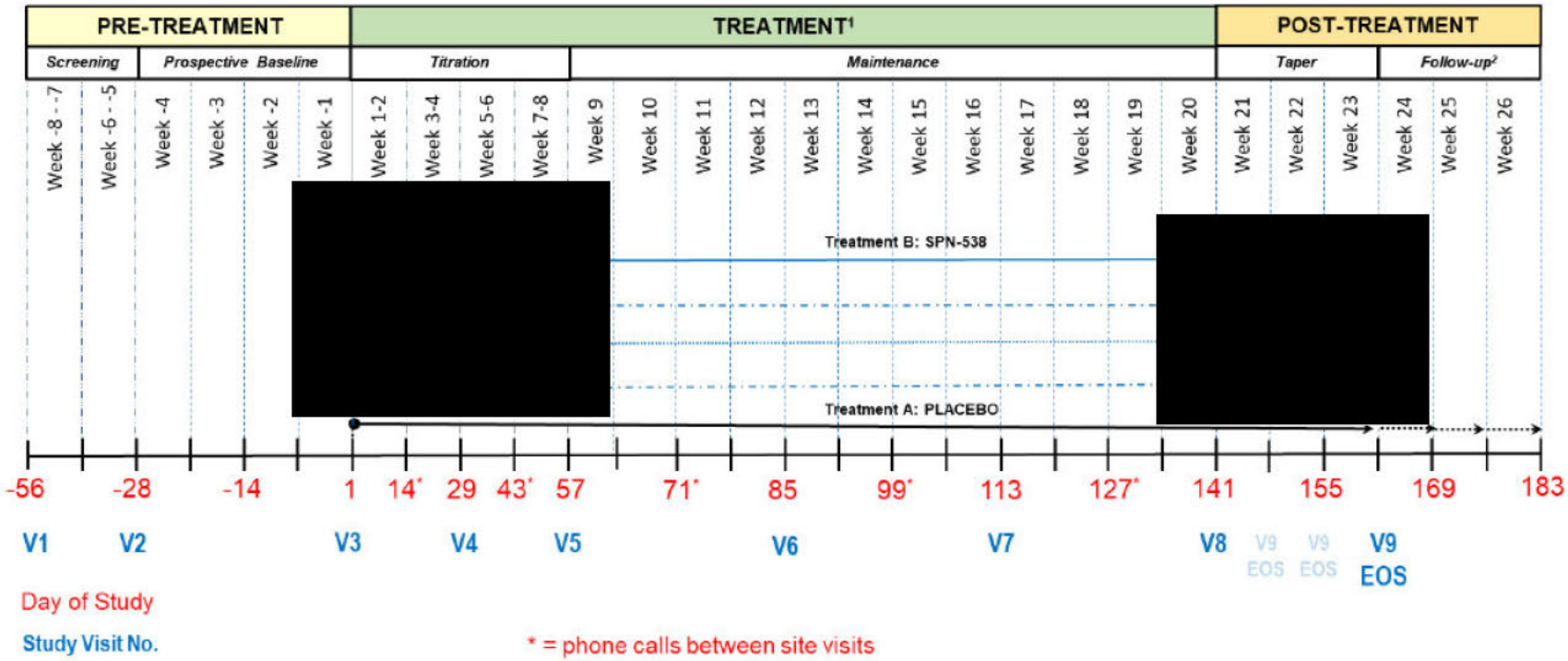
[redacted]

3. Study Description

3.1. Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel group Phase 4 study in children 6 to 11 years of age to evaluate the efficacy and safety of SPN-538 for the prevention of migraine. SPN-538 (or matching placebo) will be administered as a single oral dose once a day (QD), [redacted] The total study duration is a maximum of 34 weeks, including a Screening/Wash-out Period and Prospective Baseline Period of up to 8 weeks; a Treatment Phase of 20 weeks (8 weeks titration followed by 12 weeks of maintenance dosing); a Dose Tapering Period of 1 to 3 weeks; and a Safety Follow-up period of 1 to 3 weeks. Approximately 35 sites in the United States (US) are planned. The study schematic is shown in Figure 1 and described below

Figure 1 Study Schematic



EOS = end of study; V = visit

[redacted]

2. Subjects will receive a follow-up telephone call 1 to 3 weeks following discontinuation of study medication (Visit 9/EOS or early termination).

Table 2 Schedule of Events and Assessments

Assessments	Pre-treatment Phase		Treatment Phase					Post-treatment Phase	
	Screening/ Washout [a]	Prospective Baseline	Random-ization	Titration		Maintenance		Taper (EOS) (ET)	Safety Follow up (by phone)
Study Visit #	1	2	3	4	5	6,7	8	9	
Day of Study Visit	-56	-28	1	29	57	85,113	141	162	169-183[l]
Week of Study Visit	-8 to -5	-4 to -1	-	4 [b]	8 [b]	12,16 [b]	20 [b]	21-23	24 to 26
Study Visit Window	up to 4wks before V2	4wks before V3	+ 2 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days
Informed consent/assent	X [c]								
Demographics	X								
Retrospective 3-months headache history	X								
Randomization			X						
Inclusion/exclusion criteria	X		X						
Medical, family & psychiatric histories	X								
Physical & neurological examinations	X [d]			X [d]		X [d]	X [d]	X [d]	
Visual Neurological Exam	X							X	
Placebo Training		X		X[m]		X [V6][m]			
ECG (12-lead)	X				X			X	
Vital signs	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	
Hematology/Chemistry/ Urinalysis	X	X		X	X	X	X	X	
Serum pregnancy test	X								

Assessments	Pre-treatment Phase		Treatment Phase					Post-treatment Phase	
	Screening/ Washout [a]	Prospective Baseline	Random-ization	Titration		Maintenance		Taper (EOS) (ET)	Safety Follow up (by phone)
Study Visit #	1	2	3	4	5	6,7	8	9	
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Study Visit Window	up to 4wks before V2	4wks before V3	+ 2 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days
(FOCP only)									
Urine pregnancy test (FOCP only)		X	X	X	X	X	X	X	
Urine drug screen	X				X	X	X	X	
Eye Exam			X			X [V6]		X	
C-SSRS	X	X	X	X	X	X	X	X	
Concomitant medications	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]
Review Headache Diary		X [g]	X [g]	X [g]	X [g]	X [g]	X [g]	X [g]	
PedMIDAS	X		X		X		X	X	
PedsQL 4.0			X		X		X	X	
Cognitive assessment			X		X	X	X	X	
Dispense SM			X [h]	X	X	X	X [i]		
AEs			X	X [j]	X [j]	X [j]	X [j]	X [j]	X [j]
SM return & adherence				X	X	X	X	X	

AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination visit; FOCP = females of childbearing potential; PedMIDAS = Pediatric Migraine Disability Assessment Questionnaire; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetics; SM = study medication;

a. Subjects who had used TPM or any prophylactic migraine therapy within 4 weeks prior to Screening must complete a washout period of at least 2 weeks before the start of the Prospective Baseline Period.
b. Bi-weekly telephone contacts will occur between study visits, at Days 14, 43, 71, 99, and 127 (± 2 days).
c. Informed consent/assent to be obtained prior to performing any study procedures.
d. Physical examination (excluding genitourinary system) includes height and weight and a special assessment for the occurrence of decreased sweating and elevation in body temperature above normal. Neurological examination includes evaluation for impaired reflexes, balance problems, muscle weakness, paresthesia/numbness and tingling, speech difficulties, mental confusion or excessive fatigue.
e. Seated (5 min) pulse, blood pressure, temperature and respiratory rate. The vital signs readings, except prior to dosing, will be performed within approximately 10 minutes prior to scheduled blood draws, where applicable.
f. Concomitant medication includes headache rescue medicine (also recorded in the Headache Diary).
g. Headache Diary training will be provided at Visit 2.
h. Subjects will start the first dose on the same day of Visit 3 at the clinical site, instructions for dose titration will be provided.
i. Provide instructions for dose tapering at Visit 8.
j. Any subject who experiences an AE (whether serious or non-serious) or has a clinically significant abnormal laboratory test value will be followed by the Investigator for up to 30 days after the EOS visit. These subjects will be treated and/or followed up until the symptoms or value(s) return to normal/baseline or acceptable levels, as determined by the Investigator.

[redacted]

l. Safety Follow Up (by Phone) is not a site visit and falls within a range of 1-3 weeks after Visit 9 occurs.
m. Placebo training refresher

3.2. Study Population

The study population will comprise of children 6 to 11 years old (inclusive) with a history of migraine with or without aura, conforming to the third edition of the International Classification of Headache Disorders (ICHD-3) by the International Headache Society criteria for pediatric subjects for at least 6 months prior to Screening.

3.3. Completion and Discontinuation of Subjects

Subjects will be considered to have completed the study if they complete all visits up to and including Visit 9 (EOS).

Subjects who are randomized and dosed with SM, but who withdraw or are withdrawn from participation in the study by the Investigator prior to study completion (Week 20, Day 140), are instructed to return to the study site for an early termination (ET) visit within 1 week after discontinuation of SM. Procedures listed for Visit 9 (EOS) should be completed at the ET visit.

Subjects who exit the study early are required to gradually discontinue their SM over a period of up to 3 weeks by reducing their daily dose by one capsule every week until subjects are no longer taking the SM. The subject will return to the clinic for the EOS assessments within 1 week after discontinuation of SM. The final safety assessment will be conducted via telephone contact 1 to 3 weeks after the ET/EOS visit.

The reason for early termination will be recorded in the case report form (eCRF).

The Investigator(s) or subjects/caregivers may stop SM treatment at any time for safety or personal reasons. The subject's caregiver is free to withdraw their child from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Sponsor may also withdraw the subject at any time in the interest of subject safety. The withdrawal of a subject from the study should be discussed where possible with the Medical Monitor and/or Clinical Research Associate (CRA) before the subject discontinues taking SM. Subjects removed from the study for any reason will not be replaced.

Reasons for subject discontinuation may include:

- Withdrawal of consent and assent
- Non-compliance with study procedures
- Lack of efficacy
- Investigator decision
- Occurrence of unmanageable AEs
- Lost to follow-up
- Other

The primary reason for subject discontinuation will be recorded in the electronic case report form (eCRF). If a subject is withdrawn for more than one reason, each reason should be documented and the most medically significant reason should be entered on the eCRF.

If a subject misses any doses of SM during this study, the Investigator shall counsel the subject's caregiver on the importance of adherence. If the subject has consistently missed doses, he or she may be discontinued from the study at the discretion of the Investigator and in consultation with the Medical Monitor and the Sponsor; all procedures for discontinuation will be followed.

Efforts will be made by the study site staff to discuss with the parents/caregivers the meaning of adherence on the completion of the daily diary as at least 70% compliance with the migraine diary is requested.

3.4. Study Treatments

3.4.1. Study Medication Identity, Packaging, and Labeling

SPN-538 consists of a three-pellet composite formulation containing one enhanced immediate-release pellet type contributing 6% of the label claim, and two extended-release pellet types contributing 10% and 84% of the label claim, respectively. The drug product contains the same active pharmaceutical ingredient, TPM, as the marketed IR product Topamax.

SPN-538 25-mg capsules will be used for the study. Placebo capsules will be identical in appearance to the SPN-538 capsules but contain no TPM. Study medication (active and matching placebo capsules) will be supplied in 100-count bottles. All SM bottles will be labeled by the Sponsor in a double-blind configuration and numbered according to the randomized assignment.

3.4.2. Study Medication Administration

Study medication will be administered as a single oral dose QD with or without food, at bedtime. The capsules must be swallowed whole and intact and must not be sprinkled on food, crushed, chewed, cut or dissolved before swallowing. Subjects will take the first dose at the clinical site at Visit 3 (Day 1) and continue the day after with administration at bedtime.

3.4.3. Study Medication Dosing

The dose of SM will be flexible and optimized based on individual tolerability. The recommended target daily dose will be determined by the Investigator based on the subject's body weight and fall within the range of 2 to 3 mg/kg/day. The maximum allowed daily dose will not exceed 100 mg/day (or four 25-mg capsules once daily); the minimum daily dose may not be less than 0.5 mg/kg/day. Individual dose recommendations will be calculated based on weight and tolerability as shown in the below Table.

3.4.4. Method of Assigning Subjects to Treatment Groups

Eligible subjects will be randomized in a 1:1 ratio at Visit 3 to receive either SPN-538 or placebo. Randomization will be stratified by number of migraine days (high vs. low) at baseline to ensure treatment balance in each stratum. High monthly migraine stratum will be defined as 6 to 14 migraine days observed during the 28-day Prospective Baseline Period; and low monthly migraine stratum will be defined as 3 to < 6 migraine days during the 28-day Prospective Baseline Period.

- **Treatment A**: Placebo
- **Treatment B**: SPN-538

Allocation of study treatment will occur centrally via an interactive web response system (IWRS) using a randomization schedule to determine the SM assignment for each subject being randomized.

3.4.5. Blinding and Unblinding

Study subjects/caregivers and all personnel involved with the conduct and interpretation of the study, including the Investigators, study site personnel, the Sponsor and clinical staff, including the Medical Monitor, will be blinded to the treatment codes. Blinding will be maintained by providing capsules for placebo that are identical in appearance to the active drug. Neither the sponsor, subjects, caregivers, investigators, nor other study personnel will be aware of a subject's treatment assignment. In the event that it becomes medically necessary to identify which treatment a subject has received, the blind can be broken. The Investigator will follow the trial's randomization procedures to unblind the subject and should ensure that the code is broken only in accordance with the protocol. The Investigator will promptly document and explain to the Sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of treatment assignment.

Randomization schedule data will be kept strictly confidential, filed securely by the IWRS vendor, and accessible only to authorized persons until the time of unblinding. The IWRS manager is not required to be blinded, and he or she will have access to the study medication list and the randomization code. A limited number of Supernus personnel will perform the plasma concentration assays and interpret the results for the PK analysis and will be aware of the plasma concentration data during the study. These personnel will not have access to the randomization schedule, will not be associated with the clinical conduct of the study, and will not reveal to any clinical personnel involved in the study the treatment to which a subject is assigned.

3.5. Sample Size and Power Considerations

Based on data from previous studies conducted in adolescents and adults (MIGR-001, MIGR-002 and MIGR-003), a common SD of 3 is assumed for both the treatment and control group. Assuming a treatment difference of 1.1, a sample size of 117 subjects per arm (a total of 234 subjects) will yield 80% power to detect a non-zero difference in the mean change from baseline in the monthly migraine days between the SPN-538 and the placebo groups using a two-sample t-test at a 2-sided significance level of alpha=0.05.

Assuming that approximately 15% of subjects will drop-out before completing the study, a total sample size of 276 subjects (138 subjects per arm) will be randomized in the study.

4. Definitions and Derivations

1) Baseline: Unless specified otherwise, baseline is defined as the non-missing value collected most recent to and before the time of the very first dose of the SM.
2) The 28-day rate for the prospective baseline = (total number of migraine days during the last 4 weeks prior to randomization/ total number of days prior to randomization) *28.
3) Headache Day is any calendar day in which the subject experiences one of the following: a qualified migraine headache, a non-migraine headache that lasts continuously for more than 30 minutes, or a headache of any duration for which acute medication was used.
4) Severity of Headache is rated on a scale of 0-10: 0=None, 1- 3=Mild, 4-6=Moderate, 7-9=Severe, 10=Very severe.
5) Migraine is defined as any headache with or without aura that meets **both A and B**

criteria as described below (with matched question #s in 538P401 Protocol Appendix 2 Headache Diary).

A Criteria:

At least **one** of the following:

1) Headache duration ≥30 minutes with pain medication(s):
   Questions #2 & #3: *duration ≥30 min*
   Question #4 *checked any of the boxes or* ***Question #14*** *checked yes*
2) Headache duration ≥60 minutes with or without pain medication(s):
   Questions #2 & #3: *duration ≥60 min*

B Criteria:

At least **two** of the following:

1) Unilateral location:
   Question #7 *checked with either Right or Left.*
2) Pulsatile quality:
   Question #6 *checked with at least one of (throbbing, pounding, stabbing, constant, sharp, pressure, pulsating with the heartbeat, squeezing or other).*
3) At least moderate pain intensity:
   Question #5b *rated ≥4 in the pain scale*
4) Aggravation by physical activity:
   Question #11 *checked yes*

6) Headache/Migraine Duration is defined as the difference between the headache end date time minus start date time.
7) Change from Baseline = value at current time point – value at baseline.
8) Treatment Emergent Adverse Event (TEAE) = any adverse event with an onset date/time after first dose of study medication.
9) Duration of Adverse Event = AE end date – AE start date + 1
10) Duration of Treatment Exposure = date of last dose – date of first dose + 1
11) Percent of Study Medication Compliance is calculated as
    % compliance=100*(*Num*/*Den*), where

$$Num = \sum_{i=3}^{7} \#\ \text{of capsules dispensed at } visit_i - \#\ \text{of capsules returned at } visit_{i+1}$$

$$Den = \sum_{i=3}^{7} x_i \times (\#\ \text{of days between } visit_i \text{ and } visit_{i+1}), where$$

$$x_i = \#\ \text{of capsules per day assgined to be administered at } visit_i$$

5. Study Variables

5.1. Primary Efficacy Variable

The primary efficacy endpoint of this study is the change in the monthly (28-day) rate of migraine days (MMDs) during the last 4 weeks of the 20-week double-blind Treatment Phase relative to the Prospective Baseline Period.

The 28-day rate of monthly migraine days (MMDs) days is calculated during the last 4 weeks of Doble-blind (DBL) period as

$$\frac{\#\ of\ days\ of\ migraine}{\#\ of\ days\ with\ nonmissing\ headache\ record\ in\ the\ diary} \times 28.$$

The 28-day rate of MMDs for the prospective baseline period is calculated as in above during the last 4 weeks of 'prospective baseline'.

For MMRM analysis described in Section 7.1, the 28-day MMDs will be calculated for each visit window as depicted in the following Table.

Visit Window	Analysis Visit	Analysis Month
2 ≤ Visit ≤ 3	V3 (Prospective baseline)	Month 0
Visit 3<to ≤ Visit 4	V4 (Titration period 1)	Month 1
Visit 4<to ≤ Visit 5	V5 (Titration period 2)	Month 2
Visit 5<to ≤ Visit 6	V6 (Maintenance period 1)	Month 3
Visit 6<to ≤ Visit 7	V7 (Maintenance period 2)	Month 4
Visit 7<to ≤ Visit 8	V8 (Maintenance period 3)	Month 5

The 28-day MMDs will not be calculated after Visit 8. In other words, data from the Tapering period will not be included.

5.2. Secondary Efficacy Variables

The secondary efficacy endpoints are:

1. Responder, defined as a subject with ≥ 50% reduction in the MMDs during the last 4 weeks of the Treatment Phase relative to Prospective Baseline Period.
2. Change from baseline in the monthly migraine-specific acute rescue medication use in the last 4 weeks of the Treatment Phase.

   The 28-day rate of migraine-specific acute rescue medication (MED) days is calculated during the last 4 weeks of DBL period as

   $$\frac{\#\ of\ days\ rescue\ MED\ used}{\#\ of\ days\ with\ nonmissing\ headache\ \ record\ in\ the\ diary} \times 28$$

   The 28-day rate for the prospective baseline is calculated as in above during the 4 weeks

of 'prospective baseline'.

3. Change in the monthly rate of total headache days (migraine and non-migraine), duration and severity.
   a) Total headache days: The 28-day rate of total headache days and prospective baseline are calculated using the same formula as for the primary endpoint.
   b) Duration of headache: The 28-day duration is calculated during the last 4 weeks of DBL period as

$$\frac{sum\ of\ all\ headace\ duration}{\#of\ days\ with\ nonmissing\ headache\ record\ in\ the\ diary} \times 28$$

   The 28-day rate for the prospective baseline is calculated as in above during the 4 weeks of 'prospective baseline'.

   c) Severity of headache: The 28-day rate for severity will be calculated for each headache incidence of severity category (mild, moderate, severe, and very severe). The 28-day rate for mild severity is calculated during the last 4 weeks of DBL period as:

$$\frac{\#\ of\ days\ with\ mild\ headache\ incidence}{\#\ of\ days\ with\ nonmissing\ \text{ headache record in the Diary}} \times 28$$

   The 28-day rate for the prospective baseline is calculated as in above during the 4 weeks of 'prospective baseline'.

   The 28-day rates of moderate, severe, and very severe headache days will be calculated similarly.
4. Onset of treatment effect, defined as the time to first statistically significant treatment effect observed and maintained until the end of study in the primary endpoint.
5. Change from baseline in the Total Headache Disability Score as measured by PedMIDAS during the last 4 weeks of the Treatment Phase.
6. Change from baseline in the HRQoL as measured by the PedsQL 4.0 Total Scale Score during the last 4 weeks of the Treatment Phase for the self-report and the parent-report.

5.3. Safety Variables

The safety endpoints of this study include the following:

1. Incidence of AEs.
2. Clinical laboratory test results (blood chemistry and hematology, urinalysis).
3. Vital signs, physical and neurological examinations, eye exam and ECGs.
4. C-SSRS Assessment.
5. Cognitive Assessment.

6. Statistical Methods

6.1. General Principles

All statistical analysis, data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed using SAS version 9.4 or higher.

All tabulations of analysis results will include summaries for the two treatments: SPN-538 and placebo.

Continuous variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, interquartile range (Q1 and Q3), minimum, and maximum.

Categorical variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment groups, unless otherwise specified. The denominator for by-visit displays will be the number of subjects in the relevant study population with non-missing data at each study visit.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean, Q1, Q3, and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified and with the following exceptions: a percentage of 0% will not be displayed (i.e., only the count of 0 will be displayed), and a percentage of 100% will be displayed with 0 decimal places.

Data collected at unscheduled time points will not be summarized but will be presented in subject listings.

Categorical variables will be analyzed using Pearson's chi-squared test or Fisher's exact test if 50% the expected cell counts <5.

Treatment comparison for all efficacy variables will be evaluated based on a two-sided significance level of 0.05.

All *P* values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a *P* value less than 0.0001 occurs it will be shown in tables as <0.0001.

All collected data will be presented in listings.

6.2. Analysis Populations

The following analysis populations are planned for this study:

- **Randomized Population:** All subjects who are randomized via the IWRS.
- **Full Analysis Set (FAS):** Subjects who are randomized, received at least one dose of

study drug and have a baseline and at least one valid post-baseline assessment of monthly migraine based on the headache diary data. The FAS will be used for all efficacy analyses with treatment classification based on the randomized treatment.

- **Per Protocol Analysis Set (PPS):** includes all subjects in the FAS who have completed Visits 1-8 with no missing MMDs and no important protocol deviations. The PPS will be used for supplementary analyses of the primary and secondary efficacy endpoints with treatment classification based on the treatment received.
- **Safety Analysis Set (SAF):** includes all subjects randomized into the study who received at least 1 dose of study medication. Data will be analyzed according to the treatment received. All safety analyses will be conducted using the Safety Population.

6.3. Interim Analysis and Data Monitoring

No interim analyses are planned.

6.4. Adjustments for Covariates

Where relevant, respective baseline values will be included in the statistical models as covariates.

6.5. Hypotheses

The primary objective of this study is to test the null hypothesis (H_0) that there is no difference in the mean change from baseline in the monthly (28-day) rate of migraine days (MMDs) during the last 4 weeks of the 20-week double-blind Treatment Phase relative to the Prospective Baseline Period between the SPN-538 and placebo groups.

[redacted]

6.7. Handling of Dropouts or Missing Data

[redacted]

6.7.2. Missing Safety Variables

Missing dates for AEs and non-study concomitant medications will be imputed as described in using the following rules:

If partial AE or medication dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows.

For partial AE and medication start dates:

- If the year is unknown, then do not impute the date but assign a missing value.

- If the year is known, but the month or month and day is/are unknown, then:
    - If the year matches the year of first dose date and the end date (if present) is after first dose date, then impute as the month and day of the first dose date.
    - Otherwise, assign 01 January.
- If the year and month are known, but the day is unknown, then:
    - If the month and year match the month and year of the first dose date, then impute as the day of the first dose date.
    - Otherwise, assign 01.

For partial AE and medication end dates:

- If the year is unknown, then do not impute the date but assigned as missing value.
- If the year is known, but the month or month and day is/are unknown, then:
    - If the year matches the year of the last date of the study (date of last contact if subject lost to follow-up; date of completion or early termination), then impute as the month and day of the last date of the study.
    - Otherwise, assign 31 December.
- If the year and month are known, but the day is unknown, then:
    - If the month and year match the month and year of the last date of the study, then impute as the day of the last date of the study.
    - Otherwise, assign the last day of the month.

If partial times occur, the convention is as follows:

- if the missing time occurs on the day of the first dose and both the hour and minute are missing, then the time assigned is the time of the first dose, otherwise if both the hour and minute are missing and the date is not the date of first dose the time assigned is 12:00;
- if the date is the same as the date of the first dose and
    - only hour is missing, the hour assigned is 12 or the hour of first dose, whichever is later;
    - only the minute is missing, the minute assigned is 30 or the minute of first dose, whichever is later;
- Otherwise if the date is not the same as the date of first dose, the hour assigned is 12 if the hour is missing and the minute assigned is 30 if the minute is missing.

Missing data for all other safety endpoints will not be imputed

6.8. Analysis Visit Windows

Data from scheduled visits will be analyzed. Visits will be analyzed as scheduled. Unscheduled measurements will be excluded from the descriptive statistics and statistical analyses of efficacy data but will be included in listings. Safety data from unscheduled visits may be included in summaries and listings as appliable.

6.9. Pooling of Sites

This is a multicenter study. The primary analysis will be performed without site as a factor. Data from all sites will be pooled together for all analyses unless otherwise specified.

6.10. Study Subjects and Demographics

6.10.1. Disposition of Subjects and Withdrawals

Disposition will include tabulations of the number and percentage of subjects in each of the following categories by treatment group and overall:

- Subjects in the Randomized Population
- Subjects in the FAS
- Subjects in the PPS
- Subjects in the SAF

Within each of the previous categories, the number and percentage of subjects who completed, early discontinued and the reason for early discontinuation from the study will be summarized. The primary reason for early discontinuation may include any of the following:

- Withdrawal of consent and assent
- Lack of efficacy
- Investigator decision
- Noncompliance with study procedures
- Occurrence of unmanageable AEs
- Lost to follow-up
- Other

Subject disposition for screened subjects will be summarized. Subject enrollment distribution by site will be summarized using number and percent of subjects by each site.

Listing of screen failures among screened subjects will be presented for all screened subjects. Subject visit status at each visit and visit dates will be presented for randomized subjects.

6.10.2. Demographics and Other Baseline Characteristics

Demographic/baseline variables including age, sex, ethnicity, race, BMI, age group (6-8 vs. 9-11 years), race group (White vs non-white), Retrospective 3-months headache history score, PedMIDAS score, height and weight at screening will be summarized for the ITT population descriptive statistics for continuous variables and using counts and percentages for categorical variables and listed.

Baseline comparability among the treatment groups will be summarized using a chi-squared test for the categorical variables and using a t-test for the continuous variables. These p-values will be used for descriptive purposes and will not be considered as the formal basis for determining factors to be included in statistical analysis model.

Medical history will be coded using MedDRA version 24.1. The number and percent of subjects reporting various medical, family and psychiatric histories, grouped by MedDRA system organ class (SOC) and preferred term (PT), will be tabulated by treatment group for the safety population. The denominator used for calculating the percentages will be the total number of

subjects included in the safety population in each treatment group. Retrospective 3-month headache history will be listed.

6.10.3. Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures defined in the protocol. An important protocol deviation (IPD) is defined as a protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Potential IPDs may include, but are not limited to:

- Subjects who received the study medication but did not meet all the inclusion or met any of the exclusion criteria.
- Subjects who received non-randomized study medication.
- Subject's treatment compliance < 80% or > 120%.

Prior to the database lock and break of treatment blind, potential IPDs identified in the clinical database and/or recorded in the site deviation log will be reviewed by clinical monitor and study team for the determination of IPDs, which would lead to the exclusion from the PP Population. IPDs will be summarized and listed for the randomized population.

6.11. Exposure and Compliance

Duration of exposure is defined as the total number of days a subject is exposed to study medication (SM). This will be calculated for each subject by taking the difference between the date of SM last dose minus the date of SM first dose, plus 1 (date of last dose minus date of first dose +1).

Treatment duration will be categorized in days as: completed Day 1 to ≤ Day 28, completed Day 29 to ≤ Day 56, completed Day 57 to ≤ Day 84, completed Day 85 to ≤ Day 112, completed Day 113 to ≤ Day 141, and completed > Day141. The number and percentage of subjects in each duration group will be summarized by treatment group for the Safety population.
Duration of treatment exposure will also be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for safety population.

Percent of study drug compliance is defined in Section 4.

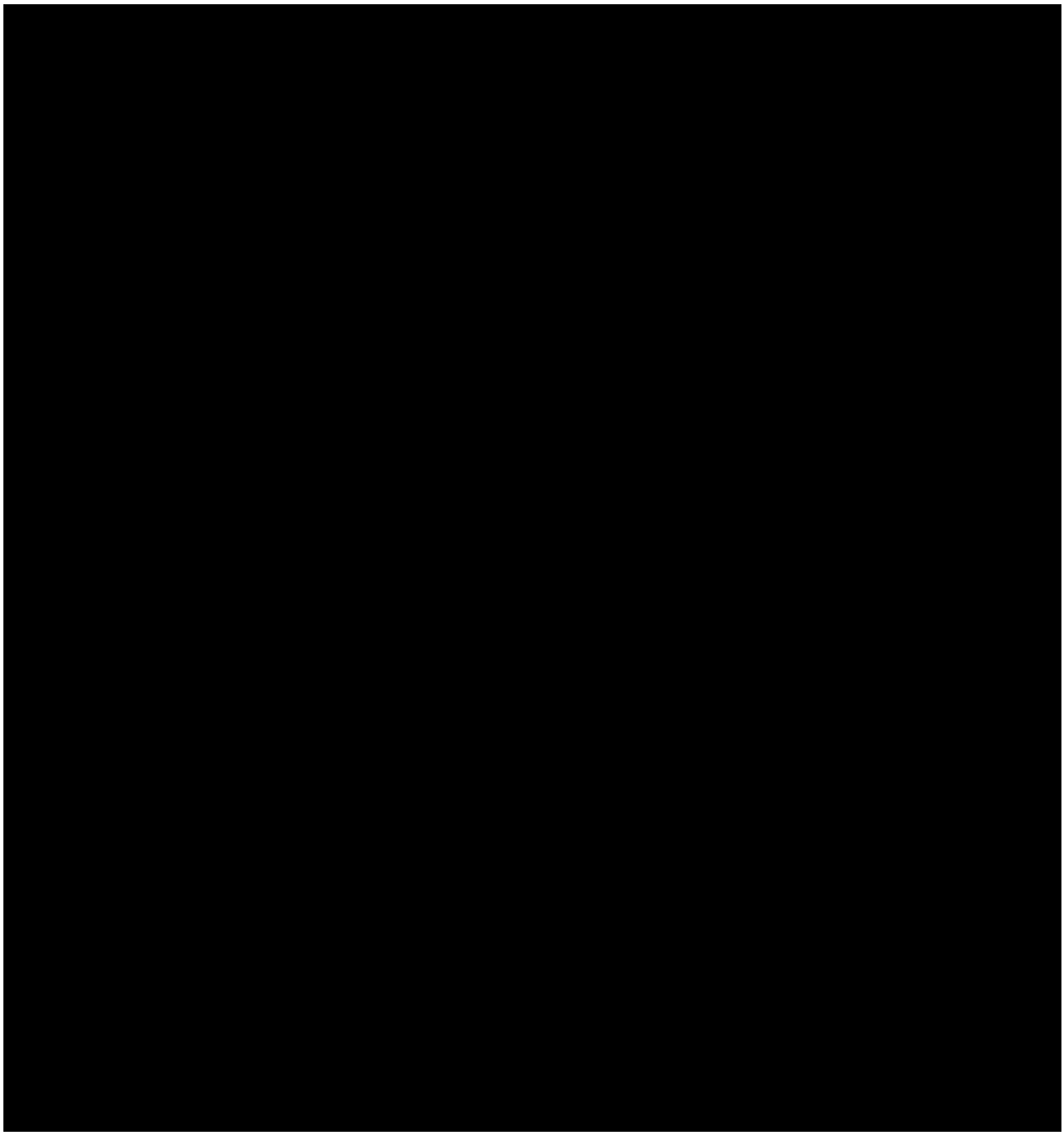
For each treatment, SM compliance will be summarized by compliance category (<80%, 80-120%, and >120%) and number of subjects in each compliance category. Study medication compliance will also be summarized as a continuous variable using descriptive statistics (number and percent for each treatment.

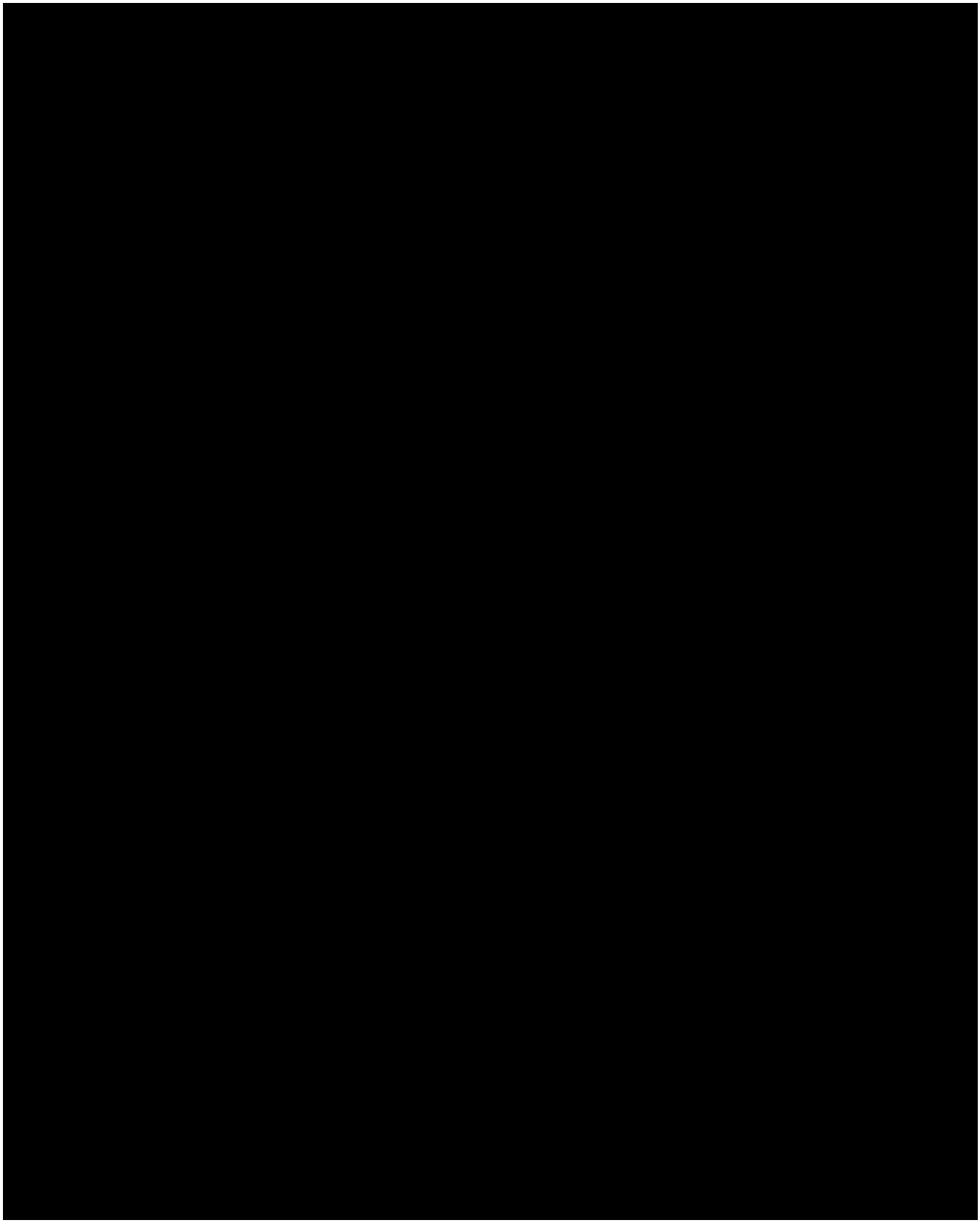
Summaries of treatment compliance and exposure will be presented separately for the Titration Period, Maintenance Period and combined Titration and Maintenance Periods.

This analysis will be conducted for the Safety Population. Derivations of duration of treatment exposure and compliance are defined in Section 4 All study medication administration, exposure, and accountability data collected will be listed.

7. Efficacy Analysis

Based on FAS, the observed value and change from baseline as well as descriptive statistics as described in Section 6.2 will be presented for all efficacy endpoints by study visit and treatment group. Subject listing of the observed value and change from baseline will be listed for all efficacy endpoints. The mean profile of 28-day MMDs will be presented by treatment group and study visit.





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9. Safety and Tolerability Analysis

All safety analyses will be performed on the Safety population. No inferential statistical tests will be performed.

9.1. Adverse Events

All adverse events (AEs) will be coded using the MedDRA Version 24.1.

A treatment-emergent adverse event (TEAE) is defined as an AE with a start date on or after the date of the first dose of study medication, or that worsened in severity following the first dose of study medication. All AEs in this study will be recorded after administration of study medication, therefore all will be considered treatment-emergent.

The Investigator is responsible for determining the relationship between the administration of SM and the occurrence of an AE as not suspected or as a suspected reaction to SM. Non-suspected AEs will be those that are determined as not related or unlikely related. Suspected AE are those that are determined as possibly related or definitely related.

Adverse event severity grades are reported as mild, moderate, or severe.

Summaries of incidence rates (frequencies and percentages) of individual TEAEs will be presented by SOC, PT, and treatment group. Such summaries will be displayed for all TEAEs, TEAEs by maximum severity, and TEAEs by relationship.

Each subject will be counted only once within each category level (SOC and PT). If a subject experiences more than 1 TEAE within each category level, the TEAE with the strongest relationship or the maximum severity, as appropriate, will be included in the summaries of relationship and severity. If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = severe, relationship = definitely related).

Incidences will be presented by descending frequency of SOC and PT within SOC, and then alphabetically within PT where the incidence is the same; this is based on overall subjects then alphabetically in case of a tie.

In addition, number and percent of patients reporting common AEs (≥5% in any treatment group) will be presented by PT.

Missing and partially missing AE start and/or stop dates and times will be imputed, for the purpose of statistical analysis, according to the specifications described in Section 6.7.2.

In the AE data listings, all AEs will be displayed.

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study medication, by treatment group, SOC, and PT will be prepared for the Safety Population.

Adverse events of special interest (AESI) include the following.

- Metabolic acidosis
- Hyperammonemia
- Oligohydrosis and hyperthermia
- Clinically significant increase in alkaline phosphatase, creatinine, or eosinophils (specifically, for patients 6 to 11 years, these were noted to be abnormally increased more frequently with TPM than with placebo)
- Clinically significant decrease in total white count or neutrophils
- Visual changes: subjects presenting with blurry vision, ocular pain, and visual field defects subjects must be discontinued early and closely followed to ensure a prompt resolution of ocular AEs.
- Suicidal behavior and ideation

- Cognitive and memory function impairments
- Nephrolithiasis

AESI for AE data will be identified in the AE eCRF page and flagged in the AE dataset. AESI for non-AE data will be identified by Supernus drug safety team based on data listings provided by statistical programming.

The incidence of AESIs based on AE data will be summarized for each treatment group by MedDRA SOC and preferred term. Supporting subject listing of AESI be presented.

A data listing of AEs leading to withdrawal of study medication will also be provided, displaying details of the event(s) captured on the CRF.

Any deaths that occur during the study will be listed. Serious adverse events will be listed and tabulated by SOC and PT and presented by treatment.

9.2. Clinical Laboratory Evaluations

Laboratory tests (chemistry, hematology, and urinalysis) will be performed at Screening, Prospective Baseline, and every visit of the Treatment Phase and Post-treatment (EOS/ET) Phase. Results will be summarized descriptively by treatment group and study visit as both observed values and change from baseline values. See Section 4 for the definition of baseline. Number and percentage of subjects with abnormal qualitative urinalysis results will be provided by treatment group and study visit.

Laboratory values for clinical chemistry and hematology will be presented by visit using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group for the actual and change from baseline values will be presented in Tables. If there are multiple values for a given visit, the worst value will be used for that visit.
Laboratory values for clinical chemistry and hematology will be flagged as abnormally low (L) if the value < lower limit of the normal range, normal (N) if the value is within normal range or abnormally high (H) if the value > upper limit of the normal range. In addition, shift tables for the change from baseline to all study visits and to the worst post-baseline will be presented.

Laboratory values will be displayed in the data listings and those that are outside the normal range will be flagged and presented along with corresponding normal ranges (if available). A separate listing of abnormal laboratory values will be provided. All study visits within a parameter for a subject will be presented if at least 1 study visit within that parameter has an abnormal result.
Urine pregnancy tests, urine drug screens and serum pregnancy test results will be listed separately.

9.3. Vital Signs

Vital signs will be collected at all study visits. Descriptive summaries of actual values and changes from baseline will be calculated for weight (kg), BMI (kg/m^2), oral body temperature (ºC), respiration rate (breaths per minute), sitting heart rate (bpm), sitting systolic blood pressure

(mmHg) and sitting diastolic blood pressure (mmHg). These summaries will be presented by study visit and treatment group. See Section 4 for the definition of baseline.

The number of subjects with vital signs values below, within, or above normal ranges, by study visit as well as to the worst post-baseline will be tabulated (shift tables) for each vital sign parameter by treatment group. Normal ranges are presented in the below table.

Vital Sign Normal Ranges

Measurement	Normal Range
Body Mass Index	18 – 35 kg/m^2
Temperature	95-100 °F (35-37.8 °C)
Diastolic blood pressure	60 – 90 mmHg
Systolic blood pressure	90 – 140 mmHg
Heart rate	50 – 100 bpm
Respiration rate	10 – 25 breaths per minute

9.4. Electrocardiograms

12-Lead ECGs will be collected at Screening, Week 8 of the Treatment Phase and Week 21-23 of the Post-treatment Phase. Descriptive summaries will be presented for heart rate (bpm), PR interval (msec), QRS duration (msec), uncorrected QT interval (msec) and QTcF (msec). These summaries will be presented by study visit and treatment group.

The number of subjects with ECG results below, within, or above normal ranges, by study visit and to the worst post-baseline will be tabulated (shift tables) for each parameter by treatment group.

Normal, abnormal but not clinically significant, and abnormal and clinically significant ECG investigator interpretation results will be flagged in the listings.

The QT and QTc parameter values will be categorized and flagged for the actual values as: ≤450 msec, 450 msec to ≤480 msec, 480 to ≤ 500 msec, and >500 msec and <= 30 msec, 30 msec to ≤ 60 msec, and >60 msec for the change from baseline. The number and percent of subjects will be presented by treatment group and visit.

9.5. Physical, Neurological and Eye Examination

Physical examinations will include assessments of all body systems except genitourinary as well as height and weight and a special assessment for the occurrence of decreased sweating and elevation in body temperature above normal. Neurological examination will include evaluation for impaired reflexes, balance problems, muscle weakness, paresthesia/numbness and tingling, speech difficulties, mental confusion or excessive fatigue. Eye examinations will measure visual acuity and visualize the optic disc through a fundoscopic exam. Subjects will be monitored for visual/ocular disturbances and potential signs of angle closure glaucoma during the participation in the study

Any findings during screening will be recorded as medical history and any clinically significant abnormal findings during treatment will be recorded as an AE. At the EOS physical and neurological examinations, only changes from the screening visit will be noted.

All physical, neurological and eye examination results will be listed.

9.6. Columbia Suicide Severity Rating Scale (C-SSRS)

Assessment of suicidal ideation and behavior will be conducted using the Columbia-Suicide Severity Rating Scale (C-SSRS) which classifies suicidal ideation and behavior events into 11 preferred categories including 5 levels of suicidal ideation, 5 levels of suicidal behavior, and the category of self-injurious behaviors with no suicidal intent. The C-SSRS will be performed at all study visits. At the Screening visit, the "baseline" version of the C-SSRS will be administered. This version assesses Suicidal Ideation and Suicidal Behavior during the subject's lifetime and during the past 6 months. At the subsequent study visits, the "since last visit" version will be administered.

The number and percentages of subjects with a response of "Yes" at any point on the suicidal ideation only, suicidal behavior only, and suicidality (ideation and behavior combined) items will be summarized by treatment group.

9.7. Cognitive Assessment

Cognitive function will be assessed by evaluating the responses to the cognitive questionnaire to which the subjects replied. Responses to the questions will be presented in subject listing and summarized by study visit and treatment group.

9.8. Concomitant Medications

Prior and concomitant medications, coded using WHO version is Global B3 September 1, 2021, will be summarized descriptively by Anatomical Therapeutic Chemical (ATC) classification Level 4 and PT (i.e., ATC classification Level 5), if applicable, using counts and percentages for the Safety Population. Concomitant medications include headache rescue medicine (also recorded in the Headache Diary).

Medications used within 30 days prior to the start of the study and during the course of the study will be listed. Medications with a valid stop date prior to the first dose date will be considered prior medications. Incidence (number and percent of subjects reporting the medication at least once during the study) will be summarized for all concomitant medications. Prior medications and concomitant medications will be summarized separately.

If a medication starts prior to the first dose and continues after the first dose it will be considered both prior and concomitant. Prior and concomitant medications will also be listed.

10. Changes from Planned Analysis

There is no change from the planned analyses specified in the protocol.

11. References

- Lu K, Mehrotra DV. Specification of covariance structure in longitudinal data analysis for randomized clinical trials. Stat Med. 2010 Feb 20;29(4):474-88.
- E9(R1) STATISTICAL PRINCIPLES FOR CLINICAL TRIALS: ADDENDUM: ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS Guidance for Industry. https://www.fda.gov/media/148473/download