TITLE PAGE

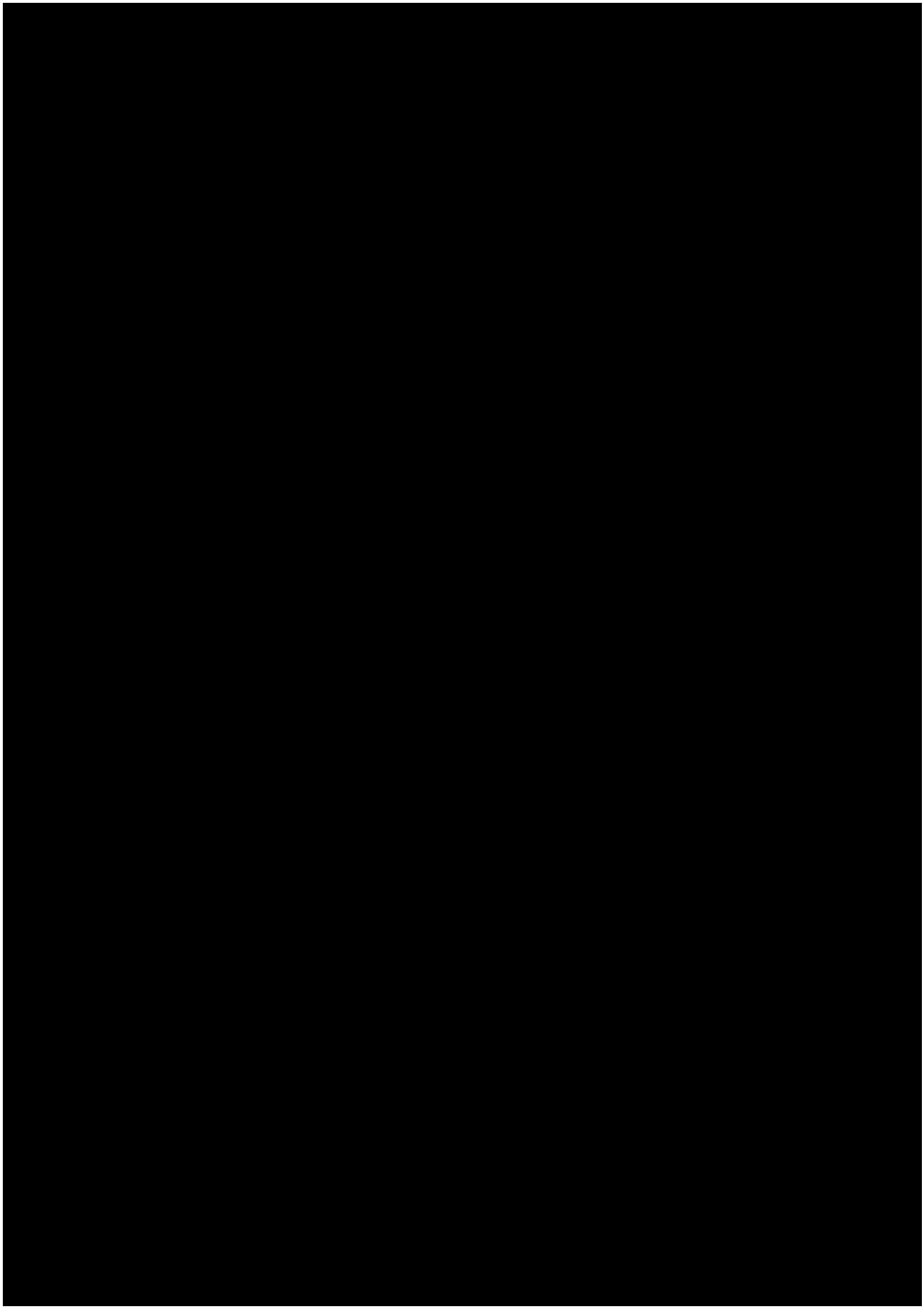
Protocol Number:	538P401
Title:	A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group Study to Evaluate the Efficacy and Safety of SPN-538 as a Therapy for the Prevention of Migraine in Subjects Ages 6-11 Years
Sponsor:	Supernus Pharmaceuticals, Inc. 9715 Key West Ave. Rockville, MD 20850 United States Phone: (301) 838-2500 Fax: (240) 403-0065
IND number:	138,790
Investigational Medicinal Product:	SPN-538 (Topiramate XR capsule)
Indication:	Prophylaxis of episodic migraine
[redacted]	
Phase:	4
Protocol Version:	Version 4.0
Date:	14 December 2022
Good Clinical Practice (GCP) Statement:	This study is to be performed in full compliance with ICH GCP and all applicable local regulations. All required study documentation will be archived as required by regulatory authorities.

INVESTIGATOR'S SIGNATURE PAGE

I, the undersigned, have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH GCP and all applicable local guidelines, including the Declaration of Helsinki and all its accepted amendments to date.

Principal Investigator's Signature	Date

Print Name



Summary of Changes

This summary table (Appendix 10.11) lists all clarifications, administrative changes or amendments to Supernus protocol 538P401. Additions are denoted by **bold** text and deletions by strikethrough.

CLINICAL PROTOCOL SYNOPSIS

Name of Company: Supernus Pharmaceuticals, Inc.	**IND Number:** 138,790
Name of Product: SPN-538 (Topiramate XR capsule)	**Name of Active Ingredient:** Topiramate (TPM)
Protocol Number: 538P401	**Phase of Development:** Phase 4
Full Title of the Study: 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	
Investigator(s)/Center(s): Approximately 35 US centers	
Number of Subjects: Approximately 276 subjects aged 6 to 11 years (inclusive) will be randomized to achieve 234 completed subjects.	

Objectives:

Primary:

- To evaluate the treatment effect of SPN-538 compared to placebo in reducing MMDs[1] in children 6 to 11 years old with migraine.

Secondary:

- 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 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.

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 (MI) under the missing not at random (MNAR) assumption. For all other missing data due to intercurrent event (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).

Safety:

- 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]

[1]*A migraine day is defined as a calendar day (12:00am to 11:59pm) in which the subject experiences a migraine attack that starts, ends or recurs within 24 hours and lasts for ≥1 hour (if untreated) or ≥30 minutes (if interrupted with rescue medication). Pain persisting for more than 1 calendar day (≥24 hours) after initial onset will be considered as a new, distinct headache day*. *MMDs are defined as the number of migraine days within 28 days or 4 weeks.*

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), starting at 25 mg/day and increasing every 2 weeks in 25 mg increments to a target dose of 2 to 3 mg/kg/day or the maximum tolerated dose (MTD), whichever is less. The total study duration is a maximum of 34 weeks including a Screening Period, 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.

Treatment Schedule:

Throughout the duration of the study, rescue medications will be allowed for symptomatic relief of headaches (migraine and non-migraine) if the pattern of use remains stable and does not meet the criteria for medication overuse (i.e., > 10 treatment days/month for ergot-containing medication or triptans; >15 treatment days/month for simple analgesics/nonsteroidal anti-inflammatory drugs (NSAIDs). Simple analgesics are allowed, but use of narcotics is not permitted (Section 4.7).

Pre-Treatment Phase (Visits 1 and 2)

Screening Period (Visit 1, up to 8 weeks before Visit 3)

At Visit 1, initial screening evaluation will be performed (Section 5.1.1). The evaluation also includes the visual neurological examination.

Prophylactic migraine treatments including daily NSAIDs, antihistamines, corticosteroids, antiemetics, high-dose magnesium supplements (≥600 mg/day), high-dose riboflavin (≥100 mg/day), coenzyme Q10, omega-3, melatonin, muscle relaxants, and β-blockers will be allowed if on a stable dose for at least 12 weeks prior to the Screening visit. The dose must remain stable (7 days/week) throughout the duration of the study (Appendix 10.9).

Prospective subjects who meet eligibility criteria at Visit 1 will be instructed to discontinue the following preventive medications 14 days prior to Visit 2 (see Exclusion Criterion #8): antipsychotics, antimanics, barbiturates, benzodiazepines, sedatives, serotonin selective reuptake inhibitors (SSRIs), non-selective reuptake inhibitor (NSRIs), amitriptyline, tricyclic antidepressants, lithium, valproic acid, AEDs, calcium channel blockers, cannabidiol (CBD) oil, calcitonin gene-related peptide (CGRP) receptor antagonists, herbal preparations/supplements such as feverfew or St John's Wort and/or any medications that could impair or decrease thinking and concentration. It is recommended to taper off antipsychotics, barbiturates, benzodiazepine, tricyclic antidepressants, lithium, amitriptyline, valproic acid, SSRIs and NSRIs as applicable (Appendix 10.10).

Re-screening is not permitted, however subjects who screen failed due to a PedMIDAS Total score > 50 under any prior version of the protocol, may be rescreened if they still meet the study eligibility criteria under this version of the protocol (Version 4.0, 14 Dec 2022).

Prospective Baseline Period (Visit 2, 4 weeks before Visit 3)

At Visit 2, in addition to routine safety assessments (Section 5.1.2), the subject's parent or guardian will be asked to maintain a daily electronic Headache Diary (completed by the parent with the subject's assistance) in which they will record daily headache-associated symptoms and the duration and severity of all headaches. Rescue medication usage during this period will also be recorded in the diary.

Treatment Phase (Visits 3 through 8)

Randomization (Visit 3, Day 1)

Upon completion of the Prospective Baseline Period, eligibility for randomization will be determined based on 1) the number of migraine episodes[2] (must be 3-12 inclusive) during Prospective Baseline Period, *and* 2) the number of total headache days (migraine and non-migraine; no more than 14 headache days) during the Prospective

Baseline Period as observed and recorded using the Headache Diary. Safety, headache disability, and HRQoL evaluations will be performed (Section 5.1.3). All eligible subjects will be randomized in a blinded fashion in a 1:1 ratio to placebo or SPN-538. Subjects will receive a 4-week supply of their assigned study medication (SM).

Titration Period (Visits 4 to 5, Weeks 1 through 8)

A dose titration schedule will be followed for the next 8 weeks to the recommended target daily dose of 2 to 3 mg/kg/day of SPN-538 (and matching placebo) or until the MTD is reached, whichever is less (Section 3.1). The target daily dose will be determined by the Investigator based on the subject's weight and will not exceed the maximum allowed dose of 100 mg (4 capsules) per day.

[redacted]

The Headache Diary will be completed daily during this period. Subjects will return to the clinic every 4 weeks for safety, headache disability, and HRQoL assessments and for guidance on dose increases or reductions (Section 5.1.4). In between monthly visits to the clinic, bi-weekly telephone calls to the subjects will assess safety and provide guidance of the SM dosage.

Maintenance Period (Visits 6 to 8, Weeks 9 through 20)

Once the target dose or MTD is reached, treatment at that dose will continue for the 12 weeks of the maintenance period; up to one dose reduction will be allowed for safety and tolerability during this period. Additional dose titration related to body weight changes will be reviewed and approved by the Medical Monitor and the Sponsor on a case by case basis. The Headache Diary will be completed daily during this period. Clinic visits will be scheduled every 4 weeks for safety, headache disability, and

[redacted]

to the clinic, bi-weekly telephone calls to the subjects will assess safety and dose reduction, if needed.

Post-Treatment Phase (Visit 9 and Telephone Follow-up)

Tapering Period (Weeks 21 through 23)

During the following 3 weeks, the daily dose of SM will be gradually reduced by 25 mg every week (1 capsule/week) until the subjects are no longer taking the SM (Section 3.1).

End of Study (Visit 9)

A final safety evaluation will occur at the end of the Tapering Period (Visit 9) for completion of the EOS procedures (Section 5.1.6).

Safety Follow-up Telephone Call (Weeks 24 through 26)

Safety follow-up over the telephone will take place 1 to 3 weeks after the EOS visit (Section 5.1.7).

[2]*Migraine episode is defined as any occurrence of a migraine that starts, ends or recurs within a 24-hour period.*

[redacted]

Duration of Treatment and Study:

The total study duration is up to 34 weeks.

Pre-Treatment Phase: 8 weeks

- Screening Period: up to 4 weeks
- Prospective Baseline Period: 4 weeks

Treatment Phase: 20 weeks

- Titration Period: 8 weeks
- Maintenance Period:12 weeks

Post-Treatment Phase: Up to 3 weeks

- Tapering Period: 1 to 3 weeks

Safety Follow-up (via telephone): 1 to 3 weeks

Investigational Medicinal Products, Reference Therapy, Dose and Mode of Administration:

Test Treatment: SPN-538, as 25 mg capsules.

Reference Treatment: Placebo in matching capsules.

All SM bottles will be labeled by the Sponsor in a double-blind configuration.

Dose: The dose will be based on body weight and optimized based on individual tolerability. Treatment will be initiated at 25 mg/day (or 1 capsule/day) and increased bi-weekly in 25 mg increments to a target dose in the range of 2 to 3 mg/kg/day. The total daily dose will not exceed 100 mg/day (or 4 x 25 mg capsules/day).

Mode of Administration: Placebo or SPN-538 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.

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

Efficacy Endpoints:

Primary Endpoint

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

Secondary Endpoints

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 mean of monthly migraine-specific acute rescue medication use in the last 4 weeks of the Treatment Phase.
3. Change in the monthly rate of total headache days (migraine and non-migraine), duration and severity.
4. Change in the time to onset of action, defined as the time to first statistically significant treatment difference observed and maintained until the EOS.
5. Change from baseline in the 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.

Safety Endpoints:

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

[redacted]

Safety Assessments:

Safety evaluations will be performed at each clinic visit. Routine safety monitoring will include monitoring, evaluation, and recording of all concomitant medications, and the evaluation of AEs, clinical laboratory test results, vital signs, 12-lead ECGs, suicidality monitoring/C-SSRS results, physical and neurological examinations. Subjects will also be monitored for visual/ocular disturbances, nephrolithiasis, oligohydrosis, hyperthermia, metabolic acidosis (serum bicarbonate), hyperammonemia, hepatic injury, and cognitive assessments.

[redacted]

Statistical Methodology:

Sample Size

Based on data from previous studies conducted in adolescents and adults (MIGR-001, MIGR-002 and MIG-003), a common standard deviation (SD) of 3 is assumed for both the treatment and control groups. 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 between the mean change from baseline in MMDs between the active treatment and the placebo groups using a two-sample t-test at a two-sided significance level of alpha=0.05.

It is assumed that approximately 15% of subjects will drop-out before completing the study, hence an adjusted total sample size of 276 subjects (138 subjects per arm) will be randomized in a 1:1 ratio to obtain 234 subjects at the completion of the study.

Analysis Populations:

The Randomized Population consists of all subjects who are randomized via the IWRS.

The Full Analysis Set (FAS) is defined as subjects who received at least one dose of study drug, have a baseline and at least one valid post-randomization assessment of monthly migraine based on diary days. The FAS will be used to assess the primary endpoint and secondary efficacy endpoints, and subjects will be included in the analyses based on randomized treatment.

The Per Protocol 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 as supplementary analysis of the primary and secondary efficacy endpoints based on the treatment received.

The Safety Analysis Set includes all subjects randomized into the study and who receive at least 1 dose of SM. Data will be analyzed according to the treatment received.

[redacted]

Efficacy Analyses: Based on the FAS, the observed value and change from baseline will be summarized using descriptive statistics and presented for all efficacy endpoints by study visit and treatment group. Subject listing of the observed value and change from baseline will be provided for all efficacy endpoints. The mean 28-day MMDs will be presented by treatment group and study visit.

Primary Endpoint Analysis:

The primary efficacy endpoint, change from the Prospective Baseline Period in the 28-day rate MMDs, will be analyzed using a MMRM, which assumes that missing data are missing at random (MAR). All post-baseline study visits will be included in the model; however, the primary comparison will be between SPN-538 and Placebo groups at Month 5 (last 4 weeks of the Maintenance Period). The model will include fixed effect terms for 28-day rate of MMDs for the Prospective Baseline Period, treatment group, Prospective Baseline monthly migraine-specific acute rescue medication (28-day rate) use, visit, and treatment-by-visit interaction as independent variables. The model parameters will be estimated using the restricted maximum likelihood method with an unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom.

If the MMRM model with the unstructured variance-covariance matrix does not converge using the default Newton-Raphson fitting algorithm by PROC MIXED in SAS, the Fisher scoring algorithm or the no-diagonal factor analytic structure will be used (Lu & Mehrotra, 2010). If the model still fails to converge, then the first (co)variance structure which does not have convergence problem will be used for the analysis from the following ordered list:

1. Heterogeneous Toeplitz,
2. Heterogeneous Autoregressive of order 1
3. Toeplitz,
4. Autoregressive of order 1
5. Compound Symmetry

The denominator degrees of freedom will be estimated using the BETWITHIN option in SAS when any of the covariance structures is used with the sandwich variance estimator.

The least square mean (LS Mean) of each treatment group (placebo and SPN-538) along with the corresponding standard error, p-values, difference in the LS Mean between SPN-538 and placebo (SPN-538 minus placebo), and 95% CIs will be computed at each visit.

Sensitivity analyses will be performed based on MI, assuming that missing data are MNAR.

Secondary Endpoint Analyses:

Secondary endpoints will be analyzed based on the FAS using appropriate statistical models.

Safety Analyses:

Safety analyses will be performed by treatment group using the Safety Analysis Set. The incidence rate, severity, and relationship to the SM for all AEs will be summarized by treatment group, system organ class (SOC), and preferred term (PT).

Descriptive statistics will be presented for demographics, data from the clinical laboratory test results, vital signs, weight, ECGs, physical, neurological and eye examinations, suicidal ideation, and cognitive assessment.

[redacted]

Inclusion Criteria:

1. Healthy male or female subjects, 6 to 11 years of age (inclusive) at Screening.
2. History of migraine with or without aura conforming to the International Headache Society (IHS) criteria for pediatric subjects (International Classification of Headache Disorders, 3rd edition [ICHD-3]) for at least 6 months prior to Screening.

3. Subjects who experience 3-12 migraine episodes and no more than 14 headache days (migraine and non-migraine) per month during the 3 months prior to Screening and during the 28-day Prospective Baseline Period (based on the Headache Diary).
4. At Screening, a PedMIDAS Disability score of ≥20 (indicating at least mild disruption of daily activities) and ≤139 (indicating severe disability that may require more comprehensive therapy).
5. Weight of at least 20 kg and no more than 60 kg (inclusive) at the Randomization visit (Visit 3).
6. Considered medically healthy by the Investigator via assessment of physical, neurological and eye examinations, medical history, clinical laboratory tests, vital signs, and ECGs.
7. Able and willing to swallow capsules whole and intact without sprinkling on food, crushing, chewing, cutting, or dissolving before swallowing.
8. Caregiver must be able to read and comprehend written instructions and be willing to supervise the completion of all headache records and questionnaires by the subject as required in the protocol.
9. Written Informed Consent obtained from the subject's parent or legal representative, and written Informed Assent obtained from the subject if required.
10. Female subjects must be premenarchal or otherwise incapable of pregnancy, or have practiced one of the following methods of contraception for at least 1 month prior to study entry:
    a. Simultaneous use of male condom, spermicide and barrier, and placement of intrauterine contraceptive device
    b. Surgically sterile male partner
    c. Simultaneous use of male condom and diaphragm with spermicide.
    d. Established hormonal contraceptive, sterility; or
    e. Be practicing abstinence and agree to continue abstinence or to use an acceptable method of contraception (as listed above) should sexual activity commence during the study.

Exclusion Criteria:

1. Subjects with chronic migraine (>14 headache days per month), cluster headaches, or migraine aura without headache, and who are unable to distinguish migraines from other headache types.
2. Subjects with more than 14 headache days during the 28-day Prospective Baseline Period (based on the Headache Diary).
3. Have taken any disallowed migraine preventive medication including TPM within 14 days prior to the start of the Prospective Baseline Period; or used onabotulinumtoxinA (Botox®) within 3 months prior to entering the Screening period.
4. Previously failed to respond to TPM prophylaxis therapy using an adequate dose (2 to 3 mg/kg/day) for an adequate period of time (minimum of 3 months), or those who have previously discontinued TPM due to AEs within 6 months prior to Screening.

5. Previously failed more than 2 adequate clinical trials (defined as non-response to treatment at a full therapeutic dose for at least 1 month) of an established prophylactic antimigraine regimen within 6 months prior to Screening.
6. Known history of allergic reaction or anaphylaxis to TPM.
7. Overuse of analgesic or migraine-specific agents for acute treatment of migraine defined as:
   a. >10 treatment days/month of ergot-containing medications or triptans
   b. >15 treatment days/month with simple analgesics (including NSAIDs)
   c. Use of narcotics
8. Subjects treated with the following prophylactic medications should discontinue the treatment 14 days prior to the Prospective Baseline Period: antipsychotics, antimanics, barbiturates, benzodiazepines amitriptyline, lithium, valproic acid, tricyclic antidepressants, AEDs, calcium channel blockers, sedatives, SSRIs, NSRIs, CGRP receptor antagonists, CBD oil, herbal preparations/supplements such as feverfew or St John's wort and/or any medications that could impair or decrease thinking and concentration. It is recommended to taper off antipsychotics, barbiturates, benzodiazepine, tricyclic antidepressants, lithium, amitriptyline, valproic acid, SSRIs and NSRIs as applicable.
   Note: Subjects must refrain from using these medications throughout the duration of the study.
9. Subjects using non-pharmacologic complementary and alternative prophylactic approaches for migraine prevention, such as neuromodulation, acupuncture, behavioral interventions, spinal manipulation, occipital nerve block and neurofeedback.
   Note: Non-pharmacologic approaches involving lifestyle modifications (e.g., trigger factor avoidance, stress reduction techniques, regular exercise, and good sleep hygiene) will be allowed if they were started at least 1 month prior to Screening and are continued throughout the study.
10. Currently on a ketogenic diet, or on a ketogenic diet within 6 months prior to Screening.
11. Significant major psychiatric disorder (e.g., psychosis, bipolar disorder, major depression and generalized anxiety disorders), or documented developmental delays or impairments (e.g., autism, cerebral palsy, or mental retardation) that, in the opinion of the Investigator, would interfere with adherence to study requirements or safe participation in the trial.
    Note: Subjects with an established diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), will be allowed if they are taking a stable dose (7 days/week) of ADHD stimulant medication (extended or controlled release) for at least 12 weeks prior to the Screening visit and refrain from changing the dose or the ADHD medication during the study duration.
12. Subjects with seizures or a history of seizure-like events within 6 months prior to Screening, or a history of seizure disorder within the immediate family (siblings, parents).
13. Known history of visual field defects regardless of etiology.
14. Presence of active liver disease (including baseline serum ammonia levels >2 times the upper limit of normal).

15. Abnormal kidney function, subjects undergoing hemodialysis, or subjects with a history of nephrolithiasis.
16. Known neurological disorder or a structural disorder of the brain from birth; head trauma or infectious disease resulting in migraine or worsening of migraine symptoms; or previous central nervous system (CNS) surgery.
17. Known history of uncontrolled asthma, uncontrolled diabetes, arrhythmias or congenital heart disease.
18. Evidence of suicidal ideation and/or suicidal behaviors within 6 months prior to Screening or during the Pre-treatment Phase.
19. Pregnancy, breastfeeding, or refusal to practice abstinence or acceptable birth control during the study for females of childbearing potential (FOCPs).
20. Known history of substance-use disorder according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) or used alcohol or illicit drugs in the 3 months prior Screening.
21. Any other reason that could interfere with the subject's participation in the study as determined by the Investigator.

<u>Note:</u> Abnormal results on screening laboratory tests and/or ECG may be repeated once per test at the discretion of the Investigator.

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LIST OF ABBREVIATIONS

ADR	adverse drug reaction
ADHD	attention-deficit/hyperactivity disorder
AE	adverse event
AED	antiepileptic drug
AESI	adverse event of special interest
ATC	Anatomical-Therapeutic-Chemical (code)
BP	blood pressure
CFR	Code of Federal Regulations
CI	confidence interval
CBD	cannabidiol
CDE	Common Data Elements
CGRP	calcitonin gene-related peptide
CNS	central nervous system
CRA	Clinical Research Associate
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
ePRO	electronic patient reported outcome
ET	early termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOCP	females of childbearing potential
GCP	Good Clinical Practice
HR	heart rate
HRQoL	health-related quality of life
IAF	informed assent form
ICE	Intercurrent events
ICF	informed consent form
ICH	International Conference on Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd edition
IHS	International Headache Society
IND	Investigational New Drug
IR	immediate release
IRB	Institutional Review Board
IWRS	interactive web response system

MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MIDAS	Migraine Disability Assessment
MMD	monthly migraine day
MMRM	Mixed Model for Repeated Measures
MNAR	Missing not at random
MTD	maximal tolerated dose
NINDS	National Institute of Neurological Disorders and Stroke
NSAID	nonsteroidal anti-inflammatory drug
NSRI	non-selective reuptake inhibitor
OD	overdose
PedMIDAS	Pediatric Migraine Disability Assessment
PedsQL 4.0	Pediatric Quality of Life Inventory, Version 4.0
PPS	Per Protocol Analysis Set
PK	pharmacokinetic
PREA	Pediatric Research Equity Act
PT	preferred term
QD	once a day
QTcF	QT interval corrected using Fridericia's method
RR	respiratory rate
SADR	suspected adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SM	study medication
SOC	system organ class
SOP	standard operating procedure
SSRI	serotonin selective reuptake inhibitors
TEAE	treatment-emergent adverse event
TPM	topiramate
TPM XR	topiramate extended release
US	United States
WBC	white blood cell
WHO DD	World Health Organization Drug Dictionary
XR	extended release

1 INTRODUCTION

Migraine is a disabling primary headache disorder characterized by recurrent attacks of predominantly unilateral headache that is pulsatile in nature, moderate to severe in intensity, and often aggravated by routine physical activity. Migraine affects up to 15% of the world population (Stovner et al., 2007). Recurrent headache is one of the most common complaints among children and adolescents, with an estimated 75% of children reporting significant headache by the age of 15 years (Antonaci et al., 2014). Moreover, approximately 4% to 11% of children between the ages of 7 and 11 years are affected by migraine, with one-third of pediatric patients meeting the criteria for pharmacologic prophylaxis (Lewis et al., 2004). The International Classification of Headache Disorders, 3rd edition (ICHD-3) summarizes definitions and diagnostic criteria for migraine with and without aura, as well as special features that are characteristic of migraine headaches in children and adolescents (Appendix 10.1).

Symptomatic manifestations of migraine are often different between adults and children. Pediatric migraine attacks are more often bilateral, of shorter duration than in adults, and have a higher prevalence of gastrointestinal complaints such as nausea, vomiting and pain (Kacperski, Kabbouche, O'Brien, & Weberding, 2016). Recurrent migraine attacks are associated with significant functional impairment, resulting in poor long-term educational, occupational, and social outlook and reduced life satisfaction (Powers, Patton, Hommel, & Hershey, 2003). The long-term outcome of childhood headaches and their progression to chronic conditions is unknown.

Treatment and management of migraine require a multilevel approach, including medication management of acute episodes, prophylactic treatment for frequent and disabling headaches, and non-pharmacologic approaches, such as cognitive and behavioral therapies, lifestyle modifications, and trigger avoidance strategies, to facilitate better therapeutic outcomes. In general, pharmacologic preventive therapies are indicated when other approaches have been ineffective (Bonfert et al., 2013).

Topiramate (TPM), an antiepileptic drug (AED), is the only drug indicated for migraine prophylaxis in the pediatric patient population, specifically for children and adolescents ≥12 years of age. The efficacy and safety of TPM in migraine prophylaxis have been clearly demonstrated in several randomized, double-blind, placebo-controlled trials in thousands of patients (Jackson et al., 2015). These studies have provided consistent evidence that TPM reduces migraine frequency and acute medication use, improves quality of life, and reduces disability in patients with episodic and in those with chronic migraine, with or without medication overuse headache. As a result, TPM has become the most commonly prescribed migraine preventative in adults and is frequently recommended for migraine prophylaxis in children and adolescents (Kacperski et al., 2016; Silberstein, 2017).

Trokendi XR® (SPN-538) was developed by Supernus Pharmaceuticals as an extended release (XR) formulation of topiramate (TPM XR), a once a day (QD) product designed to be equivalent to TPM immediate release (IR) (Topamax®, Janssen Pharmaceuticals, Inc.) administered twice daily. Currently, Trokendi XR is marketed as an AED (monotherapy and adjunctive therapy) for patients 6 years of age and older and as a preventive for migraine headaches in adults and adolescents 12 years of age and older ("National Institutes of Health-DailyMed- Trokendi XR-Prescribing Information.," 2022). United States (US) Food and Drug Administration (FDA) approval of Trokendi XR was based on the product's demonstrated bioequivalence to Topamax.

The safety and tolerability of TPM has been studied extensively in adult and pediatric patients with epilepsy but has not been definitively established for prophylaxis of migraine headache in patients younger than 12 years of age. In a meta-analysis of randomized clinical trials of TPM in children with migraine <18 years of age, the most frequently reported adverse events (AEs) included paresthesia, upper respiratory tract infections, fatigue, weight decrease, anorexia, and cognitive impairments (Le, Yu, Wang, Ali, & Guo, 2017). Most AEs, including those leading to discontinuation of TPM, occurred during the titration period and did not worsen during maintenance (Lainez et al., 2007). In pediatric patients, slow dose titration is recommended to alleviate AEs, and dose reductions may improve treatment compliance.

In previous migraine studies MIGR-001 (Silberstein, Neto, Schmitt, Jacobs, & Group, 2004), MIGR-002 (Brandes et al., 2004), MIGR-003 (Diener et al., 2004), and MIG-3006 (Lewis et al., 2009), most AEs reported with the use of TPM were mild to moderate in severity, and no unusual or unexpected safety risks were identified. However, long-term TPM treatment requires continuous assessment for AEs that are specifically attributable to this drug. These include ophthalmologic side effects (acute myopia, secondary angle closure glaucoma, and visual field defects), oligohydrosis and hyperthermia, treatment-related laboratory abnormalities (e.g., metabolic acidosis, hyperammonemia, and changes in complete blood count values), nephrolithiasis, negative effects on growth, and suicidal behavior and ideation.

Monitoring for neuropsychiatric effects and cognitive impairment is of crucial importance because of the effect of TPM on cognitive function, specifically on concentration/attention, memory, and speech/language abilities. This risk for cognitive adverse reactions is dose dependent and is greater in younger pediatric patients (6 to 11 years) than in older children (12 to 17 years)("National Institutes of Health-DailyMed- Trokendi XR- Prescribing Information.," 2022; "National Institutes of Health -DailyMed- Topamax- Prescribing Information," 2022).

Trokendi XR is an approved agent for the prophylaxis of migraine in adults and adolescents 12 years of age and older; however, its efficacy as a migraine preventative has not been established in the 6-to-11 year age range. In this study (538P401), the efficacy and safety of Trokendi XR as a preventative therapy for migraines in this younger pediatric population will be explored. The XR formulation of SPN-538 is expected to be beneficial in this patient population where, compared to the IR TPM products, it offers more constant plasma drug concentrations, less frequent dosing, and an improved AE profile (Silberstein, 2017).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To evaluate the treatment effect of SPN-538 compared to placebo in reducing MMDs in children 6 to 11 years old with migraine.

2.2 Secondary Objectives

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 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.

Primary Estimand

According to the International Conference on Harmonisation (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) as defined in Section 7.3.
4. Intercurrent event (ICE): For subjects discontinued due to AE or lack of efficacy, missing data will be imputed using MI under the MNAR assumption. For all other missing data due to ICE, missing data will not be imputed following the treatment

policy strategy, which assumes that ICE did not occur. Methods of handling missing data are described in Section 7.2.

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 MMRM as discussed in Section 7.8.1.

2.3 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]

2.5 Primary Endpoint

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

- 28-day rate of Migraine Days = (total number of migraine days during the last 4 weeks of the double-blind treatment phase/total number of days during the last 4 weeks of the double-blind treatment phase) *28.
- Prospective Baseline = total number of migraine days in the last 28 days prior to randomization.

A migraine day is defined as a calendar day (12:00 am to 11:59 pm) in which the subject experiences a migraine attack that starts, ends, or recurs within 24 hours and lasts for ≥1 hour (if untreated) or ≥30 minutes (if interrupted with rescue medication). Pain persisting for more than 1 calendar day (≥24 hours) after initial onset will be considered as a new, distinct headache day. **MMDs is defined as the number of migraine days within 28 days or 4 weeks**.

2.6 Secondary Endpoints

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.
3. Change in the monthly rate of total headache days (migraine and non-migraine), duration and severity.
4. Change in the time to onset of action, defined as the time to first statistically significant treatment effect observed and maintained until the EOS.
5. Change from baseline in the 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.

The safety endpoints are:

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

[redacted]

3 INVESTIGATIONAL STUDY PLAN

3.1 Overall Study Design and Plan

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 QD, starting at 25 mg/day and increasing every 2 weeks in 25 mg increments to a target dose of 2 to 3 mg/kg/day or the maximum tolerated dose (MTD), whichever is less. The total study duration is a maximum of 34 weeks, including a Screening Period and a 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.

Pre-treatment Phase

Screening Period (Visit 1, up to 8 weeks before Visit 3)

At Visit 1, informed consent and informed assent (if applicable) will be obtained. Initial screening evaluation includes headache history, medical, family and psychiatric histories, ECG and vital sign assessments, physical and neurological examinations,

concomitant medications, headache disability, and laboratory tests including hematology, chemistry, urinalysis, drug screen, and serum pregnancy test (females of childbearing potential [FOCPs] only). Suicidality will be evaluated using the C-SSRS, Children's version. A visual neurological examination will also be required prior to Visit 2 (Section 6.8.5).

Subjects treated with the following prophylactic medications should discontinue the treatment 14 days prior to the Prospective Baseline Period: antipsychotics, antimanics, barbiturates, benzodiazepines amitriptyline, lithium, valproic acid, tricyclic antidepressants, AEDs, calcium channel blockers, sedatives, serotonin selective reuptake inhibitors (SSRIs), non-selective reuptake inhibitor (NSRIs), calcitonin gene-related peptide (CGRP) receptor antagonists, cannabidiol (CBD) oil, herbal preparations/supplements such as feverfew or St John's wort and/or any medications that could impair or decrease thinking and concentration. It is recommended to taper off antipsychotics, barbiturates, benzodiazepine, tricyclic antidepressants, lithium, amitriptyline, valproic acid, SSRIs and NSRIs as applicable (Appendix 10.10).

Note: Subjects must refrain from using these medications throughout the duration of the study.

Non-pharmacologic approaches involving life-style modifications are allowed if initiated more than 1 month prior to Screening.

For subjects who met the eligibility criteria, prophylactic migraine treatments will be allowed if on a stable dose for at least 12 weeks prior to the Screening Visit including daily nonsteroidal anti-inflammatory drugs (NSAIDs), antiemetics, antihistamines, corticosteroids (i.e., systemic inhaled, or topical), high-dose magnesium supplements (≥600 mg/day), high-dose riboflavin (≥100 mg/day), coenzyme Q10, omega-3, melatonin, muscle relaxants and β-blockers (Appendix 10.9).

Note: The dose and the medication must remain stable (7 days/week) during the duration of the study.

During Screening, acute rescue medications (e.g., ibuprofen, acetaminophen, ergot derivates and triptans) will be allowed for symptomatic relief of headaches (migraine and non-migraine) as long as the pattern of use remains stable and does not meet the criteria for medication overuse (i.e., > 10 treatment days/month for ergot-containing medication or triptans; >15 treatment days/month for simple analgesics/NSAIDs). The use of narcotics is not permitted.

Re-screening is not permitted, however subjects who screen failed due to a PedMIDAS Total score > 50 under any prior version of the protocol, may be rescreened if they still meet the study eligibility criteria under this version of the protocol (Version 4.0, 14 Dec 2022).

Placebo Training

During Visit 2, caregivers will be asked to complete a training on the placebo effect. The training consists of three parts to be completed using the iPad: Part 1 (10 questions) illustrates what is the placebo effect (e.g., 'What is a placebo?,' 'Who knows whether your child is getting the study drug or the placebo?'); while Part 2 (6 questions) describes the importance of understanding how to use the study application/diary (e.g., 'What is the study application used for?', 'Who is collecting the data in the study application?') and Part 3 (8 questions) highlights the importance of providing accurate information about the study (e.g., 'What is a pediatric migraine?', 'What's the purpose of the trial?').

For any incorrect answer during the training, the next page will provide an explanation and the correct answer.

Refresher placebo training will be administered at Visits 4 and 6.

Prospective Baseline Period (Visit 2, 4 weeks before Visit 3)

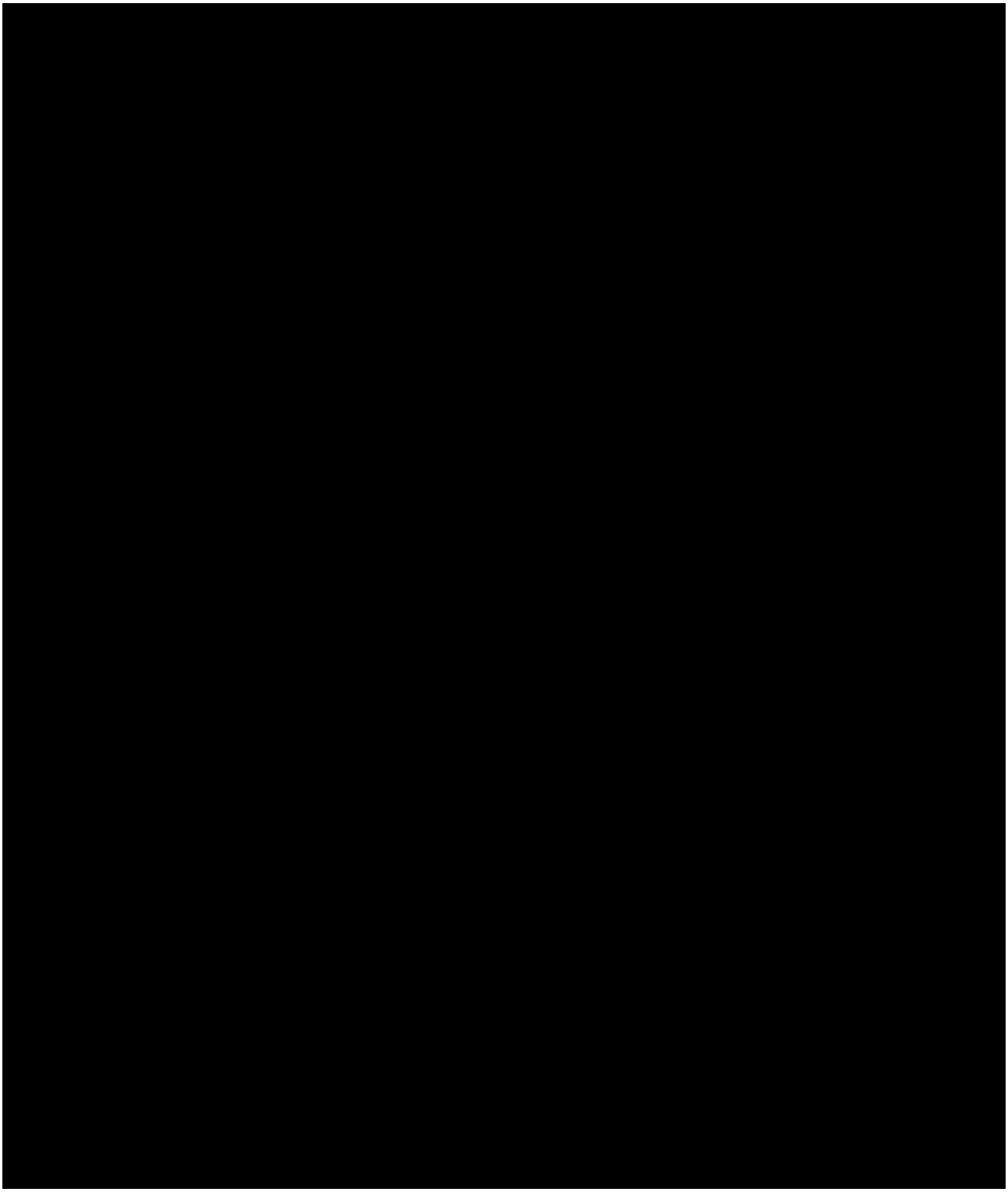
At Visit 2, the subject's parent or guardian will be asked to maintain a daily electronic Headache Diary (completed by the parent with the subject's assistance) in which they will record daily headache-associated symptoms and the duration and severity of all headaches. Rescue medication usage during the 28-day Prospective Baseline Period will also be recorded in the diary. Vital signs, concomitant medications, clinical laboratory tests, urine pregnancy test (FOCP only) and suicidality evaluation using the C-SSRS will be obtained at the visit.

Treatment Phase

Randomization (Visit 3, Day 1)

Upon completion of the Prospective Baseline Period, eligibility for randomization will be determined based on 1) the number of migraine episodes (must be 3-12 inclusive) during the Prospective Baseline Period, *and* 2) the number of total headache days (migraine and non-migraine; no more than 14 headache days) during the Prospective Baseline Period as observed and recorded using the Headache Diary.

All eligible subjects will be randomized in a blinded fashion by the interactive web response system (IWRS) in a 1:1 ratio of placebo or SPN-538. Subjects will receive a 4-week supply of their assigned study medication (SM). Safety evaluations including AEs, vital signs and suicidality evaluation (using the C-SSRS), eye examinations, concomitant medications, urine pregnancy test (FOCP only), headache disability, HRQoL, and cognitive assessments will be obtained at the visit. SM accountability and resupply will occur at each subsequent study visit.



Maintenance Period (Visits 6 to 8, Weeks 9 to 20)

Once the target dose or MTD is reached, treatment at that dose will continue for the 12 weeks of the maintenance period; up to one dose reduction will be allowed for safety

and tolerability during this period. Additional dose titration related to body weight changes will be reviewed and approved by the Medical Monitor and the Sponsor on a case by case basis. The number, severity, and symptoms of all headaches, as well as the type and dose of rescue medication and SM compliance will be recorded daily in the Headache Diary. During the Maintenance Period, clinic visits will be scheduled every 4 weeks. During each clinic visit, a 4-week supply of SM will be provided, and SM compliance and the Headache Diary will be reviewed. Safety evaluations, including vital signs, concomitant medications, cognitive assessment, C-SSRS, clinical laboratory tests (only at Visit 8), urine pregnancy test (FOCP only), urine drug screen, physical and neurological evaluations will also be performed. [redacted]

During Visit 6, the eye exam will be performed, and another refresher placebo training will be administered.

Telephone contacts will occur at the intervening 2-week periods [Days 71, 99 and 127 (±2 days)] between clinic visits for safety assessment and to provide guidance on dose reduction (as needed).

Post-Treatment Phase

Tapering Period (Weeks 21 to 23):

During the following 3 weeks the dose of SM will be gradually reduced until the subject is no longer taking the SM, so that by the end of Week 23 the subject is out of SM. Dose tapering will also be required for subjects who discontinue early during the titration period (Week 3 through Week 8) or maintenance period (Week 9 through Week 20). Subjects who discontinue early at an MTD of 25 mg/day will not undergo a dose tapering period but will return to the clinic to complete the EOS procedures (all procedures scheduled to be performed at Visit 9) within 1 week after discontinuation of SM.

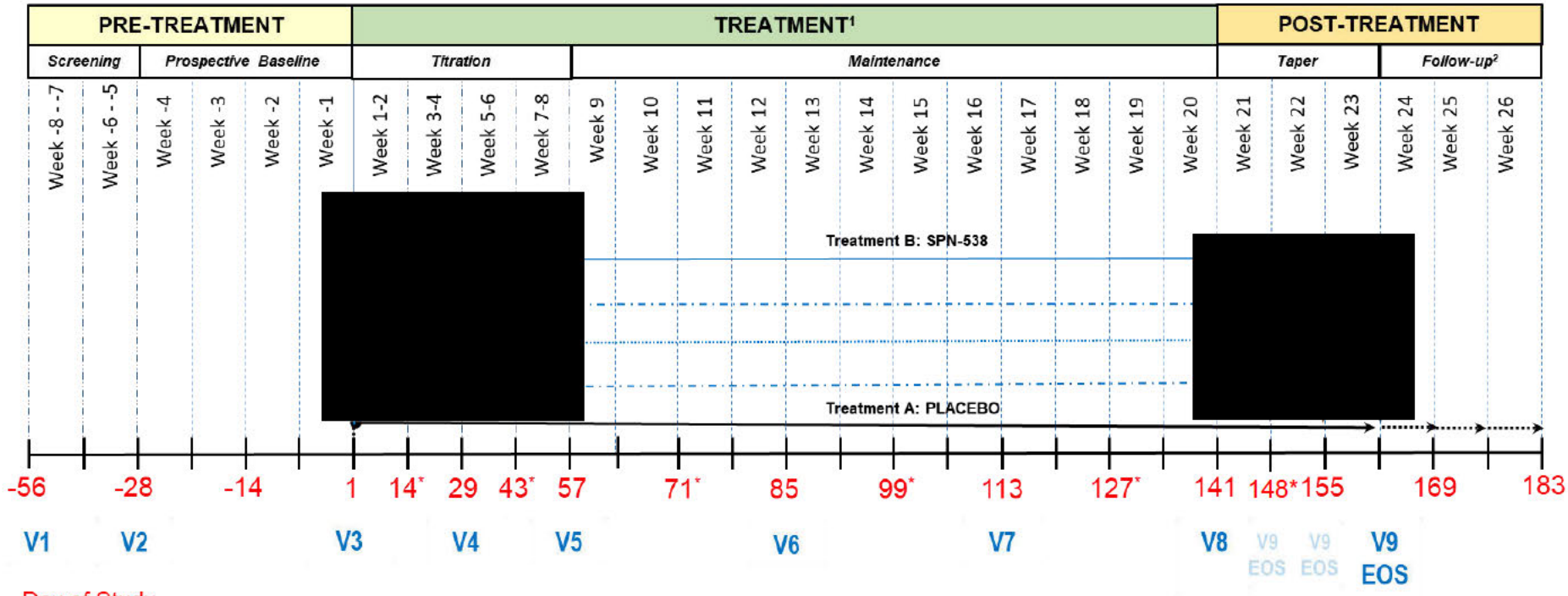
End of Study (Visit 9):

All subjects who complete the study (Week 20) will return to the clinic for a final safety evaluation at the end of the Tapering Period (Visit 9). During this visit, subjects will complete the EOS procedures: clinical laboratory tests, AE assessments, vital signs, concomitant medications review, ECG, physical and neurological evaluations, eye exam, urine pregnancy test (FOCP only) and urine drug screen, headache disability, HRQoL, C-SSRS and cognitive assessments. The remaining SM and the Headache Diary device, if applicable, will be collected, and safety follow-up instructions will be provided to caregivers.

***Safety Follow-up Telephone Call (Weeks 24 to 26)*:**

Safety follow-up over the telephone will take place 1 to 3 weeks after the EOS/early termination (ET) visit. During the telephone call, all concomitant medications, cognitive assessment and AEs will be evaluated and recorded. 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/ET visit. These subjects will be treated and/or followed up until the symptoms or laboratory values return to normal/baseline or acceptable levels, as determined by the Investigator.

Figure 1 Study Schematic



EOS = end of study; V = visit

1. Dosing will be based on weight and is flexible. [redacted], [redacted] The total daily dose will not exceed 100 mg/day (or 4 × 25 mg capsules/day). In the event of tolerability problems during titration, the Investigator may reduce the dose by 25 mg/week after Week 3. During maintenance, up to one dose reduction will be allowed for safety and tolerability during this period. Additional dose titration related to body weight changes will be reviewed and approved by the Medical Monitor and the Sponsor on a case by case basis.
2. Subjects will receive a follow-up telephone call 1 to 3 weeks following discontinuation of study medication (Visit 9/EOS or early termination).

3.2 Rationale for Study and Study Design

Preventive treatments are typically considered for patients whose migraine has a substantial impact on their lives, or whose headaches occur with sufficient frequency and severity to warrant daily medication. According to the general principles of migraine management, the goals of preventive treatment should be focused on 1) reducing the frequency, severity, and duration of attacks; 2) reducing the progression to chronic daily headache and avoiding acute headache medication escalation, and 3) decreasing the associated disability and improving the quality of life (Lewis et al., 2004). Study 538P401 aims to explore if these goals are achieved in pediatric migraine patients 6 to 11 years of age who are treated with SPN-538. The objectives of the study will address the changes in MMDs resulting from TPM therapy, as well as the effects of prophylactic SPN-538 treatment on acute rescue medication use, migraine-related disability and HRQoL, and the total number of all headaches (migraine and non-migraine). From the clinical perspective, a preventive migraine treatment is considered successful if ≥ 50% reduction in number of migraine days (as compared to baseline values) is achieved; therefore, the responder rate (a responder is a subject with ≥ 50% reduction in MMDs) is also a secondary efficacy outcome in this study.

3.2.1 Study Population

This study is a part of the Supernus PREA commitment for Trokendi XR (SPN-538), which requires that pediatric assessments are conducted for drugs that have been approved for use in adults but are also likely to be used in a substantial number of pediatric patients. Pediatric studies under PREA typically involve “assessments of safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric populations” ("Center for Drug Evaluation and Research. How to comply with the Pediatric Research Equity Act.," 2005). Trokendi XR is already approved for use in adolescents ≥12 years of age, and Supernus was granted a waiver for the study of migraine prophylaxis in the age group of birth to less than 6 years of age. The 6 to 11 years age group is an important population of migraine sufferers with an unmet need for an effective and safe medication for migraine prevention.

3.2.2 Topiramate Dose Selection

The recommended total daily dose of Trokendi XR for prophylaxis of migraine headache in adults and adolescents 12 years of age and older is 100 mg once daily. [redacted] and then gradually increased over the course of 8 weeks to the target dose of 100 mg/day [redacted] In adults 20 years of age and older, the 100 mg/day dose corresponds to approximately 0.8 to 1.8 mg/kg/day, depending on body weight (Fryar, Gu, Ogden, & Flegal, 2016).

Dosing of TPM in patients from 6 to 10 years of age is typically based on body weight. The dosage is usually increased slowly at 1 to 2 week intervals in increments of 1 to 3 mg/kg until a therapeutic target dose is reached.

For migraine prophylaxis in the pediatric age group, a dose of 2 to 4 mg/kg/day appears to be effective (Kacperski et al., 2016). In most recent randomized, controlled trials in children and adolescents 6 to 17 years of age, the target dose of TPM was 2 mg/kg/day (Powers et al., 2017) or 2 to 3 mg/kg/day (Winner et al., 2005). Other studies examined the effective dose of TPM in pediatric migraine prophylaxis and observed improvement in migraine symptoms at doses as low as 0.5 mg/kg/day (Abbaskhanian, Sadeghi, Erfani, & Rezai, 2012; Cruz et al., 2009). Daily TPM doses of > 3 mg/kg/day were also shown to be effective but were associated with a higher incidence of AEs. Based on this information, a flexible treatment dose of SPN-538 in the range of 2 to 3 mg/kg/day was selected for this study. The maximum allowed daily dose will not exceed that recommended for Trokendi XR in the treatment of adults and adolescents, i.e., 100 mg/day. This TPM dose is well within the range that is considered safe in long-term exposure for pediatric patients (i.e., up to 9 mg/kg/day or 400 mg/day for the treatment of epilepsy; ("National Institutes of Health-DailyMed- Trokendi XR- Prescribing Information.," 2022).

The AEs associated with TPM treatment are known to be dose dependent and are often transient. As the presence and severity of AEs may lessen with dose reduction, subjects will be allowed to reduce their daily TPM dose during the Titration Period until a maximum tolerated dose is found within a dosing range of [redacted]. A slower titration duration of 8 weeks is being implemented to further mitigate the potential for AEs.

3.2.3 Selection of Assessment Instruments

The assessment instruments selected for this study have been recommended by the National Institute of Neurological Disorders and Stroke (NINDS) as part of the Common Data Elements (CDEs) for Headache research, Version 2.0 ("U.S. Department of Health and Human Services - Headache,").

Headache Diary

The primary tool for collecting daily information about headaches will be the Headache Diary - Preventive Therapies. A similar diary was used in the CHAMP study by Powers et al (Powers et al., 2017). The Headache Diary will be presented in an electronic format that is uploaded on a dedicated electronic patient reported outcome (ePRO) data collection application; a device will be provided as needed. The advantages of collecting data through electronic modalities include real-time patient data monitoring, more efficient data capture within an electronic database, and improved patient compliance. Portable electronic devices also allow sending helpful reminders to complete the diary

and to enter the dosing information, which ensures more complete and timely collection of study data.

PedMIDAS and PedsQL 4.0 Questionnaires

HRQoL is emerging as an important element of clinical research in primary headache disorders. Quality of life represents the extent to which a particular illness affects a patient's life functioning and can, therefore, be very useful from a clinical perspective. Migraine is recognized as one of the most disabling pediatric conditions, as recurring headaches often have a profound impact on a child's life, affecting academic performance and interactions with family and peers, and reducing emotional well-being (Powers et al., 2003). Restoring patients' ability to function, as well as improving quality of life, is among the main objectives of migraine therapy. Hence, the International Headache Society (IHS) recommends including functionality and HRQoL measures as secondary endpoints for migraine clinical trials for the purpose of assessing changes in a subject's ability to function and enjoy life (Tfelt-Hansen et al., 2012). Topcu et al used the PedMIDAS to evaluate the effectiveness of prophylactic drugs, including TPM, in pediatric migraine studies, and saw significantly decreased disability scores demonstrating the usefulness of this questionnaire in evaluating patients' quality of life (Topcu, Hiz Kurul, Bayram, Sozmen, & Yis, 2014). The PedsQL 4.0 was an effective measure of quality of life in children with migraine demonstrating that the total score was the lowest for children with chronic headache compared to top healthy normal children, supporting the evidence that headaches in children and adolescents have a great impact similar to that found in chronic illness conditions (Powers et al., 2003). The PedMIDAS and PedsQL 4.0 questionnaires are NINDS recommended assessments for evaluating Activities of Daily Living/Performance and Quality of Life domains in headache clinical trials (Connelly & Rapoff, 2006; Hershey et al., 2001; Powers et al., 2017).

3.3 Study Population Selection

3.3.1 Number of Subjects

Approximately 276 subjects aged 6 to 11 years (inclusive) will be randomized to achieve 234 completed subjects.

3.3.2 Inclusion Criteria

1. Healthy male or female subjects, 6 to 11 years of age (inclusive) at Screening.
2. History of migraine with or without aura conforming to the IHS criteria for pediatric subjects (International Classification of Headache Disorders, 3rd edition [ICHD-3]) for at least 6 months prior to Screening.
3. Subjects who experience 3-12 migraine episodes and no more than 14 headache days (migraine and non-migraine) per month during the 3 months prior to Screening and during the 28-day Prospective Baseline Period (based on the Headache Diary).

4. At Screening, a PedMIDAS Disability score of ≥ 20 (indicating at least mild disruption of daily activities) and ≤ 139 (indicating severe disability that may require more comprehensive therapy).
5. Weight of at least 20 kg and no more than 60 kg (inclusive) at the Randomization visit (Visit 3).
6. Considered medically healthy by the Investigator via assessment of physical, neurological and eye examinations, medical history, clinical laboratory tests, vital signs, and ECGs.
7. Able and willing to swallow capsules whole and intact without sprinkling on food, crushing, chewing, cutting, or dissolving before swallowing.
8. Caregiver must be able to read and comprehend written instructions and be willing to supervise the completion of all headache records and questionnaires by the subject as required in the protocol.
9. Written Informed Consent obtained from the subject's parent or legal representative, and written Informed Assent obtained from the subject if required.
10. Female subjects must be premenarchal or otherwise incapable of pregnancy, or have practiced one of the following methods of contraception for at least 1 month prior to study entry:
    a. Simultaneous use of male condom, spermicide and barrier, and placement of intrauterine contraceptive device
    b. Surgically sterile male partner
    c. Simultaneous use of male condom and diaphragm with spermicide.
    d. Established hormonal contraceptive, sterility; or
    e. Be practicing abstinence and agree to continue abstinence or to use an acceptable method of contraception (as listed above) should sexual activity commence during the study.

3.3.3 Exclusion Criteria

1. Subjects with chronic migraine (>14 headache days per month), cluster headaches, or migraine aura without headache, and who are unable to distinguish migraines from other headache types.
2. Subjects with more than 14 headache days during the 28-day Prospective Baseline Period (based on the Headache Diary).
3. Have taken any disallowed migraine preventive medication including TPM within 14 days prior to the start of the Prospective Baseline Period; or used onabotulinumtoxinA (Botox®) within 3 months prior to entering the Screening period.
4. Previously failed to respond to TPM prophylaxis therapy using an adequate dose (2 to 3 mg/kg/day) for an adequate period of time (minimum of 3 months), or those who have previously discontinued TPM due to AEs within 6 months prior to Screening.
5. Previously failed more than 2 adequate clinical trials (defined as at least 1 month of treatment at a full therapeutic dose) of an established prophylactic anti-migraine regimen within 6 months prior to Screening.
6. Known history of allergic reaction or anaphylaxis to TPM.

7. Overuse of analgesic or migraine-specific agents for acute treatment of migraine defined as:
    a. >10 treatment days/month of ergot-containing medications or triptans;
    b. >15 treatment days/month with simple analgesics (including NSAIDs)
    c. Use of narcotics
8. Subjects treated with the following prophylactic medications should discontinue the treatment 14 days prior to the Prospective Baseline Period: antipsychotics, antimanics, barbiturates, benzodiazepines amitriptyline, lithium, valproic acid, tricyclic antidepressants, AEDs, calcium channel blockers, sedatives, SSRIs, NSRIs, CGRP receptor antagonists, CBD oil, herbal preparations/supplements such as feverfew or St John's wort and/or any medications that could impair or decrease thinking and concentration. It is recommended to taper off antipsychotics, barbiturates, benzodiazepine, tricyclic antidepressants, lithium, amitriptyline, valproic acid, SSRIs and NSRIs as applicable.

    Note: Subjects must refrain from using these medications throughout the duration of the study.
9. Subjects using non-pharmacologic complementary and alternative prophylactic approaches for migraine prevention, such as neuromodulation, acupuncture, behavioral interventions, spinal manipulation, occipital nerve block and neurofeedback.

    Note: Non-pharmacologic approaches involving lifestyle modifications (e.g., trigger factor avoidance, stress reduction techniques, regular exercise, and good sleep hygiene) will be allowed as long as they were started at least 1 month prior to Screening and are continued throughout the study.
10. Currently on a ketogenic diet, or on a ketogenic diet within 6 months prior to Screening.
11. Significant major psychiatric disorder (e.g., psychosis, bipolar disorder, major depression and generalized anxiety disorders), or documented developmental delays or impairments (e.g., autism, cerebral palsy, or mental retardation) that, in the opinion of the Investigator, would interfere with adherence to study requirements or safe participation in the trial.

    Note: Subjects with an established diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), will be allowed if they are taking a stable dose (7 days/week) of ADHD stimulant medication (extended or controlled release) for at least 12 weeks prior to the Screening visit and refrain from changing the dose or the ADHD medication during the study duration.
12. Subjects with seizures or a history of seizure-like events within 6 months prior to Screening, or a history of seizure disorder within the immediate family (siblings, parents).
13. Known history of visual field defects regardless of etiology.
14. Presence of active liver disease (including baseline serum ammonia levels >2 times the upper limit of normal).
15. Abnormal kidney function, subjects undergoing hemodialysis, or subjects with a history of nephrolithiasis.
16. Known neurological disorder or a structural disorder of the brain from birth; head trauma or infectious disease resulting in migraine or worsening of migraine symptoms; or previous central nervous system (CNS) surgery.

17. Known history of uncontrolled asthma, uncontrolled diabetes, arrhythmias or congenital heart disease.
18. Evidence of suicidal ideation and/or suicidal behaviors within 6 months prior to Screening or during the Pre-treatment phase.
19. Pregnancy, breastfeeding, or refusal to practice abstinence or acceptable birth control during the study for FOCPs.
20. Known history of substance-use disorder according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) or used alcohol or illicit drugs in the 3 months prior Screening.
21. Any other reason that could interfere with the subject's participation in the study as determined by the Investigator.

Note: Abnormal results on screening laboratory tests and/or ECG may be repeated once per test at the discretion of the Investigator.

3.4 Completion of Study

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

3.4.1 Discontinuation of Subjects

Subjects who discontinue early will complete the procedures listed for Visit 9 (Section 5.1.6).

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 (study is terminated by the Sponsor, blind is broken, subject has relocated or death etc.)

The primary reason for subject discontinuation must 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.

3.4.2 Early Termination Procedures

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

Subjects who exit the study early will also be 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 ET must be recorded in the eCRF.

4 STUDY TREATMENT

4.1 Study Medication Identity, Packaging and Labeling

SPN-538 consists of a three-pellet composite formulation containing one enhanced immediate release (IR) pellet type contributing 6% of the label claim, and two extended release (XR) 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. SM (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.

4.2 Study Medication Administration

SM 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.

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 [redacted] (Table 1). 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 (Table 1).

[redacted]

Dose optimization will be guided by clinical outcome and tolerability. During the Titration Period, subjects will be assessed during bi-weekly telephone calls, between monthly visits to the clinic, for tolerability of the SM treatment. After each telephone assessment, the Investigator will make the decision as to whether to continue increasing the dose, to maintain current dose for another 2 weeks (to allow a longer interval for dose adjustment), or to discontinue the subject early due to AEs. If a subject is to be discontinued due to AEs, an unscheduled clinic visit must be setup to perform all necessary EOS procedures.

At all dose levels, a one-step down-titration is allowed as long as the reduced SM dose does not fall outside of the allowable dose range (Table 1). Once a well-tolerated dose is achieved, the subjects will continue treatment at that dose during titration (i.e., the MTD might be achieved at Week 2 or 4 and that dose will be maintained barring any evolving AEs) until the end of Week 8. During maintenance, up to one dose reduction will be allowed for safety and tolerability. Additional dose titration related to body weight

changes will be reviewed and approved by the Medical Monitor and the Sponsor on a case-by-case basis.

Overdosage of TPM has been reported. Signs and symptoms include convulsions, drowsiness, speech disturbance, blurred vision, diplopia, impaired mentation, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. Similar signs and symptoms may occur with overdosage of SPN-538. In the event of suspected OD with SPN-538, the caregiver should be instructed to call 911 and/or the local poison control center at 1-800-222-1222.

Taking 1 or 2 more pills over the dose is considered a PD. Not every OD is a reportable event, only reportable if the overdose (OD) is a serious adverse event (SAE). Gastric lavage or induction of emesis is recommended. Activated charcoal might be considered since it has been shown to absorb TPM. Hemodialysis is also effective to remove TPM from the body.

4.4 Method of Assigning Subjects to Treatment Group

Eligible subjects will be randomized in a 1:1 ratio at Randomization Visit (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 IWRS using a randomization schedule to determine the SM assignment for each subject being randomized.

4.5 Blinding

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 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 SAE) 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 SM list and the randomization code. [redacted]

4.6 Study Medication Handling and Accountability

All SM is supplied to the Investigator by the Sponsor. SM supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the SM label.

Following Sponsor instructions and in compliance with ICH E6 as well as local, state, and federal regulations, the Investigator and study staff will be responsible for the accountability of all clinical supplies (receiving, shipment, dispensing, inventory, and record keeping). Study sites are also responsible for maintaining a SM accountability log, a copy of which will be collected by the Sponsor at the end of the study.

Under no circumstances will the Investigator allow the SM to be used in a manner other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled into the study.

An accurate and timely record of the receipt of all clinical supplies; dispensing of SM to the subject/caregiver; collection of unused supplies; and subsequent return of unused SM to the Sponsor must be maintained with dates. This SM accountability log includes but may not be limited to: (a) documentation of receipt of clinical supplies, (b) SM inventory log, (c) SM accountability log, and (d) all shipping service receipts. Forms may be provided by the Sponsor. Any comparable forms that the study site wishes to use must be approved by the Sponsor.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor, or a representative of the FDA. The assigned CRA will review these documents along with all other study conduct documents at specified intervals once SM has been received by the study site. All used, partly used, and unused clinical supplies, including empty containers, are to be returned to the Sponsor designated sites at the conclusion of the study, unless provision is made by the Sponsor for destruction of supplies and containers at the study site. Upon completion of SM accountability and reconciliation procedures by study site personnel and documentation procedures by Sponsor personnel, SM is to be returned to the Sponsor with a copy of the completed SM disposition form.

4.7 Concomitant Medications

Throughout the duration of the study, rescue migraine treatments such as simple analgesics are allowed for symptomatic relief of acute headache episodes as long as their use does not exceed 3 times per week (or 15 treatment days/month) and the pattern of use remains stable. Use of narcotics is not permitted (Appendix 10.9).

Stimulant medications (extended or controlled release formulation) for the treatment of ADHD will be allowed if initiated and maintained on a stable dose (7 days/week) for at least 12 weeks prior to the Screening Visit and continued on the same dose during the study duration (Appendix 10.9).

Prophylactic treatment for migraine is permitted if on a stable dose for at least 12 weeks prior to the Screening Visit including: daily NSAIDs, antiemetics, antihistamines, corticosteroids (i.e., systemic inhaled, or topical), high-dose magnesium supplements (≥600 mg/day), high-dose riboflavin (≥100 mg/day), coenzyme Q10, omega-3, melatonin, muscle relaxants and β-blockers. The dose and the medication must be maintained during the duration of the study (Appendix 10.9).

Triptans, ketorolac, and ergotamines must be used with caution and with a frequency that does not exceed 10 treatment days/month. Subjects will be asked to be consistent in the use of their preferred acute migraine medication and encouraged not to initiate new therapies during the course of the trial (Appendix 10.9).

If a subject exceeds rescue treatment more than 3 times per week, concomitant medication use will not be considered a protocol deviation.

Anti-asthma medication: Albuterol sulfate is the only antiasthma medication allowed as needed (PRN) to keep any respiratory conditions under control (Appendix 10.9).

Treatment for AEs other than minor transient ailments is permitted only in consultation with the Medical Monitor or his/her designee with the exception of required treatments for acute conditions in the emergency room/hospital and/or office visit as indicated.

Additional concomitant medications allowed during the study include: nutritional supplements (e.g., multivitamins), EMLA® or other numbing cream for venipuncture, routine childhood vaccinations, Coronavirus Disease 2019 (COVID-19) vaccine and mydriatics (as needed per Principal Investigator discretion) (Winner et al.).

All concomitant medications will be recorded in the eCRF. Use of rescue medication will also be recorded in the daily Headache Diary and in between visits to the clinical site.

4.8 Non-pharmacologic Adjunctive Treatments

The following complementary and alternative prophylactic approaches to migraine are prohibited during the participation in this study (and as applicable, should be recorded as part of the subject's retrospective headache history):

- Acupuncture
- Manual therapies (chiropractic spinal manipulation, occipital nerve block, massage therapy, physical therapy)
- Herbal and nutritional supplement therapies for migraine prevention (butterbur, feverfew and St. John's Wort)
- Cognitive-behavioral therapy, biofeedback, hypnosis
- Neuromodulation devices

Certain behavioral approaches (e.g., trigger factor avoidance, adequate hydration, migraine prevention diet, stress reduction techniques, regular exercise, and sleep hygiene) are allowed as long as they have been practiced for at least 1 month prior to Screening and will be continued throughout the study. These will be captured in the eCRF.

Prohibited interventions must be discontinued at least 2 weeks prior to Prospective Baseline, and no new non-pharmacologic therapies may be initiated within 1 month prior to Screening or during the study.

4.8.1 Prohibited Medications

Subjects may not be on any prohibited medication as indicated in the Inclusion/Exclusion Criteria.

Subjects treated with the following prophylactic medications should discontinue the treatment 14 days prior to the Prospective Baseline Period: antipsychotics, antimanics, barbiturates, benzodiazepines amitriptyline, lithium, valproic acid, tricyclic antidepressants, AEDs, calcium channel blockers, sedatives, SSRIs, NSRIs, CGRP receptor antagonists, CBD oil, herbal preparations/supplements such as feverfew or St John's wort and/or any medications that could impair or decrease thinking and concentration. It is recommended to taper off antipsychotics, barbiturates, benzodiazepine, tricyclic antidepressants, lithium, amitriptyline, valproic acid, SSRIs and NSRIs as applicable. (Appendix 10.10).

Note: Subjects must refrain from using these medications throughout the duration of the study.

Non-stimulant ADHD medications (e.g., clonidine, atomoxetine, viloxazine and guanfacine) must be discontinued 14 days prior the Prospective Baseline Period (Appendix 10.10).

5 STUDY METHODS

5.1 Study Visits and Procedures

All subjects who are randomized and take at least one dose of SM will be followed according to the protocol regardless of the number of doses of SM taken, unless consent for follow-up is withdrawn. The Sponsor or the Sponsor's designee must be notified of all

deviations from protocol visits or procedures, and these procedures, if applicable, will be rescheduled or performed at the nearest possible time to the original schedule. Subjects/caregivers will be instructed to call study personnel to report any abnormalities during the intervals in between study visits and to come to the study site if medical evaluation is needed and as the urgency of the situation indicates. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the Investigator or qualified designee as source data for study follow-up.

Table 2 shows the Schedule of Events and Assessments for the study. Deviations from study visit windows will be recorded in the eCRF but will not require separate notification to the Sponsor.

Study visits must be scheduled according to the Schedule of Events relative to the Randomization Visit (Visit 3). Visits must not be scheduled relative to the previous visit. Bi-weekly telephone contacts will occur between study visits at Days 14, 43, 71, 99, 127, and 148 (± 2 days).

Table 2 Schedule of Events and Assessments

Assessments	Pre-treatment Phase		Treatment Phase								Post-treatment Phase		
	Screening [a]	Prospective Baseline	Random-ization	Titration				Maintenance			Taper (EOS) (ET)		Safety Follow up (by phone)
Study Visit #	1	2	3	PC	4	PC	5*	PC	6,7	8	PC	9	
Day of Study Visit	-56	-28	1	14[b]	29	43[b]	57	71,99,127[b]	85,113	141	148[b]	162	169-183[l]
Week of Study Visit	-8 to -5	-4 to -1	-		4		8		12,16	20		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[e]				X [V6]				
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[m]	
Serum pregnancy test (FOCP only)	X												
Urine pregnancy test (FOCP only)		X	X		X		X		X	X		X	
Urine drug screen	X						X		X	X		X	

Assessments	Pre-treatment Phase		Treatment Phase								Post-treatment Phase		
	Screening [a]	Prospective Baseline	Random-ization	Titration				Maintenance			Taper (EOS) (ET)		Safety Follow up (by phone)
Study Visit #	1	2	3	PC	4	PC	5*	PC	6,7	8	PC	9	
Day of Study Visit	-56	-28	1	14[b]	29	43[b]	57	71,99,127[b]	85,113	141	148[b]	162	169-183[l]
Week of Study Visit	-8 to -5	-4 to -1	-		4		8		12,16	20		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
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	X[f]	X	X[f]	X	X[f]	X[f]	X	X[f]	X[f]
Review Headache Diary		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	X
Dispense SM			X[h]		X		X		X	X[i]			
Biweekly Phone Calls				X		X		X		X	X		
AEs			X	X	X[j]	X	X[j]	X	X[j]	X[j]	X	X[j]	X[j]
SM return & adherence					X		X		X	X		X	
PK blood sampling										X[k]			
Dose reduction instruction				X		X		X			X		

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

* Visit 5 is end of titration and beginning of Maintenance Period of the Treatment Phase hence included within Section 5.1.5 for clarification.

a. Subjects who had used TPM or any disallowed prophylactic migraine therapy must discontinue the treatment at least 2 weeks before the start of the Prospective Baseline Period, with an appropriate taper when applicable.

b. Bi-weekly telephone contacts will occur between study visits, at Days 14, 43, 71, 99, 127, and 148 (± 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 rate, 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/ET Visit occurs.
m. Subjects who discontinue from the study earlier than the EOS visit (visit 9) should undergo all EOS procedures included in visit 9 during the ET visit.

Note: Besides the testing specified during the respective visits in the Table 2 above, repeat testing for clinical laboratory parameters, vital signs, and/or ECG may be permitted, at the discretion of the Investigator. However, these repeat testing will require justification from the site and agreement with the Medical Monitor and the Sponsor on a case-by-case basis prior to conducting the tests.

5.1.1 Visit 1 – Screening (Day -56)

All reasons for screening failure will be recorded. If the subject passes screening but fails eligibility at Randomization visit (Visit 3), the reason(s) will also be recorded in the eCRF.

For subjects eligible for study participation, a Prospective Baseline Visit will be scheduled allowing for at least a 2-week/14-day washout of any disallowed migraine preventative medications the subject was receiving at Screening.

The following assessments will be conducted at this visit (screening assessments may be performed over multiple days):

- Obtain written informed consent/assent
- Obtain demographics
- Collect retrospective headache history, including non-pharmacological adjunctive treatments (last 3 months)
- Review inclusion/exclusion criteria
- Collect medical, family and psychiatric histories
- Perform physical examination (excluding genitourinary system) including height, weight and neurological examination
- Perform visual neurological exam
- Perform 12-lead ECG
- Record vital signs (pulse rate, blood pressure [BP], temperature, and respiration rate [RR])
- Collect blood samples for hematology and serum chemistry
- Collect serum sample for pregnancy testing (FOCP only)
- Collect urine sample for drug screen and urinalysis
- Administer C-SSRS
- Administer PedMIDAS scale
- Record concomitant medications

5.1.2 Visit 2 – Prospective Baseline Period (Day -28, Weeks -4 to -1)

The following assessments will be conducted at this visit**:**

- Complete caregiver placebo training
- Record vital signs (pulse rate, BP, temperature, and RR)
- Collect blood samples for hematology and serum chemistry
- Collect urine sample for urinalysis and for pregnancy testing (FOCP only)
- Administer C-SSRS
- Review and record concomitant medications
- Provide Headache Diary training to record daily headache activity/symptoms and rescue medication usage

- Download Headache Diary app on caregivers' phone

5.1.3 Visit 3 (+2 days) – Randomization (Day 1)

The following assessments will be conducted at this visit**:**

- Review inclusion/exclusion criteria
- Record vital signs (pulse rate, BP, temperature, and RR)
- Collect urine sample for pregnancy test (FOCP only)
- Administer C-SSRS
- Review and record concomitant medications
- Review Headache Diary for eligibility
- Administer PedMIDAS, PedsQL 4.0 scales
- Perform cognitive assessment
- Perform eye exam
- Record AEs
- Randomization
- Dispense SM (4-week supply) and provide instructions for dose titration

5.1.4 Titration Period (Days 1 to 56, Week 1 to end of Week 8)

Intervening Phone Calls

At Days 14 (± 2 days) and 43 (± 2 days) there will be telephone calls to subjects to assess the tolerability of the SM treatment.

The following assessments will be made during these telephone contacts**:**

- Review and record concomitant medications
- Record AEs
- Provide guidance (as needed) on dose reduction

Visit 4 (Day 29 ± 7 days)

During Treatment Phase (Visits 4 through 9), sample collection and testing have been specified for respective visits by the Sponsor. Besides the testing specified during these respective visits, repeat testing for clinical laboratory parameters, vital signs, and/or ECG may be permitted, at the discretion of the Investigator. However, these repeat testing will require justification from the site and agreement with the Medical Monitor and the Sponsor on a case-by-case basis prior to conducting the tests.

The following assessments will be conducted at this visit**:**

- Perform physical examination (excluding genitourinary system) including height and weight, and neurological examination

- Record vital signs (pulse rate, BP, temperature, and RR)
- Collect urine sample for pregnancy test (FOCP only)
- Administer C-SSRS
- Review and record concomitant medications
- Review Headache Diary
- Record AEs
- Collect SM and assess adherence; retrain as needed
- Dispense SM (4-week supply) and review medication instructions with subject and caregiver
- Placebo training refresher

5.1.5 Maintenance Period (Days 57 to 140, Week 9 to the end of Week 20)

Visit 5 (Day 57 ± 7 days)

The following assessments will be conducted at this visit**:**

- Perform 12-lead ECG
- Record vital signs (pulse rate, BP, temperature, and RR)
- Collect blood samples for hematology and serum chemistry
- Collect urine sample for urinalysis and for pregnancy test (FOCP only)
- Collect urine sample for drug screen
- Administer C-SSRS
- Review and record concomitant medications
- Review Headache Diary
- Administer PedMIDAS, PedsQL 4.0 scales
- Perform cognitive assessment
- Record AEs
- Collect SM and assess adherence; retrain as needed
- Dispense SM (4-week supply) and review medication instructions with subject and caregiver

Visits 6 (Day 85 ± 7 days) and Visit 7 (Day 113 ± 7 days)

The following assessments will be conducted at these visits**:**

- Perform physical examination (excluding genitourinary system) including height and weight, and neurological examination
- Record vital signs (pulse rate, BP, temperature, and RR)
- Collect urine sample for pregnancy testing (FOCP only)
- Collect urine sample for drug screen
- Perform eye exam (only at Visit 6)
- Administer C-SSRS
- Perform cognitive assessment

- Review and record concomitant medications
- Review Headache Diary
- Record AEs
- Collect SM and assess adherence; retrain as needed
- Dispense SM (4-week supply) and review medication instructions with subject and caregiver
- Placebo training refresher (only at Visit 6)

Intervening Phone Calls

At Days 71 (± 2 days), 99 (± 2 days) and 127 (± 2 days), there will be telephone calls to subjects to assess the tolerability of SM treatment.

The following assessments will be made during these telephone contacts**:**

- Review and record concomitant medications
- Record AEs
- Provide guidance (as needed) on dose reduction, up to one dose reduction will be allowed for safety and tolerability during this period. Additional dose titration related to body weight changes will be reviewed and approved by the Medical Monitor and the Sponsor on a case by case basis.

5.1.6 Taper Period (Days 141 to 161, Week 21 to the end of Week 23)

Intervening Phone Call

At Day 148 (± 2 days) there will be a telephone call to subjects to assess the tolerability of the SM treatment.

The following assessments will be made during these telephone contacts**:**

- Review and record concomitant medications
- Record AEs
- Provide guidance (as needed) on dose reduction

Visit 8 (Day 141 ± 7 days)

The following assessments will be conducted at this visit**:**

- Perform physical examination (excluding genitourinary system) including height and weight, and neurological examination
- Record vital signs (pulse rate, BP, temperature, and RR)
- Collect blood samples for hematology and serum chemistry
- [redacted]
- Collect urine sample for urinalysis and for pregnancy testing (FOCP only)
- Collect urine sample for drug screen
- Administer C-SSRS

- Administer PedMIDAS, PedsQL 4.0
- Perform cognitive assessment
- Review and record concomitant medications
- Review Headache Diary
- Record AEs
- Collect SM and assess adherence
- Dispense 3-week supply of SM and provide instructions for dose tapering

Visit 9 (Day 162 ± 7 days) – End of Study (EOS) Visit

The following assessments will be conducted at this visit**:**

- Perform physical examination (excluding genitourinary system) including height and weight, and neurological examination
- Perform 12-lead ECG
- Record vital signs (pulse rate, BP, temperature, and RR)
- Collect blood samples for hematology and serum chemistry
- Collect urine sample for urinalysis and for pregnancy testing (FOCP only)
- Collect urine sample for drug screen
- Perform visual neurological exam
- Perform eye exam
- Administer C-SSRS
- Review and record concomitant medications
- Administer PedMIDAS, PedsQL 4.0 scales
- Perform cognitive assessment
- Record AEs
- Collect SM and assess adherence

5.1.7 Safety Follow-up Telephone Call (Weeks 24 through 26)

The following assessments will be made during this telephone contact, at 1 to 3 weeks following the EOS/ET visit**:**

- Review concomitant medications
- Record AEs
- Perform cognitive assessment (Appendix 10.5)

[redacted]

6 STUDY VARIABLES AND ASSESSMENTS

6.1 Headache Diary– Preventive Therapies (Version 2.0)

The Headache Diary (Appendix 10.2) is the primary tool for collecting information about migraine headaches and will be used in the format recommended by the NINDS. The diary will serve as the primary source for the primary outcome measure of MMDs. The diary will be provided to caregivers in an electronic format as an application and uploaded on the caregivers' personal mobile device or on a dedicated locked mobile device in case the caregiver does not have a personal device. Reminder alarms will be programmed for diary completion and SM administration to ensure regular data entry and treatment compliance.

The caregiver will enter data with the subject's assistance every day during the Prospective Baseline Period and throughout the duration of treatment, regardless of whether they experienced a headache.

Subject's caregivers will be trained to complete a prospective 28-day headache calendar to document if a headache occurred. Based on the diagnostic criteria for migraine (ICHD-3), if the subject experienced a migraine headache as documented in the calendar, the dairy will be completed to record headache specific and detailed information.

For any given headache day, the responder will include information about the timing of the attack (when the headache started and ended and whether or not it recurred within a 24-hour period), the location and severity of the pain, premonitory and aura symptoms (nausea, photophobia and phonophobia), rescue medications (if used, selected from a list), the impact of the headache on subject's daily activities, and treatment adherence after randomization. Severity of pain will be measured on a scale of 0 to 10, where 0 = No pain and 10 = The worst pain.

6.2 Pediatric Migraine Disability Assessment Questionnaire

The PedMIDAS was developed based on the adult migraine disability assessment and measures the effect of migraine headaches on school absence, functioning during school, and disruption of home and social/recreational activities. It is the only instrument designed and validated to assess migraine disability in pediatric and adolescent patients (Hershey et al., 2001), and has been validated for the age range of 4 to 18 years.

The PedMIDAS (Appendix 10.3) is a publicly available tool that evaluates the impact of headaches on school, home, play, and social activities. It is comprised of 6 questions related to the impact of headache on school performance such as number of days missed in various activities over the past 90 days (Questions 1-3). The fourth question concerns the disability at home, while the last two questions relate to social and sport activities. The Headache Disability Score is a composite of the values for the 6 questions, where a total disability score of 0 to 10 = Little to no disability;

11 to 30 = Mild disability; 31 to 50 = Moderate disability; and >50 = Severe disability. The ratings for two additional prompts for Headache Frequency and Headache Severity are not included in the Headache Disability Score but are used for clinical reference.

The questionnaire is self-administered by the subject and may be completed in collaboration with the subject's parent or caregiver, as long as the answers are confirmed by the subject.

The PedMIDAS will be administered at the Screening Visit, Visit 3, Visit 5, Visit 8 and Visit 9.

6.3 Pediatric Quality of Life Inventory, Version 4.0

The PedsQL 4.0 is a generic measure of HRQoL that has been developed for use with children 2 to 18 years of age (Varni, Seid, & Rode, 1999). The questionnaire allows a comparison of QoL effects across acute and chronic health conditions and with healthy children and is available as child self-report and parent-proxy report. The measure has been validated in patient populations with cancer, rheumatoid disease, diabetes, and orthopedic conditions, as well as in children ages 7 to 12 years with a recurrent headache symptom.

The PedsQL 4.0 (Appendix 10.4) has two forms: a child self-report and a parent-report form. The child self-report includes 3 age ranges for young children (5-7 years), children (8-12 years), and adolescents (13-18 years). The PedsQL scale consists of 23 items (questions) comprising four areas of functioning, including physical (8 items), emotional (5 items), social (5 items), and school (5 items). The items are assessed based on the recall interval of 1 month and are scored on a 5-point Likert scale of 0 to 4, where 0= Never; 1 = Almost never; 2 = Sometimes; 3 = Often; and 4 = Almost always.

The PedsQL 4.0 will yield a total score, 2 summary scores, (the Physical Health Summary Score and the Psychosocial Health Summary Score) and 3 sub-scores (Emotional, Social and School Functioning). The Psychosocial Health Summary Score is a composite of the scores from the Emotional, Social and School Functioning scales; the Physical Health Summary Score is the same as the Physical Functioning scale score.

To obtain the total score, the items are reverse-scored and linearly transformed (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0) to a scale that ranges from 0 (worst HRQoL) to 100 (best HRQoL). The Total Scale Score is the sum of all the items in all the scales.

The parent and child should be completing their respective questionnaires independently of each other.

The PedsQL 4.0 will be administered at Visit 3, Visit 5, Visit 8 and Visit 9.

[redacted]

6.5 Safety Variables and Assessments

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Supernus or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subjects.

Safety assessments include monitoring, evaluation, and recording of all concomitant medications, and the evaluation of AEs, clinical laboratory test results, vital signs, 12-lead ECGs, suicidality monitoring/C-SSRS results, the performance of physical and neurological examinations, and cognitive assessment as detailed in the Schedule of Events and Assessments (Table 2). Subjects will also be monitored for visual/ocular disturbances, nephrolithiasis, oligohydrosis, hyperthermia, metabolic acidosis (serum bicarbonate), hyperammonemia, and hepatic injury.

6.6 Adverse Events

As defined by the ICH Guideline for GCP, an AE is any untoward medical occurrence in a patient or clinical investigation subject who was administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment.

An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease, intercurrent injuries, or exacerbation of an existing disease.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG) that results in symptoms, a change in treatment, or discontinuation from SM.
- Recurrence of an intermittent medical condition (e.g., muscle pain) not present at baseline.

Surgical procedures are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period.

6.6.1 Causality

AEs may be categorized as either ADRs or SADRs based on their relationship to SM and the degree of certainty about causality.

SADRs are a subset of AEs for which there is evidence to suggest a causal relationship between the drug and the AE, i.e., there is a reasonable possibility that the drug caused the AE.

ADRs are a subset of all SADRs for which there is reason to conclude that the drug caused the event.

6.6.2 Recording and Evaluation of Adverse Events

All subjects who provided written Informed Consent (Visit 1) and prior to randomization, will be questioned regarding the occurrence of AEs which will be captured as medical history. TEAEs are AEs that occur after study treatment has started, or an already present event that worsens either in intensity or frequency following the study treatment.

At each subsequent visit or contact with the subject, after the first administration of SM, the investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the appropriate AE module of the eCRF. All clearly related signs, symptoms, and abnormal results for diagnostic procedures should be recorded in the source document, though they may be grouped under one diagnosis. For example, fever, elevated WBC count, cough, abnormal chest X-ray, etc., may be reported as a single AE of "pneumonia". The clinical course of each AE will be followed for at least 30 days after subject's early discontinuation/EOS, until resolution (AEs in general) or based on the medical judgment of the Investigator, the event has stabilized or is assessed as chronic.

The Investigator is responsible for evaluating AEs and determining the following:

- **Serious vs. Non-serious**: Is the event an SAE?
- **Causality**: Was AE related or not related to the SM?
- **Severity**: How pronounced is the incapacity/discomfort caused by an AE?

6.6.3 Criteria for Assessing Severity

The Investigator will evaluate the comments of the subject and the response to treatment in order that he or she may judge the true nature and severity of the AE. Severity refers to the accumulated intensity of discomfort/impairment of health since the last recording of AEs and will be assessed according to the following criteria:

- **Mild:** Awareness of sign, symptom, or event, but easily tolerated
- **Moderate:** Discomfort enough to interfere with usual activity and may warrant intervention
- **Severe:** Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention

The criteria for assessing severity are different from those used for seriousness.

6.6.4 Criteria for Assessing Causality

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. These are defined as follows:

Not suspected: The temporal relationship of the AE to SM administration makes a causal relationship unlikely, or other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

- **Not related:** Temporal relationship to SM administration is missing or implausible, or there is an evident other cause.
- **Unlikely related:** Temporal relationship to SM administration makes a causal relationship improbable; and other drugs, chemicals, or underlying disease provide plausible explanations.

Suspected: The temporal relationship of the AE to SM administration makes a **causal relationship possible**, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

- **Possibly related:** Temporal relationship to SM administration is plausible, but concurrent disease or other drugs or chemicals could also explain event. Information on drug withdrawal may be lacking or unclear. This will be reported as a **SADR**.
- **Definitely related**: Temporal relationship to SM administration is plausible, and concurrent disease or other drugs or chemicals cannot explain event. The response to withdrawal of the medication (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary. This will be reported as an **ADR**.

6.6.5 Serious Adverse Events

AEs are classified as serious or non-serious. An AE or ADR is considered “serious” if, in the view of either the investigator or Sponsor, it results in one of the following outcomes:

- death
- life-threatening AE (i.e., the subject was at immediate risk of death from the AE as it occurred. This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death.)
- in-patient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening or result in death or hospitalization but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, blood dyscrasias, a seizure that did not result in in-patient hospitalization or intensive treatment for allergic bronchospasm in an emergency department would typically be considered serious.

6.6.6 Investigator Responsibilities for Reporting SAEs

AEs will be followed for at least 30 days after subjects' early discontinuation/EOS or until resolution (AEs in general). SAEs will be followed until resolution or until no further/additional information can be obtained regarding the event.

The Investigator must immediately report to the Sponsor all SAEs, regardless of whether the Investigator believes they are drug related.

All SAEs must be reported to the Drug Safety Contact within 24 hours of first becoming aware of the SAE. The Investigator must complete an SAE Form and include a detailed description of the SAE, as well as other available information pertinent to the case (e.g., hospital records, autopsy reports and other relevant documents as applicable). The investigator will keep a copy of this SAE Report form on file at the study site.

The Investigator or study physician, after thorough consideration of all facts that are available, must include an assessment of causality of an AE to SM in the report to the Sponsor.

Follow-up information, or new information available after the initial report, should be actively sought and reported to the Sponsor, as it becomes available, using the SAE Report Form.

6.6.7 Other Events Requiring Immediate Reporting

The Investigator must report a pregnancy that occurs in a subject during a clinical study to the Drug Safety Contact within 24 hours of first becoming aware of the event. Pregnancy should be reported on a Pregnancy Report Form. The Investigator should discuss the case with the Medical Monitor; the Investigator must follow any pregnant subject for 3 months after the child is born. Any AEs concerning the pregnancy of the subject during pregnancy or the child after birth must be documented and reported to the Sponsor.

Acute suicidal crisis or clinically significant suicidal behavior or ideation should be reported to the Drug Safety Contact within 24 hours of first becoming aware of the event.

6.6.8 Sponsor Responsibilities for Reporting SAEs

The Sponsor will inform Investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (i.e., within specific timeframes). For this reason, it is imperative that study sites submit SAE information to the Sponsor in the manner described above.

Investigators must comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB. Investigators must also submit the safety information provided by the Sponsor to the IRB unless the country legal regulation requires that the Sponsor should be responsible for the safety reporting to the IRB.

It is the responsibility of the Sponsor to notify all participating investigators, in a written IND safety report, of any SADR that is both serious and unexpected. The Sponsor will also notify participating investigators if applicable of any findings that suggest a significant risk for human subjects. Such findings will typically lead to safety-related changes in the study protocol, Informed Consent, and/or Investigator's Brochure.

6.6.9 Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulatory agencies, IRB, etc.) might also be warranted.

Several AEs are known to be associated with the long-term use of TPM and can be expected with treatment with SPN-538 ("National Institutes of Health-DailyMed- Trokendi XR- Prescribing Information.," 2022). Consistent monitoring is required for the following AESIs:

- Metabolic acidosis (serum bicarbonate)
- 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 cell count or neutrophils
- Visual changes: subjects presenting with blurry vision, ocular pain, and visual field defects must be discontinued early and closely followed to ensure a prompt resolution of ocular AEs.

- Suicidal behavior and ideation
- Serious skin reactions (TPM should be discontinued at the first sign of rash, unless rash is not drug-related)
- Negative effect on growth (weight and height)
- Cognitive and memory function impairments
- Nephrolithiasis

The Site Investigator must report all AESIs to Supernus drug safety team within 24 hours of becoming aware of the information using the SAE/AESI Report form.

6.7 Treatment-Emergent Suicidal Ideation

Prospective assessment of suicidal ideation and suicidal behavior is a mandatory part of the safety evaluations for any drugs developed for epilepsy and psychiatric indications ("Center for Drug Evaluation and Research. Suicidal Ideation and Behavior," 2012). In this study, the initial evaluation of subjects will be conducted prior to enrollment to assess lifetime suicidal ideation and to identify subjects who must not participate in the trial due to pre-existing suicidality risk. The assessment will then be repeated at each subsequent study visit (except telephone contacts) to monitor the occurrence of new suicidal and self-injurious tendencies.

6.7.1 Columbia Suicide Severity Rating Scale (C-SSRS)

Assessment of suicidal ideation and behavior will be conducted using the C-SSRS (Appendix 10.6). The C-SSRS is an FDA-recommended prospective assessment instrument that directly 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 instrument has been validated and used successfully in both children and adolescent patients with various psychiatric disorders that do not involve cognitive impairment. The C-SSRS outcomes that can be used for clinical management and safety monitoring are suicidal lethality rating, suicidal ideation score, and suicidal ideation intensity rating. In this study, the Children's Baseline version (Appendix 10.6.1) will be used at Screening, and the Children's Since Last Visit version (Appendix 10.6.2) will be used at each subsequent clinic visit.

6.7.2 Suicide Risk Management Plan

The protocol procedures related to clinical care of patients with treatment-emergent suicidal ideation and behavior must be implemented to ensure proper management of the event and protection of subjects' safety. If a disclosure of suicidal ideation is revealed as part of the C-SSRS questionnaire or when a subject spontaneously expresses that he/she may be a threat to him/herself, the study team should be

prepared to quickly evaluate the event and to determine the appropriate course of action.

6.7.3 Assessment of Suicide Risk

Any indication of suicidal ideation should be evaluated as soon as possible by appropriately trained staff. The Investigator is responsible for making the final judgment regarding potential suicide risk and need for subsequent action.

6.7.4 Acute Suicidal Crisis

A person evaluated as being at high risk should be transferred to an immediate care facility. The Investigator will guide intervention as clinically indicated and follow up with the subject within 1 week and/or refer him/her to a qualified mental health professional.

6.7.5 Non-acute Suicidal Risk

The Investigator will conduct safety planning with the subject and will follow up within 1 week. Reference materials for subjects and caregivers should include lists of mental health organizations and professionals, outpatient behavioral services, local crisis, and peer support groups and Suicide/Crisis Hotlines.

6.8 Clinical Measurements

6.8.1 Laboratory

All clinical laboratory tests will be performed by a central laboratory as specified in the reference binder.

Details for collecting, handling, and shipping samples (including shipment addresses) will be detailed in a separate clinical laboratory manual. The Schedule of Events and Assessments (Table 2) shows the time points at which blood and urine samples will be collected for clinical laboratory tests.

Table 3 presents the clinical laboratory tests to be performed.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Red blood cell count, hemoglobin, hematocrit, platelets count, and white blood cell count with differential
Serum Chemistry	**Electrolytes**: Na^+, K^+, phosphate, chloride, bicarbonate
	Liver function tests: alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, gamma-glutamyl transpeptidase
	Renal function parameters: blood urea nitrogen, creatinine
	Other: glucose, Ca^{2+}, albumin, total protein, ammonia

Category	Parameters
Urinalysis and urine pregnancy test (FOCP only)	Complete urinalysis with microscopic examination, human chorionic gonadotropin
Urine Drug Screen	Cocaine, amphetamines, barbiturates, benzodiazepines, cannabinoids, opioids, phencyclidine, propoxyphene, methadone and alcohol
Serum Pregnancy Test (FOCP only)	Human chorionic gonadotropin

6.8.2 Vital Signs

Vital signs' measurements (e.g, BP, pulse rate, temperature, and RR) will be obtained at each visit. BP and pulse rate will be measured after the subject has been sitting for 5 minutes. Route of temperature may be oral or temporal, per clinical practice, but should remain consistent throughout the subject's participation. Vital signs may be taken at any other time, as deemed necessary by the Investigator.

6.8.3 Medical and Psychiatric History

Medical and psychiatric history will be collected at Screening as per the Schedule of Events and Assessments (Table 2).

6.8.4 Retrospective 3-months Headache History

Retrospective 3-months headache history will be collected at Screening to record the first onset of migraine headache diagnosis, including the duration, frequency and location of the experienced migraine. Furthermore, if potential triggers such as food, medication, and symptoms associated with the migraine attack are known, these will be documented.

6.8.5 Physical and Neurological Examinations

The physical examination conducted at Screening will include assessments of all body systems other than genitourinary and at visits designated on the Schedule of Events and Assessments (Table 2). Measurement of height, and weight will be performed to monitor for signs of growth retardation. A special assessment will be made regarding the occurrence of decreased sweating and an elevation in body temperature above normal. 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 examination, only changes from baseline (Screening visit) will be noted.

Routine neurological exam at Screening will be aimed at detecting any possible causes of headache other than migraine. After the initiation of treatment, a neurological evaluation will help to assess for effects of SPN-538 on the nervous system, such as

impaired reflexes, balance problems, muscle weakness, paresthesia/numbness and tingling, speech difficulties, mental confusion or excessive fatigue. As part of the visual neurological examination, the following will be assessed at Visits 1 and 9: extraocular movements, pupils and confrontation visual fields for each eye (Appendix 10.7). Equipment necessary for this part of the examination listed in the next section under Eye Exam.

6.8.6 Eye Exam

An eye examination (does not include intraocular pressure) will be performed at Visits 3, 6 and 9 (EOS). It will measure visual acuity and visualize the optic disc through a fundoscopic exam (Appendix 10.8). Subjects will be monitored for visual/ocular disturbances and potential signs of angle closure glaucoma during the participation in the study. If signs or symptoms of angle closure glaucoma (see below) develop and are observed during the clinical visits or reported at the intervening phone calls, subjects will be instructed to stop the SM immediately and be referred to an ophthalmologist or optometrist for priority exams (see below) as needed. If the subject goes to the ED, an exam by an ophthalmologist (preferred) or optometrist should be performed within 24 hours of the presentation.

Equipment at the site necessary to perform the visual neurological and eye exam consists of the following:

- Near card
- Wall Snellen Chart (optional, at Investigator's discretion based on outcome from routine eye exam)
- Penlight
- Hand help Ophthalmoscope (direct or Panoptic)
- Amsler grid (optional, at Investigator's discretion based on outcome from routine eye exam)

The Wall Snellen Chart uses a geometric scale to measure visual acuity, with normal vision at a distance being set at 20/20. The numerator represents the distance that the patient is standing from the chart (in feet), while the denominator represents the distance from which a person with perfect eyesight is still able to read the smallest line that the patient can clearly visualize.

The Amsler grid could be used to help detect early signs of retinal disease and monitor changes in vision after diagnosis.

Note: The Sponsor has appended Snellen chart (Appendix 10.8.1) and Amsler grid (Appendix 10.8.2) for every participating site as a tool to be used by the investigator if further examination is deemed necessary after a routine eye exam outcome.

Symptoms and signs of Angle Closure Glaucoma that might develop within the first 2-3 weeks of starting the medication, consist of the following:

- Rapid onset of pain that is often severe (typically, both eyes are affected)
- Headache (may be different from usual migraine)
- Nausea and/or vomiting
- Blurred vision, worse at distance and better at near
- Cloudy vision
- Halos around lights
- Conjunctival injection (redness)
- Mid-dilated and fixed or poorly reactive pupils

If symptomatic, the Sponsor recommends an urgent referral to an ophthalmologist or optometrist for priority exams (marked with asterisk):

- Best corrected visual acuity at far distance, usual correction at near distance*
- Pupil exam (Equal? Reaction to light? Afferent pupillary defect?) *
- Eye movements (up, down, horizontal) *
- Slit lamp exam (for corneal edema and narrow angle) *
- Intraocular pressure (applanation, air puff or Tonopen) *
- Anterior segment ocular coherence tomography (OCT) to confirm angle closure*
- Gonioscopy if intraocular pressure is elevated
- Dilated fundus exam (if possible) or B-scan ultrasound (for choroidal effusions)

6.8.7 Cognitive Assessment

Cognition refers to the mental processes involved in gaining knowledge and comprehension such as thinking, knowing, remembering, judging, and problem solving. These higher-level functions of the brain encompass language, imagination, perception, and the planning and execution of complex behaviors. Monitoring for cognitive/neuropsychiatric effects is recommended as part of standard clinical practice in TPM use ("National Institutes of Health-DailyMed- Trokendi XR- Prescribing Information.," 2022). The sponsor created a checklist (Appendix 10.5) of questions related to the subject's daily activities; subjects are asked to rate each question on a scale from 0 to 3 where 0 means never and 3 very often based on his/her recollection of the past weeks since the last visit. It is recommended to conduct the assessment with the parent(s) first. If discrepancies are found between different sources of information, the study staff will have to use their best clinical judgement.

Changes in cognitive function will be assessed at Visit 3, Visits 5 through 9 and at the safety follow-up phone call after the EOS.

6.8.8 Electrocardiograms (ECGs)

A 12-lead ECG will be obtained as per the Schedule of Events and Assessments (Table 2). Additional ECGs may be performed at other times if deemed necessary by the Investigator.

The ECG will be recorded while the subject is resting in a supine position. The ECG will electronically measure the PR, QRS, QT, and QTc intervals, and HR. All ECG tracings will be reviewed within 24 hours by the Investigator or qualified Sub-Investigator. PR intervals will be determined for each of these ECGs from a single reading. Invalid measurements will be repeated. QTc will be reported as QTcF.

7 STATISTICAL METHODS

7.1 General Considerations

All data will be analyzed using SAS® (SAS Institute, Inc., Version 9.3 or later).

In general, continuous variables will be summarized using standard descriptive statistics including number of subjects (n), mean (S), median, interquartile range (Q1, Q3) minimum, and maximum. Categorical variables will be summarized with frequencies and percentages.

The data summaries will be accompanied by individual subject data listings, as specified in Sections 16.2 and 16.4 of ICH Guidance E3, sorted by unique subject identifier. All data available from the electronic CRFs will be listed. Unscheduled measurements will be excluded from the descriptive statistics and statistical analysis but will be included in listings.

Categorical variables will be analyzed using categorical statistical methods such as Pearson's Chi-square test or Fisher's exact test as appropriate.

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

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.

Complete details of the statistical analysis will be provided in a separate SAP.

7.2 Handling of Missing Data

Missing endpoint values in this study may result from subjects discontinuing from the study prematurely or missing intermediate assessments while remaining on study. The primary efficacy analysis method will be based on a Mixed Model for Repeated Measures (MMRM) which utilizes all available data (complete and partial) from subjects included in an analysis set. The MMRM-based approach assumes that missing diary data are MAR. MAR refers to a missingness mechanism that is independent of missing responses, conditionally on observed response history and covariates. That is, given the observed data, the reason for the missing data does not depend on the underlying unseen data.

For primary analysis, missing 28-day MMDs for subjects discontinued due to AE or lack of efficacy will be explicitly imputed by the mean values obtained from MI under the missing not at random (MNAR) assumption before implementing the MMRM. Missing 28-day MMDs for subjects discontinued due to reasons other than AE or lack of efficacy will not be imputed for the primary efficacy analysis.

Sensitivity analyses of the primary endpoint to investigate robustness to missing primary endpoint data will be performed by assuming that missing diary data are MNAR,

meaning that the probability that an observation is missing may depend on its underlying unobserved value. Missing data handling for safety data will be described in the SAP.

7.3 Analysis Populations

The **Randomized Population** consists of all subjects who are randomized via the IWRS.

The **Full Analysis Set (FAS)** is defined as subjects who received at least one dose of study drug and have a baseline and at least one valid post-randomization assessment of monthly migraine based on diary days. The FAS will be used to assess the primary endpoint and secondary efficacy endpoints, and subjects will be included in analyses based on randomized treatment.

The **Per Protocol Set (PPS)** includes all subjects in the FAS who have completed Visits 1-8 with no missing MMDs and no important protocol deviations. PPS will be used as supplementary analysis of the primary and secondary efficacy endpoints with treatment classification based on the treatment received.

The **Safety Analysis Set** includes all subjects randomized into the study who received at least 1 dose of SM. Data will be analyzed according to the treatment received.

[redacted]

7.4 Demographics and Baseline Analysis

Demographic/baseline variables including age, sex, ethnicity, race, height, and weight at screening, and medical and neurological histories will be summarized using descriptive statistics for continuous variables and counts and percentages for categorical variables. Descriptive summaries will be presented by treatment group for FAS, PPS, and Safety Analysis Set.

7.5 Subject Disposition

A disposition of subjects will include the number and percentage of subjects in each of the following categories:

- Subjects in the Randomized Population
- Subjects in the FAS
- Subjects in the PP Analysis Set
- Subjects in the Safety Analysis Set

[redacted]

Within each of the previous categories, the number and percentage of subjects who completed and discontinued from the study and primary reason for early discontinuation

will be summarized. The 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 (study is terminated by the Sponsor, blind is broken, subject has relocated or death etc.)

7.6 Study Medication Exposure and Compliance

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

Duration of treatment exposure will also be summarized using descriptive statistics.

Percent of SM Compliance is calculated as % compliance=100*(*Num*/*Den*), where

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

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

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

For each treatment, SM compliance will be summarized by compliance category (< 80%, 80-120%, and >120%) and number of subjects in each compliance category. SM compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, minimum, and maximum) 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.

7.7 Concomitant Medications

Prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary (WHO DD) and summarized descriptively by ATC classification level 4 and preferred term for the Safety Population. 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 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.

7.8 Efficacy Analysis

Based on the FAS, the observed value and change from baseline will be summarized using descriptive statistics as described in Section 7.1 and 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.

7.8.1 Primary Efficacy Analysis

The primary efficacy endpoint, change from the Prospective Baseline Period in 28-day rate MMDs, will be analyzed using MMRM, which assumes that missing data are MAR. All post-baseline study visits will be included in the model; however, the primary comparison will be between SPN-538 and placebo at Month 5 (last 4 weeks of the Maintenance Period). The model will include fixed effect terms for 28-day rate of MMDs for the Prospective Baseline Period, treatment group, Prospective Baseline monthly migraine-specific acute rescue medication (28-day rate) use, visit, and treatment-by-visit interaction as independent variables. The model parameters will be estimated using restricted maximum likelihood method with an unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom.

If the MMRM model with the unstructured variance-covariance matrix does not converge using the default Newton-Raphson fitting algorithm by PROC MIXED in SAS, then the Fisher scoring algorithm or the no-diagonal factor analytic structure will be used (Lu & Mehrotra, 2010). If the model still fails to converge, then the first (co)variance structure which does not have convergence problem will be used for the analysis from the following ordered list:

1. Heterogeneous Toeplitz
2. Heterogeneous Autoregressive of order 1
3. Toeplitz
4. Autoregressive of order 1
5. Compound Symmetry

The denominator degrees of freedom will be estimated using the BETWITHIN option in SAS when any of the covariance structures is used with the sandwich variance estimator.

The least square mean (LS Mean) of each treatment group (placebo and SPN-538) along with the corresponding standard error, p-values, difference in the LS Mean between SPN-538 and placebo (SPN-538 minus placebo), and 95% CIs will be computed at each visit.

To assess the robustness of the primary analysis under the MAR assumption, two sensitivity analyses will be performed based on multiply imputed data assuming missing data are MNAR. The first sensitivity analysis will be based on placebo-based MI in which missing values for the subjects in the SPN-538 treatment group would adopt the outcome model estimated from the placebo arm. The second sensitivity analysis will be performed using a 'tipping point' methodology to assess the assumption of MAR in the primary analysis. The tipping point analysis will progressively impose increasing shift parameters to the imputed observations under the MNAR assumption in the active treatment arm, not to the placebo arm, to assess how severe departures from MAR must be to overturn the conclusion from the primary analysis.

The details for both approaches will be provided in the SAP.

7.8.2 Multiple Comparisons

The overall type I error rate for the study will be preserved at the two-sided 5% significance level by using a sequential (hierarchical) testing for the primary and secondary endpoints. The details will be provided in the SAP

7.8.3 Secondary Efficacy Analyses

Secondary endpoints will be analyzed based on the FAS using appropriate statistical models based on the type of endpoints.

Analyses of Secondary Endpoints

1. Monthly Migraine Responders: For each subject, a binary response variable for change from baseline in the MMDs during the last 4 weeks of the Treatment Phase relative to baseline will be set to 'YES' if a subject's % reduction is ≥ 50% or 'NO' otherwise. The proportion of responders will be presented for each treatment group. The 2-sided 95% CI around the difference in proportions (SPN-538 dose minus Placebo) and the p-value from Pearson's Chi-squared Test or Fisher's Exact Test will be presented.
2. Migraine-Specific Acute Rescue Medication: The change from Prospective Baseline in the 28-day rate of migraine-specific acute rescue medication use in the last 4 weeks of the Treatment Phase will be analyzed using the same analysis method (MMRM) as for the primary efficacy endpoint. The contrast of interest will be at Month 5 for the SPN-538 group compared with placebo.
3. Total Headache Days, Duration, and Severity: The change from Prospective Baseline in the 28-day rate of total headache days, duration of headache days (migraine and non-migraine) in the last 4 weeks of the Treatment Phase will be analyzed using the same analysis method (MMRM) as for the primary efficacy endpoint. The contrast of interest will be at Month 5 for the SPN-538 group compared with placebo.

The change from Prospective Baseline in the 28-day rate for severity in the last 4 weeks of the Treatment Phase will be summarized using descriptive statistics by severity (mild, moderate, severe, very severe).

4. Onset of action: The time to first significant treatment effect in the MMDs will be based on the MMRM analysis of the primary endpoint. The first month at which a statistically significant difference in the change from baseline in 28-day MMDs is observed and maintained until the EOS between SPN-538 and placebo will be claimed as the first month for the onset of treatment effect.
5. Headache disability: The change from baseline in the Headache Disability Score as measured by PedMIDAS during the last 4 weeks of the Treatment Phase will be summarized using descriptive statistics by visit.
6. HRQoL: The change from baseline in the HRQoL as measured by the PedsQL4.0 Total Scale Score during the last 4 weeks of the Treatment Phase for the self-report and the parent-report will be summarized using descriptive statistics by visit.

7.9 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 groups. 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 between the mean change from baseline in the MMDs between the active treatment and the placebo groups using a two-sample t-test at a 2-sided significance level of alpha=0.05.

It is assumed that approximately 15% of subjects will drop-out before completing the study, hence an adjusted total sample size of 276 subjects (138 subjects per arm) will be randomized in a 1:1 ratio to obtain 234 subjects at the completion of the study.

[redacted]

7.11 Safety Analysis

Safety analysis as described below will be conducted using the Safety Analysis Set. All safety analyses will be performed on the Safety Analysis Set.

The incidence rate of AEs will be calculated by treatment group for each System Organ Class (SOC) and Preferred Term (PT). The severity of the AEs and the relationship to

SM will be summarized by treatment group for each SOC and PT. AEs will be summarized using discrete summaries at the subject and event level by SOC and PT, and by severity and relationship separately for each treatment group. Verbatim description and MedDRA SOCs and PTs for all AEs will be contained in the subject data listings.

All AEs occurring after randomization and throughout the study period will be recorded. For subjects who receive SM, TEAEs will be collected starting after the first dose of SM (Visit 3) to the end of the study. These AEs include those that emerge during treatment or worsen in severity during treatment. These AEs will be tabulated, listed and analyzed.

The incidence of AESIs based on AE data will be summarized for each treatment group by MedDRA SOC and PT. Supporting subject listing of AESI will be presented. For AESIs, percentages of subjects experiencing visual/ocular disturbances, oligohydrosis, hyperthermia, metabolic acidosis (serum bicarbonate), hyperammonemia, nephrolithiasis, and hepatic injury will be summarized using descriptive statistics by treatment and collection time point. Clinical laboratory values will be summarized by visit and treatment group using descriptive statistics. For quantitative laboratory parameters, both actual values and change from baseline (values collected at Screening) will be summarized.

Vital signs will be summarized by visit by treatment group using descriptive statistics. Both actual values and change from baseline will be summarized.

ECG results will be summarized by visit by treatment group using descriptive statistics (for quantitative ECG parameters) and frequency tables (for qualitative ECG parameters, including the overall ECG finding).

C-SSRS outcomes will be summarized using number and percent of subjects by categories for suicidal ideation only, suicidal behavior only and suicidality (ideation and behavior combined). The summary will be presented by treatment groups.

For physical, neurological, and eye examinations, change in status from baseline to the EOS will be summarized by body system for each treatment group.

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

8 DOCUMENTATION

8.1 Adherence to the Protocol

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described within and to the principles of ICH GCP as well as all governing local regulations and principles for medical research.

The protocol, ICF/IAF, and appropriate related documents must be reviewed and approved by an IRB constituted and functioning in accordance with ICH E6 and any local regulations. Documentation of IRB compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB must be sent to the Investigator with a copy to the Sponsor prior to study start and the release of SM to the site by the Sponsor or its designee. If the IRB decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the IRB to the Sponsor.

8.2 Changes to the Protocol

Changes to the protocol will not be made without written approval from the Sponsor.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRB, and in some cases, filings to the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Medical Monitor and IRB must be notified promptly.

Changes to the protocol that are administrative in nature do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such changes. In these cases, the Sponsor will send a letter to the IRB detailing such changes.

8.3 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site visit audits may be made periodically by the Sponsor’s Quality Assurance team or qualified designee, which is an independent function from the study conduct team.

8.3.1 Data Collection

The primary source document will be the subject’s medical record. If separate research records are maintained by the Investigator(s), both the medical record and the research

record will be considered the source documents for the purposes of monitoring and auditing the study.

Electronic data collection techniques will be used to collect data directly from the study sites using eCRFs. The electronic data will be stored centrally in a fully validated clinical database.

Data recorded on source documents will be transcribed into the eCRFs in accordance with the eCRF Completion Instructions that are provided to the study sites. The Investigator is responsible for ensuring that all sections of each eCRF are completed correctly, and that entries can be verified against source documents. The eCRFs will be monitored for completeness and accuracy against the source documents by the CRA(s) on a regular basis. Inconsistencies between the eCRFs and source documents will be resolved in accordance with the principles of GCP.

8.3.2 Clinical Data Management

Data from eCRFs and other external data (e.g., laboratory data) will be entered into or merged with a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

8.3.3 Database Quality Assurance

In accordance with the vendor’s procedures, the clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. The procedure for handling missing data will be addressed in the SAP. Data queries requiring clarification will be documented and returned to the study site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

8.3.4 Bioanalytical Sample Handling

Topiramate (TPM) concentrations in plasma samples will be determined using a validated chromatographic method. Details on the analytical methodology, the method of validation, and the analytical within-study quality control procedures will be included in the clinical study report for this study.

8.4 Retention of Records

The Investigator has the responsibility to retain all study “essential documents”, as described in ICH E6 for at least 2 years after approval of a marketing application or after formal discontinuation of the clinical program. Essential documents include but are not limited to the protocol, eCRFs, source documents, laboratory test results, SM inventory records, Investigator's Brochure, regulatory agency registration documents (e.g., FDA form 1572, ICFs, and IRB correspondence). The Investigator must obtain written permission from Supernus prior to the destruction of any study document.

8.5 Auditing Procedures

In addition to the routine monitoring procedures, the Sponsor's Corporate Quality Assurance department or qualified designee may conduct audits of clinical research activities in accordance with the Sponsor's written SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator must inform the Sponsor immediately that this request has been made.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with the US 21 CFR 312.68 or other national or foreign regulatory authorities in accordance with regulatory requirements.

8.6 Publication of Results

Any presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the Investigator(s) and the appropriate personnel at the Sponsor's site. Authorship will be determined by mutual agreement. All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor, prior to submission for publication or presentation. No publication or presentation with respect to the study shall be made until Sponsor comments on the proposed publication or presentation have been addressed to the Sponsor's satisfaction.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be outlined in the agreement between each Investigator and the Sponsor or designee.

8.7 Financing and Insurance

Financing and Insurance information will be set forth in a separate document between the Investigator and Sponsor (provided by the Sponsor or designee).

8.8 Disclosure and Confidentiality

The contents of this protocol, any amendments, and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and the IRB and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will appear in any written work, including publications, without the written consent of Sponsor.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and Sponsor.

8.9 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical or administrative reasons at any time. The Investigator will be reimbursed for reasonable expenses covering subjects, use of live-in facilities, laboratory tests, and other professional fees. The Investigator will refund the excess of payments made in advance.

The Investigator reserves the right to discontinue the study as per his/her judgment. The Investigator will notify the IRB in case of study discontinuation. Study records must be retained as noted above.

9 ETHICS

9.1 Institutional Review Boards

The IRB that approved this study and the approval letters will be included in the clinical study report for this protocol.

The protocol, any protocol amendments, and the ICF/IAF will be reviewed and approved by the appropriate IRB before subjects are enrolled. The Investigators or Sponsor will submit, depending on local regulations, periodic reports and inform the IRB of any reportable AEs per ICH guidelines and local IRB standards of practice.

9.2 Ethical Conduct of the Study

This study will be conducted in accordance with SOPs from both the Sponsor. These SOPs are designed to ensure adherence to GCP guidelines as required by:

- Declaration of Helsinki, 1964 (“Recommendations Guiding Physicians in Biomedical Research Involving Human Patients”), and all its accepted amendments to date concerning medical research in humans.
- ICH Guideline for GCP (Committee for Proprietary Medicinal Products/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.
- United States (US) CFR dealing with clinical studies (21 CFR, including parts 50 and 56 concerning Patient Informed Consent/Assent and IRB regulations).
- Local, national legal guidelines.

9.3 Investigators and Study Personnel

This study will be conducted by qualified Investigators under the sponsorship of Supernus Pharmaceuticals, Inc. (Sponsor).

Contact persons at the Sponsor and the qualified personnel from the site or designee are listed in the reference binder provided to each investigational site. The study will be monitored by qualified personnel from the Sponsor or their designees. Medical writing, data management, and statistical analyses will be performed by the qualified personnel

or designee. Laboratory tests will be conducted by a central laboratory as designated in the reference binder.

The study will be monitored by qualified personnel from Supernus or designee for data management and biostatistics groups.

9.4 Subject Information and Consent

The Investigator (or designee) will inform the caregiver and subject of all aspects pertaining to the subject's participation in the study and will provide oral and written information describing the nature and duration of the study, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort.

The process for obtaining informed consent/assent will be in accordance with all applicable regulatory requirements. The Investigator (or designee) and subject/caregiver must sign and date the ICF/IAF before the subject can participate in the study. The caregiver/subject will be given a copy of the signed and dated ICF/IAF and the original will be retained in the investigational site study records.

The decision regarding subject participation in the study is entirely voluntary. The Investigator (or designee) must emphasize to the subject/caregiver that consent, regarding study participation, may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF/IAF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF/IAF by the IRB and use the amended ICF (including ongoing subjects).

10 APPENDICES

10.1 Study Definitions and ICHD-3 Diagnostic Criteria

Study Definitions

ICHD-3 outlines special features that are characteristic of migraine headaches in children and adolescents (aged under 18 years), including the following:

- In children and adolescents, migraine attacks may last 2-72 hours.
- In children and adolescents, migraine headache is often bilateral; unilateral pain usually emerges in late adolescence or early adult life.
- In children and adolescents, aura may be represented by less typical bilateral visual symptoms.
- In children, migraine headache is usually frontotemporal. Occipital headache is rare and calls for diagnostic caution.
- In young children, photophobia and phonophobia may be inferred from their behavior.

Migraine episode is defined as the occurrence of any migraine that starts, ends or recurs within a 24-hour period. Migraine episodes that persist or recur within a 24-hour period are considered the same episode.

Monthly migraine is measured by the number of migraine days within 28 days. A migraine day is defined as a calendar day (12:00 am to 11:59 pm) in which the subject experiences a migraine attack that starts, ends or recurs within 24 hours and lasts for ≥ 1 hour (if untreated) or ≥ 30 minutes (if interrupted with rescue medication). Pain persisting for more than 1 calendar day (≥ 24 hours) after initial onset will be considered as a new, distinct headache day.

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.

ICHD-3 Diagnostic Criteria

Per the IHS Criteria for Classification of Migraines in Children and Adolescents (aged less than 18 years) (*https://www.ichd-3.org/; Headache Classification Committee of the International Headache (IHS), Cephalalgia, 2018, 38 (1): 1-211*).

Migraine Without Aura

Previously used terms:

Common migraine; hemicrania simplex.

Description:

Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

A. At least five attacks [Note #1] fulfilling criteria B-D
B. Headache attacks lasting 4-72 h (untreated or unsuccessfully treated) [Notes #2; #3]
C. Headache has at least two of the following four characteristics:
    - unilateral location
    - pulsating quality
    - moderate or severe pain intensity
    - aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
    - nausea and/or vomiting
    - photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. One or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for 1.1 *Migraine without aura* but have had fewer than five attacks should be coded 1.5.1 *Probable migraine without aura*.
2. When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening.
3. In children and adolescents (aged under 18 years), attacks may last 2-72 hours (the evidence for untreated durations of less than two hours in children has not been substantiated).

Migraine With Aura

Previously used terms:

Classic or classical migraine; ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine; migraine accompagnée; complicated migraine.

Description:

Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other CNS symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
   - visual
   - sensory
   - speech and/or language
   - motor
   - brainstem
   - retinal
C. At least three of the following six characteristics:
   - at least one aura symptom spreads gradually over ≥5 minutes
   - two or more aura symptoms occur in succession
   - each individual aura symptom lasts 5-60 minutes Note #1
   - at least one aura symptom is unilateral Note #2
   - at least one aura symptom is positive Note #3
   - the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. When for example three symptoms occur during an aura, the acceptable maximal duration is 3×60 minutes. Motor symptoms may last up to 72 hours.
2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.
3. Scintillations and pins and needles are positive symptoms of aura.

10.2 Headache Diary – Preventive Therapies (Version 2.0)

Instructions: This form should be completed by the participant for each day the participant/subject experienced a headache/migraine.

1. Did you experience a headache today? ☐ Yes ☐ No
2. What time did your headache start? ☐ (24 hour clock) ☐ Woke up with this headache
3. What time did your headache end? ☐ (24 hour clock) ☐ Headache resolved after falling asleep
4. What acute pain medication(s), in addition to the study drug, did you take? (Choose all that apply)
   - ☐ Acetaminophen
   - ☐ Almotriptan
   - ☐ Aspirin
   - ☐ Dihydroergotamine (DHE)
   - ☐ Eletriptan
   - ☐ Ergotamine tartrate (ET)
   - ☐ Frovatriptan
   - ☐ Ibuprofen
   - ☐ Naproxen
   - ☐ Naratriptan
   - ☐ Rizatriptan
   - ☐ Sumatriptan
   - ☐ Zolmitriptan
   - ☐ Other, specify:
5. Describe the worst severity of your headache today? Complete **one** of the following pain severity scales:
   a. Which word describes the severity of your headache?
      ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Very Severe (for cluster headaches)

   b. Rate your overall worst pain for this headache on a scale of 0-10: ("0" = no pain & "10" = the worst pain): ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
6. Do any of the following describe your pain? (Choose all that apply)
   - ☐ Throbbing
   - ☐ Pounding
   - ☐ Stabbing
   - ☐ Constant
   - ☐ Sharp
   - ☐ Pressure
   - ☐ Pulsating with the heart beat
   - ☐ Squeezing
   - ☐ Other, specify:
7. Where is the location of your headache pain? (Choose one)
   ☐ Right ☐ Left ☐ Bilateral (both sides)
8. Where is the location of your headache pain that hurts the most? (Choose all that apply)
   - ☐ Top
   - ☐ One Eye (specify, ☐ left ☐ right)
   - ☐ Around Eyes
   - ☐ Behind Eyes
   - ☐ Back
   - ☐ Neck
   - ☐ All over
   - ☐ Right Temple
   - ☐ Left Temple
   - ☐ Front
   - ☐ Other, specify:
9. Does sound aggravate or make your headache worse? ☐ Yes ☐ No
10. Does light aggravate or make your headache worse? ☐ Yes ☐ No

11. Does routine physical activity (e.g. walking, climbing stairs) aggravate or make your headache worse? ☐ Yes ☐ No

12. Optional - Did you have any symptoms that came before and warned that this headache was going to start?

    ☐ Yes ☐ No ☐ Unknown

    a. If premonitory symptoms (symptoms that come *before* headache), which of the following did you experience? (Choose all that apply)

    ☐ Fatigue
    ☐ Difficulty concentrating
    ☐ Irritability
    ☐ Mood Changes
    ☐ Food Cravings
    ☐ Nausea
    ☐ Yawning
    ☐ Neck stiffness / pain
    ☐ Blurred vision
    ☐ Hypersensitivity to light
    ☐ Hypersensitivity to noise
    ☐ Other symptoms, specify:

    b. If aura symptoms (neurological symptoms that come before or during headache), which type of aura did you have? (Choose all that apply)

    ☐ Visual aura (flashing lights, zig zag lines, dots, stars, sparkles, blind spots, shape and size distortion, temporary blindness, shimmering patches, tunnel vision, etc.)
    ☐ Sensory aura (numbness, pins and needles)
    ☐ Language/Speech aura (trouble understanding speech or producing it)
    ☐ Motor aura (paralysis/muscle weakness of face, arm, or leg on one side)
    ☐ Brainstem aura (double-vision, tinnitus or ringing in the ears, increased sense of hearing, unsteadiness when walking, slurred speech, vertigo or spinning sensation, or decreased level of alertness)

13. Did this headache reduce your ability to function? ☐ Yes ☐ No

    a. How would you describe your abilities to perform your usual daily activities at the onset of this headache?

    ☐ Able to work and function normally
    ☐ Working ability or activity impaired to some degree
    ☐ Working ability or activity severely impaired
    ☐ Bed rest required

14. Did you receive acute headache treatment for your headache? ☐ Yes ☐ No

15. Complete one of the following questions:

    a. What time did this headache end? (24 hour clock)

    b. Headache ended after falling asleep? ☐ Yes ☐ No

Additional Pediatric-specific Elements

16. Did the headache change the participant's activity level (i.e., stop playing)? ☐ Yes ☐ No
17. Does activity or playing make the participant's headache worse? ☐ Yes ☐ No
18. How did today's headache affect the following school and other activities:

School
a. Participant missed a full day of school? ☐ Yes ☐ No
b. Participant missed a half or part of the day of school? ☐ Yes ☐ No
c. Functioned at less than half of participant's ability at school? ☐ Yes ☐ No

Home
d. Participant could not do things at home (chores, homework, etc.)? ☐ Yes ☐ No

Other Activities
e. Participant could not participate in other activities (sports, play, etc.)? ☐ Yes ☐ No
f. Participant functioned at less than half of his/her ability? ☐ Yes ☐ No

10.3 Pediatric Migraine Disability Assessment Questionnaire (PedMIDAS)

PedMIDAS

Headache Disability.

The following questions try to assess how much the headaches are affecting day-to-day activity. Your answers should be based on the last three months. There are no "right" or "wrong" answers so please put down your best guess.

1. How many full school days of school were missed in the last 3 months due to headaches? _____

2. How many partial days of school were missed in the last 3 months due to headaches (do not include full days counted in the first question)? _____

3. How many days in the last 3 months did you function at less than half your ability in school because of a headache (do not include days counted in the first two questions)? _____

4. How many days were you not able to do things at home (i.e., chores, homework, etc.) due to a headache? _____

5. How many days did you not participate in other activities due to headaches (i.e., play, go out, sports, etc.)? _____

6. How many days did you participate in these activities, but functioned at less than half your ability (do not include days counted in the 5th question)? _____

Total PedMIDAS Score _____

Headache Frequency _____

Headache Severity _____

10.4 Pediatric Quality of Life Inventory, Version 4.0 (PedsQL, 4.0)

ID# _____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

CHILD REPORT (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

ID# _____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month,** how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

YOUNG CHILD REPORT (ages **5-7**)

Instructions for interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show the child the template and point to the responses as you read.

If it is <u>not at all</u> a problem for you, point to the smiling face

If it is <u>sometimes</u> a problem for you, point to the middle face

If it is a problem for you <u>a lot</u>, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.

	Not at all	Sometimes	A lot
Is it hard for you to snap your fingers	☺	😐	☹

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

PedsQL 2

Think about how you have been doing for the last few weeks. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

PHYSICAL FUNCTIONING ***(problems with…)***	Not at all	Some-times	A lot
1. Is it hard for you to walk	0	2	4
2. Is it hard for you to run	0	2	4
3. Is it hard for you to play sports or exercise	0	2	4
4. Is it hard for you to pick up big things	0	2	4
5. Is it hard for you to take a bath or shower	0	2	4
6. Is it hard for you to do chores (like pick up your toys)	0	2	4
7. Do you have hurts or aches (***Where?*** _____)	0	2	4
8. Do you ever feel too tired to play	0	2	4

Remember, tell me how much of a problem this has been for you for the last few weeks.

EMOTIONAL FUNCTIONING ***(problems with…)***	Not at all	Some-times	A lot
1. Do you feel scared	0	2	4
2. Do you feel sad	0	2	4
3. Do you feel mad	0	2	4
4. Do you have trouble sleeping	0	2	4
5. Do you worry about what will happen to you	0	2	4

SOCIAL FUNCTIONING ***(problems with…)***	Not at all	Some-times	A lot
1. Is it hard for you to get along with other kids	0	2	4
2. Do other kids say they do not want to play with you	0	2	4
3. Do other kids tease you	0	2	4
4. Can other kids do things that you cannot do	0	2	4
5. Is it hard for you to keep up when you play with other kids	0	2	4

SCHOOL FUNCTIONING ***(problems with…)***	Not at all	Some-times	A lot
1. Is it hard for you to pay attention in school	0	2	4
2. Do you forget things	0	2	4
3. Is it hard to keep up with schoolwork	0	2	4
4. Do you miss school because of not feeling good	0	2	4
5. Do you miss school because you have to go to the doctor's or hospital	0	2	4

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **YOUNG CHILDREN** (ages **5-7**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores, like picking up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with school activities	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

10.5 Cognitive Assessment

Subject I.D._____ Visit Date_____

Cognitive Assessment

This assessment is administered by asking the child questions related to his/her daily activities in the past weeks since the last visit.
To obtain accurate information, we suggest conducting the assessment with the parent(s) first. If discrepancies are found between different sources of information, the study staff will have to use his/her best clinical judgement.

Since your last visit to the study doctor, please answer the following questions:
On a scale from 0 to 3, where 0= never, 1= sometimes (once or twice a week), 2=often (more than 3 times a week), 3= very often (every day)

N.	Question	Answer
1.	Do you have trouble remembering things that your mom, teacher or friends have said to you?	
2.	Do you have trouble recognizing objects and remembering how they look?	
3.	Do you feel that you sometimes don't know what to do especially at school?	
4.	Do you have trouble answering questions or find it difficult to respond to questions?	
5.	Do you feel unusually tired or sleepy?	
6.	Do you feel that your activity has recently slowed down?	
7.	Do you have trouble paying attention and concentrating: a. at school? b. at home while doing your homework? c. when playing with your friends?	

Ver. 1.0 Date 25 June 2019

10.6 Columbia-Suicide Severity Rating Scale

10.6.1 C-SSRS - Children's Baseline

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Baseline

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you ever wish you weren't alive anymore?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., ***"I've thought about killing myself"***) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, ***"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*** ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to ***"I have the thoughts but I definitely will not do anything about them."*** ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you ever decided how or when you would make yourself not alive anymore/kill yourself? Have you ever planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you ever <u>do anything</u> to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you ever hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, <u>not at all</u> to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself) - like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

10.6.2 C-SSRS - Children's Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:
This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS-Children-Since Last Visit - United States/English - Mapi.
C-SSRS-Children-SinceLastVisit_AU3.0_eng-USori.doc

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** **Has subject engaged in Self-Injurious Behavior, intent unknown?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Completed Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

10.7 Visual Neurological Exam Checklist

VISUAL NEUROLOGICAL EXAM CHECKLIST

Instructions:

Please complete checklist based on observations during physical exam at **Visits 1 and 9.**

EXAM	
Extraocular Movements	
Right Eye	☐ Normal
	☐ Abnormal (if abnormal, describe)
Left Eye	☐ Normal
	☐ Abnormal (if abnormal, describe)
Pupils	
Size	☐ Equal
	☐ Unequal (if unequal, describe)
Reaction to light	☐ Normal
	☐ Abnormal (if abnormal, describe)
Afferent pupillary defect present?	☐ No
	☐ Yes (If yes, right eye or left eye)?
Confrontation Visual Field (for each eye)	
Right Eye	☐ Normal
	☐ Abnormal (if abnormal, describe)
Left Eye	☐ Normal
	☐ Abnormal (if abnormal, describe)

10.8 Eye Exam Checklist

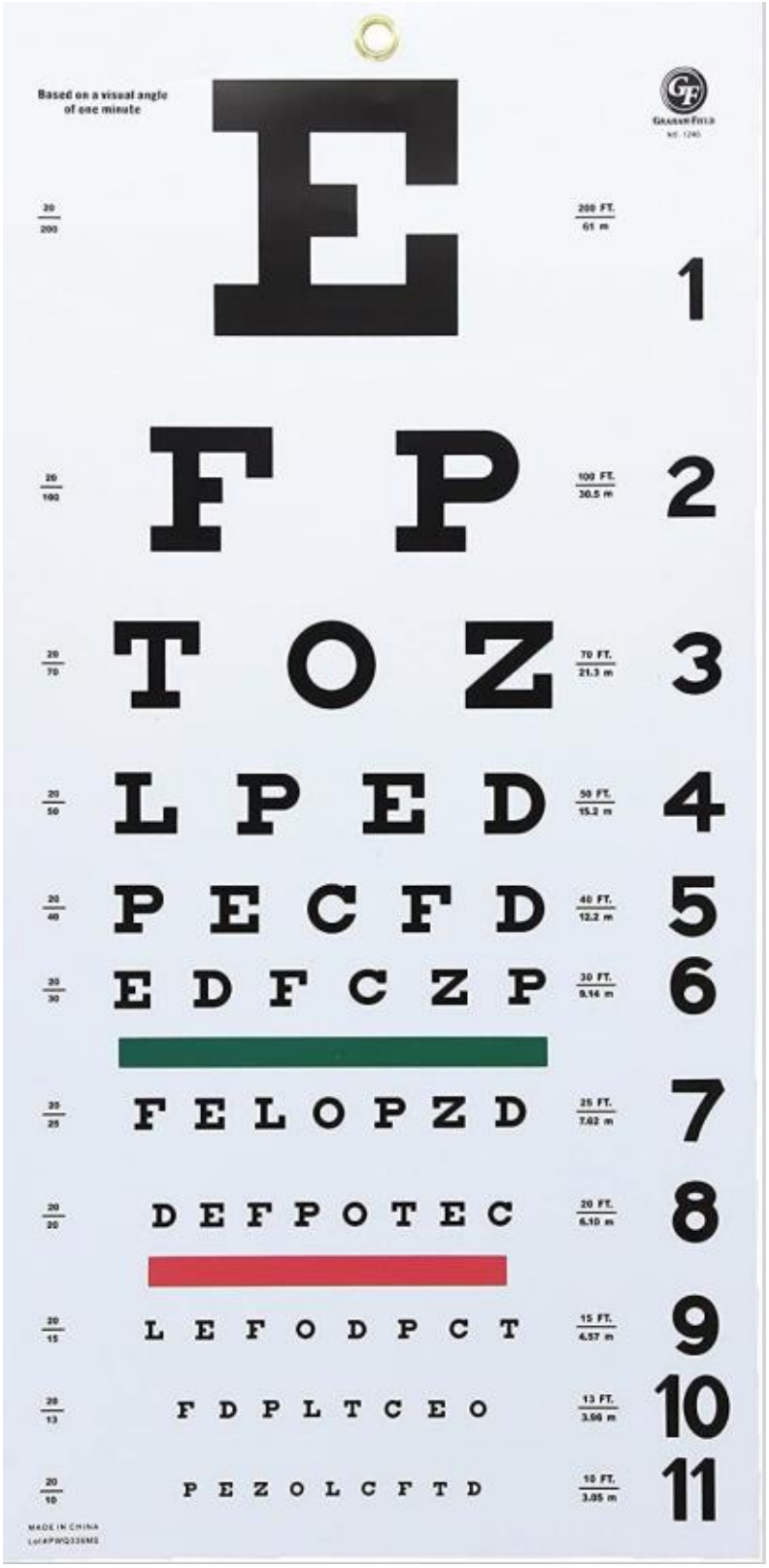
EYE EXAM CHECKLIST

Instructions:

Please complete checklist based on observations during **Visits 3, 6 and 9**.

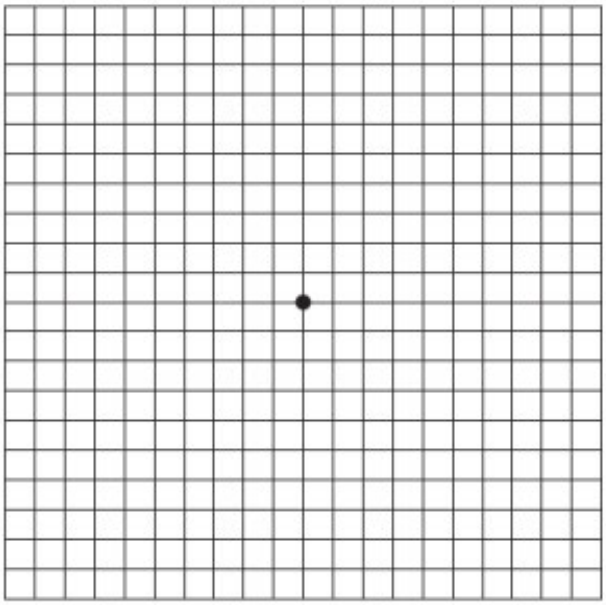
FUNDOSCOPIC EXAM			
Optic Disc			
	RIGHT Eye:		**LEFT Eye:**
Color	☐ Normal	Color	☐ Normal
	☐ Pale		☐ Pale
Contour	☐ Flat	Contour	☐ Flat
	☐ Edema		☐ Edema
	☐ [redacted]		☐ [redacted]
VISUAL ACUITY			
Snellen Wall Chart	Right eye: _/_		Left eye: _/_
Near Card	Right eye: J ___		Left eye: J ___

10.8.1 Wall Snellen Chart



10.8.2 Amsler Grid Test

Amsler Grid



Use this Amsler grid to check your vision every day.

How to use:

- Wear the eyeglasses you normally wear when reading.
- Position the chart 14 inches away from your face.
- Cover one eye at a time with your hand.
- Stare at the dot in the center. Do not let your eye drift from the center dot.
- Contact your eye care doctor immediately if any of the straight lines appear wavy or bent, any of the boxes differ in size or shape from the others, or any of the lines are missing, blurry or discolored.

Monitoring your vision every day is important - print out this grid and keep it in a convenient place.

Visit MyVisionTest.com to test your vision with an online computerized version of the Amsler grid.

myvisiontest.com

10.9 Concomitant Medications

This list of medications is not all inclusive: please contact the Medical Monitor for any questions related to the subject's current concomitant medication(s). Additional concomitant medication (s) may be allowed on a case-by-case basis at the discretion of the Investigator, the Medical Monitor and the Sponsor.

Migraine Prophylactic Medications:	
Daily NSAIDs Antiemetics Antihistamines Magnesium supplements (≥600 mg/day) Riboflavin (≥100 mg/day) Coenzyme Q10 Omega-3 Melatonin Muscle relaxants β-blockers	Allowed if treatment is on a stable dose for at least 12 weeks before the Screening Visit
Rescue Migraine Treatments:	
Ibuprofen Acetaminophen	Use should not exceed 3 times per week (or 15 treatment days/month)
Triptans Ketorolac Ergotamines	Use should not exceed 10 treatments days/month
Antiasthma Medications:	
Albuterol sulfate	As needed (PRN)
Corticosteroids (systemic, inhaled or topical)	Allowed if treatment is on a stable dose for at least 12 weeks before the Screening Visit
ADHD medications:	
Stimulants (i.e., amphetamines, methamphetamine), extended or control release formulations	Allowed if on a stable dose for at least 12 weeks prior to the Screening visit
Other Concomitant medications:	
Nutritional supplement (e.g., vitamins)	PRN
EMLA or other numbing cream	PRN
Childhood vaccinations, including COVID vaccine	PRN
Mydriatics	PRN

10.10 Prohibited Medications

The medications in the following list are not permitted and treatment should be discontinued 14 days prior to the Prospective Baseline Period. It is recommended to taper off antipsychotics, barbiturates, benzodiazepine, tricyclic antidepressants, lithium, amitriptyline, valproic acid, SSRIs and NSRIs as applicable per the discretion of the Investigator.

Migraine Prophylactic:
Antipsychotics
Antimanics
Barbiturates
Benzodiazepines
Sedatives
Serotonin Selective Reuptake Inhibitors (SSRIs)
Non-Selective Reuptake Inhibitors (NSRIs)
Amitriptyline
Tricyclic antidepressants
Lithium
Valproic acid
Antiepileptic drugs (AEDs)
Calcium channel blockers
Cannabidiol (CBD) oil
CGRP receptor antagonists
Narcotics
Herbal preparations/supplements (including feverfew or St John's Wort)
Any medications that could impair or decrease thinking and concentration
ADHD Medications:
Non-stimulants (e.g., clonidine, atomoxetine, viloxazine and guanfacine)

10.11 Summary of Changes

Protocol Number, Version, and Date:

Protocol 538P401, Version 4.0, dated 14 Dec 2022

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

Version	Version Number	Version Date
Amended Protocol	4.0	14 Dec 2022
Old Protocol (prior to amendment)	3.0	29 Jun 2021

Section and page numbers are references to the amended protocol.

Administrative changes: Minor changes involving grammar, wordsmithing, punctuation, spelling, formatting, correction of typographical errors, and other editorial changes for further clarification and/or consistency have been made throughout the document. This includes changes to document version number and date, all that is related to abbreviations/spelling out of abbreviations in the list of abbreviations as well as synopsis and main text, all that is related to references and citations, all things related to cross reference and hyperlinks, and personnel changes (Sponsor, Investigator, and/or Vendors/Consultants). Movement of intact sections (e.g., an appendix to main text or renumbering of appendices) are also considered administrative. All these changes except formatting changes are identified in the track-changes version of the amendment.

Section	Page	Description of Change	Rationale for Change
Synopsis 2.2	5 25	Secondary (Objectives) 1. Responder rate~~,~~ **with a responder** defined as **a subject with** at least a 50% reduction in ~~the average of~~ monthly migraine days (MMDs). 4. Onset of action, defined as the **time to** ~~month of the Treatment Phase in which~~ first statistically significant ~~difference is~~ **treatment effect** observed ~~between SPN-538~~ and ~~placebo in the primary endpoint~~ **maintained until the end of study (EOS)**.	Major change for clarification
Synopsis 2.2	5-6 25-26	**Primary Estimand (new section)** **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 (MI) under the missing not at random (MNAR) assumption. For all other missing data due to intercurrent event (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).**	Changed to align with statistical analysis plan (SAP) per FDA request
Synopsis 2.3	6 26	Safety (Objectives) 4. C-SSRS **assessment**. **5. Cognitive assessment.**	Minor change for clarification
Synopsis 2.4	6 26	[redacted]	Minor change for clarification

Section	Page	Description of Change	Rationale for Change
Synopsis	7	Treatment Schedule Throughout the duration of the study, rescue medications will be allowed for symptomatic relief of headaches (migraine and non-migraine) if the pattern of use remains stable and does not meet the criteria for medication overuse~~.~~ **(i.e., > 10 treatment days/month for ergot-containing medication or triptans; >15 treatment days/month for simple analgesics/nonsteroidal anti-inflammatory drugs (NSAIDs)**. Simple analgesics ~~(e.g., ibuprofen, acetaminophen)~~ are allowed, but use of narcotics is not permitted (Section 4.7).	Clarified the definition of overdose
Synopsis	7	Screening~~/Wash Out~~ Period (Visit 1, up to 8 weeks before Visit 3) ~~Prospective subjects who meet initial eligibility criteria will be instructed to discontinue any preventive medications for a 14-day wash-out period before returning to the clinic for Visit 2.~~ **Prophylactic migraine treatments including daily NSAIDs, antihistamines, corticosteroids, antiemetics, high-dose magnesium supplements (≥600 mg/day), high-dose riboflavin (≥100 mg/day), coenzyme Q10, omega-3, melatonin, muscle relaxants, and β-blockers will be allowed if on a stable dose for at least 12 weeks prior to the Screening visit. The dose must remain stable (7 days/week) throughout the duration of the study (Appendix 10.9).** **Prospective subjects who meet eligibility criteria at Visit 1 will be instructed to discontinue the following preventive medications 14 days prior to Visit 2 (see Exclusion Criterion #8): antipsychotics, antimanics, barbiturates, benzodiazepines, sedatives, serotonin selective reuptake inhibitors (SSRIs), non-selective reuptake inhibitor (NSRIs), amitriptyline, tricyclic antidepressants, lithium, valproic acid, AEDs, calcium channel blockers, cannabidiol (CBD) oil, calcitonin gene-related peptide (CGRP) receptor antagonists, herbal preparations/supplements such as feverfew or St John's Wort and/or any medications that could impair or decrease thinking and concentration. It is recommended to taper off antipsychotics, barbiturates, benzodiazepine, tricyclic antidepressants, lithium, amitriptyline, valproic acid, SSRIs and NSRIs as applicable (Appendix 10.10).** **Re-screening is not permitted, however subjects who screen failed due to a PedMIDAS Total score > 50 under any prior version of the protocol, may be rescreened if they still meet the study eligibility criteria under this version of the protocol (Version 4.0, 14 Dec 2022).**	Major change to facilitate study conduct

Section	Page	Description of Change	Rationale for Change
Synopsis 3.1	8 30-31	Maintenance Period (Visits 6 to 8, Weeks 9 through 20) Once the target dose or MTD is reached, treatment at that dose will continue for the 12 weeks of the maintenance period; up to one dose reduction will be allowed for safety and tolerability during this period. **Additional dose titration related to body weight changes will be reviewed and approved by the Medical Monitor and the Sponsor on a case by case basis**. The Headache Diary will be completed daily during this period. Clinic visits will be scheduled every 4 weeks for safety, headache disability, and HRQoL assessments (Section 5.1.5). [redacted]	Minor change per site clarification
Synopsis 2.5	10 26	The primary efficacy outcome measure is the ~~mean~~ change in the monthly (28-day) rate of MMDs 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)~~.	Minor change for clarification
Synopsis 2.6	10 26-27	Secondary Endpoints 2. ~~Percentage of responders~~ **Responder, defined as a subject** with ~~a~~ ≥ 50% reduction in the ~~average of monthly~~ **MMDs** during the last 4 weeks of the Treatment Phase relative to ~~baseline~~ **Prospective Baseline Period**. 7. Change from baseline in the mean of monthly migraine-specific acute rescue medication use in the last 4 weeks of the Treatment Phase. 8. Change in the monthly rate of total headache days (migraine and non-migraine), duration and severity. 9. ~~The first month~~**Change in the time to onset** of ~~treatment including the last 4 weeks of~~ **action, defined as** the ~~Treatment Phase in which a~~ **time to first** statistically significant **treatment** difference ~~in the change from baseline in monthly migraine days is~~ observed ~~between SPN-538~~ and ~~placebo~~ **maintained until the EOS**.	Major change for clarification
Synopsis 2.6	10 27	Safety Endpoints: 4. C-SSRS **assessment**. **5. Cognitive assessment.**	Minor change for clarification

Section	Page	Description of Change	Rationale for Change
Synopsis 3.3.2	13 37	Inclusion Criteria 4. At Screening, a PedMIDAS Disability score of ~~>10~~ **≥20** (indicating at least mild disruption of daily activities) and ≤ ~~50~~**139** (~~where a score greater than 50 indicates~~ indicating severe disability that may require more comprehensive therapy). 5. Weight of at least 20 kg and no more than 60 kg (inclusive) at the ~~Screening and Baseline visits~~ **Randomization visit (Visit 3)**.	Major change to facilitate study conduct
Synopsis 3.3.3	13-15 37-39	Exclusion Criteria 3. Have taken any **disallowed** migraine preventive medication including TPM within 14 days prior to the start of the Prospective Baseline Period; or used onabotulinumtoxin A (Botox®) within 3 months prior to entering the Screening period. 8. ~~Inability to washout of current~~ **Subjects treated with the following prophylactic** medications **should discontinue the treatment** 14 days ~~before prospective baseline including~~ **prior to the Prospective Baseline Period**: antipsychotics, antimanics, barbiturates, benzodiazepines, ~~muscle relaxants, β-blockers,~~ **amitriptyline, lithium, valproic acid**, tricyclic antidepressants, AEDs, calcium channel blockers, ~~corticosteroids (i.e., systemic, inhaled or topical), daily NSAIDs,~~ sedatives, SSRIs, NSRIs, ~~high-dose magnesium supplements (≥600 mg/day), high-dose riboflavin (≥100 mg/day),~~ CGRP receptor antagonists, ~~omega-3, melatonin,~~ CBD oil, herbal preparations/supplements such as feverfew or St John's wort and/or any medications that could impair or decrease thinking and concentration. **It is recommended to taper off antipsychotics, barbiturates, benzodiazepine, tricyclic antidepressants, lithium, amitriptyline, valproic acid, SSRIs and NSRIs as applicable.** *Note: ~~The use of these medications should be discontinued at least 14 days before Prospective Baseline Period and refrain from using throughout duration of study~~.**Subjects must refrain from using** these medications throughout **the** duration of **the** study.* 11. Significant major psychiatric disorder (e.g., psychosis, bipolar disorder, major depression~~,~~ **and** generalized anxiety disorders~~, ADHD~~), or documented developmental delays or impairments (e.g., autism, cerebral palsy, or mental retardation) that, in the opinion of the Investigator, would interfere with adherence to study requirements or safe participation in the trial. ***Note: Subjects with an established diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), will be allowed if they are taking a stable dose (7 days/week)***	Major change to facilitate study conduct

Section	Page	Description of Change	Rationale for Change
		of ADHD stimulant medication (extended or controlled release) for at least 12 weeks prior to the Screening visit and refrain from changing the dose or the ADHD medication during the study duration. 16. Known neurological disorder or a structural disorder of the brain from birth; head trauma or ~~past infection (within 6 months prior to Screening)~~ **infectious disease resulting in migraine or worsening** of ~~the~~ **migraine symptoms; or previous** central nervous system (CNS)~~, or previous CNS~~ surgery. 18. Evidence of suicidal ideation and/or suicidal behaviors within 6 months prior to Screening or during the ~~Screening period~~ Pre-treatment Phase. *Note: Abnormal results on screening laboratory tests **and/or ECG** may be repeated once per test at the discretion of the Investigator.*	
1	24	Introduction These include ophthalmologic side effects (acute myopia, secondary angle closure glaucoma, and visual field defects), oligohydrosis and hyperthermia, treatment-related laboratory abnormalities (e.g., metabolic acidosis, hyperammonemia, and changes in complete blood count values), nephrolithiasis, **negative effects on growth**, and suicidal behavior and ideation.	Changed to provide additional safety information
3.1	27-28	Pre-treatment Phase Screening~~/Wash-Out~~ Period (Visit 1, up to 8 weeks before Visit 3) ~~Prospective subjects who meet initial eligibility criteria will discontinue any preventive~~ **Subjects treated with the following prophylactic** medications ~~for a 14-day wash-out period. All ongoing pharmacological therapies used for migraine prophylaxis (except~~ **should discontinue the treatment 14 days prior to the Prospective Baseline Period: antipsychotics, antimanics, barbiturates, benzodiazepines amitriptyline, lithium, valproic acid, tricyclic antidepressants, AEDs, calcium channel blockers, sedatives, serotonin selective reuptake inhibitors (SSRIs), non-selective reuptake inhibitor (NSRIs), calcitonin gene-related peptide (CGRP) receptor antagonists, cannabidiol (CBD) oil, herbal preparations/supplements such as feverfew or St John's wort and/or any medications that could impair or decrease thinking and concentration. It is recommended to taper off antipsychotics, barbiturates, benzodiazepine, tricyclic antidepressants, lithium, amitriptyline, valproic acid, SSRIs and NSRIs as applicable. (Appendix 10.10)** ***Note: Subjects must refrain from using these medications throughout the duration of the study***.	Major change to facilitate study conduct

Section	Page	Description of Change	Rationale for Change
		Non-pharmacologic approaches involving life-style modifications **are allowed if** initiated more than 1 month prior to Screening. **For subjects who met the eligibility criteria, prophylactic migraine treatments** will be ~~discontinued~~ **allowed if on a stable dose** for at least ~~14 days before the start of the Prospective Baseline Period. If a subject does not need to wash out from any medications, he/she may enter the Prospective Baseline Period within a~~ **12 weeks prior to the Screening Visit including daily nonsteroidal anti-inflammatory drugs (NSAIDs), antiemetics, antihistamines, corticosteroids (i.e., systemic inhaled, or topical), high-dose magnesium supplements (≥600 mg/day), high-dose riboflavin (≥100 mg/day), coenzyme Q10, omega-3, melatonin, muscle relaxants and β-blockers (Appendix 10.9).** ***Note: The dose and the medication must remain stable (7 days/***week***) during the duration*** of ~~Visit 1 if the laboratory test results are normal~~ ***the study.*** During Screening, acute rescue medications (e.g., ibuprofen, acetaminophen, ~~Non-Steroidal Anti-Inflammatory Drugs (NSAIDs),~~ ergot derivates and triptans) will be allowed for symptomatic relief of headaches (migraine and non-migraine) as long as the pattern of use remains stable and does not meet the criteria for medication overuse (i.e., > 10 treatment days/month for ergot-containing medication or triptans; >15 treatment days/month for simple analgesics/NSAIDs). The use of narcotics is not permitted. **Re-screening is not permitted, however subjects who screen failed due to a PedMIDAS Total score > 50 under any prior version of the protocol, may be rescreened if they still meet the study eligibility criteria under this version of the protocol (Version 4.0, 14 Dec 2022).**	
3.1	29	Randomization (Visit 3, Day 1) All eligible subjects will be randomized in a blinded fashion by the interactive web response system (IWRS) in a 1:1 ratio of placebo or SPN-538. Subjects will receive a 4 week supply of their assigned study medication (SM). Safety evaluations including **AEs,** vital signs and suicidality evaluation (using the C-SSRS), **eye examinations,** concomitant medications, urine pregnancy test (FOCP only), headache disability, HRQoL, and cognitive assessments will be obtained at the visit. SM accountability and resupply will occur at each subsequent study visit.	Minor changes for completeness

Section	Page	Description of Change	Rationale for Change
3.1	30	Titration Period (**Visits 4 to 5**, Weeks 1 through 8) • During ~~the visits~~ (Visit 4 ~~and Visit 5)~~, SM supply will be provided, ~~and~~ SM compliance**,** and the Headache Diary will be reviewed. Safety assessment including AEs, vital signs, concomitant medications, ~~clinical laboratory tests,~~ urine pregnancy test (FOCP only) and suicidality evaluation (using the C-SSRS) will be obtained. Physical and neurological evaluations **will be performed, and a refresher placebo training will be administered** ~~will be performed~~. • During the last visit of the titration period (Visit 5), ~~in~~ **SM supply will be provided, SM compliance and the Headache Diary will be reviewed. In** addition to safety evaluations **(i.e., AEs, vital signs and concomitant medications)**, ECG, headache disability, HRQoL, **C-SSRS** and cognitive assessments will be performed; **urine pregnancy test (FOCP only), clinical laboratory tests,** and a urine drug screen sample will be collected.	Minor changes for completeness and/or clarification
3.1	30-31	Maintenance Period (**Visits 6 to 8,** Weeks 9 to 20) Once the target dose or MTD is reached, treatment at that dose will continue for the 12 weeks of the maintenance period; up to one dose reduction will be allowed for safety and tolerability during this period. **Additional dose titration related to body weight changes will be reviewed and approved by the Medical Monitor and the Sponsor on a case by case basis.** The number, severity, and symptoms of all headaches, as well as the type and dose of rescue medication and SM compliance will be recorded daily in the Headache Diary. During the Maintenance Period, clinic visits will be scheduled every 4 weeks. During each clinic visit, a 4-week supply of SM will be provided, and SM compliance and the Headache Diary will be reviewed. Safety evaluations, including **vital signs,** concomitant medications, cognitive assessment, **C-SSRS,** clinical laboratory tests **(only at Visit 8)**, urine pregnancy test (FOCP only), urine drug screen, physical and neurological evaluations will also be performed.[redacted] **During Visit 6, the eye exam will be performed, and another refresher placebo training will be administered.** Telephone contacts will occur at the intervening 2-week periods [Days 71, 99 and 127 (±2 days)] between clinic visits for safety assessment and to provide guidance on dose reduction (as needed).	Minor changes for completeness and/or clarification

Section	Page	Description of Change	Rationale for Change
3.1	30-31	Tapering Period (Weeks 21 to 23): During the following 3 weeks the dose of SM will be gradually reduced until the subject is no longer taking the SM, so that by the end of Week 23 the subject is out of ~~capsules~~**SM**. Dose tapering will also be required for subjects who discontinue early during the titration period (Week 3 through Week 8) or maintenance period (Week 9 through Week 20). Subjects who discontinue early at a**n** MTD of 25 mg/day will not undergo a dose tapering period but will return to the clinic to complete the ~~end of study (~~EOS~~)~~ procedures (**all procedures scheduled to be performed at** Visit 9) within 1 week after discontinuation of SM.	Minor changes for clarification
3.1	31	End of Study (Visit 9): All subjects who complete the study (Week 20) will return to the clinic for a final safety evaluation at the end of the Tapering Period (Visit 9). During this visit, subjects will complete the EOS procedures: clinical laboratory tests, **AE assessments, vital signs, concomitant medications review,** ECG, physical and neurological evaluations, eye exam, urine pregnancy test (FOCP only) and **urine** drug screen, headache disability, HRQoL, **C-SSRS** and cognitive assessments. The remaining SM and the Headache Diary device, if applicable, will be collected, and safety follow-up instructions will be provided to caregivers.	Minor changes for completeness and/or clarification
3.1	32	Safety Follow-up Telephone Call (Weeks 24 to 26): Safety follow-up over the telephone will take place 1 to 3 weeks after the EOS/**early termination (ET)** visit. During the telephone call, all concomitant medications, **cognitive assessment** and AEs will be evaluated and recorded. 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**/ET** visit. These subjects will be treated and/or followed up until the symptoms or laboratory values return to normal/baseline or acceptable levels, as determined by the Investigator.	Minor changes for completeness and/or clarification
3.1	33	Figure 1 (Study Schematic) Footnote 1. Dosing will be based on weight and **is** flexible. [redacted] whichever is less. The total daily dose will not exceed 100 mg/day (or 4 × 25 mg capsules/day). In the event of tolerability problems during titration, the Investigator may reduce the dose [redacted] During	Minor change per site clarification

Section	Page	Description of Change	Rationale for Change
		maintenance, up to one dose reduction will be allowed for safety and tolerability **during this period. Additional dose titration related to body weight changes will be reviewed and approved by the Medical Monitor and the Sponsor on a case by case basis.**	
3.4.1	39	Discontinuation of Subjects 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 **(study is terminated by the Sponsor, blind is broken, subject has relocated or death etc.)**	Minor change for completeness and/or clarification
4.3	41-42	Study Medication Dosing During maintenance, up to one dose reduction will be allowed for safety and tolerability. **Additional dose titration related to body weight changes will be reviewed and approved by the Medical Monitor and the Sponsor on a case-by-case basis.**	Minor change per site clarification
4.7	44	Concomitant Medications ~~Subjects may not be on any prohibited medication as indicated in the Inclusion/Exclusion Criteria.~~ Throughout the duration of the study, rescue migraine treatments such as simple analgesics ~~(e.g., ibuprofen and acetaminophen)~~ are allowed for symptomatic relief of acute headache episodes as long as their use does not exceed 3 times per week (or 15 treatment days/month) and the pattern of use remains stable. Use of narcotics is not permitted (**Appendix 10.9**). **Stimulant medications (extended or controlled release formulation) for the treatment of ADHD will be allowed if initiated and maintained on a stable dose (7 days/week) for at least 12 weeks prior to the Screening Visit and continued on the same dose during the study duration (Appendix 10.9).** **Prophylactic treatment for migraine is permitted if on a stable dose for at least 12 weeks prior to the Screening Visit including: daily NSAIDs, antiemetics, antihistamines, corticosteroids (i.e., systemic inhaled, or topical), high-dose**	Major change to facilitate study conduct

Section	Page	Description of Change	Rationale for Change
		magnesium supplements (≥600 mg/day), high-dose riboflavin (≥100 mg/day), coenzyme Q10, omega-3, melatonin, muscle relaxants and β-blockers. The dose and the medication must be maintained during the duration of the study (Appendix 10.9). Triptans, ketorolac, ~~antiemetics,~~ and ergotamines must be used with caution and with a frequency that does not exceed 10 treatment days/month. Subjects will be asked to be consistent in the use of their preferred acute migraine medication and encouraged not to initiate new therapies during the course of the trial (**Appendix 10.9**). **Anti-asthma medication: Albuterol sulfate is the only antiasthma medication allowed as needed (PRN) to keep any respiratory conditions under control (Appendix 10.9).** Treatment for AEs other than minor transient ailments is permitted only in consultation with the Medical Monitor or his/her designee with the exception of required treatments for acute conditions in the emergency room/hospital and/or office visit as indicated. ~~No additional concomitant medications are allowed during the study, with the following exceptions:~~ ~~• Nutritional supplements (e.g., multivitamins), except those listed in Section 4.8 • EMLA® or other numbing cream for venipuncture • Routine childhood vaccinations~~ ~~• Mydriatics are allowed on as needed basis per PI's discretion~~ **Additional concomitant medications allowed during the study include: nutritional supplements (e.g., multivitamins), EMLA® or other numbing cream for venipuncture, routine childhood vaccinations, Coronavirus Disease 2019 (COVID-19) vaccine and mydriatics (as needed per Principal Investigator (Winner et al.) discretion).**	
4.8	44-45	The following complementary and alternative prophylactic approaches to migraine are prohibited during the participation in this study (and as applicable, should be recorded as part of the subject's retrospective headache history): • Acupuncture • Manual therapies (chiropractic spinal manipulation, occipital nerve block, massage therapy, physical therapy)	Minor change

Section	Page	Description of Change	Rationale for Change
		• Herbal and nutritional supplement therapies for migraine prevention (butterbur, feverfew~~, high-dose magnesium supplements, riboflavin, and coenzyme Q10~~) and St. John's Wort) • Cognitive-behavioral therapy, biofeedback, hypnosis • Neuromodulation devices	
4.8.1	45	**4.8.1 Prohibited Medications (new section)** **Subjects may not be on any prohibited medication as indicated in the Inclusion/Exclusion Criteria.** **Subjects treated with the following prophylactic medications should discontinue the treatment 14 days prior to the Prospective Baseline Period: antipsychotics, antimanics, barbiturates, benzodiazepines amitriptyline, lithium, valproic acid, tricyclic antidepressants, AEDs, calcium channel blockers, sedatives, SSRIs, NSRIs, CGRP receptor antagonists, CBD oil, herbal preparations/supplements such as feverfew or St John's wort and/or any medications that could impair or decrease thinking and concentration. It is recommended to taper off antipsychotics, barbiturates, benzodiazepine, tricyclic antidepressants, lithium, amitriptyline, valproic acid, SSRIs and NSRIs as applicable. (Appendix 10.10).** ***Note: Subjects must refrain from using these medications throughout the duration of the study.*** **Non-stimulant ADHD medications (e.g., clonidine, atomoxetine, viloxazine and guanfacine) must be discontinued 14 days prior the Prospective Baseline Period (Appendix 10.10).**	Major change for consistency/study conduct facilitation
5.1	46	Study Visits and Procedures Study visits must be scheduled according **to** the Schedule of Events relative to the ~~Baseline~~ **Randomization** Visit (Visit 3). Visits must not be scheduled relative to the previous visit. **Bi-weekly telephone contacts will occur between study visits, at Days 14, 43, 71, 99, 127, and 148 (± 2 days).**	Major change to provide clarification on telephone contacts and add telephone contact at Day 148
Table 2	47-49	The Schedule of Events and Assessments was updated for consistency with changes to the protocol, especially those detailed in Sections 3.1 and 5. The following changes were made to the table footnotes. *** Visit 5 is end of titration and beginning of Maintenance Period of the Treatment Phase hence included within Section 5.1.5 for clarification.** a. Subjects who had used TPM or any **disallowed** prophylactic migraine therapy ~~within 4 weeks prior to Screening~~ must ~~complete a washout period of~~	Major and minor changes for completeness and/or clarification and to add Day 148 telephone contact

Section	Page	Description of Change	Rationale for Change
		discontinue the treatment at least 2 weeks before the start of the Prospective Baseline Period**, with an appropriate taper when applicable**. b. Bi-weekly telephone contacts will occur between study visits, at Days 14, 43, 71, 99, ~~and~~ 127, **and 148** (± 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 **rate**, 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**/ET Visit** occurs. m. ~~Placebo training refresher~~ **Subjects who discontinue from the study earlier than the EOS visit (visit 9) should undergo all EOS procedures included in visit 9 during the ET visit.** **Note: Besides the testing specified during the respective visits in the** Table 2 **above, repeat testing for clinical laboratory parameters, vital signs, and/or ECG may be permitted, at the discretion of the Investigator. However, these repeat**	

Section	Page	Description of Change	Rationale for Change
		testing will require justification from the site and agreement with the Medical Monitor and the Sponsor on a case-by-case basis prior to conducting the tests.	
5.1.1	50	Visit 1 – Screening (Day -56) All reasons for screening failure will be recorded. If the subject passes screening but fails eligibility at ~~baseline~~ **Randomization visit (Visit 3)**, the reason(s) will also be recorded in the eCRF. For subjects ~~provisionally~~ eligible for study participation, a Prospective Baseline Visit will be scheduled allowing for at least a 2-week/**14-day** washout of any **disallowed** migraine preventative ~~drug therapy~~ **medications** the subject was receiving at Screening.	Major change to provide clarification
5.1.3	51	Visit 3 (+2 days) – Randomization (Day 1) The following assessments will be conducted at this visit: • Review inclusion/exclusion criteria • Record vital signs (pulse **rate**, BP, temperature, and RR) • Collect urine sample for pregnancy test (FOCP only) • Administer C-SSRS • Review and record concomitant medications • Review Headache Diary for eligibility • Administer PedMIDAS, PedsQL 4.0 scales • Perform cognitive assessment • Perform eye exam • **Record AEs** • Randomization • Dispense SM (4-week supply) and provide instructions for dose titration	Minor change for completeness

Section	Page	Description of Change	Rationale for Change
5.1.4	51-52	Titration Period (Days 1 to 56, Week 1 to end of Week 8) Visit 4 (Day 29 ± 7 days) **During Treatment Phase (Visits 4 through 9), sample collection and testing have been specified for respective visits by the Sponsor. Besides the testing specified during these respective visits, repeat testing for clinical laboratory parameters, vital signs, and/or ECG may be permitted, at the discretion of the Investigator. However, these repeat testing will require justification from the site and agreement with the Medical Monitor and the Sponsor on a case-by-case basis prior to conducting the tests.** The following assessments will be conducted at this visit: • Perform physical examination (excluding genitourinary system) including height and weight, and neurological examination • Record vital signs (pulse rate, BP, temperature, and RR) • ~~Collect blood samples for hematology and serum chemistry~~ • Collect urine sample for ~~urinalysis and for~~ pregnancy test (FOCP only) • Administer C-SSRS • Review and record concomitant medications • Review Headache Diary • Record AEs • Collect SM and assess adherence; retrain as needed • Dispense SM (4-week supply) and review medication instructions with subject and caregiver • Placebo training refresher	Minor change for completeness and/or clarification

Section	Page	Description of Change	Rationale for Change
5.1.5	52-53	Maintenance Period (Days 57 to 140, Week 9 to the end of Week 20) Visits 6 (Day 85 ± 7 days) and Visit 7 (Day 113 ± 7 days) The following assessments will be conducted at these visits: • Perform physical examination (excluding genitourinary system) including height and weight, and neurological examination • Record vital signs (pulse rate, BP, temperature, and RR) • ~~Collect blood samples for hematology and serum chemistry~~ • Collect urine sample for ~~urinalysis and for~~ pregnancy testing (FOCP only) • Collect urine sample for drug screen • Perform eye exam **(only at Visit 6)** • Administer C-SSRS • Perform cognitive assessment • Review and record concomitant medications • Review Headache Diary • Record AEs • Collect SM and assess adherence; retrain as needed • Dispense SM (4-week supply) and review medication instructions with subject and caregiver • Placebo training refresher **(only at Visit 6)**	Minor change to align with Table 2
5.1.5	53	Maintenance Period (Days 57 to 140, Week 9 to the end of Week 20) Intervening Phone Calls At Days 71 (± 2 days), 99 (± 2 days) and 127 (± 2 days), there will be telephone calls to subjects to assess the tolerability of SM treatment. The following assessments will be made during these telephone contacts: • Review and record concomitant medications • Record AEs • Provide guidance (as needed) on dose reduction, up to one dose reduction will be allowed **for safety and tolerability during this period. Additional dose titration related to body weight changes will be reviewed and approved by the Medical Monitor and the Sponsor on a case by case basis.**	Minor change per site clarification

Section	Page	Description of Change	Rationale for Change
5.1.6	54	Taper Period (Days 141 to 161, Week 21 to the end of Week 23) **Intervening Phone Call** **At Day 148 (± 2 days) there will be a telephone call to subjects to assess the tolerability of the SM treatment.** **The following assessments will be made during these telephone contacts:** • **Review and record concomitant medications** • **Record AEs** • **Provide guidance (as needed) on dose reduction** <u>Visit 9 (Day 162 ± 7 days) – End of Study (EOS) Visit</u> The following assessments will be conducted at this visit: • Perform physical examination (excluding genitourinary system) including height and weight, and neurological examination • Perform 12-lead ECG • Record vital signs (pulse rate, BP, temperature, and RR) • Collect blood samples for hematology and serum chemistry • Collect urine sample for urinalysis and for pregnancy testing (FOCP only) • Collect urine sample for drug screen • Perform visual neurological exam • Perform eye exam • Administer C-SSRS • Review and record concomitant medications • ~~Review Headache Diary~~ • ~~Remove app from caregiver's phone~~ • Administer PedMIDAS, PedsQL 4.0 scales • Perform cognitive assessment • Record AEs • Collect SM and assess adherence	Minor change for completeness and clarification
5.1.7	54	Added 3rd bullet to assessments at Safety Follow-up Telephone Call (Weeks 24 through 26) **Perform cognitive assessment (Appendix 10.5)**	Major change

Section	Page	Description of Change	Rationale for Change
6.6	58	Adverse Events An AE can be: • Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • Any new disease, intercurrent injuries, or exacerbation of an existing disease. • Any deterioration in a laboratory value or other clinical test (e.g., ECG) that results in symptoms, a change in treatment, or discontinuation from SM. • Recurrence of an intermittent medical condition (e.g., ~~headache~~ **muscle pain**) not present at baseline.	Minor change
6.6.2	59	Recording and Evaluation of Adverse Events The Investigator is responsible for evaluating AEs and determining the following: • Serious vs. Non-serious: Is the event an SAE? • Causality: Was AE related or ~~possibly~~ **not** related to the SM? • Severity: How pronounced is the incapacity/discomfort caused by an AE?	Major change
6.6.9	62-63	Adverse Events of Special Interest Several AEs are known to be associated with the long-term use of TPM and can be expected with treatment with SPN-538 ("National Institutes of Health-DailyMed-Trokendi XR- Prescribing Information.," 2022). Consistent monitoring is required for the following AESIs: • Metabolic acidosis **(serum bicarbonate)** • 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 **cell** 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	Major change to align with the updated Prescribing Information

Section	Page	Description of Change	Rationale for Change
		• **Serious skin reactions (TPM should be discontinued at the first sign of rash, unless rash is not drug-related)** • **Negative effect on growth (weight and height)** • Cognitive and memory function impairments • Nephrolithiasis	
6.8.6	66	Eye Exam Equipment at the site necessary to perform the visual neurological and eye exam consists of the following: • Near card • Wall Snellen Chart **(optional, at Investigator's discretion based on outcome from routine eye exam)** • Penlight • Hand help Ophthalmoscope (direct or Panoptic) • **Amsler grid (optional, at Investigator's discretion based on outcome from routine eye exam)** **The Wall Snellen Chart uses a geometric scale to measure visual acuity, with normal vision at a distance being set at 20/20. The numerator represents the distance that the patient is standing from the chart (in feet), while the denominator represents the distance from which a person with perfect eyesight is still able to read the smallest line that the patient can clearly visualize.** **The Amsler grid could be used to help detect early signs of retinal disease and monitor changes in vision after diagnosis.** ***Note: The Sponsor has appended Snellen chart (Appendix 10.8.1) and Amsler grid (Appendix 10.8.2) for every participating site as a tool to be used by the investigator if further examination is deemed necessary after a routine eye exam outcome.***	Major change for completeness and/or clarification
6.8.7	67	Cognitive Assessment Changes in cognitive function will be assessed at Visit 3, Visits ~~6~~**5** through 9 **and at the safety follow-up phone call after the EOS.**	Major change

Section	Page	Description of Change	Rationale for Change
7.1	69	~~All data analyses will be performed by qualified personnel as identified by the Sponsor after the study is completed and the database is released.~~ All data will be analyzed using SAS® (SAS Institute, Inc., Version 9.3 or later). In general, continuous variables will be summarized using standard descriptive statistics including number of subjects (n), mean, ~~standard deviation (~~SD~~)~~, median, **interquartile range (Q1, Q3),** minimum, and maximum. Categorical variables will be summarized with frequencies and percentages. The data summaries will be accompanied by individual subject data listings, as specified in Sections 16.2 and 16.4 of ICH Guidance E3, sorted by unique subject identifier. All data available from the electronic CRFs will be listed. Unscheduled measurements will be excluded from the descriptive statistics and statistical analysis but will be included in listings. Categorical variables will be analyzed using categorical ~~response~~ **statistical** methods such as Pearson's Chi-square test or Fisher's exact test as appropriate. Treatment comparison for all efficacy variables will be evaluated based on a two-sided significance level of 0.05 ~~and the interaction effects at 0.10~~. 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. ~~Subject baseline measurements are assumed to be comparable at the start of the study, as randomization is designed to ensure balance between the groups on the baseline characteristics, so no formal statistical group comparisons will be conducted on the subject characteristics.~~ ~~The test for the normality of the change in the monthly migraine days during the last 4 weeks of the Treatment Phase relative to the Prospective Baseline Period will be checked using the Shapiro-Wilks test. If the test does not detect departures from normality, then the primary and sensitivity analyses will be performed using parametric methods for estimation and hypothesis testing. Otherwise, the primary and sensitivity analysis endpoints will be analyzed using the non-parametric Wilcoxon rank-sum test to compare the median SPN-538 dose with the median of the Placebo. The Hodges-Lehmann estimate of the difference (SPN-538 minus placebo) and the associated 95% confidence interval (CI) around the difference will be calculated.~~ Complete details of the statistical analysis will be provided in a separate ~~statistical analysis plan (~~SAP~~)~~. ~~The statistical analysis methods described in the SAP will supersede the statistical methods described in this protocol.~~	Changed to align with SAP per FDA request

Section	Page	Description of Change	Rationale for Change
7.2	69-70	~~Baseline:~~ ~~For baseline, missing baseline data will not to be imputed.~~ ~~Primary and Secondary Efficacy Endpoints:~~ ~~For the primary efficacy endpoint, monthly migraine days during the treatment period will be calculated over the number of days with non-missing migraine diary data in the Treatment Phase.~~ ~~Missing diary data for the analysis in the calculations of monthly measurements about subjects' migraine will be handled by the following method:~~ ~~1. Monthly intervals with diary compliance ≥ 50% (i.e., ≥ 14 days of diary days out of 28 days during the Treatment Phase):~~ ~~a) Monthly measurements (including migraine days, headaches days duration of migraine, or acute medication use) will be prorated to 28-day equivalents.~~ ~~b) Monthly average severity of migraine pain, migraine related symptoms and monthly average scale of migraine interference with daily activity will be calculated as the average of observed scores.~~ ~~2. Monthly intervals with diary compliance < 50% (i.e., < 14 days of diary days out of 28 days); all monthly measurements will be set as missing.~~ **Missing endpoint values in this study may result from subjects discontinuing from the study prematurely or missing intermediate assessments while remaining on study. The primary efficacy analysis method will be based on a Mixed Model for Repeated Measures (MMRM) which utilizes all available data (complete and partial) from subjects included in an analysis set. The MMRM-based approach assumes that missing diary data are MAR. MAR refers to a missingness mechanism that is independent of missing responses, conditionally on observed response history and covariates. That is, given the observed data, the reason for the missing data does not depend on the underlying unseen data. For primary analysis, missing 28-day MMDs for subjects discontinued due to AE or lack of efficacy will be explicitly imputed by the mean values obtained from MI under the missing not at random (MNAR) assumption before implementing the MMRM. Missing 28-day MMDs for subjects discontinued due to reasons other than AE or lack of efficacy will not be imputed for the primary efficacy analysis. Sensitivity analyses of the primary endpoint to investigate robustness to missing primary endpoint data will be performed by assuming that missing diary data are MNAR, meaning that the probability that an observation is missing may depend**	Changed to align with SAP per FDA request

Section	Page	Description of Change	Rationale for Change
		on its underlying unobserved value. Missing data handling for safety data will be described in the SAP.	
7.3	70	The **Per-Protocol ~~(PP) Population~~** ~~is the subset of~~ **Set (PPS) includes all** subjects in the FAS who ~~are free of major~~ **have completed Visits 1-8 with no missing MMDs and no important** protocol deviations. ~~Analysis of~~ **PPS will be used as supplementary analysis of the primary and secondary** efficacy **endpoints with treatment classification**-based on the ~~PP Population is not a sensitivity analysis, but it will be used to support the primary analysis to describe the treatment effects under idealized conditions of full or partial compliance. Subjects will be analyzed according to the~~ treatment received. The **Safety Analysis Set ~~(SAS)~~** includes all subjects randomized into the study who received at least 1 dose of **SM**. ~~study medication. Subjects~~ **Data** will be analyzed according to the treatment received. [redacted]	Changed to align with SAP per FDA request
7.4	70	Demographic/baseline variables including age, sex, ethnicity, race, height and weight at screening, and medical and neurological histories will be summarized using descriptive statistics for continuous variables and counts and percentages for categorical variables. Descriptive summaries will be presented by treatment group for ~~the~~ FAS, ~~PP Population~~ **PPS,** and ~~SAS~~ **Safety Analysis Set**.	Minor changes
7.5	70-71	A disposition of subjects will include the number and percentage of subjects in each of the following categories: • Subjects in the Randomized Population • Subjects in the FAS • Subjects in the PP ~~Population~~ **Analysis Set** • Subjects in the ~~SAS~~**Safety Analysis Set** [redacted] Within each of the previous categories, the number and percentage of subjects who completed and discontinued from the study and primary reason for early discontinuation will be summarized. The reason for early discontinuation may include any of the following: • Withdrawal of consent and assent	Changed to align with SAP per FDA request

Section	Page	Description of Change	Rationale for Change
		• Lack of efficacy • Investigator decision • Noncompliance with study procedures • Occurrence of unmanageable AEs • Lost to follow-up • ~~Other~~ **Other (study is terminated by the Sponsor, blind is broken, subject has relocated or death etc.)**	
7.6	71	Duration of exposure is defined as the total number of days a subject is exposed to any study treatment. This will be calculated for each subject by taking the difference between the date of last dose minus the date of the first dose, plus 1 (date of last dose minus date of first dose +1). Duration of treatment exposure will also be summarized using descriptive statistics ~~(n, mean, SD, median, minimum, and maximum)~~. Percent of ~~study drug~~ **SM Compliance is calculated as %** compliance ~~is defined as {(number of capsules dispensed minus number of capsules returned) / (date of last dose minus date of first dose + 1)}*~~ 100% ***(Num/Den), where** ~~If the date of last dose is not available, then it will be imputed by the subject's last visit in the study.~~ $\boldsymbol{Num} = \sum_{i=3}^{7} \#\ \textbf{of capsules dispensed at}\ \boldsymbol{visit_i} - \#\ \textbf{of capsules returned at}\ \boldsymbol{visit}_{i+1}$ $\boldsymbol{Den} = \sum_{i=3}^{7} \boldsymbol{x_i} \times (\#\ \textbf{of days between}\ \boldsymbol{visit_i}\ \textbf{and}\ \boldsymbol{visit_{i+1}}), \boldsymbol{where}$ $\boldsymbol{x_i} = \#\ \textbf{of capsules per day assgined to be administered at}\ \boldsymbol{visit_i}$ For each treatment, SM compliance will be summarized by compliance category (<80%, 80-120%, and >120%) and number of subjects in each compliance category. **SM** ~~Study medication~~ compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, ~~standard deviation~~ **SD**, median, minimum, and maximum) 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.	Changed to align with SAP per FDA request

Section	Page	Description of Change	Rationale for Change
7.7	71-72	Prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary (WHO DD)~~. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. A tabular summary of concomitant medications by drug class will be presented for the SAS~~ **and summarized descriptively by ATC classification level 4 and preferred term for the Safety Population**. 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 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.	Changed to align with SAP per FDA request
Synopsis & 7.8	11, 72	**Based on the FAS, the observed value and change from baseline will be summarized using descriptive statistics as described in Section 7.1 and 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.**	Changed to align with SAP per FDA request
Synopsis & 7.8.1	11-12, 72-73	The primary efficacy ~~outcome measure is the~~ **endpoint,** change ~~in the mean monthly (28-day) rate of migraine days (MMDs) during the last 4 weeks of the 20-week double-blind Treatment Phase relative to~~ **from** the Prospective Baseline Period ~~based on the FAS.~~ ~~The test for the normality of the change in the monthly migraine days during the last 4 weeks of the Treatment Phase relative to the Prospective Baseline Period will be checked using the Shapiro-Wilks test. If the test does not detect departures from normality, then the primary and sensitivity analyses will be performed using parametric methods for estimation and hypothesis testing. Otherwise, the primary and sensitivity analysis endpoints~~ **in 28-day rate MMDs,** will be analyzed using ~~the non-parametric Wilcoxon rank-sum test to compare the median SPN-538 dose with the median of the Placebo. The Hodges-Lehmann estimate of the difference (SPN-538 minus placebo) and the associated 95% confidence interval (CI) around the difference will be calculated.~~ ~~If departures from normality in the number of migraine days per month are not detected, then the primary endpoint will be analyzed using a Mixed Model for Repeated Measures (~~MMRM~~) analysis of covariance (ANCOVA)~~, which assumes that missing data are ~~missing at random (~~MAR~~)~~. **All post-baseline study visits will**	Changed to align with SAP per FDA request

Section	Page	Description of Change	Rationale for Change
		be included in the model; however, the primary comparison will be between SPN-538 and placebo at Month 5 (last 4 weeks of the Maintenance Period). The model will include fixed effect terms for ~~the prospective baseline migraine days,~~ **28-day rate of MMDs for the Prospective Baseline Period,** treatment group, **Prospective Baseline monthly migraine-specific acute** rescue medication **(28-day rate)** use ~~(Yes or No)~~, visit ~~(5 monthly visits)~~, and treatment-by-visit interaction as ~~covariates~~ **independent variables**. The model parameters will be estimated using restricted maximum likelihood method with **an** unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom. ~~In case there is a convergence problem in the MMRM model with the unstructured variance-covariance matrix,~~ **If the MMRM model with the unstructured variance-covariance matrix does not converge using the default Newton-Raphson fitting algorithm by PROC MIXED in SAS, then the Fisher scoring algorithm or the no-diagonal factor analytic structure will be used (Lu & Mehrotra, 2010). If the model still fails to converge, then** the first (co)variance structure which does not have convergence problem will be used for the analysis from the following ordered list: ~~a) Toeplitz, b) Autoregressive of order 1, c) Compound symmetry.~~ ~~The treatment differences in terms of mean change from the Prospective Baseline Period to the post-randomization migraine days will be estimated and tested from this model from the treatment-by-visit interaction.~~ **6. Heterogeneous Toeplitz** **7. Heterogeneous Autoregressive of order 1** **8. Toeplitz** **9. Autoregressive of order 1** **10. Compound Symmetry** **The denominator degrees of freedom will be estimated using the BETWITHIN option in SAS when any of the covariance structures is used with the sandwich variance estimator.** The ~~adjusted mean (~~least square mean **(**~~[~~LS Mean~~]~~) of each treatment group (~~P~~**p**lacebo and SPN-538~~dose~~) along with the corresponding standard error, p-values, difference **in the LS Mean** between ~~the LS Mean of~~ SPN-538 ~~dose~~ and placebo (SPN-538 ~~dose~~ minus ~~P~~placebo), and 95% CIs will be computed **at each visit**.	

Section	Page	Description of Change	Rationale for Change
		~~Sensitivity~~ **To assess the robustness of the primary analysis under the MAR assumption, two sensitivity** analyses will be performed based on multiply imputed data assuming missing data are ~~missing not at random (~~MNAR~~)~~. The ~~change in the mean 28-day rate of migraine days during the last 4 weeks of the Treatment Phase relative to the Prospective Baseline~~ **first sensitivity analysis will be** based on **placebo-based MI in which missing values for the subjects in** the ~~FAS will be analyzed using ANCOVA with treatment as a fixed classification variable and~~ SPN-538 treatment group would adopt the ~~Prospective Baseline migraine days as a covariate.~~ **outcome model estimated from the placebo arm. The second sensitivity analysis** This will be ~~implemented~~ **performed** using ~~SAS® PROC MI and SAS® PROC MIANALYZE (SAS/STAT Software)~~ **a 'tipping point' methodology to assess the assumption of MAR in the primary analysis. The tipping point analysis will progressively impose increasing shift parameters to the imputed observations under the MNAR assumption in the active treatment arm, not to the placebo arm, to assess how severe departures from MAR must be to overturn the conclusion from the primary analysis.** **The details for both approaches will be provided in the SAP**.	
7.8.2	73	~~This is a 2-arm treatment study and hence, no multiplicity adjustment is needed.~~ **The overall type I error rate for the study will be preserved at the two-sided 5% significance level by using a sequential (hierarchical) testing for the primary and secondary endpoints. The details will be provided in the SAP.**	Changed to align with SAP per FDA request
7.8.3	73-74	Secondary endpoints will be analyzed based on the FAS using appropriate statistical models based on the type of endpoints. Analyses of Secondary Endpoints 1. **Monthly Migraine Responders:** For each subject, a binary response variable for change from baseline in the ~~monthly migraine days~~ MMDs during the last 4 weeks of the Treatment Phase relative to baseline will be set to 'YES' if a subject's % reduction is ≥ 50% or 'NO' otherwise. The proportion of responders will be presented for each treatment group. The 2-sided 95% CI around the difference in proportions (SPN-538 dose minus Placebo) and the p-value from Pearson's Chi-squared Test or Fisher's Exact Test will be presented. 2. **Migraine-Specific Acute Rescue Medication: The change from Prospective Baseline in the 28-day rate of migraine-specific acute rescue medication use in the last 4 weeks of the Treatment Phase will be analyzed using the same analysis method (MMRM) as for the primary efficacy endpoint. The**	Changed to align with SAP per FDA request

Section	Page	Description of Change	Rationale for Change
		contrast of interest will be at Month 5 for the SPN-538 group compared with placebo. ~~Change from baseline in the number of days per month with acute rescue medication use in the last 4 weeks of the Treatment Phase will be analyzed using parametric ANCOVA, assuming normality assumption, with treatment as a fixed classification variable and baseline as a covariate. The SPN-538 dose will be compared with placebo. The p-values, LS Means of the treatment groups, differences between the LS treatment means and placebo (SPN-538 dose minus Placebo), and 95% CIs for the treatment differences will be computed. If data are not normal, then non-parametric method will be used.~~ 3. **Total Headache Days, Duration, and Severity: The change from Prospective Baseline in the 28-day rate of total headache days, duration of headache days (migraine and non-migraine) in the last 4 weeks of the Treatment Phase will be analyzed using the same analysis method (MMRM) as for the primary efficacy endpoint. The contrast of interest will be at Month 5 for the SPN-538 group compared with placebo.** ~~Change in the monthly rate of total headache days (migraine and non-migraine), duration and severity will be analyzed using the methods described above.~~ ~~4~~. **Onset of action: The time to first significant treatment effect in the MMDs will be based on the MMRM analysis of the primary endpoint. The first month at which a statistically significant difference in the change from baseline in 28-day MMDs is observed and maintained until the EOS between SPN-538 and placebo will be claimed as the first month for the onset of treatment effect.** ~~Change from baseline in monthly migraine days from the first month of treatment and the last 4 weeks of the Treatment Phase will be evaluated for a statistically significant difference between SPN-538 and placebo in the primary analyses.~~ 5. **Headache disability: The** change from baseline in the Headache Disability Score as measured by PedMIDAS during the last 4 weeks of the Treatment Phase will be **summarized using descriptive statistics by visit.** ~~analyzed using the methodology described in item 2 above~~ 6. **HRQoL: The** change from baseline in the HRQoL as measured by the PedsQL4.0 Total Scale Score during the last 4 weeks of the Treatment Phase for the self-report and the parent-report will be ~~analyzed~~ **summarized** using ~~the methodology described in item 2 above~~ **descriptive** statistics **by visit**.	

Section	Page	Description of Change	Rationale for Change
Synopsis & 7.8.4	12, 74	~~Descriptive statistics and modeling will be used for exploratory analyses of other efficacy endpoints. Multiple Type 1 error rates will not be controlled.~~	Administrative change resulting from changes to align with SAP per FDA request
Synopsis	12	Descriptive statistics will be presented for demographics, data from the clinical laboratory test results, vital signs, weight, ECGs, physical, neurological and eye examinations**, suicidal ideation, and cognitive assessment**.	Major change for completeness
7.11	74-75	Safety analysis as described below will be conducted using ~~the~~ SAS. **All safety analyses will be performed on the Safety Analysis Set**. The incidence rate of AEs will be calculated by treatment group for each System Organ Class (SOC) and Preferred Term (PT). The severity of the AEs and the relationship to SM will be summarized by treatment group for each SOC and PT. AEs will be summarized using discrete summaries at the subject and event level by SOC and PT, and by severity and relationship separately for each treatment group. Verbatim description and ~~Medical Dictionary for Regulatory Activities (~~MedDRA~~)~~ SOCs and PTs for all AEs will be contained in the subject data listings. All AEs occurring after randomization and throughout the study period will be recorded. For subjects who receive SM, TEAEs will be collected starting after the first dose of SM (Visit 3) to the end of the study. These AEs include those that emerge during treatment or worsen in severity during treatment. These AEs will be tabulated, listed and analyzed. **The incidence of AESIs based on AE data will be summarized for each treatment group by MedDRA SOC and PT. Supporting subject listing of AESI will be presented**. For AESIs, percentages of subjects experiencing visual/ocular disturbances, oligohydrosis, hyperthermia, metabolic acidosis (serum bicarbonate), hyperammonemia, nephrolithiasis, and hepatic injury will be summarized using descriptive statistics by treatment and collection time point. Clinical laboratory values will be summarized by visit and treatment group using descriptive statistics. For quantitative laboratory parameters, both actual values and change from **baseline (values collected at** Screening**)** ~~values~~ will be summarized. Vital signs will be summarized by visit by treatment group using descriptive statistics. Both actual values and change from baseline will be summarized.	Minor changes for completeness and/or clarification

Section	Page	Description of Change	Rationale for Change
		ECG results will be summarized by visit by treatment group using descriptive statistics (for quantitative ECG parameters) and frequency tables (for qualitative ECG parameters, including the overall ECG finding). C-SSRS outcomes will be summarized using number and percent of subjects by categories for suicidal ideation only, suicidal behavior only and suicidality (ideation and behavior combined). The summary will be presented by treatment groups. For physical, neurological, and eye examinations, change in status from baseline to the ~~end of study~~ **EOS** will be summarized by body system for each treatment group. **Cognitive function will be assessed by evaluating the responses from subject responses to the cognitive questionnaire. Responses to the questions will be presented in subject listing and summarized by study visit and treatment group**.	
10.6	98-103	10.6 ~~(Appendix 6)~~ Columbia-Suicide Severity Rating Scale **10.6.1 C-SSRS - Children's Baseline (new section)** **10.6.2 C-SSRS - Children's Since Last Visit (new section)**	Major Change Version 3.0 contained only the Children's Baseline version. Appendix 10.6 has the Children's Baseline and Children's Since Last Visit versions in two subsections.
10.8	105-107	10.8 ~~(Appendix 7b)~~ Eye Exam Checklist **10.8.1 Wall Snellen Chart (new section)** **10.8.2 Amsler Grid Test (new section)**	Major Change Version 3.0 contained only the Eye Exam Checklist. Version 4.0 contains the Eye Exam Checklist and the two additional listed items in the subsections.
10.9	108	**10.9 Concomitant Medications (new section)**	Major Change
10.10	109	**10.10 Prohibited Medications (new section)**	Major Change

Section	Page	Description of Change	Rationale for Change
10.11	110-139	**10.11 Summary of Changes (new section)**	Major Change – put Summary of Changes at the end to prevent pagination changes during the process of creating the Summary of Changes

Section and page numbers refer to the amended protocol.
Changes in figures and tables are described rather than reproduced as marked up text.

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