STATISTICAL ANALYSIS PLAN

Protocol Title Open-label Study of Safety and Tolerability of Chronic Intermittent Usage for 6 or 12 Months of Intranasal Dihydroergotamine Mesylate (DHE) Administered by the I123 Precision Olfactory Delivery (POD®) Device [INP104, POD-DHE] in Patients with Migraine Headache

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PROTOCOL TITLE	Open-label Study of Safety and Tolerability of Chronic Intermittent Usage for 24 or 52 Weeks of Intranasal Dihydroergotamine Mesylate (DHE) Administered using I123 Precision Olfactory Delivery (POD®) Device [INP104, POD-DHE] in Patients with Migraine Headache
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Chief Medical Officer

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LIST OF ABBREVIATIONS

AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CRF	Case report form
DHE	Dihydroergotamine mesylate
ECG	Electrocardiogram
EAER	Exposure Adjusted Event Rate
HIT-6	Headache Impact Test
ICH	International Conference on Harmonisation
IP	Investigational Product
MBS	Most Bothersome Symptom
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment
POD	Precision Olfactory Delivery
PT	Preferred term
QSS-NM	Quantitative scoring scale of evaluation of the nasal mucosa
SAE	Serious adverse event
SOC	System organ class
TEAE	Treatment-emergent adverse events
UPSIT	University of Pennsylvania Smell Identification Test
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

Migraine is experienced by more than 80 million people in the United States and European Union. It is a common and disabling neurologic disorder (Hansen 2016; Manzoni 2010). Acute treatment of migraine remains a clinical challenge despite the availability of multiple treatment options. More than 40% of respondents in a population survey of acute migraine claimed to have at least one unmet need in their acute migraine treatment, and a large percentage (37.4%) of respondents' report dissatisfaction with current treatment options, suggesting the opportunity for outcome improvement in acute migraine subjects (Lipton 2013).

D.H.E. 45® Injection, USP is the brand name of the dihydroergotamine mesylate product first approved in 1946 for injection (D.H.E. 45® Prescribing Information). Dihydroergotamine mesylate (DHE), in all current formulations, is an acute (abortive) therapy and will not prevent headaches. Common side effects of D.H.E. 45® Injection include dizziness, drowsiness, headache, nausea, vomiting, diarrhea, flushing (redness or tingly feeling under the skin), increased sweating, anxiety, or skin rash. Though effective, many patients do not like injections, and they commonly require a healthcare professional to administer them.

Migranal® Nasal Spray is the brand name of a DHE product administered by a nasal spray applicator and was approved by the United States Food and Drug Administration (FDA) in August 1997 (Migranal US Prescribing Information). Unfortunately, the bioavailability of DHE via intranasal spray (32%) is poor compared to the injectable product, and side effects of taste disturbance and rhinitis are frequent (Migranal® US Prescribing Information). It is hypothesized that absorption of drug could be improved with a targeted delivery of drug to the upper nasal cavity in a manner that avoids loss of drug through dripping out from the nose or into the throat.

The INP104 product utilizes hydrofluoroalkane-134a propellant to deliver the same formulation of DHE as contained in Migranal® Nasal Spray, for a total target dose of 1.45 mg (administered in two sprays, one per nostril), after which the product is discarded. The I123 POD® Device used in INP104 has been specifically designed to propel liquid formulations in a focused stream, as a narrow plume, to the epithelium of the upper nasal cavity. This narrow stream is intended to minimize deposition in the nasal vestibule and to avoid loss of drug before absorption.

One clinical trial (Protocol INP104-101) was completed with DHE delivered by the I123 POD® Device (i.e. with INP104). This study compared the bioavailability of DHE following single dose administration by INP104 to that of D.H.E. 45® Injection, USP and to Migranal® Nasal Spray in healthy adult subjects. Safety data indicate that when DHE is delivered by intranasal administration, adverse events (AEs) other than increased nausea tend to be localized to the nose and throat and include minor nose and throat irritation, nasal congestion, and bad taste in the mouth. In the phase I study (Protocol INP104-101), administration of INP104 or Migranal® resulted in fewer AEs compared to D.H.E. 45® Injection administered intravenously. The established safety of Migranal Nasal Spray and D.H.E. 45 (dihydroergotamine mesylate) Injection, USP supports further clinical development of the INP104 product.

This study is focused on the safety and tolerability of chronic intermittent usage for 24 or 52 weeks of nasal DHE administered using the I123 POD® device [INP104 or POD-DHE] in subjects with migraine. The Statistical Analysis Plan (SAP) provides details of the analyses and data presentations regarding the endpoints identified in the protocol.

2. OBJECTIVES

2.1. Primary Objectives

The primary objective of this study is to evaluate the safety and tolerability of the investigational product (IP; INP104 or POD-DHE):

- Number of subjects with serious and non-serious treatment emergent adverse events
- Change in nasal mucosa
- Change in olfactory function

2.2. Secondary Objectives

The secondary objectives are

(1) To evaluate the efficacy of INP104 as assessed by change from baseline in migraine measures over 24 and 52 weeks of treatment.

(2) To further assess safety and tolerability by:

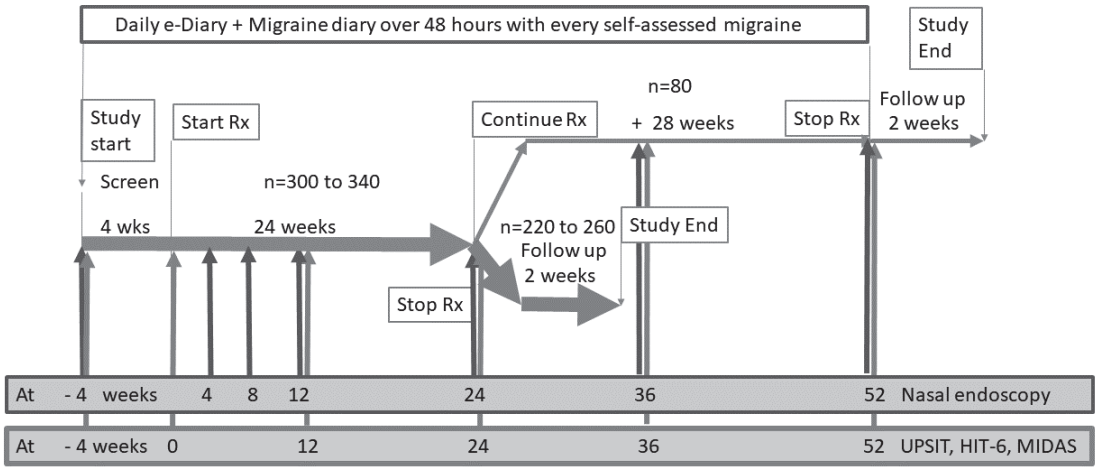
- Change in vital signs
- Change in physical examinations
- Change in 12-lead electrocardiogram (ECG)
- Change in laboratory evaluations (hematology, clinical chemistry, and urinalysis)

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is an interventional, open-label, single-group assignment, safety, tolerability, and exploratory efficacy study. The study will comprise a 4-week screening period, a 24-week treatment period for all subjects, with a treatment continuation to 52 weeks for a subset of the subjects who reach Week 24, and a 2-week post-treatment follow-up period. Approximately 340 subjects will be enrolled to achieve at least 150 subjects in the primary safety set (Section 4.3.4) and a subset will continue into the second half of the study with the aim of at least 60 subjects completing 52 weeks of exposure. Suitable subjects continuing to the 52-week endpoint will be re-consented at 24 weeks.

Figure 1: Study Design Flow Chart



The study is an outpatient study in subjects who suffer frequent migraines (currently suffering a minimum of 2 migraines/per month) but not diagnosed with chronic headache by International Classification of Headache Disorder version 3 beta (ICHD3b) criteria. During the screening period, subjects will be required to complete a daily migraine diary and record at least 2 migraine attacks. If they are eligible at Visit 2, they will be enrolled and provided with a POD device for training purposes and a supply of INP104 (up to 3 doses per week) and instructed to use no more than 2 doses within a 24-hour period, 3 doses in a 7-day period and 12 doses per 4-week period for their usual migraines. All subjects will self-administer INP104 nasally (1.45 mg in a divided dose, one actuation per nostril).

During the treatment period, all subjects will record all migraines experienced over 24 weeks. A subset of subjects with sufficient IP exposure and diary compliance will enter an additional 28-week treatment period to allow data collection for 52 weeks of total exposure. Study subjects will record all headache episodes (frequency and severity) in an electronic diary and undergo periodic evaluation by Migraine Disability Assessment (MIDAS; Appendix 14.4) and Headache

Impact Test (HIT-6™ ; Appendix 14.3) questionnaires. Subjects will also return to the clinic for periodic evaluations of safety, which will include collection of vital signs, physical examinations, nasal endoscopy, the University of Pennsylvania Smell Identification Test (UPSIT), electrocardiography, recording of AEs, laboratory evaluations, and concomitant medications.

3.1.1. Primary Endpoints

The primary endpoints for the study are listed below and the analyses are documented in the Safety Analysis section:

- Number of subjects with serious and non-serious treatment emergent adverse events (Section 10.1)
- Change in nasal mucosa as detected by nasal endoscopy (Section 10.6)
- Change in olfactory function (Section 10.7)

3.1.2. Secondary Endpoints

The secondary endpoints for the study include additional safety and tolerability as assessed by:

- Change from baseline in vital signs (Section 10.3)
- Change from baseline in physical examinations (Section 10.4)
- Change from baseline in 12-lead ECG (Section 10.5)
- Change from baseline in laboratory evaluations (hematology, clinical chemistry and urinalysis) (Section 10.2)

3.1.3. Exploratory Endpoints

The exploratory endpoint of this study includes:

- Change from baseline in healthcare utilization for migraine (Section 10.8)
- Product acceptability questionnaire (Section 10.9)

Exploratory efficacy endpoints include:

- Change from baseline in rate of freedom from headache pain at 2 hours after IP administration (Section 9.1.1)
- Change from baseline in Most Bothersome Symptom (MBS) at 2 hours after IP administration (Section 9.1.1)
- Change from baseline in frequency and severity of headache pain (over other time points) after IP administration (Section 9.1.1)
- Change from baseline in MBS at other time points after IP administration (Section 9.1.1)
- Change from baseline in frequency and severity of migraine (measured by headache pain, nausea, phonophobia and photophobia) by diary (Section 9.1.1 and)

- Incidence of pain relapse within 24 and 48 hours after IP administration (Section 9.1.1 and)
- Change from baseline in MIDAS and HIT-6 questionnaires (Section 9.1.2)
- Change in concomitant migraine medication use (Section 9.1.1 and)

4. GENERAL CONSIDERATIONS

- Continuous data will be described using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum).
- Categorical data will be described using the subject count and percentage in each category.
- For the summary statistics of all numerical variables, unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation / standard error will be displayed to two levels of precision greater than the data collected.
- Confidence intervals will be presented as 2-sided 95% CIs to one level of precision greater than the data reported.
- Subjects will be identified in the listings by the concatenation of the site number with the subject identification number.
- Listings will be sorted by subject id and record date. Demographic information will be included at the subject level in all listings.
- When count data are presented, the percentage will be suppressed when the count is zero to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where needed to account for dropouts and missing values.
- The denominator for all percentages will be the number of subjects within the analysis set of interest, unless otherwise specified.
- Unless specified otherwise all references to a migraine and summaries of migraines will be for migraine attack and not migraine days.

4.1. Sample Size

Approximately 300 to 340 subjects will be enrolled in the study. All subjects enrolled are planned for the 24-week treatment period, with the goal of having at least 150 subjects being in the primary safety set (Section 4.3.4). Additionally, a subset of subjects will be enrolled into an additional 28-week period with the goal of having at least 60 subjects who complete a total of 52 weeks of treatment, with each individual subject having an average of at least 2 migraines per 28 day period. At least 30 subjects of each gender will be enrolled in the initial 300 to 340 subjects.

4.2. Treatment Groups

This is an open-label study with only one arm: 1.45 mg of DHE.

Subjects in both the 24-week and 52-week exposure groups, will all receive the same treatment.

4.3. Analysis Set

Separate analysis populations will be created to account for the fact that all treated subjects will be in the initial 24-week period but only a subset of these will be treated for the full 52 weeks.

Additionally, as the primary objective of this study is to evaluate safety in subjects with sufficient exposure, analysis populations have been created for all treated subjects and for the subset of subjects with sufficient exposure to IP. These subset populations are called 'Primary Safety Sets' as they are the primary focus of this study.

4.3.1. Enrolled Set

The Enrolled Set will include all subjects who sign the informed consent form and are provided IP.

4.3.2. 52-Week Enrolled Set

The 52-Week Enrolled Set will include all subjects who sign the additional informed consent at the Week 24 visit and are provided IP.

4.3.3. 24-Week Full Safety Set

The 24-Week Full Safety Set will include all subjects who are enrolled and receive at least 1 dose of INP104. The summaries of the 24-Week Treatment Period will be based on 24-Week Full Safety Set.

4.3.4. 24-Week Primary Safety Set

The 24-Week Primary Safety Set will include all subjects who have an average of two or more treatments with INP104 per 28 day period during the 24-Week Treatment Period. Specifically, inclusion into this group will require that the subject remain in the study and attend the Week 24 visit and receive twelve or more INP104 treatments by the Week 24 Visit.

4.3.5. 52-Week Full Safety Set

The 52-Week Full Safety Set will include all subjects who sign the additional informed consent at 24 weeks and receive at least one dose of INP104 in the additional 28-Week treatment period. The summaries of the 52-Week Treatment Period will be based on the 52 Week Full Safety Set.

4.3.6. 52-Week Primary Safety Set

The 52-Week Primary Safety Set will include all subjects who sign the additional informed consent at 24 weeks and have an average of two or more treatments with INP104 per 28 day period during the full 52-Week treatment period. Specifically, inclusion into this group will require that the subjects remain in the study and attend the Week 52 visit, have received at least 26 INP104 treatments during the full 52-Week treatment period, and have received at least 7 INP104 treatments between Weeks 24 and 52.

4.4. Analysis Periods

Selected study elements will be summarized by analysis periods as outlined below. The 24-Week Treatment Period starts on Day 0. The end date is dependent upon if the subject consents for the additional 28-Week treatment period

- If the subject does not continue into the additional 28-Week treatment period, all data after Day 0 are included in the 24-Week Treatment Period

– If the subject consents to continue into the additional 28-Week treatment period, then the 24-Week Treatment Period ends on the date of the Week 24 visit.

The 52-Week Treatment Period starts on Day 0 and includes all data after Day 0.

4.5. Analysis Window/Interval

Trial endpoints will be reported within analysis windows or analysis intervals based upon the actual date of the assessment. Assignment of results to these time points is based upon the trial day.

Trial day = date of assessment – date of study enrollment

Analysis windows used to report non-diary endpoints are outlined in Table 1.

Table 1: Analysis Windows

Visit	Range	Target Day	If more than one which one is used for analyses
Screening	< Day 0		Last Value
Day 0	Day 0 to Day 7	Day 0	Day 0
Week 4	Day 8 to Day 42	Day 28	Closest to Target Day*
Week 8	Day 43 to Day 70	Day 56	Closest to Target Day*
Week 12	Day 71 to Day 98	Day 84	Closest to Target Day*
Week 16	Day 99 to Day 126	Day 112	Closest to Target Day*
Week 20	Day 127 to Day 154	Day 140	Closest to Target Day*
Week 24	Day 155 to Day 171	Day 168	Closest to Target Day*
Week 26	Day 172 to Day 200	Day 182	Closest to Target Day*
Week 36	Day 201 to Day 273	Day 252	Closest to Target Day*
Week 42	Day 274 to Day 329	Day 294	Closest to Target Day*
Week 52	Day 330 to Day 375	Day 364	Closest to Target Day*
Week 54	> Day 375	Day 378	Closest to Target Day*
End of Period (24-WkTrt)	Last assessment with non-missing value during the 24-Week Treatment Period		
End of Period (Overall)	Last assessment with non-missing value over the entire study		

*Note: If two observations exist with same distance to target day, use first observation.

For the diary data used to produce the migraine endpoints the analysis intervals specified in Table 2 will be used to collapse the daily data into 4-week intervals.

Table 2: Diary Headache/ Migraine Endpoint Analysis Intervals

Weeks	Trial Time	Comments
Baseline	The 28 days before Day 0	Day 0 = Date of enrollment
Week 1-4	Days: 0-28	
Week 5-8	Days: 29-56	
Week 9-12	Days: 57-84	
Week 13-16	Days: 85-112	
Week 17-20	Days: 113-140	
Week 21-24	Days: 141-168	End of the 24-Week Treatment Period
Week 25-28	Days: 169-196	Start of the additional 28-Week treatment period
Week 29-32	Days: 197-224	
Week 33-36	Days: 225-252	
Week 37-40	Days: 253-280	
Week 41-44	Days: 281-308	
Week 45-48	Days: 309-336	
Week 49-52	Days: 337-364	End of the 52-Week Treatment Period

4.6. Baseline

Unless otherwise specified, baseline, for non-diary based endpoints, will be the last observation prior to or on subject enrollment to the study on Day 0. If no measurement of a parameter is collected before subject enrollment to study on Day 0, then the baseline measurement will be missing.

For diary based endpoints baseline will be calculated for each subject by averaging the results recorded within 28 days prior to subject enrollment to the study on Day 0. For endpoints which incorporate the timing after IP administration (e.g. change from baseline in rate of freedom from headache pain at 2 hours after IP administration), the baseline period is from prior to subject having access to IP. In this case, baseline will be based upon the assessments following the non-IP acute treatment the subject used for their migraine within the baseline period. Hence, baseline represents the subject usual treatment and will be based upon data following various acute treatment.

5. SUBJECT DISPOSITION

5.1. Disposition

The eligibility criteria failed will be summarized based on subjects who have failed any Inclusion or Exclusion criteria. The number and percentage of subjects will be summarized for each exclusion criteria met and/or inclusion criteria failed.

The number of subjects who signed informed consent on Day 0, the number of subjects who were enrolled and not enrolled (screen failures) in the 24-Week Treatment Period, the number of subjects included in the 24-Week Full and Primary Safety sets will be summarized for all screened subjects.

The number of subjects who signed informed consent on the Week 24 visit and the number of subjects who are included in the 52-Week Full and Primary Safety sets will be summarized for all subjects who continue to the additional 28 weeks of treatment.

Subject disposition (entered the Week 24 period/enrolled, entered the 52 Week period, completed the Week 24/52 period, discontinued treatment/study, along with primary reason for discontinuation of treatment/study) will be summarized based on the Enrolled Set and 52-Week Enrolled Set.

Primary reasons for treatment and study discontinuation in the 24-Week Treatment Period and 52-Week Treatment Period collected on the Study Disposition eCRF will be summarized with the following categories:

- Adverse Event
- Non-Compliance/Protocol Violation
- Sponsor Decision
- Physician Decision
- Lost to Follow-up
- Consent Withdrawn
- Death
- Other
  - Lack of Efficacy

A by-subject listing will be provided for enrolled subjects.

5.2. Protocol Deviations

The protocol deviations will be identified and assessed by a clinical research physician or designee following company standard operating procedure. The protocol deviations will be summarized by using the Enrolled Set for the 24 Week Treatment Period and the 52-Week Enrolled set for the 52-Week Treatment Period. Protocol deviations will be listed.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized descriptively using the 24-Week Full and Primary Safety Sets for the 24-Week Treatment Period and the 52-Week Full and Primary Safety sets for the 52-Week Treatment Period. Subject data listings will be provided. Diary baseline assessments will be summarized by first finding the frequency, average or percentage within the 28 days prior to subject's enrollment to the study on Day 0 for a subject and then averaging across subjects.

6.1. Demographics

The following characteristics will be summarized as continuous variables:

- Age (years)
- Baseline body weight (kg)
- Baseline height (cm)
- Baseline body mass index (BMI, kg/m^2)

The following characteristics will be summarized as categorical variables:

- Sex (male, female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Collected or Reported, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not reported, Unknown)
- Categorical baseline BMI (< 18.5, $18.5 - < 25$, $25 - < 30$, $30 - < 35$, and ≥ 35 kg/m^2)

6.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized as continuous variables:

- Duration of migraine history (years)
  - Duration of migraine will be calculated as Age at informed consent – Age at diagnosis.
- Baseline MIDAS
- Baseline HIT-6
- Number of non-migraine headaches during screening (at baseline)
- Number of migraine headaches during screening (at baseline)
- Percentage of pain free at 2 hours after non-IP migraine medication among all treated migraines at baseline
- Percentage of MBS free at 2 hours after non-IP migraine medication among all treated migraine at baseline
- Percentage of migraines with aura at baseline

- Percentage of migraines without aura at baseline
- The maximum severity of a symptom (headache pain, MBS, nausea, photophobia, phonophobia) will be summarized at subject level. For each subject, the maximum severity of a symptom is the worst severity score among all migraines within 28 days prior to subject's enrollment Day 0. For each migraine, the worst severity score is identified including any time point during the time course of a migraine event (i.e. the onset, time when any medication was taken, any post-dose time point of 15 min, 30 min, 1, 2, 4, 8, 24, 48 hours post-dose).

The following baseline disease characteristics will be summarized as categorical variables:

- Categorical duration of migraine history (< 2, $2 - < 4$, $4 - < 7$, ≥ 7 years)
- The maximum severity of headache pain (by subject) at baseline (None, Mild, Moderate, Severe)
- The frequency of MBS sub-categories (by subject) at baseline
  - Nausea
  - Vomiting
  - Photophobia
  - Phonophobia
  - Visual changes
  - Dizziness/vertigo
  - Fatigue
  - Slowed/foggy thinking
  - Sensitivity to Touch
  - Other
- The maximum severity of MBS (by subject) at baseline (None, Mild, Moderate, Severe).
- The maximum severity of nausea (by subject) at baseline (None, Mild, Moderate, Severe)
- The maximum severity of phonophobia (by subject) at baseline (None, Mild, Moderate, Severe)
- The maximum severity of photophobia (by subject) at baseline (None, Mild, Moderate, Severe)
- Migraine medication usage at baseline from diary:
  - Ergots other than IP
  - Triptans
  - Acetaminophen

- NSAID
- Opioid
- Barbiturate
- Combination Analgesic
- Other Medication

6.3. Social History

The social history includes the usage history of cigarettes, smokeless tobacco/nicotine, alcohol, marijuana, cocaine, amphetamines, barbiturate, and opiates. Social history will be summarized by using 24-Week Full and Primary Safety Sets for the 24-Week Treatment Period and 52-Week Full and Primary Safety sets for the 52-Week Treatment Period. The number and percentages of subjects with usage status (current vs former) for each will be presented. Subject social history data listings will be provided.

6.4. Medical History

Medical history will be summarized by using 24-Week Full and Primary Safety Sets for the 24-Week Treatment Period and 52-Week Full and Primary Safety sets for the 52-Week Treatment Period, respectively. Medical history will be coded according to Medical Drug Regulatory Activities (MedDRA) version 21.0 and will be summarized by system organ class (SOC) and preferred term (PT), with SOCs sorted alphabetically and PTs within each SOC sorted in descending order of frequency. Subject medical history will be provided based on 24-Week Full Safety Set and 52-Week Full Safety Set. Migraine history data listings will be provided.

7. TREATMENTS AND MEDICATIONS

The medication summarized in this section will be collected from migraine medical history and concomitant medication CRF pages. The medication collected in the diary will be analyzed separately.

Partial missing dates will be imputed based on Appendix 14.2.

7.1.1. Prior Medications and Migraine Procedures

Prior medications are defined as those with a start date before the date of the first dose of INP104 (whether or not the end date is before the date of the first dose of INP104). Prior medications that continue on or after the date of the first dose of INP104 will be reported as both prior and concomitant medications. The Anatomical Therapeutic Chemical (ATC) coding scheme of the latest World Health Organization Drug Dictionary (WHODD) will be used to group medications into relevant categories. Prior medications will be summarized by using the 24-Week Full and Primary Safety Sets for the 24-Week Treatment Period and 52-Week Full and Primary Safety sets for the 52-Week Treatment Period. Prior medications will be summarized by ATC2 level and standardized medication name, with ATC2 levels sorted alphabetically and standardized medication names within each ATC2 level sorted in descending order of frequency.

Prior migraine procedures are collected within the migraine history data as directed questions about specific procedures. These procedures will not be coded and will be summarized based upon the procedure names provided within the CRF .

7.1.2. Concomitant Medications and Procedures

Concomitant medications and procedures will be summarized by using 24-Week Full and Primary Safety Sets for the 24-Week Treatment Period and 52-Week Full and Primary Safety sets for the 52-Week Treatment Period. For the 52-Week Treatment Period summary, the concomitant medication and procedures that occur during the 24-Week Treatment Period and 52-Week Treatment Period will be summarized.

Concomitant medications for the 24-Week Treatment Period are defined as non-study medications with any amount taken between the first dose date in the 24-Week Treatment Period and the end date of the 24-Week Treatment Period.

Concomitant medications for the 52-Week Treatment Period are defined as non-study medications with any amount taken between the first dose date in the 24-Week Treatment Period and end date of the 52-Week Treatment Period.

The ATC coding scheme of the latest version of the World Health Organization Drug Dictionary (WHODD) will be used to group medications into relevant categories. Concomitant medications will be summarized by ATC2 level and standardized medication name, with ATC2 levels sorted alphabetically and standardized medication names within each ATC2 level sorted in descending order of frequency.

Concomitant medications and/or treatments or procedures for the prevention of migraine and acute migraine treatment will be summarized similarly. Number and percentage of subjects with at least one concomitant migraine medications will be presented.

Concomitant procedures are defined similarly to concomitant medications. Concomitant procedures will be coded according to the MedDRA version 21.0 and summarized within study period and overall by SOC and PT, with SOCs sorted in alphabetical order and PTs within each SOC in descending order of frequency.

By-subject listings of medications and procedures will be provided.

7.2. Investigational Product

INP104 will be dispensed at Baseline, every 4 weeks in the 24-Week Treatment Period, and Weeks 24, 36 and 42 for subjects enrolled in the 28-Week treatment period. Use of the investigational product is recorded by the subject in the eDiary. Investigational product recorded in the headache diary, Evening Diary and the Study Medication Intake Report will all be used for exposure summary Investigational product will be summarized by using the 24-Week Full and Primary Safety Sets for the 24-Week Treatment Period and 52-Week Full and Primary Safety sets for the 52-Week Treatment Period.

7.2.1. Extent of Exposure

The total number of INP104 doses taken will be summarized for the 24-Week Treatment Period in the following categories:

- < 12 doses
- 12 – 24 doses
- > 24 doses

and the 52-Week Treatment Period in the following categories:

- < 12 doses
- 12 – 24 doses
- 25 – 36 doses
- 37 – 48 doses
- > 48 doses

Number of INP104 doses taken per 28 day period will be summarized descriptively in both the 24-Week Treatment Period and 52-Week Treatment Period.

By-subject listings of IP exposure records will be provided.

8. DIARY

Data will be collected in a validated electronic diary. It will include a daily evening diary, a headache diary where use of and timing of acute medication is recorded along with headache start and end date and time, a post-dose diary that records severity measurements at 15 min, 30 min, 1 hour, 2 hours, 8 hours, 24 hours, and 48 hours, and a Study Intake Medication Report. A detailed discussion on data collected by diary is documented in Appendix 14.5. The summaries of the diary are based on analysis intervals defined in Section 4.5.

8.1. Diary Compliance

Diary compliance rate will be summarized descriptively per analysis interval, 24-Week Treatment Period, and 52-Week Treatment Period.

The electronic diary compliance per every 28 day interval is defined as the following:

- Number and percent of calendar days where the subject completed the evening diary or headache diary in 4-week interval / duration in days on study in 4-week interval

The electronic diary compliance rate in the 24-Week Treatment Period is defined as the following:

- Number and percent of calendar days where the subject completed the evening diary or headache diary in the 24-Week Treatment Period / Duration of the 24-Week Treatment Period

The electronic diary compliance rate in the 52-Week Treatment Period is defined as the following:

- Number and percent of calendar days where the subject completed the evening diary or headache diary in the 52-Week Treatment Period / Duration of the 52-Week Treatment Period

Diary compliance of every 28 day interval will also be listed. The diary calculated compliance results are provided to the sites to allow the decisions concerning entry into or continuation in the study to be made by the sites. These compliance calculations are different from and separate from the calculations outlined above.

9. EFFICACY ANALYSIS

All efficacy analyses are exploratory with no testing.

9.1. Efficacy Endpoints

Efficacy analyses will be summarized by using the 24-Week Full and Primary Safety Sets for the 24-Week Treatment Period and the 52-Week Full and Primary Safety sets for the 52-Week Treatment Period. Efficacy data will be listed as well as summarized as outlined below.

Efficacy endpoints pertain to migraine headaches experienced by subjects, and the primary source for all headache (migraine and non-migraine) data is the headache diary, which contains subject-completed details about all headaches (migraine and non-migraine) experienced.

Missing post-dose diaries at 15 min, 30 min, 1 hour, 2 hours, 8 hours, 24 hours, and 48 hours will be imputed as follows:

1) Missing values for post-dose timepoints that occur after the resolution of the current headache and prior to the start of a subsequent headache will be imputed to a value of zero (no pain, no MBS).
2) Missing values for post-dose timepoints that occur on or after the start of a subsequent headache will be left missing and will not be imputed.

Within the efficacy analyses a migraine headache is any headache that the subject has identified as being a migraine.

9.1.1. Monthly Migraine Measures

The principal efficacy summarization method will be to summarize diary results by analysis interval (see Table 2). For each 4-week interval (e.g., Baseline, Weeks 1-4, 5-8, etc.) the following will be summarized by first finding the frequency, average or percentage within the 4-week interval for a subject and then averaging across subjects. For efficacy assessments regarding severity of a symptom, maximum severity of a symptom, percentage of a symptom free, summaries are only based on the migraines treated with INP104.

1. Number of headaches (migraine vs non-migraine)
2. Number of treated headaches (migraine vs non-migraine)
    a. Timing of IP (< 2 hours, 2-4 hours, > 4 hours) will be summarized for treated migraines
3. Percentage of migraines that become headache pain free at 2 hours after IP administration
4. Percentage of migraines with MBS free at 2 hours after IP administration
5. The pain severity at 15 min, 30 min, 1, 2, 8, 24 and 48 hours after IP administration. For each subject, the pain severity at the 15 min post-IP timepoint is the average of no-missing pain severity at the 15 min post-IP timepoint of all IP treated migraines during the 4-week interval. The same algorithm will be applied to other post-IP timepoints and other symptoms (MBS, nausea, phonophobia, photophobia).
6. The MBS severity at 15 min, 30 min, 1, 2, 8, 24 and 48 hours after IP administration

7. The nausea, phonophobia, photophobia severity at 15 min, 30 min, 1, 2, 8, 24 and 48 hours after IP administration
8. Maximum severity for pain, nausea, phonophobia, photophobia and the MBS. The maximum severity of a symptom (headache pain, MBS, nausea, photophobia, phonophobia) will be summarized at the subject level. For each subject, the maximum severity of a symptom is the worst severity score among all migraines in each 4- weeks interval. For each migraine treated with INP104, the worst severity is identified by using any timepoint during the course of a migraine event (i.e., 15 min, 30 min, 1 hour, 2 hours, 4 hours, 8 hours, 24 hours, and 48 hours post-IP as well as the more global pain questions asked by the diary).
9. The percentages of migraines with pain relapse at 24 hours and at 48 hours after IP administration. This is defined as a migraine that was pain free at 2 hours after IP administration and then was not pain free before or at 24 and/or 48 hours after IP administration, or there is onset of a new headache prior to 24 or 48 hours after IP administration.
10. Number and percentage of migraines with a need for rescue medication
    a. A summary of type of rescue medication collected in the diary will also be provided.
11. Number of calendar days of triptan usage and percentage of migraines for which a triptan is used will be summarized.
    a. Calendar day of triptan usage is defined as the day on which a triptan is documented as medication taken in either evening diary, headache diary, or post-dose diary.
    b. The percentage of migraines for which a triptan is used will be computed by averaging the migraines for which a triptan is documented in medication taken report in 4-week interval for a subject and then averaging across subjects.

These subject level values will be summarized (including 95% confidence intervals) as well as the change from baseline. For item 1, only change from baseline of headache, migraine and non-migraine will be presented. For the average percentage and severity, the 95% confidence interval of change from baseline will be calculated by using Wald's method. Subjects with no treated migraines within the 4-week interval will not be included in the summary measures for migraine specific measures (i.e. items 3-9).

9.1.2. MIDAS and HIT-6

Descriptive statistics will be presented for the MIDAS and HIT-6 total scores (see endpoint 7 from Section 3.1.2). These statistics will be presented at baseline, each scheduled time-point and EOT.

The MIDAS total score will be derived as the sum of non-missing results from questions 1 to 5. The statistics will be presented based upon the derived values as well as the change from baseline. 95% confidence interval of change from baseline will be calculated by using Wald's method for each scheduled post-baseline time point. Total score will also be summarized into the following categories (Table 3) by time-point.

For the HIT-6 the following life impact ranges (Table 4) will be summarized by time-point.

Table 3: MIDAS Category Range

Score Range	Grade	Definition
0-5	I	Minimal or infrequent disability
6-10	II	Mild or infrequent disability
11-20	III	Moderate disability
21-40	IVa	Severe disability – subgroup a
41-270	IVb	Severe disability – subgroup b

Table 4: HIT-6 Category Range

Score Range	Life Impact
≥ 60	Severe
56-59	Substantial
50-55	Some
≤ 49	Little to None

10. SAFETY ANALYSIS

Safety will be evaluated using descriptive statistics. Unless otherwise specified, safety analyses will be summarized by using the 24-Week Full and Primary Safety Sets for the 24-Week Treatment Period and the 52-Week Full and Primary Safety sets for the 52-Week Treatment Period.

10.1. Adverse Events

Adverse events will be coded according to MedDRA version 21.0. Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs sorted in the alphabetical order and PTs within each SOC in descending order of subject incidence. Partial missing adverse event start dates will be imputed based on Appendix 14.2.

The summary of the 24-Week Treatment Period includes all AEs that started during the 24-Week Treatment Period, and the summary of the 52-Week Treatment Period includes all AEs that started during the 52-Week Treatment Period.

In the AE summarization, each AE will be summarized only once per period. AE period is assigned based on the start date of the AE event. All the AEs will be summarized by using the 24-Week Full and Primary Safety Sets for the 24-Week Treatment Period and the 52-Week Full and Primary Safety sets for the 52-Week Treatment Period. For the 52-Week Treatment Period summary, the adverse events that occur during the 24-Week Treatment Period and 52-Week Treatment Period will be summarized.

A TEAE is defined as an AE that starts or an existing AE that worsened on or after the first dose of IP.

By-subject listings of adverse event records will be provided.

10.1.1. Incidence of Adverse Events

An overall summary of the following TEAE categories for each period and overall will be provided:

- Any TEAE
- Any IP -related TEAE
- Any nasal related TEAE
- Any nasal IP-related TEAE
- Any study procedure-related TEAE
- Any severe TEAE
- Any serious TEAE
- Any serious IP related TEAE
- Any serious nasal related TEAE
- Any serious nasal IP-related TEAE
- Any serious study procedure-related TEAE

- Any TEAE leading to IP interruption
- Any TEAE leading to IP withdrawal

A separate summary of TEAE's will be provided by SOC and PT.

10.1.2. Relationship of Adverse Events

IP-related TEAEs will be summarized by SOC and PT. A TEAE will be considered related if the relationship to IP or the device is of 'Definite', 'Probable' or 'Possible'. AEs assessed as 'Not Related' or 'Unlikely' for both the device and IP will be considered unrelated for reporting purposes.

10.1.3. Adverse Events by Extent of Exposure

TEAEs will be summarized by the extent of exposure categories outlined in Section 7.2.1, and by SOC and PT.

10.1.4. Relationship of Adverse Events to Study Procedure

Study Procedure-related TEAEs will be summarized by SOC and PT. Study procedure-related AEs are those with a relationship to study procedure of 'Definite', 'Probable' or 'Possible' on the eCRF. AEs assessed as 'Not Related' or 'Unlikely' will be considered unrelated for reporting purposes.

10.1.5. Severity of Adverse Event

Severity of AEs will be graded by the Investigator as one of:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

All TEAEs will be summarized by maximum severity (mild, moderate, severe, and, if needed, missing). If a subject reports multiple occurrence of a specific event, the subject will be counted only once by the maximum severity. If the severity is missing for one or more of the occurrences, the maximum severity of the remaining occurrences will be used.

10.1.6. Serious Adverse Events

Serious TEAEs will be summarized by SOC and PT. Serious AEs are those identified on the eCRF as meeting the protocol definition of serious. A subject data listing of all serious AEs (both TEAEs and non-TEAEs) will be provided.

10.1.7. Adverse Events Leading to Treatment Discontinuation

The TEAEs leading to IP discontinuation will be summarized by SOC and PT. A subject data listing of all adverse events leading to IP withdrawal will be provided.

Nasal TEAEs leading to IP discontinuation will be summarized by SOC and PT.

10.1.8. Adverse Events Leading to Study Discontinuation

The TEAEs leading to study withdrawal will be summarized by SOC and PT. A subject data listing of all adverse events leading to study withdrawal will be provided.

10.1.9. Death

All adverse events leading to death will be included within the SAE listings

10.1.10. Nasal Related AE

Nasal related AEs will be identified using a custom MedDRA query list generated through an iterative process as outlined in the medical monitoring document *Identification of Nasal Related Adverse Events* Appendix 14.6. The custom MedDRA query list will be finalized prior to database lock and used to generate a summary table of nasal related AEs by SOC and PT. A subject data listing will also be provided. .

10.1.11. Adverse Events Associated with Olfactory Test or Nasal Endoscopy

An olfactory test meeting shift criteria is defined as an UPSIT score decrease from the average of screening and baseline of 5 or more points on any single olfactory test. Upper nasal endoscopy meeting shift criteria is defined as a total QSS-NM score (summed from left and right upper nasal cavity scores) exceeding 7, an individual score of 2 or more on any one of the 5 items (Mucosal Irritation, Epistaxis, Mucosal Edema, Nasal Discharge, Mucosal Crusting) or an overall impression of 'Abnormal, Clinically Significant', at any time upper endoscopy is performed. Lower nasal endoscopy meeting shift criteria is defined based on an overall impression of 'Abnormal, Clinically Significant' within the QSS-NM scale.

Subjects with at least one nasal AE other than those coded as olfactory test abnormal will be summarized. Similarly, subjects with AEs coded to olfactory test abnormal will also be summarized. Within each group of subjects, summaries of shift criteria met will also be presented.

Adverse events associated with UPSIT score, upper nasal endoscopy, and lower nasal endoscopy will be identified by a clinical review of adverse event, UPSIT and QSS-NM data performed by the medical monitor. These associations will be summarized.

Subjects with AEs related to at least one shift criteria met for UPSIT score, upper nasal endoscopy, or lower nasal endoscopy will be summarized.

10.2. Clinical Laboratory Evaluations

Central clinical laboratory evaluations will include hematology, serum chemistry, and urinalysis.

For the continuous laboratory parameters, summary statistics of observed values and changes from baseline will be provided by time point (including the end of period and the post-treatment

observational follow-up visit). Continuous laboratory records will also be categorized as low, normal, and high based on normal reference range. Frequency summaries (shift tables) of shift from baseline to the worst post-baseline value by category of low, normal, high, and both low and high, will be provided.

By-subject listings of laboratory records will be provided.

10.2.1. Hematology

Hematology assessments (including analysis of hemoglobin, hematocrit, erythrocytes, platelets, and leukocytes, eosinophils, neutrophils, basophils, lymphocytes, monocytes and reticulocytes) will be performed according to the study schedule Appendix 14.1.

10.2.2. Serum Chemistry

Serum chemistry assessments (including analysis of blood urea nitrogen, creatinine, total bilirubin and direct bilirubin, urate, albumin, total protein, alkaline phosphatase, creatine kinase, gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, glucose, sodium, potassium, calcium, chloride, phosphate, and bicarbonate) will be performed according to the study schedule Appendix 14.1.

10.2.3. Urinalysis

Urinalysis assessments (including analysis of pH, specific gravity, protein, glucose, ketones, total bilirubin, occult blood, nitrite, urobilinogen, and leukocytes) will be performed according to the study schedule Appendix 14.1.

10.2.4. Pregnancy Testing

A serum pregnancy test will be performed at screening and urine pregnancy tests will be performed at all other study visits for women of child-bearing potential only, according to the study schedule (Appendix14.1). Serum FSH will be measured in post-menopausal women.

A subject data listing of pregnancy test records will be provided.

10.3. Vital Sign Measurements

For vital signs, summary statistics of observed values and changes from baseline will be provided by time point according to the study schedule Appendix 14.1.

By-subject listings of vital signs records will be provided.

10.4. Physical Examination

The complete physical examination will include: general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, lymph nodes, and other.

The directed physical examination will include: head, ears, eyes, nose, throat, chest (heart, lungs), abdomen, skin, musculoskeletal, lymph nodes, and any pertinent system based on any prior findings.

For physical examinations, summary measure of the number and percent of subject who shift from normal to abnormal / abnormal clinically significant at any point post baseline will be provided.

By-subject listings of physical examination records will be provided.

10.5. Electrocardiogram

For ECG, summary statistics of observed values and changes from baseline will be provided by time point according to the study schedule Appendix 14.1. A frequency summary of ECG overall interpretation (normal; abnormal, not clinically significant; and abnormal, clinically significant) will be provided at each time point.

By-subject listings of ECG records will be provided.

10.6. Nasal Endoscopic Examination

Nasal endoscopic examination will include endoscopic evaluation of both the lower and upper nasal mucosa, using the QSS-NM (Table 3)

Table 3: Quantitative Scoring Scale for Evaluation of Nasal Mucosa (QSS-NM)

Finding	Grading Criteria	Score
Mucosal Irritation	0 = None	0
	Grade 1A = focal irritation	1
	Grade 1B = superficial mucosal erosion	2
	Grade 2 = moderate mucosal erosion	3
	Grade 3 = ulceration	4
	Grade 4 = septal perforation	5
Epistaxis (frank bleeding or dried blood clot)	None	0
	Mild = self-limited	1
	Moderate = significant, prevents daily activity	2
	Severe = Emergency Room visit or hospitalization	3
Mucosal Edema	None	0
	Mild	1
	Moderate	2
	Severe	3
Nasal Discharge	None	0
	Mild	1
	Moderate	2
	Severe	3

Mucosal Crusting	None	0
	Mild	1
	Moderate	2
	Severe	3

Nasal endoscopy will be performed in all subjects as outlined in the schedule of events. For those subjects who are noted to have clinically significant changes from baseline on nasal endoscopy of the upper nasal space, or have reported a clinically significant AE related to the nose, nasal endoscopy will be repeated at 2-week intervals until the change has resolved or been otherwise explained.

All endoscopic exams will be scored and summed for the upper nasal cavity (right side + left side) and similarly for the lower nasal cavity using the scale above. Summary statistics of total score and changes from baseline will be provided by time point according to the study schedule Appendix 14.1. A frequency summary of each sub-score will be provided by time point.

A subject data listing of all nasal examination records will be provided.

10.7. Olfactory Function Changes (UPSIT)

Olfactory function will be assessed using the University of Pennsylvania Smell Identification Test (Doty 1984).

The full test consists of 4 booklets with a total of 40 scratch-and-sniff odorants to correctly identify in a multiple-choice format. The full 40-question exam will be administered as outlined in the schedule of events. A reduction from baseline in absolute test score of 5 or more points on any single test will be recorded as an AE and will trigger repeat tests.

The baseline of UPSIT will be defined as the average screening and baseline UPSIT test scores, providing data for both tests is available. If one test is missing, then the baseline will be set as the non-missing result.

Summary statistics of UPSIT score and changes from baseline will be provided by time point according to the study schedule Appendix 14.1.

10.8. Healthcare Utilization

The healthcare utilization will be collected at screening on ‘Healthcare Utilization’ CRF pages, and post-baseline on the eDiary. The Exposure Adjusted Event Rate (EAER) at baseline and post-baseline for each of the following events of interest will be summarized,

- Hospitalization
- Emergency room visit
- Urgent care visit
- Unplanned clinic/physician office visit

New or changed non-IP acute/preventive migraine medication or preventive procedure at post-baseline will not be summarized as indicated in the protocol. Only baseline values for these parameters will be reported.

The EAER per 100-person years is interpreted as the expected number of specific events per 100-person years of exposure. It is defined as 100 times the number of events with the specific event divided by the total exposure time (in years) among subjects included in the analysis. Subjects with multiple occurrences of the specific event will be counted multiple times in the numerator. For baseline, the exposure time for subjects is 12 months. For post-baseline, the exposure time for a subject is based upon the duration of time on study. The total exposure time in years is calculated by dividing the sum of exposure time in days overall all subjects included in the safety set being summarized by 365.25.

A subject data listing of all healthcare utilization records will be provided.

10.9. Product Acceptability Questionnaire

Product Acceptability Questionnaire will be distributed and collected at week 24 and week 52, and summarized by frequency at each of these scheduled visits.

By-subject listings will be provided.

11. INTERIM ANALYSIS

There are no formally planned interim analyses for this study.

12. CHANGES IN THE PLANNED ANALYSIS

- Change from baseline in healthcare utilization for migraine will not be presented. Result for each time interval will be reported.
- New or changed non-IP acute/preventive migraine medication or preventive procedure at post-baseline will not be summarized as indicated in the protocol. Only baseline values for these parameters will be reported. The data capture post baseline was insufficient to allow for these post baseline measures.
- Within the protocol the primary safety sets referenced the number of IP treated migraines, however within this analysis plan this has been expanded to include all IP treatments. This change has been made as it more accurately reflects the exposure subjects have had to treatment.

13. REFERENCES

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14. APPENDICES

14.1. Schedule of Study Procedures

Period	Screening	Baseline	Treatment Period										Follow up
Week	**-4**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**26[1]**	**36**	**42**	**52/ET**	**54**
Days	**-28**	**0**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	**252**	**294**	**364**	**378**
Window (days)	**-7**		**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±10**	**±10**	**±10**	**±10**	**+ 14**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**99a**	**99b**	**10**	**11**	**12**
Informed consent	X							X[8]					
Medical history	X												
Confirmation of Eligibility	X	X											
Height	X												
Weight	X							X				X	
Vital signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[2]	X	X						X[9]				X[9]	
Physical exam	X							X	X			X	X
Directed exam		X	X	X	X	X	X			X	X		
Nasal endoscopy[3]	X[3]		X	X	X			X		X		X	
UPSIT4	X	X			X			X		X		X	
MIDAS and HIT-6	X	X			X			X		X		X	
Hematology and chemistry labs	X	X			X			X	X	X		X	X
Urinalysis[5]	X	X			X			X	X	X		X	X
Serology	X												
Urine drug screen	X												
Serum pregnancy test[6]	X												
Urine pregnancy test[6]		X	X	X	X	X	X	X	X	X	X	X	X
Serum FSH[7]	X												
Diary training & distribution	X												
Diary check		X	X	X	X	X	X	X		X	X	X	
Training on POD®		X											
Diary Review		X	X	X	X	X	X	X		X	X	X	
Dispense IP		X	X	X	X	X	X	X[10]		X	X		
Collect unused IP			X	X	X	X	X	X		X	X	X	
AE collection	X	X	X	X	X	X	X	X	X	X	X	X	X

Concomitant (and rescue) medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Diary collection								X				X	
IP questionnaire (usability and effectiveness)								X				X	

Abbreviations: AE = adverse event; ECG = electrocardiogram; EOT = end-of-treatment; FSH = follicle stimulating hormone; HIT-6 = Headache Impact Test; IP = investigational product; MIDAS = Migraine Disability Assessment; POD = Precision Olfactory Delivery; UPSIT = University of Pennsylvania Smell Identification Test

1. Follow up visit for subjects not continuing through 52 weeks treatment
2. Participants should be rested in a supine position for ≥ 5 minutes prior to recording of ECGs and ≥ 3 minutes prior to taking vital signs. ECGs and vital signs should be assessed prior to blood draws.
3. Nasal endoscopy will be performed by a trained otolaryngologist within visit windows as specified. Procedures conducted by otolaryngologists are not required to be carried out on the same day as those carried out by the investigational site provided all study procedures are carried out within the specified visit windows. Off schedule assessments triggered by findings on the UPSIT or nasal endoscopy, or as a result of reported AEs are specified in Section 6.4.2 of the protocol.
4. UPSIT testing will be performed at visits as specified. Off schedule assessments triggered by findings on the UPSIT or nasal endoscopy, or as a result of reported AEs are specified in Section 6.4.3 of the protocol.
5. Blood samples will be collected for hematology and chemistry tests, and a urine sample will be collected for urinalysis.
6. Women of childbearing potential only.
7. Post-menopausal women only.
8. Subjects continuing to 52 weeks of treatment will be re-consented at their 24-week visit.
9. If ECG at Week 24 (for subjects ceasing treatment at that visit) or Week 52 shows potentially significant abnormalities, this should be repeated at Week 26 or Week 54, respectively.
10. IP dispensed to subjects continuing to 52 weeks of treatment only.

14.2. Guideline of Missing Date Imputation for Safety

14.2.1. Impute Missing Adverse Events/ Prior or Concomitant Medications

A. <u>Incomplete Start Date:</u>

If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first doing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date, i.e. set to the stop date.

Missing day, month, and year

- No imputation is needed; the corresponding AE will be included as TEAE provided the end date of the AE is after the first dose date or the end date is also missing.

B. <u>Incomplete End Date:</u>

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date and prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

14.2.2. Prior/Concomitant Procedures

Prior/concomitant procedures are defined as surgeries, other medical procedures (e.g., acupuncture, chiropractic TMS, and others) and transplants such as stem-cell transplants.

Partially missing start/stop dates for prior/concomitant procedures will be imputed in the analysis dataset for prior/concomitant procedures. If the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant procedure stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

14.2.3. Impute Partial IP Dosing Date and Time

Missing time only

- No imputation is needed; the corresponding IP dose will be summarized by dosing date.

Missing day and time only

- If the year and month are the **same** as the year and month of the first IP dispense date, then the first IP dispense date will be assigned to the missing IP dosing date.
- If the year and month are the **same** as the year and month of the IP discontinuation date, then the date of treatment discontinuation will be assigned to the missing IP dosing date.
- If the year and month is **after** the year and month of the first IP dispense date and **before** the year and month of the treatment discontinuation date, then 15th day of the month will be assigned to the missing IP dosing date.

Missing month, day and time

- If only year is present and drug dispense and return data shows a subject took IP, then the first IP dispense date will be assigned to the missing IP dosing date.

14.3. Headache Impact Test (HIT-6™)

The HIT-6™ will be licensed for use in this study from Optum Inc. Below is an example of the questions.

HIT is a tool used to measure the impact headaches have on your ability to function on the job, at school, at home and in social situations. Your score shows you the effect that headaches have on normal daily life and your ability to function. HIT was developed by an international team of headache experts from neurology and primary care medicine in collaboration with the psychometricians who developed the SF-36® health assessment tool. This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

1. When you have headaches, how often is the pain severe?

never	rarely	sometimes	very often	always

2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

never	rarely	sometimes	very often	always

3. When you have a headache, how often do you wish you could lie down?

never	rarely	sometimes	very often	always

4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

never	rarely	sometimes	very often	always

5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

never	rarely	sometimes	very often	always

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

never	rarely	sometimes	very often	always
Column 1 *6 points each*	*Column 2* *8 points each*	*Column 3* *10 points each*	*Column 4* *11 points each*	*Column 5* *13 points each*

To score, add points for answers in each column. TOTAL SCORE: _____

14.4. Migraine Disability Assessment Test (MIDAS)

The Migraine Disability Assessment Test

The **MIDAS** (Migraine Disability Assessment) questionnaire was put together to help you measure the impact your headaches have on your life. The information on this questionnaire is also helpful for your primary care provider to determine the level of pain and disability caused by your headaches and to find the best treatment for you.

INSTRUCTIONS

Please answer the following questions about ALL of the headaches you have had over the last 3 months. Select your answer in the box next to each question. Select zero if you did not have the activity in the last 3 months. Please take the completed form to your healthcare professional.

_____ 1. On how many days in the last 3 months did you miss work or school because of your headaches?

_____ 2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)

_____ 3. On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?

_____ 4. How many days in the last 3 months was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)

_____ 5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

_____ Total (Questions 1-5)

What your Physician will need to know about your headache:

_____ A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day.)

_____ B. On a scale of 0 - 10, on average how painful were these headaches? (where 0=no pain at all, and 10= pain as bad as it can be.)

Scoring: After you have filled out this questionnaire, add the total number of days from questions 1-5 (ignore A and B).

MIDAS Grade	Definition	MIDAS Score
I	Little or No Disability	0-5
II	Mild Disability	6-10
III	Moderate Disability	11-20
IV	Severe Disability	21+

If Your MIDAS Score is 6 or more, please discuss this with your doctor.

14.5. Diary Data

14.5.1. Evening Diary

Subjects are to complete evening diary items daily, each evening. These items include the following:

- Confirmation of whether or not a headache occurred that day
- Status of each headache experienced that day (i.e., ended or ongoing)
- Confirmation of whether or not an aura occurred
- Recording of which if any of the prespecified medications were taken that day

The evening diary serves as a triggering diary where if subjects report having a headache during the day, then they will be directed to the Headache diary later.

14.5.2. Headache Diary

Subjects are to complete headache diary entries on an episodic basis whenever there is one to report. The following information will be collected in the headache diary:

- Confirmation of whether any headache during the last 24 hours along with its start and end time/date and the status of headache
- The medication usage including the name of the medication and the dose/time take for each of them
- The maximum severity (none, mild, moderate, severe) of each of symptoms (headache pain, nausea, vomiting, photophobia, phonophobia) both prior to IP self-administration and then at prespecified (post dose) time points after IP has been taken
- Whether subject experienced aura along with characteristics of the aura
- Self-identify whether the headache event is a migraine

The headache diary serves as a triggering diary: if subjects report any migraine medication (IP or non-IP), then they will be directed to the post-dose diary. The trigger mechanism is as follows:

- If all medications documented in the headache diary are non-IP, then the first medication documented will trigger the post-dose diary
- If at least one IP is documented in headache diary, then the first IP will trigger the post-dose diary

14.5.3. Post-Dose Diary

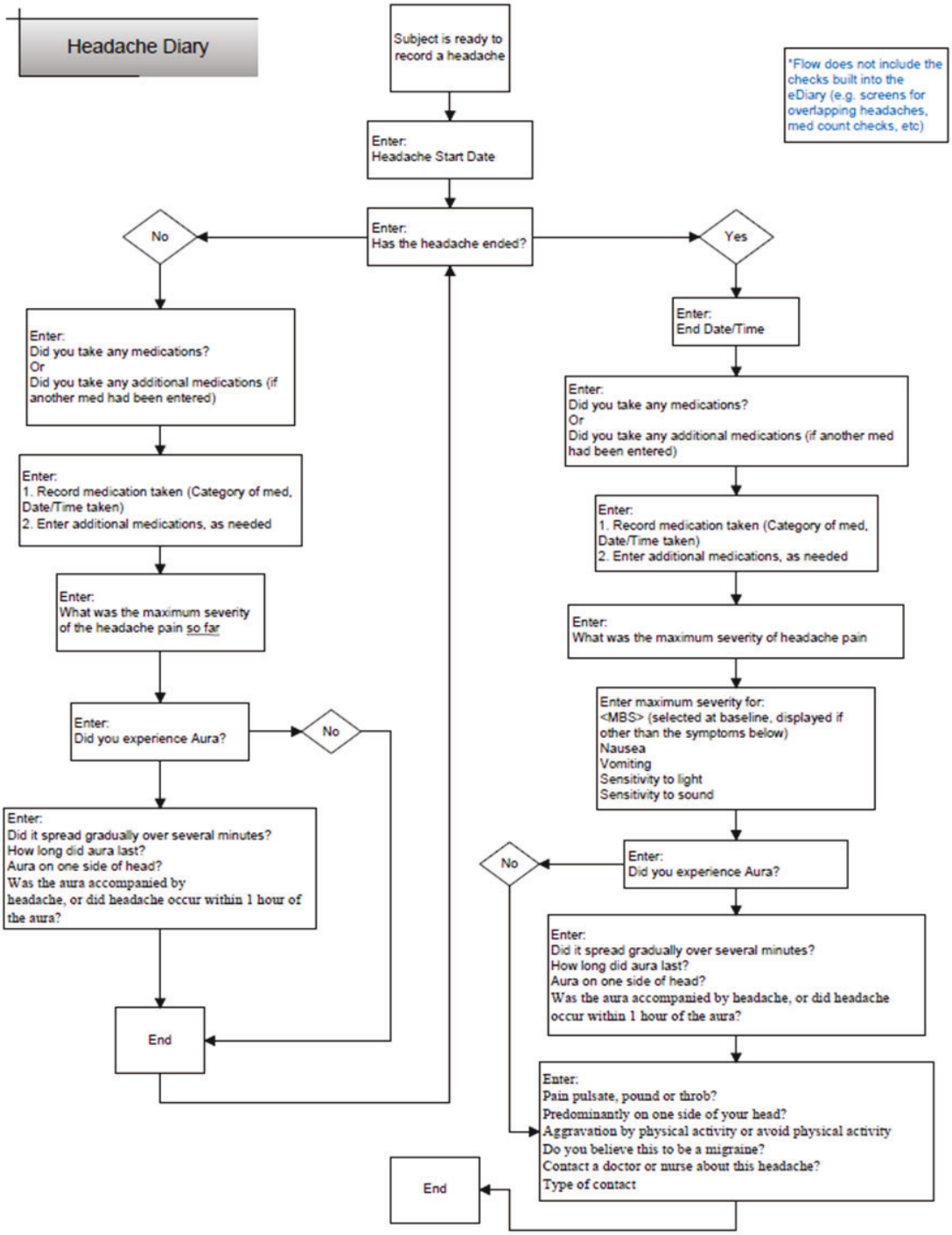
Subjects are to complete post-dose diary at 15 min, 30 min, 1 hour, 2 hours, 4 hours, 24 hours, and 48 hours post-dose time points up to end of headache.

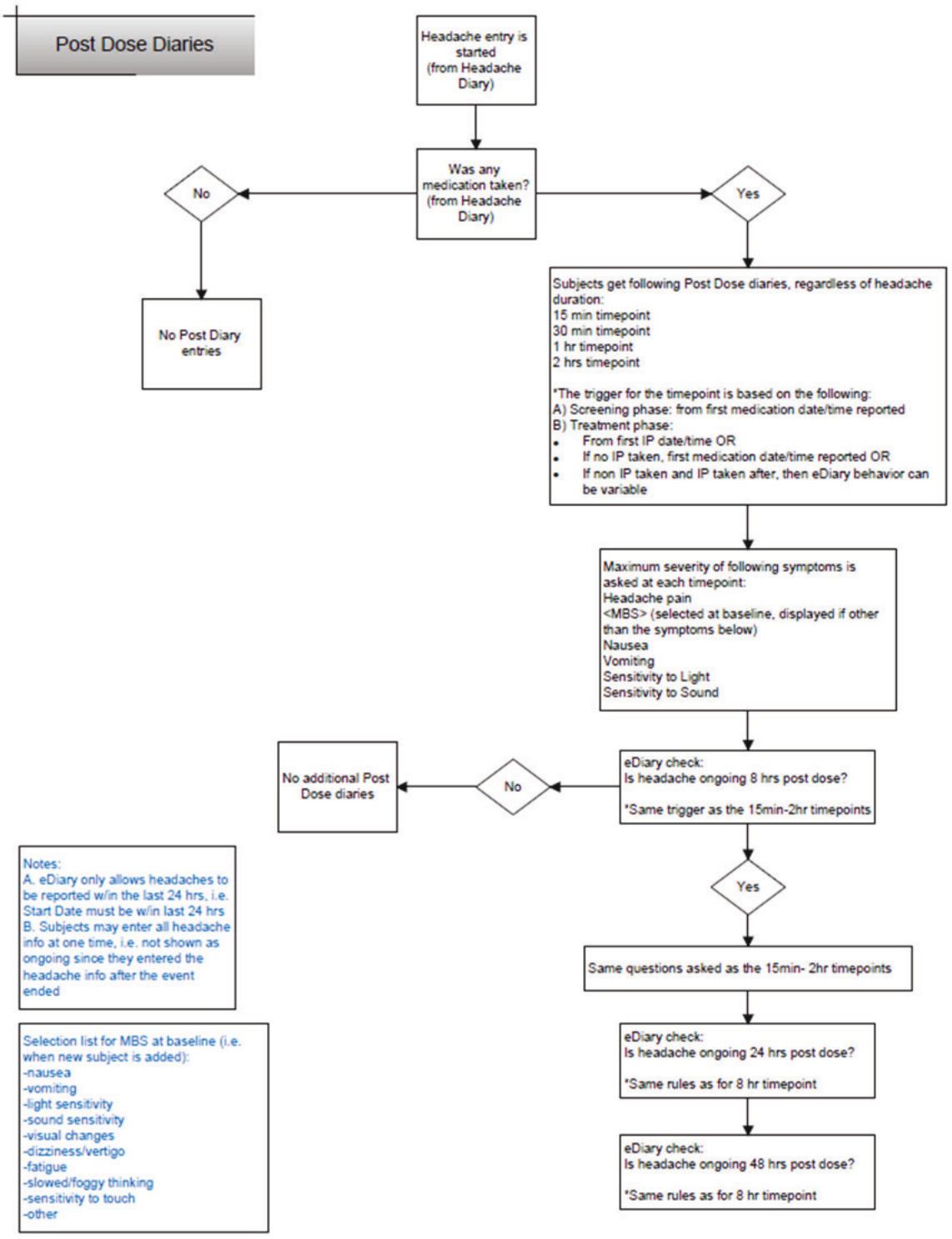
At each post-dose time point, subjects will be asked to rate the severity (none, mild, moderate, severe) of symptoms (headache pain, nausea, vomiting, photophobia, phonophobia).

14.5.4. Study Intake Medication Report

There will also be the opportunity to document IP usage that was not recorded in the Headache or Evening diaries. This IP usage will be recorded in the Study Intake Medication Report.

14.5.5. eDiary Flow Diagram




Post Dose Diaries
Headache entry is started (from Headache Diary)
Was any medication taken? (from Headache Diary)
No
Yes
No Post Diary entries
Subjects get following Post Dose diaries, regardless of headache duration:
15 min timepoint
30 min timepoint
1 hr timepoint
2 hrs timepoint
*The trigger for the timepoint is based on the following:
A) Screening phase: from first medication date/time reported
B) Treatment phase:
From first IP date/time OR
If no IP taken, first medication date/time reported OR
If non IP taken and IP taken after, then eDiary behavior can be variable
Maximum severity of following symptoms is asked at each timepoint:
Headache pain
<MBS> (selected at baseline, displayed if other than the symptoms below)
Nausea
Vomiting
Sensitivity to Light
Sensitivity to Sound
eDiary check:
Is headache ongoing 8 hrs post dose?
*Same trigger as the 15min-2hr timepoints
No
No additional Post Dose diaries
Yes
Same questions asked as the 15min- 2hr timepoints
eDiary check:
Is headache ongoing 24 hrs post dose?
*Same rules as for 8 hr timepoint
eDiary check:
Is headache ongoing 48 hrs post dose?
*Same rules as for 8 hr timepoint
Notes:
A. eDiary only allows headaches to be reported w/in the last 24 hrs, i.e. Start Date must be w/in last 24 hrs
B. Subjects may enter all headache info at one time, i.e. not shown as ongoing since they entered the headache info after the event ended
Selection list for MBS at baseline (i.e. when new subject is added):
-nausea
-vomiting
-light sensitivity
-sound sensitivity
-visual changes
-dizziness/vertigo
-fatigue
-slowed/foggy thinking
-sensitivity to touch
-other

14.6. Identification of Nasal-Related Adverse Events

14.6.1. Introduction

The purpose of this document is to provide additional details about the identification of nasal-related adverse events and their correlation with abnormal olfaction as measured using the University of Pennsylvania Smell Identification Test (UPSIT) and abnormal nasal endoscopy, quantified using the Quantitative Scoring Scale-Nasal Mucosa (QSS-NM), for Study INP104-301.

14.6.2. Nasal-Related Adverse Events

Nasal-related adverse events, defined as adverse events associated with the nose in any way, were identified through a custom MedDRA query list, as these adverse events could be coded under more than one system organ class. Special care was taken to ensure that adverse events that might manifest as abnormal findings on olfactory testing or nasal endoscopy were included.

The custom MedDRA query list was generated and finalized using an iterative process. First, the medical monitor reviewed select sections of the MedDRA coding dictionary to identify high level terms (HLT), preferred terms (PT) and lower level terms (LLT) indicating a relationship with the nose to generate an initial custom MedDRA query list of nasal-related adverse events. Then the medical monitor was provided with a tabular summary of subjects having any one of the following: a nasal-related adverse event per MedDRA query, total UPSIT score decreased ≥ 5 points, total upper QSS-NM score > 7 (summed from left + right upper nasal cavity scores), individual upper QSS-NM score of ≥ 2, abnormal clinically significant overall assessment of upper endoscopy, or abnormal clinically significant overall assessment of lower endoscopy. Summarized data was matched by subject, with a separate row for each unique combination of abnormal olfactory test or endoscopy and nasal-related adverse event. Each row included the date and study visit of the abnormal olfactory test or endoscopy, as well as the start date and PT of the adverse event.

The medical monitor reviewed these data to indicate which adverse events were related to each abnormal olfactory test and each abnormal endoscopy. If no nasal-related adverse event could be correlated with an abnormal olfactory test or endoscopy, the medical monitor reviewed all adverse events for the subject, and if applicable, added the corresponding terms to the MedDRA query list so that the adverse event would be designated as nasal-related upon next review. If there was no temporally related adverse event that could explain the abnormal olfactory test or endoscopy, the site was advised to enter an applicable adverse event or the abnormal result as an adverse event per protocol, and if necessary, the coded terms were added to the MedDRA query list. This process was repeated until all nasal-related adverse events were captured in the final custom MedDRA query list Appendix 14.6.3.

Prior to database lock, the final custom MedDRA query list was used to identify all nasal-related TEAEs reported in the study by flagging adverse events matching each combination of HLT, PT and LLT. In some cases, all adverse events coded under the HLT (e.g., HLT-Nasal disorders NEC) were designated as nasal-related, regardless of the PT or LLT. In other cases, only adverse events which matched the specific combination of HLT, PT and LLT (HLT-Atopic disorders/PT-Seasonal allergy/LLT-Seasonal rhinitis) were designated as nasal-related. The custom MedDRA query list was designed to be both comprehensive, including some PTs and LLTs which were not reported in the study, and specific, excluding PTs and LLTs that were not considered nasal-related. If additional terms need to be added to the final MedDRA query list after finalization of this document, the attachment may be updated.

Nasal-related adverse events, identified using this custom MedDRA query list, will be listed and summarized as outlined in the Statistical Analysis Plan. In addition, the subset of nasal-related adverse events associated with abnormal olfactory testing or abnormal endoscopy as determined by the medical monitor, will be listed and summarized.

14.6.3. Final Custom Nasal MedDRA Query List

System Organ Class Name	High Level Group Term	High Level Term	Preferred Term	Lower Level Term
Immune system disorders	Allergic conditions	Atopic disorders	Seasonal allergy	Allergic rhinitis due to pollen
Immune system disorders	Allergic conditions	Atopic disorders	Seasonal allergy	Hay fever
Immune system disorders	Allergic conditions	Atopic disorders	Seasonal allergy	Rhinitis seasonal
Immune system disorders	Allergic conditions	Atopic disorders	Seasonal allergy	Seasonal allergic rhinitis
Immune system disorders	Allergic conditions	Atopic disorders	Seasonal allergy	Seasonal allergy
Immune system disorders	Allergic conditions	Atopic disorders	Seasonal allergy	Seasonal nasopharyngitis
Immune system disorders	Allergic conditions	Atopic disorders	Seasonal allergy	Seasonal rhinitis
Infections and infestations	Infections - pathogen unspecified	Upper respiratory tract infections	Nasal abscess	
Infections and infestations	Infections - pathogen unspecified	Upper respiratory tract infections	Nasal vestibulitis	
Infections and infestations	Infections - pathogen unspecified	Upper respiratory tract infections	Rhinitis	
Infections and infestations	Bacterial infectious disorders	Bacterial infections NEC	Bacterial rhinitis	
Infections and infestations	Fungal infectious disorders	Fungal infections NEC	Fungal rhinitis	
Infections and infestations	Fungal infectious disorders	Candida infections	Nasal candidiasis	
Infections and infestations	Viral infectious disorders	Viral infections NEC	Viral rhinitis	
Infections and infestations	Infections - pathogen unspecified	Upper respiratory tract infections	Acute sinusitis	
Infections and infestations	Infections - pathogen unspecified	Upper respiratory tract infections	Chronic sinusitis	
Infections and infestations	Infections - pathogen unspecified	Upper respiratory tract infections	Nasopharyngitis	
Infections and infestations	Infections - pathogen unspecified	Upper respiratory tract infections	Rhinolaryngitis	

System Organ Class Name	High Level Group Term	High Level Term	Preferred Term	Lower Level Term
Infections and infestations	Infections - pathogen unspecified	Upper respiratory tract infections	Rhinotracheitis	
Infections and infestations	Infections - pathogen unspecified	Upper respiratory tract infections	Sinusitis	
Infections and infestations	Infections - pathogen unspecified	Upper respiratory tract infections	Upper respiratory tract infection	
Infections and infestations	Viral infectious disorders	Viral infections NEC	Respiratory tract infection viral	
Infections and infestations	Viral infectious disorders	Viral infections NEC	Viral sinusitis	
Infections and infestations	Viral infectious disorders	Viral infections NEC	Viral upper respiratory tract infection	
Infections and infestations	Bacterial infectious disorders	Bacterial infections NEC	Upper respiratory tract infection bacterial	
Infections and infestations	Bacterial infectious disorders	Bacterial infections NEC	Sinusitis bacterial	
Infections and infestations	Fungal infectious disorders	Fungal infections NEC	Upper respiratory fungal infection	
Infections and infestations	Fungal infectious disorders	Fungal infections NEC	Sinusitis fungal	
Injury, poisoning and procedural complications	Injuries NEC	Site specific injuries NEC	Nasal injury	
Investigations	Physical examination and organ system status topics	Physical examination procedures and organ system status	Ear, nose and throat examination abnormal	
Investigations	Investigations, imaging and histopathology procedures NEC	Imaging procedures NEC	Endoscopy abnormal	
Investigations	Respiratory and pulmonary investigations (excl blood gases)	Respiratory tract and thoracic imaging procedures	Nasoendoscopy	

System Organ Class Name	High Level Group Term	High Level Term	Preferred Term	Lower Level Term
Investigations	Respiratory and pulmonary investigations (excl blood gases)	Respiratory tract and thoracic imaging procedures	Nasopharyngoscopy	
Investigations	Respiratory and pulmonary investigations (excl blood gases)	Respiratory tract and thoracic imaging procedures	Rhinoscopy	
Investigations	Neurological, special senses and psychiatric investigations	Special sense investigations NEC	Olfactory test abnormal	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Respiratory and mediastinal neoplasms malignant and unspecified	Paranasal sinus and nasal cavity neoplasms malignant and unspecified		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Respiratory and mediastinal neoplasms benign (excl mesotheliomas)	Nasal and paranasal sinus neoplasms benign		
Nervous system disorders	Cranial nerve disorders (excl neoplasms)	Olfactory nerve disorders		
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract disorders (excl infections)	Nasal congestion and inflammations		
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract disorders (excl infections)	Nasal disorders NEC		
Respiratory, thoracic and mediastinal disorders	Respiratory tract signs and symptoms	Upper respiratory tract signs and symptoms	Nasal crease	
Respiratory, thoracic and mediastinal disorders	Respiratory tract signs and symptoms	Upper respiratory tract signs and symptoms	Nasal discharge discolouration	
Respiratory, thoracic and mediastinal disorders	Respiratory tract signs and symptoms	Upper respiratory tract signs and symptoms	Nasal discomfort	
Respiratory, thoracic and mediastinal disorders	Respiratory tract signs and symptoms	Upper respiratory tract signs and symptoms	Nasal obstruction	

System Organ Class Name	High Level Group Term	High Level Term	Preferred Term	Lower Level Term
Respiratory, thoracic and mediastinal disorders	Respiratory tract signs and symptoms	Upper respiratory tract signs and symptoms	Nasopharyngeal reflux	
Respiratory, thoracic and mediastinal disorders	Respiratory tract signs and symptoms	Upper respiratory tract signs and symptoms	Rhinalgia	
Respiratory, thoracic and mediastinal disorders	Respiratory tract signs and symptoms	Upper respiratory tract signs and symptoms	Rhinorrhoea	
Respiratory, thoracic and mediastinal disorders	Respiratory tract signs and symptoms	Upper respiratory tract signs and symptoms	Upper airway obstruction	
Respiratory, thoracic and mediastinal disorders	Respiratory tract signs and symptoms	Upper respiratory tract signs and symptoms	Upper-airway cough syndrome	
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract disorders (excl infections)	Paranasal sinus disorders (excl infections and neoplasms)		