CLINICAL STUDY PROTOCOL

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 the I123 Precision Olfactory Delivery (POD®) Device [INP104, POD-DHE] in Patients with Migraine Headache **STOP 301** Trial (Safety and Tolerability of POD-DHE)
Protocol Number	INP104-301

Product	INP104 [POD-DHE]
Indication	Migraine
Development Phase	Phase 3
Sponsor	Impel NeuroPharma Inc. 201 Elliott Ave West, Suite 260 Seattle, Washington 98119 USA
Medical Monitor	Dr Andrew Graber MD PPD Medical Monitor PPD Pharmacovigilance Hotline: +1-(888) 483-7729 Safety Email: wilsafety@ppdi.com
Version	Amendment 03 (A03) - Final v4.0
Effective Date	26 April 2019

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This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research, as set out in the current Declaration of Helsinki and the guidelines on Good Clinical Practice (GCP), as per ICH Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2) (2015) and applicable local regulations.

DocuSigned by Stephen Shrewsbury

Stephen Shrewsbury | I approve this document 4/26/2019 2:35:25 PM PDT

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26-Apr-2019 | 14:40 PDT

Dr. Stephen Shrewsbury (MD), Chief Medical Officer, Impel NeuroPharma Inc.	Date

DECLARATION OF THE INVESTIGATOR

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

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure(s) (IB), Case Report Forms (CRFs), and scientific data not in the public domain.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB, except where necessary to avert an immediate hazard to the subjects.

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki, concerning medical research in humans (recommendations guiding physicians in biomedical research involving human subjects), ICH Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2) (2015) and applicable local regulations.

I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Name (Print)	Investigational Site / Site Number
Investigator Signature	Date

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STUDY SYNOPSIS

Title	Open-label Study of Safety and Tolerability of Chronic Intermittent Usage for 24 or 52 Weeks of Intranasal Dihydroergotamine Mesylate (DHE) Administered using the I123 Precision Olfactory Delivery (POD®) Device [INP104, POD-DHE] in Patients with Migraine Headache
Protocol number	INP104-301
Sponsor	Impel NeuroPharma Inc. Seattle, Washington USA
Study medication	INP104 (POD-DHE)
Clinical phase	3
Study sites	Approximately 40 sites in the United States of America
Study objectives	**Primary Objectives:** Safety and tolerability as assessed by: • Number of subjects with serious and non-serious treatment emergent adverse events • Change in nasal mucosa • Change in olfactory function. **Secondary Objectives:** • Efficacy of INP104 as assessed by change from baseline in migraine measures at 24 and 52 weeks of treatment • Additional safety and tolerability as assessed by: o Change in vital signs o Change in physical examinations o Change in 12-lead electrocardiogram o Change in laboratory evaluations (hematology, clinical chemistry, and urinalysis).
Patient population	Adult male and female subjects 18 to 65 years of age, with a minimum of 2 migraine attacks per month.
Number of subjects	Approximately 300 to 340 subjects will be enrolled: • At least 150 subjects will receive 24 weeks of treatment • At least 60 subjects (of the 300 to 340 enrolled) will receive up to 52 weeks of treatment At least 30 of each gender will be enrolled.
Study design	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, and a 2-week post-treatment follow-up period for all subjects. A subset of these subjects will complete a 52-week treatment period.
Methodology	Study assessments will include evaluations of clinical measures, laboratory findings, and safety reporting. • Specific assessments to evaluate treatment safety will include nasal endoscopy, University of Pennsylvania Smell Identification Test, and the frequency and type of adverse events

	• Clinical evaluations will include collection of medical history, concomitant medication use, height and weight, physical examination, 12-lead electrocardiograms, and vital signs • Laboratory evaluations will include hematology, serum chemistry, urinalysis, serology, and pregnancy testing for women of childbearing potential
Key inclusion criteria	1. Adult males and females, 18 to 65 years of age at the time of screening. 2. Documented diagnosis of migraine (by International Classification of Headache Disorders version 3 beta criteria) with or without aura, with at least 2 attacks/month for previous 6 months. 3. At least two migraine attacks during the 28-day screening period (treated with subject's usual treatment). Subjects who cannot meet this criteria cannot be rescreened. 4. Participants must be in good general health, with no significant medical history (excluding migraine), and have no clinically significant abnormalities on physical examination at screening or baseline visits.
Key exclusion criteria	1. Subjects with trigeminal autonomic cephalalgias (including cluster headache, hemicrania syndromes and short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing), migraine aura without headache, hemiplegic migraine or migraine with brainstem aura (previously referred to as basilar migraines), as per by International Classification of Headache Disorders version 3 beta criteria. 2. Subjects with chronic migraines, medication overuse headache or other chronic headache syndromes, as per International Classification of Headache Disorders version 3 beta criteria. 3. Positive test for human immunodeficiency virus, hepatitis B surface antigen, or hepatitis C antibodies. 4. Subjects with ischemic heart disease or subjects who have clinical symptoms or findings consistent with coronary artery vasospasm, including Prinzmetal's variant angina. 5. Subjects with significant risk factors for coronary artery disease or medical history of diabetes or smoking, known peripheral arterial disease, Raynaud's phenomenon, sepsis or vascular surgery (within 3 months prior to study start), or severely impaired hepatic or renal function. Subjects with a history of hypertension may be enrolled if the hypertension is stable and well-controlled on current therapies for > 6 months, provided no other risk factors for coronary artery disease are present. 6. Significant nasal congestion, physical blockage in either nostril, significantly deviated nasal septum, septal perforation, or any pre-existing upper nasal mucosal abnormality on endoscopy scoring 1 or more (except score 1 allowed for mucosal edema). 7. Subjects who have previously shown hypersensitivity to ergot alkaloids or any of the ingredients in the drug product. 8. Subjects who have previously failed to respond to intravenous DHE for treatment of migraine. 9. Use of > 12 days per month of triptan or ergot-based medication in the 2 months prior to screening or during screening period
Study drug administration	INP104 drug-device combination product will be used to administer 1.45 mg DHE intranasally.

	Subjects will be instructed to use no more than 2 doses of INP104 within a 24-hour period, 3 doses in a 7-day period, and 12 doses per 4-week period.
Treatment assignment	Single group: All study subjects will receive INP104.
Outcome measures	**Primary Endpoints:** • Number of subjects with serious and non-serious treatment emergent adverse events • Change in nasal mucosa as detected by nasal endoscopy • Change in olfactory function **Secondary Endpoints (including additional safety and tolerability endpoints):** • Change from baseline in vital signs • Change from baseline in physical examinations • Change from baseline in 12-lead electrocardiogram • Change from baseline in laboratory evaluations (hematology, clinical chemistry and urinalysis) **Exploratory Endpoints:** • Change from baseline in healthcare utilization for migraine • Product acceptability questionnaire Exploratory Efficacy Endpoints: • Change from baseline in rate of freedom from headache pain at 2 hours after INP104 administration • Change from baseline in Most Bothersome Symptom (MBS) at 2 hours after INP104 administration • Change from baseline in frequency and severity of headache pain (over other time points) after INP104 administration • Change from baseline in MBS at other time points after INP104 administration • Change from baseline in frequency and severity of migraine (measured by headache pain, nausea, phonophobia and photophobia) by diary • Incidences of pain relapse within 24 and 48 hours after INP104 administration • Change from baseline in Migraine Disability Assessment (MIDAS) and Headache Impact Test (HIT)-6 questionnaires • Change in concomitant migraine medication use
Statistical analysis	Statistical analyses will be descriptive in nature. All subjects who receive any amount of study drug (Safety Population) will be included in the analyses. Safety and tolerability will be analyzed based upon the reporting of adverse events, nasal endoscopy, laboratory findings, vital sign assessments, and electrocardiogram parameters. Continuous safety data will be summarized with descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum). Categorical safety data will be summarized with frequency counts and percentages.

	Exploratory efficacy analyses will focus on summarizing the following over time: • Frequency and severity of migraine symptoms captured in the migraine diary • MIDAS and HIT-6 questionnaire scores • Use of concomitant migraine medications
Study duration	Maximum of 30 weeks for subjects receiving 24 weeks of treatment and 58 weeks for subjects receiving 52 weeks of treatment

LIST OF TERMS AND ABBREVIATIONS

AE	adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	body mass index
CRO	contract research organization
CSR	Clinical study report
DHE	dihydroergotamine mesylate
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	Electronic data collection
eDiary	electronic diary
EOT	end-of-treatment
FDA	United States Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBsAG	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HFA	hydrofluoroalkane-134a (propellant)
HIT-6	Headache Impact Test
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICH	International Council for Harmonisation
ICHD3b	International Classification of Headache Disorders version 3 beta
IFU	Instructions For Use
IHS	International Headache Society
IM	Intramuscular
IP	investigational product
IRB	Institutional Review Board
IV	Intravenous
LPLV	Last patient last visit
MBS	Most Bothersome Symptom
MedDRA	Medical Dictionary for Regulatory Affairs
MIDAS	Migraine Disability Assessment
NSAID	Non-steroidal anti-inflammatory drug
PI	Principal Investigator
POD	Precision Olfactory Delivery
PPD	Pharmaceutical Product Development, LLC
PRN	as necessary
PVG	Pharmacovigilance
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SP	Safety Population
SSRI	selective serotonin reuptake inhibitor
TEAE	Treatment Emergent Adverse Event
UPSIT	University of Pennsylvania Smell Identification Test
WHO	World Health Organization
WOCBP	women of childbearing potential

1 BACKGROUND

1.1 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).

The purpose of this study is to evaluate the investigational product (IP; INP104 or POD-DHE), which is a drug-device combination product comprised of the active ingredient, dihydroergotamine mesylate (DHE), administered intranasally by a Precision Olfactory Delivery (POD®) device (I123 POD device). The indication for INP104 is for the treatment of acute migraine headache with or without aura.

D.H.E. 45® (dihydroergotamine mesylate) Injection, USP is the brand name of the dihydroergotamine mesylate product first approved in 1946 for injection (D.H.E. 45® Prescribing Information). 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 (HFA) 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 nasal epithelium. This narrow stream is intended to minimize deposition in the nasal vestibule and to avoid loss of drug before absorption.

1.2 Clinical overview

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 (dihydroergotamine mesylate) 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 for 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.

1.3 Summary of potential risks and benefits

The risk/benefit profile of DHE is well known and is described in the D.H.E. 45 (dihydroergotamine mesylate) Injection, USP and Migranal US Prescribing Information.

INP104 drug substance and drug product are manufactured by the same contract manufacturer using the same equipment and same process as the approved drug substance and drug product in Migranal Nasal Spray. Given that there are no differences to the chemistry and manufacturing of these two products, no additional toxicology risks due to sourcing are anticipated by the Sponsor.

1.4 Proposed dosage and treatment period

D.H.E. 45 (dihydroergotamine mesylate) Injection, USP is approved for intravenous (IV), intramuscular (IM), and subcutaneous (SC) injections at a dose of 1 mg. This dose can be repeated at 1 hour intervals up to a maximum of 3 mg by IM or SC injection, or a maximum of 2 mg by IV injection per any 24-hour period. The total dose should not exceed 6 mg in a week. Migranal Nasal Spray is approved for dosing with 2 mg with a maximum dose of 3 mg per 24-hour period and 4 mg in any 7-day period.

It is proposed that INP104 will be administered using the I123 POD device where the dose will be 1.45 mg of DHE. Subjects will be allowed to self-administer a maximum number of 3 doses in a 7-day period (with no more than 2 doses in a 24-hour period). The minimum planned treatment period for all enrolled subjects will be 24 weeks, with a subset of at least 60 (of an estimated 80 enrolled into this period) continuing through to 52 weeks of treatment.

1.5 Patient population

This study will be conducted in subjects diagnosed with a history of migraine per International Headache Society (IHS) criteria (Headache Classification Committee of the International Headache Society, 2018) with or without aura, with an average of at least 2 migraine attacks per month in the previous 6 months, and who meet all of the inclusion criteria and none of the exclusion criteria. This population is appropriate for a Phase 3

study investigating safety and tolerability, as well as changes in migraine frequency and severity, changes in the disabling effects of migraine, and changes in concomitant medication use.

2 OBJECTIVES

2.1 Primary objectives

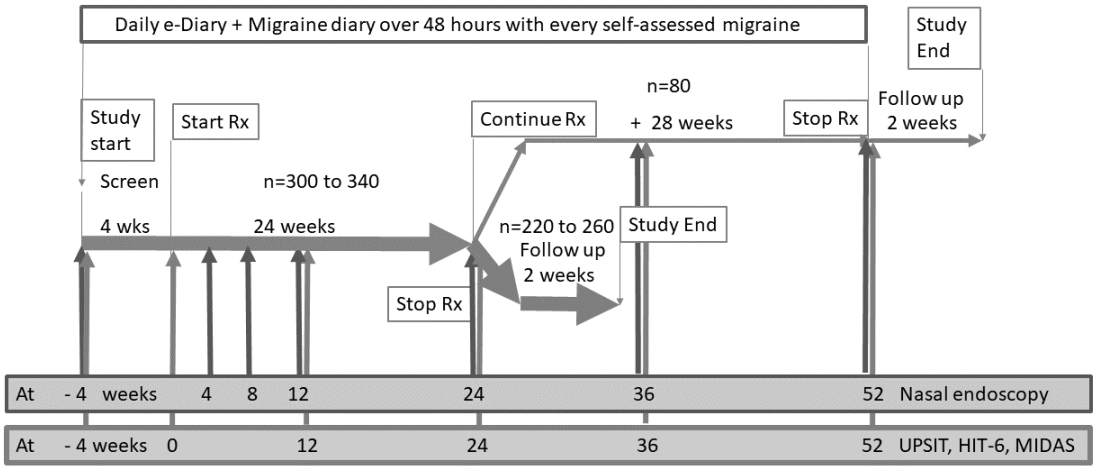
Safety and tolerability as assessed by:

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

2.2 Secondary objectives

- Efficacy of INP104 as assessed by change from baseline in migraine measures (Section 3.3) at 24 and 52 weeks of treatment
- Additional safety and tolerability as assessed 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 STUDY DESIGN



3.1 Overview

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, and a 2-week post-treatment follow-up period. Approximately 300 to 340 subjects will be enrolled to allow for a 25% drop-out rate over the 24-week study, to achieve at least 150 completing treatment at 24 weeks and 80 subjects continuing 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.

The study is an outpatient study in frequent migraineurs (currently suffering a minimum of 2 migraines per month) but not diagnosed with chronic headache by International Classification of Headache Disorders version 3 beta (ICHD3b) criteria. During the screening period, they 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 INP104 when they experience a recognizable migraine. They will be 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 intranasally (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 suffering from an average of at least 2 migraines per 28-day period between Weeks 12 and 24 (i.e., each subject will record a minimum of 6 migraine attacks over this 12-week period) and demonstrating at least 80% diary

compliance will enter an extension treatment period to allow data collection for 52 weeks of total exposure. Study subjects will record all migraine attacks (frequency and severity) in a migraine diary and undergo periodic evaluation by Migraine Disability Assessment (MIDAS; Appendix 4) and Headache Impact Test (HIT-6™; Appendix 5) questionnaires. Subjects will also return to the clinic for periodic evaluations of safety, which will include collection of vital signs, physical examinations, nasal endoscopy, UPSIT smell test, electrocardiography, and recording of AEs, laboratory evaluations, and concomitant medications.

After the last study treatment visit, subjects will return two weeks later for a post-treatment follow-up visit.

If a higher than anticipated drop-out rate is experienced or enrolled subjects experience fewer than 2 migraine events per 28 days on treatment, consideration will be given to amending the protocol to increase the number of enrolled subjects, or to modify the inclusion criteria to require a higher frequency of migraines, or both.

3.2 Primary endpoints

The primary endpoints for the study are listed below:

- Number of subjects with serious and non-serious treatment emergent adverse events
- Change in nasal mucosa as detected by nasal endoscopy
- Change in olfactory function.

3.3 Secondary endpoints

The secondary endpoints for the study include additional safety and tolerability endpoint:

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

3.4 Exploratory endpoints

The exploratory endpoints for the study include:

- Change from baseline in healthcare utilization for migraine
- Product acceptability questionnaire.

Exploratory efficacy endpoints include:

- Change from baseline in rate of freedom from headache pain at 2 hours after INP104 administration
- Change from baseline in Most Bothersome Symptom (MBS) at 2 hours after INP104 administration
- Change from baseline in frequency and severity of headache pain (over other time points) after INP104 administration
- Change from baseline in MBS at other time points after INP104 administration
- Change from baseline in frequency and severity of migraine (measured by headache pain, nausea, phonophobia and photophobia) by diary
- Incidence of pain relapse within 24 and 48 hours after INP104 administration
- Change from baseline in MIDAS and HIT-6 questionnaires
- Change in concomitant migraine medication use.

4 STUDY POPULATION

4.1 Population size

Approximately 300 to 340 subjects in the United States will be enrolled in the study at approximately 40 study sites. All 300 to 340 subjects are planned for the 24-week treatment period (the primary safety assessment period), to ensure that at least 150 will complete that period. At least 80 of these subjects will be enrolled into an extension of the treatment period to ensure 60 will complete a total of 52 weeks of treatment. At least 30 subjects of each gender will be enrolled in the initial 300 to 340 subjects enrolled.

4.2 Inclusion criteria

In order to be eligible for participation in this study, potential subjects must meet all of the following criteria:

1. Adult male and females, 18 to 65 years of age (inclusive) at the time of screening.
2. Documented diagnosis of migraine (by ICHD3b criteria) with or without aura, with at least 2 attacks/month for previous 6 months.
3. Must have experienced at least 2 migraine attacks as defined by ICHD3b criteria during the 28 days of screening prior to Visit 2. All migraines experienced during the screening period must be recorded in the diary. Subjects who do not meet this criterion cannot be rescreened.
4. Must have completed daily diary entries on 23 of the 28 days of screening prior to Visit 2.
5. Participants must be in good general health, with no significant medical history (excluding migraine), have no clinically significant abnormalities on physical examination or laboratory value at baseline visit.
6. Negative urine drug screen at screening. Positive urine drug screens with a medical explanation may be discussed with the Medical Monitor for potential inclusion.
7. Participants must have the ability and willingness to attend the necessary visits to the study center.
8. Written informed consent must be given, signed, and documented prior to entry into the study.
9. Female subjects of childbearing potential must agree to use adequate contraception (as defined in the protocol) during the study and for 30 days after the last dose of study drug.
10. Male subjects and their partners must agree to use effective contraception (as defined in the protocol) during the study and for 30 days after study completion. Males must refrain from sperm donation for 30 days after study completion.

4.3 Exclusion criteria

In order to be eligible for participation in this study, potential subjects may not meet any of the following criteria:

1. Subjects with trigeminal autonomic cephalalgias (including cluster headache, hemicrania syndromes and short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing), migraine aura without headache, hemiplegic migraine or migraine with brainstem aura (previously referred to as basilar migraines), as per ICHD3b criteria.
2. Subjects with chronic migraines, medication overuse headache or other chronic headache syndromes (and/or subjects with ≥ 15 headache days per 28 days in screening), as per ICHD3b criteria.
3. Subjects with status migrainosus in the 3 months prior to screening or during screening period.
4. Positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (HCV).
5. Subjects with ischemic heart disease or subjects who have clinical symptoms or findings consistent with coronary artery vasospasm, including Prinzmetal's variant angina.
6. Subjects with significant risk factors for coronary artery disease, current use of tobacco products, smoking history (of at least 10 or more cigarettes per day within the last 12 months prior to screening), or history of diabetes, known peripheral arterial disease, Raynaud's phenomenon, sepsis or vascular surgery (within 3 months prior to study start), or severely impaired hepatic or renal function. Subjects with a history of hypertension may be enrolled if the hypertension is stable and well-controlled on current therapies for > 6 months, provided no other risk factors for coronary artery disease are present.
7. Subjects with potentially unrecognized coronary arterial disease as demonstrated by history, physical examination, or screening ECG.
8. Abnormal, clinically significant laboratory tests at screening, including but not limited to:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2X upper limit of normal.
    - Serum creatinine > 1.5X upper limit of normal.
9. Any acute illness or uncontrolled infection within 28 days prior to Day 1; however, potential subjects who have experienced a mild self-limiting illness that has resolved at least 7 days prior to Day 1 may be included.
10. Subjects with recurrent sinusitis or epistaxis, or chronic rhinosinusitis with nasal polyp (unless surgically resolved > 3 months prior to screening).

11. Significant nasal congestion, physical blockage in either nostril, significantly deviated nasal septum, septal perforation, or any pre-existing upper nasal mucosal abnormality on endoscopy scoring 1 or more (except score 1 allowed for mucosal edema).
12. Subjects who have previously shown hypersensitivity to ergot alkaloids or any of the ingredients in the drug product. For ingredients, refer to the INP104 Investigational Brochure.
13. Subjects who have previous documented failure of response to IV DHE for treatment of migraine.
14. Use of any triptan or ergot-based medication or medication strongly or moderately affecting CYP3A4 Cytochrome P450 metabolic pathway within 2 days prior to the Baseline Visit (Visit 2). This exclusion criteria does not apply to prescription contraceptives.
15. Use of any medications prohibited by protocol (see Section 4.4).
16. Use of > 12 days per month of triptan or ergot-based medication in the 2 months prior to screening or during screening period.
17. Use of barbiturates/barbiturate containing compounds or opiates (including tramadol or tapentadol) greater than 7 days per month (cumulative) or unstable usage pattern in the 2 months prior to screening or during screening.
18. History or presence of alcoholism or drug abuse within the 2 years prior to the first study drug administration or a positive result on the urine drug test at the Screening Visit (positive urine drug screens with a medical explanation may be discussed with the Medical Monitor for potential inclusion).
19. Females who are pregnant, or planning to get pregnant, or are lactating while participating in this clinical study.
20. Treatment with another investigational drug, investigational device, or approved therapy for investigational use within 28 days or 5 half-lives (whichever is longer) prior to screening is prohibited.
21. Subjects with any underlying physical, psychological, or medical condition that, in the opinion of the investigator, would make it unlikely that they would comply with the study.
22. Failure to satisfy the Investigator of fitness to participate for any other reason.

4.4 Concomitant medications

A list of permitted concomitant migraine medications is provided in Appendix 1.

All medications including over-the-counter medications and herbal supplements taken during the 28 days prior to the Screening Visit (Visit 1) and continuing through the screening period will be recorded and reviewed by the Investigator to determine whether the subject is suitable for inclusion. In addition, all migraine medications taken within 12 months before the Screening Visit will be recorded.

Routine migraine prevention treatment (e.g., beta-blocker or tricyclic antidepressant) may be continued if stable > 30 days prior to screening unless they are contraindicated for concomitant use with an ergot derivative. Other acute migraine treatment may be used in the screening period.

While on study, only non-ergot, non-triptan acute migraine treatment may be used and only after 2 hours from study drug administration has elapsed. After 2 hours, non-ergot, non-triptan analgesics may be used as rescue medication for subjects who still have headache pain. Alternatively, a single further dose of Investigational Product may be taken at 2 hours. The use of such rescue medications must be recorded in the diary.

Use of any triptan or ergot (other than IP) acute migraine treatment within 2 days prior to Baseline Visit (Visit 2) and through end of study treatment is prohibited.

Intranasal use of saline is allowable. Intranasal use of corticosteroids and antihistamines are allowable if usage pattern is stable for at least 2 months prior to screening and throughout trial. Other concomitant medications via intranasal route are prohibited during trial.

Macrolide antibiotics, protease inhibitors, and other medications affecting the CYP3A4 metabolite pathway (including verapamil) are prohibited, with the exception of oral contraceptives, during the course of this study (Appendix 2).

Peripheral vasoconstrictors are prohibited, as well as nicotine from smoking or other sources.

Caution should be advised when a selective serotonin reuptake inhibitor (SSRI) is being used due to rare events with weakness, hyperreflexia and incoordination when 5-HT agonists have been co-administered with SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline). There have been no spontaneous reported cases of drug interaction between SSRIs and Migranal Nasal Spray or D.H.E. 45 for Injection.

Beta-blockers are allowed (if being taken for migraine prophylaxis, but not for hypertension), however caution should be advised due to their potential to block the vasodilatory properties of epinephrine.

All medications including over-the-counter medications and herbal supplements (other than the IP) taken by subjects during the course of the study will be recorded. Concomitant medications will be recorded and will be coded using the most current World Health Organization (WHO) drug dictionary.

4.5 Diet, activity, and other restrictions

The are no diet or activity restrictions; however, dosing with INP104 more than twice in 24 hours, and more than 3 times within a 7-day period is not allowed.

4.6 Contraceptive requirements

Subjects must be willing to comply with the contraceptive requirements of the study as detailed below:

(a) Female subjects

Women will be defined as of non-childbearing potential if post-menopausal (12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with FSH levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy or hysterectomy).

Women of childbearing potential (WOCBP) must not become pregnant and must use adequate contraceptive during the study and for 30 days after the last dose of IP. Adequate contraception is defined as one of:

- Birth control pills
- Depo Shot or injectable birth control (e.g., Implanon)
- Intrauterine Device
- Condom with spermicide
- Diaphragm with spermicide
- NuvaRing®
- Documented evidence of surgical sterilization at least 6 months prior to Screening Visit, i.e., tubal ligation or hysterectomy for women or vasectomy of a male partner.

These allowed methods of contraception are only effective when used consistently, correctly, and in accordance with the product label. The Investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

(b) Male subjects

To prevent pregnancy in a female (WOCBP) partner, male subjects must agree to use effective contraception (as defined in the protocol) during the study and for 30 days after study completion for all sexual intercourse (see Section 8.8).

Males must also not donate sperm during the study or for 30 days after study completion.

5 INVESTIGATIONAL PRODUCTS

The IP is INP104. INP104 is a drug-device combination product that includes a drug component: DHE drug product and a device component: I123 POD® Device. Specific instructions regarding the storage, preparation, and administration of INP104 are provided in the Investigator's Brochure, Pharmacy Manual, and Instructions For Use (IFU). The IFU will be provided to all participating subjects.

5.1 Study medication identification

The device component, I123 POD device, is a handheld, manually actuated, metered-dose administration device intended to deliver a drug solution to the nasal cavity.

The drug component, DHE drug product, is a 3.5-mL amber glass vial filled with 1 mL of DHE 4 mg/mL solution. The DHE drug product vial attaches to the I123 POD device forming the fully assembled INP104 product. A single manual actuation of INP104 by the user results in delivery of the DHE solution to the nasal cavity of the user. INP104 is designed to be disposed of after single-dose drug delivery of 1.45 mg DHE delivered as two actuations, one to each nostril.

Additional information about INP104 and its components are provided in the INP104 Investigational Brochure.

5.2 Dosage and administration

INP104 will be self-administered. The dose will be split between nostrils, with one spray in each nostril delivering a target total dose of 1.45 mg DHE.

Subjects will be instructed to use INP104 when they experience a recognizable migraine. Study drug should be the first acute treatment medication administered unless daily or weekly dosage limits have been reached. INP104 should not be used as second-line therapy for acute migraines.

Rescue medication: While on study, only non-ergot, non-triptan acute migraine treatment may be used and only after 2 hours from study drug administration has elapsed. After 2 hours, non-ergot, non-triptan analgesics may be used as rescue medication for subjects who still have headache pain. The use of such rescue medications must be recorded in the diary. Subjects will be instructed to use no more than 2 doses of INP104 within a 24-hour period, 3 doses in a 7-day period, and 12 doses per 4-week period.

5.2.1 Study supplies

The Sponsor will supply all IP through a third-party vendor, Almac Group (Craigavon, Northern Ireland), to the investigational site(s). The DHE drug product provided for this study will be manufactured under current Good Manufacturing Practices, will be subject to release, and will be suitable for human use. The I123 POD device will be manufactured under controlled conditions and assembled into kits under clean room conditions.

Almac will be responsible for the packaging and labelling of the IP. The Sponsor will be responsible for providing details of batch numbers, safety, and stability data.

Almac will label the products in accordance with local regulatory requirements.

5.2.2 Investigational product storage, dispensing, and accountability

Investigational product must be stored at controlled room temperature, between 15°C and 25°C, in original packaging as provided (not refrigerated or frozen) upon receipt at the investigational site. A record will be maintained by the investigational site, which will account for all dispensing and return of any used and unused IP. At the end of the study, the IP will be reconciled, and a copy of the record given to the Study Monitor.

Upon completion of the study, any surplus IP will be returned to an appropriate storage facility as indicated by the Sponsor. If no supplies remain, this will be documented in the disposition record.

The Investigator will be fully responsible for the security, accessibility, and storage of the IP while it is at the investigational site.

Subjects may be assigned a POD training device to assist with training. The training device will not contain any study medication, however, while training with the POD device, subjects may be exposed to HFA gas (the propellant of the POD device) if the device is actuated while the tip is placed in the naris.

Following training on the use of INP104 by an authorized Sponsor trainer, the Investigator is responsible for the education of study staff and study subjects in the correct administration of the IP.

6 STUDY PROCEDURES

6.1 Medical history

Medical history (focused on migraine diagnosis) and concomitant medication use (especially for the prevention or treatment of migraine; see Section 4.4) will be recorded at screening and will include the collection of previous and current illnesses and surgeries, as well as a medication history. Any ongoing events should be recorded as baseline medical history.

Information about healthcare utilization over the previous 12 months (for migraine) will be collected if available.

6.2 Demographics

Date of birth, age (calculated), sex, ethnicity, and race will be recorded at screening.

6.3 Body weight and height or body mass index

Body mass index is calculated by dividing the subject's body weight in kilograms by the subject's height in meters squared (BMI = kg/m^2). Body height (centimeters) and body weight (kilograms) will be measured at the time points delineated in the study schedules. Body weight and height will be obtained with the subject's shoes and jacket or coat removed.

6.4 Safety assessments

This study will assess the safety and tolerability of INP104. Safety will be determined by evaluating physical examination findings, nasal endoscopy, and testing of olfactory function, ECGs, vital signs, clinical laboratory parameters, concomitant medication usage, and AEs.

6.4.1 Physical examination

Complete physical examinations may be performed by a licensed physician (or by a nurse practitioner or physician's assistant delegated by the Principal Investigator if permitted by local law), at the time points specified in Table 7-1.

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

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

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

6.4.2 Nasal endoscopic examination

Nasal endoscopic examinations will be performed by a board certified/board eligible otolaryngologist at the specified visits (or within specified nasal endoscopy time windows).

The nasal endoscopy will include endoscopic evaluation of both the lower and upper nasal mucosa, using either a flexible or rigid 30-degree nasal endoscope (with a diameter between 2.5 and 4 mm), with special attention paid to identifying any trauma, inflammation, crusting, epistaxis, ulceration, or other changes to the mucosa as listed in Table 6-1. Every attempt must be made to ensure the same investigator assess the same subject at each visit with the same equipment.

Nasal endoscopy will be performed in all subjects during Screening (before visit 2) and then at 4, 8, and 12 weeks. If no adverse changes to the upper nasal cavity mucosa are detected on nasal endoscopy, and the subjects have not reported any AEs related to the nose, then all subjects will have further nasal endoscopy at 24 weeks and at 36 and 52 weeks for those continuing through 52 weeks of treatment. For those subjects who are noted to have clinically significant changes on nasal endoscopy or have reported a clinically significant AE related to the nose, and nasal endoscopy will be repeated at 2-week intervals until the change has resolved or been otherwise explained. If the changes have not resolved or have worsened at the first repeat endoscopy, treatment should be discontinued, unless changes are otherwise explained and approved by medical monitor to continue treatment.

Otolaryngologists will conduct the nasal endoscopy and will follow the study Nasal Examination Manual (Appendix 3) and scoring grid outlined in Table 6-1.

Table 6-1: Quantitative Scoring Scale for Evaluation of the 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*

Table 6-1: Quantitative Scoring Scale for Evaluation of the Nasal Mucosa (QSS-NM)

Finding	Grading Criteria	Score
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*

* A total score exceeding 7 (summed from left + right upper nasal cavity scores), or an individual score of 2 or more on any one of the 5 items at any time point will trigger a repeat examination 2 weeks later.

All endoscopic examinations will be scored and summed for the upper nasal cavity (left side + right side) using the scale above. The lower nasal cavity scores will not be summed or used for making study treatment discontinuation decisions. Follow-up of any changes in the lower nasal space will be at the discretion of the otolaryngologist. Findings (in the upper nasal cavity) causing a change in score as defined above will require a follow-up endoscopy within 14 days. The purpose of the endoscopic examination is to ensure subjects are not experiencing untoward events that may be associated with the POD delivery of DHE, and that any subject with endoscopic findings considered clinically significant will be followed for 28 days or until resolution (refer to Section 8.7). The purpose of the scale is to quantify changes from baseline.

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.

Further details of the nasal endoscopy procedure and scoring can be found in the Nasal Examination Manual (Appendix 3).

6.4.3 Olfactory changes (UPSIT)

Olfactory changes will be assessed using the University of Pennsylvania Smell Identification Test (Doty 1984), as described in the Nasal Examination Manual (Appendix 3).

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 examination will be administered at screening and at 0, 12, and 24 weeks. Absent any significant changes in test scores at any of these time points (where a significant change will be defined as greater than or equal to a 5-point reduction in absolute test score compared to averaged screening and baseline UPSIT scores for that subject), thereafter the test will be administered at 36 and 52 weeks for the subset of subjects enrolled through 52 weeks of the study. A reduction in absolute test score of greater than or equal to 5 points on any single test will be recorded as an AE and will trigger a repeat test 4 weeks later. If the UPSIT score is still 5 or more points below baseline for that subject 4 weeks later, the subject will be discontinued from any further treatments with INP104 but will continue to return for scheduled study visits until olfaction returns to baseline or they have completed their participation in the study (whichever occurs sooner).

6.4.4 Electrocardiogram

A 12-lead ECG will be collected at the time-points delineated in the study schedule Table 7-1. Additional ECG monitoring may be performed at other times if deemed necessary.

ECGs will be performed with subjects in a supine position. Subjects must be in this position for at least 5 minutes before the reading is taken. When the time of ECG monitoring coincides with a blood draw, the ECG will be conducted first.

All ECG tracings will be reviewed by the PI or his/her designate.

6.4.5 Vital signs

Subjects should rest for at least 3 minutes prior to and during the collection of vital signs. Blood pressure and heart rate should be measured when the subject is in a supine or seated position. When the time of vital signs measurement coincides with a blood draw, the vital signs will be taken before the scheduled blood draw.

Additional vital signs may be performed at other times if deemed necessary.

6.4.6 Laboratory investigations

Safety laboratory tests (hematology, chemistry, and urinalysis) will be performed at the time points specified in Table 7-1.

Medically indicated laboratory tests (emergency) can be conducted at a local laboratory, but repeat and unscheduled tests should be conducted at the central laboratory.

6.4.6.1 Hematology and serum chemistry

A blood sample will be taken from each subject for hematology and serum chemistry analysis at the time points delineated in the study schedule in Table 7-1. Laboratory parameters will include:

- hematology
- hemoglobin
- hematocrit
- erythrocytes
- platelets
- leukocytes with differential (including eosinophils, neutrophils, basophils, lymphocytes, monocytes, and reticulocytes)

Serum chemistry

- 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
- bicarbonate

Additional clinical laboratory tests may be performed at other times if deemed necessary.

6.4.6.2 Urinalysis

A urinalysis test (dipstick) will be performed for each subject. Urinary analyses will be performed at the Screening Visit and at other times according to the study schedule (Table 7-1).

Macroscopic

- pH
- specific gravity
- protein
- glucose
- ketones
- total bilirubin
- occult blood
- nitrite
- urobilinogen
- leukocytes

If an abnormality is noted for protein, blood, nitrite or leukocyte esterase, a microscopic examination of red blood cells, white blood cells, bacteria, and casts will be performed.

6.4.6.3 Serology

Serologic testing for HBsAg, anti-HCV, and HIV antibody testing will be performed at the Screening Visit.

6.4.6.4 Urine drug screen

A urine drug screen will be performed at the Screening Visit. This will include screening for:

- Cocaine
- Amphetamines
- Barbiturates
- Opiates

6.4.6.5 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 childbearing potential only, according to the study schedule (Table 7-1). Serum FSH will be measured in post-menopausal women (who have not had a period for at least 12 months).

6.5 Efficacy assessments

6.5.1 MIDAS and HIT-6 questionnaires

The MIDAS (Appendix 4) and HIT-6 (Appendix 5) Questionnaires provide tools for the assessment of headache-related disability. The MIDAS questionnaire (Stewart 1999) includes 5 scored questions that measure the number of days in the past 3 months that the subject experienced limitations in daily activities resulting from migraine. The HIT-6 questionnaire (Yang 2011) includes 6 scored questions that measure the impact headaches have on activities of daily living, with 3 of the questions asking for data from the past 4 weeks. These questionnaires will be completed by study subjects at baseline, selected study visits (Table 7-1), and end-of-treatment (EOT).

6.5.2 Migraine diary

The primary modality for diary data collection will be a validated electronic diary (eDiary), though a paper diary may be implemented as a back-up if needed (eg, if technology issues interfere with eDiary data collection). An eDiary (or, alternatively, a paper diary if needed) entry will be completed by subjects for every migraine they experience during the study, whether or not they treat it.

At least 2 such migraines must be experienced in the 28-day screening period, and the subject must record details about them in the migraine diary. Only subjects who successfully complete their diary during at least 2 migraines during the screening period will be enrolled.

Once enrolled, subjects will record all headaches experienced. When a subject experiences a recognizable migraine, it will be recorded in the diary and the subject will take the study medication (or alternative, if they have already reached their maximum permitted use of IP). Subjects will answer a series of questions about the severity of headache and presence and severity of associated symptoms (nausea, phonophobia, and photophobia). These questions will be used to determine if the headache qualifies as a migraine as per ICHD-3b. The same questions will be answered and recorded in the diary at various time points post-dosing.

If the migraine has not resolved at 2 hours post IP administration, subjects are allowed to take their usual (non-ergot, non-triptan) migraine treatment and will then continue scoring the headache diary up to 48 hours.

At each visit, staff will check that all migraines have been recorded in the diary and whether the subject has any questions or concerns.

6.5.3 Subject's impression of INP104 usability/effectiveness

A questionnaire asking subjects to assess the usability and effectiveness of the INP104 product will be administered at the 24-week and 52-week time points (Appendix 6).

7 STUDY SCHEDULE

7.1 Study flow

A tabular display of study events is provided in Table 7-1.

Table 7-1: Time and Event Schedule

Period	**Screening**	**Baseline**	**Treatment Period**										**Follow-up**
Week	**-4**	**0**	**4**	**8**	**12**	**16**	**20**	**24/EOT**	**26[1]**	**36**	**42**	**52/EOT**	**54**
Days	**-28**	**0**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	**252**	**294**	**364**	**378**
Window (days)	**-12**		**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±10**	**±10**	**±10**	**±10**	**+ 14**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9a**	**9b**	**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 examination	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	
UPSIT[4]	X	X			X			X		X		X	
MIDAS and HIT-6	X	X			X			X		X		X	
Hematology and chemistry labs[5]	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												

Table 7-1: Time and Event Schedule

Period	Screening	Baseline	Treatment Period										Follow-up
Week	**-4**	**0**	**4**	**8**	**12**	**16**	**20**	**24/EOT**	**26[1]**	**36**	**42**	**52/EOT**	**54**
Days	**-28**	**0**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	**252**	**294**	**364**	**378**
Window (days)	**-12**		**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±10**	**±10**	**±10**	**±10**	**+ 14**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9a**	**9b**	**10**	**11**	**12**
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. Participants should be seated or supine for ≥ 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. The baseline endoscopy may be performed at any time between Visit 1 and Visit 2. 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 nasal endoscopy, or as a result of reported AEs are specified in Section 6.4.2 of this protocol.
4. UPSIT testing will be performed at visits as specified. Off schedule assessments triggered by findings on the UPSIT, or as a result of reported AEs are specified in Section 6.4.3 of this 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 on 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 on to 52 weeks of treatment only.

7.2 Study activities

7.2.1 Consent and screening

Prior to enrolling in the study, and before performing any study-related procedures, potential subjects will attend a Screening Visit within 28 days (-12 days) of the start of the treatment period, at which time they will be provided with the Informed Consent Form. Prior to being asked to sign the consent form, subjects will be given time to review study information and ask any questions. Subjects continuing on through 52 weeks of treatment will be reconsented at their 24-week visit. This option will be offered to those subjects complying with diary completion criteria (at least 80% compliance) and recording on average a minimum of 2 migraine diaries per 4-week period during the period from 12 to 24 weeks (i.e., each individual subject records at least 6 migraine attacks over the 12-week period). Once approximately 80 subjects have agreed to continue through to 52 weeks, to allow for 60 to complete this period of the study, no further subjects will be enrolled in this period.

After the consent form is signed, subjects will be sequentially assigned a subject identification number. The subject identification number will remain the same throughout the study. Screening assessments will be carried out as follows:

- Review of all prior and concomitant medications for the 28 days prior to screening (12 months for migraine medications), medical history, and inclusion/exclusion criteria
- Measurement of height and weight
- Recording demographic information
- Complete physical examination
- Nasal endoscopy (to occur once anytime between the Screening and Baseline Visits)
- UPSIT evaluation, MIDAS, and HIT-6 questionnaires
- Vital signs (body temperature, blood pressure, heart rate, and respiratory rate)
- 12-lead ECG
- Clinical laboratory testing (hematology, serum chemistry and urinalysis)
- HIV, Hepatitis B, and Hepatitis C screen
- Urine drug screen
- Serum pregnancy test (women of childbearing potential only)
- Follicle stimulating hormone (FSH; post-menopausal women only)
- Collection of pre-treatment AEs
- Distribution of the migraine diary and training in its use

Data from screen failures (basic demographics, migraine history and reason for screen fail) will be recorded in the electronic case report form (eCRF).

7.2.2 Baseline

Subjects who qualify for inclusion in the study but are not enrolled within 28 days (+12 days), may be re-consented, assigned a new screening number, and re-screened once. Subjects who do not qualify for inclusion in the study for reasons other than failing to meet screening period migraine attack requirement may be re-screened once if approved by the study Medical Monitor. Subjects who do not qualify for inclusion in the study because of failure to meet screening period migraine attack requirement may not be re-screened.

Enrolled subjects will undergo the following procedures to collect baseline (Day 0) data:

- Review to determine whether the subject continues to satisfy the study inclusion and exclusion criteria (including diary record of at least 2 migraines during screening period)
- 12-lead ECG
- Vital signs (body temperature, blood pressure, heart rate, and respiratory rate)
- Directed physical examination
- UPSIT evaluation, MIDAS and HIT-6 questionnaires
- Clinical laboratory testing (hematology, serum chemistry, and urinalysis)
- Urine pregnancy test (women of childbearing potential only)
- Pre-treatment AEs
- The subject's concomitant medications, including non-prescription medications including complementary medicines and herbal preparations
- Demonstration and training in use of POD device
- Dispensation of IP.

7.2.3 Treatment period visits

Treatment period visits will occur on Week 4 (±5 days), Week 8 (±5 days), Week 12 (±5 days), Week 16 (±5 days) and Week 20 (±5 days), and additionally at Week 24 (±5 days), Week 36 (±10 days) and Week 42 (±10 days) for those subjects who receive 52 weeks of treatment. The following procedures will be performed at each visit:

- Vital signs (body temperature, blood pressure, heart rate, and respiratory rate)
- Directed physical examination
- Nasal endoscopy performed at selected visits as specified in Table 7-1

- UPSIT evaluation, MIDAS and HIT-6 questionnaires (at selected visits as specified in Table 7-1)
- Clinical laboratory testing (hematology, serum chemistry, and urinalysis) (at selected visits as specified in Table 7-1)
- Urine pregnancy test (women of childbearing potential only)
- Adverse events
- The subject's concomitant medications, including rescue medications, non-prescription medications including complementary medicines and herbal preparations
- Check of the migraine diary
- Collect unused IP and dispense new supply. IP to be dispensed at Week 24 (±5 days) only for subjects continuing to 52 weeks of treatment.

7.2.4 End-of-treatment visits

End-of-treatment (EOT) visits will take place at Week 24 (± up to 5 days) for those subjects who receive 24 weeks of treatment and at Week 52 (± up to 10 days) for those subjects who receive 52 weeks of treatment. In case a subject is withdrawn from treatment at any time (Early Termination), these procedures should be undertaken and the subject asked to return 2 weeks later for an early termination follow-up. The following procedures will be performed at each EOT visit:

- Body weight
- Vital signs (body temperature, blood pressure, heart rate, and respiratory rate)
- 12-lead ECG
- Complete physical examination
- Nasal endoscopy
- UPSIT evaluation, MIDAS and HIT-6 questionnaires
- Clinical laboratory testing (hematology, serum chemistry, and urinalysis)
- Urine pregnancy test (women of childbearing potential only)
- Adverse events
- The subject's concomitant medications, including non-prescription medications including complementary medicines and herbal preparations
- Check and collection of the migraine diary. The diary should only be collected at Week 24 from subjects who are not continuing to 52 weeks of treatment.
- Extension informed consent for subjects continuing to 52 weeks of treatment
- INP104 Product Questionnaire

- Return of unused study medication.

7.2.5 Post-treatment follow-up visits

Safety follow-up visits will take place 2 weeks following the EOT visits, at Week 26 (+ up to 10 days) for those subjects who only receive 24 weeks of treatment and at Week 54 (+ up to 14 days) for those subjects who receive 52 weeks of treatment, or 2 weeks after last dose for subjects who have an early termination from the study. The following procedures will be performed at each safety follow-up visit:

- Vital signs (body temperature, blood pressure, heart rate, and respiratory rate)
- Complete physical examination
- Clinical laboratory testing (hematology, serum chemistry and urinalysis)
- 12 lead ECG, if preceding ECG showed a potentially clinically significant abnormality
- Urine pregnancy test (women of childbearing potential only)
- Adverse events
- The subject's concomitant medications, including non-prescription medications including complementary medicines and herbal preparations.

8 SAFETY

In this study, AEs will be reported by all subjects from time of consent until the completion of the last study follow-up visit. Serious adverse events will be reported in all subjects (enrolled and not enrolled) from the time of consent. However, AEs recorded during the screening period or prior to first dose of IP will not be listed as treatment-emergent AEs (TEAEs). TEAEs will be evaluated from first exposure to IP until the end of study visit. Adverse events that are ongoing at the end of study visit will be marked as ongoing on the AE eCRF page.

Specific TEAEs of olfactory test abnormal (measured by UPSIT) or a significant change in Quantitative Scoring Scale for Evaluation of the Nasal Mucosa (QSS-NM, as detected on nasal endoscopy) – as outlined in the Nasal Examination Manual (Appendix 3) will be recorded and the following medication stopping rules applied:

- A TEAE will be recorded for any change in UPSIT score of 5 points or more. If the change is unresolved at a repeat UPSIT 4 weeks later, study medication will be discontinued.

- A TEAE will be recorded for any QSS-NM score of ≥ 2 in any one criterion, or a total score > 7 summed from left + right upper nasal cavity scores. If the change remains unresolved at the first follow-up endoscopy 2 weeks later, study medication will be discontinued.

All spontaneously volunteered and enquired for, as well as observed, AEs will be recorded in the subject's medical records and the eCRF. Migraine headaches will be recorded separately from the AE eCRF pages; they will not be recorded as AEs but as manifestations of the underlying disease unless they are more severe than generally experienced by that subject.

The primary safety analysis will take place when all subjects have completed at least 24 weeks of treatment. Additional safety analyses will also be performed when all subjects who undergo 52 weeks of treatment have completed their treatment.

8.1 Definition of an adverse event

As stated above, for the purposes of this study, a migraine will not meet the definition of an AE.

An AE is any event, side-effect, or other untoward medical occurrence that is temporally associated with a study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events that do not meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Hospitalization for elective procedures scheduled prior to start of trial participation, or for treatment of the target disease for the study unless associated with worsening of the condition.

If there is evidence of an AE through report or observation, the Investigator or designee will evaluate further and record the following information:

- Time of onset and resolution

- Severity
- Causality/relation to IP
- Causality/relation to study procedures or participation
- Action taken regarding IP
- Outcome.

8.1.1 Severity of an adverse event

Severity of adverse events 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.

8.1.2 Causal relationship of an adverse event

The Investigator will assess the relationship between IP or study procedures/participation and the occurrence of each AE. The Investigator's assessment of the relationship of each AE to IP will be recorded in the source documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to the IP should be considered and investigated, if appropriate. The following definitions are general guidelines to help assign grade of attribution:

- Not related: The event is clearly related to other factors such as the subject's environment or clinical state, therapeutic interventions or concomitant drugs administered to the subject. This is especially so when an event occurs prior to the commencement of treatment with the study medication.
- Unlikely: The event was most likely produced by other factors such as the subject's environment or clinical state, therapeutic interventions, or a concomitant drug administered to the subject and does not follow a known response to the study medication.
- Possible: The event follows a reasonable temporal sequence from the time of study medication administration or follows a known response to the study medication but could have been produced by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.

- Probable: The event follows a reasonable temporal sequence from the time of study medication administration and follows a known response to the study medication and/or cannot be reasonably explained by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.

Events assessed as not related or unlikely related will be considered unrelated for reporting purposes, and events assessed as possibly or probably related will be assessed as related for reporting purposes

8.1.3 Action taken with investigational products

Should the Investigator need to alter the administration of the IP from the procedure described in the protocol due to the well-being and safety of the subject, then the action taken with IPs will be recorded on the AE eCRF page, as one of the following options:

- Dose Reduced
- Dose Interrupted
- Dose Withdrawn
- Not Applicable
- Unknown

8.1.4 Outcome

Outcome of an AE will be recorded on the AE eCRF as follows:

- Recovered / Resolved or attributable to other (defined) cause
- Recovering / Resolving
- Recovered / Resolved with Sequelae
- Not Recovered / Not Resolving, up to a 28-day follow-up period
- Fatal
- Unknown (or subject lost to follow-up after 4 attempts at contact over a period of 28 days).

8.2 Definition of a serious adverse event

An SAE is any untoward medical occurrence that at any dose meets any of the following criteria:

- Results in death.
- Is life-threatening. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It

does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity. The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Other situations. Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.2.1 Notification of a serious adverse event

In order to meet the requirements for expedited reporting of serious adverse events (SAEs) to applicable regulatory authorities and IRBs, all SAEs must be entered on the appropriate AE eCRF in the electronic data collection (EDC) system within 24 hours from the time the site investigational team first become aware of the event. Should the EDC system not be available, the SAE can be reported via paper SAE report form and faxed to Pharmaceutical Product Development, LLC (PPD) Pharmacovigilance (PVG). In the event of fax failure or any questions, the site investigational team should contact PPD PVG via the SAE hotline.

SAE Hotline: 800-201-8725

SAE Faxline: 888-488-9697

As further information regarding the SAE becomes available, such follow-up information should be updated in the EDC system. After review by the Medical Monitor, additional information may be requested. Any requested source documentation should be faxed to PPD PVG accordingly.

Withdrawal from the study in the event of an SAE and the therapeutic measures taken shall be at the discretion of the Investigator. A full explanation for the discontinuation from the study should be made in the subject's medical records and in the eCRF.

8.3 Clinical laboratory abnormalities and other abnormal assessments as adverse events and serious adverse events

Abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECG and vital signs) are not reported as AEs. However, those abnormal findings that are deemed clinically significant or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (and recorded as an SAE if they meet the criteria of being serious) as described previously. Clinically significant abnormal laboratory or other abnormal findings that are detected after consent or that are present at baseline and worsen after consent are to be included as AEs (and SAEs if serious).

The Investigator should exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom, or be likely to result in an evident sign or symptom in the near term, to be considered clinically significant. A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize the subject and may require intervention to prevent immediate consequences. For example, a markedly low serum glucose concentration may not be accompanied by coma or convulsions, yet be of a magnitude to require glucose administration to prevent such sequelae.

8.4 Documenting adverse events

Any AE occurrence during the study must be documented in the subject's medical records in accordance with the Investigator's normal clinical practice and on the AE page of the eCRF where applicable. Serious adverse events that occur during the study must be documented in the subject's medical record, on the AE eCRF, and on the SAE report form.

Migraine headaches will be recorded separately from the AE eCRF pages; they will not be recorded as AEs but as manifestations of the underlying disease unless they are more severe than expected for the participant's condition.

The Investigator should attempt to establish a diagnosis of the event based on the signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE (and SAE if serious) and not the individual signs/symptoms. If a diagnosis cannot be made, a syndrome may be specified in the case of several related symptoms, rather than the individual symptoms.

If a clinically significant abnormal laboratory finding or other abnormal assessment meets the definition of an AE, then the AE eCRF page must be completed as appropriate. In addition, if the abnormal assessment meets the criteria for being serious, the SAE report form must also be completed. A diagnosis (if known, or clinical signs or symptoms, if the diagnosis is unknown, rather than the clinically significant laboratory finding or abnormal assessment) should be used to complete the AE/SAE page. If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding should be recorded. If an SAE report form is completed, pertinent laboratory data should be recorded on the SAE report form, preferably with baseline values and copies of other relevant laboratory reports.

The SAE page should be completed as thoroughly as possible and signed by the Investigator before transmittal to PPD. *It is very important that the Investigator provide an assessment of the causal relationship between the event and the IP at the time of the initial report, as this is required for submissions to regulatory authorities*.

8.5 INP104 combination product technical complaints

An INP104 product technical complaint will be defined as:

- Any malfunction or deterioration in the characteristics and/or performance of INP104 as well as any inadequacy in the labeling or the instructions for use.

Documentation of an INP104 product incident will include:

- Completion of a technical complaint form and follow-up documentation.
- For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE eCRF page and an SAE report form (if meets SAE criteria) will be completed.

8.6 Regulatory authorities

The reporting of any SAEs to applicable regulatory authorities will be the responsibility of Impel in compliance with applicable country regulations.

All SAEs must be reported to the IRB by the Investigator in accordance with their reporting requirements.

8.7 Follow-up of adverse events and serious adverse events

All AEs and SAEs will be followed for 28 days after the last visit of the dosing period, until the condition resolves or stabilizes, until the event is otherwise explained, or until the subject dies or is lost to follow-up (whichever happens first). The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, it should be reported to the Sponsor immediately. The Sponsor should be provided with a copy of any post-mortem findings, including histopathology.

8.8 Pregnancy

Any pregnancy that occurs during the treatment period and at any time during the 28 days following the last dose of IP must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to PPD within 24 hours of the Investigator learning of its occurrence. The pregnancy should be followed up to determine outcome (including premature termination) and status of mother and child. The subject will be requested to provide written informed consent to enable collection of information pertaining to the outcome of the pregnancy. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as possibly related to the IP must be promptly reported to PPD.

In addition, the Investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to PPD as described above.

All pregnancy related events must be communicated by the Investigator to PPD within 24 hours of receipt of notification of an event.

8.9 Safety data review

Study progress and safety will be reviewed by the Medical Monitor and Sponsor's Medical Expert on an ongoing basis (at not less than monthly frequency) as described in the Safety and Medical Management Plan and Data Validation Manual. At a minimum, safety review will focus on adverse events (AEs) with cross reference to medical history and concomitant medication. Additional safety parameters that will be reviewed include nasal endoscopic examination grading and olfactory changes.

There will be two safety analysis time points in this study:

1) A Primary Safety Analysis will be conducted once all 300 to 340 enrolled subjects have completed (or withdrawn early from) the 24-Week Treatment Period. This will include the 26-Week visit for those subjects exiting the study after the 24-Week Treatment Period (who do not continue on into the 52-Week Treatment Period).

2) A Secondary Safety Analysis will be conducted once the subset of 80 subjects continuing into the 52-Week Treatment Period have completed (or withdrawn early from) the study through the 54-Week follow-up visit.

All subjects who receive any amount of study drug will be included in these analyses.

In addition to the routine medical monitoring safety reviews, an independent evaluation with specific attention to the nasal examination grading and olfactory changes, will be performed as part of each of the two safety analysis time points noted above. This review will be performed centrally by three independent otolaryngologist consultants to the study. A summary of relevant review findings will be provided in an expert report and included in the interim and the final clinical study report(s).

9 STUDY DURATION

The study will comprise 3 periods: screening, treatment, and safety follow-up. The screening period will occur 28 days prior to the start of treatment. The treatment period will provide for 24 weeks of treatment for all 300 to 340 enrolled subjects entering the study (to ensure at least 150 complete) and 52 weeks of treatment for approximately 80 subjects entering the 52-week treatment period to ensure 60 complete. The safety follow-up period will extend for 2 weeks after the cessation of treatment for each group of subjects. The overall study duration will be 58 weeks (+ up to a 14-day window) maximum per subject, with the majority completing 30 weeks.

All subjects will complete 9 visits, with the subjects continuing treatment through 52 weeks completing 12 visits in total.

In the event a subject discontinues the study early for any reason after Visit 2, an Early Termination Visit (see Section 7.2.4) will be performed (as per Table 7-1). The subject should also return 2 weeks after the last dose of study drug to complete the Post-Treatment Follow-up Visit procedures (see Section 7.2.5).

9.1 Subject withdrawal

In accordance with applicable regulations, a subject has the right to withdraw from the study at any time and for any reason, without prejudice to his/her future medical care.

Subjects may be withdrawn from the study for any of the following reasons:

- Subject is unable or unwilling to continue participation in the study
- Adverse event (whether or not related to IP) that precludes further participation in the study in the judgment of the investigator and/or sponsor
- Protocol noncompliance
- A male subject's partner becomes pregnant
- The investigator considers that it is in the subject's best interest for the subject not to continue participation in the study.

Subjects must be withdrawn from the study in the event that:

- A subject becomes pregnant
- Informed consent is withdrawn.

If a subject is withdrawn because of an AE, the Investigator must arrange for the subject to have appropriate follow-up care until the AE is resolved, has been attributed to another cause or has stabilized. Unresolved AEs will be followed until the last scheduled follow-up visit or until the PI and Medical Monitor determine that further follow-up is no longer indicated. In addition to AEs, other reasons for removal of subjects from the study might include, but are not limited to:

- Withdrawal of consent
- Administrative decision by the investigator or the sponsor
- Protocol deviation
- Subject noncompliance.

If a subject asks or decides to withdraw from the study, all efforts will be made to complete and report the observations, especially the listed primary and secondary objectives, as thoroughly as possible up to the date of withdrawal. The primary reason for withdrawal will be identified and recorded on the appropriate eCRF, along with the date of withdrawal.

9.2 Subject replacement

Once subjects initiate the dosing period of the study they will not be replaced if discontinued for any reason.

10 STUDY CLOSURE

The Sponsor, Investigator, and the IRB reserve the right to terminate or suspend the study at any time; however, this should be discussed between the relevant parties beforehand and the reason for such decision recorded. Should this occur, all data available will be recorded in the eCRFs. The Investigator should notify the relevant institutional IRB in writing of the study's completion or early discontinuation.

In the event of a study closure, the Sponsor and Investigator will arrange appropriate follow-up care for any subject who has an ongoing AE.

11 STUDY MONITORING AND DATA MANAGEMENT

11.1 Study monitoring

The Sponsor has appointed a qualified CRO (PPD) to manage and monitor the study so as to assure the adequate conduct of the study and to act as the contact with the investigational site. Study Monitors will be identified and will be responsible for liaison with, and for support of, investigational sites.

The Study Monitors and regulatory authority inspectors will contact and visit investigational sites for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs, essential documentation, and other pertinent data) provided that subject confidentiality is respected.

11.2 Access to study documents and personnel

The Sponsor, Sponsor's agents, CRO Study Monitors, IRB, and applicable regulatory agencies may require access to all study documents held at the investigational site, as well as access to all members of the investigational site personnel. It is expected that such access would normally be arranged by agreement with the investigational site.

11.3 Source document and data verification

The Study Monitor will visit the investigational site periodically where s/he shall:

- Meet with the Investigator and any other applicable site staff.
- Verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research.
- Review subject medical records and other study-related records needed to perform source verification of data entered into the eCRFs. The Study Monitor will raise queries for correction by the site and ensure that details of changes are recorded accordingly. The Investigator will cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved and that eCRF data entry is performed in a timely manner. The monitor will identify any data to be recorded directly into the eCRFs (i.e., no prior written or electronic record of data) and to be considered to be source data.
- Review the investigational site file and regulatory documentation.
- Collect relevant documents for use by the appointed data management group and retention by the Study Sponsor.
- Verify disposition of the IP, ensuring that IPs have been stored and handled appropriately, and have been administered correctly to eligible subjects.

11.4 Data management

All data will be recorded in individual source documents. An eCRF will be created using a validated system for recording of the required data in the study database. All eCRF information is to be filled in by site staff. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The data entered into the eCRF will be subject to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site for response. The investigator will ensure prompt resolution of data queries before the database is locked and released for statistical analysis.

12 STATISTICAL ANALYSES

A detailed SAP will be prepared for approval by the study Sponsor, will be shared with the FDA, and any changes will be incorporated prior to database lock.

There will be two safety analysis time points in this study:

1) A Primary Safety Analysis will be conducted once all 300 to 340 enrolled subjects have completed (or withdrawn early from) the 24-Week Treatment Period. This will include the 26-Week visit for those subjects exiting the study after the 24-Week Treatment Period (who do not continue on into the 52-Week Treatment Period).

2) A Secondary Safety Analysis will be conducted once the subset of 80 subjects continuing into the 52-Week Treatment Period have completed (or withdrawn early from) the study through the 54-Week follow-up visit.

12.1 Sample size calculation

Since this is an open-label safety study, the sample size calculation is not based on statistical inference (Type I error or power considerations). Approximately 300 to 340 subjects will be enrolled in the study with the goal of having at least 150 subjects complete 24 weeks of treatment; where each individual subject within these 150 subjects has an average of 2 or more migraines per 28-day period. Additionally, at least 80 subjects will be enrolled into an additional 28 weeks of treatment with the goal of having at least 60 subjects complete a total of 52 weeks of treatment, with each individual subject having an average of 2 or more migraines per 28 days period. At least 30 subjects of each sex will be enrolled in the initial 300 to 340 subjects.

12.2 Subjects to analyze

Analysis sets will include:

A 24-Week Enrolled Set which includes all subjects who sign the informed consent form and are provided IP.

A 52-Week Enrolled Set which includes all subjects who sign an extension informed consent at 24 weeks and are provided IP.

Full Safety Sets (for each of the 24-Week and 52-Week treatment periods) which will include all subjects who are enrolled and receive at least 1 dose of INP104.

Primary Safety Sets (for each of the 24-Week and 52-Week treatment periods) which will include all subjects with an average of 2 or more migraines and/or headaches treated with INP104 on average per 28 day period during the identified study periods.

12.3 Study endpoints

Please refer to sections 3.2, 3.3 and 3.4 for information on the primary, secondary and exploratory endpoints, respectively.

12.4 Exploratory efficacy analysis

All efficacy analyses are exploratory in nature with no testing and will be performed for the 24-week treatment period and 52-week treatment period on the Full and Primary Safety Set for each identified study period.

Descriptive statistics (n, mean, standard deviation, standard error, median, minimum, maximum) will be presented. For percentages, severity of symptom, MIDAS and HIT-6 scores, the 95% confidence intervals of average and change from baseline will be provided.

The components of the migraine diary (i.e., pain, nausea, photophobia, and phonophobia) are measured as ordinal variables that vary from 0 to 3 (0 being none present). During screening, the MBS of the migraine will be determined at the subject level. Type of rescue medication (e.g., ergots other than IP, triptans, acetaminophen) will also be collected in the migraine diary.

All migraine diary related efficacy endpoints will be summarized by monthly measures (i.e., per 4-week interval of baseline, week 1-4, week 5-8, etc.).

For analysis by monthly migraine measures, for each 4-week interval, number of headache and treated headache for those migraine(s) and non-migraine(s) will be summarized. Subject level percentage of symptom-free migraine and severity of each symptom at each 4-week interval are calculated as the average of all IP treated migraines within each 4-week interval. Subject level maximum severity of a symptom at each 4-week interval will be identified among all timepoints through the course of all IP treated migraine events during each 4-week interval.

Number and percentage of migraines with a need for rescue medication, number of calendar days of triptan usage and percentage of migraine for which triptan is ever used will be summarized for each 4-week interval.

Descriptive statistics (including 95% confidence interval) will be presented for the MIDAS and HIT-6 total score at baseline, each scheduled visit and EOT. These statistics will be presented based upon the observed values as well as the change from baseline. MIDAS and HIT-6 total score will also be summarized by category at the same visit as above.

12.5 Safety analysis

No formal inferential statistics will be performed on safety assessments and will be evaluated via descriptive statistics and point estimates. Safety analyses will be performed for the 24-week treatment period and for the 52-week treatment period on the Full and

Primary Safety Set for each identified study period. Summaries of the overall study period will also be provided. Safety and tolerability will be analyzed based upon the reporting of AEs, SAEs, nasal endoscopy, change in sense of smell (UPSIT), vital sign assessments, laboratory findings, and electrocardiogram parameters. Continuous safety data will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical safety data will be summarized with frequency counts and percentages.

Adverse events will be coded using the most current Medical Dictionary for Regulatory Affairs (MedDRA®) version available. A by-subject SAE and AE data listing, including verbatim term, preferred term, system organ class, treatment, severity, and relationship to IP drug, IP device and IP procedure, leading to treatment and/or study discontinuation, and leading to death will be provided. The number of subjects experiencing SAEs and/or AEs and number of SAEs/AEs will be summarized by system organ class and preferred term using frequency counts. Adverse events will also be summarized by severity, relationship to IP drug, IP device, IP procedure, leading to treatment discontinuation, study discontinuation, and death. Adverse events of olfactory test abnormal or a significant change in quantitative scoring scale of evaluation of the nasal mucosa will also be summarized. In addition, each SAE will include a narrative.

Individual nasal endoscopy evaluation results will be listed for each subject. Summaries of nasal assessments will include observed values and changes from baseline for each parameter, with any other cause noted (e.g., recurrent allergic rhinitis, etc.).

Individual sense of smell (UPSIT) results will be listed for each subject. Summaries of sense of smell will include observed values and changes from baseline for total UPSIT result.

Individual vital signs assessments will be listed for each subject. Summaries of vital signs will include descriptive statistics of observed values at each scheduled timepoint and changes from baseline for each parameter.

Changes in physical examinations will be listed for each subject and described in the text of the final report where appropriate. Number and percentage of subjects who shift from normal to abnormal/abnormal clinically significant at any post-baseline time point will be summarized.

Individual ECG results will be listed for each subject. Summaries of ECGs will include descriptive statistics of observed values and changes from baseline for each parameter. A frequency summary of ECG overall interpretation (normal, abnormal not clinically significant, and abnormal clinically significant) will be summarized at each scheduled time point.

Individual clinical laboratory results will be listed for each subject. Summaries of clinical laboratory results will include descriptive statistics at each timepoint evaluated, changes from baseline, as well as a shift table of counts of the number of values out of normal range at each scheduled time point.

Individual clinical laboratory results will be listed for each subject. Summaries of clinical laboratory results will include descriptive statistics at each timepoint evaluated, changes from baseline, as well as a shift table of counts of the number of values out of normal range at each scheduled time point. Individual time course profiles will be presented for subjects with clinical laboratory results deemed clinically significant.

Prior and concomitant medications or/and procedures collected from CRFs will be listed by subject and coded using the most current WHO drug dictionary. The number of subjects who use any prior or concomitant medication will be summarized by ATC2 level and standardized medication name using frequency counts.

12.6 Exploratory analysis

Product Acceptability Questionnaire will be summarized for the frequency of response for each question (strongly agree, agree, neutral, disagree, strongly disagree) and will be summarized at the scheduled time point. A listing for Product Acceptability Questionnaire will also be provided.

Healthcare utilization will be summarized for the overall study period by exposure adjusted event rate at baseline and post-baseline for each of the events (i.e., hospitalization, emergency room visit, urgent care visit, unplanned clinic/physician office visit, new or changed prescription for acute migraine, prescription for preventive migraine, and preventive procedures for migraines).

13 REGULATORY REQUIREMENTS

13.1 Regulatory approvals

This study will be conducted in the United States under an Investigational New Drug application. It will be the first study conducted with INP104 in the United States and, as such, the protocol will be submitted to and reviewed by the FDA prior to conducting the study. Comments from the FDA as part of preliminary reviews have been incorporated. It is anticipated that the data from this study will be significant and relevant to a subsequent New Drug Application for INP104.

13.2 Ethics committees

The investigator must obtain IRB approval to conduct the study. Prior to initiation of the study, the Sponsor must receive a copy of the communication from the IRB to the investigator indicating approval of the protocol and consent form. All changes to the protocol must be reviewed and approved by the IRB prior to implementation, except for administrative changes to correct errors or to update study personnel or contact information or where necessary to eliminate apparent immediate hazards to subjects.

13.3 Subject informed consent

The Principal Investigator (or delegated study site staff) is responsible for obtaining and documenting informed consent per GCP. Once a subject is referred for consideration in the study, the subject's history and status will be completely evaluated, and study treatment will be discussed thoroughly with the subject and the risks and hazards of the IP explained. The investigator shall seek consent only under circumstances that provide the subject sufficient opportunity to consider whether or not to participate. The information that is given to the subject shall be in language understandable to the subject. No informed consent may include any language through which the subject is made to waive or appear to waive any of their legal rights, or releases or appears to release the investigator, the Sponsor, the institution, or its agents from liability for negligence.

The subject must be able to comprehend and sign the informed consent form prior to enrollment. The subject will then receive a signed copy of the consent form.

13.4 Data protection

Subjects will be informed that data will be held on file at the investigational site and the otolaryngology site and may be viewed by study/site staff, Sponsor staff, Data Management/CRO staff, including the Study Monitor, and by auditors and/or monitors on behalf of the Sponsor and appropriate regulatory authorities. Subjects will also be informed that a study report will be prepared and may be submitted to regulatory authorities and for publication; however, subjects will be anonymous in such reports, only being identified by subject identification number, gender, and age. All subject data will be held in strict confidence.

14 ADMINISTRATIVE PROCEDURES

14.1 Liability/indemnity/insurance

The Sponsor will ensure sufficient insurance is available to enable it to indemnify and hold the Investigator(s) and relevant staff, as well as any hospital, institution, IRB or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by the IP but only to the extent that the claim is not caused by the fault or negligence of the subject or Investigator(s).

14.2 Recording of data and retention of records

All source data, clinical records and laboratory data relating to the study will be archived after the completion of the study in accordance with applicable regulatory requirements. All data will be available for retrospective review or audit.

Source documents are original documents, data, and records from which the subjects' eCRF data are obtained. These include, but are not limited to: hospital records, clinical and office charts, laboratory and pharmacy records, paper diaries, eDiaries, microfiches, radiographs, angiograms, study medication accountability logs, and correspondence. Electronic CRF entries may be considered source data if the eCRF is the repository of the original recording (i.e., there is no other written or electronic record of data). In this case, a Source Document Agreement should indicate which eCRFs are considered source documents for the study.

The Investigator and study staff are responsible for maintaining a comprehensive filing system of all study-related (essential) documentation. These include, but are not limited to: IRB correspondence, study medication accountability logs, and *curricula vitae* of all personnel participating in the study. These files must be available for inspection at any time by the Sponsor, monitor, and/or applicable regulatory authorities. All essential documentation will be retained by the institution in accordance with applicable regulatory requirements.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. If the Investigator wishes to assign the study records to another party or move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

14.3 Publication of results

Publication and reporting of results and outcomes of this trial will be accurate and honest, undertaken with integrity and transparency and in accordance with the Sponsor's Publication Policy.

Publication of results will be subjected to fair peer-review. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation.

All conflicts arising through disputes about authorship will be reviewed by the Sponsor.

Acknowledgment will be given to collaborating institutions and hospitals and other individuals and organizations providing finance or facilities. Subject confidentiality will be maintained by referring to individual subjects by their subject identification number used in the trial. In the case of no publication, information will only be released to the public and media in accordance with the Sponsor's policies.

The study protocol and results summary will be posted to https://clinicaltrials.gov/.

14.4 Disclosure and confidentiality

By signing this protocol, the Investigator agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by the Sponsor (protocol, IB, eCRFs, etc.) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the Investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

The Investigator must ensure that the subject's anonymity is also maintained. Subjects should only be identified by their initials and a subject identification number on the eCRFs and other source documents. Other study-related documents (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Compliance with Good Clinical Practice

The study will be carried out in accordance with the current version of the Declaration of Helsinki, concerning medical research in humans (recommendations guiding physicians in biomedical research involving human subjects), ICH Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2) (2015), and applicable local regulations.

15.2 Archiving and regulatory inspection

All study-related documents and records are to be retained according to applicable regulatory authority requirements after trial completion. Written agreement from the Sponsor must precede destruction of the same.

In accordance with ICH GCP, this study may be selected for audit. Inspection of site facilities (e.g., pharmacy, medication storage areas, laboratories) and review of study-related records may occur by the Sponsor, Sponsor's representative, or regulatory authority to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The Investigator, by signing this protocol, agrees to fully cooperate with any such inspection.

16 CLINICAL STUDY REPORT

A clinical study report (CSR) will be prepared with reference to ICH Guidance E3 (1995) to include:

- Details of where the study was carried out
- A description of the study methods used
- Dates of the start and completion of each period of the study
- Details of the study medication and a statement of production
- A statement confirming that the applicable IRB gave written approval for the study in accordance with local regulations
- A demographic listing for all subjects
- A list of all adverse events
- Details of any occurrences which may be of significance to the study outcome
- Details of all operations, calculations, and transformations performed on the reported data
- A SAP
- All data from any withdrawn subject not included in the statistical analysis, not including screen failures
- A scientific interpretation of the results.

The CSR will focus on the Primary Safety Analysis (see Section 12). The Secondary Safety Analysis will either be included in the primary CSR or may be presented in a supplementary or separate CSR as defined in the SAP.

The report(s) will be issued under the study Sponsor's responsibility.

Where required by the applicable regulatory requirements, an Investigator's signature will be required for the approval of the CSRs. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results. The Sponsor will also provide the Investigator with the full summary of study results.

17 SPONSOR AND INVESTIGATOR OBLIGATIONS

17.1 Protocol amendments

Neither the Investigator nor the Sponsor will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial subjects. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

17.2 Protocol deviations

A protocol deviation is any unplanned excursion from, or noncompliance with, the protocol.

All protocol deviations should be reported to the Study Monitor as soon as is reasonably practical. Important deviations that potentially affect the safety of a subject and the reason for their occurrence must be documented and reported to the relevant IRB (as per the IRB's requirements). Important protocol deviations will be summarized and listed in the clinical study report.

18 REFERENCES

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Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the Migraine Disability assessment score in a population-based sample of headache sufferers. Cephalalgia 1999; 19(2):107-114

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19 APPENDICES

19.1 Appendix 1 – List of Permitted Migraine Medications

Permitted concomitant medications include:

- Acetaminophen, when necessary (PRN)
- Aspirin – regular low dose or full dose PRN
- Ibuprofen PRN (or other NSAIDs PRN)
- Regular migraine preventative treatment (if the dose is stable and subjects have been receiving for at least 30 days before screening and still meet all entry criteria) may be continued at stable dose throughout the study.
- If headache pain does not resolve within 2 hours after treatment with IP (or if IP cannot be used due to dose limitation) then a rescue medication such as acetaminophen, an NSAID (e.g., ibuprofen), an opioid or a barbiturate containing medication may be administered (per the Investigator's instruction and normal practice).
- Other prescribed medications may be continued throughout the study at the discretion of the Investigator (unless they are excluded or prohibited – Sections 4.3 and 4.4, respectively). All such medication use should be documented.

Subjects should record their use of ALL rescue medications during every migraine they treat while on study.

If subjects attend an emergency room or other healthcare provider, they MUST disclose that they have taken study medication.

19.2 Appendix 2 – Examples of CYP3A4 Inhibitors

Strong inhibitors:

- Atazanavir
- Clarithromycin
- Darunavir
- Indinavir
- Itraconazole
- Ketoconazole
- Lopinavir
- Nefazodone
- Nelfinavir
- Ritonavir
- Saquinavir
- Telithromycin
- Tipranavir

Moderate Inhibitors:

- Amiodarone
- Amprenavir
- Conivaptan
- Delavirdine
- Diltiazem
- Erythromycin
- Fluconazole
- Fosamprenavir
- Miconazole
- Verapamil

19.3 Appendix 3 – Nasal Examination Manual

Refer to attached INP104-301 Nasal Examination Manual

19.4 Appendix 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.

19.5 Appendix 5 – 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.

To complete, please circle one answer for each question.

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

never	rarely	sometimes	very often	always

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

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

never	rarely	sometimes	very often	always

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

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

never	rarely	sometimes	very often	always

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	*Column 2*	*Column 3*	*Column 4*	*Column 5*
6 points each	*8 points each*	*10 points each*	*11 points each*	*13 points each*

To score, add points for answers in each column.

If your HIT-6 is 50 or higher: TOTAL SCORE:_____

You should share your results with your doctor. Headaches that stop you from enjoying the important things in life, like family, work, school or social activities could be migraine.

19.6 Appendix 6 – Product Acceptability Questionnaire

The following is an example of the Questions.

Check the box that most closely matches your experience with the investigational product:

1. The study drug is easy to use.

- Strongly Agree
- Agree
- Neutral
- Disagree
- Strongly Disagree

2. The investigational product works faster compared to my previous prescription migraine medication(s).

- Strongly Agree
- Agree
- Neutral
- Disagree
- Strongly Disagree

3. The investigational product keeps my migraine from coming back for a longer time than previous prescription migraine medications I've used.

- Strongly Agree
- Agree
- Neutral
- Disagree
- Strongly Disagree

4. With the investigational product I can return to normal activities faster (school/work/leisure activities) compared to my previous prescription migraine medication(s).

- Strongly Agree
- Agree
- Neutral
- Disagree
- Strongly Disagree

5. Compared to previous migraine prescription medications, the investigational product more consistently relieves each one of my migraine headaches.

- Strongly Agree
- Agree
- Neutral
- Disagree
- Strongly Disagree

6. The investigational product was very convenient to carry with me and use outside of my home.

- Strongly Agree
- Agree
- Neutral
- Disagree
- Strongly Disagree
- I never used it outside my home

7. Insertion of this device into my nose caused discomfort or hurt compared to other nasal migraine medications I've used.

- Strongly Agree
- Agree
- Neutral
- Disagree
- Strongly Disagree
- I have never used a nasal migraine medication before this study

8. The investigational product produced a bad taste compared to other nasal migraine medications.

- Strongly Agree
- Agree
- Neutral
- Disagree
- Strongly Disagree
- I have never used a nasal migraine medication before this study

9. If the INP104 Product were commercially available, I would request a prescription for it from my physician.

- Strongly Agree
- Agree
- Neutral
- Disagree
- Strongly Disagree

Add any additional comments on your experience with the investigational product: