CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213436Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	213436
Priority or Standard	Standard
Submit Date(s)	November 6, 2020
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Division/Office	Division of Neurology 2/Office of New Drugs
Reviewer Name(s)	Ryan Kau, MD
Review Completion Date	August 30, 2021
Established/Proper Name	Dihydroergotamine mesylate and Precision Olfactory Delivery device
(Proposed) Trade Name	Trudhesa
Applicant	Impel NeuroPharma, Incorporated
Dosage Form(s)	Nasal Spray
Applicant Proposed Dosing Regimen(s)	Single dose of 1.45 mg nasal spray; Maximum dose in 24-hours period of 2.90 mg; Maximum dose in 7-day period of 4.35 mg
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine with or without aura
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Acute treatment of migraine with or without aura in adults

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

INP104, is a combination product consisting of dihydroergotamine (DHE) and what the applicant refers to as I123 Precision Olfactory Delivery (POD) device. DHE belongs to a class of drugs called ergots and is a 5-hydroxytryptamine $(HT)_{1D\alpha}$ and $5\text{-}HT_{1D\beta}$ receptor agonist. The applicant plans to market INP104 for the acute treatment of migraine with and without aura in adults. The DHE drug component is identical to the DHE formulation used in the commercially available Migranal nasal spray product. The applicant relies on the Migranal and D.H.E. 45 injection to support the efficacy and systemic safety of INP104, respectively. The I123 POD device component is designed to administer DHE into the upper nasal space using hydrofluoroalkane-134a (HFA) gas as a propellant. The proposed dosing regimen is a single total dose of 1.45 mg DHE nasal spray divided over two sprays (one spray to each nostril), with a maximum of two doses (total of 2.90 mg) over 24 hours, and a maximum of three doses (total of 4.35 mg) over 7 days.

DHE is a drug product that is FDA-approved as a nasal spray for the acute treatment of migraine headaches with and without aura, and as an injection for the acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes. Please refer to Section 3.1 of this review for details of these applications.

1.2. Conclusions on the Substantial Evidence of Effectiveness

As a 505(b)(2) application, the effectiveness of INP104 (Trudhesa) is based on comparing DHE bioavailability (BA) to listed drugs (LDs). A BA study was used to bridge efficacy of INP104 nasal spray to the LD, Migranal, for which efficacy has been established for the acute treatment of migraine (NDA 020148). The Office of Clinical Pharmacology (OCP) has reviewed the results of the pivotal bioavailability study (INP104-101), and found that the study showed that the upper bound of the 90% confidence interval for the geometric mean ratios for AUC ($AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$) and C_{max} of DHE between INP104 nasal spray and D.H.E 45 was ≤ 125%, suggesting that it is appropriate to bridge safety information from D.H.E 45; and the lower bound of the 90% confidence interval for the geometric mean ratios for AUC ($AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$) and C_{max} of DHE between INP104 nasal spray and Migranal was ≥ 80%, suggesting that it is appropriate to bridge efficacy information from Migranal. In summary, OCP concludes that these results demonstrate that an adequate PK bridge between INP104 and the LDs has been established (i.e., the exposures from INP104 is bracketed by those from the two LDs), allowing the applicant to rely on the safety and efficacy information, as appropriate, from the respective LDs.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

INP104 is a combination product consisting of dihydroergotamine (DHE) and what the applicant refers to as I123 POD device. INP104 is to be used for the acute treatment of migraine with and without aura in adults. DHE belongs to a class of drugs called ergots. INP104 is administered as a single total dose of 1.45 mg INP104 nasal spray divided over two sprays (one to each nostril). The I123 POD device is designed to apply DHE higher in the nasal cavity than typical nasal spray devices (although any clinical advantages to such administration have not been established).

Migraine is a common, chronic, neurologic disorder that can be a serious and a potentially disabling condition affecting patient's quality of life. The severity and frequency can vary, with patients typically experiencing recurrent, moderate to severe headaches. There are multiple FDA-approved therapies for acute treatment of migraines such as triptans, ergots, calcitonin gene-related peptide (CGRP) receptor antagonists, and NSAIDs. INP104 may offer a practical advantage to patients by allowing for a complete single dose to be administered at one time, instead of over two separate administrations separated by 15 minutes as is required by the currently approved DHE nasal spray.

The applicant's 505(b)(2) application includes a bioavailability study (INP104-101) to bridge the efficacy and safety of INP104 to Migranal nasal spray and D.H.E. 45 injection, respectively. The Office of Clinical Pharmacology (OCP) has reviewed the results of the pivotal bioavailability study and concluded that the study demonstrated that it is appropriate to bridge safety and efficacy information of INP104 from D.H.E. 45 and Migranal, respectively. The applicant also submitted an open-label long-term safety study (INP104-301) to evaluate local toxicity.

DHE has been marketed in the United States since 1946 and has a well-established safety profile. In the postmarketing setting, INP104 is expected to have the same safety profile as other approved DHE products, except for possibly local adverse reactions given that INP104 is to be applied higher in the nasal cavity compared to a typical nasal spray.

The INP104 labeling and routine postmarketing surveillance will address INP104 safety issues. The INP104 label will contain both the well-characterized safety profile of D.H.E. 45 as well as the local toxicity safety data of INP104 and Migranal. In study INP104-301 the most common associated local irritation adverse events were nasopharyngitis, nasal congestion, nasal discomfort, and product taste abnormal.

Based on the INP104 bioavailability study results, prior approval of other DHE products, well-characterized safety profile of DHE, and review of the local toxicity safety data from study INP104-301, the overall benefit-risk assessment of INP104 is unchanged from previously FDA-approved DHE products.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Migraine is a common, chronic, neurologic disorder. • Migraine is characterized by recurrent, moderate to severe headaches. • Migraine attacks typically are unilateral headaches associated with other symptoms, such as nausea, vomiting, phonophobia, or photophobia. • Minor physical activity can exacerbate headaches, which may last from 4 to 72 hours. • A migraine with aura is typically characterized by symptoms of visual, sensory, language, or brainstem dysfunction associated disturbances lasting between 5-60 minutes before onset of headache.	Migraine significantly affects patients' ability to perform daily activities. Migraine can be a serious and potentially disabling condition affecting the patient's quality of life.
Current Treatment Options	• There are multiple FDA-approved therapies for acute treatment of migraines such as triptans, ergots, calcitonin gene-related peptide (CGRP) receptor antagonists, and NSAIDs.	A DHE nasal spray formulation that allows for a single dose to be administered at one time (with one spray to each nostril) may offer a practical advantage over the current dosing of Migranal, in which a single dose is two sprays (one spray in each nostril) followed by a 15-minute waiting period then another two sprays

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		(one spray in each nostril).
Benefit	• It can be concluded that INP104 1.45 mg nasal spray would have a similar benefit as Migranal in adult patients for treating acute migraine, since efficacy of INP104 has been bridged from Migranal.	INP104 has established efficacy through reliance on Migranal. The efficacy of the LD (Migranal) for acute treatment of migraines has been demonstrated.
Risk and Risk Management	The safety profile of INP104 can be expected to be consistent with the approved formulations of DHE and is supported by reliance on D.H.E. 45 Injection as the LD to support safety. In study INP104-301 the most common associated local irritation adverse events were nasopharyngitis, nasal congestion, nasal discomfort, and product taste abnormal.	INP 104 has established safety through reliance on D.H.E. 45 Injection and local toxicity data. INP104 labeling and routine postmarketing surveillance will address INP104 safety issues. INP104 labeling will contain both the well-characterized safety profile of D.H.E. 45 Injection as well as the local toxicity safety data of INP104 and Migranal.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
x	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Migraine is a common, chronic, neurologic disorder that can be a serious and potentially disabling condition affecting the patient's quality of life. The severity and frequency can vary, with patients typically experiencing recurrent, moderate to severe headaches. In the United States, approximately 21% of women and 10.7% of men have migraine headaches (Burch 2018), and many of migraine patients report reduced work or school productivity. The prevalence of migraine is highest between the ages of 25 and 55 years, then decreases with age (Dodick, 2018). A migraine aura may occur prior to or at onset of headache and may occur in the absence of pain. Patients may have aura lasting minutes, of unilateral reversible visual, sensory, or other central nervous system symptoms one or two days prior to onset of the headache.

The International Headache Society (IHS) has established the International Classification for Headache Disorders (ICHD-3) which include the diagnostic criteria for migraine with and without aura. Per the ICHD-3 definition, a migraine is a recurrent headache disorder presenting with episodes lasting 4-72 hours. The headaches should have two of the four characteristics of unilateral, pulsating, moderate or severe intensity, or aggravated by routine physical activity. In addition, the headache should have nausea and/or vomiting, or photophobia and phonophobia. Lastly the symptoms are not better accounted for by another ICHD-3 diagnosis.

2.2. Analysis of Current Treatment Options

There are multiple FDA-approved and off-label therapies for acute treatment of migraines. Options for treatment of acute migraines include drugs such as triptans, ergots, calcitonin gene-related peptide (CGRP) receptor antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen and ibuprofen combination. Triptan and ergot usage can be limited due to restriction in patients with cardiovascular disease. DHE can be administered by nasal spray, subcutaneous injection, intramuscular injection, or intravenous infusion. Migranal nasal spray is labeled for administration of one spray in each nostril followed by another one spray in each nostril 15 minutes later, for a total dosage of four sprays (2mg).

There are multiple options for the acute treatment of migraine, however safety and tolerability may limit usage of current FDA-approved treatments.

Table 1 Summary of Acute Treatment for Migraine*

Product (s) Name	Year of Approval for Migraine	Route	Important Safety and Tolerability Issues	Other Comments (for example, subgroups addressed)
FDA Approved Treatments				
ERGOTS				
Dihydroergotamine (DHE) Nasal Spray 2 mg	1997	Intranasal	CYP3A4 inhibitor interaction;	

			contraindicated with cardiovascular disease; fibrotic complications	
DHE 1 mg injection	1946	Sub-cutaneous, Intravenous, and intramuscular	CYP3A4 inhibitor interaction; contraindicated with cardiovascular disease; fibrotic complications	
Ergotamine 2 mg	1982	Sublingual		
Ergotamine/caffeine (Oral 1mg/100mg, Rectal 2 mg/100mg)	1948	Oral and Rectal		
TRIPTANS				
Almotriptan 12.5 mg	2001	Oral Tablet	Contraindicated in patients with coronary artery disease, coronary artery vasospasm, conduction pathway disorders, cerebrovascular disease, hemiplegic or basilar migraine, peripheral vascular disease, ischemic bowel disease or uncontrolled hypertension; Warnings/precautions in patients with history of myocardial ischemia, arrhythmias, cerebral hemorrhage, subarachnoid hemorrhage, or stroke	Indicated for patients age 12 to 17 years old
Eletriptan 20, 40 mg	2002	Oral Tablet		Interacts with CYP3A4 inhibitors
Frovatriptan 2.5 mg	2001	Oral Tablet		
Naratriptan 1, 2.5 mg	1998	Oral Tablet		
Rizatriptan 5, 10 mg	1998	Oral Tablet		Indicated for patients age 6 to 17 years old
Sumatriptan Oral 25, 50, 100mg	1992	Oral Tablet		
Sumatriptan Nasal Spray 10, 20 mg		Intranasal		
Sumatriptan Nasal Powder 22 mg	2016	Intranasal		
Sumatriptan SC 4, 6 mg	2009	Sub-cutaneous		
Zolmitriptan NS 2.5, 5 mg	2015	Intranasal		Indicated for patients 12 years of age or older
Zolmitriptan ZMT 1.25, 2.5, 5 mg	2001	Oral Disintegrating tablet		
Zolmitriptan Oral 2.5, 5 mg	1997	Oral Tablet		
Sumatriptan/naproxen 85/500 mg (NSAID included)	2008	Oral Tablet		Indicated for patients 12 years and older; Cardiovascular risk, increased risk of bleeding due to naproxen component
NSAIDS				
Diclofenac (Cambia) 50 mg	2009	Oral (Packet)	Cardiovascular risk for thrombotic events, myocardial infarction, and stroke; gastrointestinal	

			adverse events, especially in elderly	
Celecoxib oral solution (Elyxyb)	2020	Oral Solution	Cardiovascular risk for thrombotic events, myocardial infarction, and stroke; gastrointestinal adverse events, especially in elderly, dysgeusia	
5-HT1F receptor agonists				
Lasmiditan	2019	Oral	Driving impairment for up to 8 hours; May lower heart rate; Adverse events include dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, muscle weakness;	
CGRP antagonist				
Ubrogepant 50 mg, 100 mg	2019	Oral	Nausea, somnolence, dry mouth	Interacts with CYP3A4 Inhibitors/inducers; substrate of BCRP and P-gp efflux transporters
Rimegepant 75 mg	2020	Oral	Nausea	Interacts with CYP3A4 Inhibitors/inducers; inhibitors of BCRP and P-gp efflux transporters
Devices				
GammaCore device	2017	Device		
Cerena device	2013	Device	Contraindicated in patients with magnetic metals in head, neck or upper body, or pacemakers, or other implanted devices	
Cefaly ACUTE device	2017	Device	Contraindicated with recent trauma to skull/face or with skin conditions/rashes	
Nonprescription, FDA approved				
NSAIDs (ibuprofen)	2000 (Advil Migraine)	Oral Tablet, Capsule	Gastrointestinal toxicity, bleeding complications	Advil Migraine is a nonprescription drug indicated for the treatment of migraine.

Acetaminophen/aspirin/caffeine	1998 (Excedrin Migraine)	Tablet	Overuse, see effects for individual categories	Excedrin Migraine is a nonprescription drug indicated for the temporary relief of mild to moderate pain associated with migraine headache.

*Modified from Dr. Viveca Livezy's clinical review of NDA 212157.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

DHE, initially marketed as D.H.E. 45, received marketing authorization for subcutaneous, intramuscular, and intravenous administration for the acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes, on April 12, 1946, (NDA 005929). On December 8, 1997, Migranal (NDA 020148), a DHE nasal spray, received marketing authorization for acute treatment of migraine headaches with or without aura. A boxed warning was added on June 29, 2001 to both D.H.E. 45 and Migranal labels regarding the risk of serious and/or life-threatening peripheral ischemia associated with the coadministration of DHE with potent CYP3A4 inhibitors, due to CYP3A4 inhibition elevating serum levels of DHE. A warning describing the risk of cardiac valvular fibrosis was also added.

3.2. Summary of Presubmission/Submission Regulatory Activity

The investigational new drug (IND) application 130133 was opened for INP104 on April 26, 2018, to conduct studies to evaluate INP104 for the acute treatment of migraine. At that time the applicant established that they planned to demonstrate efficacy and safety of INP104 by bridging to Migranal nasal spray, and to D.H.E. 45, respectively. On May 11, 2018, a "May Proceed" letter was issued.

The device component of INP104, is a novel nasal spray device that applies the drug higher in the nasal cavity than a typical spray, such as the one used with Migranal. Therefore, the Division identified local toxicity and smell preservation as areas of special interest that needed to be addressed in the safety evaluation of INP104. At the Pre-IND meeting, on May 12, 2016, the Division recommended that the applicant "conduct a long-term safety study to evaluate local toxicity of DHE on the olfactory and nasal epithelia, including long-term effects on the sense of smell. At a minimum, [the applicant] will need to provide local toxicity data on at least 150 patients, treating on average a minimum of two migraine attacks per month for 6 months, and 50 patients up to one year."

In addition, the Division determined that the Pediatric Research Equity Act (PREA) was triggered due to the proposed dosing regimen being a new dosing regimen, and the applicant submitted an Initial Pediatric Study plan and was issued an agreement letter on November 26, 2019 based on its plan for a waiver of studies for children 0 to <6 years of age and a deferral for pediatric clinical studies in patients 6 to <18 years of age until additional adult safety data is evaluated.

At the Pre-NDA meeting on, July 16, 2020, the Division informed the applicant that although the single dose of 1.45 mg intranasal (IN) DHE divided into 1 spray in each nostril, in a 24-hour period, appeared acceptable based on the comparative bioavailability study results, the applicant should provide justification or safety information to support the administration of a second or third dose in the NDA application.

At the Pre-NDA meeting the Division informed the applicant that the proposed safety package appeared to be acceptable with final determination to be made at the time of filing.

At the Pre-NDA meeting, the applicant proposed that the labeling for INP104 should not include (b) (4) In response the Division, stated that the applicant would need to provide detailed data demonstrating (b) (4)

Summary of dates for regulatory interactions:
Pre-IND meeting: May 12, 2016
Initial IND: May 11, 2018
Pre-NDA meeting: July 16, 2020
NDA filing: November 6, 2020

3.3. Foreign Regulatory Actions and Marketing History

This product is not currently marketed in any foreign country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No inspections by OSI are required. In addition, the Office of Study Integrity and Surveillance

(OSIS) has declined to inspect the site. Please refer to a memo from Dr. Folaremi Adeyemo on January 27, 2021 for further details.

4.2. Product Quality

Please refer to the Chemistry, Manufacturing, and Controls review by the Office of Product Quality (OPQ) for further details.

4.3. Clinical Microbiology

N/A

4.4. Nonclinical Pharmacology/Toxicology

The applicant is relying on the FDA's findings of safety for D.H.E. 45. Please refer to the review by Dr. Edmund Nesti, nonclinical reviewer.

4.5. Clinical Pharmacology

DHE belongs to a class of drugs called ergots and its therapeutic effect is thought to be due to its high affinity binding as an agonist at 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors. Although the exact mechanism of DHE is unknown, DHE is an agonist to serotonin receptor, induces vasoconstriction of the intracranial blood vessels, and interacts with dopamine and adrenergic receptors, centrally.

The applicant has conducted a Phase 1, 3-period, 3-way, 6-sequence, randomized, open-label, single-dose, crossover, comparative bioavailability bridging study. The applicant is relying on the FDA's findings of efficacy and safety for Migranal and D.H.E. 45, respectively. The Office of Clinical Pharmacology (OCP) found that the results from Study INP104-101 "showed that the upper bound of the 90% confidence interval for the geometric mean ratios for AUC ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) and C_{max} of DHE between INP104 nasal spray and D.H.E 45 was ≤ 125%, suggesting that it is appropriate to bridge safety information from D.H.E 45; and the lower bound of the 90% confidence interval for the geometric mean ratios for AUC ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) and C_{max} of DHE between INP104 nasal spray and Migranal was ≥ 80%, suggesting that it is appropriate to bridge efficacy information from Migranal." Please refer to the OCP review by Dr. Xiaohan Cai.

4.6. Devices and Companion Diagnostic Issues

INP104 is a single-use, metered dose nasal DHE combination product consisting of DHE drug constituent in a vial and the I123 POD device. The I123 POD device uses HFA gas as the propellant to apply the DHE into the superior nasal cavity. It allows administration of INP104 to be used without requiring coordinated sniffing. Please refer to the review from CDRH by device

reviewer, Ms. Michaela Schulman.

4.7. Consumer Study Reviews

N/A

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 Clinical Trials Relevant to NDA 213436

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety							
INP104-301	Open-label, 24- or 52-week safety study	INP104 One spray per nostril (1.45 mg total nasal DHE); maximum of 2 doses per 24-hour period and maximum of 3 doses per 7-day period	Number of patients with serious and nonserious TEAEs Change in nasal mucosa (with nasal endoscopy) Change in olfactory function	24 weeks or 52 weeks	360 enrolled; 354 exposed to one or more doses	Adult patient with migraine headache	38 sites/United States (US)
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
INP104-101-	3-period, 6 sequence, 3-way, randomized, open-label, single-dose, crossover comparative BA study.	INP104 One spray per nostril (1.45 mg total nasal DHE); Nasal D.H.E. 45 Injection 1 mg DHE (1-min infusion of 1 mL); IV Migranal nasal spray	Analysis of dihydroergotamine PK after a single dose of INP104, D.H.E. 45, and Migranal including plasma C_{max}, T_{max}, $AUC_{0\text{-}last}$, kel, $t_{1/2}$, $AUC_{0\text{-}inf}$, and CL/F (CL for IV	22 days	36	Healthy Adults	1 site/US

		Two sprays to each nostril followed by a 15-min wait, and then 2 additional sprays per nostril (2 mg total); Nasal	administration).				
INP104-IAA-2009-	Human factors validation study	INP104 in tertiary packaging including instructions for use (IFU), with an empty drug vial (representative of the DHE vial). No drug product was administered.	Validation of the summative protocol for simulated-use and knowledge-task human factors	1 hour	30; 15 with previous nasal spray experience including 5 with Migranal experience	Adult patients with migraine headache	1 site/US

Note: Throughout this review I will used refer to study INP104-301 as "301," INP104-101 as "101," and INP104-IAA-2009 as "IAA-2009."

5.2. Review Strategy

The efficacy and safety of INP104 are established through reliance on the LDs. Please refer to the OCP review for details of their conclusions in this regard. The approach to this review is to evaluate the safety data from this development program with particular attention to the local toxicity with this product. Please refer to Section 7.1 for additional details.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. INP104-101

6.1.1. Study Design

Overview and Objective

This study is a bioavailability study to bridge INP104 efficacy to Migranal nasal spray and safety to D.H.E. 45. Please refer to the clinical pharmacology review by Dr. Xiaohan Cai.

7. Review of Safety

7.1. Safety Review Approach

The following safety review includes studies 101 and 301. Study 101 was a 3-period, 6 sequence, 3-way, randomized, open-label, single-dose, crossover comparative bioavailability study. Subjects were given a single dose of either 1.45 mg intranasal INP104, 1 mg IV D.H.E. 45, or 2 mg intranasal Migranal over three periods. For each period a different drug was given in one of six sequences. There were no nasal specific exams in this study.

Study 301 was an open-label, single-group assignment, long-term safety and tolerability study lasting 24 week or 52 weeks. Adult migraine patients were to self-administer one spray in each nostril of INP104 when the patient experienced a recognizable migraine. No more than 2 doses were to be taken in a 24-hour period and no more than 3 doses were to be taken in a 7-day period. There was no stated minimum time interval needed before taking a second dose when administered within 24 hours. Patients who enrolled would complete at least a 24-week treatment period, with a subset continuing treatment to 52 weeks. To evaluate local toxicity, nasal endoscopy, and the University of Pennsylvania Smell Identification Test (UPSIT) (for

further details regarding UPSIT refer to section 7.4.9) were utilized. Nasal endoscopy was performed at screening, week 4, week 8, week 12, and week 24. The UPSIT was administered at screening, baseline, week 12, and week 24. If patients participated in the additional 28-week portion of the trial the UPSIT and nasal endoscopy would be completed at weeks 36 and 52. If there was any clinically significant change on nasal endoscopy a repeat nasal endoscopy were completed at 2-week intervals until resolved or trial period completed. If during the study there was a reduction in the UPSIT score of ≥5 point, INP104 was to be stopped and 4 weeks later another UPSIT would be administered, with continued scheduled visits until olfaction returns or study participation is completed.

DHE has an established safety profile as both an injection, as well as a nasal spray. INP104 is a drug-device combination product, using a new device, referred to by the applicant as a POD device, which is to deliver the same DHE formulation as Migranal, but higher in the nasal cavity compared to typical nasal spray devices, such as the one used with Migranal. Therefore, the safety review will focus on the local toxicity of INP104and focus on study 301.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

Table 3 Studies 101 and 301 - Safety Population

Clinical Trial Groups	INP104 (n=385)	Migranal Nasal Spray (n=34)	D.H.E. 45 Injection (n=32)
Study 101 Open-label crossover	31	34	32
Study 301 Open-label long-term safety At least one INP104 dose	354	N/A	N/A
Study 301 Open-label long-term safety ≥2 INP104 doses on average per 28-day for 24 weeks	185	N/A	N/A
Study 301 Open-label long-term safety ≥2 INP104 doses on average per 28-day period for 52 weeks	55	N/A	N/A
At least one dose of INP104 (Safety Set)	385	N/A	N/A

At the Pre-IND meeting, the Division recommended that the applicant provide safety data for 150 and 50 evaluable patients who treated an average of two migraine attacks a month with

INP104, for 6 and 12 months, respectively. The 12-month data would be required if a safety signal that requires further evaluation and longer monitoring is seen in the 6-month data. The applicant prospectively planned to administer INP104 to patients for 12 months even if there was no safety signal. In study 301, of the 354 patients enrolled, 185 patients and 55 patients treated an average of ≥2 migraines a month for 24 and 52 weeks, respectively, therefore meeting the requirements set by the Division for a long-term safety database to evaluate local toxicity. 354 patients administered at least one dose of INP104.

7.2.2. Relevant characteristics of the safety population:

Migraine is more prevalent in woman than men at a ratio of approximately 2:1. In study 301 the ratio of women to men is 6:1. Therefore, the demographic characteristics of the long-term safety study 301, are not entirely representative of the intended treatment population. However, there are enough male patients in this open-label trial to provide adequate safety information.

Table 4 Summary of Demographic Characteristics for Study 301

Demographic Parameters	**INP104** **Study 301** N=354 n (%)
Sex	
Male	50 (14.1%)
Female	304 (85.9%)
Age	
Mean years (SD)	41.2 (11.1)
Median	40.5
Min, Max	18, 66
Race	
American Indian or Alaska Native	3 (0.9%)
Asian	3 (0.9%)
Black	79 (22.3%)
Native Hawaiian or Pacific Islander	1 (0.3%)
White	266 (75.1%)
Other	2 (0.6%)
Weight (kg)	
Mean (SD)	84.3 (21.0)

This table was created by the reviewer using ADBL where FSA01FL=Y

7.2.3. Adequacy of the safety database:

The applicant has provided safety data of 185 patients who have treated an average of ≥2 migraines a month with INP104 for 24 weeks and 55 patients who have treated an average of ≥2 migraines a month with INP104 for 52 weeks. This meets the recommendation of data for 150 patients for 6 months and 50 patients for 12 months and would be adequate to provide sufficient safety data to evaluate the local toxicity of INP104.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

There were no concerns regarding the data quality and integrity.

7.3.2. Categorization of Adverse Events

Applicant's Definitions of AEs, SAEs, and TEAEs

All AEs from the time of consent until completion of the last study visit were reported. An AE was any event, side-effect, or other untoward medical occurrence that was temporally associated with a study intervention, irrespective if the AE is considered related to the study intervention.

SAEs from the time of consent until completion of the last study visit were reported in all patients irrespective if they were enrolled or not enrolled.

An SAE was any untoward medical occurrence that at any dose met any of the following criteria:

- Death
- Life-threatening
- Required inpatient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly/birth defect
- Other situations where medical or scientific judgment was exercised to decide

A TEAE was defined as an AE that started after the first dose of IP or an existing AE that worsened after the first dose of IP. TEAEs were evaluated from the first dose of IP until the end-of-study visit.

Process of Recording, Coding, and Categorizing AEs

If there was evidence of an AE through report or observation, the investigator or designee evaluated further and recorded the time of onset, resolution, severity, causality/relation to IP, causality/relation to study procedures or participation, action taken regarding IP, other action taken, and outcome.

All AEs that were spontaneously reported, obtained via inquiry, or observed were recorded in the patient's medical records and the eCRF. Adverse events, medical history, and concomitant procedures were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

Assessment of the Applicant's Verbatim Terms and Coding
The applicant provided verbatim terms and translated them to preferred terms. I reviewed all AEs in the ADAE dataset for studies 101 and 301 to see if recoding or adding terms was needed. Overall, the coding appeared acceptable.

AEs of interest
The following AEs were considered events of special interest: local toxicity AEs and change in smell.

Nasal related AEs were defined as AEs associated with the nose in any way and were identified using a custom MedDRA query list generated through an iterative process.

7.3.3. Routine Clinical Tests

For study 301 the safety assessments included nasal endoscopy, physical examination, UPSIT, labs, urinalysis, urine pregnancy test, ECG, medication review, and adverse event review. Vital signs, urine pregnancy tests, medication review, and AE review occurred at each visit, which included monthly visits and a 26-week follow-up for patients in the 24-week treatment period, and at 36, 42, 52, 54 weeks for the patients who participated in the 52-week treatment period.

ECGs were completed at baseline and either at the 24-week, 52 week, or end of treatment period visits.

7.4. Safety Results

7.4.1. Deaths

There were no deaths reported in the safety database for this application.

7.4.2. Serious Adverse Events

Study 301: There were 10 SAEs reported by 7 patients: spontaneous abortion, status migranosis, ovarian mass, pulmonary embolism, visual impairment, clavicle fracture, rib fracture, intestinal obstruction. The only SAE to occur in two patients was spontaneous abortion. One patient experienced intestinal obstruction twice separated by 7 days of resolution from the first incident. There were no reported SAEs related to local toxicity.

The following are select narratives for patients who experienced a SAE:

Spontaneous abortion

A 37-year-old female patient with a positive serum pregnancy test 34 days ((b) (6)) after her second and last dose of INP104, presented with a threatened abortion on (b) (6) . Pelvic ultrasound demonstrated slow fetal heart tones, two areas with chorioangioma, and an ovarian cyst. The patient had a negative screening serum pregnancy test and a negative urine pregnancy test 27 days prior to the positive serum pregnancy test. Her last menstrual period was on (b) (6) with the first dose and second dose of INP104 administered 18 days prior and 9 days after, respectively. The patient was scheduled for a 1-week follow-up with recommendation of dilation and curettage. The patient experienced a spontaneous abortion on (b) (6), 49 days after last investigational product dose, and subsequently underwent a dilation and curettage. The chromosome analysis revealed a normal karyotype 46, XX (female). The investigator and the applicant assessed the event to be not related to the investigational product or study procedures.

A 45-year-old female patient taking an oral contraceptive and a negative serum pregnancy test at screening presented with a spontaneous abortion one day after administrating their 25th INP104 dose on (b) (6). Her 25th dose was her 4th dose since her last menstrual period. Three days prior she had spotting and assumed she was having her period. The patient then experienced extreme cramping and passed blood clots which was suspected to be the onset of a spontaneous abortion. She did not call her obstetrician/gynecologist because the bleeding stopped. On (b) (6), at the week 42 visit, a urine pregnancy test was positive, and the investigational product was discontinued. An ultrasound demonstrated mildly thickened endometrium consistent with a missed pregnancy and the patient underwent dilation and curettage. The investigator and applicant assessed the event to be not related to the investigational product or study procedures.

Reviewer comments: The first patient described had her last dose of the investigational product 36 days prior to the diagnosis of the AE. Based on her last menstrual period, only the second and last dose could have been given to her during her pregnancy. However, the patient was unlikely to be pregnant during administration of the last dose since it was only 7 days after her last menstrual period. Although the investigational product cannot be completely ruled out as related to the spontaneous abortion, I believe it is unlikely.

The second patient administered her 25th dose of the investigational product one day before diagnosis of spontaneous abortion. She had also received 3 other doses since her last menstrual period. Given the proximity to doses of the investigational product and the onset of symptoms, the relationship of the event to the study drug administration cannot be ruled out.

The LD label states that DHE may cause fetal harm when administered to a pregnant woman. It notes DHE's oxytocic properties and notes that no adequate studies of DHE in human pregnancy have occurred. It also states that developmental toxicity has been demonstrated in animal

models. DHE nasal spray was also noted to cause decreased fetal body weights in rats and delayed fetal skeletal ossification in rats and rabbits. I believe that the first spontaneous abortion described is unlikely related to the investigational product, while the second described spontaneous abortion is possibly related to the investigational product. Labeling will describe the potential risks of use during pregnancy, which are also described in the D.H.E. 45 prescribing information.

Pulmonary embolism and visual impairment

A 52-year-old female patient presented with moderate influenza 15 days after the 11th dose of INP104, which progressed to bronchitis, and was later diagnosed with a pulmonary embolism. The influenza was initially treated with oseltamivir. After, the symptoms worsened, she was treated with amoxicillin for severe bronchitis. Four days after the 12th and last dose of INP104 her symptoms were not improved and a computed tomography (CT) scan of the chest demonstrated findings consistent with bronchiolitis that involved the right upper lobe and subtle findings for a tiny thrombus in the descending left pulmonary artery, which could have been a chronic thrombus. The patient was diagnosed with a pulmonary embolism, which was considered secondary to unresolved bronchitis. The investigator noted that the patient was very active and healthy and did not smoke, but she did have a family history of blood clots. The patient was discharged from the hospital after 4 days and the pulmonary embolism event was considered resolve. No action was taken with the investigational product. The investigator attributed the pulmonary embolism to prolonged infection, which continued for a month and did not respond to antibiotics.

Three days after discharge and 11 days after self-administrating the 12th and last dose of INP104, the patient experienced visual impairment of dark shadows around a horizon-type image. She was hospitalized to evaluate for stroke, which was eliminated as a diagnosis and event resolved after 20 minutes. The patient was discharged the next day and the visual impairment was considered resolved. The investigator and applicant assessed the event of visual impairment to be not related to the investigational product or study procedures.

Reviewer comments: The SAE of pulmonary embolism occurred 15 days after a dose of INP104 in a setting of an influenza diagnosis. Therefore, it is unlikely related to the INP104.

The transient visual impairment occurred 11 days after a dose of INP104. Stroke was ruled out and the symptoms resolved. This SAE is unlikely related to INP104.

Intestinal obstruction

A 49-year-old female with a history of recurrent intestinal obstruction, irritable bowel syndrome, megacolon, and colectomy, presented with two episodes of small bowel obstruction, 3 days after self-administration of the 20th dose of INP104. A CT scan demonstrated small bowel obstruction and the patient was diagnosed with a moderate SAE of

intestinal obstruction and was hospitalized. The patient was treated and received a peripherally inserted central catheter for total parenteral nutrition and eventually started on a soft diet. Her laboratory tests normalized, an abdominal X-ray showed improvement, and the patient declined surgery. The patient was discharged and on (b) (6) the event was considered resolved. No action was taken with the investigational product in response to the event and the patient continued in the study.

On (b) (6), the patient returned to the emergency room with abdominal pain (19 days after the patient's 20th dose of INP104). The next day, the patient was diagnosed with a severe SAE, which was a recurrence of the intestinal obstruction and was hospitalized. On (b) (6), the patient had laparoscopic lysis of adhesions performed and was discharged three days later. On (b) (6) it was considered resolved. The investigator and the applicant assessed the intestinal obstruction to be not related to the investigational product or study procedures. Both events were thought to be related to the patient's medical history since the patient had recurrent events of bowel obstruction since (b) (6)

Reviewer comments: The patient had a history of multiple bowel obstructions since (b) (6). Treatment required lysis of adhesions. Therefore, this SAE is unlikely related to INP104.

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study 301: Of 354 patients who received at least one dose of INP104 there were 25 patients (7.1%) who had TEAEs that led to IP discontinuation and 23 patients (6.5%) who had TEAEs that led to study withdrawal. These TEAEs included 5 events of nasal congestion, 4 events of nasal discomfort, 4 events of nausea, 2 events of sinus congestion, and one event of each of the following: vomiting, drug hypersensitivity, migraine, parosmia, product taste abnormal, anxiety, nasal edema, rhinitis allergic, pruritus generalized, and asymptomatic olfactory test abnormal. Only 3 TEAEs leading to study discontinuation did not lead to study withdrawal. This included TEAEs of moderate nausea, severe vomiting, and mild asymptomatic olfactory test abnormal. The patient with severe vomiting withdrew from the study due to worsening migraine.

No SAE led to IP discontinuation or study withdrawal.

7.4.4. Significant Adverse Events

Severity categorization

The investigator rated the severity of AEs by the following:

- Mild: A type of AE that was usually transient and required only minimal treatment or therapeutic intervention. The event did not generally interfere with usual activities of daily living.
- Moderate: A type of AE that was usually alleviated with additional specific therapeutic intervention. The event interfered with usual activities of daily living, causing discomfort

but posed no significant or permanent risk of harm to the research patient.
- Severe: A type of AE that interrupted usual activities of daily living, or significantly affected clinical status, or required intensive therapeutic intervention.

Study 301: There were four TEAEs of anosmia, septal perforation, and two patients with hyposmia, that were not considered severe nor serious, but I note as significant.

Anosmia

A 44-year-old female with a history of a normal baseline average UPSIT score of 36.5 (score of 37 at screening and 36 at baseline), a normal baseline overall assessment on upper nasal endoscopy, and a normal baseline overall assessment on lower nasal endoscopy, presented with a mild AE of anosmia. The patient had no post-baseline UPSIT, upper nasal endoscopy, or lower nasal endoscopy results before the start date of the event. The patient self-administered the first dose of INP104 and experienced anosmia that resolved the same day without treatment. Ten days later the patient self-administered a second dose of INP104, which coincided the same day of a clinic visit with an UPSIT score of 34 (mild microsmia). The patient reported no subjective decrease in olfaction. The patient decided to withdraw from the study due to lack of efficacy.

Reviewer comments: Given the resolution of the anosmia on the same day and lack of UPSIT testing with symptoms it is difficult to determine if this was true anosmia. However, based on the timing I cannot rule out that that there is relationship between the study drug and the reported anosmia.

Septal perforation

A 49-year-old patient with history of sinus and septal surgery, and seasonal allergies, was found to have a mild AE of nasal septal perforation and moderate AE of sinusitis 11 days after administering a second and last dose of INP104, and 25 days since the first dose. The perforation had not been documented to be present on screening examination. There is no report of epistaxis or pain noted. The septal perforation was noted to be not new and well-healed on examination and was judged to be due to previous history of septal and sinus surgery. No other description of the septal perforation was available such as size or location. The investigator assessed the events of sinusitis and nasal septal perforation to be not related to the IP or study procedures. It was noted that the septal perforation was considered to be present but not properly documented on the first visit.

Reviewer comment: Following review of the details of this case, I am unable to definitively conclude that this perforation is not related to study drug administration, yet my impression is that this event is unlikely related to study drug, for the following reasons.

The lack documentation of the septal perforation at the first visit allows for a question of whether the perforation was a newly formed between the first and second examination. However, given that it was well healed 25 days and 11 days after administration of the first and second dose, respectively, it would be unlikely that INP104 cause the perforation since it would typically take longer for the perforation to form and then completely heal. Furthermore, most septal perforations due to medication are due to chronic frequent nasal spray use, while this patient had only administered the medication twice. In addition, there were no reported symptoms related to the septal perforation, although it is not clear if directed questions were asked about symptoms.

I did request from the applicant to provide the size, appearance, and any images of the perforation from the applicant, as well as any AEs reported by the patient after identification of the perforation. The applicant reported that the size and images were not available. The applicant replied that "This was not a new finding, it was considered present at screening, but not properly documented." The applicant reported that no TEAEs were "reported that would indicate that the septal perforation detected by nasal endoscopy was a new lesion (e.g., no reports of epistaxis and pain) following initiation of treatment."

Additionally, the caudal septum typically is the location more susceptible to formation of a perforation. INP104 differentiates itself from the approved Migranal nasal spray in that it applies the dose higher in the nasal cavity. In addition, the formulation of the DHE in INP104 is the same as Migranal. However, as of this review, I could not find a reported incident of septal perforation due to Migranal. Lastly, septal surgery would be the more likely cause of a septal perforation when compared to drug-induced septal perforations. Therefore, it is unlikely that the nasal septal perforation was study drug related.

Hyposmia

A 50-year-old female with a history of recent onset of menopause (study day 165) and baseline average UPSIT score of 36.5 (normosmia), reported that one day after 45th dose of INP104 (study day 193) she experienced a mild AE of hyposmia. The hyposmia was not reported until after a follow-up UPSIT was completed on study day 365, with a score of 31 (mild microsmia), because the patient thought the hyposmia was related to menopause. She did have an UPSIT score of 34 on study day 247 (mild microsmia) during the time between the onset of hyposmia and the report of the symptom. The patient continued use of INP104. The patient had a follow-up UPSIT score of 29 (moderate microsmia) on study day 393 and 34 (mild microsmia) on study day 421 at which time the event of hyposmia was considered resolved.

Reviewer comment: Given the onset of symptoms, one day after a dose of INP104 was administered, it is possible that the hyposmia could be related to use of INP104. The patient did have onset of menopause 28 days prior to symptoms. Menopause can be associated with olfactory dysfunction; thus, this case may be confounded by the onset of menopause. However,

if due to menopause, the symptom of hyposmia would likely not resolve. Based on the timing of drug administration and onset of hyposmia, there is likely a relationship between the study drug and the reported hyposmia.

In another case, a 44-year-old female with a baseline average UPSIT score of 35.5 (normosmia) reported experiencing hyposmia with an UPSIT score of 30 (moderate microsmia) on study day 169 (9 days after 34th and last dose), at which point the 24-week treatment period was completed. Subsequently, on study day 188 that patient had an UPSIT score of 29 (moderate microsmia). At the time of last patient contact the event was ongoing, and the investigator deemed it not related to the investigational product.

Reviewer comment: The onset of hyposmia was 9 days after the administration of the last dose of INP104. Therefore, an association between the study drug and hyposmia is less likely. However, a relationship between the study drug and reported hyposmia cannot be definitively ruled out.

Neither of the above patients' experiences with hyposmia can be definitively stated to be not associated with the study drug. In section 7.4.5 I recommend that "change in smell" be described in the labeling.

7.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Study 301: Of the 354 patients who received at least one dose of INP104, 185 (52%) experienced at least one local irritative TEAE. I did review the TEAEs other than the local irritative AEs and did not find a substantially different percentage than what is described in the labels of the referenced drugs. Therefore, the focus of TEAE was on local irritative TEAEs. My safety analysis grouped the following preferred terms under a single term, because they were clinically similar:

- **Change in smell**: Combines the preferred terms **hyposmia, parosmia,** and **anosmia**
- **Ear discomfort:** Combines the preferred terms **ear pain** and **ear discomfort**
- **Nasal Discomfort**: combines the preferred terms **rhinalgia**, and **nasal discomfort**
- **Nasopharyngitis**: Combines the preferred terms **nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection,** and **respiratory tract infection viral**
- **Pharyngitis:** Combines the preferred terms **pharyngitis** and **pharyngitis streptococcal**
- **Product taste abnormal/Dysgeusia:** Combines the preferred terms **product taste abnormal** and **dysgeusia**
- **Rhinitis:** Combines the preferred terms **rhinitis allergic**, **rhinitis, nasal congestion, nasal edema,** and **seasonal allergy**

- **Sinus discomfort**: Combines the preferred terms **sinus congestion, sinus pain, sinus headache** and **paranasal sinus discomfort**
- **Sinusitis:** Combines the preferred terms **sinusitis** and **acute sinusitis**

The local irritative TEAEs of patient who administered at least one dose of INP104 in study 301 are listed in Table 5 below.

Table 5 Local Irritative TEAEs of Patients Receiving At Least One Dose of INP104 in Study 301

Adverse Event Term	Patients who received at least one dose INP104 (N = 354)
Total Subjects with any local irritative AE	185 (52.3%)
Nasopharyngitis	75 (21.2%)
Rhinitis	68 (19.2%)
Nasal discomfort	23 (6.5%)
Product taste abnormal/Dysgeusia	21 (5.9%)
Sinusitis	17 (4.8%)
Sinus discomfort	15 (4.2%)
Olfactory test abnormal	14 (4.0%)
Epistaxis	10 (2.8%)
Pharyngitis	9 (2.5%)
Nasal mucosal disorder	6 (1.7%)
Change in smell	4 (1.1%)
Ear discomfort	4 (1.1%)
Rhinorrhea	4 (1.1%)
Throat irritation	3 (0.8%)
Nasal dryness	2 (0.6%)
Nasal injury	2 (0.6%)
Oropharyngeal pain	2 (0.6%)
Intranasal hypoesthesia	1 (0.3%)
Nasal septum perforation	1 (0.3%)
Nasal varices	1 (0.3%)

This table was adapted from the ADAE data set and the applicant's ad-hoc analyses.

The most common local irritative symptoms events (at least 1 % of patients) were nasopharyngitis (21.2%;), rhinitis (19.2%), nasal discomfort (6.5%), product taste abnormal/dysgeusia (5.9%), sinusitis (4.8%), sinus discomfort (4.2%), olfactory test abnormal (4.0%), epistaxis (2.8%), pharyngitis (2.5%), nasal mucosal disorder (1.7%), change in smell (1.1%), ear discomfort (1.1%), and rhinorrhea (1.1%). Of local irritative TEAEs, one (0.5%) was reported to be severe which was nasal congestion. This TEAE resolved without treatment during the same day of onset.

Reviewer comments: I recommend that the local irritative TEAEs occurring in at least 1% of patients be described in labeling.

Nasal related TEAEs by dosing frequency subgroups

My safety analyses included evaluating nasal related TEAEs of study 301 patients who administered 2 or more doses in 24 hours. To evaluate the local toxicity, specifically the nasal related TEAEs, I examined the subgroups of patients in study 301 who administered no more than 1 dose in a 24-hour period, 2 or more doses in a 24-hour period, a second dose 0 to 1 hours after the first dose, a second dose >1 to 2 hours after the first dose, a second dose 0 to2 hours after the first dose, and a second dose >2 to 24 hours after the first dose.

When comparing nasal related TEAEs of patients who never administered more than one dose per 24-hour period during the study to those who administered 2 or more doses in a 24-hour period, the only nasal related TEAE that had a difference of ≥2% points between the two subgroups were upper respiratory tract infection, nasal congestion, nasal discomfort, rhinorrhea, and nasal mucosal disorder (Table 6). Of the five nasal related TEAEs only one occurred more frequently in the ≥2 doses in a 24-hour period subgroup, which was nasal mucosal disorder.

Table 6 Nasal Related TEAEs with ≥2% Point Difference Between Patients Who Received a Maximum of 1 Dose in a 24-Hour Period and Patients Who Received a Maximum of ≥2 Doses in a 24-Hour Period During Study 301

	Maximum Doses in 24 Hours	
Preferred Term	1 Dose (N=178) n (%)	≥2 Doses* (N=175) n (%)
Upper respiratory tract infection	24 (13.5)	17 (9.7)
Nasal congestion	35 (19.7)	25 (14.3)
Nasal discomfort	14 (7.9)	5 (2.9)
Rhinorrhea	4 (2.2)	0
Nasal mucosal disorder	1 (0.6)	5 (2.9)

This table was created from data from an Adhoc subgroup analysis provided by the applicant
* Four patients in the study administered 3 doses in less than 24 hours despite instructions that the maximum dose in 24 hours was 2 doses.

Reviewer comments: The subgroup data in Table 6 does not appear to demonstrate an increased rate of nasal related TEAE in patients who administered a maximum of 2 or more doses in a 24-hour period during the study compared to patients who never used more than 1 dose in a 24-hour period. Therefore, no specific clinical safety concerns were identified to oppose the applicant's proposed maximum dose of 2 doses in a 24-hour period.

In Table 7, the patients who took 2 or more doses in 24 hours during the study were divided by the timing of the second dose to evaluate whether patients who administered a second dose at a shorter time interval would be more likely to have a nasal related TEAE. There were two nasal related TEAEs that occurred at a higher percentage in both the 0 to 1 hours and the >1 to 2 hours subgroups compared to the >2 to 24 hours subgroup, which were upper respiratory tract infections and rhinitis allergic. The other nasal related TEAEs had a lesser percentage of occurrence in the >1 to 2 subgroup compared to the two other subgroups. Upper respiratory tract infection occurring in the 0 to 1 hour and >1 to 2 hours subgroups had a similar percentage of occurrence as patients only receiving one dose in 24 hours. Epistaxis did occur at a higher percentage in the 0 to 1 hour subgroup compared to the >2 to 24 hours subgroup.

Table 7 Nasal Related TEAEs with ≥2% Point Difference Between Second Dose at 0 to 1 Hours After First Dose and >2 to 24 Hours After First Dose During Study 301

	Maximum Doses in 24 Hours		The Second Dose at the Time After First Dose		
Preferred Term	1 Dose (N=178) n (%)	≥2 Doses* (N=175) n (%)	0-1 Hour** (N=22) n (%)	>1-2 Hours** (N=22) n (%)	>2-24 Hours** (N=161) n (%)
Nasopharyngitis	14 (7.9)	17 (9.7)	3 (13.6)	1 (4.5)	14 (8.7)
Upper respiratory tract infection	24 (13.5)	17 (9.7)	3 (13.6)	3 (13.6)	16 (9.9)
Hyposmia	0	2 (1.1)	1 (4.5)	0	2 (1.2)
Epistaxis	4 (2.2)	6 (3.4)	2 (9.1)	0	4 (2.5)
Nasal discomfort	14 (7.9)	5 (2.9)	1 (4.5)	0	4 (2.5)
Rhinitis allergic	1 (0.6)	2 (1.1)	1 (4.5)	1 (4.5)	1 (0.6)
Sinus congestion	6 (3.4)	5 (2.9)	1 (4.5)	0	4 (2.5)

This table was created from data from an Adhoc subgroup analysis provided by the applicant
* Four patients in the study administered 3 doses in less than 24 hours despite instructions that the maximum dose in 24 hours was 2 doses.
** Patients appear in multiple columns if they had pairs of IP treatments that occurred within multiple

of the specified intervals

Reviewer comments: When comparing the 0 to 1 hour subgroup to the >2 to 24 hours subgroup, there is a notable difference in the percentage of patients who experienced epistaxis and nasopharyngitis. However, given the small number of patients in the 0 to 1 hour subgroup, there were only 2 patients who experienced epistaxis and 3 patients who experienced nasopharyngitis. Therefore, it is not clear whether this is a significant difference.

In Table 8, the patients who took 2 or more doses in 24 hours during the study were divided by the timing of the second dose. There were four nasal related TEAEs that occurred at a ≥2% point difference between the subgroup consisting of patients who administered a second dose 0-2 hours after the first dose at any time during the trial, and the subgroup of patients who administered a second dose within 24 hours of the first dose but more than 2 hours after the first dose. Three of the TEAEs occurred at a higher percentage in the subgroup with the shorter interval between doses, and included upper respiratory tract infection (URI), epistaxis and rhinitis allergic.

Table 8 Nasal Related TEAEs with ≥2% Point Difference Between Second Dose at 0 to 2 Hours After First Dose and >2 to 24 Hours After First Dose During Study 301

	Maximum Doses in 24 Hours		The Second Dose at the Time After First Dose	
Preferred Term	1 Dose (N=178) n (%)	≥2 Doses* (N=175) n (%)	0-2 Hours** (N=40) n (%)	>2-24 Hours (N=135) n (%)
Upper respiratory tract infection	24 (13.5)	17 (9.7)	5 (12.5)	12 (8.9)
Epistaxis	4 (2.2)	6 (3.4)	2 (5.0)	4 (3.0)
Nasal mucosal disorder	1 (0.6)	5 (2.9)	0	5 (3.7)
Rhinitis allergic	1 (0.6)	2 (1.1)	2 (5.0)	0

This table was created from data from an Adhoc subgroup analysis provided by the applicant
* Four patients in the study administered 3 doses in less than 24 hours despite instructions that the maximum dose in 24 hours was 2 doses.
** If a patient administered a second dose 2 hours or less after the first dose at any time during the study, the patient was only counted in the 0-2 hours group.

Reviewer comments: When comparing the 0-2 hours subgroup to the >2 to 24 hours subgroup, the largest differences in TEAE occurrence between the two subgroups are with URI and nasal mucosal disorder. Regarding the URI TEAEs, the percentage of patient in the 0-2 hours subgroup is similar to the percentage of URI TEAEs of patients receiving only 1 dose in 24-hour intervals. Nasal mucosal disorder occurred at greater frequency in the >2 to24 hours group than the 0-2

hours subgroup.

Epistaxis occurred in 5% of the patients in the 0 to 2 hours subgroup which is higher than the 2.2% noted in the patients using only 1 dose in 24 hours. However, in the 0 to 2 hours subgroup there were only 2 patients who experienced epistaxis. Due to the small number of patients experiencing epistaxis it difficult to determine the significance of the difference. Allergic rhinitis also occurred more frequently in the 0 to 2 hours subgroup versus the 1 dose in 24 hours subgroup. However, given the low occurrence in both subgroups it is difficult to conclude that this is a significant difference.

Overall, there does not appear to be a significant increase in nasal related TEAEs in patients administering a second dose 0 to 2 hours after the first dose compared to those administering the second dose >2 to 24 hours after the first dose, and to those administering 1 dose in 24 hours. Therefore, I would recommend that labeling be consistent with the LD that states that a second dose be administered after a minimum of 1 hour following the first dose, if needed. I have also recommended earlier in this section epistaxis, nasopharyngitis (which includes URI), and rhinitis be described in labeling.

7.4.6. Laboratory Findings

In study 301, patients had laboratory assessments that included hematology, chemistry, and urinalysis completed at screening, baseline, 12 weeks, and 24 weeks. If the patient participated up to 52 weeks, laboratory assessments were obtained at 26, 36, 42, and 52 weeks as well as at the follow-up visit. I reviewed the applicant's analyses of laboratory findings and did not conduct independent analyses of laboratory data. No relevant trends were noted.

7.4.7. Vital Signs

In study 301, vital signs were obtained at screening, baseline and at monthly intervals. Vital signs included systolic and diastolic blood pressure, pulse rate, temperature, respiratory rate, and weight. I reviewed the applicant's analyses of vital sign and no relevant trends were noted.

Reviewer comments: Of note five patients did have a reported TEAE of hypertension. Increase in blood pressure is included in the D.H.E. 45 label in the warning sections and DHE is contraindicated in patients with uncontrolled hypertension. This warning will remain in the label for INP104.

7.4.8. Electrocardiograms (ECGs) and QT

In study 301, a 12-lead ECG was completed at screening, baseline, 24 weeks, and 52 weeks. No patient had an TEAE associated with abnormal ECG. I reviewed the applicant's ECG analyses by the applicant but did not conduct independent analyses of the ECG intervals.

One patient found to have QT prolongation (QT interval, 510 ms) at screening, had a normal ECG at baseline (QT interval, 445 ms), and a recurrence of QT prolongation (QT interval, 491 ms) at week 24. By week 52 the QT prolongation had normalized (QT interval, 459 ms). Another patient had a newly identified incomplete right bundle-branch block, long QT interval (QT interval, 457 ms) at week 24 and was unchanged at week 52.

Reviewer comments: Cardiac events and fatalities, and disturbances of cardiac rhythm are included in the D.H.E. 45 label in the warning section. This should remain the in the PI.

7.4.9. University of Pennsylvania Smell Identification Test

The UPSIT is used to assess the patient's olfactory function. It utilizes a 40-item scratch and sniff test with a four-choice multiple choice question for each item. Scores range from 0 to 40 (one point for each correct response) with a higher score indicating better smell function. The categorization in adults is based on the score and the sex of the patient. In adults, the scores are categorized as normosmia (35-40 in females, 34-40 in males), mild microsmia (31-34 in females, 30-33 in males), moderate microsmia (26-30 in females, 26-29 in males), severe microsmia (19-25 in females and males), total anosmia (6-18 in females and males), or probably malingering (0-5 in females and males).

In study 301, the safety endpoint is change in olfactory function. Throughout the study there were fluctuations in UPSIT scores. At 24 weeks, patients who had at least one dose of INP104 demonstrated a mean and median change from baseline in UPSIT score of -0.2 and 0, respectively. For patients who administered on average of ≥2 doses every 28-day period, the mean and median change after 24 weeks was -0.3 and 0, respectively. For patients who administered on average of ≥2 doses every 28-day period the mean and median change after 52 weeks was -0.9 and -1.0, respectively.

Table 9 24-Week At Least One Dose of INP104 UPSIT Scores

	Actual Value	Change from Baseline
Baseline		
n	354	
Mean (SD)	35.25 (2.998)	
Median	36	
Min, Max	16.0, 40.0	
Week 24		
N	206	206
Mean (SD)	35.03 (3.182)	-0.22 (2.270)
Median	35.5	0
Min, Max	25.0, 40.0	-6.5, 11.5

This table was adapted from the applicant's materials from the CSR for study 301.

Table 10 52-Week Two or More INP104 Doses on Average Every 28 Days UPSIT Scores

	Actual Value	Change from Baseline
Baseline		
N	55	
Mean (SD)	35.09 (2.541)	
Median	35.5	
Min, Max	27.0, 39.5	
Week 24		
N	54	54
Mean (SD)	34.11 (3.289)	-0.91 (2.746)
Median	34	-1
Min, Max	25.0, 40.0	-8.0, 6.5

This table was adapted from the applicant's materials from the CSR for study 301.

The applicant used a decrease of 5 points or greater on the UPSIT as an UPSIT score shift criterion and considered this shift to be an AE. Patients who had no other nasal related TEAE but had a decrease of 5 or greater on the UPSIT score would have a TEAE labeled as "olfactory test abnormal." Of patients who received at least one dose of INP104, 25 patients met UPSIT shift criterion. Of those, 2 patients noted a smell change, diagnosed as hyposmia, with one case considered resolved 228 days after onset of symptoms. Of note a patient reporting parosmia and another reporting anosmia did not have an UPSIT assessment during the time of symptoms as the smell changes resolved the same day as onset.

Reviewer comments: Without a placebo arm it is difficult to conclude whether the decreases noted in the UPSIT score are clinically significant. The mean and median score decreases are small.

Regarding the UPSIT shift criterion, only two of the 25 patients who had decreases of 5 points or greater on the UPSIT, reported of smell change associated with them. Therefore, the applicant defined UPSIT shift criterion, may not be a reliable criterion for a clinically meaningful olfactory function change. The report of anosmia and a report of parosmia were not tested since the symptoms resolved as the same day as onset. Therefore, I believe the focus should be on the symptomatic smell changes noted by the patients.

Overall, of the 4 patients with symptomatic change in smell TEAE patients, three had resolved while one was ongoing at the end of the study. I believe that this does not warrant label recommendation.

7.4.10. Immunogenicity

N/A

7.5. Analysis of Submission-Specific Safety Issues

DHE is approved as an injection and nasal spray. The applicant conducted a long-term safety study to evaluate the local toxicity of the product.

7.5.1. Local Toxicity

Local toxicity is discussed in sections 8.4.4 and 8.4.5.

7.6. Safety Analyses by Demographic Subgroups

I examined the five most common TEAEs and conducted subgroup analyses of the open-label long-term safety study, study 301, using the ADAE dataset and not counting duplicate AEs for a single patient. The subgroups evaluated were by sex (M/F), age (≥40 or <40), race (black or white, since all other groups were <1% of study population).

Table 11 Subgroup Analysis of Most Common TEAEs (≥5%) in Study 301

	Sex		Age		Race	
Adverse Event Term	Females N (%)	Males N (%)	≤40 years N (%)	>40 years N (%)	White N (%)	Black N (%)
N	304	50	177	177	266	76
Nasopharyngitis*	63 (21.0%)	12 (24.0%)	42 (23.7%)	33 (18.6%)	56 (21.1%)	15 (19.7%)
Rhinitis**	57 (18.5%)	11 (22.0%)	37 (20.9%)	31 (17.5%)	51 (19.2%)	15 (19.7%)
Nasal Discomfort***	21 (6.9%)	2 (4.0%)	10 (5.6%)	13 (7.3%)	17 (6.4%)	6 (7.9%)
Product Taste Abnormal/Dysgeusia	21 (6.9%)	0	15 (8.5%)	6 (3.4%)	16 (6.0%)	5 (6.6%)
Sinusitis****	16 (5.3%)	1 (2.0%)	8 (4.5%)	9 (5.1%)	16 (6.0%)	1 (1.3%)

This table was created by the reviewer, using datasets ADAE and ADSL.
*Includes the following preferred terms: nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, and respiratory tract infection viral.
**Includes the following preferred terms: rhinitis allergic, rhinitis, nasal congestion, nasal edema, and seasonal allergy
***Includes the following preferred terms: nasal discomfort, and rhinalgia
****Includes the following preferred terms: sinusitis and acute sinusitis.

Reviewer comments: The study 301 is an open-label study and some of the subgroups such as male and Black groups are considerably smaller than the female group and White group, respectively. Therefore, subgroup analyses are unlikely to lead to clinically interpretable findings. The table above demonstrates that the product taste abnormal/dysgeusia tended to occur more often in females and patients 40 years and younger, compared to males and those over 40 years of age, respectively.

However, the overall number of male patients was small, making it is difficult to draw conclusions. It is possible that nasopharyngitis, nasal congestion, and product taste abnormal/dysgeusia may be more common in younger patients. However, without a placebo arm it is difficult to conclude whether these differences are associated with INP104 administration. Overall, the data is not compelling enough to support statements in the label regarding these differences based on any of the subgroup analyses.

7.7. Specific Safety Studies/Clinical Trials

Other than the study 301 to evaluate local toxicity, there were no other special clinical safety studies conducted as part of this new drug application.

7.8. Additional Safety Explorations

7.8.1. Human Carcinogenicity or Tumor Development

The application is relying of previously approved product for safety.

7.8.2. Human Reproduction and Pregnancy

Patients who were pregnant or lactating were excluded from study 101 and 301. Information on pregnancy/lactation will be informed by the FDA approved label for D.H.E. 45.

7.8.3. Pediatrics and Assessment of Effects on Growth

Pediatric studies were not conducted for this product. The FDA-approved label for D.H.E. 45 states that the safety and effectiveness in pediatric patients have not been established.

7.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No studies of abuse potential were conducted. No potential for abuse has been identified with the use of DHE.

7.9. Safety in the Postmarket Setting

7.9.1. Safety Concerns Identified Through Postmarket Experience

DHE has been marketed since 1946 and the safety profile has been well-established. A warning describing the risk of cardiac valvular fibrosis and a boxed warning regarding the risk of serious and/or life-threatening peripheral ischemia associated with the coadministration of DHE with potent CYP3A4 inhibitors was added to the label in the postmarket setting.

7.9.2. Expectations on Safety in the Postmarket Setting

The systemic safety of INP104 in the postmarket setting is expected to be the same as other DHE products. The local adverse reactions may be different given the difference in targeted location of application in the nasal cavity compared to Migranal.

7.9.3. Additional Safety Issues From Other Disciplines

At the time of this review, I am unaware of additional safety issues from other disciplines.

7.10. Integrated Assessment of Safety

D.H.E 45 was approved by the FDA in 1946 and the safety profile has been well-established. The product has been scientifically bridged for efficacy and safety to Migranal and D.H.E. 45, respectively. Therefore, the product can rely on the label of D.H.E. 45 for the systemic safety. Safety data related to the local toxicity of the product cannot completely rely on the label of either Migranal or D.H.E. 45 since INP104 is a nasal spray that targets the upper nasal cavity for application. The review of the open-label long-term safety study (study 301) did not identify safety concerns that would change the overall benefit-risk assessment.

8. Advisory Committee Meeting and Other External Consultations

N/A

9. Labeling Recommendations

9.1. Prescription Drug Labeling

The applicant has submitted a 505(b)(2) application and is demonstrating efficacy of INP104 by bridging to Migranal, and safety by bridging to D.H.E. 45. The label will be largely consistent with the FDA approved label for D.H.E. 45 and Migranal prescribing information. The label will be formatted in a Physician Labeling Rule (PLR) format. In addition, I recommend including the local toxicity data from study 301 as discussed in section 8.4.5 in the final approved label.

9.2. Nonprescription Drug Labeling

N/A

10. Risk Evaluation and Mitigation Strategies (REMS)

N/A

11. Postmarketing Requirements and Commitments

PREA has been determined to be triggered because the proposed dosing regimen is a new dosing regimen. There is an agreed upon Initial Pediatric Safety Plan for a full waiver for patient less than 6 years old and a deferral for ages 6 through 17 years. The applicant is required to complete a juvenile animal toxicology study in one species as well as a three period clinical study to evaluate: 1) pharmacokinetics in patients age 6 to less than 12 years, 2) the efficacy and safety for the treatment of acute migraine with or without aura in patients ages 6 through 17 years with a randomized double blind design with an initial single-blind placebo lead-in to identify patients who respond to placebo, and 3) (b) (4)

12. Appendices

12.1. References

Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: Updated age, sex, and socioeconomic-specific estimates from government health surveys. Headache. 2021 Jan;61(1):60-68. doi: 10.1111/head.14024. Epub 2020 Dec 21. PMID: 33349955.

Dodick, D. Migraine. Lancet. 2018 March 31; 391(10127):1315-30

12.2. Financial Disclosure

Only Study 101 would qualify as a "covered clinical study" under 21 CFR 54, as it is used to establish the scientific bridge from the applicant's product (INP104) to an already approved effective product (Migranal nasal spray).

Covered Clinical Study (Name and/or Number): INP104-101

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

		Applicant)
Total number of investigators identified: 10		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RYAN L KAU
09/02/2021 01:42:52 PM

HEATHER D FITTER
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