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APPLICATION NUMBER:

206099Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	206099
Priority or Standard	Standard
Submit Date(s)	January 27, 2014
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PDUFA Goal Date	November 26, 2014
Division / Office	Division of Neurology Products
Reviewer Name(s)	Suhail Kasim, MD MPH
Review Completion Date	September 30, 2014
Established Name	Sumatriptan Succinate
(Proposed) Trade Name	Onzetra Xsail breath powered delivery device
Therapeutic Class	Triptan agonist
Applicant	Avanir Pharmaceuticals, Inc.
Formulation(s)	Pre-filled nosepiece containing encapsulated sumatriptan succinate nasal powder
Dosing Regimen	Onzetra 22 mg administered through two 11 mg nosepieces, one per nostril
Indication(s)	Acute migraine
Intended Population(s)	Adult patients with migraine

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval action is recommended for NDA 206099 Onzetra (sumatriptan nasal powder), 22 mg AVP-825 to be used with the proprietary Xsail breath powered delivery device for the indication, acute treatment of migraine with or without aura.

1.2 Risk Benefit Assessment

Onzetra (sumatriptan nasal powder), 22 mg (AVP-825) for use with the proprietary Xsail breath powered delivery device should benefit adult migraineurs for the acute treatment of migraine with or without aura considering the relative bioavailability established to Imitrex, the reference listed drug. In addition, the effectiveness of AVP 825 was demonstrated in the phase 3 study OPN-SUM-MIG-3301 for the primary endpoint headache relief at 120-minutes, with supportive evidence of nominal treatment difference for the migraine associated symptoms and other secondary endpoints.

The risks with use of the product for the intermittent treatment of moderate to severe migraine episodes appear to be similar to available migraine nasal spray products where patients experienced nasal discomfort or irritation locally at the site of administration in addition to product unpleasantness as it transits the oropharynx. Differences in the systemic toxicity profile are not expected with the nasally administered sumatriptan product. The prescriber information from Imitrex label is applicable for the safe use of AVP 825 submitted to the 505(b)(2) NDA 206099.

Even though there is concern regarding the ease of use of the device, which requires several steps prior to use during a migraine event and whether the patients follow through on adequate dosing recommendations as directed, it appears most subjects did not experience difficulty operating the device, or report evidence of discomfort in the phase 3 study OPN-SUM-MIG-3301 where device use education was provided prior to use. However, unpleasant taste was reportedly higher for the AVP 825 22 mg treated patients, which may be their reason for the equivocal response for product preference. Adequate patient education with clear instructions for use and counselling on appropriate device use is recommended to avoid dosing errors that a patient may likely experience when there is insufficient indication that the drug is dispensed or whether the encased capsule in the disposable nosepiece is pierced.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine postmarketing surveillance is appropriate.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

Avanir Pharmaceuticals (Avanir) submitted 505(b)(2) new drug application (NDA 206099) on January 27, 2014 for Onzetra (sumatriptan nasal powder), 22 mg AVP-825 to be used with the proprietary Xsail breath powered delivery device for the proposed indication, acute treatment of migraine with or without aura. AVP-825 is a combination product comprised of a drug product and a delivery device, which was developed by Optinose US. Optinose US filed IND 110,090 on November 11, 2011. In 2013, Optinose US transferred the ownership of IND 110,090 to Avanir Pharmaceuticals.

The sponsor references the following information for AVP-825 Onzetra 505(b)(2) NDA that relies on previous findings pertaining to sumatriptan safety and efficacy from

- Imitrex Nasal Spray (NDA 020626 [local exposure and efficacy])
- Imitrex oral tablet (NDA 020132 [systemic exposure])
- Imitrex injectable, subcutaneous (NDA 020080 [systemic exposure])

Avanir Pharmaceuticals has not received right of reference from GlaxoSmithKline for the above referenced Imitrex NDAs. Avanir has the right of reference to IND 110,090.

2.1 Product Information

AVP-825 is a drug-device combination product intended for self-administration of sumatriptan succinate, for the acute treatment of migraine headache with or without aura. The *drug delivery system* consists of a reusable device body incorporating a flexible mouthpiece device and a disposable, pre-filled nosepiece containing encapsulated drug as sumatriptan succinate nasal powder (15.4 mg of sumatriptan succinate, equivalent to 11 mg sumatriptan base), which is then individually packaged in a foil (b) (4) pouch. Each nosepiece contains 11 mg of sumatriptan (base equivalent) and two nosepieces (one used in each nostril) constitute a full, 22 mg dose of AVP-825.

The drug (sumatriptan succinate) is contained within a [redacted] capsule housed within the nosepiece, and there are no excipients. The sponsor refers to the units as the Xsail breath powered delivery device (previously called [redacted]). For commercial distribution, the sponsor expects the kit will contain two AVP-825 devices (one for immediate use and a spare) with either 12-18 pouched nosepieces representing six and nine doses, respectively.

POWDER DELIVERY DEVICE

The powder delivery device of AVP-825 is reusable and is comprised of [redacted] flexible mouthpiece; mouthpiece insert; [redacted] and button piercing assembly. Please see Figure 1 for images of the device with and without the nosepiece. See Figure 2 for a diagram of the nosepiece.

Figure 1: NDA 206099 Photograph of AVP-825 Nosepiece, Breath-Powered Powder Device with Cover and the Device Assembled with the Nosepiece

Disposable Nosepiece | Flexible Mouthpiece Device with Cover | Assembled AVP-825 Device

Ref: eCTD seq 0000; Module 3.2.P.1, Sponsor's Figure 3.2.P.1-1

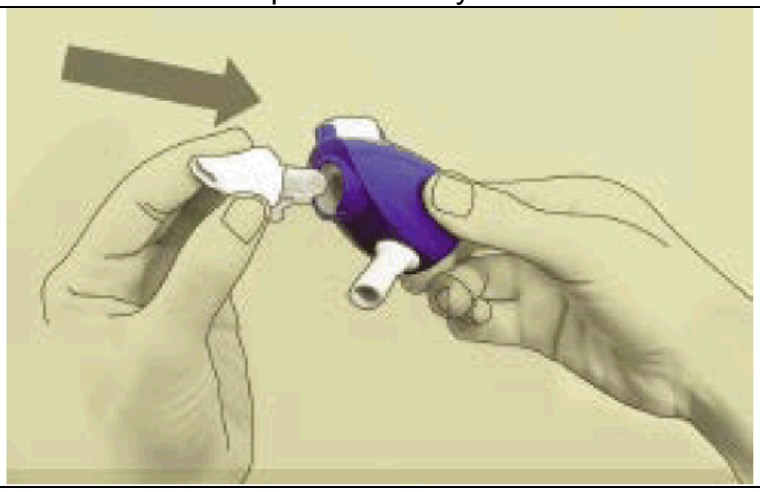
DISPOSABLE NOSEPIECE

The nosepiece, including the sub-parts is the disposable component of the AVP-825 device. Each fully assembled disposable nosepiece includes the [redacted] nozzle, [redacted], chamber and the capsule packaged individually as a unit dose in a foil [redacted] pouch. The disposable nosepiece is intended for a single dose administration and it is not refillable. Each disposable nosepiece contains a [redacted] capsule filled with 15.4 mg sumatriptan succinate (equivalent to 11 mg Sumatriptan base). *The drug-filled capsule is not removable from the nosepiece.*

Figure 2: NDA 206099 AVP-825 Nosepiece Components

(b) (4)

Figure 3: NDA 206099 Insertion of the Disposable Nosepiece into the Reusable Flexible Mouthpiece Delivery Device



Ref: eCTD seq 0000; Module 2.5, Sponsor's Figure 2.5-2

Device Use and Device Development

Device Use

For administration, the disposable nosepiece that contains the encapsulated sumatriptan succinate is inserted into the drug delivery device body (Figure 1 – blue reusable device, and Figure 3). A (white) button integrated in the device body is then pressed fully and released to pierce the capsule in the disposable nosepiece. The nosepiece of the device is then inserted into the nose to make a complete seal. The mouthpiece is then rotated, and, flexing the mouthpiece as necessary, the mouth piece is inserted between the lips. *Exhalation into the mouthpiece propels the sumatriptan*

powder into the nasal cavity through the attached disposable nosepiece. The disposable nosepiece (including the now dose-expended drug-containing capsule) is then removed and discarded, and a second nosepiece is used similarly to deliver the remainder (i.e. a second 11 mg nosepiece) into the opposite side of the nose to complete the dosing.

Drug dispensing mechanics/description: When the piercing button on the side is depressed, (b) (4) pins (b) (4) pierce the capsule (b) (4). The nosepiece is then inserted into the user's nose and the mouthpiece into the mouth and the user blows into the device mouthpiece. (b) (4) the user blows into the device the airflow lifts the capsule (b) (4). (b) (4)

(b) (4): the user is required to blow forcefully for 2-3 seconds. The four steps required to operate the delivery system, from insertion of the Disposable Nosepiece to completion of administration of a dose, are provided in the eCTD submission under Instructions for Use (Section 1.14.1.3).

Device Changes during Development

The clinical studies conducted to support this NDA submission used a drug delivery device with a fixed (rigid) mouthpiece. In order to accommodate a wider range in size and physical characteristics of patients, the design of the delivery device was modified for commercialization to include a *flexible mouthpiece*.

According to the sponsor, the design of the Flexible Mouthpiece Device is nearly identical to the Fixed Mouthpiece Device, with the exception of the mouthpiece and minor modifications to the shell necessary to accommodate the flexible mouthpiece (Figure 4). The parts of the Flexible Mouthpiece Device that receives the disposable nosepiece, and which contain the capsule piercing mechanism are identical in the Flexible Mouthpiece Device and the Fixed Mouthpiece Device. Both the Fixed Mouthpiece Device and the Flexible Mouthpiece Device also utilize the same disposable nosepiece. These are identically inserted, secured, and released from the device. Therefore, the Flexible Mouthpiece Device should be identical in all respects to the Fixed Mouthpiece Device from the point where drug is released from the capsule to the point where the drug leaves the device and enters the patient's nostril, and is identical in the manner in which the patient inserts the nosepiece and pierces the capsule.

Figure 4: NDA 206099 Fixed Mouthpiece (A) and Flexible Mouthpiece Device (B)

Ref: eCTD seq 0000; Module 2.5, Sponsor's Figure 2.5-3

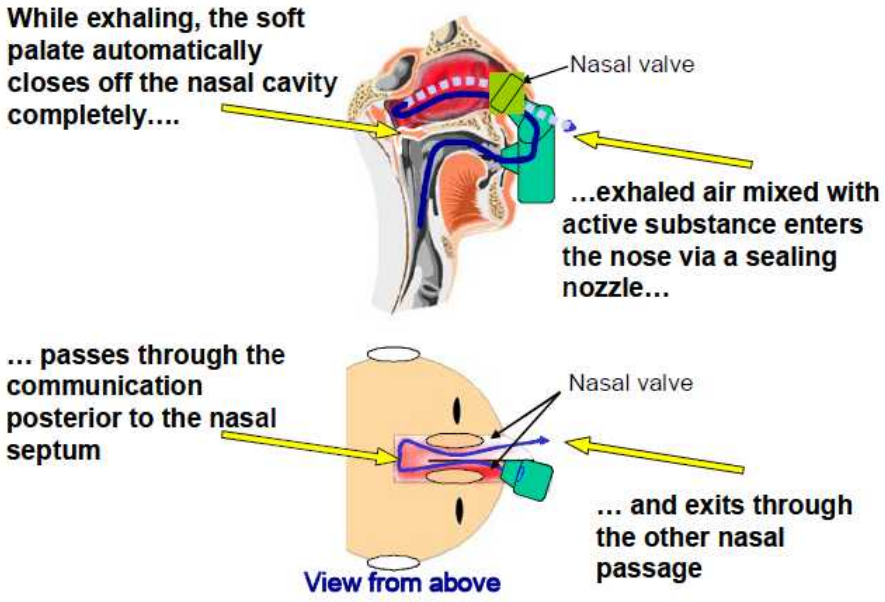
Bi-Directional Drug Delivery System

Product development rationale

According to the sponsor, nasal drug delivery can be difficult. The drug delivery should occur to the most effective location without undue loss through the mouth or into the lungs. With existing nasal sprays, the sponsor believes the drug is largely delivered to the anterior third of the nasal passage in the nasal valve (the anterior triangular narrow segments in the nose). Ideally, inhaled products should make it possible to improve delivery beyond the nasal valve by using smaller particles and asking people to inhale when the spray is actuated (Figure 5). The use of smaller particles results in up to 60% of the dose being delivered to the lungs, which may not be desired [1] [2]. Drug intended for nasal delivery is lost, and there may be undesired pulmonary side effects. See additional discussion towards the end of section 7.3.5. The sponsor believes the current nasal sprays may be compromising efficient nasal delivery: whilst producing smaller particles will improve deposition beyond the nasal valve, this will correspondingly increase the risk of lung inhalation.

[1] Suman JD, Laube BL, Dalby R. Comparison of nasal deposition and clearance of aerosol generated by nebulizer and an aqueous spray pump. *Pharm Res*, 16, (1999) 1648-1652.
[2] Djupesland PG, Skretting A, Windern M, Holand T. A novel concept for nasal delivery of aerosols can prevent lung inhalation. *Aerosol Med*, (2004) 17 (3), 249-59.

Figure 5: NDA 206099 Description of the Bi-directional Nasal Delivery Principle



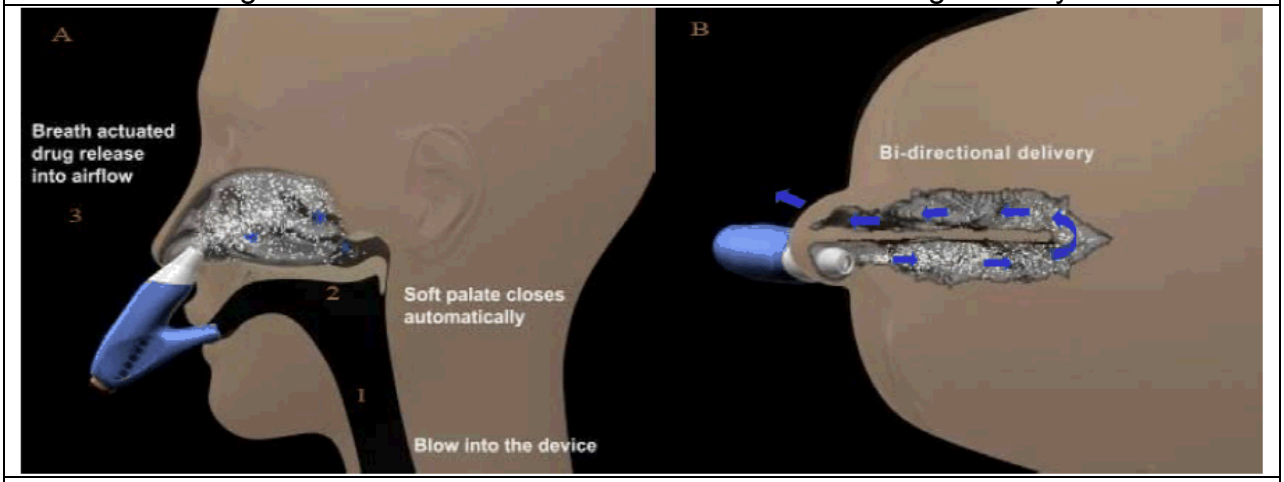
Ref: IND 110,090, Study Report OPTUK-MSPP-PRO-002. Figure 1

Avanir reports that currently nasal spray pumps must have a mean particle size large enough (b) (4) to limit the fraction of respirable particles to (b) (4)%, and that this particle size is incompatible with efficient delivery to the posterior two thirds of the nose beyond the nasal valve. Furthermore, sniffing during actuation will cause additional narrowing of the elastic tissues of the valve and suck a large part of the dose along the floor of the nose to the mouth, to be lost to swallowing.

Bi-Directional Drug Delivery System
The bi-directional delivery system used in the tested device (previously called (b) (4)) uses two aspects of nasal anatomy to address some of these issues (Figure 5). **First**, during exhalation against a resistance the soft palate closes due to positive pressure, separating the nasal and oral cavities. Consequently, it becomes possible to use smaller particles in a nasal spray and still avoid lung deposition by exhaling through the mouth during nasal administration. **Second**, during closure of the soft palate there is a communication pathway between the two nostrils, located behind the walls separating the two passages. *Under these circumstances, it is possible for airflow to enter via one nostril and leave by the other*.

The sponsor believes the bi-directional delivery concept combines these two anatomical facts into one fully functional device. A sealing nozzle is inserted into one nostril and the subject blows into the mouth-piece. The combination of closed soft palate and sealed nozzle creates an airflow, which enters one nostril, turns 180° through the communication pathway and exits through the other nostril (bi-directional flow - Figure 6). Since delivery occurs during exhalation, the small particles are not expected to enter the lungs.

Figure 6: NDA 206099 AVP-825 Bi-Directional Drug Delivery



Ref: eCTD seq 0000; Module 3.2.R, Sponsor's Figure 3.2.R.4.1-1

A flexible mouthpiece with specific asymmetrically tapered nosepiece geometry creates a seal and reduces undesirable obstruction of the (pre-filled) drug-containing disposable nosepiece outlet by nosepiece compression of soft tissues in the nose. By these means, the AVP-825 device uses the patient's exhaled breath and taking advantage of the naturally occurring balanced soft palate closure that prevents lung inhalation (Figure 6).

According to the sponsor, the device part of AVP-825 is a Class 1 nasal administration device in accordance with 21 CFR 874.5220 that is exempt from pre-market notification and GMP regulations, except for the general requirements concerning records and complaint files. Please refer to CDRH reviews for further information on the drug delivery device.

2.2 Tables of Currently Available Treatments for Proposed Indication

Avanir Pharmaceuticals (Avanir) submitted 505(b)(2) new drug application (NDA 206099) to obtain approval for use of Onzetra (sumatriptan nasal powder), 22 mg (AVP-825) to be used with the proprietary Xsail breath powered delivery device for the proposed indication of the acute treatment of migraine with or without aura. The safety and efficacy of sumatriptan (Imitrex) has been demonstrated for the treatment of acute migraine headache and in patients where there is a clear diagnosis of cluster headache.

The following (modified) Table 1 summarizes medications that are being used to treat acute migraine. However, please note that not all the products are FDA approved for treating acute migraine headache.

Table 1: US Headache Consortium: Acute Therapies for Migraine Headaches

Group 1*	Group 2†	Group 3‡	Group 4§	Group 5¶
Specific Almotriptan PO Eletriptan PO Frovatriptan PO Naratriptan PO Rizatriptan PO Sumatriptan SC, IN, PO, Sumavel DosePro injection Sumatriptan Iontophoretic Transdermal System Zolmitriptan PO, IN DHE SC, IM, IV, IN DHE IV, plus antiemetic Nonspecific Acetaminophen, aspirin, plus caffeine PO Aspirin PO Butorphanol IN Ibuprofen PO Naproxen sodium PO Prochlorperazine IV	Acetaminophen plus codeine PO Butalbital, aspirin, caffeine, plus codeine PO Butorphanol IM Chlorpromazine IM, IV Diclofenac K, PO Ergotamine plus caffeine plus pentobarbital plus Bellafoline PO Flurbiprofen PO Isometheptene CPD, PO Ketorolac IM Lidocaine IN Meperidine IM, IV Methadone IM Metoclopramide IV Naproxen PO Prochlorperazine IM, PR	Butalbital, aspirin, plus caffeine PO Ergotamine PO Ergotamine plus caffeine PO Metoclopramide IM, PR	Acetaminophen PO Chlorpromazine IM Granisetron IV Lidocaine IV	Dexamethasone IV Hydrocortisone IV

Modified Table. Reference: Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000 Sep 26;55(6):754-62
* Proven, pronounced statistical and clinical benefit (at least two double-blind, placebo-controlled studies and clinical impression of effect).
† Moderate statistical and clinical benefit (one double-blind, placebo-controlled study and clinical impression of effect).
‡ Statistically but not proven clinically or clinically but not proven statistically effective (conflicting or inconsistent evidence).
§ Proven to be statistically or clinically ineffective (failed efficacy versus placebo).
¶ Clinical and statistical benefits unknown (insufficient evidence available).

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient is sumatriptan in this drug-device combination product for the acute treatment of migraine headache with or without aura, which consists of a reusable device body incorporating a flexible mouthpiece device and a disposable, pre-filled nosepiece containing encapsulated drug (sumatriptan succinate).

Sumatriptan was initially approved in 1992 under the trade name Imitrex (NDA 020080) by GlaxoSmithKline. It is widely available in the United States in various formulations including tablets, nasal spray, subcutaneous injection, as an iontophoretic transdermal patch, and as a combination product with naproxen sodium.

The following is a listing of all currently available formulations of sumatriptan in the United States:

- Oral tablets (GlaxoSmithKline and generics): 25, 50, and 100 mg oral tablets containing sumatriptan succinate
- Oral fixed dose combination (GlaxoSmithKline): Treximet oral tablets containing 85 mg sumatriptan succinate and 500 mg naproxen
- Nasal spray (GlaxoSmithKline and generics): 5 and 20 mg nasal spray containing sumatriptan succinate
- Subcutaneous injection (GlaxoSmithKline and generics): 4 mg (8 mg/mL) and 6 mg (12 mg/mL) containing sumatriptan succinate
- Iontophoretic transdermal system (sumatriptan patch): Zecuity (Teva Pharmaceuticals) delivers 6.5 mg of sumatriptan over 4 hours

2.4 Important Safety Issues With Consideration to Related Drugs (Triptans)

Sumatriptan is a chemical analog of the class of products - 'triptans', developed for their potent cranial vasoconstrictor properties. Triptans are selective 5-HT1B/1D receptor agonists and mediate their vasoconstrictor activity via 5-HT1B receptors expressed on vascular smooth muscle.

While triptans are generally recognized as safe and effective, there have been class concerns raised as large numbers of patients were exposed to triptans, that their vasoconstrictor mechanism of action also conferred a risk of serious cardiovascular adverse events, some fatal. Consistent with their common pharmacology, sumatriptan, zolmitriptan, rizatriptan, eletriptan and naratriptan induced comparable dose-dependent contraction of isolated human coronary arteries. Because triptans are known to cause coronary vasospasm, they are contraindicated in patients with known coronary artery disease (CAD). It is strongly recommended that 'triptans' are not prescribed to patients with risk factors for undiagnosed CAD (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, male over 40 years of age) without first undergoing a thorough cardiovascular evaluation. It is recommended that the first dose of a triptan should be given in a physician's office, and preferably followed by an electrocardiogram (ECG).

Treatment of migraineurs with known cardiovascular disease and cardiovascular risk factors is particularly challenging because the incidence of myocardial infarction, stroke, claudication, diabetes, hypertension, and hypercholesterolemia are all higher in individuals with migraine compared with the general population (Bigal et al, 2010; Table 2). Migraineurs who were previously eligible for triptan therapy may become ineligible as they age and develop cardiovascular disease and/or associated risk factors.

Table 2: Cardiovascular Disease and Cardiovascular Risk Factors in Migraineurs

		Control N (%)	Migraine N (%)
Cardiovascular Disease	Myocardial Infarction	100 (1.91)	249 (4.08)
	Stroke	66 (1.26)	123 (2.02)
	Claudication	48 (0.92)	157 (2.57)
Cardiovascular Risk Factors	Diabetes	492 (9.38)	768 (12.59)
	Hypertension	1350 (25.75)	2021 (33.12)
	High Cholesterol	1343 (25.62)	1995 (32.69)

(Modified Table) Reference: Bigal ME et al. Migraine and cardiovascular disease: a population-based study. *Neurology*. 2010 Feb 23;74(8):628-35.

The current label recommends patients who are intermittent long-term users of sumatriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use the drug.

Cerebrovascular events and fatalities (cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events) have also been described, but this relationship is confounded by the presence of these complications in the migraine population in general. Other (non-coronary artery) vasospasm-type events are known with triptan use including peripheral vascular and colonic ischemia and (rarely) transient and permanent blindness. Migraine patients are already at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack). The incidence of all of these disorders remains low, when the widespread use of triptans is considered.

The development of a potentially life-threatening serotonin syndrome may occur with triptans, including sumatriptan, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Development of AVP-825 (sumatriptan nasal powder), to be used with the proprietary Xsail breath powered delivery device was performed under IND 110,090. The sponsor at the time, Optinose US, met with Division of Neurology Products (DNP) for initial pre-IND discussions on November 22, 2010. In 2013, Optinose US transferred the ownership of IND 110,090 to Avanir Pharmaceuticals. Avanir Pharmaceuticals has the right of reference to this IND 110,090 and for NDA 206099. The following meetings were held between the sponsor and DNP during the development of this product:

Table 3: NDA 206099 FDA-Sponsor Interactions		
Interaction	**Purpose**	**Date**
Type B Pre-IND Meeting	Regulatory, Clinical, Nonclinical, CMC	November 22, 2010
FDA responses to Optinose questions	Clinical, Nonclinical	February 22, 2012
Type C Clinical Meeting	Clinical question, exposure database	June 14, 2012
Type C CMC Meeting	CMC	April 10, 2013
Type B Pre-NDA Meeting Minutes	Clinical, Nonclinical, CMC	July 22, 2013
Ref: eCTD seq 0000; Module 1.6.3, Sponsor's Table 1		

Avanir provided summary of the key discussions, and I have abstracted these in Table 4 and Table 5 under sections pertaining to 'regulatory and procedural' and 'clinical' discussions. The clinical discussions focused primarily on developing AVP-825 through the 505(b)(2) regulatory pathway: method for establishment of clinical efficacy, and reliance on safety exposures from labeled Imitrex products with adequate exposure information to the local/nasal mucosa.

Table 4: NDA 206099 FDA-Sponsor Regulatory and Procedural Interactions	
Discussion Topic/FDA Feedback	**Sponsor Response/Action**
November 22, 2010 pre-IND Meeting/ 505(b)2 regulatory pathway (b) (4) SUMATRIPTAN is intended for the same indication as the reference listed drug (Imitrex® Nasal Spray NDA 20-626, Imitrex® oral NDA 20-132 and Imitrex® injection NDA 20-080) and matches the approved dose (20 mg). (b) (4) SUMATRIPTAN is administered via the same route of administration. (b) (4) SUMATRIPTAN differs from the reference listed drug in that a novel nasal delivery system is used, the form of delivery is changed from liquid to powder and the succinate salt of sumatriptan, as approved in the Imitrex Tablet and Imitrex sub-cutaneous injection, is administered. OptiNose believes that these product presentation differences are within the scope of a 505(b)(2) application. Does the Division agree that OptiNose can pursue marketing approval for the treatment of migraine headache via a section 505(b)(2) application referencing Imitrex Nasal Spray (NDA 20-626), Imitrex® Tablet (NDA 20-132) and Imitrex® injection (NDA 20-080)? ***FDA Response:*** *In this case, you should establish a "bridge" (e.g., relative bioavailability study) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is appropriate. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.*	Avanir conducted a comparative pharmacokinetic study (module 5.3.1.2 OPN-SUM-1302) to bridge AVP-825 to approved Imitrex formulations and a single Phase 3 efficacy and safety study (module 5.3.5.1 OPN-SUM-MIG-3301) to provide evidence of safety and efficacy. See 2.7.2 Clinical Pharmacology, and section 2.7.3 Summary of Clinical Efficacy.
November 22, 2010 pre-IND Meeting/ 505(b)2 regulatory pathway ***FDA Response****: On face, that (the Phase 1 PK) study would be appropriate for that purpose, but that local toxicity issues need to be addressed separately, as PK alone does not fully address local (nasal) exposure to the product.*	See 2.7.3 Summary of Clinical Efficacy, and section 2.7.4 Summary of Clinical Safety.
Ref: eCTD seq 0000; Module 1.6.3, Sponsor's Table 2	

Table 5: NDA 206099 FDA-Sponsor Clinical Development Discussions

Discussion Topic/FDA Feedback	Sponsor Response/Action
November 22, 2010 pre-IND Meeting pre-IND/Efficacy Endpoint ***Preliminary Agency Response****: Please note that an efficacy study may not be necessary if you are able to establish bioequivalence between* (b) (4) *SUMATRIPTAN and an approved dosing form of IMITREX. The study design for the pivotal trial appears generally acceptable. The division prefers the 2-hour pain-free rate as primary endpoint. Please also record headache intensity, associated symptoms (nausea, photophobia and phonophobia) presence or absence, and use of rescue medication at 4h, 8h, 16h and 24 h after administration of study medication.* ***Meeting Discussion****: The sponsor stated that the majority of migraine products, including Treximet and Zomig, are approved on the basis of 2-hour pain relief (headache response: reductions in severity from moderate or severe to mild or no pain). Therefore, the sponsor asked whether it is still acceptable to pursue approval on the basis of pain relief. The Agency replied that pursuing approval on the basis of pain relief was acceptable*.	A single pivotal efficacy trial was performed. See 2.7.3 Summary Clinical Efficacy for evidence of the efficacy and 2.7.4 Summary of Clinical Safety for evidence of the safety of AVP-825 for the treatment of acute migraine with or without aura in adults.
February 2, 2012 FDA Advice/ Efficacy Endpoint ***Meeting Discussion****: As discussed at the Pre-IND meeting, an efficacy study may not be needed if you are able to show bioequivalence between your product and one of the dosage forms of Imitrex. Also, while pain relief is acceptable, we recommend pain freedom as primary assessment of migraine pain. Unless your product is bioequivalent to (or has higher exposure than) another approved dosage form of Imitrex, we would require statistical significance on migraine associated symptoms as well*.	See 2.7.2 Summary of Clinical Pharmacology for data demonstrating that AVP-825 produces a higher exposure than Imitrex Nasal Spray and 2.7.3 Summary of Clinical Efficacy for data demonstrating that AVP-825 is statistically superior to placebo in producing pain relief and complete relief at 2 hours post dosing.
July 22, 2013 pre-NDA meeting/ Efficacy Studies The clinical efficacy program conducted with (b) (4) SUMATRIPTAN in support of the proposed NDA is comprised of a single adequate and well-controlled Phase 3 study (OPN-SUMMIG-3301) and a supportive Phase 2 study (OPTUK-MSPP PRO 002). The Sponsor believes that results from these studies provide sufficient evidence of efficacy in the treatment of patients with acute migraine to justify submission of an NDA for the proposed use. Does the Division agree? ***FDA Preliminary Response****: In form, your clinical studies can potentially provide sufficient evidence of efficacy and therefore support the submission of your planned NDA.* ***Meeting Discussion****: The agency confirmed that provided AVP-825 was shown to be bioequivalent or produced higher exposure than another approved dosage form of Imitrex, showing a statistical significance on migraine associated symptoms would not be required*.	Please see 2.7.2 Summary of Clinical Pharmacology and 2.7.4 Summary of Clinical Safety.
November 22, 2010 pre-IND Meeting/ Statistical Analysis Plan (SAP) ***FDA Response****: Your data analysis plan will be reviewed when you submit the study protocol to the IND*.	See 5.3.5.1 OPN-SUM-MIG-3301 SAP
November 22, 2010 pre-IND Meeting/ Nasal Mucosa Exposure and Local Safety Assessments ***FDA Response****: The design of the Phase I study intended to determine the comparative pharmacokinetics of* (b) (4) *SUMATRIPTAN, Imitrex Nasal Spray, Imitrex Injection, and Imitrex Oral Tablet appears to be reasonable.* *Again, an efficacy study may not be needed if you are able to show bioequivalence between your product and one of the dosage forms of Imitrex. In addition, your product appears to potentially expose a greater surface area of the nasal mucosa*	The systemic exposure of sumatriptan with AVP-825 has been demonstrated to be well within the range of the approved sumatriptan formulations. The bioavailability of

Table 5: NDA 206099 FDA-Sponsor Clinical Development Discussions	
Discussion Topic/FDA Feedback	**Sponsor Response/Action**
than the currently approved intranasal IMITREX, and it is unclear that you will be able to rely on the previous findings of safety of IMITREX to support the local long-term safety (at the site of administration) of (b) (4) SUMATRIPTAN. Therefore, further assessment of local toxicity with chronic use of (b) (4) SUMATRIPTAN may be needed. The typical requirement is for data on at least 300 patients followed for 6 months, and 100 followed for 12 months, treating on average at least 2 migraine attacks per month. ***Meeting Discussion**: The sponsor made the following points:* • *(b) (4) SUMATRIPTAN is not deposited in any area of nasal epithelium which is not exposed to Imitrex Nasal Spray. Deposition differences described in the briefing book refer primarily to initial deposition (first few minutes).* • *Because of normal ciliary clearance, powder and nasal spray medications are rapidly cleared so that by 30 minutes after treatment, the total and regional distribution are indistinguishable.* • *Initial deposition to a greater surface area would reduce the level of local epithelial exposure.* *The sponsor asked whether the Agency could consider the argument as outlined above and allow (b) (4) SUMATRIPTAN to rely on the previous findings of safety of IMITREX to support the local long-term safety (at the site of administration). The Agency stated that the sponsor should submit their full argument in the IND, and it will be reviewed at that time*.	AVP-825 (AUC $_{0-\infty}$ and C_{max}) are similar to or higher than IMITREX®, nasal spray and less than 6 mg of the IMITREX® SC Injection and 100 mg IMITREX® Oral Tablets. Bioequivalence between AVP-825 and an approved formulation of sumatriptan was not established. Therefore, a pivotal efficacy trial was performed. See 2.7.3 Summary of Clinical Efficacy for evidence of the efficacy and safety of AVP-825 for the treatment of acute migraine with or without aura. AVP-825 exposes the same or smaller surface area of the nasal mucosa than the currently approved intranasal Imitrex. Therefore, further assessment of local toxicity is not required. See 2.7.4 Summary of Clinical Efficacy, 5.3.5.4 OPT-SUM-GAM-001 and 5.3.5.4 OPT-SUM-GAM-002
<u>February 22, 2012 30-day Review Comments/ 505(b)(2) safety exposures & Comparative Nasal Epithelial Exposures</u> ***FDA Response**: You stated that your studies "found that (b) (4) bi-directional delivery does not deposit medication to an area of the nose not already reached with traditional nasal spray delivery, does not produce longer total exposure, and does not produce significantly greater exposure in any region of the nose beyond the first minutes following administration; rather the relative proportion of administered dose in each area of the nasal cavity is initially different and the pattern of delivery is more consistent across subjects. An important point regarding relative local exposure within the nasal cavity between (b) (4) SUMATRIPTAN and Imitrex Nasal Spray is that the former will produce markedly less local exposure given that only half the dose is administered to a given nostril. Specifically, (b) (4) SUMATRIPTAN is used in divided doses of 10 mg per nostril, where Imitrex Nasal Spray delivers 20 mg into a single nostril. Although (b) (4) SUMATRIPTAN is administered as a powder it is expected to enter into solution rapidly once in the nasal cavity (15 mg dissolves in 250 µL of water in less than 30 seconds). Thus, there is potential for much less local sumatriptan nasal exposure with (b) (4) SUMATRIPTAN than with the approved Imitrex Nasal Spray."* *If the data submitted in your NDA support that the local and systemic exposure with (b) (4) SUMATRIPTAN is no*	

Table 5: NDA 206099 FDA-Sponsor Clinical Development Discussions

Discussion Topic/FDA Feedback	Sponsor Response/Action
greater than with Imitrex Nasal Spray, then it would be acceptable to rely on long term safety data from Imitrex Nasal Spray. Importantly, you would also need to make the case that contact with the olfactory epithelium is no higher (in extent and/or duration) with your product than with Imitrex Nasal Spray.	
June 14, 2012 Clinical Meeting/ Comparative Nasal Epithelial Exposures Regarding local site of administration safety assessment, OptiNose has presented its approach for addressing the question from the FDA regarding comparative nasal epithelial exposures (including the olfactory region) for (b) (4) SUMATRIPTAN versus Imitrex Nasal Spray. • Can the FDA confirm if this approach, including these types of data and this justification, does or does not support the conclusion that no clinical safety data beyond what is proposed will be required? • If not, can the FDA please clarify what increment to the clinical safety exposure database (numbers of patients and duration of use and/or numbers of migraines irrespective of duration of use) would constitute an adequate NDA safety package to address local site of administration tolerability? ***FDA Response**: On face, your approach supports the conclusion that no clinical safety data beyond what is proposed will be required. Please include the relevant study reports and data with your NDA submission.*	No further action required. Please see 2.7.4 Summary of Clinical Safety, Section 2.7.4.1.3.
July 22, 2013 pre-NDA Meeting/ Number of subjects A total of 222 subjects will have received a least a single dose of (b) (4) SUMATRIPTAN in the clinical program conducted in support of the proposed NDA. For the proposed (b) (4) SUMATRIPTAN NDA, the Sponsor intends to incorporate by reference via the 505(b)(2) pathway data in the NDA 020080 (Imitrex for injection; Glaxo Smithkline), NDA 020132 (Imitrex tablet; GSK) for systemic exposure and NDA 020626 (Imitrex nasal spray; GSK) for local exposure. These references are being done in order to fulfil the requirements of the ICH E1A Guideline for Industry "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Longterm Treatment of Non-Life-Threatening Conditions" for the active drug, sumatriptan succinate. Clinical pharmacokinetic and scintigraphy studies provide evidence that exposure to sumatriptan from administration of (b) (4) SUMATRIPTAN does not exceed that of the reference product systemically or to the site of administration in the nasal cavity. Therefore, the Sponsor believes that requirements for population exposure are met by referencing the cited marketing applications of previous innovator products via the 505(b)(2) pathway. Does the Division agree with the proposed 505(b)(2) approach to meet the requirements for the extent of exposure of sumatriptan succinate in support of the proposed NDA? ***FDA Response**: We agree, on face, with the proposed 505(b)(2) approach in support of the NDA. Adequacy of the population exposure to sumatriptan, however, is a review issue and will be determined during the NDA review process.*	No action required.
November 22, 2010 pre-IND Meeting/ Repeat (second) dose and labelling Sumatriptan has been well studied and shown to be safe and effective across 3 different dosage forms within a wide range of systemic exposure. The systemic exposure of sumatriptan with (b) (4) SUMATRIPTAN has been demonstrated to be well within the range of the approved sumatriptan formulations. In fact, the PK profile closely matches that of the already approved intranasal formulation where the maximum plasma concentrations (Cmax) as well as overall exposure (area under the plasma concentration-time curve extrapolated to infinity [AUCo-∞]) values are substantially lower than that observed with the injection and oral tablets of sumatriptan. In the already completed Phase II study, 78 subjects were treated with (b) (4) SUMATRIPTAN. The proposed Phase III study will have 100 subjects per treatment arm,	The OPN-SUM-MIG-3302 study allows a second dose of AVP-825 120 minutes after the first dose. Please see the progress report (5.3.5.4 OPN-SUM-MIG-3302) The full OPN-SUM-MIG-3302 CSR will be submitted when the study has completed.

Table 5: NDA 206099 FDA-Sponsor Clinical Development Discussions	
Discussion Topic/FDA Feedback	**Sponsor Response/Action**
therefore it is anticipated that at its completion the total number of subject exposures to (b) (4) SUMATRIPTAN within the NDA submission will be approximately 178. In the Phase III study subjects will be permitted to use a second dose of medication if there is no relief after 2 hours or there is a reoccurrence of headache. Given that the systemic exposure of sumatriptan with (b) (4) SUMATRIPTAN is well within that observed with the approved dosage forms and the submission will be a 505(b)(2) referencing the extensive amount of safety information within the Imitrex Nasal Spray, oral and injection NDAs, does the Division agree that the proposed number of subjects as outlined is acceptable? ***Preliminary FDA Response****: (Also, see responses to Nasal Mucosa Exposure and Local Safety Assessments addressed during the meeting). Additionally, to support language suggesting that a second dose may be beneficial, you will need to demonstrate safety and efficacy of a second dose, e.g. by re-randomizing patients who had an inadequate response to drug or placebo, and assessing the response to a second dose.* ***Meeting discussion****: The sponsor reported that the approved product label for Imitrex Nasal Spray states, "if the headache returns, the dose may be repeated once after 2 hours". The sponsor asked whether their study, as described, is appropriate to support similar language.* ***FDA Response****: The Agency said no and reiterated that the sponsor would have to show an actual benefit from a getting a second dose. As mentioned above, this would entail conducting a study assessing the benefits of a second dose. A multiple dose PK study may also be required. In addition, the Agency suggested the sponsor review the label for Sumavel Dosepro as an example of what would be acceptable language regarding a second dose treatment, absent data supporting the efficacy of a second dose*.	
February 2, 2012 FDA Advice/ OPNSUM-1302 ***FDA Response****: We have completed our 30-day safety review of your application and, as communicated to you on December 14, 2011, have concluded that you may proceed with your proposed clinical investigation for the acute treatment of migraine. In addition, we have the following comments for your consideration, regarding Study OPNSUM-1302:* *1. You should take T_{max} into consideration when comparing your product to Imitrex Nasal Spray.* *2. Variability in PK parameters following administration of your product ranges from 30%-60%. Provide a justification for your sample size (n=20) selection*.	See OPNSUM-1302, Section 11.
July 22, 2013 pre-NDA Meeting/ ISE For the NDA, the Sponsor intends to summarize efficacy results from the single adequate and well-controlled Phase 3 study (OPN-SUM-MIG-3301) and the supporting Phase 2 study (OPTUK-MSPP PRO 002) separately. No integration or pooling of data from these two studies is planned. Does the division agree with the proposed analysis plan for efficacy data? ***FDA Response****: We agree*.	No further action required
July 22, 2013 pre-NDA Meeting/ ISE and Summary of Clinical Efficacy As described in Question 5, the Sponsor does not intend to integrate efficacy data across studies and, therefore, does not intend to provide a separate ISE document. All efficacy results will be summarized in Section 2.7.3 Clinical Summary of Efficacy, and efficacy data will be provided in Module 5. Does the Division agree with the Sponsor's plan to discuss the efficacy analyses in Section 2.7.3 rather than in a separate document?	No further action required. See 2.7.3 Summary of Clinical Efficacy

Table 5: NDA 206099 FDA-Sponsor Clinical Development Discussions	
Discussion Topic/FDA Feedback	**Sponsor Response/Action**
***FDA Response**: We agree*.	
July 22, 2013 pre-NDA Meeting/ ISS For the NDA, the Sponsor intends to integrate and summarize safety results from the Phase 3 study (OPN-SUM-MIG-3301) and the supporting Phase 2 study (OPTUK-MSPP PRO 002). Safety data from Phase 1/Bioavailability studies (OPTUK-MSPP PRO 001 in migraine patients and OPN-SUM-1302 in healthy subjects) will be summarized separately with no data integration. Does the division agree with the analysis plan for safety data? ***FDA Response**: We agree*.	No further action required
July 22, 2013 pre-NDA Meeting/ ISS and Summary of Clinical Safety The Sponsor proposes to integrate the planned ISS analyses into Section 2.7.4 Clinical Summary of Safety and will not provide a separate ISS document. The size of the clinical program suggests that the ISS will be small enough to allow incorporation into Section 2.7.4 and therefore, a separate ISS document is not necessary. Results of the ISS analyses will be provided in Module 5. Does the Division agree with the Sponsor's plan to incorporate the results of the ISS analyses in Section 2.7.4 rather than in a separate document? ***FDA Response**: We agree*.	No further action required. See 2.7.4 Summary of Clinical Safety
July 22, 2013 pre-NDA Meeting/ CRFs During clinical trials of (b) (4) SUMATRIPTAN, there were no deaths or discontinuations due to an adverse event, and therefore, no CRFs are planned to be submitted in the NDA. Are there any other categories, beyond deaths or discontinuations due to AEs, for which the Division would like CRFs to be submitted? During pivotal clinical trials of (b) (4) SUMATRIPTAN, there were no deaths, discontinuations due to AEs, or SAEs reported, and therefore, no patient narratives are planned to be provided in the NDA. Are there any other categories of adverse events for which the Division would like narratives submitted in the NDA? ***FDA Response**: Your comments (for parts b and c) in this question imply that there were SAEs reported in the supportive study. Therefore, we request that you provide CRFs and patient narratives of SAEs for the pivotal and supportive clinical studies.* ***Meeting Discussion**: FDA agreed that while there have been no SAEs to date, Sponsor will provide patient narratives and CRFs of any SAEs reported from the ongoing supportive clinical study*.	There were no SAEs in any of the clinical studies conducted to support this NDA.
July 22, 2013 pre-NDA Meeting/ CRTs The Sponsor intends to submit Case Report Tabulation (CRT) as part of the NDA package. The CRT will include documentation of data (define.xml) and Study Data Tabulation Model (SDTM) for clinical studies OPTUK-MSPP PRO 002, OPN-SUM-MIG-3301, and OPN- SUM-1302. In addition, the Sponsor plans to submit analysis data published in scientific data set format (SDS 1.6 – ADaM IG 1.0) along with source data published in SDS 1.6 (ADaM IG). ***FDA Preliminary Response**: While we agree in form to your proposal, we may have additional specific instructions related to data organization. If so, these will be included in the final pre-NDA meeting minutes.* ***Meeting Discussion**: We agree with your proposal and have no further requests*.	No further action required.
January 7, 2014 Email/CRTs In our NDA, we are submitting both the SDTM and ADaM data sets for the two safety and efficacy studies (OPTUK-MSPP PRO 002, OPN-SUM-MIG-3301). For the Phase 1 OPN-SUM-1302 pharmacokinetic study, because we plan to submit the	No further action required.

Table 5: NDA 206099 FDA-Sponsor Clinical Development Discussions	
Discussion Topic/FDA Feedback	**Sponsor Response/Action**
SDTM datasets that include the necessary derived PK variables (e.g. Cmax, AUC, t1/2 etc), we do not plan to submit ADaM datasets for this study in the NDA. ***FDA Response**: We agree*.	
July 22, 2013 pre-NDA Meeting/120 Day Safety Update The clinical program in support of the planned NDA is complete and safety data from these studies will be summarized and integrated as appropriate and provided in the initial NDA submission. Additionally, a Phase 3 study (OPN-SUM-MIG-3302) comparing (b) (4) SUMATRIPTAN to oral sumatriptan is ongoing and all then-available blinded safety data from this study will be summarized in the initial NDA submission as a progress report. The Sponsor believes that safety information from this study is not pivotal to an assessment of safety of (b) (4) SUMATRIPTAN in the marketing application, which references safety information for innovator products via the 505(b)(2) pathway. The Sponsor does not intend to incorporate safety results from this study once completed and unblinded into the integrated safety analyses conducted for the NDA. Accordingly, the Sponsor proposes that a full 120 day safety update is not needed and proposes to submit the CSR for Study OPN-SUM-MIG-3302 as the 120-day safety update. Does the Division agree to accept the CSR for the ongoing blinded study to meet the requirement for a 120 day safety update? ***FDA Response**: We agree*.	No further action required.
Ref: eCTD seq 0000; Module 1.6.3 Correspondence regarding meetings. Sponsor's Table 3	

2.6 Other Relevant Background Information

None submitted and none required.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the submission was acceptable. The NDA was submitted in eCTD format and conformed to CDISC SDTM standards. The information required for the review of the NDA was well-organized, easy to navigate, and complete.

3.2 Compliance with Good Clinical Practices

The sponsor affirms that ethics committees or institutional review boards approved all studies in the clinical development program. The studies were in compliance with Good Clinical Practice (GCP) standards according to the ICH guidelines and the Declaration of Helsinki. Written informed consent was obtained for all subjects prior to any study related procedure.

3.3 Financial Disclosures

The sponsor provided required information regarding financial disclosure and there was no evidence that any study investigators had financial arrangements that may have introduced significant bias into the results of this trial. Form FDA 3454 provided information for the clinical studies with no disclosable financial interests related to the sponsor of the covered study. Since there were no principal investigators participating who had disclosable financial (royalty), proprietary (patent), and equity (stock holder) interests of concern, Form FDA 3455 was not included. Please see additional Clinical Investigator final disclosure document completed for NDA 206099. EDR location \\CDSESUB1\evsprod\NDA206099\206099.enx; Module 1.3.4.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to Chemistry Manufacturing and Controls review.

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

Avanir is relying on the nonclinical sections of the labeling for the Imitrex nasal spray label for previous findings of safety and efficacy (NDA 020626).

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

No new data was acquired for this 505(b)(2) study.

4.4.2 Pharmacodynamics

No new data was acquired for the 505(b)(2) study.

4.4.3 Pharmacokinetics

Pharmacokinetic studies were reviewed by Dr. Jagan Parepally, Ph.D., Office of Clinical Pharmaceutics. The reader is referred to Dr. Parepally's review for details and for any confirmation of sponsor's findings.

The Division of Neurology Products previously discussed the clinical development program for AVP-825 22 mg with the sponsor (Table 4 and Table 5). Briefly, the pharmacokinetic profile of AVP-825 was characterized in studies OPTUK MSPP IMP 001 and OPN-SUM-1302. OPN-SUM-1302 was a relative bioavailability (BA) study designed to compare the PK of AVP-825 with Imitrex 6 mg injection, 100 mg tablet, and the 20 mg nasal spray formulations. These results provide the required sumatriptan

systemic exposure link between AVP-825 (sumatriptan nasal spray) 22mg and the Imitrex formulations for the approval for AVP-825, 505(b)(2) application.

According to the sponsor, AVP-825 produced a higher and earlier peak exposure (C_{max}), and a higher early exposure (AUC_{0-30} min) relative to 20 mg Imitrex nasal spray, indicating that a greater proportion of sumatriptan was absorbed from the nasal cavity following administration of AVP-825 in the first 30 minutes compared to Imitrex nasal spray in Study OPN-SUM-1302 (Table 6). The overall systemic exposure ($AUC_{0-\infty}$) of AVP-825 was slightly higher than 20 mg Imitrex nasal spray. In contrast, AVP-825 was lower in terms of peak and overall systemic exposure compared to both 100 mg Imitrex Oral Tablet and 6 mg Imitrex SC Injection.

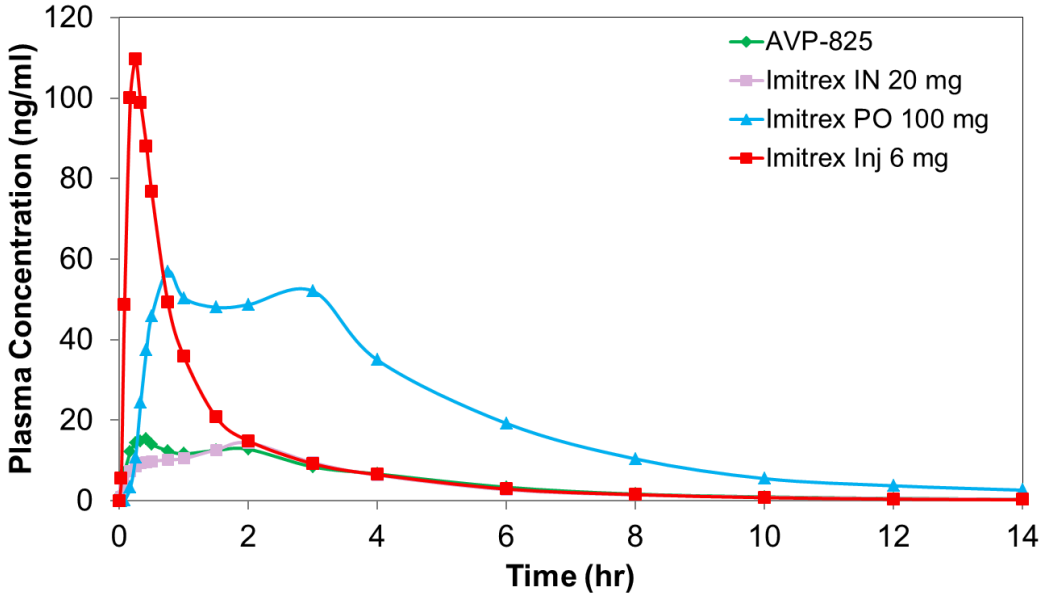
Table 6: NDA 206099 Summary of Mean (SD) Plasma Sumatriptan PK Parameters

	Key Pharmacokinetic Parameters By Rank Order			Increasing Values
	C_{max} (ng/mL)	**AUC_{0-30} min (ng·hr/mL)**	**AUC0-inf (ng·hr/mL)**	
Imitrex Nasal Spray, 20 mg	16.39 ± 5.70	3.59 ± 1.89	61.06 ± 17.78	↓
AVP-825 22 mg	20.78 ± 12.2	5.79 ± 4.11	64.91 ± 20.58	
Imitrex Oral Tablet, 100 mg	70.17 ± 25.3	8.11 ± 4.97	128.22 ± 17.36	
Imitrex Injection, 6 mg	111.63 ± 21.6	39.66 ± 7.09	308.83 ± 92.35	

Ref: eCTD seq 0000; Sponsor's Table 2.7.3 - 2. (Cmax and AUC) by Treatment for Study OPN-SUM-1302 (N=20 for all Treatments)

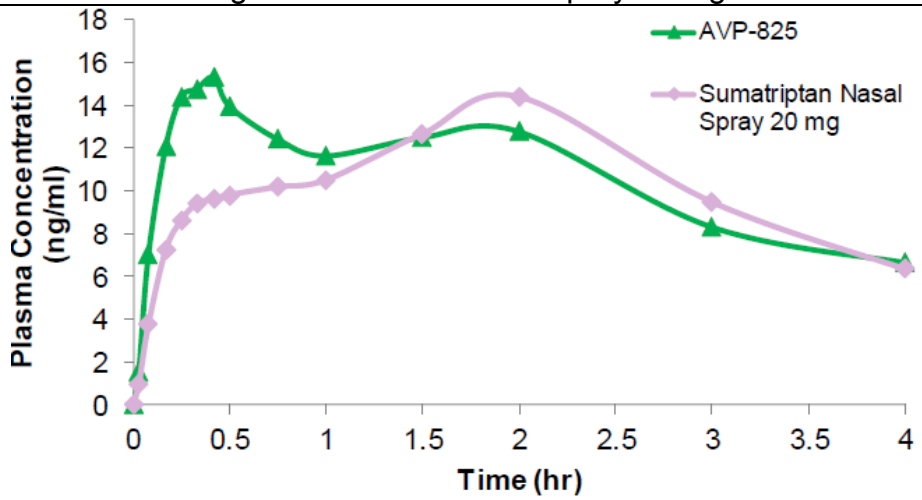
Absorption of sumatriptan following AVP-825 administration occurs within a median T_{max} of 20 to 40 minutes. For Imitrex nasal spray, T_{max} was reached at later time points, between 1 and 1.5 hours after administration. The total bioavailability relative to subcutaneous injection was low, approximately 19% when corrected for emitted dose. The sponsor reported relative bioavailability of AVP-825 was approximately 130% of the relative bioavailability reported for the oral tablet (14.4%) and nasal spray (14.6%). The plasma half-life of AVP-825 was between 2.5 and 3 hours.

Figure 7: NDA 206099 Sumatriptan Plasma Concentration-Time Profiles AVP-825 22 mg versus Imitrex Formulations



Ref: eCTD seq 0000; Sponsor's Figure 2.7.2 - 8. Source: Study Report No. OPN-SUM-1302
Concentration-Time profiles over the entire 14 hour sampling period for AVP-825, Imitrex 20 mg nasal spray, Imitrex 100 mg tablet and Imitrex 6 mg subcutaneous injection - (Linear Scale)

Figure 8: NDA 206099 Sumatriptan Plasma Concentration-Time Profiles AVP-825 22 mg versus Imitrex nasal spray 20 mg



Ref: eCTD seq 0000; Sponsor's Figure 2.7.2 - 9. Source: Study Report No. OPN-SUM-1302
Concentration-Time profiles over the first-4 hours sampling period for AVP-825 compared with Imitrex 20 mg nasal spray

The efficacy data from a single phase 3 study (OPN-SUM-MIG-3301) and supportive data from a phase 2 study (OPTUK-MSPP-PRO-002) is submitted to provide the additional clinical evidence necessary to support approval of AVP 825.

5 Sources of Clinical Data

All documents and datasets reviewed for this NDA submission are in electronic format. The path to this information in the CDER Electronic Document Room is: \\CDSESUB1\evsprod\NDA206099\206099.enx

5.1 Tables of Studies/Clinical Trials

Abbreviations used: AC=active controlled; DB=double-blind; DD=double dummy; PBO= placebo; PO=per oral; hrs=hours; mg=milligram; Rand=randomized; BA=Bioavailability; SC=sub-cutaneous; SD=single dose; IN=intranasal; CSR=clinical study report; PO=oral; Cont.= controlled; F=female; M=male

Table 7: NDA 206099 Overview of Clinical Studies

Study Number/Study Dates	Study Objectives	Study Design	Study Population	N Total Enrolled and Dosed	Test Product(s); Dosage Regimen	Demo-graphics
Bioavailability						
OPN-SUM-1302	Relative BA to Imitrex Oral Tablet, SC, and Nasal Spray	Single-center, open-label, randomized, single-dose, 4-way crossover study	Healthy volunteers	20 5/dose group	AVP-825 intranasal powder 22 mg Imitrex 20 mg Nasal Spray Imitrex 100 mg Tablets Imitrex 6 mg Injection	F=3 (15%) M=17 (85%) Mean age 37 (range 20-54 years)
OPTUK-MSPP IMP-001 (Non-IND)	Relative BA to SC	Open-label, active-treatment controlled, randomized, 3 way cross-over study	Glyceryltrinitrate challenge (on all 3 dosing periods) to induce headache in migraineurs for the effects on quantitative wake EEG of intranasal sumatriptan in subjects with history of migraine	12	AVP-825 intranasal powder 11 mg and 22 mg doses Imitrex SC Injection 6mg Glyceryltrinitrate challenge: sublingual administration of 0.9 mg	F=11 (92%) M=1 (8%) Mean age 31 (±6.5 years)
Efficacy and Safety						
OPN-SUM-MIG-3301 (Phase 3 study)	Headache relief 2-hrs after dosing	Rand, DB, PBO Cont., parallel	15 US sites Patients with Migraine Headache	N=112 per treatment arm	AVP-825 powder 22 mg SD, IN	F=187 (83.9%) M=36 (16.1%)

Table 7: NDA 206099 Overview of Clinical Studies

Study Number/Study Dates	Study Objectives	Study Design	Study Population	N Total Enrolled and Dosed	Test Product(s); Dosage Regimen	Demo-graphics
December 2011 to May 2012		Group			PBO powder SD, IN	Mean age 42 (19-64 yrs)
OPTUK-MSPP PRO-002 (Supportive Phase 2 study) April 2007 to September 2007	Pain Free 2-hrs after dosing	Rand, DB, PBO Cont., parallel group	10 sites Czech Republic Patients with Migraine Headache	N=39 per treatment arm	AVP-825 powder 22 mg SD, IN AVP-825 powder 11 mg, SD, IN PBO powder SD, IN	F=100 (85%) M=17 (15%) Mean age 43 (18-64 yrs)
OPN-SUM-MIG-3302 (Ongoing study)	Headache relief 30-min after dosing	Rand, DB, DD, AC, *cross-over* Patients instructed to treat up to 5 migraine attacks within 3 months		N=275 randomized; N=185 patients treated migraines in both 3-month treatment periods	AVP-825 powder 22 mg SD, IN; PBO powder, SD, IN; Sumatriptan tablet 100mg SD, PO; PBO tablet PO	Not Available
Nasal Exposure/Gamma Scintigraphy studies						
OPT-SUM-GAM-001	Compare the intranasal distribution of an IN delivered dose within the nasal cavity for Imitrex Nasal Spray device and bi-directional device	Cross-over	Healthy volunteers	N=10	Tc ^{99m} labeled *Budesonide powder*, IN Bi-directional delivery device; Tc ^{99m} *labeled DTPA*, Imitrex Nasal Spray device	
OPT-SUM-GAM-002	Compare the intranasal distribution of an IN delivered dose within the nasal cavity for traditional Nasal Spray and bi-directional device	Cross-over	Healthy volunteers	N=7	Tc ^{99m} labeled *lactose powder*, IN Bi-directional delivery device; Tc ^{99m} *labeled DTPA*, traditional Nasal Spray device	

Ref: eCTD seq 0000; Sponsor's Table 2.7.3 – 1. Completed Clinical Study Reports submitted to IND 110,090 and cross-referenced electronically in NDA 206099
*Headache Relief was defined as patients with a baseline headache pain score of moderate (2) or severe (3) improving to either mild (1) or none (0)

5.2 Review Strategy

The clinical program for AVP-825 is primarily relying on establishing relative bioavailability between AVP 825 and Imitrex, the reference listed drug (RLD) conducted under IND 110,090 (see section 4.4.3). Supportive evidence of efficacy of AVP-825 for the treatment of migraine with and without aura is provided from the phase 3 study OPN-SUM-MIG-3301 and the phase 2 study OPTUK-MSPP PRO 002, which are reviewed in Sections 5.3 and 6.

- Phase 3 study (OPN-SUM-MIG-3301): A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of a Single 22 mg Dose of Sumatriptan Powder Delivered Intranasally with the Bi-directional Device in Adults with Acute Migraine With or Without Aura.

- Phase 2 study (OPTUK-MSPP-PRO002): A Double-Blind, Placebo-Controlled Evaluation of Intranasal Sumatriptan Delivered with the (b) (4) Powder Device in the Treatment of Acute Migraine.

Safety information for 22 mg AVP-825 delivered intranasally to be used with the proprietary Xsail breath powered delivery device for the proposed indication of the acute treatment of migraine with or without aura is presented in Section 7, Review of Safety. In addition, cross over studies using Gamma Scintigraphy method for the comparison of nasal deposition patterns with available spray pump and the AVP 825 bi-directional delivery device are summarized in the safety evaluation of the product.

Dr. Jingyu (Julia) Luan, Ph.D. Division of Biometrics performed the statistical analysis for this submission. Applicable portions of her efficacy review have been referenced and incorporated in this review

The doses described in the completed study reports for the studies in Table 7 above refer to 20 mg AVP 825 OR (b) (4) Sumatriptan in the actual study report text, while the product was under development by Optinose US. However, this review refers to the LABELED DOSE AVP 825 (ONZETRA) 22 mg. During prior FDA-sponsor meetings, DNP recommended use of AVP 825 22 mg for clarity. Please refer to explanation in section 6.1.8. The AVP 825 22 mg dose is used in the review to avoid the reader any confusion, and for consistency with previous discussions.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol OPN-SUM-MIG-3301

Title
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of a Single 22 mg Dose of Sumatriptan Powder Delivered Intranasally with the Bi-directional Device in Adults with Acute Migraine With or Without Aura

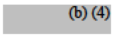
Study Sites
15 centers in the USA

Objective
To compare headache relief (defined as a reduction from moderate [Grade 2] or severe [Grade 3] pain to none [Grade 0] or mild [Grade 1] pain) at 120-minutes following a dose of AVP 825 22 mg with placebo in the acute treatment of a single migraine attack

Design and Methodology
This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and tolerability of a single 22 mg dose of AVP 825 (sumatriptan powder), delivered intranasally with the bi-directional device, during a single migraine episode. Subjects were instructed to use the study drug to treat the first qualifying migraine headache that they experienced following the randomization visit and to initiate treatment as soon as the headache severity reached moderate (Grade 2) or severe (Grade 3) intensity. If for any reason a subject was unable to treat the first attack with study drug, the subject was instructed to use the study drug to treat the next attack. Subjects completed all assessments in the electronic diary for 120 minutes after study drug administration. Subjects completed the electronic diary before taking rescue medication in the event of headache recurrence or if symptom relief was inadequate. If a subject did not experience a qualifying headache within 8 weeks of the randomization visit, he/she was discontinued from the study. The end-of-study visit could occur from 48 hours after treatment of the qualifying migraine headache to 7 days after treatment, when the subjects returned the electronic diary.

Study Schema

Figure 9: NDA 206099 Study Design OPN-SUM-MIG-3301



Ref: eCTD seq 0000; Module 5.3.5.1. Source: Study Report OPN-SUM-MIG-3301. Figure 9.1

Duration
Total time on study = 12-weeks
Treatment period = 8 weeks

Sample Size
Up to 200 subjects randomized to complete the Treatment Period.

Key Inclusion Criteria
1. Patients with episodic migraine with or without aura fulfilling the International Headache Society (IHS) diagnostic criteria 1.1, 1.2.1 and 1.2.3 (International Headache Classification (ICHD)- 2nd Ed, 1st revision 2005)
2. History of 1 – 8 migraine attacks per month for the past 12 months (< 15 headache days per month)
3. Male or female patients aged 18 years or above
4. Have verified airflow through both nostrils and an ability to close the soft palate
5. Demonstrate the ability to use the bi-directional delivery device correctly

Key Exclusion Criteria
1. Inability to distinguish other headaches from migraine
2. Experiences headache of any kind at a frequency greater than or equal to 15 days per month

3. History of resistance to sumatriptan, or non-response to 2 or more other triptans, defined as subjects who have not responded to an adequate dose and duration of treatment
4. Current use of medication for migraine prophylaxis that has not been stable (no dose adjustment) for 30 days prior to screening
5. Chronic opioid therapy (>3 consecutive days in the 30 days prior to screening)
6. Current treatment with monoamine oxidase A (MAO-A) inhibitors or use within 4 weeks before randomization.
7. Current treatment with antipsychotic medications (taken for any indication), or use within 4 weeks before randomization
8. Have hemiplegic or basilar migraine
9. History, symptoms or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort, vasospastic forms of angina such as the Prinzmetal variant), all forms of myocardial infarction and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, Raynaud syndrome
10. Uncontrolled hypertension (screening systolic/diastolic blood pressure >140/95 mmHg)
11. Have severe hepatic impairment
12. Have history of epilepsy or conditions associated with a lowered seizure threshold
13. History (within 2 years) of drug or alcohol abuse as defined by DSM-IV criteria
14. Has any systemic disease which in the opinion of the Investigator would contraindicate participation
15. History of a neurological or psychiatric condition which in the opinion of the Investigator would contraindicate participation
16. History of hypersensitivity or intolerance to sumatriptan, any of its components, or Sulphonamides
17. Known nasal obstruction due to nasal septum deviation, polyposis, severe mucosal swelling, or any other reason
18. Current uncontrolled nasopharyngeal illness
19. Known velum insufficiency, i.e., those with cleft palate and/or structural abnormalities in the soft palate and nasopharynx

Reviewer Comment

The sponsor excludes migraineurs who have a history of resistance to sumatriptan, or non-response to two or more other triptans. The failure to respond to a triptan on one or more migraine occurrences does not predict non-response on subsequent occasion. Protocol OPN-SUM-MIG-3301 is not adequately designed to infer treatment effects in non-responders.

Concomitant Medications
Please see inclusion exclusion criteria.

Rescue Medication
For subjects whose migraine headache persists or worsens after treatment, rescue medication (excluding ergotamine/ergot-type medications) was allowed 120 minutes after treatment. The 120 minute headache assessments in the electronic diary was completed before taking any rescue medication.

Subject Diary
Subjects were asked to assess their headache severity at specified time points: 0 (pre dose), 0.5, 1, 1.5, 2, 3, 4 and 24 and 48 hours post dose using the IHS four point headache severity rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain). Recurrence of pain was assessed between 4 and 24 hours and at 48 hours. Recurrence of pain and second dosing of study medication was assessed between 2 and 24 hours and at 48 hours. At the same time points, 0 (pre dose), 0.5, 1, 1.5, 2, 3, 4 and 24 and 48 hours, subjects were graded the degree of interference with normal activities and the presence or absence (yes/no) of accompanying symptoms: phonophobia, photophobia, nausea. Subjects' diary recorded the exact time at which headache relief became meaningful to them and the time at which they become headache free.

The use of rescue medication was recorded if taken after headache pain free is not achieved at 2 hours. If migraine recurs within 48 hours of dosing, the patient noted the exact time when the headache returns to mild, moderate, or severe intensity after being pain free. Subjects documented the use of any rescue medication and any other symptoms they experienced.

Schedule of Assessments

Table 9.2: Schedule of Procedures and Assessments

Phase	Pretreatment		Double-Blind Treatment[a]			Post-treatment Follow-up
Visit	1	2	Pre-Dose	Post-Dose		3
Procedures and assessments	Screening	Randomization	Onset of Moderate/Severe Migraine Headache Attack	10, 15, 30, 45, 60, 90, and 120 Minutes	After 120 Minutes Through 48 Hours	End-of-Study[b]
Informed consent	X					
Medical and migraine history	X					
Prior medication history	X					
Inclusion and exclusion criteria	X	X				
Pregnancy test (women only)	X (serum)	X (urine)				X (urine)
Hematology, serum chemistry and urinalysis	X					X
Urine drug screen	X					
Full physical examination	X[c]					X
Electrocardiogram	X					X
Blood pressure, pulse measurements	X					X
Randomization/IWRS[d]		X				
Dispense study drug		X				
Collect study drug						X
Provide/collect electronic diary		X				X
Record efficacy/dosing (diary)						
Headache Severity Score			X	X		
Clinical Disability Score			X	X		
Nausea, photophobia, phonophobia, vomiting			X	X		
Time of study drug dose			X			
Time of meaningful relief				X		
Time of recurrence of headache				X	X[e]	
Rescue medication information					X	
Short Form Health Survey (SF-36)		X				
Headache Impact Text (IT-6)		X				
Resource utilization		X				
Notify study site of occurrence of headache/schedule Visit 3					X[f]	
Weekly telephone contact			X[g]			
Completion of Subject Preference Questionnaire						X
Adverse event inquiry[h]	X	X				X
Concomitant medication inquiry	X	X				X

[a] Double-blind treatment phase lasted until subject treated a single migraine headache or until 8 weeks were reached without treating a migraine headache
[b] 48 hours up to 7 days after treatment
[c] Included height and weight at screening only
[d] The interactive web-based response system (IWRS) was contacted at Visit 2 to randomly assign subjects to treatment
[e] Through 24 hours after treatment
[f] Subjects scheduled Visit 3 within 24 hours after treating migraine headache, or the next working day
[g] Clinic to contacted the subject via phone at least once a week during this phase to insure subject had not treated a migraine and forgotten to notify the site staff
[h] Adverse events were monitored from the time the informed consent was signed through completion of the study. Serious adverse events were reported through 30 days after the last dose of study drug administration

Protocol Amendments

The original protocol (August 19, 2011) was amended three times during the study. There were no clinically relevant modifications identified during the review. Copies of the original protocol and amendments are presented in Appendix 16.1.1 of protocol OPN-SUM-MIG-3301 (eCTD module 5.3.5.1).

Efficacy Endpoints and Analysis

Primary Efficacy Endpoint

Percentage of subjects with Headache Pain Relief at 2 hours (120 minutes) after treatment with study drug, defined as a reduction from moderate [Grade 2] or severe [Grade 3] pain to none [Grade 0] or mild [Grade 1] pain.

Headache Severity Scale	
Grade	Definition
0	None
1	Mild
2	Moderate
3	Severe

The migraine-associated symptoms of nausea, phonophobia, and photophobia were evaluated although these endpoints were not prospectively analyzed for efficacy.

The Full Analysis Dataset (FAD) included all subjects who were randomized, received study drug, and recorded at least one post-treatment assessment of pain severity. The treatment group assignment in this population was designated according to the treatment received. The FAD served as the basis for the analysis of efficacy. The primary efficacy analysis compared AVP 825 treatment group to the placebo treatment group using a chi-square test (continuity-corrected).

Key Secondary Efficacy Endpoints

These endpoints were not pre-specified for secondary analyses or multiplicity testing.

- Headache relief at 10, 15, 30, 45, 60, and 90 minutes after treatment
- Complete relief (i.e., pain free, defined as moderate [Grade 2] or severe [Grade 3] reduced to none [Grade 0]) at 10, 15, 30, 45, 60, 90 and 120 minutes after treatment
- Headache severity (0=none, 1= mild, 2=moderate, 3=severe) changes from baseline at 10, 15, 30, 45, 60, 90, and 120 minutes after treatment
- Clinical disability changes from baseline at 10, 15, 30, 45, 60, 90, and 120 minutes after treatment, as measured by the Clinical Disability Scale (0=no disability, 1=mildly impaired, 2= moderately impaired 3= severely impaired)

- Sustained pain-free plus no adverse events (SPFNAE) at 120 minutes after treatment and through 24 and 48 hours
- Presence of nausea, photophobia, phonophobia, or vomiting at 10, 15, 30, 45, 60, 90 and 120 minutes after treatment
- Meaningful relief (subject interpretation) and time to meaningful relief within 120 minutes of treatment
- Maintenance of headache relief over 24, and 48 hours following treatment, where maintenance of headache relief was defined as moderate (Grade 2) or severe (Grade 3) headache pain at baseline going to none (Grade 0) or mild (Grade 1) pain at 2 hours after dosing with no recurrence of headache, or rescue medication up to 24, and 48 hours
- Time to recurrence of headache, defined as an increase from none (Grade 0) or mild (Grade 1) pain to moderate (Grade 2) or severe (Grade 3) pain within 24 hours of treatment
- Use of and time to rescue medication

Safety Monitoring

Safety was monitored with physical examinations, vital signs, ECGs, clinical laboratory testing, and AE/SAE assessments. A nasal examination using a speculum was conducted to ensure that the subject did not have nasal obstruction due to nasal deviations, polyposis, severe mucosal swelling, or any other reason.

Table 1: Laboratory Measurements

Hematology	Serum chemistry	Urine analysis (dipstick)
Hemoglobin Hematocrit RBC count WBC count (total and differential) Platelet count	Urea Creatinine Alkaline phosphatase Alanine aminotransferaseAspartate aminotransferase Total bilirubin γ-Glutamyl Transpeptidase Glucose Electrolytes (Na,K,Cl,Ca) Albumin Total protein	pH Protein Glucose Ketone bodies Indicators of blood and white blood cells

Adverse events (AEs) were coded by MedDRA preferred terms.

Study Results - OPN-SUM-MIG-3301

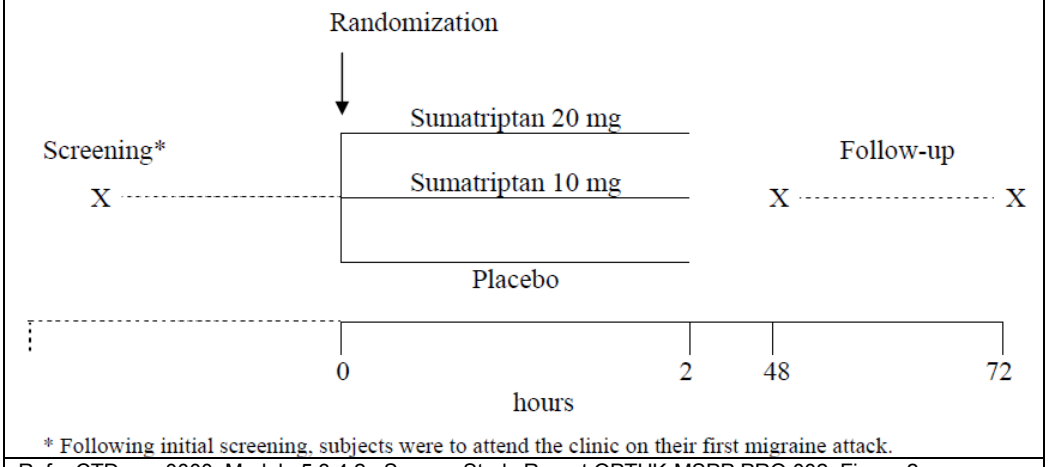
Please see section 6 of this review.

5.3.2 Protocol OPTUK-MSPP PRO 002

This was a multicenter, double-blind, randomized, placebo-controlled dose-ranging, parallel group evaluation of the efficacy and tolerability of either 11 mg or 22 mg AVP-825 during a single migraine episode.

The study subjects included migraineurs ages 18–65 years with International Headache Society criteria of moderate (Grade 2) or severe (Grade 3) headache pain intensity with history of migraine headaches for at least 1 year, with a 3-month, well-documented retrospective history. These migraineurs should have an average of >1 and <6 migraine attacks per month for the past 6 months. Study OPTUK-MSPP PRO 002 required that subjects should report the migraine attack and that they attend the clinic within 4 hours of the onset of the attack. The study exclusion criteria was similar to that described earlier in section 5.3.1 for the phase 3 study (OPN-SUM-MIG-3301).

Figure 10: NDA 206099 Study Design OPTUK-MSPP PRO 002



Ref: eCTD seq 0000; Module 5.3.4.2. Source: Study Report OPTUK-MSPP PRO 002. Figure 2

N=120 subjects were randomized 1:1:1 to each treatment arm. Subjects attended for an initial screening (Visit 1) at which a number of assessments were made and, received instruction on the use of the intranasal device. The subjects were to contact the clinic as soon as they had their next migraine attack. On the treatment day (Visit 2) the subjects attended the clinic and were randomized to receive an intranasal administration of either 11 mg AVP-825, 22 mg AVP-825 or placebo using the device. They were assessed prior to administration, and at 15, 30, 60, 90, and 120 minutes after administration. Headache severity, functional disability and other symptoms (nausea, vomiting, phonophobia and photophobia), and vital signs were assessed at these time points. The subject was asked to measure the time to meaningful relief of the headache using a stopwatch. After treatment the subject returned home and then reported to the study center for follow-up (Visit 3) between 48 to 72 hours later. The safety parameters measured were AEs, physical examination, vital signs, ECG, and clinical laboratory tests.

Study Dosing and Blinding

The dose of 22 mg AVP-825 was given using 2 nosepieces each containing 11 mg AVP-825 with one administration made to each nostril. Where the treatment consisted of a single 11 mg AVP-825, the administration was to the nostril on the same (ipsilateral) side as the migraine headache. Placebo treatment used an identical device to the active treatment, but it contained an empty capsule and no drug. To maintain blinding, half the placebo group subjects received a single placebo administration to one nostril and the other half of the placebo group received 2 administrations, one to each nostril. Again, where the treatment consisted of a single use of AVP-825, the administration was to the nostril on the same (ipsilateral) side as the migraine headache. After the 120-minute assessments if the subject still had a moderate to severe headache (Grade 2 or 3) they were provided with rescue medication.

Table 8: NDA 206099 Dose Exposure OPTUK-MSPP PRO 002

11 mg AVP-825		**22 mg AVP-825**		**Placebo**	
Number of Subjects	Number of Administrations	Number of Subjects	Number of Administrations	Number of Subjects	Number of Administrations
39	39[a]	39	78[b]	39	59[c]

Ref: eCTD seq 0000; Sponsor's Table 2.7.4 – 7. *Data source: 5.3.4.2 OPTUK-MSPP PRO 002, Table 16.4.11
[a]39 administrations to one nostril (one nosepiece) = 39 doses
[b]78 administrations to two nostrils (one nosepiece per nostril) = 39 doses
[c] Approximately half of the subjects assigned to placebo received two administrations to maintain blinding.

Reviewer Comment

The study was inadequately blinded to doses administered. The enrolled patients' and the study site personnel may have been aware of the dosing particularly when the 11 mg dose was administered to one side of the nostril as opposed to two sides in the 22 mg AVP 825 and when half of the patients in the placebo groups received two sides dosage administration. Moreover, the doses were required to be administered at the study site after the subject developed a moderate to severe headache pain.

Primary Efficacy Endpoint

Percentage of subjects with Headache *Pain-Free* at 2 hours (120 minutes) after treatment with study drug, defined as a reduction from moderate [Grade 2] or severe [Grade 3] pain to no [Grade 0] pain.

Headache Severity Scale	
Grade	Definition
0	None
1	Mild
2	Moderate
3	Severe

The migraine-associated symptoms of nausea, phonophobia, and photophobia were evaluated although these endpoints were not prospectively analyzed for efficacy.

The Modified Intent-to-Treat (mITT) population included all subjects who presented with a migraine, received study medication, and had a post-dose primary efficacy evaluation.

Key Secondary Efficacy Endpoints

These endpoints were not pre-specified for secondary analyses or multiplicity testing.

- Headache relief at 10, 15, 30, 45, 60, and 90 minutes after treatment
- Complete relief (i.e., pain free, defined as moderate [Grade 2] or severe [Grade 3] reduced to none [Grade 0]) at 10, 15, 30, 45, 60, 90 and 120 minutes after treatment
- Presence of nausea, photophobia, phonophobia, or vomiting at 10, 15, 30, 45, 60, 90 and 120 minutes after treatment

Study Results

Baseline Demographics

There were no differences in baseline demographics between subjects in the treatment groups. Overall, patients had mean age 36.8 years and 60% were African American with the majority of patients being males (85%). Subjects experienced mean duration of 18-years of experiencing migraine, and they usually had <3 migraine attacks per month at baseline with most of these subjects experiencing moderate headache pain. The following table summarizes the pre-dose headache assessment on the day the patients reported with the migraine headache for study treatment.

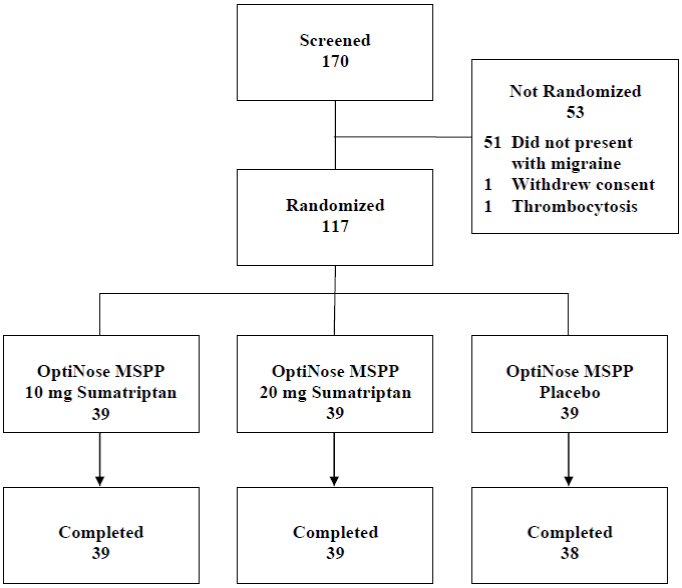
AE Profile	OptiNose MSPP 10 mg Sumatriptan n = 39 n (%)	OptiNose MSPP 20 mg Sumatriptan n = 39 n (%)	Placebo n = 39 n (%)
Migraine Type			
With aura	4 (10.3)	4 (10.3)	2 (5.1)
Without aura	35 (89.7)	35 (89.7)	37 (94.9)
Duration of migraine attack before study medication			
< 4 hours	38 (97.4)	38 (97.4)	38 (97.4)
> 4 hours	0 (0.0)	1 (2.6)	0 (0.0)
Not recorded	1 (2.6)	0 (0.0)	1 (2.6)
Presence of [1]:			
Nausea	32 (82.1)	35 (89.7)	30 (76.9)
Vomiting	2 (5.1)	2 (5.1)	1 (2.6)
Phonophobia	25 (64.1)	22 (56.4)	23 (59.0)
Photophobia	35 (89.7)	35 (89.7)	28 (71.8)
Associated symptoms	3 (7.7)	3 (7.7)	6 (15.4)
Headache severity			
Mild	1 (2.6)	4 (10.3)	7 (17.9)
Moderate	35 (89.7)	30 (76.9)	29 (74.4)
Severe	3 (7.7)	5 (12.8)	3 (7.7)
Functional disability score			
No disability	4 (10.3)	3 (7.7)	3 (7.7)
Daily activities mildly impaired	5 (12.8)	4 (10.3)	10 (25.6)
Daily activities moderately impaired	28 (71.8)	29 (74.4)	23 (59.09)
Daily activities severely impaired	2 (5.1)	3 (7.7)	3 (7.7)
[1]A subject may have had more than one of the listed symptoms.			
Source: Table 14.2.4, Section 14			

Ref: eCTD seq 0000; Module 5.3.4.2. Source: Study Report OPTUK-MSPP PRO 002: Table 10

Subject Disposition

All but one of the subjects randomized completed the study. One subject in the placebo group attended the treatment day, was randomized and treated, but did not attend the follow-up visit scheduled for 48 to 72 hours later.

Twelve subjects (1 in 11 mg group, 4 in the 22 mg group, and 7 in the placebo group) reported experienced mild pain prior to treatment. This was identified as a *major protocol deviation* prior to unblinding and database lock.



Primary Efficacy Endpoint Analysis

All randomized patients (N=39 per treatment-arm) were part of the modified intent-to-treat (mITT) population - subjects who presented with a migraine, received study medication, and had a post-dose primary efficacy evaluation.

The primary endpoint was the proportion of subjects treated with sumatriptan that were pain-free at 120 minutes post-dose compared with placebo. Pain-free was defined as moderate (=2) to severe (=3) headache pain to none (=0).

A greater proportion of subjects in both the 11 mg sumatriptan (53.8% vs 33.3%; p=0.1094) and 22 mg sumatriptan (56.4% vs 33.3%; p=0.0679) groups were pain-free at 120 minutes compared with placebo; however, the differences did not reach statistical significance *using the initially panned mITT population*.

The sponsor also presented in the summary of clinical efficacy, the results from the Full Analysis Dataset (FAD or per protocol). The FAD analyzed population excluded from the mITT population the 12 subjects identified with major protocol deviation (1 in 11 mg group, 4 in the 22 mg group, and 7 in the placebo group) who reported only mild pain prior to treatment. The sponsor believes the FAD population is similar to the population used in Phase 3 study, OPN-SUM-MIG-3301, enabling a comparison of the results across the OPN-SUM-MIG-3301 and the OPTUK-MSPP-PRO002 study. In that case, using the FAD dataset, there is a greater proportion of subjects in both the 11 mg sumatriptan (54.1% vs 25.0%; p=0.0261) and 22 mg sumatriptan (57.1% vs 25.0%; p=0.0127) groups who were pain-free at 120 minutes compared with placebo.

Table 9: NDA 206099 Subjects (%) with Pain Free OPTUK-MSPP PRO 002

The proportion of subjects pain-free over Time	Dose			p-value	
	11 mg N=38	22 mg N=35	Placebo N=32	11 mg	22 mg
60 minutes	11 (29.7%)	12 (34.3%)	6 (18.8%)	-	-
90 minutes	18 (48.6%)	18 (51.4%)	8 (25%)	-	-
120 minutes*	20 (54.1%)	20 (57.1%)	8 (25.0%)	p=0.0261	p=0.0127

Ref: eCTD seq 0000; Sponsor's Table 2.7.3 – 11.
*Data source: 5.3.4.2 OPTUK-MSPP PRO 002, Table 14.2.6A, p-values, comparing with placebo group, are based on Fisher's exact test; Full Analysis Dataset; Subject 001-11 in Sumatriptan 10 mg used rescue medication within 120 minutes post-dose and is not included in analysis. Headache relief is defined as a reduction from moderate (Grade 2) or Severe (Grade 3) pain to none (Grade 0) or mild (Grade 1) pain.

The secondary endpoint headache pain relief at 120 minutes was nominally superior for both tested doses 11 mg (82.1% vs 35.9%; p=0.0001) and 22 mg (82.1% vs 35.9%; p=0.0029) AVP 825 compared to placebo. Headache relief was defined as a reduction in headache severity from moderate (Grade 2) or severe (Grade 3) to none (Grade 0) or mild (Grade 1).

Table 10: NDA 206099 Subjects (%) with Pain Relief OPTUK-MSPP PRO 002

The proportion of subjects pain-relief over Time	Dose			p-value	
	11 mg N=38	22 mg N=35	Placebo N=32	11 mg	22 mg
60 minutes	27 (73%)	26 (74.3%)	12 (37.5%)	-	-
90 minutes	29 (78.4%)	27 (77.1%)	13 (40.6%)	-	-
120 minutes	31 (83.8%)	28 (80.0%)	14 (43.8%)	0.0008	0.0027

Ref: eCTD seq 0000; Sponsor's Table 2.7.3 – 12. Source: 5.3.4.2 OPTUK-MSPP-PRO-002, Table 14.2.7A . p-values, comparing with placebo group, are based on Fisher's exact test; Full Analysis Dataset; Subject 001-11 in Sumatriptan 10 mg used rescue medication within 120 minutes post-dose and is not included in analysis. Headache relief is defined as a reduction from moderate (Grade 2) or Severe (Grade 3) pain to none (Grade 0) or mild (Grade 1) pain.

Reviewer Comment

The results of study OPTUK-MSPP PRO 002, which was conducted in the Czech Republic, may be supportive evidence as a dose finding study. Issues regarding study blinding discussed earlier and the reliance on data from OPTUK-MSPP PRO 002 whether this is an adequately powered study to interpret the treatment difference observed is questionable. However, these results are supportive of the observed efficacy information in the phase 3 study OPN-SUM-MIG-3301. As discussed elsewhere in the review, it was previously communicated to the sponsor that a controlled efficacy study in migraineurs, OR demonstration of statistically significant reduction in migraine associated symptoms compared with placebo would not be required, provided AVP-825 produced a systemic exposure that was equivalent to or higher than an approved dose of Imitrex Nasal Spray. These study results are not recommended for inclusion in the products prescriber information.

6 Review of Efficacy

Efficacy Summary

The clinical program for AVP-825 is primarily relying on establishing relative bioavailability between AVP 825 and Imitrex, the reference listed drug (RLD) conducted under IND 110,090 (see section 4.4.3). Supportive evidence of efficacy of AVP-825 for the treatment of migraine with and without aura is provided from the phase 3 study OPN-SUM-MIG-3301 and the phase 2 study OPTUK-MSPP PRO 002 reviewed in Sections 5.3.2.

The sponsor has adequately demonstrated a statistically significant superiority of AVP 825 over placebo for the primary endpoint (headache pain relief), and the results of study OPN-SUM-MIG-3301 suggest that AVP 825 is effective, as compared to placebo, in adults with acute migraine with or without aura.

Phase 3 study (OPN-SUM-MIG-3301): A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of a Single 22 mg AVP 825 Dose of Sumatriptan Powder Delivered Intranasally with the Bi-directional Device in Adults with Acute Migraine With or Without Aura.

It was previously communicated to the sponsor that a controlled efficacy study in migraineurs, OR demonstration of statistically significant reduction in migraine associated symptoms compared with placebo would not be required, provided AVP-825 produced a systemic exposure that was equivalent to or higher than an approved dose of Imitrex Nasal Spray. See summary discussions in Table 5.

6.1 Indication

The proposed labeling for Onzetra (sumatriptan nasal powder), 22 mg (AVP-825) to be used with the proprietary Xsail breath powered delivery device is for the acute treatment of migraine with or without aura in adults.

6.1.1 Methods

Phase 3 study OPN-SUM-MIG-3301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and tolerability of a single 22 mg AVP 825 dose, delivered intranasally with the bi-directional device, during a single migraine episode. Subjects were randomized in a 1:1 ratio and continued treatment until they treated a single attack or until 8 weeks after randomization, whichever occurred first. The study included a pretreatment screening phase, a double-blind phase, and a post treatment follow-up phase. Rescue medication (excluding

ergotamine) was permitted 120 minutes after the dose of study drug if symptom relief was inadequate. At the screening visit, following informed consent procedures, subjects provided a detailed medical and headache history and a diagnosis of migraine was established in accordance with the International Classification of Headache Disorders-2 (ICHD-2) prepared by the International Headache Society. Subjects were eligible for the study if they had a history of migraine for at least 1 year and a 3-month well documented history with an average of >1 and ≤8 migraine attacks per month for the past 12 months. Subjects must have had the ability to distinguish other headaches from migraine and not have had headaches on 15 or more days per month. Subjects were not to be enrolled into the study if they had a history of resistance to sumatriptan, defined as subjects who have not responded to an adequate dose and duration of treatment. Subjects who are using medications for migraine prophylaxis were permitted to participate in this study.

Following a physical examination, subjects were instructed on the use of the AVP-825 breath powered delivery device. The capsules contained within the nosepieces in the training devices were empty. Once a subject demonstrated the ability to appropriately use the device, blood and urine samples for clinical laboratory assessments were taken and an electrocardiogram (ECG) was performed. At the randomization visit, eligible subjects were assigned to receive either 22 mg AVP-825 or placebo using the interactive web-based response system (IWRS). Following randomization, subjects were provided with and trained on the use of an electronic diary and the assigned study drug was dispensed.

The subjects were instructed to treat the first qualifying migraine headache that they experienced following the randomization visit and to initiate treatment as soon as the headache severity reached moderate (Grade 2) or severe (Grade 3) intensity, with the attack not spontaneously improving prior to dosing. However, if for any reason any subject was unable to treat the first attack with study drug, the subject was instructed to use the study drug to treat the next attack. Subjects were instructed to complete all diary information for the 120-minute assessment time point prior to taking rescue medication in the event of headache recurrence or inadequate symptom relief. Achievement of meaningful relief was recorded. If any subject did not treat a headache within 8 weeks of the randomization visit, he/she was discontinued from the study.

6.1.2 Demographics

Overall, patients were 19 to 64 years of age (mean, 42 years) and 85.8% were Caucasian with the majority of patients being female (83.5%). Subjects had a mean of 4.5 migraine attacks per month in the treated groups.

Baseline Migraine Severity
There was no difference in the baseline severity for the migraine headache treated in this study with moderate headache pain reported for 83% of subjects and severe for 17% of subjects.

Table 11: NDA 206099 Baseline Migraine Characteristics OPN-SUM-MIG-3301

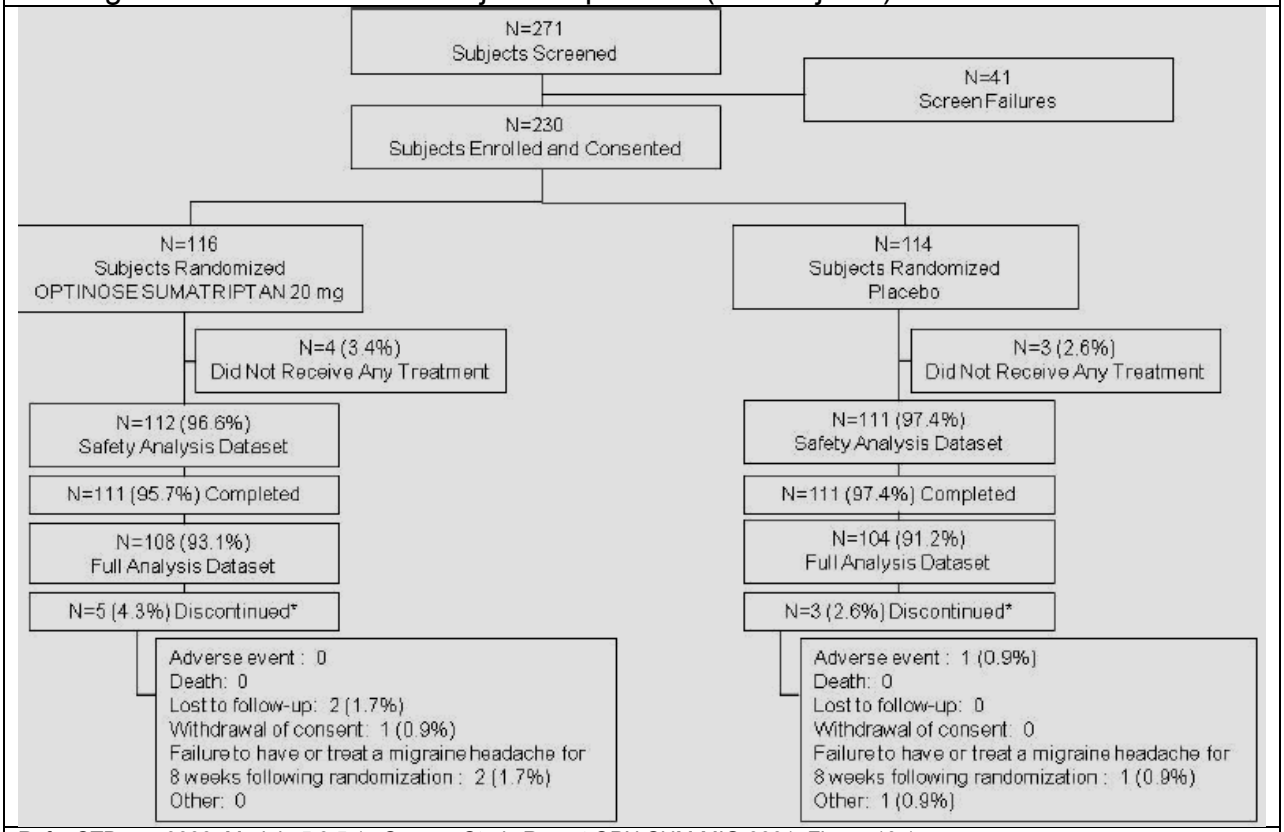
Migraine Headache History	**AVP 825 (%)**	**Placebo (%)**
Vomiting (Past 6-months)	42 (38.9%)	30 (28.8%)
Moderate to severe Photophobia (Past 6-months)	62 (57.4%)	51 (49.1%)
Moderate to severe Phonophobia (Past 6-months)	88 (78.7%)	72 (69.2%)
Prior Intranasal Medication	17 (15.7%)	16 (15.4%)
Ref: NDA 206099 (Full Analysis Dataset; Table 14.1.3)		

6.1.3 Subject Disposition

N=271 subjects were screened, and there were 41 screening failures. Even though 230 subjects were randomized, five subjects (4 untreated) discontinued in the 22 mg AVP 825 group, while 3 subjects (all untreated) discontinued in the placebo group. One subject (Subject 13023) in the placebo group discontinued due to an AE (pregnancy). However, this subject had not taken any study medication.

N=212 subjects (108 AVP-825, 104 Placebo) met the criteria and these subjects were included in the analysis for efficacy, Full Analysis Dataset (FAD). The FAD included all subjects who were randomized, received study drug, and recorded at least one post-treatment assessment of pain severity and served as the basis for the analysis of efficacy. As shown in Figure 11, protocol deviations excluded eleven subjects including placebo treated were excluded from the FAD population. Three subjects randomized to AVP 825: subjects 10003, 13020, and 15017 and seven subjects randomized to placebo: subjects 02003, 05009, 06008, 13021, 13024, 15012 and 15029, took study medication before completing their baseline diary and did not record post-baseline assessments. Another AVP 825 subject (Subject 02010) did not record any post baseline pain assessments.

Figure 11: NDA 206099 Subject Disposition (All Subjects) OPN-SUM-MIG-3301



Ref: eCTD seq 0000; Module 5.3.5.1. Source: Study Report OPN-SUM-MIG-3301. Figure 10.1
*All discontinued subjects were randomized; 4 of the 5 discontinued AVP 825 subjects, and all 3 of the discontinued Placebo subjects were untreated.
Notes: Percentage of subjects were calculated out of the total number of randomized subjects per treatment group.
The Safety Analysis Dataset included all randomized subjects who received at least one dose of study drug. The Full Analysis Dataset (FAD) included all subjects who were randomized, received study drug, and recorded at least one post-treatment assessment of pain severity and served as the basis for the analysis of efficacy. The treatment group assignment for both populations was defined by the treatment received.

Dr. Luan's review notes, "The sponsor presented "Completers Dataset" as a subset of "Randomized Dataset" instead of a subset of "Full Analysis Dataset." Dr. Luan's re-analysis is shown below, where only one patient in the Full Analysis Dataset discontinued from the study (22 mg AVP 825).

Table 12: NDA 206099 Subject Disposition (All Subjects) OPN-SUM-MIG-3301

Dataset	**22 mg AVP 825**	**Placebo**
Randomized Dataset	116	114
Safety Dataset	112	111
Full Analysis Dataset	108	104
Completer Dataset	107	104

Ref: NDA 206099 Dr. Luan's Statistical Review

Compliance and Consistency of Delivered Inhaled Dose
Based on laboratory analysis of drug residuals remaining in nosepieces from 19 subjects, the mean (SD) amount of sumatriptan delivered to the patient was 7.49 mg (4.46, 9.28) per nosepiece and an average of 14.98 mg for both nosepieces or 74.9% of the nominal dose (22 mg). This data was presented in Table 2.7.3 – 7, Summary of Clinical Efficacy. Treatment compliance was rated at 96% after visual observation of empty medication capsules; one subject (Subject 05008) in the AVP 825 group "did not return" and therefore did not return any capsules.

6.1.4 Analysis of Primary Endpoint(s)

I concur with the sponsors analysis that there was a statistically significant mean between-group treatment difference in the 22 mg AVP-825 group, 73 (67.6%) subjects, who reported pain relief at 120 minutes versus the placebo group, 47 (45.2%) subjects (p=0.0016). Headache relief was defined as a reduction in headache severity from moderate (Grade 2) or severe (Grade 3) to none (Grade 0) or mild (Grade 1). Although, headache pain-free is the preferred endpoint, in the treatment of migraine headache applications, 'headache relief' is an acceptable endpoint.

Since the sponsor used the LOCF imputation for handling missing data, Dr. Luan's re-analysis of the full analysis dataset did not produce different results since only one subject discontinued from study OPN-SUM-MIG-3301.

Table 13: NDA 206099 Subjects (%) with Pain Relief OPN-SUM-MIG-3301

Proportion of Subjects with Headache Pain Relief	Dose		p-value
	AVP 825 20 mg N=108	Placebo N=104	
30 minutes	45 (41.7%)	28 (26.9%)	0.032
45 minutes	51 (47.2%)	34 (32.7%)	0.043
60 minutes	60 (55.6%)	38 (35.6%)	0.008
90 minutes	72 (66.7%)	43 (41.3%)	0.0004
120 minutes	73 (67.6%)	47 (45.2%)	0.001

Ref: eCTD seq 0000; Sponsor's Table 2.7.3 – 8. Source Data: 5.3.5.1 OPN-SUM-MIG-3301 End-of-Text Table 14.2.1.
Headache relief is defined as a reduction from moderate (Grade 2) or Severe (Grade 3) pain to none (Grade 0) or mild (Grade 1) pain. FAD = full analysis dataset. The Last Observation Carried Forward (LOCF) imputation was used. P-value was calculated by chi-square test (continuity-corrected).

6.1.5 Analysis of Secondary Endpoints(s)

Pain-Free (OR Complete Headache pain Relief)
Complete Relief was defined as a reduction in pain from moderate (Grade 2) or severe (Grade 3) to none (Grade 0), which is also referred to as pain-free. Although the endpoint was not prospective analyzed, there was nominally greater response at 120-

minutes in the AVP 825 treated group compared to placebo treated migraineurs, 34.3% Versus 17.3%.

Migraine Associated Symptoms

DNP previously discussed with the sponsor that provided AVP-825 was shown to be bioequivalent or produced higher exposure than another approved dosage form of Imitrex, showing a statistical significance on migraine associated symptoms would not be required. I concur with the sponsor's analysis of efficacy. The migraine-associated symptoms were not required for establishing efficacy of AVP 825 and there was demonstration of treatment difference on the endpoint evaluating pain relief.

Even though these endpoints were not prospectively analyzed for efficacy, comparisons between treatment groups for the proportion of subjects with each of the migraine symptoms at 120 minutes post dose is presented in Table 14. Except for the very low incidence of vomiting, the proportion of patients with migraine related symptom was numerically lower in the 22 mg AVP 825 group than in the placebo group.

Table 14: NDA 206099 Migraine Associated Symptoms OPN-SUM-MIG-3301

Migraine Associated Symptoms	**Dose**		**p-value**
	22 mg AVP 825 N=108	**Placebo** N=104	
Nausea-free	88 (81.5%)	82 (78.8%)	0.75
Photophobia-free	56 (51.9%)	42 (40.4%)	0.12
Phonophobia-free	73 (67.6%)	56 (55.6%)	0.10
No Vomiting	106 (98.1%)	104 (100%)	0.49

Ref: eCTD seq 0000; Source Data: 5.3.5.1 OPN-SUM-MIG-3301 End-of-Text Table 14.2.8, 14.2.9, 14.2.10 and 14.2.11

6.1.6 Other Endpoints

The following table is reproduced from the sponsor's submission summarizing the endpoints evaluated.

Table 2.7.3 - 5 Endpoints and Results (OPN-SUM-MIG-3301)

Endpoints	Dose		p-Value
	20 mg N=108	Placebo N=104	
Primary Endpoint			
The comparison of the percentage of subjects in each treatment group who had headache relief* at 120 minutes after treatment with study drug.	73 (67.6%)	47 (45.2%)	p=0.0016
Secondary Endpoints (120 minutes unless indicated otherwise)			
Complete relief	37 (34.3%)	18 (17.3%)	0.0079
Meaningful relief within 120 minutes of treatment	76 (70.4%)	47 (45.2%)	0.0004
Time to meaningful Relief	47 min	>120 min	0.0003
Headache severity **	-1.1 (0.95)	-0.7 (0.83)	0.0018
Clinical disability scores **	-0.8 (0.89)	-0.4 (0.87)	0.0045
Individual migraine related symptoms over time (any non-headache migraine symptom)	66 (61.1%)	79 (76.0%)	0.0275 (60 minutes)
Comparison of the proportion of subjects with nausea between treatment groups	20 (18.5%)	22 (21.2%)	0.7574
Comparison of the proportion of subjects with photophobia between treatment groups	52 (48.1%)	62 (59.6%)	0.1245
Comparison of the proportion of subjects with phonophobia between treatment groups	35 (32.4%)	46 (44.2%)	0.1031
Sustained pain-free, no adverse events (SPFNAE) state over time, 120 minutes	24 (22.2%)	17 (16.3%)	0.3634
Maintained headache relief for 24 hours after treatment among subjects with headache relief at 120 min	48 (65.8%)	25 (53.2%)	0.1693
Maintained headache relief for 48 hours after treatment among subjects with headache relief at 120 min	37 (50.7%)	21 (44.7%)	0.3847
Recurrence of headache within 24 hours of treatment among subjects with headache relief at 120 min	18 (24.7%)	18 (38.3%)	0.1693
Recurrence of headache within 48 hours of treatment among subjects with headache relief at 120 min	24 (32.9%)	21 (44.7%)	0.3847
Rescue medication usage	40 (37.0%)	54 (51.9%)	0.0224

Data Source: 5.3.5.1 OPN-SUM- MIG-3301

6.1.7 Subpopulations

I concur with the sponsor's subgroup analyses based on demographic and baseline values. Dr. Luan presented the results of subgroup analysis by sex, race, and age group in Table 9 of the statistical review for study OPN-SUM-MIG-3301. The results have been consistent with 'triptan' migraine products in demonstrating that the treatment effect is nominally superior in a greater proportion of males and females across age groups and race who responded better to AVP 825 compared to the placebo response.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The proposed labeling for Onzetra (sumatriptan nasal powder), 22 mg (AVP-825) to be used with the proprietary Xsail breath powered delivery device is for the acute treatment of migraine with or without aura in adults.

The amount of sumatriptan succinate contained in each capsule along with the base equivalent released *in vitro* and *in vivo* is presented in Table 15 for each of the clinical studies conducted.

The sponsor provided the following explanation for difference in the doses described in the completed studies (20 mg) and the final product labeled dose (22 mg). In the early studies (OPTUK-MSPP-PRO-001 and OPTUK-MSPP-PRO-002) conducted in Europe prior to the IND being submitted, each capsule within a given nosepiece was loaded with (b) (4) sumatriptan base (b) (4) (b) (4). This fill weight was slightly increased to 11 mg of sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder) for the later phase 3 clinical studies conducted under the U.S. IND (OPN-SUM-MIG-3301 and OPN-SUM-MIG-3302). For commercialization, the sponsor plans to use the same capsule fill weight of 11 mg of sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder). Thus combined delivered dose through 2-nosepieces = 22 mg.

Furthermore, the amount of powdered sumatriptan base delivered *in vivo* identified after the analyses of residual sumatriptan powder in nosepieces used to treat a migraine by subjects in the OPTUK MSPP PRO 002 and OPN-SUM-MIG-3301 clinical studies demonstrated that the actual mean delivered dose was 7.5 mg ± 1.1 mg and 8.1 mg ± 1.1 mg.

DNP communicated at the April 10, 2013 Type C meeting (see Table 5) that the labeled dose be based on the amount of powder sumatriptan base filled into a capsule (i.e., 11 mg), rather than on the amount of drug delivered from the device during *in vitro* testing (i.e., 10 mg) or the amount delivered *in vivo* by migraine patients treating a migraine episode (7.5±1.2 mg). Therefore, the proposed labeling refers to the administration of

drug from two nosepieces (one per nostril) for the treatment of an acute migraine headache as a dose of 22 mg (see proposed Labeling Text). However, the sponsor acknowledges that the clinical study reports, which were prepared before adoption of this dose description, generally refer to a dose of 10 or 20 mg. Table 15 reviews all the capsule fill weights and dose notations used during the development program.

Table 15: NDA 206099 Sumatriptan Dose per Nosepiece in Clinical Study Reports

Parameter	Dose of Sumatriptan in OPN-SUM-3301	Dose of Sumatriptan in OPTUK MSPP IMP 002
Capsule Fill of Sumatriptan, Succinate Salt	(b) (4)	
Capsule Fill of Sumatriptan, Base Equivalent		
Mean (target) Dose of Sumatriptan Base Delivered by AVP 825 *in vitro* when tested at a flow rate of 30 L/min for 4 seconds (2 L total delivered volume)	10 mg	NA
Mean (SD) Dose of Sumatriptan (Base) Delivered per Nosepiece in Migraineurs	7.5 (b) (4) mg	8.1 (b) (4) mg
Dose Descriptions Used in Clinical Study Reports	20 mg (2 nosepieces)	10 mg (1 nosepiece) 20 mg (2 nosepieces)
Labeled Dose	22 mg (2 nosepieces)	22 mg (2 nosepieces)

Ref: eCTD seq 0000; Sponsor's Table 2.5.3 – 3

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Due to the short-term nature of this trial, no comment may be made upon persistence of therapeutic efficacy or tolerance effects of AVP 825.

6.1.10 Additional Efficacy Issues/Analyses

No additional pre-specified efficacy issues or analyses were performed. Subjects were required to complete a Subject Preference Questionnaire at the end-of-study visit (Visit 3). The questionnaire assessed the subject's preference (e.g., taste, ease of use) of the study drug compared with previous medications that they would have received for treatment of migraine headaches. It appears most subjects did not experience difficulty operating the device, or report evidence of discomfort. However, unpleasant taste was reportedly higher for subjects in the AVP 825 22 mg group, which may be the reason for the equivocal response for product preference when it should become available.

Table 16: NDA 206099 Summary of Product Preference Questionnaire

Preference Questionnaire	AVP 825 22 mg	Placebo
How easy to use the study device Very Difficult	0	0

Table 16: NDA 206099 Summary of Product Preference Questionnaire

Preference Questionnaire	AVP 825 22 mg	Placebo
Somewhat difficult	5 (4.6%)	3 (2.9%)
Neither difficult nor easy	12 (11.1%)	5 (4.8%)
Somewhat easy	22 (20.4%)	24 (23.1%)
Very easy	68 (63.0%)	72 (69.2%)
How comfortable to use the study device		
Very uncomfortable	4	5 (4.8%)
Somewhat uncomfortable	16 (14.8%)	9 (8.7%)
Neither uncomfortable nor comfortable	13 (12.0%)	9 (8.7%)
Somewhat comfortable	32 (29.6%)	34 (32.7%)
Very comfortable	42 (38.9%)	47 (45.2%)
How would you describe the taste you experienced when you using the device		
Very unpleasant	22 (20.4%)	1 (1.0%)
Unpleasant	55 (50.9%)	5 (4.8%)
Neither unpleasant nor pleasant	20 (18.5%)	39 (37.5%)
No taste at all	10 (9.3%)	59 (56.7%)
How do you rate the study medication in terms of pain relief		
Poor	39 (36.1%)	63 (60.6%)
Fair	25 (23.1%)	16 (15.4%)
Good	28 (25.9%)	16 (15.4%)
Excellent	15 (9.3%)	9 (8.7%)
How likely is it that you would choose to use the study medication to treat your migraine if it were available		
Very unlikely	36 (33.3%)	44 (42.3%)
Somewhat unlikely	18 (16.7%)	9 (8.7%)
Neutral	18 (16.7%)	22 (21.2%)
Somewhat likely	16 (14.8%)	13 (12.5%)
Very likely	19 (17.6%)	16 (15.4%)

Ref: eCTD seq 0000; Source: 5.3.5.1 OPN-SUM-MIG-3301; End-of-Text Table 14.2.19. Denominators are the number of subjects for the specified population. Data Source: Listing 16.2.6.9. Full Analysis Set. The questionnaire assessed the subject's preference (e.g., taste, ease of use) of the study drug compared with previous medications that they would have received for treatment of migraine headaches.

7 Review of Safety

Safety Summary

The safety of AVP 825 discussion includes the product safety evaluation relating to systemic exposure, local nasal cavity exposure and any of pulmonary safety concerns that may be from product exposure via nasal inhalation.

The sponsor references the following information for AVP-825 Onzetra 505(b)(2) NDA that relies on previous findings pertaining to sumatriptan safety and efficacy from

- Imitrex Nasal Spray (NDA 020626 [local exposure and efficacy])
- Imitrex oral tablet (NDA 020132 [systemic exposure])
- Imitrex injectable, subcutaneous (NDA 020080 [systemic exposure])

DNP informed the sponsor during previous communications, that if the data submitted in the NDA support that the local and systemic exposure with AVP 825 sumatriptan is no greater than with Imitrex, then it would be acceptable to rely on long-term safety data from Imitrex labeled information for their 505(b)(2) NDA. The evaluation will also take into account the nasal olfactory epithelial surface contact in extent and/or duration between AVP 825 and Imitrex (see discussion in section 7.3.5).

There is higher amount of AVP 825 absorbed after nasal delivery and the systemic exposure of sumatriptan is higher than Imitrex nasal spray, although lower than for Imitrex 100 mg tablet and the Imitrex 6 mg SC injection (Table 6), therefore the NDA may rely on referencing the systemic safety data for Imitrex tablets. Reliance on the nasal exposure information for Imitrex nasal spray is acceptable. It does not appear the sponsor requires additional studies in order to fulfil the requirements of the ICH E1 for population exposure.

Please see Table 5 for FDA-sponsor communications regarding discussions for adequate safety evaluation of AVP 825.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

AVP 825 for the treatment of migraine headache has been evaluated in four clinical studies (Table 7): one study in healthy volunteers (OPN-SUM-1302) and one study in migraineurs in whom a migraine was induced by nitroglycerine (OPTUK-MSPP-PRO-001) and two studies where the patients treated a migraine with AVP-825 (OPN-SUM-MIG-3301 and OPTUK-MSPP-PRO-002). A fifth study, OPN- SUM-MIG-3302, which is a multiple-dose double-blind, randomized, active comparator (to oral sumatriptan) study in migraineurs is ongoing.

Information from the phase 3 study OPN-SUM-MIG-3301 is primarily included for additional safety information in the 505(b)(2) NDA review. The results for the pooled studies (OPTUK-MSPP-PRO-002 and OPN-SUM-MIG-3301) for AVP 825 22 mg dose are in section 7.1.3.

In order to provide information on the nasal distribution pattern to estimate safety at the site of administration, the sponsor conducted intranasal deposition studies utilizing gamma scintigraphy to compare relative intranasal distribution patterns associated with a breath-powered intranasal delivery device versus standard nasal spray devices (OPT-SUM-GAM 001 and OPT-SUM-GAM 002). Please additionally refer to section 2.1 of the review regarding the device and its operational mechanics. While ***sumatriptan was not used*** in the gamma scintigraphy studies, the gamma scintigraphy data using the

AVP-825 breath-powered device and the Imitrex nasal spray device were to predict sumatriptan distribution and an understanding of the extent and pattern of local exposure of sumatriptan when delivered via AVP-825 Xsail breath-powered delivery device. The relevant data from OPT-SUM-GAM-001 and OPT-SUM-GAM-002 evaluating local exposure in the nasal cavity are discussed in Section 7.3.5.

Overall, the safety data analyzed in this review were derived primarily from the phase 3 study OPN-SUM-MIG-3301. Since the sponsor is relying on pharmacokinetic information (Table 6) from the RLD for their 505(b)(2) NDA, there was no long-term repeat dose administration study.

7.1.2 Categorization of Adverse Events

OPN-SUM-MIG-3301 adverse events (AEs) were coded to MedDRA dictionary 13.1 and study OPTUK-MSPP-PRO-002 was coded using MedDRA dictionary 13.1. However, since the studies were conducted at different times and to ensure coding consistency, the AEs across the two studies were recoded using version 14.1 of the MedDRA dictionary. Coding included system organ class (SOC) and preferred term (PT). All verbatim descriptions and coded terms were listed.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Study treatments across the two randomized controlled studies (OPTUK-MSPP-PRO-002 and OPN-SUM-MIG-3301) included AVP-825 (11 mg and 22 mg) and placebo. The treatment groups to which the subjects in each individual study were exposed are summarized in Table 17.

Table 17: NDA 206099 Pooled Studies Treatment Information

Study Number	Treatment Groups	Exposures
OPTUK-MSPP-PRO-002	22 mg AVP-825 11 mg AVP-825 Placebo	39 39 39
OPN-SUM-MIG-3301	22 mg AVP-825 Placebo	112 111

Ref: eCTD seq 0000; Sponsor's Table 2.5 – 14

Adverse events for the AVP-825 22 mg dose groups were pooled separately from the AVP-825 11 mg dose group. There were no long-term safety studies due to reliance on the safety information for the RLD. Adverse event data from the pooled studies is listed in section 7.4.1 of the review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

N=222 subjects have been exposed to a single dose of AVP-825 (Table 18). Of these exposures, during controlled studies (Table 17) N=151 subjects received AVP 22 mg (total labeled dose) administered to both nostrils, and N=39 subjects received administration to only one-nostril (AVP 11 mg).

Study OPN- SUM-MIG-3302, which is a multiple-dose randomized, double-blind, double dummy, active comparator (to oral sumatriptan 100 mg tablets) cross over study in migraineurs is ongoing. During each 3-month treatment period, patients were instructed to treat up to five migraine attacks; 185 patients treated migraines in both 3-month treatment periods (full analysis set population). The final report is pending submission at the time of the review.

Table 18: NDA 206099 AVP 825 Subject Exposures by Study

Study Number	Status	Type of Study	Number of Doses	AVP 825 Dose	Number Exposed
OPN-SUM-1302 (healthy subjects)	Completed	PK	Single Dose	22 mg	20
OPTUK-MSPP-IMP-001	Completed	PK	Single Dose	22 mg	12
OPTUK-MSPP-PRO-002	Completed	Dose response	Single Dose	11 mg 22 mg	39 39
OPN-SUM-MIG-3301	Completed	Efficacy & Safety	Single Dose	22 mg	112
				TOTAL	**222**
OPN-SUM-MIG-3302	Ongoing	Efficacy & Safety	Single Dose	22 mg	112

Ref: eCTD seq 0000; Sponsor's Table 2.5 – 13.

Please see patient demographics discussion in section 5.3.2 for study OPTUK-MSPP-PRO-002, and section 6.1.2 for study OPN-SUM-MIG-3301.

7.2.2 Explorations for Dose Response

NDA 206099 (Labeled dose = AVP-825 Onzetra 22 mg) is filed as a 505(b)(2) NDA based on bioequivalence to the referenced listed drug, Imitrex, (sumatriptan succinate) for the acute intermittent use in migraine headache. Single dose of AVP-825 Onzetra 22 mg was evaluated in controlled study OPN-SUM-MIG-3301, and AVP-825 11 mg dose was evaluated in N=39 subjects with a similar number of subjects exposed to placebo and AVP-825 22 mg in study OPTUK MSPP PRO 002.

7.2.3 Special Animal and/or In Vitro Testing

The sponsor conducted a non-GLP, in vitro local tolerance study of the effect of sumatriptan succinate powder AVP-825 and a batch of the solvent precipitated dry formulation (SP25) on mucociliary transport in isolated frog palates. However, it was discussed during the pre-NDA meeting (July 22, 2013) that no additional nonclinical studies will be needed to support an NDA, provided there are no safety concerns (e.g., impurities, leachables/extractables) that would require nonclinical assessment. Based on discipline reviews, nonclinical assessments are not required since no drug product quality issues that raise safety concerns have been identified.

7.2.4 Routine Clinical Testing

The routine clinical safety testing in the NDA 206099 clinical studies seemed appropriate and capable of identifying major safety signals. Analyses performed for this safety summary primarily from the phase 3 clinical study OPN-SUM-MIG-3301 are as follows in.

- Demographics and baseline characteristics (age, race, sex, height, weight, and body mass index [BMI]).
- Treatment-emergent AEs (TEAEs), including:
  - Common AEs (occurring in ≥2% of subjects in any treatment group).
  - Serious AEs.
  - TEAEs that led to treatment discontinuation.
- Vital signs, Electrocardiograms (ECGs), Physical examinations
- TEAEs of special interest (i.e., nasal discomfort, nasal mucosal disorder [erythema] and rhinalgia). A nasal examination (at screening (Visit 1) and at the end-of-study visit (Visit 3)) using a speculum was conducted to ensure that the subject did not have nasal obstruction due to nasal septum deviations, polyposis, severe mucosal swelling, or any other reason.
- Laboratory variables (hematology, serum chemistry, and urinalysis) including summaries of values and change from baseline, shifts based on normal range values, and the frequency of abnormal and markedly abnormal values
- Use of concomitant medications
- Pregnancy testing
- Technical device issues - If a device was suspected of having technical issues (e.g., damaged device, missing parts, inoperable device), the nature of the technical issue was reviewed by the Investigator to determine if the issue resulted in an AE or SAE.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Please see Review Section 2.4, for triptan class relevant safety issues. There were no major issues reported in NDA 206099.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported during the clinical development program of AVP 825 Onzetra 22 mg.

7.3.2 Nonfatal Serious Adverse Events

There were no reports of serious adverse events (21 CFR 312.32(a); 314.80(a)) reported in the studies submitted to NDA 206099.

7.3.3 Dropouts and/or Discontinuations

Phase 3 Study OPN-SUM-MIG-3301
Please refer to Figure 11 and section 6.1.3 of the review that discussed subject disposition for study OPN-SUM-MIG-3301. N=116 were randomized to the AVP 825 treatment and N=114 to placebo. The sponsor's safety analysis dataset included all randomized subjects who received study drug (AVP 825 = 112, Placebo = 111). 4 of the 5 randomized subjects to the AVP 825 group were listed as discontinued and not included in the safety/efficacy analysis because they did not receive study treatment (did not experience migraine), similar to 3 subjects listed as discontinued in the placebo arm (see Figure 11 and Table 12). There were no subjects with serious treatment emergent adverse events and no subjects with treatment emergent adverse events leading to discontinuation.

Study OPTUK-MSPP PRO 002
Please refer to section 5.3.2.

7.3.4 Significant Adverse Events

Phase 3 Study OPN-SUM-MIG-3301

N=45 (40.2%) subjects in the AVP 825 22 mg dose group experienced treatment emergent adverse events (TEAEs) compared to N=15 (13.5%) in the placebo group. No technical device issues or unanticipated adverse device effects were reported during the study.

Table 19: NDA 206099 TEAEs by Maximum Severity AVP 825 22 mg

System Organ Class Preferred Term Maximum Severity	AVP 825 22 mg (N=112)	Placebo (N=111)
Subjects with any TEAE	45 (40.2%)	15 (13.5%)
Mild	31 (27.7%)	14 (12.6%)
Moderate	11 (9.8%)	1 (0.9%)
Severe	3 (2.7%)	0
General disorders and administration site conditions		
Product Taste Abnormal	25 (22.3%)	4 (3.6%)
Mild	19 (17.0%)	4 (3.6%)
Moderate	5 (4.5%)	0
Severe	1 (0.9%)	0
Infections and infestations		
Rhinitis	3 (2.7%)	0
Mild	0	0
Moderate	2 (1.8%)	0
Severe	1 (0.9%)	0
Sinus headache	1 (0.9%)	0
Mild	0	0
Moderate	0	0
Severe	1 (0.9%)	0
Respiratory, thoracic and mediastinal disorders		
Nasal Discomfort	15 (13.4%)	2 (1.8%)
Mild	9 (8.0%)	2 (1.8%)
Moderate	6 (5.4%)	0
Severe	0	0

Ref: eCTD seq 0000; Source: 5.3.5.1 OPN-SUM-MIG-3301; End-of-Text Table 14.3.1-1.7.

Subject who received AVP 22 mg reported the following TEAEs (not listed above), relevant to the product administration and safety. Mild Epistaxis N=1, Rhinalgia N=2, Rhinorrhea mild N=5 and moderate N=1. Please see additional patient reported nasal adverse events listed in Table 22.

7.3.5 Submission Specific Primary Safety Concerns

During regulatory communications, DNP informed the sponsor that the 505(b)(2) NDA needs to support that the local and systemic exposure with AVP 825 is no greater than with Imitrex and the need to make the case that contact with the olfactory epithelium is no higher (in extent and/or duration) in comparison to Imitrex nasal spray.

With regard to systemic exposure, AVP 825 is relatively bioavailable to Imitrex, therefore relying on long-term safety data from Imitrex labeled information for their 505(b)(2) NDA 206099.

Estimating Actual Nasal Exposure With AVP 825

If the AVP 825 bi-directional device delivery (to one nostril) produced a greater extent of exposure to the nasal mucosa, then adequate safety exposure evaluation would apply requiring up to 300 patients treated for 6 months and 100 treated for 12 months with AVP 825 device. However, the proposed labeled dose delivered to the site of administration with AVP 825 (11 mg *to each nostril*) is less than the highest approved dose of Imitrex Nasal Spray (20 mg to one nostril). In that case, there may still be concern from the differential fractional distribution (extent) including the deposition profiles and the duration of exposure between the sumatriptan (inhaled) products, particularly with regard to olfactory region, which are discussed further in this section.

The relative bioavailability study OPN-SUM-1302 (Table 7) evaluated the amount of residual powder remaining in the capsules and disposable nosepieces from the devices used by the subjects. The average amount of residual drug in the capsule and disposable nosepiece was (b) (4) mg of the 11 mg loaded in the capsule. Similar findings were observed from the phase 2 study OPTUK MSPP PRO 002, where approximately (b) (4) % of the nominal dose was delivered to the patient. This represented an average delivery of (b) (4) mg to each nostril ((b) (4) mg to the whole nose) indirectly demonstrating that AVP 825 should produce ~ (b) (4) % lower mucosal exposure than the approved Imitrex nasal spray for the entire nose and, 60% lower exposure for the mucosal surfaces within a given side of the nose ((b) (4)).

Concerns have risen since anosmia was reported with intranasal zinc containing products [3]. In order to evaluate the nasal olfactory epithelial surface contact in extent and/or duration between AVP 825 and Imitrex, the sponsor provided supportive information comparing the AVP 825 bi-directional device to information from traditional spray device use.

Overview of Olfactory Epithelium and Nasal Cavity

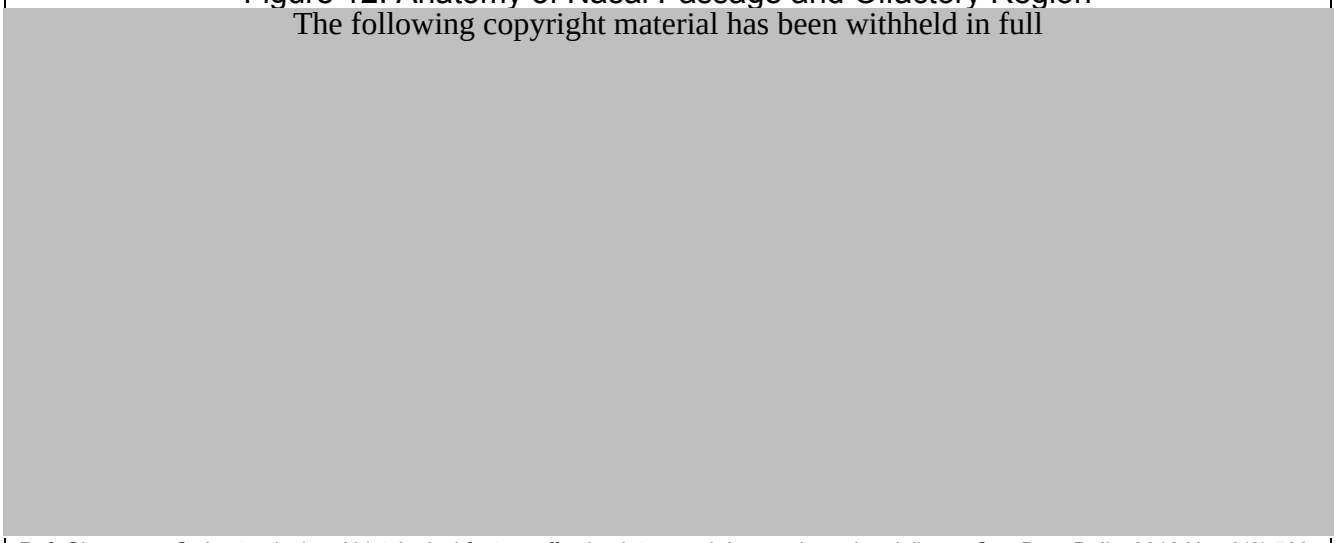
The volume of the human nasal cavity is 15-20 mL. The nasal cavity is much narrower where the olfactory region is located (Figure 12 and Figure 13), which is about 3% of the nasal surface area (total surface area = 150 cm^2). The first cranial nerve (olfactory nerve), however, is the target when direct absorption into the brain is the goal, since this is the only site in the body where the central nervous system is directly expressed on the mucosal surface [4]. Some of the six nerves that serve the nasal cavity cause many of the side effects seen following intranasal administration. Cranial nerve V (trigeminus

[3] http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm166931.htm. October 9, 2014

[4] Gizurarson S. Anatomical and histological factors affecting intranasal drug and vaccine delivery. *Curr Drug Deliv*. 2012 Nov;9(6):566-82.

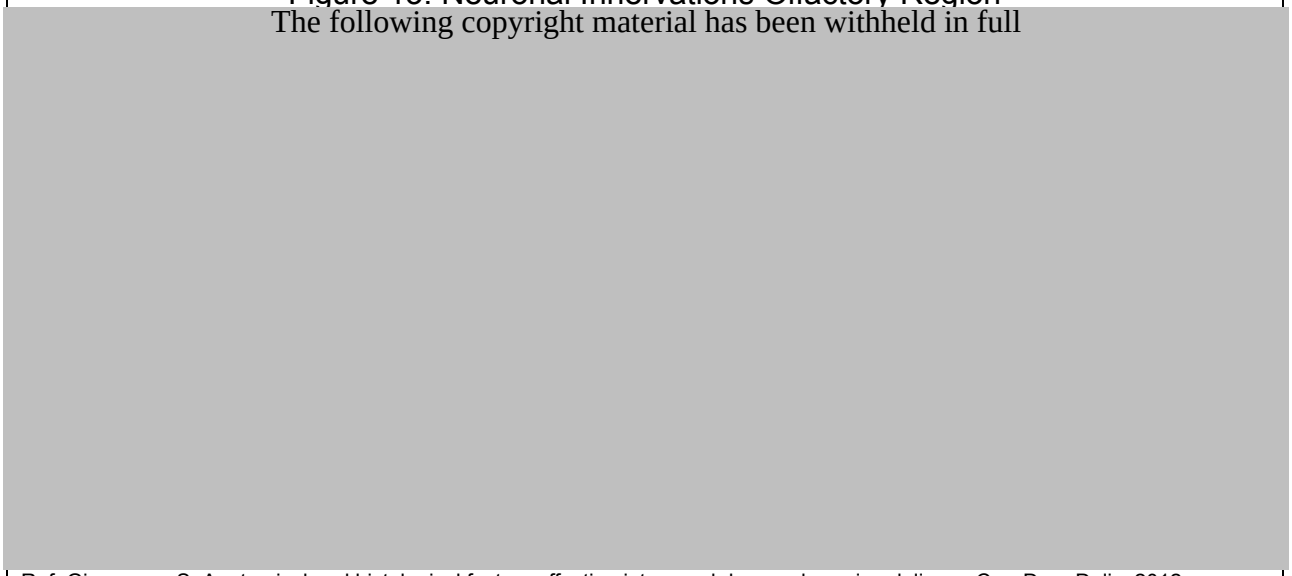
nerve) senses pain and irritation following nasal administration and the cranial nerve VII (facial nerve) will respond to such irritation by stimulating nasal glands to secrete mucus, which dilutes the irritant, facilitating removal rapidly to the nasopharynx and swallowed, also reducing nasal absorption.

Figure 12: Anatomy of Nasal Passage and Olfactory Region



Ref: Gizurarson S. Anatomical and histological factors affecting intranasal drug and vaccine delivery. Curr Drug Deliv. 2012 Nov;9(6):566-82.

Figure 13: Neuronal Innervations Olfactory Region



Ref: Gizurarson S. Anatomical and histological factors affecting intranasal drug and vaccine delivery. Curr Drug Deliv. 2012 Nov;9(6):566-82. Sagittal section of the nasal cavity showing the neuronal innervations, to the lateral wall and the nasal septum

The sense of smell is not derived only from the olfactory nerve as is often considered. The ophthalmic and maxillary divisions of the trigeminal nerve participate in olfaction by

mediating a "common chemical sense".[5] These branches of the trigeminal nerve broadly innervate the nasal cavity at all levels and all methods of nasal administration would expose these neurons to an administered drug. The interaction between the olfactory and trigeminal systems influences perception of odors. Therefore, if a substance were toxic to neurons its negative impact on the sense of smell would likely manifest itself no matter the regional deposition profile within the nose.

Extent and Duration of Exposure to Olfactory Epithelium

In order to determine the intranasal distribution and clearance pattern associated with delivery of a powder from the AVP 825 bidirectional device compared with traditional nasal sprays, the sponsor provided information from gamma scintigraphy studies although these studies did not provide information using sumatriptan product exposure specifically[6]. Gamma scintigraphy is an in vivo imaging tool combined with MRI scan that quantifies amount of drug formulation delivered to target sites.

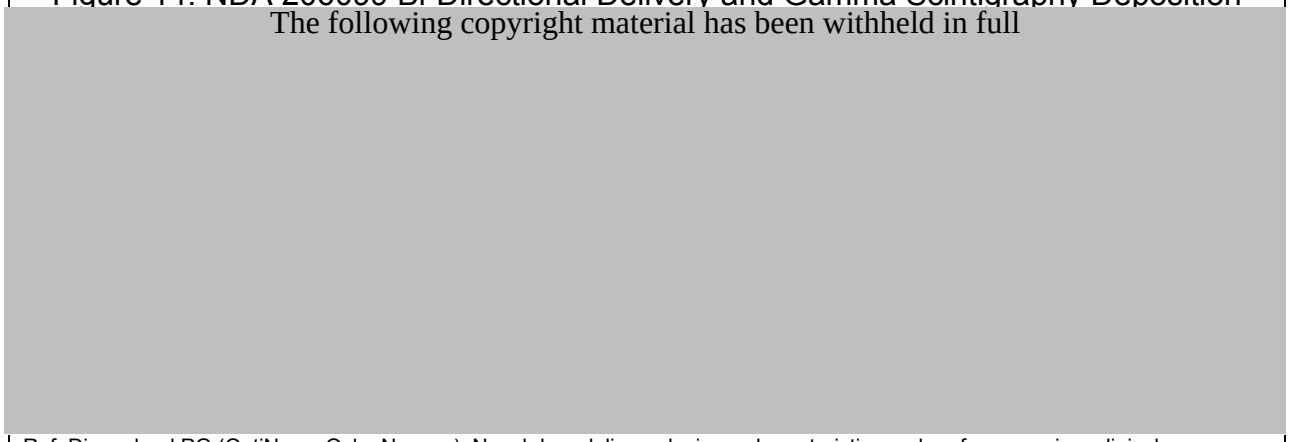
OPT-SUM-GAM-001 compared a *prototype* bi-directional powder delivery device to the same spray pump used with Imitrex Nasal Spray. Budesonide powder was labeled with technetium-99m (Tc^{99m}) and used in the powder device while Tc^{99m} labeled diethylene triamine pentaacetic acid (DTPA) solution was used in the liquid spray pump. The second study, OPT-SUM-GAM-002, compared the final AVP 825 powder delivery device with a standard nasal spray device. Tc^{99m} labeled lactose powder was used in the powder device while Tc^{99m} labeled DTPA solution was used in the spray.

The gamma scintigraphy studies (Figure 14) show the deposition patterns of bi-directional delivery and traditional nasal sprays (product used in that study – budesonide and lactose).

[5] Sahin-Yilmaz A1, Naclerio RM. Anatomy and physiology of the upper airway. *Proc Am Thorac Soc*. 2011 Mar;8(1):31-9.

[6] Djupesland PG, Skretting A. Nasal deposition and clearance in man: comparison of a bidirectional powder device and a traditional liquid spray pump. *J Aerosol Med Pulm Drug Deliv*. 2012 Oct;25(5):280-9.

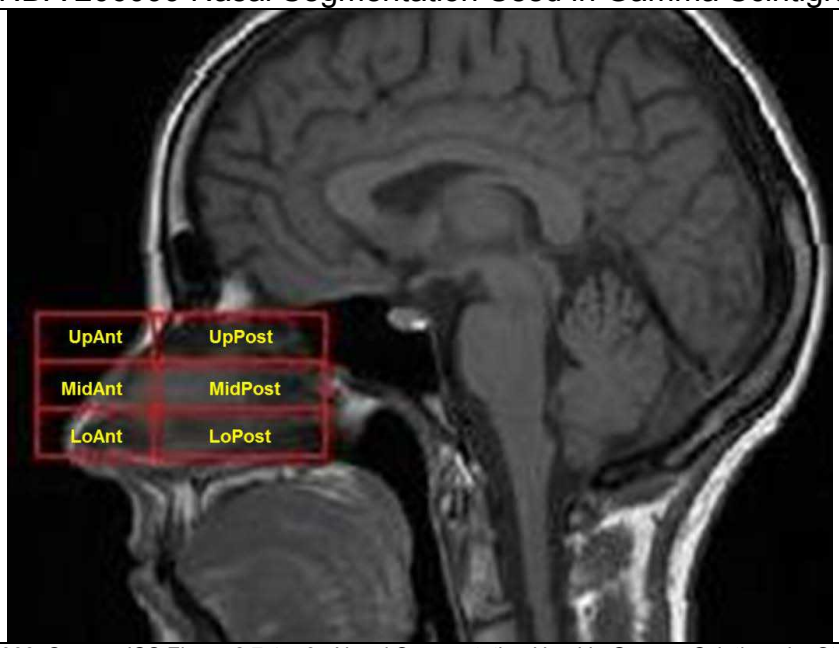
Figure 14: NDA 206099 Bi-Directional Delivery and Gamma Scintigraphy Deposition



Ref: Djupesland PG (OptiNose, Oslo, Norway). Nasal drug delivery devices: characteristics and performance in a clinical perspective-a review. *Drug Deliv Transl Res*. 2013 Feb;3(1):42-62. Epub 2012 Oct 18.
Comparison of deposition patterns with traditional spray pump and bi-directional delivery device incorporating the same spray pump. Gamma camera image information (logarithmic "hot iron" intensity scale) from the nasal cavity is superimposed on the corresponding sagittal MRI section
The initial deposition following traditional spray (A) was greatest in the lower anterior regions of the nose, whereas deposition with the Bi-Directional delivery devices (B) was greatest in the upper posterior regions of the nose. The less broad distr bution following breath-powered Bi-Directional powder device (B) is believed to be due to the slower clearance for powder the first 6–8min, reflecting the dissolution of the powder into the mucosal layer.

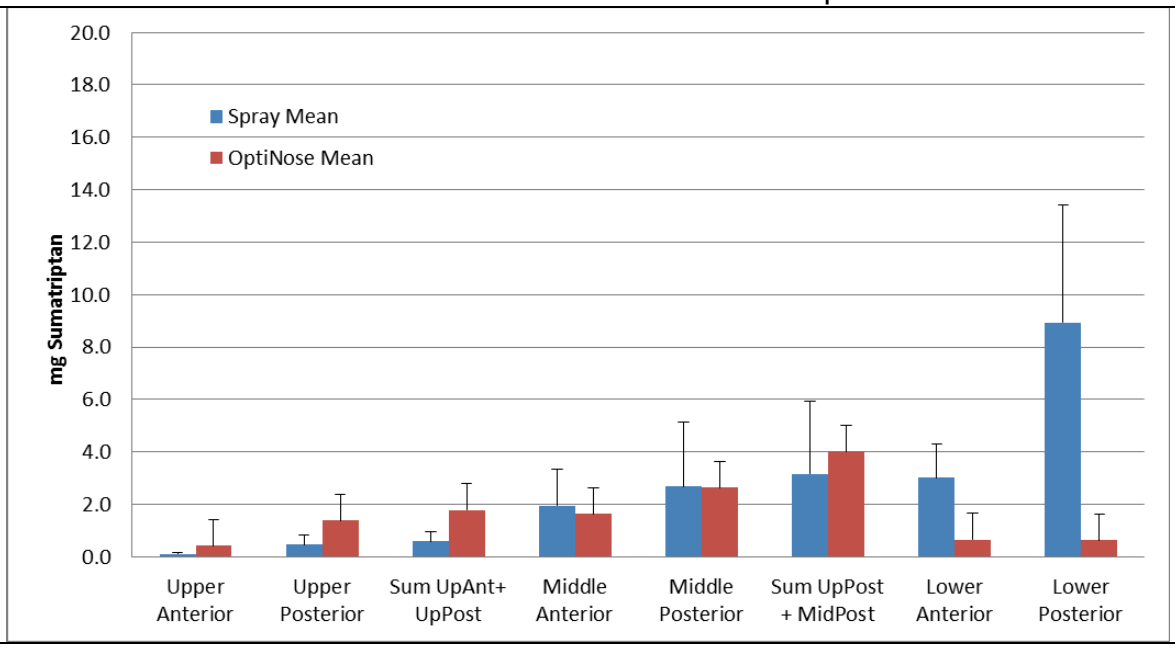
The *distribution patterns* associated with each delivery method show that both methods of administration deposit drug similarly into all areas of the nasal cavity (Figure 16). Although, the bi-directional method deposited on average a smaller percentage of the delivered drug in the (lower) anterior region and a larger proportion in the (upper and middle) posterior region (Figure 16). In addition, there was less *variability* in deposition to the (upper and middle) posterior region for the bi-directional powder delivery compared with the spray (data not shown).

Figure 15: NDA 206099 Nasal Segmentation Used in Gamma Scintigraphy Study



Ref: Ref: eCTD seq 0000; Source: ISS Figure 2.7.4 – 8. Nasal Segmentation Used in Gamma Scintigraphy Study OPT-SUM-GAM-002 – Comparison of AVP-825 and a Standard Nasal Spray

Figure 16: NDA 206099 Distribution Within the Nasal Cavity Adjusted for Mean Calculated Delivered Dose of Sumatriptan

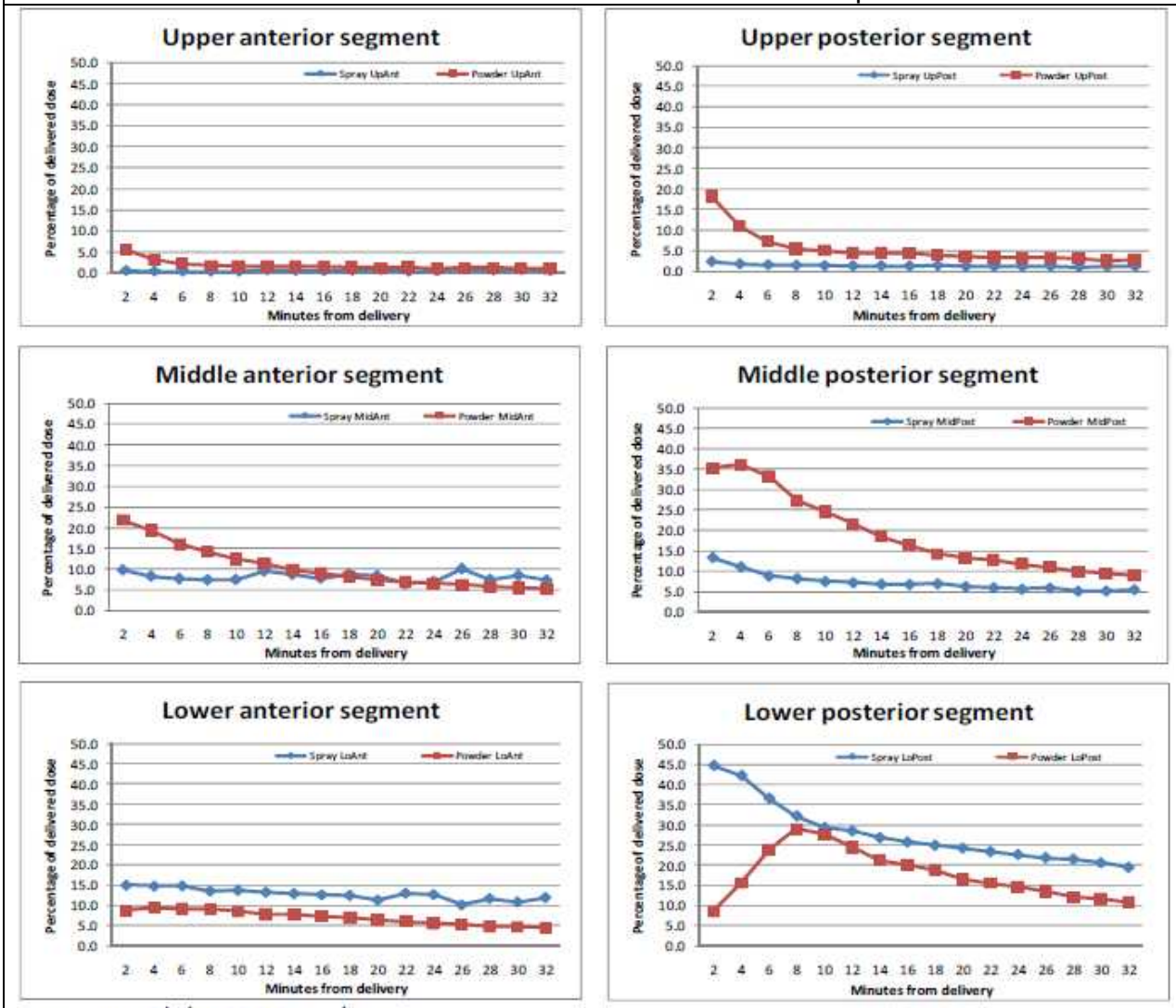


Ref: Ref: eCTD seq 0000; Source: ISS Figure 2.7.4 – 10. Study OPT-SUM-GAM-002 - Initial Distribution Within the Nasal Cavity Adjusted for Mean Calculated Delivered Dose of Sumatriptan with AVP-825 and Imitrex Nasal Spray (mg ±SD)

The upper posterior region clearance
The (upper and middle) posterior region received a proportionally higher fraction of the dose as delivered by the bi-directional device than by the nasal spray, with early clearance observed in the first 10-20 minutes, possibly resulting in relatively similar fractions of the delivered dose remaining in the region thereafter, regardless of delivery mechanism (Figure 17). The normal mucociliary clearance processes likely moved deposited drug onward into the lower posterior region, where an initially lower fraction of drug was deposited by bi-directional delivery as is suggestive from the reported product preference questionnaire (Table 16).

Sumatriptan is freely water soluble. Mucosal contact for affecting olfactory or trigeminal nerve dysfunction in the nasal epithelium requires at least some lipophilicity to facilitate transport. Moreover, there was no difference observed with the AVP 825 sumatriptan that will affect mucociliary transport and clearance which in this case was rapid (normal human mucociliary transit time between 13-15 minutes), and therefore absorption in comparison to Imitrex, the RLD should remain the same.

Figure 17: NDA 206099 Projected Clearance From the Olfactory Region Adjusted for Mean Calculated Delivered Dose of Sumatriptan



Data source: Listing 16.1.4, Section 16.1

UpAnt = upper anterior
MidAnt = middle anterior
LoAnt = lower anterior

UpPost = upper posterior
MidPost = middle posterior
LoPost = lower posterior

Ref: Ref: eCTD seq 0000; Source: Study report OPT-SUM-GAM-002 - Projected Clearance from the Nose Adjusted for Mean Calculated Delivered Dose of Sumatriptan with AVP-825 (OptiNose) and Imitrex Nasal Spray

Since the olfactory epithelium is mostly located in the (upper and middle) posterior region of the nasal cavity, the sponsor extrapolates exposure information to the mucosal surfaces within a given side of the nose using residual capsule estimates of AVP 825 (b) (4) mg vs. Imitrex Nasal Spray 20 mg (Table 15). It was estimated that in the initial 0-2 minutes the mean deposition to the nasal region containing the olfactory epithelium after bidirectional powder delivery was (b) (4) % of the delivered dose (AVP 825 (b) (4) mg)

compared to (b) (4) % for the nasal spray device (Table 20). The sponsor predicts that, on average, AVP 825 bi-directional powder delivery device would deliver (b) (4) mg of sumatriptan to the region of the olfactory epithelium and Imitrex Nasal Spray would deliver (b) (4) mg (Table 20). However, as mentioned earlier, there appears to be more variation in deposition across subjects when using the nasal spray device, where some subjects may have higher (upper) posterior region sumatriptan exposure.

Table 20: NDA 206099 Mean Fraction of Delivered Dose and Calculated Dose of Sumatriptan Deposited in the Region of Olfactory Epithelium*

Parameter	AVP 825	Nasal Spray Pump
Fraction of delivered dose	(b) (4)	
Expected dose of sumatriptan delivered		

Ref: eCTD seq 0000; Source: ISS Table 2.7.4-12.
*Calculated from subject individual normalized counts observed in 0-2 min in the *upper and middle posterior regions*, (Figure 15) by first calculating a percent delivered dose to the region (count/100,000*100) then applying that percentage to the anticipated delivered dose of sumatriptan with the given device: (b) (4) with AVP-825 and (b) (4) with Imitrex Spray Pump.

Particle Size of Budesonide and Lactose Powder Used in Gamma Scintigraphy Study

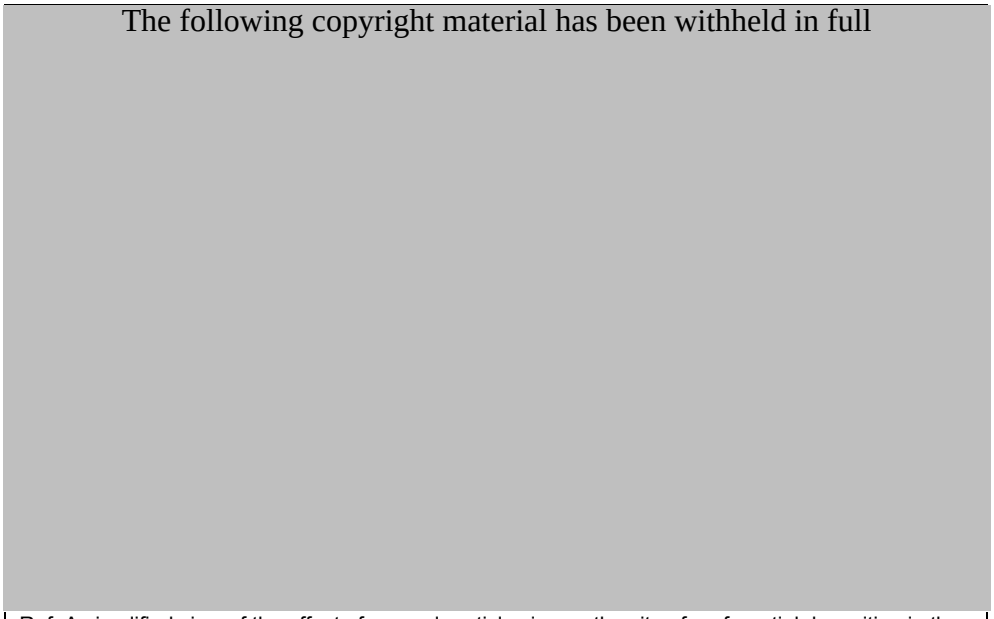
The sponsor reports that even though budesonide powder (4 mg) was used, which is relatively insoluble and the results from study OPT-SUM-GAM-001 probably reflect how an insoluble powder will behave in terms of deposition and clearance. However, results using a soluble powder (capsule filled with 16 mg of technetium-99m (Tc^{99m}) lactose powder) from OPT-SUM-GAM-002 showed similar deposition and clearance patterns to those observed for budesonide in the study OPT-SUM-GAM-001 suggesting that dissolution may not affect clearance from the posterior regions of the nose. Prior studies evaluating impact of particle size distribution showed no difference in deposition to the nasal regions, suggesting that particle size was not a critical factor in determining regional deposition patterns when administered using closed-palate bi-directional delivery.

Even though the powder and liquid used in gamma scintigraphy studies were not sumatriptan, one would expect the actual clearance of sumatriptan may be different. However, since sumatriptan powder is highly water soluble and with close replication of results using different powders that have varied solubility, the clearance from the olfactory region following delivery of sumatriptan from both of these devices is expected to occur at equivalent rates.

Aerosol Particle Size & Lower Airways Deposition

For an aerosol particle to be considered within a respirable range or having the potential to reach the lungs and airways, mechanisms come into play as aerosol particles are inhaled orally or through the nose, when aerosolized medications must be deposited

past the oropharyngeal region[7]. Particle size plays an important role. Larger particles (> 10 µm, 10–100 µm) are deposited mostly in the nose and are filtered in the nose and/or the oropharynx, largely by inertial impaction. Particles of 5–10 µm generally reach the proximal generations of the lower respiratory tract, and particles of 1–5 µm reach to the lung periphery (Figure 18).



Ref: A simplified view of the effect of aerosol particle size on the site of preferential deposition in the airways. Figure 1 A Guide to Aerosol Delivery Devices for Respiratory Therapists, 3rd Edition © 2013

The sponsors study on the effect of flow rate on particle size distribution used flow rates of 15 L/min, 30 L/min, and 45 L/min. The CMC review notes (page 34 of 126) that the particle size fraction with mean D10, D50, and D90 tend to decrease slightly with increasing flow rate whereas the mean percentage of particles less than 10 µm increases slightly. Despite these observed small changes, it appears that the flow rate within the test ranges do not have significant effect on the emitted dose particle size distribution. The particle size is characterized in Table 21.

Table 21: NDA 206099 AVP 825 Sumatriptan Particle Size

AVP 825 Sumatriptan (Stage of Development)	DS Lot #	DP (Capsule Lot #)	%D_{10}	% D_{50}	% D_{90}
Phase I	0370905 (R66172B)	0609004	(b) (4)		
Pivotal	SUM/0110211 (1010748, 1010749, 1010750)	FVTK			
Registration	SUM/0520812	0032R			
Specification	For both DS and DP emitted dose		NMT (b) (4)		NMT

[7] https://www.aarc.org/education/aerosol_devices/aerosol_delivery_guide2.pdf.

		µm	(b) (4) µm	(b) (4) µm

Ref: NDA 206099 CMC review, Section P.2.2.1.
Note: The lot number is (b) (4) lot # and those in parenthesis are (b) (4) lot numbers.

In addition, it appears the device may be used in different positions with no significant effect, as there was no significant difference in the emitted dose content uniformity and emitted dose particle size distribution if flexible mouthpiece device was oriented in different positions (CMC reviewer's notes page 41 of 126).

Lung Deposition
There were no signs of lung deposition evident from the images and it is unlikely mechanistically with the instructed method for device use that this should be of concern.

Treatment-Emergent Adverse Events Of Special Interest
All subjects who were randomized and received treatment recorded use of a nose piece for administration to each nostril, except for subject 08008 where only one nose piece was punctured upon device inspection (although reported as administered dose). This information is listed in the CSR for OPN-SUM-MIG-3301 Listing 16.2.5.2. The sponsor presented treatment-emergent adverse events of special interest (i.e., nasal discomfort, nasal mucosal disorder [erythema] and rhinalgia). There were no AEs reported suggestive of olfactory dysfunction.

Table 22: NDA 206099 Nasal Adverse Events OPN-SUM-MIG-3301

Subject	Verbatim Term	Preferred Term	Severity	Duration (days)	Relatedness to Study Drug
AVP 825 22 mg					
01001	Nasal burning	Nasal discomfort	Moderate	1	Yes
01002	Nasal cavity erythema	Nasal mucosal disorder	Mild	15	Yes
01005	Nasal burning	Nasal discomfort	Moderate	1	Yes
01009	Nasal erythema during current migraine attack	Nasal mucosal disorder	Mild	1	Yes
01013	Nasal burning on left	Nasal discomfort	Mild	1	Yes
01014	Nasal burning	Nasal discomfort	Mild	1	Yes
01020	Nasal burning	Nasal discomfort	Mild	1	Yes
05019	Burning sensation in the nose	Nasal discomfort	Mild	1	Yes
09007	Stinging-bilateral nares	Rhinalgia	Mild	1	Yes
09008	Nasal burning	Nasal discomfort	Moderate	1	Yes
09010	Stinging-bilateral nares	Rhinalgia	Mild	1	Yes
10001	Bilateral nasal burning	Nasal discomfort	Moderate	1	Yes
10005	Burning sensation in the nose	Nasal discomfort	Mild	1	Yes
10009	Nasal burning	Nasal discomfort	Moderate	1	Yes
10012	Nasal burning sensation	Nasal discomfort	Moderate	1	Yes
12001	Nasal irritation	Nasal discomfort	Mild	1	Yes
12004	Burning in nose	Nasal discomfort	Mild	1	Yes
14003	Bilateral burning in nostrils	Nasal discomfort	Mild	1	Yes
14013	Burning sensation bilateral nostrils	Nasal discomfort	Mild	1	Yes

Table 22: NDA 206099 Nasal Adverse Events OPN-SUM-MIG-3301

Subject	Verbatim Term	Preferred Term	Severity	Duration (days)	Relatedness to Study Drug
PLACEBO					
01007	Nasal burning	Nasal discomfort	Mild	1	Yes
01007	Erythema nasal cavity during migraine	Nasal mucosal disorder	Mild	1	Yes
10017	Nasal cavity irritation	Nasal discomfort	Mild	1	Yes
01010	Nasal mucosal erythema	Nasal mucosal disorder	Mild	1	Yes

Ref: eCTD seq 0000; Study report OPN-SUM-MIG-3301. Sponsor's Table 12.4. Source Data: Listing 16.2.7

Reviewer Comment

Onzetra (sumatriptan nasal powder), 22 mg AVP-825 to be used with the proprietary Xsail breath powered delivery device for the proposed indication of the acute treatment of migraine with or without aura is an acute intermittent use product. If sumatriptan were toxic to the neurons that affect the sense of smell (olfactory or trigeminal pathways) this effect would likely have become apparent with the use of Imitrex nasal spray. When considering differences in the delivered dose, the whole nose exposure, and individual nostril exposure, it appears to be lower with AVP 825 than with Imitrex nasal spray. Exposure of the region containing the olfactory epithelium to sumatriptan with AVP 825 was within the range of exposures produced by Imitrex nasal spray (Table 20). In addition, the nasal clearance is rapid following both delivery methods (Figure 17), and the duration of exposure to the nasal regions between the sumatriptan products appears to be similar. The local nasal mucosal safety information for AVP 825 22 mg should be comparable to Imitrex nasal spray with the available information, and additionally as noted in Table 22, severe and unexpected events were not observed in the single use controlled study OPN-SUM-MIG-3301.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events for the AVP-825 22 mg dose groups were pooled separately from the AVP-825 11 mg dose group from the two randomized controlled studies (OPTUK-MSPP-PRO-002 and OPN-SUM-MIG-3301. There were no long-term safety studies due to reliance on the safety information for the RLD. In addition, please refer to discussions for local nasal safety in sections 7.3.4 and 7.3.5 of the review.

Table 23: NDA 206099 TEAEs ≥ 2% of Patients, Pooled Data OPTUK-MSPP-PRO-002 and OPN-SUM-MIG-3301

Adverse Event	**AVP 825 22 mg** (N=151)	**AVP 825 11 mg** (N=39)	**Placebo** (N=150)
Abnormal Taste (Includes both abnormal product taste and dysgeusia)	20%	10%	3%
Nasal Discomfort	11%	3%	1%
Rhinorrhea	5%	0	2%
Rhinitis	2%	0	0%
Ref: eCTD seq 0000; Source: Module 2.7.4 Table 2.7.4 – 17			

AE coding dictionary MedDRa 13.1 was used to code adverse event verbatim terms in the Phase 2 (OPTUK-MSPP-PRO-002) and Phase 3 (OPN-SUM-MIG-3301) studies. In the Phase 2 study, a verbatim term of "bitter taste" or "bad taste" was coded to "dysgeusia." In the Phase 3 OPN-SUM-MIG-3301 study, the term "bad taste" or "bitter taste" was coded to "taste abnormal." In the adverse event tables, frequency counts of dysgeusia and taste abnormal were combined.

7.4.2 Laboratory Findings

OPN-SUM-MIG-3301

During the phase 3 study OPN-SUM-MIG-3301, the following laboratory tests were performed at screening (Visit 1) and the end-of-study visit (Visit 3) using standard methods:

- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count [total and differential], platelet count;
- Serum chemistry: urea, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, gamma-glutamyl transpeptidase, glucose, electrolytes (sodium, potassium, chloride, calcium, albumin, total protein; and
- Urinalysis: Urine samples were analyzed by dipstick and a microscopic analysis was performed if the results of dipstick indicated abnormalities requiring further investigation.

The review of shift tables did not identify clinically significant changes in laboratory values.

7.4.3 Vital Signs

OPN-SUM-MIG-3301

During the phase 3 study OPN-SUM-MIG-3301, vital signs were collected at screening (Visit 1) and at the end-of-study visit (Visit 3). The assessments performed were systolic BP, diastolic BP, and heart rate. There were no clinically significant changes identified.

7.4.4 Electrocardiograms (ECGs)

OPN-SUM-MIG-3301

During the phase 3 study OPN-SUM-MIG-3301, a 12-lead resting ECG was obtained at screening (Visit 1) and the end-of-study visit (Visit 3) with the subject in the supine position. At both screening and the end-of-study visit, ECGs were classified as normal, abnormal/not clinically significant, or abnormal/clinically significant. There were no clinically significant ECG abnormalities after dosing (reference: Module 5.3.5.1 study report OPN-SUM-MIG-3301, End-of-Text Table 14.3.4).

7.4.5 Special Safety Studies/Clinical Trials

Please see section 7.3.5 of the review addressing nasal/local exposure safety and any evidence of local nasal irritation.

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The proposed labeled dose is AVP 825 22 mg Onzetra. Adverse events for the AVP-825 22 mg dose groups were pooled separately from the AVP-825 11 mg dose group from the two randomized controlled studies (OPTUK-MSPP-PRO-002 and OPN-SUM-MIG-3301 as described in section 7.4.1 of the review. There were N=39 subjects exposed to the AVP 825 11 mg Onzetra dose as shown in Table 23.

7.5.2 Time Dependency for Adverse Events

Please see section 7.3.5 of the review.

7.5.3 Drug-Demographic Interactions

Treatment emergent adverse events were analyzed by subgroups based on gender and race for the two randomized controlled studies (OPTUK-MSPP-PRO-002 and OPN-SUM-MIG-3301 (data not presented in this review). Since the majority of subjects were white (85.8%), females (83.5%), any meaningful differences are difficult to determine regarding differential effects of gender and race on adverse events for AVP-825, when there have been no differences observed for sumatriptan products in product safety based on demographic differences.

7.5.4 Drug-Disease Interactions

No formal drug-disease interaction studies have been conducted with AVP-825. Since NDA 206099 is a 505(b)(2) application, it relies on the recommendations and cautions described in the prescriber information of the reference listed drug, Imitrex.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies have been performed with AVP-825.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were conducted for this NDA.

7.6.2 Human Reproduction and Pregnancy Data

There were no exposures to AVP 825 in order to evaluate pregnancy outcomes. NDA 206099 relies on the recommendations and cautions described in the prescriber information of the reference listed drug, Imitrex.

7.6.3 Pediatrics and Assessment of Effects on Growth

The clinical development program for AVP 825 was performed in adults above the age of 18. The sponsor proposed conducting pediatric clinical studies in patients 6-17 years old, and submitted their initial Pediatric Study Plan (as per FDASIA) for PeRC review.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
No overdoses in clinical studies are reported with either AVP-825 22 mg (highest dose) or AVP-825 11 mg. Since the half-life of elimination of AVP-825 is about 3 hours, the sponsor recommends monitoring patients after overdose with AVP-825 for at least 15 hours or while symptoms persist. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.

Drug abuse, withdrawal and rebound
No studies have been conducted evaluating drug abuse, withdrawal, or rebound effects of AVP-825. There is no evidence of abuse potential based on the package insert for the reference listed product, Imitrex.

NDA 206099 relies on the recommendations and cautions described in the prescriber information of the reference listed drug, Imitrex.

7.7 Additional Submissions / Safety Issues

There were no data from submissions other than those noted above.

8 Postmarket Experience

AVP 825 is not approved for use and therefore post-marketing data is not available. NDA 206099 relies on the prescriber information of the reference listed drug, Imitrex.

9 Appendices

9.1 Literature Review/References

Citations are noted as footnotes in the review.

9.2 Labeling Recommendations

The labeling should be consistent with other 5HT1 receptor agonists for the treatment of acute migraine headache, and the clinical sections should remain consistent with RLD, Imitrex nasal spray for the 505(b)(2) NDA. Several multidisciplinary labeling meetings were held during the review cycle and the available data supports the use of AVP 825

22 mg dose administered using two 11 mg nosepieces to each nostril, and for up to 44 mg (4-nosepieces in 24 hours. DMEPA found the proposed proprietary name, Onzetra, as acceptable.

9.3 Advisory Committee Meeting

No advisory committee meeting was held because the drug product has already been approved at similar doses for other routes of administration and there were no unexpected safety issues.

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/s/

SUHAIL KASIM
11/13/2014

ERIC P BASTINGS
11/16/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	November 12, 2014
To:	Billy Dunn, M.D. Acting Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Robin Duer, MBA, BSN, RN Acting Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, BSN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	Onzentra (sumatriptan nasal powder), 22 mg
Dosage Form and Route:	Xsail Breath Powdered Delivery Device
Application Type/Number:	NDA 206099
Applicant:	Avanir Pharmaceuticals

1 INTRODUCTION

On January 22, 2014, Avanir, submitted for the Agency's review an Original New Drug Application for Onzentra (sumatriptan nasal powder), 22 mg in the Xsail Breath Powered Delivery Device. Onzentra is indicated for the acute treatment of migraine with or without aura. On February 4, 2014, DNP requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Onzentra (sumatriptan nasal powder), 22 mg in the Xsail Breath Powdered Delivery Device.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for Onzentra (sumatriptan nasal powder), 22 mg in the Xsail Breath Powdered Delivery Device.

2 CONCLUSIONS

Due to outstanding human factor study deficiencies, DNP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

TWANDA D SCALES
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Food and Drug Administration
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
Division of Ophthalmic and Ear, Nose and Throat Devices
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Response to Consultation Request

DATE:	March 11, 2014
TO:	Vandna Kishore Senior Regulatory Project Manager Division of Neurology Products Office of Drug Evaluation I Center for Drug Evaluation and Research
THROUGH:	Srinivas Nandkumar, PhD Ear, Nose and Throat Device Branch Chief, DOED/ENTB Eric Mann, MD, PhD Deputy Director (Clinical), DOED Malvina B. Eydelman, MD Director, DOED
FROM:	Sageev T. George, PhD Biomedical Engineering Scientific Reviewer, DOED/ENTB
SUBJECT:	Consultative Review of NDA 206-099
APPLICATION/DRUG:	AVP-825 22mg drug-device combination product
Applicant:	Avanir Pharmaceuticals
APPLICATION/DRUG:	AVP-825 22mg drug-device combination product

Executive Summary

CDER's Division of Neurology Products requested DOED's input regarding an application by Avanir Pharmaceuticals, Inc., the Sponsor, for the use of AVP-825 (sumatriptan nasal powder) 22mg, a drug-device combination product intended for the self-administration of Sumatriptan Succinate, USP. Two capsule/nosepieces containing 11mg each of Sumatriptan base per administration (one per nostril) provides 22mg equivalent of Sumatriptan base constituting a full dose of AVP-825 for the acute treatment of migraine headache with or without aura. DNP requests a review of the delivery system from DOED.

Device Description

The drug delivery system consists of a reusable device body incorporating a flexible mouthpiece (Flexible Mouthpiece Device) and a disposable, pre-filled drug-containing nosepiece (Disposable Nosepiece). For administration, the disposable nosepiece that contains the encapsulated Sumatriptan Succinate, USP is inserted into the drug delivery device body. A button integrated in the device body is then pressed and released to pierce the capsule in the disposable nosepiece. The nosepiece of the device is then inserted into the nose and the mouthpiece inserted into the mouth. Exhalation into the mouthpiece propels the sumatriptan powder into the nasal cavity through the attached disposable nosepiece. The disposable nosepiece (including the now dose-expended drug containing capsule) is then removed and discarded, and a second nosepiece is used to similarly deliver the remainder (i.e. a second 11 mg nosepiece) into the opposite side of the nose to complete the dosing.

The majority of the delivery system components are custom molded. Mold capability studies using key component dimensions have been performed on all individual injection molded components. (b) (4) components (b) (4) are supplied to controlled specifications.

Disposable Nosepiece Components

The nosepiece, including sub-parts thereof (Figure 3.2.R.4.3-1), is the disposable component of the AVP-825 device. It is intended for a single dose administration and it is not refillable. Each disposable nosepiece contains a (b) (4) capsule filled with 15.4 mg Sumatriptan Succinate, USP (equivalent to 11 mg Sumatriptan base). The drug filled capsule is not removable from the nosepiece. Each fully assembled disposable nosepiece, which includes the plastic nozzle, (b) (4) and capsule is packaged individually in a foil (b) (4) pouch.

Figure 3.2.R.4.3-1 Disposable Nosepiece Components

Flexible mouthpiece device Components

The Flexible mouthpiece device including sub-parts thereof (see Figure 3.2.R.4.3-3), is the reusable component of the AVP-825 drug delivery system. The disposable nosepiece component is designed to fit into the Flexible mouthpiece device (see Figure 3.2.R.4.3-4). (b) (4) (b) (4). The functional parts of the Flexible mouthpiece device include a button and piercing mechanism. When the button is pressed (b) (4) two (b) (4) pins enter the chamber (b) (4). When fully depressed the pins (b) (4) piercing the capsule. The button is then released, retracting the pins from the capsule.

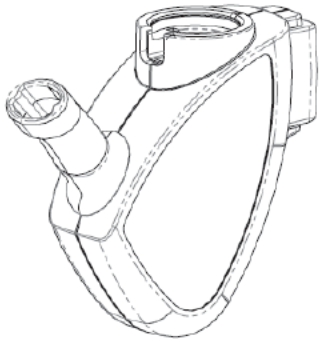

Figure 3.2.R.4.3-3 Flexible Mouthpiece Device

Device Usage

A Disposable Nosepiece is inserted into the Flexible mouthpiece device as shown in Figure 3.2.R.4.3-4. When the piercing button on the side is depressed, (b) (4) pins connected to the button pierce the capsule and are retracted when the button is released. The nosepiece is then inserted into the user's nose and the mouthpiece into the mouth and the user blows into the device mouthpiece. (b) (4) As the user blows into the device the airflow lifts the capsule until it hits the grid at the top of the capsule. (b) (4) (b) (4)The repeated rising and falling of the capsule creates the energy to disperse the powder into the flow and may create a characteristic rattling sound, which

also serves to indicate that the device is functioning correctly. When in use, the user is required to blow forcefully in order to generate the air flow and efficiently empty the powder from the capsule. Emptying of the capsule into the air flow is achieved within a short period of time: the user is required to blow forcefully for 2-3 seconds.

Device Verification Summary

The sponsor provides the following verification tests to demonstrate that the device conforms to predefined performance specifications:

1. Flow Efficiency
2. Pressure Drop / Flow Resistance

The results are summarized below:

Specification	Acceptance Criteria	Description	Test Results
Pressure Drop/Flow Resistance	Pressure Drop must be less than (b) (4) at a flow rate into mouthpiece of **30 L/min**	Baseline Pressure Drop Characterization Study (Flow 30 L/min) ENS-2149-R1	Pass
		Unpackaged Drop Test of AVP-825 ENS-2168-R1	Pass
Flow Efficiency	Flow efficiency (outlet to inlet ratio) through the device at a flow rate of 30l/min at the mouthpiece (b) (4)	Baseline Flow Efficiency Testing TRP-1525-R1	Pass
		Humidification Study (b) (4) TRP-1521-R1	Pass
		Unpackaged Drop Test of Flexible Mouthpiece Device TRP-1523-R1	Pass

Device Characterization and Performance Verification Tests

Table 3.2.R.4.9-1 Device Characterization and Performance Verification Tests Conducted which are Described in 3.2.P.2.2 Pharmaceutical Development.

Section number	Device characterization and performance verification test description
DRUG CHARACTERIZATION STUDIES	
2.2.1.6.1.1	The effect of high humidity on the emitted dose content uniformity (EDCU)
2.2.1.6.1.3	The effect of high humidity on the emitted particle size distribution (PSD)
2.2.1.6.2	The effect of cold devices and nose pieces on emitted dose content uniformity and emitted dose particle size distribution
2.2.1.6.3	The effect of flow rates at 15, 30 and 45 L/min on emitted dose particle size distribution
2.2.1.6.4	The effect of flow rate (i.e., 15, 30 and 45 L/min) on emitted dose content uniformity
2.2.1.6.5	The effect of flexible mouth piece position on emitted dose content uniformity
2.2.1.6.6	The effect of flexible mouth piece position on emitted dose particle size distribution
2.2.1.6.7	Robustness of the device pin piercing mechanism
2.2.1.6.8	Drop test studies to the assembled device unit (nose piece attached to device body), and unpackaged nose pieces to assess ruggedness
2.2.1.6.10	The effect of unprotected nose pieces on emitted dose particle size distribution
2.2.1.6.11	The effect of unprotected nose pieces on emitted dose content uniformity
2.2.1.6.12	Effect of device orientation on emitted dose content uniformity
2.2.1.6.13	Effect of device orientation on emitted dose size distribution
2.2.2	Flow rate and pressure drop study
2.2.3.1	Device comparison on emitted dose content uniformity study
2.2.3.2	Device comparison emitted dose particle size distribution study

NOTE TO TEAM: It is recommended that CDER review the outcomes of the above tests in which the content uniformity and particle size distribution are measured as a function of the various testing conditions. The following tests are those in which the robustness of the device are determined:

Drop test studies to the assembled device unit (nose piece attached to device body), and unpackaged nose pieces to assess ruggedness

A study examined the functionality of the Breath-Powered™ powder delivery device with flexible mouthpiece after drop conditioning the device with the nosepiece and drop testing only the nosepiece. The testing approach was adapted from ISO 11608-1:2000, Pen-Injectors for Medical Use.

The study measured the effect of dropping the device with nosepiece unit dropped once in one of three orientations from a height of one meter onto a 3 mm thick steel plate using 3 devices and 30 drug product nosepieces (10 nosepieces per device) using AVP-825 batch 0012R. The drop height was set such that the lowest part of the device was a minimum of one meter above the test surface.

- Horizontal orientation, side impact (10 nosepieces)
- Vertical 1 Orientation, bottom impact (10 nosepieces)
- Vertical 2 Orientation, top impact (10 nosepieces)

Drug product was stored at ambient lab conditions. The study evaluated after dropping:

- That the nosepiece was properly seated and firmly attached to the device.
- The piercing pin button force, with an acceptance criterion of the button force is less than (b) (4)

The flexible mouthpiece devices exhibited no apparent damage after falling from one meter. During one of the thirty flexible mouthpiece device drop tests the nosepiece unit fell out of the device upon impact. No physical damage was observed on the nosepiece or flexible mouthpiece device and the nosepiece unit reattached firmly to the device. All other devices remained intact during drop and exhibited no visible damage.

Pressure drop was measured pre- and post-drop at an inlet flow rate of 30.0 ± 0.5 L/min. The pressure either decreased or remained the same for every device after dropping. Table 3.2.P.2.2–23 summarizes the mean results. The downward shift in pressure occurred independent of drop orientation (Figure 3.2.P.2.2-5) displays the pressure drop measurements before and after drop in relation to the (b) (4) specification limit. As shown in Table 3.2.P.2.2–23, there is a difference in mean of (b) (4) which is approximately one standard deviation of the dataset. Based on the spread of the data, a one-way ANOVA detects this difference in means as statistically significant, yielding a p-value of less than 0.001, as reported in Table 3.2.P.2.2–24.

2.2.1.6.8.1 Button Force Testing After Device Drop Testing

Button force measurements taken after dropping each flexible mouthpiece device remained well within specification. The data fit a normal distribution and all force measurements were below the (b) (4) spec limit. Calculating the tolerance interval yields a 95% confidence that 99% of the population will not exceed a button force of (b) (4) after drop. The button force data is summarized in Table 3.2.P.2.2–25.

2.2.1.6.8.2 Nosepiece Drop Test Results

Dropping individual nosepiece units in all three orientations showed no observable damage on any nosepiece after dropping and each nosepiece seated properly and firmly attached to the flexible mouthpiece device. Button force measurements were made after dropping the nosepieces. Table 3.2.P.2.2–26 summarizes the button force data. The data fits a normal distribution and all force measurements are below the (b) (4) spec limit. The calculated tolerance interval yields a 95% confidence that 99% of the population will not exceed a button force of (b) (4) after drop.

Flow Rate and Pressure Drop Testing

2.2.2 Flow Rate And Pressure Drop Testing

A study was performed to investigate the comparability of the pressure drop and flow resistance between the Breath-Powered™ Powder delivery device with flexible mouthpiece and the device with fixed mouthpiece. Testing included 30 devices with fixed mouthpieces and 30 (b) (4) devices with flexible mouthpieces and 60 AVP-825 nosepieces (batch 0012R). The sample size was selected to be sufficient to detect a difference between two means of one standard deviation at 90% power using one-way ANOVA.

2.2.2.1 Test Procedure

The pressure drop test equipment was initially set up to insure that the system did not leak. The test device sample was then installed into the pressure drop test equipment and each device with nosepiece was tested three times at the flow rates shown in Table 3.2.P.2.2–32.

2.2.2.3 Test Results

The purpose of the study was to compare the pressure drop and flow resistance characteristics of the Fixed Mouthpiece Device and the Flexible Mouthpiece Device specifically at inlet flow rates 20, 30, and 40 L/min. The study found there was not a significant difference between the devices at 20 L/min or 30 L/min. However, at 40 L/min, Welch's t-tests determined there was a statistically significant difference between the mean pressure drop and flow resistance of the two devices returning p-values of less than 0.001. The results are summarized in Table 3.2.P.2.2–33.

At the 20 L/min flow rate, the mean pressure drop for the fixed mouthpiece device is (b) (4) (b) (4) while the mean for the flexible mouthpiece device is (b) (4). The two means are nearly equal. The t-test performed on the data, Table 3.2.P.2.2–33 shows a p-value of 0.945, showing that at 20 L/min there is no significant difference in mean pressure drop between the two devices. The results of the power analysis for the hypothesis test using the 20 L/min data are shown in Table 3.2.P.2.2–34. The power analysis shows there is high probability for the t-test to detect a difference in means down to (b) (4) Therefore, there is high confidence in the conclusion drawn by the t-test.

At the 30 L/min flow rate, there is small difference (b) (4) in the mean pressure drop. This difference is not statistically significant ($p>0.05$) showing that there was no significant difference between the mean pressure drop of the fixed mouthpiece device and the flexible mouthpiece device. The t-test performed on the data, Table 3.2.P.2.2–33 shows a p-value of 0.222, showing that at 30 L/min there is no significant difference in mean pressure drop between the two devices. The results of the power analysis for the hypothesis test using the 30 L/min data are shown in Table 3.2.P.2.2–35. The power analysis shows there is high probability for the t-test to detect a difference in means down to (b) (4). Therefore, there is high confidence in the conclusion drawn by the t-test.

At the 40 L/min flow rate, there is a slight difference (b) (4) in the mean pressure drop between the fixed mouthpiece device and the flexible mouthpiece device. There is an overlap in the range of individual pressure drop for the two devices of (b) (4). The t-test (Table 3.2.P.2.2–33) found the difference in the means between the two devices to be statistically significant ($p<0.001$). The power analysis for the 40 L/min data, Table 3.2.P.2.2–36 shows high probability for the t-test to detect a difference in means down to (b) (4)

The flow resistance characteristics for the fixed mouthpiece device and the flexible mouthpiece device are shown in Figure 3.2.P.2.2-6. Both devices also show a clear linear relationship between flow rate and square root of pressure drop with high coefficients of correlation (R^2 values of 0.9327 and 0.9531).

2.2.2.4 Conclusions

At flow rates of 20 L/min and 30 L/min, there are no significant differences between the mean pressure drop or flow resistance of the fixed and flexible mouthpiece devices. The 30L/minute flow rate is used for *in vitro* performance testing of the flexible mouthpiece device that was chosen to be representative of the average peak expiratory flow rate in adults.

At 40 L/min, hypothesis testing determined that the (b) (4) difference between the pressure drop means is statistically significant, but is modest in light of the difference in the mean pressure drop and flow resistance of (b) (4) respectively. These values represent about a (b) (4)% difference in mean pressure drop and a (b) (4)% difference in mean flow resistance between the fixed and flexible mouthpiece devices. Further, this difference is not considered clinically significant as there is little sensitivity in the E-DCU and the ED-PSD to flow rates of 20 L/min to 45 L/min (see 3.2.P.2.2.1.6.3, 3.2.P.2.2.1.6.4).

Conclusions

The tests provided by the sponsor to demonstrate that the device conforms to flow efficiency, flow rate and pressure drop are adequate, and demonstrate conformance with device specifications. The tests provided by the sponsor to demonstrate the robustness of the device to drops are adequate, demonstrating that there are no significant effects on button force, or flow rate at 20 or 30 L/min. Although the drop tests do indicate a statistically significant changes to the device post-drop at 40L/min, the sponsor's arguments that this is not clinically significant is acceptable.

The submission contains adequate mechanical engineering testing to demonstrate device effectiveness through normal use conditions. There are no further concerns.

Reviewer Sign-Off:	Sageev George -S 2014.03.11 17:34:01 -04'00'
Branch Chief Sign-Off:	Srinivas Nandkumar -S 2014.09.19 17:47:15 -04'00'

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10/22/2014