

Published: September, 30, 2022

**Citation:** Shrewsbury SB, Davies G, et al., 2022. The Pharmacokinetics of Drug Delivery to the Upper Nasal Space: A Review of INP105 Development, Medical Research Archives, [online] 10(9). <https://doi.org/10.18103/mra.v10i9.2971>

Copyright: © 2022 European Society of Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI  
<https://doi.org/10.18103/mra.v10i9.2971>

ISSN: 2375-1924

## RESEARCH ARTICLE

### The Pharmacokinetics of Drug Delivery to the Upper Nasal Space: A Review of INP105 Development

1. **Stephen B. Shrewsbury**, MBChB, Impel Pharmaceuticals Inc., Seattle, WA, USA
2. **Greg Davies**, BSc (Hons), Impel Pharmaceuticals Inc., Seattle, WA, USA
3. **Lisa McConnachie**, PhD, Impel Pharmaceuticals Inc., Seattle, WA, USA
4. **John Hoekman**, PhD, Impel Pharmaceuticals Inc., Seattle, WA, USA

#### ABSTRACT

Nasal drug delivery presents a potential opportunity for achieving rapid, extensive drug absorption via a nonoral route by 1) avoiding degradation within the gastrointestinal tract and first-pass metabolism in the liver and 2) facilitating faster onset via rapid absorption into the bloodstream. However, the site of drug deposition within the nasal cavity may impact drug pharmacokinetics. Precision Olfactory Delivery (POD®) by Impel Pharmaceuticals Inc. is a new technology that provides handheld, manually actuated, propellant-powered drug delivery to the upper nasal space for rapid and efficient absorption. Rapid onset of effect can be a major advantage in many clinical applications where quick and effective administration is needed (eg, alleviating agitation in emergency settings or reducing debilitating migraine symptoms). Here, we review the pharmacokinetic profile of INP105, which is being developed to deliver olanzapine (OLZ) by POD to treat agitation in patients with autism. Because formulation can play a large role in the pharmacokinetic profile of a nasally administered drug, we provide a comprehensive review of both published and previously unpublished preclinical data outlining how the INP105 formulation was developed and optimized for study in humans. Multiple formulation carriers and excipients were tested to find a stable INP105 formulation with a desirable nasal absorption profile. Because the nasal architecture in nonhuman primates (NHPs) is similar to humans, the pharmacokinetics and tolerability of an INP105 combination product (NHP-INP105) using a clinical formulation combined with a device specifically designed for NHPs has been investigated in preclinical NHP studies, providing translational data for human studies and the pathway for testing novel products and formulations. The pharmacokinetics and tolerability of INP105 were then evaluated in an early clinical study in humans, demonstrating favorable pharmacokinetic and pharmacodynamic profiles. In this review, we aim to illustrate how delivery of therapeutics to the upper nasal space using POD, such as with agents like INP105, has the potential to optimize nasal delivery and unlock the potential of delivery-limited drugs to provide patients with rapid onset of effect, ease of use, and convenience.

**Keywords/Phrases:** Precision Olfactory Delivery, upper nasal space, pharmacokinetics, translational research, nasal delivery, INP105

**Abbreviations:** ADME = absorption, distribution, metabolism, and elimination; AUC = area under the concentration-time curve; AUC<sub>0-last</sub> = area under the concentration-time curve from time 0 to the last measurable concentration; AUC<sub>inf</sub> = area under the concentration-time curve from time 0 to infinity; AE = adverse event; C<sub>max</sub> = maximum plasma concentration; DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; Exp = experiment; GI = gastrointestinal; HPMC = hydroxypropyl methylcellulose; IM = intramuscular; IV = intravenous; NHP = nonhuman primate; ODT = oral disintegrating tablet; OLZ = olanzapine; PET = positron emission tomography; POD® = Precision Olfactory Delivery; PF68 = Pluronic F-68; SC = subcutaneous; SD = standard deviation; TEAE = treatment-emergent adverse event; T<sub>max</sub> = time to reach the maximum plasma concentration

## 1. INTRODUCTION

Within early stages of drug development, clinical research is preceded by preclinical animal studies that attempt to predict how a drug will behave within humans by evaluating absorption, distribution, metabolism, and elimination (ADME).<sup>1-3</sup> Understanding the pharmacokinetics of a therapeutic, such as C<sub>max</sub> (maximum plasma concentration) or AUC (area under the concentration–time curve), is one of the first clinical steps for successful drug development and translation to humans.<sup>1,2,4</sup> Pharmacokinetic data provide key information on the concentrations that can be achieved by a drug with respect to the intensity and duration of that drug's effect in humans.<sup>3</sup> Importantly, these data not only provide information on the effective plasma concentrations of a drug or the rate of metabolism and elimination, but they also shed light on drug properties associated with the emergence of potential side effects.<sup>3,4</sup>

The pharmacokinetics of an agent can be influenced by many factors, one of which is the method of delivery, whether it is oral, buccal, rectal, transdermal, injection (eg, intravenous [IV], intramuscular [IM], subcutaneous [SC]), inhaled, or nasal.<sup>5-7</sup> However, the full profile of a therapeutic and its mode of delivery goes well beyond C<sub>max</sub> and T<sub>max</sub> values, encompassing ease of administration and patient-oriented parameters.<sup>3</sup> Despite the popularity of oral drugs in this regard, their utility can be limited by several factors, including their solubility, degradation within the gastrointestinal (GI) tract or first-pass metabolism through the liver, and potential impaired processing

in disease states where GI motility and function may be compromised or where patient cooperation may be suboptimal and oral products may be spat out, such as with agitation.<sup>7-9</sup> Furthermore, certain clinical situations may necessitate faster drug absorption than oral agents can provide. Such is the case in disabling migraine attacks, with agitation in mental health care settings, or in disabling “off” episodes in Parkinson's disease.<sup>7,10-14</sup> Therefore, there is a great unmet need in a variety of clinical settings for nonoral, noninjectable delivery methods that offer fast, efficient absorption of drug with ease of administration suitable for use in the community.

Despite a long history of nasal therapeutics in medicine, the marked differences in the speed and extent of absorption of certain drugs when delivered to different parts of the nasal mucosa is still not appreciated or well understood.<sup>8,15-17</sup> Achieving fast absorption through a nonoral route requires a drug to be delivered directly onto an absorptive surface, which generates early and high C<sub>max</sub> and an adequate AUC.<sup>3,7,18</sup> Such parameters are seen with IV administration but may come with systemic side effects from anticipated higher C<sub>max</sub> and can also come with potential needle-related issues.<sup>7,18,19</sup> This clinical challenge extends beyond a need for ease of administration—many clinical settings require effective, systemic levels of a given drug to be reached rapidly.<sup>8</sup> Nasal drug delivery offers many benefits for these applications, including its noninvasiveness, absence of potential needlestick injury, rapid delivery of drug without requiring sterile technique, and a nonoral option that carries a lower risk for systemic side effects.<sup>7,8,11,20,21</sup> Nasal delivery of drugs can be especially advantageous in many challenging clinical scenarios. For example, these drugs can be self-administered or given by a caregiver in multiple settings, including less controlled situations, such as emergency departments, acute crisis, or urgent psychiatric situations where it may be difficult or unsafe to administer an injection.<sup>7,11,22</sup> Importantly, nasal delivery is typically associated with a low risk for GI side effects and these medications do not need to be taken separate from, or with, meals (as is the case with some oral medications).<sup>16,20,23</sup> Nasal delivery results in absorption across the nasal mucosa into the bloodstream and avoids first-pass hepatic metabolism, which can result in higher bioavailability than most oral methods, facilitating rapid absorption and onset of action.<sup>8,21</sup>

An important feature of nasal drug delivery is the site of drug deposition within the nose, which can differ in epithelia type, mucociliary function, and vascular supply, and can affect drug pharmacokinetics.<sup>8,20,23-27</sup> The nose can be divided into the upper and lower nasal space. The lower nasal space includes structures such as the vestibule, which is lined with a nonciliated squamous epithelium that is not well suited for effective drug absorption and includes a narrow, constricted region called the nasal valve. The nasal turbinates within the lower nasal space are covered by ciliated pseudostratified cuboidal-columnar respiratory epithelium and are coated with mucus that along with the motile cilia, can lead to rapid drug clearance.<sup>8,16,20,27,28</sup> The upper nasal space is partially lined with olfactory epithelium, which may be more permeable than the respiratory epithelium in the lower nasal space, and nonmotile cilia that greatly reduce mucociliary clearance. These allow drugs to enter the bloodstream more effectively via the rich vascular supply to this part of the nose.<sup>20,23,24,27,29-31</sup> Although these attributes make the upper nasal space an attractive target for drug delivery, reaching the upper nasal space is challenging because of its complex architecture,<sup>23</sup> which includes navigating the narrow nasal valve.

The unique anatomy and physiology of the upper nasal space, including the olfactory mucosa, can be strategically employed to formulate drugs that maximize absorption and bioavailability while reducing mucociliary clearance. These strategies include the addition of mucoadhesive excipients (eg, chitosan, Carbopol®, carboxymethylcellulose, polyacrylic acid), absorption enhancers (eg, cyclodextrins, bile salts, fatty acids), and preservatives that inhibit mucociliary clearance, thus prolonging the opportunity for absorption.<sup>24</sup> Moreover, semisolid drug formulations containing thickening agents, such as hydroxypropyl methylcellulose (HPMC), have proved particularly well suited for nasal administration. Their high viscosity makes them less susceptible to the rapid mucociliary clearance of the lower nasal space and gravitational effects than liquid formulations.<sup>24</sup> By targeting both the upper nasal space with its reduced mucociliary clearance and optimizing drug formulation, nasally administered drugs possess the capability of producing injection-like pharmacokinetic and pharmacodynamic profiles.<sup>32</sup>

## 2. AIM, SCOPE, AND METHODOLOGY OF THIS REVIEW

Here we provide a comprehensive review of the considerations that must be made during the

formulation development and optimization of upper nasal-targeted drugs, specifically in the context of INP105 for Precision Olfactory Delivery (POD®)-mediated delivery of olanzapine (OLZ). While a comprehensive review of how the POD device technology specifically deposits drug within the upper nasal space has been provided elsewhere (Cooper W. et al, 2022 *in press*),<sup>33</sup> this review illustrates how the formulation of POD-delivered agents can also be optimized to maximize upper nasal drug delivery and achieve injection-like pharmacokinetic profiles. We aim to review the rationale for upper nasal drug delivery and the issues POD technology was developed to address, as well as the rationale behind applying POD technology to the delivery of OLZ for agitation. In order to provide further context on how the INP105 formulation was optimized for upper nasal drug delivery, we review the clinical formulation development process of INP105, including previously unreported preclinical data evaluated in nonhuman primates (NHPs). We further review the pharmacokinetics of INP105, including previously unpublished pharmacokinetic data from these preclinical NHP studies and a published phase 1 clinical study.

## 3. UPPER NASAL DRUG DELIVERY

### 3.1. Rationale and goal of POD technology for upper nasal drug delivery

Nasal delivery of drugs by traditional nasal sprays creates a diffuse cloud of drug particles (powder formulations) or droplets (liquid formulations) and mostly delivers drug to the lower nasal space, which may result in variable drug absorption due to rapid mucociliary clearance, swallowing, or expectoration.<sup>8,15,20,23,24,31,34,35</sup> This delivery method facilitates ~5% of drug particles to pass through the nasal valve and enter the upper nasal space.<sup>36</sup> Industry has developed robust solutions for alternative drug delivery, employing pulmonary delivery and various platforms for nasal delivery, but it is now well established that nasal delivery is more complicated than previously thought and that the efficiency of absorption through different compartments of the nasal cavity may vary.<sup>7,8,15,17,20</sup> Further, pulmonary delivery may require a forced inspiratory maneuver (thus requiring a conscious patient) and complex manufacturing of a propellant suspension, or several steps may be needed to ensure powder particles are of the correct aerodynamic size to be entrained into the air stream and carried to the alveolae to be deposited.<sup>24,37,38</sup> For example, the upper nasal-targeting drug delivery platform ONZETRA® (sumatriptan, Currax Pharmaceuticals

LLC, Morristown, NJ, USA) for the acute treatment of migraine is a breath-powered device requiring coordinated breathing from a conscious/cooperative patient for proper drug delivery.<sup>38,39</sup>

Impel Pharmaceuticals Inc. (Seattle, WA, USA) has developed devices and methods to enable differential delivery of drugs to the previously unexplored upper nasal space – for instance, the POD nasal drug platform was developed to improve drug bioavailability by effectively and consistently delivering drugs through the nasal valve and into the upper nasal space. Devices that utilize POD technology are handheld, manually actuated, propellant powered, and designed to gently deliver a narrow, focused stream-like plume of liquid droplets or powder particles to the upper nasal space.<sup>23,32,40</sup> POD is compatible with a variety of propellants, including hydrofluoroalkane and more environmentally friendly options such as nitrogen. In all cases, the drug formulation and propellant are stored separately in the POD device and only make contact with each other at the time of administration, thus eliminating the need for the drug product to be formulated in the propellant.<sup>23,38,39</sup>

### 3.2. Application of POD technology to the delivery of olanzapine

POD was combined with OLZ, a well-characterized, second-generation antipsychotic with known efficacy and safety, to explore the potentially significant benefits of upper nasal space drug delivery for acute agitation episodes.<sup>32</sup> Agitation episodes are characterized by heightened states of motor activity and irritability and often pose a physical risk to patients and care providers alike, and they may result in visits to hospital emergency departments.<sup>41-43</sup> Since it was first approved by the FDA in 1996,<sup>44</sup> OLZ has often been used to treat acute agitation associated with illnesses such as schizophrenia or bipolar disorder, but it is also used off-label to treat patients with underlying autism and is commonly administered by IM injection to obtain rapid onset of effect.<sup>41,44,45</sup> The administration of OLZ via IM or oral routes is long-standing in clinical practice.<sup>32,46</sup> However, both routes of administration have significant drawbacks. Although IM OLZ has a rapid onset time of 15 to 45 minutes,<sup>46</sup> the injection of a patient experiencing agitation requires physical restraint or patient cooperation and carries several risks, including patient or caregiver injury, mental trauma, and short- and long-term damage to patient-physician relationships.<sup>32,41</sup> OLZ delivered as an oral

disintegrating tablet (ODT) provides an alternative delivery option but is associated with a slow onset time and erratic absorption. Thus, it often requires extended patient observation time.<sup>32,41</sup> Therefore, there is a need for fast-acting, safer, noninjectable alternatives of OLZ.

The availability of upper nasal administration of OLZ would present an opportunity to simultaneously address the shortcomings of existing delivery methods. INP105—OLZ delivered by POD—uses an optimized, spray-dried powder formulation of OLZ to produce an injection-like pharmacokinetic profile while remaining noninvasive, demonstrating the promise of upper nasal space delivery.<sup>32</sup>

## 4. PRECLINICAL DEVELOPMENT OF INP105

### 4.1. Translational considerations for upper nasal drug delivery: Preclinical POD technology

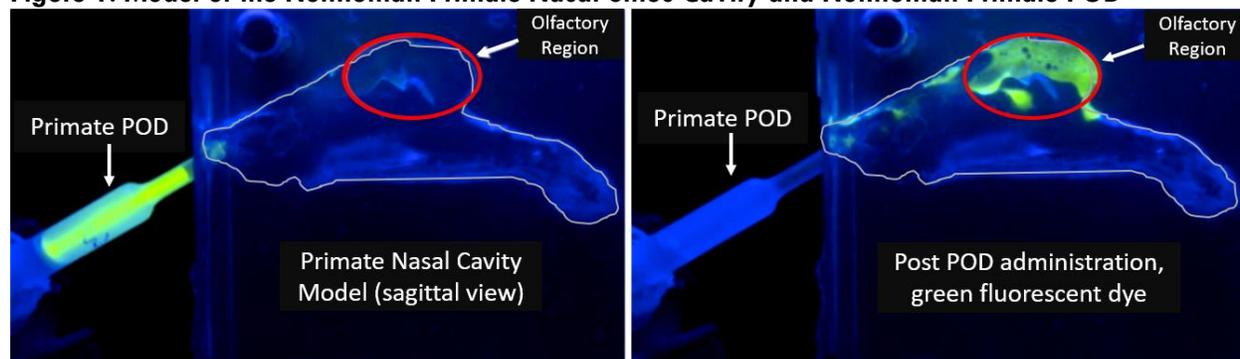
New drugs and new formulations of existing drugs, like INP105, must pass through numerous stages of development and testing to establish preliminary safety before human testing.<sup>2-4,15,47</sup> Therefore, it is critical to select the proper animal model (eg, mouse, rat, rabbit, canine, large mammal, or even primate) to ensure that data are clinically relevant and translatable to humans.<sup>2,4,47</sup> However, selecting the appropriate animal model to investigate drugs delivered to the upper nasal space is a challenge.<sup>48,49</sup> Adaptations to the POD delivery system have been specifically developed for preclinical evaluation in multiple animal models to assess general ADME.<sup>3,50,51</sup> Although preclinical animal studies are typically conducted in rodents, rabbits, or canines, results with nasally delivered products may be less readily translatable to humans from these species because of significant differences in nasal anatomy and the macroscopic nature of these animal models.<sup>48,49</sup> Microscopic humans have a relatively unsophisticated sense of smell and a small surface area of olfactory epithelium compared with the more complex architecture of other more macroscopic animals, such as rodents and canines, who have more discriminating olfactory function.<sup>48,49</sup> NHPs are similar to humans in this regard, having a more limited olfactory epithelium.<sup>52</sup> NHPs also possess a complex nasal architecture that more closely resembles humans' than other mammals', produces mucus in an increasing anterior-to-posterior gradient like humans', and—in some NHPs—is adapted for both oral and nasal breathing (compared with other mammals, such as rodents, which are obligate nose breathers).<sup>52</sup> Therefore, given the shared nasal characteristics and architecture between humans and NHPs, in order to

understand and optimize nasal drug delivery in humans, preliminary preclinical studies were conducted in NHPs using a specially developed NHP-INP105 drug-device combination.<sup>48,50-52</sup>

The NHP POD device is based on the same mode of action as the human device; using a propellant to deliver drug into the upper nasal space, but scaled to the anatomy of the NHP nose. As part of the preclinical development process, the pattern of INP105 deposition within the nasal space of NHPs was evaluated, with the intention of generating key relevant data for translation to humans. A radiolabeled tracer was nasally administered in NHPs using the NHP POD device and was detected in the upper nasal space using positron emission tomography (PET) imaging (**Figure 1**). Histological evaluation indicated that no damage or irritation was sustained through repeated POD dosing in NHPs, demonstrating that POD delivery was well tolerated. Overall, no major safety concerns were identified in preclinical studies of POD in NHPs, and

drug absorption was rapid when delivered to the upper nasal space (detailed below)—emphasizing that proper selection of animal models before clinical testing is critical to translate results to human studies.<sup>32</sup> Limitations of this preclinical work included a lack of data of any impact of the POD device on olfaction in NHPs; however, clinical data in humans (a 52-week study) assessing olfactory function (with a liquid POD-delivered formulation) suggest little impact of POD-mediated drug delivery on olfaction.<sup>53</sup> This product, INP104, or TRUDHESA®, received regulatory approval in the United States for the acute treatment of migraine in September 2021.<sup>54</sup> Collectively, these data indicate that upper nasal drug deposition can be safely achieved with the POD device. The early NHP-INP105 preclinical studies were a crucial step along the development of an agent for upper nasal drug delivery and allowed for the testing of multiple iterations of OLZ powder formulations over a highly accelerated time frame.

**Figure 1: Model of the Nonhuman Primate Nasal-Sinus Cavity and Nonhuman Primate POD**



Caption: Using cadaver nasal casts from nonhuman primates, a species-specific model was developed for deposition testing of the nonhuman primate POD®. Left panel: Aqueous fluorescein loaded into POD. Right panel: Tracer delivered to olfactory region (upper nasal space) of NHP. POD = Precision Olfactory Delivery.

#### 4.2. Optimizing agents for upper nasal drug delivery: Formulation development of INP105

The formulation of INP105 was optimized for upper nasal delivery over the course of a rigorous development program, including pharmacokinetic analysis in NHPs across formulations that allowed for rapid transition to clinical testing. OLZ is a crystalline solid with poor solubility yet high permeability. Various initial formulations investigated preparations of OLZ combined with 1) different surfactants to increase OLZ “wettability” and solubility or 2) a heated-solution approach to create a homogenous solution, which can then be spray dried into an amorphous drug product with improved solubility (amorphous solid dispersion). All formulations were spray dried with a GEA PSD1 spray dryer and included HPMC as a vehicle and

stabilizer, which is commonly used in powder formulations. Powder formulations reduce drippage and gravitational effects, and as noted above, the mucoadhesive properties of HPMC make it well suited for nasal drug delivery, as it is less prone to the rapid mucociliary clearance seen during lower nasal space delivery.<sup>24</sup> Each tested formulation therefore was aimed at optimizing the properties affecting drug absorption within the upper nasal space.

With the surfactant approach, 2 nonionic surfactants were tested: n-dodecyl β-D-maltoside and poloxamer 188 (Pluronic PF68). The formulation containing n-dodecyl β-D-maltoside was discontinued because it was sticking within the drying chamber of the spray dryer, while the PF68

formulation (OLZ:HPMC:PF68) was tested further. For the amorphous solid dispersion method, the spray dryer included an in-line heat exchanger to test 2 formulations, 1 with the permeation enhancer 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC, a phospholipid) and 1 without. OLZ:HPMC:DSPC was further developed by screening numerous solvent systems to improve the solubility profile, increase the particle size, and minimize the residual solvent, among other parameters. After screening with n-propanol, isopropanol, methanol, ethanol, dichloromethane, and acetone, a mixture of isopropanol and water was selected as the solvent. Further studies optimized solvents for increasing the solid content of the formulation for spray drying, resulting in an increased particle size. This process therefore sought to optimize both particle size and solubility for upper nasal drug delivery.

Based on this formulation development program, in a subsequent preclinical study, the NHP-POD device (NHP-INP105) was used to examine pharmacokinetic parameters of the powdered OLZ formulations described above (with nonionic

surfactant, OLZ:HPMC:PF68; and with permeation enhancer, OLZ:HPMC:DSPC) compared with IM OLZ in NHPs. Doses of 2 mg OLZ administered as commercial crystalline OLZ (not reformulated), OLZ:HPMC:PF68, and OLZ:HPMC:DSPC were tested using NHP-INP105. Blood samples were obtained at suitable intervals for pharmacokinetic assessment. The  $T_{max}$  (ie, time to reach  $C_{max}$ , the maximum concentration) of OLZ from the DSPC formulation was comparable with that of IM OLZ. However, the  $T_{max}$  was over twice as long for the PF68 formulation as well as for crystalline OLZ compared with that of IM OLZ delivery (**Table 1**). Notably, NHPs were heavily sedated at  $T_{max}$  for IM OLZ. Moreover, although the  $C_{max}$  of IM OLZ was over 5-fold higher compared with the DSPC formulation for NHP-INP105, the total exposure during plasma sampling (as measured by area under the concentration-time curve [AUC]) for the DSPC formulation was nearly identical to that of IM OLZ (**Table 1**;  $352 \pm 89$  ng\*hr/mL and  $371 \pm 55$  ng\*hr/mL, respectively). Based on this optimal pharmacokinetic profile, the OLZ:HPMC:DSPC formulation was pursued further.

**Table 1. Mean Pharmacokinetic Parameters of Olanzapine in the Cynomolgus Monkey**

Formulation	AUC <sub>last</sub> (ng*hr/mL)	C <sub>max</sub> (ng/mL)	Median T <sub>max</sub> (hr)	t <sub>1/2</sub> (hr)
Commercial OLZ for IM injection	371 ± 55	338 ± 121	0.31 ± 0.13	3.7 ± 0.5
OLZ:HPMC:PF68 (50:19:31 w/w%)	285 ± 65	35.0 ± 4.9	0.81 ± 0.83	4.3 ± 0.4
OLZ:HPMC:DSPC <sup>Exp. 1</sup> (50:42:8 w/w%)	352 ± 89	64.6 ± 18.8	0.31 ± 0.13	5.0 ± 1.0
OLZ:HPMC:DSPC <sup>Exp. 2</sup> (50:42:8 w/w%)	257 ± 62	77 ± 41	0.26 ± 0.18	4.0 ± 0.4
OLZ:HPMC:DSPC (30:62:8 w:w%)	268 ± 34	60 ± 12	0.31 ± 0.13	3.7 ± 0.3
OLZ:HPMC:DSPC:Citric Acid (41:34.5:6.5:18 w:w%)	184 ± 13	47 ± 6.2	0.81 ± 0.24	3.7 ± 0.3
OLZ:HPMC:DSPC:Maltoside (50:41:8:1 w:w%)	276 ± 75	89 ± 63	0.34 ± 0.19	3.9 ± 0.2

Abbreviations: AUC<sub>last</sub> = area under the concentration time curve to the last measurable time point; C<sub>max</sub> = maximum plasma concentration; DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; Exp = experiment; HPMC = hydroxypropyl methylcellulose; hr = hour; IM = intramuscular; OLZ = olanzapine; PF68 = Pluronic F-68; SD = standard deviation; t<sub>1/2</sub> = terminal half-life; T<sub>max</sub> = time to reach the maximum plasma concentration.

A subsequent preclinical study in NHPs examined pharmacokinetic parameters of 2 constitutions of OLZ:HPMC:DSPC with varying ratios of drug content (50:42:8 w/w and 30:62:8 w/w), a third formulation with the addition of citric acid to improve solubility (OLZ:HPMC:DSPC:Citric acid; 41:34.5:6.5:18), and a fourth formulation with maltoside added as a permeation enhancer

(OLZ:HPMC:DSPC:Maltoside), all delivered by NHP-POD. Of the 4 formulations tested, the OLZ:HPMC:DSPC (50:42:8 w/w) formulation had the lowest (shortest) median T<sub>max</sub> (0.26 hr ± 0.18) and a comparable maximum concentration and total exposure to the other formulations (full pharmacokinetic profile summarized in **Table 1**).

This preclinical work in NHPs provided crucial pharmacokinetic data on multiple formulations of OLZ delivered via POD, with the OLZ:HPMC:DSPC (50:42:8 w/w) spray-dried powder formulation providing improved absorption compared with other formulations, while producing comparable exposure to IM OLZ. This formulation was also found to be stable for up to 6 months as well as having the strongest reproducibility across preclinical studies. Because this formulation, containing HPMC and DSPC, achieved the desired pharmacokinetic profile (similar to that of OLZ IM administration, see **Table 1**) without the need for further mucoadhesive or absorption-enhancing additives, it was selected for testing in a phase 1 human trial as INP105.

### 5. INP105 CLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS IN HUMANS: REVIEW OF THE SNAP 101 TRIAL

INP105 is a drug-device combination product that delivers an OLZ powder formulation (optimized through the process described above) to the upper nasal space using POD and has been investigated in a phase 1 clinical trial. SNAP 101 (NCT03624322) was a phase 1, 2-period, incomplete-block, placebo- and comparator-controlled 1-way crossover study that assessed the safety, pharmacokinetics, and pharmacodynamics of INP105 in healthy adult participants. Blood samples for pharmacokinetic analysis were collected at regular intervals before dosing and during the 120 hours after dosing in each period. Plasma OLZ concentrations were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS), and pharmacokinetic

measurements were obtained for  $C_{max}$ ,  $T_{max}$ ,  $t_{1/2}$  (terminal half-life),  $CL/F$  (apparent clearance),  $AUC_{0-last}$  (area under the concentration-time curve from 0 to the last measurable time point),  $AUC_{0-inf}$  (area under the concentration-time curve from 0 to infinity),  $V_z/F$  (apparent volume of distribution at the terminal phase), and  $k_{el}$  (apparent terminal elimination rate constant). All randomized participants who received any study drug comprised the safety population, which included INP105 5 mg (n=10), INP105 10 mg (n=9), INP105 15 mg (n=8), and placebo POD (n=10), IM OLZ 5 mg (n=20), IM OLZ 10 mg (n=2) and ODT OLZ 10 mg (n=18).<sup>32</sup>

Pharmacokinetic data from the SNAP 101 trial identified that the absorption of OLZ was faster following administration of INP105 compared with OLZ IM or OLZ ODT. For INP105, the median  $T_{max}$  was 9.5 to 15 minutes for all doses, compared with 15 to 20 minutes for all OLZ IM doses and 120 minutes for OLZ ODT. For all doses of INP105,  $\geq 40\%$  of participants had  $T_{max} / C_{max}$  by the first time point of 5 minutes, suggesting that maximal concentrations can be achieved within 5 minutes of administration of INP105. The mean  $C_{max}$  for INP105 5 mg was comparable with OLZ IM 5 mg and approximately 1.6-fold greater than OLZ ODT 10 mg; the mean  $C_{max}$  for INP105 10 mg was 2.6-fold higher than INP105 5 mg, and for INP105 15 mg, the mean  $C_{max}$  was 3-fold higher than INP105 5 mg. Exposure ( $AUC_{0-last}$  and  $AUC_{0-inf}$ ) was similar for INP105 5 mg and OLZ IM 5 mg, suggesting comparable levels of systemic OLZ exposure (**Table 2**).<sup>32</sup>

**Table 2. SNAP 101 – Comparative Pharmacokinetic Parameters (PK Population)<sup>32</sup>**

Parameter, Mean $\pm$ SD (CV%)	OLZ IM 5 mg (n=20)	INP105 5 mg (n=10)	OLZ IM 10 mg (n=2)	INP105 10 mg (n=9)	OLZ ODT 10 mg (n=18)	INP105 15 mg (n=8)
$C_{max}$ , ng/mL	24.8 $\pm$ 11.7 (47.3)	28.7 $\pm$ 16.4 (57.3)	73.1 $\pm$ 12.2 (16.6)	74.5 $\pm$ 43.0 (57.8)	17.5 $\pm$ 7.0 (40.2)	88.8 $\pm$ 32.8 (37.0)
$AUC_{0-inf}$ , ng*h/mL	314 $\pm$ 111 (35.4)	328 $\pm$ 161 (49.0)	470 $\pm$ 0.4 (0.09)	720 $\pm$ 340 (47.2)	563 $\pm$ 241 (42.7)	811 $\pm$ 263 (32.4)
$T_{max}$ median (min, max), min	20.0 (10, 360)	15.0 (5, 360)	15.0 (15, 15)	10.0 (5, 15)	120.0 (45, 361)	9.5 (4, 15)
$t_{1/2}$ , hours	41.2 $\pm$ 9.7 (23.4)	40.5 $\pm$ 12.1 (29.8)	33.2 $\pm$ 3.1 (9.5)	36.8 $\pm$ 6.4 (17.4)	37.1 $\pm$ 9.2 (24.7)	38.5 $\pm$ 11.8 (30.8)
$k_{el}$ , L/hour	0.020 $\pm$ 0.004 (22.0)	0.019 $\pm$ 0.006 (30.2)	0.021 $\pm$ 0.002 (9.5)	0.019 $\pm$ 0.004 (18.5)	0.020 $\pm$ 0.005 (23.4)	0.019 $\pm$ 0.005 (25.4)
CL/F, L/hour	17.8 $\pm$ 5.9 (33.2)	18.0 $\pm$ 7.2 (39.9)	21.3 $\pm$ 0.02 (0.09)	17.1 $\pm$ 8.2 (48.3)	21.1 $\pm$ 8.9 (42.0)	20.0 $\pm$ 5.6 (28.0)
$V_z/F$ , L	1044 $\pm$ 446 (42.7)	979 $\pm$ 307 (31.4)	1020 $\pm$ 95 (9.4)	862 $\pm$ 325 (37.7)	1077 $\pm$ 425 (39.5)	1059 $\pm$ 257 (24.3)

$AUC_{0-inf}$  = area under the concentration-time curve from time 0 to infinity;  $CL/F$  = apparent clearance;  $C_{max}$  = maximum observed plasma concentration; CV = coefficient of variation; h = hour;  $k_{el}$  = apparent terminal elimination rate constant; max = maximum; min = minimum; ODT, orally disintegrating tablet;

OLZ = olanzapine; PK = pharmacokinetic; SD = standard deviation;  $t_{1/2}$  = apparent elimination half-life;  $T_{max}$  = time to maximum plasma concentration;  $V_z/F$  = apparent volume of distribution at the terminal phase.

Treatment-emergent adverse events (TEAEs) were mostly mild and were reported for 100% of participants for OLZ IM 10 mg, 90% for OLZ IM 5 mg, and 83.3% for OLZ ODT, compared with 80% for INP105 5 mg, 66.7% for INP105 10 mg, 75% for INP105 15 mg, and 10% for placebo. There were no severe or serious TEAEs or drug-related discontinuations with any of the INP105 doses, and nasal adverse events (AEs) were minimal. No clinically significant changes were observed in electrocardiogram or vital sign assessments after dosing. Two of the 4 participants who had been dosed in the double-blind Period 2 before dosing in the open-label Period 1 (some subjects were dosed in Period 2 and then returned to Period 1 after  $\geq 14$  days) developed postural dizziness, and 1 developed orthostatic tachycardia after INP105 5 mg administration. One of the 2 participants first dosed with INP105 10 mg developed hypotension and bradycardia (see further below).<sup>32</sup>

Pharmacodynamic effects were assessed on 3 scales designed to measure sedation and attention: the visual analog scale (VAS), the agitation/calmness evaluation scale (ACES), and the digit symbol substitution test (DSST). VAS is a self-reported scale, ACES is investigator evaluated, and DSST is an objective psychomotor assessment. Compared with placebo, INP105 produced significantly reduced scores on all 3 assessments that were comparable in magnitude to OLZ IM, indicating a similar pharmacodynamic profile to injected OLZ. Moreover, changes from placebo were evident at the first 15-minute time point for all doses of INP105 and for OLZ IM 5 mg but not for OLZ ODT, which was consistent with pharmacokinetic data showing rapid absorption and drug action for INP105 and OLZ IM administration. Of note, the 2 participants who received OLZ IM 10 mg had significant hypotension, which prevented pharmacodynamic assessments to be made, and the treatment arm was subsequently discontinued.<sup>32</sup> There was a notable delay in peak pharmacodynamic effects compared with  $T_{max}$  (~15-30 minutes), but this delay was evident in all treatment groups and is believed to be drug specific. Finally, the pharmacokinetic-pharmacodynamic relationship obtained with OLZ IM and INP105 was similar at matching doses, and the observed pharmacodynamic effects were adequately explained by measured plasma concentrations. The similarity of the

pharmacokinetic-pharmacodynamic relationship between the IM and nasal routes suggest that pharmacodynamic effects were likely driven by distribution of drug through plasma, as opposed to direct transport from the nasal cavity to the brain along olfactory pathways.

The results of SNAP 101 indicate that INP105 is a viable alternative to IM- or ODT-administered OLZ, producing a similar pharmacodynamic profile with rapid pharmacokinetic onset and exposure while displaying neither of the primary drawbacks of IM and ODT administration: invasiveness and slow onset, respectively. These data support that in healthy participants, at equivalent doses of 5 mg, INP105 had similar  $AUC_{0-last}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  as OLZ IM, but with a faster median  $T_{max}$  and lower incidence of AEs (80% vs 90%, respectively). Moreover, 3 different pharmacodynamic assessments indicated that all doses of INP105 produced injection-like changes in pharmacodynamic profile within 15 minutes, consistent with the rapid pharmacokinetic onset time (ie,  $T_{max}$ ). These results suggest that the pharmacokinetic and pharmacodynamic profile of INP105 may allow for a more rapid onset of effect, which would be beneficial in the context of acute agitation, using a noninvasive delivery method of OLZ to the upper nasal space via POD. A phase 2, proof-of-concept study (CALM 201, NCT05163717) is now investigating the efficacy and safety of a further optimized formulation of INP105 in adolescent patients with autism spectrum disorder who have been hospitalized for management of repeated bouts of acute agitation.<sup>55</sup>

## 6. CONCLUSION

Although nasal delivery of drugs is not a new concept, the site of drug deposition in the nose is underappreciated and undervalued. The ability to reach the upper, deeper cavities of the nasal space is challenging and requires careful selection of preclinical animal models to appropriately modify delivery technology and facilitate translation to humans. As described here, use of the NHP model enabled optimization of the formulation ultimately used in the initial clinical trial of INP105. Delivery of drug to the upper nasal space can allow for rapid, extensive absorption that is injection-free and easy to administer by patients, clinicians, and caregivers. POD technology allows for the delivery

of clinically relevant doses of OLZ (INP105) to the upper nasal space and is supported by a phase 1 study that indicated INP105 exhibits a favorable pharmacokinetic profile, including rapid and consistent absorption of drug into the blood. These phase 1 data followed preclinical formulation development, optimization, and pharmacokinetic characterization in NHP models. Collectively, these data have demonstrated the potential for the broad applicability of POD to treat a number of disease states exhibiting agitation.

**Conflict of Interest Statement:**

Stephen B. Shrewsbury, Greg Davies, Lisa McConnachie, and John Hoekman are full-time

employees and stockholders of Impel Pharmaceuticals. John Hoekman and Stephen B. Shrewsbury are officers of Impel Pharmaceuticals.

**Funding:** This work was funded by Impel Pharmaceuticals Inc.

**Acknowledgments:**

Writing and editorial assistance was provided by IMPRINT Science, New York, NY, and supported by Impel Pharmaceuticals Inc. The authors are fully responsible for the content, editorial decisions, and opinions expressed in this article.

## REFERENCES

1. Vugmeyster Y, Harrold J, Xu X. Absorption, distribution, metabolism, and excretion (adme) studies of biotherapeutics for autoimmune and inflammatory conditions. *AAPS J.* 2012;14(4):714-727. DOI: 10.1208/s12248-012-9385-y
2. Tang C, Prueksaritanont T. Use of in vivo animal models to assess pharmacokinetic drug-drug interactions. *Pharm Res.* 2010;27(9):1772-1787. DOI: 10.1007/s11095-010-0157-z
3. Yacobi A, Skelly JP, Shah VP, Benet LZ, eds. *Integration of pharmacokinetics, pharmacodynamics, and toxicokinetics in rational drug development.* Springer; 1993.
4. Tuntland T, Ethell B, Kosaka T, et al. Implementation of pharmacokinetic and pharmacodynamic strategies in early research phases of drug discovery and development at novartis institute of biomedical research. *Front Pharmacol.* 2014;5:174. DOI: 10.3389/fphar.2014.00174
5. Price G, Patel DA. Drug bioavailability. In: *Statpearls publishing.* Treasure Island, FL 2020.
6. Jin JF, Zhu LL, Chen M, et al. The optimal choice of medication administration route regarding intravenous, intramuscular, and subcutaneous injection. *Patient Prefer Adherence.* 2015;9:923-942. DOI: 10.2147/PPA.S87271
7. Shrewsbury S, Hocevar-Trnka J, Hoekman J. Drug delivery via the upper nasal space: A novel route for anesthesiologists, intensivists and emergency department physicians? *J Clin Anesth Intensive Care.* 2021;2(1):8-14.
8. Djupesland PG, Messina JC, Mahmoud RA. Breath powered nasal delivery: A new route to rapid headache relief. *Headache.* 2013;53(Suppl 2):72-84. DOI: 10.1111/head.12186
9. Homayun B, Lin X, Choi HJ. Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. *Pharmaceutics.* 2019;11(3):129. DOI: 10.3390/pharmaceutics11030129
10. Citrome L. Addressing the need for rapid treatment of agitation in schizophrenia and bipolar disorder: Focus on inhaled loxapine as an alternative to injectable agents. *Therapeutics and clinical risk management.* 2013;9:235-245. DOI: 10.2147/TCRM.S31484
11. Rech MA, Barbas B, Chaney W, Greenhalgh E, Turck C. When to pick the nose: Out-of-hospital and emergency department intranasal administration of medications. *Ann Emerg Med.* 2017;70(2):203-211. DOI: 10.1016/j.annemergmed.2017.02.015
12. Simonet C, Tolosa E, Camara A, Valldeoriola F. Emergencies and critical issues in parkinson's disease. *Pract Neurol.* 2020;20(1):15-25. DOI: 10.1136/practneurol-2018-002075
13. Lipton RB, Munjal S, Buse DC, et al. Unmet acute treatment needs from the 2017 Migraine In America Symptoms And Treatment Study. *Headache.* 2019;59(8):1310-1323. DOI: 10.1111/head.13588
14. Detke HC, Millen BA, Zhang Q, et al. Rapid onset of effect of galcanezumab for the prevention of episodic migraine: Analysis of the evolve studies. *Headache.* 2020;60(2):348-359. DOI: 10.1111/head.13691
15. Rygg A, Hindle M, Longest PW. Absorption and clearance of pharmaceutical aerosols in the human nose: Effects of nasal spray suspension particle size and properties. *Pharm Res.* 2016;33(4):909-921. DOI: 10.1007/s11095-015-1837-5
16. Djupesland PG. Nasal drug delivery devices: Characteristics and performance in a clinical perspective-a review. *Drug Deliv Transl Res.* 2013;3(1):42-62. DOI: 10.1007/s13346-012-0108-9
17. Dhuria SV, Hanson LR, Frey WH, II. Intranasal delivery to the central nervous system: Mechanisms and experimental considerations. *J Pharm Sci.* 2010;99(4):1654-1673. DOI: 10.1002/jps.21924
18. Mignani S, Shi X, Karpus A, Majoral JP. Non-invasive intranasal administration route directly to the brain using dendrimer nanoplatfoms: An opportunity to develop new cns drugs. *Eur J Med Chem.* 2021;209:112905. DOI: 10.1016/j.ejmech.2020.112905
19. Kellerman DJ, Forst A, Combs DL, Borland S, Kori S. Assessment of the consistency of absorption of dihydroergotamine following oral inhalation: Pooled results from four clinical studies. *J Aerosol Med Pulm Drug Deliv.* 2013;26(5):297-306. DOI: 10.1089/jamp.2012.0999

20. Martin V, Hoekman J, Aurora SK, Shrewsbury SB. Nasal delivery of acute medications for migraine: The upper versus lower nasal space. *J Clin Med.* 2021;10(11):2468. DOI: 10.3390/jcm10112468
21. Musumeci T, Bonaccorso A, Puglisi G. Epilepsy disease and nose-to-brain delivery of polymeric nanoparticles: An overview. *Pharmaceutics.* 2019;11(3):118. DOI: 10.3390/pharmaceutics11030118
22. Miller JL, Ashford JW, Archer SM, Rudy AC, Wermeling DP. Comparison of intranasal administration of haloperidol with intravenous and intramuscular administration: A pilot pharmacokinetic study. *Pharmacotherapy.* 2008;28(7):875-882. DOI: 10.1592/phco.28.7.875
23. Hoekman J, Ray S, Aurora SK, Shrewsbury SB. The upper nasal space—a novel delivery route ideal for central nervous system drugs. *US Neurol.* 2020;16(1):25-31.
24. Gänger S, Schindowski K. Tailoring formulations for intranasal nose-to-brain delivery: A review on architecture, physico-chemical characteristics and mucociliary clearance of the nasal olfactory mucosa. *Pharmaceutics.* 2018;10(3):116. DOI: 10.3390/pharmaceutics10030116
25. Djupesland PG, Messina JC, Mahmoud RA. The nasal approach to delivering treatment for brain diseases: An anatomic, physiologic, and delivery technology overview. *Ther Deliv.* 2014;5(6):709-733. DOI: 10.4155/tde.14.41
26. Crowe TP, Greenlee MHW, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. *Life Sci.* 2018;195:44-52. DOI: 10.1016/j.lfs.2017.12.025
27. Chamanza R, Wright JA. A review of the comparative anatomy, histology, physiology and pathology of the nasal cavity of rats, mice, dogs and non-human primates. Relevance to inhalation toxicology and human health risk assessment. *J Comp Pathol.* 2015;153(4):287-314. DOI: 10.1016/j.jcpa.2015.08.009
28. Chari S, Sridhar K, Walenga R, Kleinstreuer C. Computational analysis of a 3D mucociliary clearance model predicting nasal drug uptake. *J Aerosol Sci.* 2021;155(5):105757. DOI: <https://doi.org/10.1016/j.jaerosci.2021.105757>
29. Escada PA, Lima C, da Silva JM. The human olfactory mucosa. *Eur Arch Otorhinolaryngol.* 2009;266(11):1675-1680. DOI: 10.1007/s00405-009-1073-x
30. Ladel S, Schlossbauer P, Flamm J, Luksch H, Mizaikoff B, Schindowski K. Improved in vitro model for intranasal mucosal drug delivery: Primary olfactory and respiratory epithelial cells compared with the permanent nasal cell line RPMI 2650. *Pharmaceutics.* 2019;11(8):367. DOI: 10.3390/pharmaceutics11080367
31. Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. *Adv Drug Deliv Rev.* 2012;64(7):614-628. DOI: 10.1016/j.addr.2011.11.002
32. Shrewsbury SB, Hocevar-Trnka J, Satterly KH, Craig KL, Lickliter JD, Hoekman J. The snap 101 double-blind, placebo/active-controlled, safety, pharmacokinetic, and pharmacodynamic study of inp105 (nasal olanzapine) in healthy adults. *J Clin Psychiatry.* 2020;81(4). DOI: 10.4088/JCP.19m13086
33. Cooper W, Ray S, Aurora SK, et al. Delivery of dihydroergotamine mesylate to the upper nasal space for the acute treatment of migraine: Technology in action. *Journal of Aerosol Medicine and Pulmonary Drug Delivery.* 2022; In Press.
34. Morgan KT, Jiang XZ, Patterson DL, Gross EA. The nasal mucociliary apparatus. Correlation of structure and function in the rat. *Am Rev Respir Dis.* 1984;130(2):275-281. DOI: 10.1164/arrd.1984.130.2.275
35. Silberstein SD, Shrewsbury SB, Hoekman J. Dihydroergotamine (dhe) — then and now: A narrative review. *Headache.* 2020;60(1):40-57. DOI: 10.1111/head.13700
36. Hoekman JD, Ho RJ. Effects of localized hydrophilic mannitol and hydrophobic Nelfinavir administration targeted to olfactory epithelium on brain distribution. *AAPS PharmSciTech.* 2011;12(2):534-543. DOI: 10.1208/s12249-011-9614-1
37. Darquenne C. Aerosol deposition in health and disease. *J Aerosol Med Pulm Drug Deliv.* 2012;25(3):140-147. DOI: 10.1089/jamp.2011.0916
38. Djupesland PG, Skretting A, Winderen M, Holand T. Breath actuated device improves

- delivery to target sites beyond the nasal valve. *Laryngoscope*. 2006;116(3):466-472. DOI: 10.1097/01.mlg.0000199741.08517.99
39. Onzetra® Xsail® [package insert]. Currax™ Pharmaceuticals LLC; 2019.
40. Shrewsbury SB, Jeleva M, Satterly KH, Lickliter J, Hoekman J. Stop 101: A phase 1, randomized, open-label, comparative bioavailability study of inp104, dihydroergotamine mesylate (dhe) administered intranasally by a 1123 precision olfactory delivery (POD®) device, in healthy adult subjects. *Headache*. 2019;59(3):394-409. DOI: 10.1111/head.13476
41. Zeller SL, Citrome L. Managing agitation associated with schizophrenia and bipolar disorder in the emergency setting. *West J Emerg Med*. 2016;17(2):165-172. DOI: 10.5811/westjem.2015.12.28763
42. Dundar Y, Greenhalgh J, Richardson M, Dwan K. Pharmacological treatment of acute agitation associated with psychotic and bipolar disorder: A systematic review and meta-analysis. *Hum Psychopharmacol*. 2016;31(4):268-285. DOI: 10.1002/hup.2535
43. Klein LR, Driver BE, Miner JR, et al. Intramuscular midazolam, olanzapine, ziprasidone, or haloperidol for treating acute agitation in the emergency department. *Ann Emerg Med*. 2018;72(4):374-385. DOI: 10.1016/j.annemergmed.2018.04.027
44. Zyprexa [Prescribing information]. Indianapolis, In: Eli Lilly and Company; 2009.
45. Wilson MP, Pepper D, Currier GW, Holloman GH, Jr., Feifel D. The psychopharmacology of agitation: Consensus statement of the American Association For Emergency Psychiatry Project Beta Psychopharmacology Workgroup. *West J Emerg Med*. 2012;13(1):26-34. DOI: 10.5811/westjem.2011.9.6866
46. Battaglia J. Pharmacological management of acute agitation. *Drugs*. 2005;65(9):1207-1222. DOI: 10.2165/00003495-200565090-00003
47. Hanson LR, Fine JM, Svitak AL, Faltsek KA. Intranasal administration of CNS therapeutics to awake mice. *J Vis Exp*. 2013(74):4440. DOI: 10.3791/4440
48. Rouquier S, Blancher A, Giorgi D. The olfactory receptor gene repertoire in primates and mouse: Evidence for reduction of the functional fraction in primates. *Proceedings of the National Academy of Sciences*. 2000;97(6):2870-2874. DOI: 10.1073/pnas.040580197
49. Takahashi R. The formation of the human paranasal sinuses. *Acta Otolaryngol Suppl*. 1984;408:1-28. DOI: 10.3109/00016488409121162
50. Gajera B, Satterly KH, McKennon M, Muppaneni S, Wright J, Hoekman J. Formulation development and physicochemical characterization of a CNS drug product delivered intranasally by precision olfactory delivery (POD®) device technology. Presented at: American Association of Pharmaceutical Scientists Annual Meeting; November 4-7, 2018.
51. Brown V, Liu F. Intranasal delivery of a peptide with antidepressant-like effect. *Neuropsychopharmacology*. 2014;39(9):2131-2141. DOI: 10.1038/npp.2014.61
52. Harkema JR, Carey SA, Wagner JG. The nose revisited: A brief review of the comparative structure, function, and toxicologic pathology of the nasal epithelium. *Toxicol Pathol*. 2006;34(3):252-269. DOI: 10.1080/01926230600713475
53. Smith TR, Winner P, Aurora SK, Jeleva M, Hocevar-Trnka J, Shrewsbury SB. Stop 301: A phase 3, open-label study of safety, tolerability, and exploratory efficacy of inp104, precision olfactory delivery (POD®) of dihydroergotamine mesylate, over 24/52 weeks in acute treatment of migraine attacks in adult patients. *Headache*. 2021;61(8):1214-1226. DOI: 10.1111/head.14184
54. Trudhesa. [Prescribing information]. Manufactured in: Mipharm, S.p.A, Milano, Italy for Impel Neuropharma Inc., Seattle, WA. 2021.
55. Clinicaltrials.Gov. "INP105 proof-of-concept study for the acute treatment of agitation in adolescents with ASD (CALM 201)". NCT05163717 (<https://clinicaltrials.gov/ct2/show/study/NCT05163717>), accessed July 26, 2022.