Development of a Precision Olfactory Delivery (POD®)-Olanzapine Drug-Device Product for Agitation

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Abstract

Background: Impel NeuroPharma is developing INP105 (POD-Olanzapine [OLZ]), a drug-device combination product consisting of a novel OLZ powder formulation for nasal administration by the POD device, designed to provide a dosage form with rapid onset of agitation relief comparable to intramuscular injection and the ease of use of oral therapy. POD technology is designed to deliver drugs to the upper nasal mucosa for rapid and consistent systemic absorption with minimal effort or user coordination.

Methods: OLZ formulations were designed and manufactured to optimize powder characteristics and device compatibility. Formulations were characterized by analytical methods and in rat and non-human primate (NHP) pharmacokinetic (PK) studies.

Results: Approximately 30 formulations were designed for nasal delivery by the POD device, manufactured, and assessed by analytical chemistry techniques and device compatibility. The lead formulation was tested to 5 months on stability, had >99% assay and <1% total impurities over the storage period, and exhibited a T_{max} of 17 min in NHP, similar to that reported for intramuscular OLZ, and a C_{max} of 71 ng/mL, ~3-fold higher than the C_{max} following intramuscular OLZ in patients. This lead formulation was selected for clinical development in the INP105-101 study.

Conclusions: This series of preclinical development studies, where powder OLZ formulations were manufactured for delivery by a POD device to preclinical models and were tested by chemical and pharmacokinetic properties, led to the identification of a lead formulation to be tested in the INP105-101 proof-of-concept clinical study and for further development by Impel NeuroPharma.

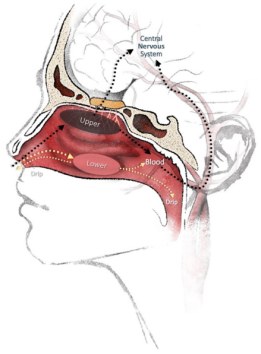
Introduction

Acute agitation is a cluster of behaviors observed in multiple psychiatric diseases, with up to 7 million episodes reported per year in the US, and which can increase the likelihood of violent behavior. Atypical antipsychotics, including oral and intramuscular OLZ, have been approved for chronic and acute agitation treatment, respectively, for schizophrenia and bipolar I disorder in the US for over 20 years. During acute agitation episodes, intramuscular OLZ is preferred over oral treatments due to a shorter T_{max}. However, intramuscular OLZ is invasive and is predominately administered in Emergency Room (ER) or other acute hospital settings and may require restraint if the patient is uncooperative, potentially reducing trust between patient and medical personnel and increasing the likelihood of injuries. When possible, non-injectable routes of administration are preferred during agitation events; however, slower onset oral products often require labor intensive observation of the medicated patient until adequate resolution of the acute episode occurs.

Impel NeuroPharma is developing INP105 (POD-OLZ), a drug-device combination product consisting of a novel OLZ powder formulation for nasal administration by the POD device (Figure 1a), designed to provide a dosage form with the rapid onset of agitation relief comparable to intramuscular injection and the ease of use of oral therapy. The POD device technology is designed to deliver drug to the upper nasal mucosa for rapid and consistent systemic absorption with minimal effort or user coordination (Figure 1b).

Figure 1a. Image of the Clinical Research INP105 (POD-OLZ) Drug-Device Combination Product Used in the INP105-101 Clinical Study

Figure 1b. Diagram of the Nasal Space: "Lower" Is the Target of Typical Nasal Sprays; "Upper" Is the Target for POD Delivery



Methods

Manufacturing and Analytical Testing

Figure 2. Image of the NHP-POD Device

- OLZ formulations were designed and manufactured for upper nasal cavity delivery:
  - Powder characteristics were optimized for POD device compatibility
  - Stabilizers, enhancers, particle size and manufacturing were screened as part of the formulation development process
- Formulations were characterized by the following test methods:
  - Assay and related substances by an Impel-developed high pressure liquid chromatography/diode array detector method optimized for Impel's OLZ formulations
  - Solid state by X-ray diffraction and differential scanning calorimetry [data not shown]
  - Moisture content by Karl Fischer titration or loss on drying
  - POD device compatibility for species specific (rat-POD and NHP-POD), clinical, and to-be-marketed devices: a gravimetric method was used to determine compatibility through residual and variability in delivery (coefficient of variation)
  - Short-term (1 week) stability under accelerated conditions (40 °C/75% RH) and longer term stability under standard conditions (25 °C/75% RH) were used to assess formulation stability ahead of and in parallel with the PK studies

Pharmacokinetic Studies

- Lead formulations were evaluated in single dose rat [data not shown] and NHP PK studies:
  - Powder olanzapine formulations were administered nasally to NHP by Impel's non-human primate NHP-POD device (Figure 2)
  - Per formulation, 2 male and 2 female *Cynomolgus* macaques were assigned to each group
  - Formulations were delivered through 1 spray to a single naris to deliver 2 mg OLZ
  - Blood samples were collected at 0 (pre-dose), 0.05, 0.117, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 10, 18, and 24 hours post dose into K_2EDTA tubes with OLZ stabilizer
  - Plasma was isolated from blood and OLZ was measured by a liquid chromatography mass spectrometry (LC/MS/MS) method optimized to measure OLZ
  - PK parameter calculations were performed by non-compartmental analysis using Phoenix WinNonlin (v6.3, v8.0)
  - Observations of tolerability and the pharmacodynamic impact of each nasal OLZ formulation administered were collected throughout the study

Results

- Approximately 30 formulations were designed for nasal delivery by the POD device, optimized through the manufacturing process, and characterized by analytical chemistry techniques and device compatibility.
- In total, 20 of the designed and optimized formulations were evaluated in single dose rat [data not shown] and NHP PK studies.

Table 1. Summary of Select Formulation Stability Results under Accelerated (40 °C/75% RH) Storage Conditions

	F-OLZ #1	F-OLZ #2	F-OLZ #3	F-OLZ #4	F-OLZ #5	F-OLZ #6
Manufacturing Process	NA[1]	B	A	C	A	A
Purity % T=0	99.8	99.8	100.5	94.9	96.1	ND[2]
Purity % T=1 week	99.8	100	112	91.6	98.7	ND[2]
NHP-POD Device Compatibility (% Variability, N=5)	± 21%	± 6%	± 6%	± 10%	± 10%	± 30%

[1]Not applicable. [2]Not determined.

- Short-term formulation stability results for 6 lead formulations are shown in Table 1 for formulations tested in both rat and NHPs. These stability results demonstrate good purity over the brief accelerated period. Powder flow characteristics impact device compatibility as shown by differences in variability.
- One lead formulation, F-OLZ #2, was tested to 5 months on stability and had >99% assay and <1% total impurities over the storage period. Further, device compatibility results for F-OLZ #2 over 5 months were excellent, demonstrating that even with minor changes to powder characteristics (eg, moisture content), the formulation continues to perform well with POD technology (Table 2). These results demonstrate a good shelf-life for POD-OLZ is feasible, especially considering that the stability study was conducted without the opportunity to fully optimize packaging at this early stage.

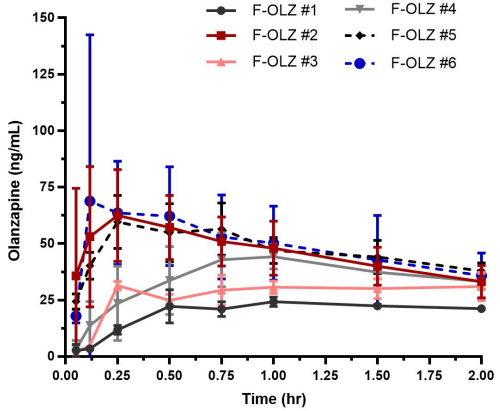
Table 2. Summary of Lead Formulation F-OLZ #2 Stability Results at Room Temperature Storage Conditions (25 °C/60% RH) in Early Stage[1] Packaging

	T=0	T=1 month	T=2 months	T=3 months	T=5 months
Purity %	96.5	99.0	99.7	99.1	99.3
Related Substances (Total %)	0.3	0.2	0.4	0.6	0.9
Device Compatibility	10.6 mg ± 6%	9.7 mg ± 6%	9.9 mg ± 4%	9.9 mg ± 5%	10.1 mg ± 6%
Moisture Content %	0.8	1.6	2.2	2.2	2.1

[1]Early stage packaging has not been optimized, and this data represents worst case scenario compared to the intended commercial packaging.

- In total, 10 OLZ formulations were tested in single dose NHP PK studies. The plasma concentration time curves from PK blood draws following administration of 6 different OLZ formulations are shown in Figures 3 and 4.
- Delivery of formulations F-OLZ #2, F-OLZ #5 and F-OLZ #6 to NHP via the NHP-POD device resulted in rapid uptake with short time to median T_{max} (15, 15 and 23 min, respectively) and less than 7 min to exceed 40 ng/mL, which is approximately the C_{max} achieved in patients following a 10 mg intramuscular injection (Zyprexa NDA 21253).
- Delivery of formulations F-OLZ #1, F-OLZ #3 and F-OLZ #4 to NHP via the NHP-POD device resulted in slower plasma uptake compared to the other 3 formulations, but still resulted in median T_{max} of 30-60 min (Table 3), which is significantly faster than time to peak plasma concentration for oral OLZ tablets or disintegrating tablets (T_{max} ~5-8 hrs in patients).
- The lead formulation, F-OLZ #2, was selected for clinical development in the INP105-101 study.

Figure 3. Mean (± SD) Plasma Concentrations of OLZ Following Administration of Nasal Powder Formulations Delivered to NHP by the POD Device (Time displayed 0-2 hours)



- All 6 formulations delivered by the NHP-POD device were well tolerated following single dose administration to NHP. No visible irritation was observed immediately following administration or 24 hours after delivery. Additionally, though not shown in this report, 14-day subchronic toxicity in rat was studied with nasal OLZ delivery. No macroscopic or microscopic findings were reported suggesting that acute and repeat nasal exposure OLZ will be well tolerated.
- The pharmacodynamic effects of each nasal OLZ formulation administered to NHP were collected throughout each study. For lead formulations with shorter time to T_{max}, visible calming, though not excessive sedation, was observed in NHPs by the 7 min blood draw station, and the effect continued through 24 hours. This reported calming effect was observed in all groups that received nasal OLZ, though the time to onset was delayed and effect was less pronounced in groups with slower time to peak plasma concentration and with lower peak exposure.

Figure 4. Mean (± SD) Plasma Concentrations of OLZ Following Administration of Nasal Powder Formulations Delivered to NHP by the POD Device (Time displayed 0-10 hours)

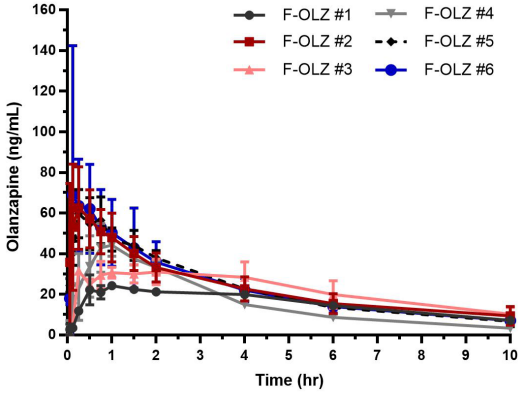


Table 3. PK Parameters Following POD-OLZ Administration to NHP

Formulation	Median T_{max} (min) [min, max]	C_{max} (ng/mL) (Avg ± SD)	$AUC_{0\text{-}24hr}$ (ng*hr/mL) (Avg ± SD)	$t_{1/2}$ (hr) (Avg ± SD)
F-OLZ #1	60 [30, 60]	26 ± 4.4	201 ± 21	4.7 ± 0.6
F-OLZ #2	15 [3, 30]	71 ± 30	297 ± 62	4.5 ± 0.9
F-OLZ #3	30 [15, 120]	35 ± 4.9	279 ± 65	4.3 ± 0.4
F-OLZ #4	54 [30, 60]	47 ± 6.2	184 ± 13	3.7 ± 0.3
F-OLZ #5	15 [15, 30]	60 ± 12	285 ± 34	3.7 ± 0.3
F-OLZ #6	23 [7.2, 30]	89 ± 63	276 ± 75	3.9 ± 0.2

Conclusions

- Impel NeuroPharma is developing INP105, a POD-OLZ drug-device combination product, which will administer powder OLZ drug product to the vascular-rich upper nasal space with the novel POD device, a needle-free, easy self- or care-giver administered, and potentially rapidly effective OLZ treatment to abort episodes of acute agitation in the low-intensity community clinic or ER setting.
- This series of preclinical development studies demonstrates:
  - The chemical stability of a lead OLZ powder formulation has excellent purity and device compatibility over at least 5 months, suggesting a reasonable shelf-life will be feasible for a powder nasal OLZ product.
  - Nasal delivery of OLZ by the POD device results in rapid uptake across the nasal epithelium in NHP, with lead formulations resulting ~15 minutes to maximum plasma concentration, comparable with intramuscular injection of OLZ.
  - OLZ nasal formulations delivered by NHP-POD device were well tolerated and exhibited rapid calming effects, both positive attributes of a potential treatment for acute agitation.
- The results from these development studies has led to the identification of a lead formulation to be tested in the INP105-101 proof-of-concept clinical study and for further development.

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