Snap 101: Randomized, Crossover, Active and Placebo-Controlled, Safety, Pharmacokinetic, and Pharmacodynamic Study of Three Ascending Doses of INP105 - Novel Precision Olfactory Delivery (POD) of a Nasal Formulation of Olanzapine

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Abstract

Background: INP105 is a drug-device combination product consisting of a novel, proprietary powder formulation of olanzapine and a research form of the Precision Olfactory Delivery (POD®) device (I231 POD device) that delivers olanzapine (OLZ) to the vascular rich upper nasal space. It is being developed for rapid control of agitation to provide fast onset of relief in an accessible, needle-free, dosage form.

Objective: The objectives of this study were to evaluate the safety and tolerability of single ascending doses of INP105; to compare the pharmacokinetics (PK) of INP105 doses with OLZ intramuscular (IM) and OLZ oral disintegrating tablet (ODT); to compare pharmacodynamic (PD) effects of INP105 and comparators; and to explore PK/PD and dose-response relationships for INP105.

Methods: This was a Phase 1, randomized, double-blind, placebo- and active comparator-controlled, ascending-dose, 2-way, 2 period, incomplete block, crossover study in healthy subjects. Subjects were randomized to single doses of INP105, OLZ IM, and OLZ ODT. Period 1 was open label to evaluate OLZ IM 5 mg and 10 mg and OLZ ODT 10 mg. Period 2 was a double-blind phase to compare INP105 5 mg, 10 mg, and 15 mg or placebo with doses of OLZ IM and OLZ ODT used in Period 1. The effects of all treatments on sedation and attention using a visual analog scale (VAS), Agitation/Calmness Evaluation Scale (ACES), and Digit Symbol Substitution Test (DSST) were assessed.

Results: T_{max} was reached within 9.5 to 15 minutes with INP105 vs. 20 minutes with OLZ IM 5 mg and 120 minutes with OLZ ODT. Exposure (AUC_{0-last} and AUC_{0-inf}) was similar for INP105 5 mg and OLZ IM 5 mg; C_{max} with INP105 5 mg was similar to OLZ IM 5 mg and greater than OLZ ODT 10 mg, while C_{max} for 10 and 15 mg doses of INP105 were at least 3-fold higher than for OLZ IM 5 mg. A comparison of C_{max} and AUC for INP105 showed that at equivalent doses, INP105 provided similar exposure to OLZ IM and OLZ ODT; an increase in exposure occurred at each dose level of INP105. Effects on the pharmacodynamic measures (VAS, ACES, and DSST) were greater with INP105 than placebo and OLZ ODT 10 mg and comparable to OLZ IM 5 mg. Mean maximum change from baseline for ACES was significantly (p<0.0001) improved vs. placebo with all 3 doses of INP105. The incidence of treatment-emergent AEs was highest with OLZ IM and OLZ ODT; most common events were related to dizziness, hypotension, and orthostasis, but the majority occurred with OLZ IM or ODT. Headache occurred in 6 (33.3%) of subjects with OLZ ODT 10 mg.

Conclusion: INP105 has a rapid T_{max} and corresponding onset of effect and may represent an effective alternative for treating acutely agitated patients and a valuable option for self or caregiver administration in the home environment.

Introduction

- On average, patients with schizophrenia or bipolar I disorder, experience 12 agitation events/year ranging from mild to severe.[1]
- Severely agitated patients are a common cause of workplace violence against healthcare professionals in the emergency department (ED).[2,3]
- There are 1.7M ED visits/year related to agitation in patients with either schizophrenia or bipolar I disorder and over 10M inpatient treatment facility admissions/year lasting 6-10 days per visit with multiple agitation events requiring treatment related to agitation.[4]
- Treatment for acute agitation in the ED includes antipsychotics and benzodiazepines, however, the use of either have limitations.[2,5]
- The ideal acute agitation therapy would provide rapid de-escalation, be safe, be delivered non-invasively and create a tranquil state for patients versus unconsciousness.[6]
- Olanzapine (OLZ) intramuscular (IM) is often used because of a more rapid onset than oral tablets or orally-disintegrating tablets (ODT).[6,7]
- INP105 is a drug-device product consisting of a powder form of OLZ and a POD® device (I231 POD device) that delivers OLZ to the vascular rich upper nasal space.[8]
- INP105 may represent a rapid, reliable and relevant option for patients needing OLZ in the ED, during psychiatric hospitalization, community care or even when living at home.

Objectives

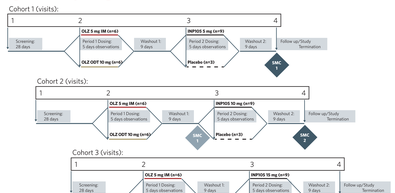
- Evaluate the safety and tolerability of 3 single ascending doses of INP105 in healthy subjects
- Compare the PK and PD effects of 3 INP105 doses with OLZ IM (5 and 10 mg) and OLZ ODT 10 mg
- Explore PK/PD and dose-response relationships for INP105

Methods

Study Design

- Phase 1, randomized, double-blind, placebo- and active comparator-controlled, ascending-dose, 2-way, 2 period, incomplete block, crossover study in healthy subjects (**Figure 1**)
  - Period 1 (open label) evaluated OLZ IM 5 mg and 10 mg (quickly abandoned) and OLZ ODT 10 mg
  - Period 2 (double-blind) compared INP105 5 mg, 10 mg, and 15 mg or placebo with doses of OLZ IM and OLZ ODT
- OLZ or matched placebo were delivered nasally using the POD device
- All subjects were observed as in-patients for at least 72 hours post-dosing, and follow-up occurred at 4, 5, and 14 days after dosing for each study period

Figure 1. Study Design



Subject Selection

- Adult male or female subjects ages 18 to 55 years inclusive and with a body mass index (BMI) of 18 to 32 kg/m² inclusive who were in good general health
- Subjects were excluded for hypersensitivity to OLZ or OLZ use within the past 3 months

Study Assessments

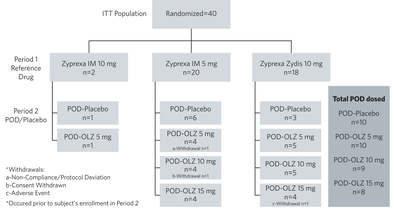
- Safety was assessed from physical examination, vital signs, body temperature, 12-lead electrocardiogram (ECG), nasal examination and clinical laboratory tests
- Subjective assessments of sedation and attention taken pre- and postdose:
  - Agitation/Calmness Evaluation Scale (ACES) on a 9-point scale
  - Visual Analog Scale (VAS) level of sedation on three 10 cm scales using the descriptive terms Alert / Drowsy, Foggy/Clear-headed, and Energetic / Lethargic
  - Digit Symbol Substitution Test (DSST) assessed response speed, sustained attention, visual spatial skills, and set shifting
- Blood samples for determining OLZ levels were collected pre-dose and at frequent intervals out to 120 hours after each dose

Results

Subject Disposition

- The OLZ IM 10 mg group was discontinued during Period 1 due to excessive hypotension
- 40 subjects were randomized, and all 40 were included in the Safety and PK Population and 37 subjects were included in the Per Protocol Population having received both reference and study drug (**Figure 2**)

Figure 2. Subject Disposition



- Treatment groups were generally comparable for baseline characteristics (**Table 1**)

Table 1. Baseline Demographic Characteristics (Subjects Receiving IM OLZ 10 mg Excluded)

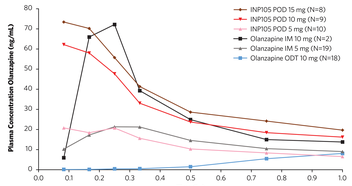
Period 1	OLZ IM 5 mg				OLZ ODT 10 mg				
Period 2	INP105 5 mg (n=5)	INP105 10 mg (n=5)	INP105 15 mg (n=4)	Placebo (n=6)	INP105 5 mg (n=5)	INP105 10 mg (n=5)	INP105 15 mg (n=5)	Placebo (n=3)	Overall (n=38)
Age, years[a]	26.4 ± 4.9	25.8 ± 3.0	26.5 ± 4.5	26.2 ± 3.9	32.0 ± 12.4	25.6 ± 5.1	27.6 ± 5.9	33.7 ± 12.5	27.5 ± 6.7
Female, *n* (%)	3 (60.0)	1 (20.0)	2 (50.0)	4 (66.7)	3 (60.0)	3 (60.0)	1 (20.0)	2 (66.7)	20 (50.0)
Race, *n* (%)									
White	4 (80.0)	3 (60.0)	3 (75.0)	3 (50.0)	4 (80.0)	4 (80.0)	3 (60.0)	3 (60.0)	28 (70.0)
Asian	0	1 (20.0)	1 (25.0)	2 (33.3)	0	1 (20.0)	2 (40.0)	0	7 (17.4)
Other	1 (20.0)	1 (20.0)	0	1 (16.7)	1 (20.0)	0	0	0	5 (12.5)
Weight, kg[a]	78.6 ± 14.9	76.7 ± 14.6	76.5 ± 8.3	71.2 ± 18.0	73.9 ± 13.1	73.4 ± 11.4	76.8 ± 17.9	64.4 9.0	74.4 ± 13.3
BMI, kg/m²[a]	26.3 ± 3.8	23.8 4.4	26.3 ± 1.4	24.1 ± 2.1	25.2 ± 3.6	23.9 ± 1.9	24.3 ± 3.9	24.0 ± 3.9	24.7 ± 3.0

[a]Mean ± standard deviation; BMI – body mass index

Pharmacokinetics

- Peak plasma OLZ concentrations were achieved within 20 minutes for all treatment groups except for OLZ ODT 10 mg (**Figure 3**)

Figure 3. Mean Plasma OLZ Concentrations From 0-1 Hour



- Median T_{max} was reached within 9.5 to 15 minutes with INP105 vs. 20 minutes with OLZ IM 5 mg and 120 minutes with OLZ ODT 10 mg (**Table 2**)
- C_{max} with INP105 5 mg was similar to OLZ IM 5 mg and approximately 2-fold greater than OLZ ODT 10 mg

Table 2. Summary of Pharmacokinetic Parameters (PK Population)

	Mean ± Standard Deviation (CV%)					
	Period 1			Period 2		
	OLZ IM 5 mg (n=20)	OLZ IM 10 mg (n=2)	OLZ ODT 10 mg (n=18)	INP105 5 mg (n=10)	INP105 10 mg (n=9)	INP105 15 mg (n=8)
C_{max}, ng/mL	24.8 ± 11.7 (47.3)	73.1 ± 12.2 (16.6)	17.5 ± 7.0 (40.2)	28.7 ± 16.6 (57.3)	74.5 ± 43.1 (57.8)	88.8 ± 32.8 (37.0)
AUC_{0-last}, h*ng/mL	275 ± 90 (32.7)	450 ± 12 (2.6)	499 ± 201 (40.2)	269 ± 84 (31.3)	649 ± 299 (46.0)	719 ± 180 (25.1)
AUC_{0-inf}, h*ng/mL	314 ± 111 (35.4)	470 ± 0.4 (0.09)	563 ± 241 (42.7)	328 ± 161 (49.0)	720 ± 340 (47.2)	811 ± 263 (32.4)
T_{max}, h[a]	20.0 (10, 360)	15.0 (15, 15)	120.0 (45, 361)	15.0 (5, 360)	10.0 (5, 15)	9.5 (4, 15)
$T_{1/2}$, h	41.2 ± 9.7 (23.4)	33.2 ± 3.1 (9.5)	37.1 ± 9.2 (24.7)	40.5 ± 12.1 (29.8)	36.8 ± 6.4 (17.4)	38.5 ± 11.8 (30.8)
K_{el}, L/h	0.018 ± 0.004 (22.0)	0.02 ± 0.002 (9.5)	0.02 ± 0.005 (23.4)	0.019 ± 0.006 (30.2)	0.02 ± 004 (18.5)	0.02 ± 0.005 (25.4)
CL/F, L/h	17.8 ± 5.9 (33.2)	21.3 ± 0.02 (0.09)	21.1 ± 8.9 (42.0)	18.0 ± 7.2 (39.9)	17.1 ± 8.2 (48.3)	20.0 ± 5.6 (28.0)
Vz/F, L	1044 ± 446 (42.7)	1020 ± 95 (9.4)	1077 ± 425 (39.5)	979 ± 307 (31.4)	862 ± 325 (37.7)	1059 ± 257 (24.3)

[a]median (min, max)

- Exposure (AUC_{0-last} and AUC_{0-inf}) was similar for INP105 5 mg and OLZ IM 5 mg (**Table 3**) and higher for INP105 10 mg compared to OLZ ODT 10 mg

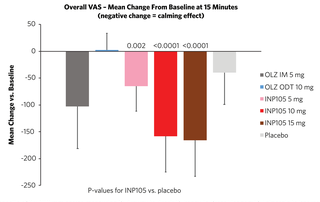
Table 3. Ratio of PK Parameters for INP105 vs. Olanzapine

		Ratio of Mean ± Standard Deviation (CV%)		
Treatment Groups	Number of Subjects	C_{max}, ng/mL	AUC_{0-last}, h*ng/mL	AUC_{0-inf}, h*ng/mL
INP105 5 mg vs. OLZ 5 mg IM	4	0.88 ± 0.73 (82.9)	0.85 ± 0.38 (44.6)	0.92 ± 0.43 (46.5)
INP105 10 mg vs. OLZ 5 mg IM	4	4.28 ± 3.57 (83.5)	2.49 ± 0.36 (14.3)	2.36 ± 0.28 (11.7)
INP105 15 mg vs. OLZ 5 mg IM	4	5.21 ± 5.28 (101.5)	2.97 ± 0.38 (12.7)	2.95 ± 0.36 (12.2)
INP105 5 mg vs. OLZ ODT 10 mg	5	1.79 ± 0.68 (37.7)	0.57 ± 0.18 (31.4)	0.59 ± 0.18 (31.3)
INP105 10 mg vs. OLZ ODT 10 mg	5	4.05 ± 2.13 (52.8)	1.16 ± 0.13 (11.4)	1.15 ± 0.12 (10.3)
INP105 15 mg vs. OLZ ODT 10 mg	4	10.50 ± 5.50 (52.4)	2.07 ± 0.16 (7.6)	2.03 ± 0.13 (6.6)

Pharmacodynamics

- A significant (p<0.05) change in drowsiness was observed for mean change from baseline to 15 minutes for the VAS score with 10 and 15 mg doses of INP105 and with OLZ IM 5 mg (**Figure 4**)
- The mean maximum change in VAS scores showed greater sedation/cognition impairment than placebo (p<0.05) among active treatment groups

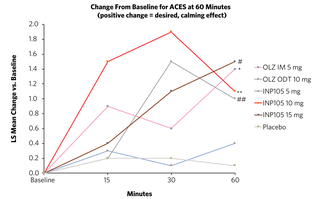
Figure 4. Mean Overall Change From Baseline at 15 Minutes for VAS



VAS = composite of 3 x 100 mm scales measuring 1) Drowsy to Alert; 2) Foggy to Clear Headed; 3) Lethargic to Energetic

- For ACES, mean change from baseline over the first 60 minutes increased (improved) 1 to 2 points with all doses of INP105 (p<0.05) and OLZ IM 5 mg (p<0.05), but was unchanged with OLZ ODT 10 mg and placebo (**Figure 5**)

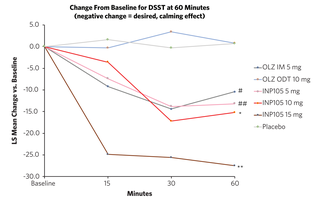
Figure 5. Mean Change From Baseline Over 1 Hour for ACES



#p=0.003; **p=0.008; *p<0.0001, **p=0.006 vs. placebo

- Mean change over 60 minutes vs. baseline for DSST decreased (desired effect) for all doses of INP105 (p<0.05) and OLZ IM (p<0.05) (**Figure 6**)

Figure 6. Mean Change From Baseline Over 1 Hour for DSST



#p=0.003; **p=0.001; *p=0.0007; **p<0.0001 vs. placebo

Safety/Tolerability

- The incidence of reported TEAEs was higher in subjects who received OLZ IM (20/22 [90.1%]) and OLZ ODT (15/18 [83.3%]) (**Table 4**)
- The most commonly reported TEAEs of dizziness, hypotension, and orthostasis, occurred in 75% with OLZ IM or ODT and 52% with INP105
- Headache occurred in 6 (33.3%) of subjects with OLZ ODT 10 mg and 2 (7.4%) with INP105
- Other AEs occurred in no more than 2 subjects each
- No subjects were withdrawn due to treatment-related AEs and no serious AEs were observed

Table 4. Incidence of Treatment-Emergent Adverse Events With at Least 2 Events in any Group (Safety Population)

	Number (%) of Subjects						
	OLZ IM 5 mg (n=20)	OLZ IM 10 mg (n=2)	OLZ ODT 10 mg (n=18)	INP105 5 mg (n=10)	INP105 10 mg (n=9)	INP105 15 mg (n=8)	Placebo (n=10)
Any adverse event	18 (90.0)	2 (100)	15 (83.3)	8 (80.0)	6 (66.7)	5 (62.5)	1 (10.0)
Dizziness	4 (20.0)	1 (50.0)	0	1 (10.0)	2 (22.2)	0	0
Dizziness postural	6 (30.0)	1 (50.0)	8 (44.4)	2 (20.0)	1 (11.1)	1 (12.5)	0
Fatigue	0	0	0	2 (20.0)	0	0	2 (7.4)
Headache	2 (10.0)	0	6 (33.3)	1 (10.0)	0	1 (12.5)	0
Hypotension	1 (5.0)	2 (100)	2 (11.0)	0	2 (22.2)	0	0
Nasal congestion	0	0	0	0	1 (11.1)	2 (25.0)	0
Nausea	0	0	2 (11.0)	0	1 (11.1)	0	0
Orthostatic hypotension	3 (15.0)	0	0	1 (10.0)	0	2 (25.0)	0
Orthostatic tachycardia	2 (20.0)	0	0	1 (10.0)	0	0	0
Restlessness	1 (5.0)	0	2 (11.0)	0	1 (11.1)	0	0
Rhinorrhea	2 (10.0)	0	0	0	0	0	0

Summary

- INP105 may offer a well tolerated, non-invasive method of delivery of OLZ with rapid absorption
- OLZ exposure with INP105 was similar to IM delivery at the same dose, but achieved T_{max} in half the time and exposure exceeded that of OLZ ODT at the same dose
- PD measures of sedation and attention exhibited clinically meaningful effects with INP105 compared to placebo within 15 minutes

Conclusions

- INP105 delivers OLZ into the upper nasal cavity enabling faster absorption than ODT and IM OLZ with similar C_{max} and AUC to the same mg dose
- INP105 was well tolerated in healthy subjects after a single dose with a comparable safety profile to ODT and IM OLZ
- INP105 represents a potentially rapid acting and effective option for treating acutely agitated patients and could represent a valuable option for self or caregiver administration in the home environment
- INP105 may be suitable for early use by patients (or administered by their carers) who have insight into their condition and recognize early symptoms of agitation before escalating uncontrolled agitation leads to violence and injury to the patient, their caregivers, and/or healthcare workers

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