SNAP 101 study were the following: 1) Establish safety and tolerability of three single, ascending doses of INP105; 2) compare pharmacokinetic (PK) data for OLZ)from three INP105 doses with OLZ IM (5 and 10 milligrams [mg]) and orally disintegrating tablets (OLZ-ODT) 10 mg; 3) establish and compare pharmacodynamic (PD) effects of INP105 to OLZ IM and OLZ-ODT; and 4) explore PK/PD and dose-response relationships for INP105.

Methods: SNAP 101 was a randomized, double-blind, placebo- and active comparator-controlled, ascending-dose, 2-way, 2 period, incomplete block, crossover Phase 1 trial to compare the safety, tolerability, PK and PD of three doses of INP105 (5 mg, 10 mg and 20 mg) with two doses of OLZ IM (5 mg and 10 mg) and one dose of OLZ-ODT (10 mg).

Period 1 was open label; Period 2 was double-blind with at least 14 days between dosing in the two periods. Dose escalation was staggered across cohorts to allow a monitoring committee to assess safety and tolerability of INP105 between doses.

Following all dosings in both periods, PD assessments were made by frequent and regular vital signs recordings as well as visual analogue scale for subjective assessment of sedation, the Agitation/Calmness Evaluation Scale, an objective assessment by the investigator, and the timed Digit Symbol Substitution Test. Blood was drawn at frequent timepoints over the 120 hours post dosing for PK evaluation.

All subjects were observed as inpatients for at least 72 hours post-dosing of reference therapy and IP. Follow-up occurred four, five and 14 days after dosing for each study period. The first two subjects receiving 10 mg OLZ IM had clinically significant hypotensive events following administration, and thus the study design was immediately changed with the remaining 36 subjects (12 per cohort) being randomized to OLZ 5 mg IM or OLZ ODT 10 mg. After each block of 12 subjects completed period 1 dosing, five days of observation and nine days of washout, they returned for period 2 dosing when they received INP105 (n=9) or placebo. After a further five days of observations and nine days of washout, a safety monitoring committee (SMC) reviewed the safety data before allowing dose to be escalated to the next level, ie, SMC 1 approved proceeding from INP105 5 mg to INP105 10 mg; but at SMC 2, the decision was made to reduce the dose for cohort 3 from INP105 20 mg (four capsules) to 15 mg (three capsules) due to the frequent but not substantial drops in blood pressure noted after cohort 2, period 2 dosing.

Conclusion: This SNAP 101 study (completed in 2018 with results expected in December), which administered OLZ to the vascular-rich, upper nasal space with the novel POD® device, should guide further clinical development for a needle-free, easy self- or caregiver-administered, rapidly effective OLZ treatment to abort episodes of acute agitation in low-intensity community or ED settings. Safety signals (blood pressure drops) suggestive of appreciable pharmacodynamic effects of OLZ were noted with OLZ IM 5 mg and with cohort 2 and 3, period 2 dosings (INP105 at 10 and 15 mg doses or placebo) at the SMCs. Their formal analysis, along with other PD measures and PK data, is anticipated.

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

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Introduction: Agitation is a cluster of behaviors observed in multiple psychiatric diseases, which can increase the likelihood of violent behavior. Atypical antipsychotics, including oral and intramuscular (IM) olanzapine (OLZ), have been approved for chronic and acute agitation treatment, respectively, for schizophrenia and bipolar I disorder in the U.S. for over 20 years. During acute agitation episodes, IM OLZ is preferred over oral treatments due to a shorter Tmax. However, IM OLZ is invasive, predominantly administered in a hospital setting, 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 symptom resolution.

Impel NeuroPharma is developing INP105, a drug-device combination product consisting of a novel OLZ powder formulation for upper nasal cavity administration using precision olfactory delivery (POD®) technology. This rescue therapy is designed to provide non-invasive, rapid relief of acute agitation comparable to IM injection, without excessively sedating the patient, in a reasonably safe and tolerable manner. POD technology is designed to deliver drug to the upper nasal mucosa with minimal effort or coordination for self or caregiver administration.

Methods: OLZ formulations were designed and manufactured to optimize powder characteristics and device compatibility. Formulations were characterized by analytical methods to assess chemical and physical state as well as device compatibility. Lead formulations were evaluated in rat and non-human primate (NHP) pharmacokinetic (PK) studies, where dose was administered by species-specific POD devices, and plasma samples for PK analysis were analyzed by liquid chromatography mass spectrometry. Formulation selection for further evaluation was based on analytical and PK properties, and a single formulation was identified for inclusion in the INP105-101 proof-of-concept, clinical study.

Results: Approximately 30 formulations designed for nasal delivery by POD technology were manufactured and then assessed using analytical chemistry techniques and device-compatibility testing. Twenty of the formulations were evaluated in rat and NHP PK models. Short-term stability tests and device compatibility testing were used to further narrow down formulations for additional PK studies. The lead formulation was tested to five months of stability with >99% assay, <1% total impurities, and positive device compatibility over the storage period. All formulations tested in NHP PK studies resulted in a Tmax of less than 53 minutes and a Cmax greater than 26 nanograms per milliliter (ng/mL). The lead formulation, selected for clinical development in the INP105-101 study, exhibited a Tmax of 17 minutes, similar to that reported for IM OLZ, and a Cmax of 71 ng/mL, approximately threefold higher than the reported Cmax in patients receiving 10 milligrams (mg) IM OLZ.

Conclusion: Impel NeuroPharma is developing a drug-device combination product that will administer powder OLZ to the vascular-rich, upper nasal space with a novel precision olfactory delivery (POD®) device. It is needle-free, easily administered by self or caregiver, and a potentially rapidly effective OLZ treatment to abort episodes of acute agitation in the low-intensity community clinic or emergency department setting. This series of preclinical development studies has led to the identification of a lead formulation to be tested in the INP105-101 proof-of-concept clinical study for further development.

9 Heroin Abstinence: A Case Report of Kratom in the Emergency Department and Beyond

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Introduction: Kratom, an herb that was traditionally used by Southeast Asians to boost energy, is increasingly being used in the United States. According to the American Kratom Association, an estimated two to three million chronic pain sufferers resort to kratom as a "safe," natural alternative to prescription opioids. Some of the reported beneficial effects include analgesic effects, muscle relaxation, and anti-inflammatory properties. In the drug addiction world however, kratom is being propagated as a legal alternative to getting high that is undetectable on routine drug screen. Kratom, or mitragynine, is a major psychoactive alkaloid. Several studies have found that kratom has stimulant effects in small doses but sedative effects in large doses, binding to mu and kappa receptors (Yusoff et al. 2014). Kratom causes cravings and an array of opioid-like withdrawal symptoms when users attempt to decrease usage. Withdrawal symptoms include restlessness, severe bone pain, muscle aches, tearing or runny nose, gastrointestinal (GI) symptoms, blurred vision, depression, irritability, and changes in mood. This case report documents one patient who used kratom as an alternative to heroin use. We also describe its subsequent addictive potential and the successful management of his withdrawal symptoms with an opioid detoxification protocol.

Case Presentation: Our patient was an adult Caucasian male with a past psychiatric history of depression and severe opioid use disorder identified by appropriate history- taking. The patient recounted that he had been using kratom for the prior two and a half years as a "legal alternative" to heroin, motivated by his partner. At the time of encounter, he reported "strong cravings" and withdrawal symptoms when he attempted to abstain from kratom. Urine drug screen was negative. A quick Clinical Opioid Withdrawal Scale (COWS) evaluation was noted to be 30, and inpatient detoxification was deemed appropriate. He admitted to using initially four capsules per day, which increased up to 30 capsules a day over the 30-month time period. He reported having spent a lot of money to feed his habit and noted weight loss and decreased appetite. He reported, "I felt high," and maintained that he had abstained from illicit heroine use. The patient admitted that he had not known kratom had addictive properties and reported that the withdrawal symptoms were more protracted – as long as two months post his last use when compared to that of heroin after being "hard stopped" during a brief incarceration. We used a COWS assessment and scoring to determine management of his withdrawal symptoms at initial presentation and over a short period of time. We measured vital signs, hepatic function, and management of withdrawal symptoms daily two hours after the delivery of daily buprenorphine and naloxone (using tapering protocol) for five days. We also administered clonidine at a dose of 0.1 milligrams (mg) by mouth every six hours (PO q6h), baclofen 10 mg PO for muscle spasms, chlorproamazine/ diphenhydramine 50mg as needed (PRN) for agitation, and ibuprofen 600mg PO q6h PRN for generalized joint pain. We monitored his symptomology by patient evaluation, daily vital signs, and a physician-guided questionnaire.

Results: Electrolytes, renal function and liver studies were found to be within normal limits; however, his heart rate was elevated at 100 beats per minute on day of admission. Blood pressure was 122/75 millimeters of mercury and temperature was 97.5° Fahrenheit with a body mass index of 21.5. Urine toxicology was negative for all drugs of abuse including methadone and opiates. The patient's pupils were constricted and there was profuse diaphoresis visible over his forehead. He also reported joint pain throughout his body, and he was unable to sit still. His eyes were tearing, he had uncontrollable yawning, and complained of "skin crawl." The patient denied having any GI symptoms such as diarrhea or nausea, and he also denied having tremors. No tremors were observed, although muscle twitching of his forearm and biceps was noted. His COWS score was noted to be 30 on day one, and considered moderately severe. HIS COWS score