especially when transfer to another facility is required. Therefore, improvements in the efficiency of evaluation, treatment and disposition of psychiatric patients benefit both patients and the EDs that care for them.

Methods: To improve throughput and reduce wait times in the ED at our Level I trauma center located in the Upstate region of South Carolina, we implemented several improvements. We then tracked pre- and post-intervention metrics, including LOS and the time from ED consultation order to the completion of psychiatric consultant documentation. The intervention consisted of several protocols with various checkpoints for required documentation necessary for progression through overall mental health evaluation and treatment. In addition, structured psychiatrist and social worker evaluation-note templates were standardized to improve documentation accuracy, consistency, efficiency and overall patient safety. A separate tracking system is monitored by a dedicated psychiatric advanced practice provider to ensure compliance on note completion and order set utilization. The time from ED consult order to completion of psychiatric consultant documentation and mean LOS (in hours +/-standard deviation [SD]) were measured for six months before (10/2016 to 03/2017) and eight months after (4/2017 to 11/2017) institution of these protocols. We then compared pre- and post-intervention measures using Student's t-test ($p<0.05$).

Results: The number of ED patients seen by a psychiatrist were 3,331 and 4,482 in the pre- and post-intervention time frames, respectively. Overall mean LOS significantly decreased from 38.2 (SD+57.5) to 24.9 (SD+37.6) hours after institution of these new protocols. In addition, mean LOS for patients discharged to home or to a psychiatric facility also significantly decreased from 36.9 (SD+53.7) to 21.8 (SD+30.7) and 42.8 (SD+66.5) to 31.8 (SD+49.1) hours, respectively. Time from consult order to completion of ED psychiatrist documentation significantly decreased from 11.3 (SD+9.8) to 6.2 (SD+6.9) hours. All four comparisons were significantly different with p-values ≤ 0.01.

Conclusion: The implementation of these protocols showed a rapid, sustained improvement in overall efficiency of evaluation and disposition of psychiatric patients in our ED. The decrease in time to evaluation for patients discharged home, as well as a decreased time to transfer to inpatient level of care for those requiring hospitalization made for greater throughput and decreased demand on ED resources. Of note, this improvement in efficiency was observed despite an increase in the volume of psychiatric patients seen by the ED over the course of the study. Our institution continues to track outcomes and has implemented further changes including hiring several dedicated ED psychiatrists, with a goal of providing 24/7 availability of in-house psychiatrists embedded in the ED in an effort to further decrease LOS and improve patient care.

Given the shortage of psychiatrists and declining numbers of psychiatric hospital beds, until an alternative solution for this difficulty of access to psychiatric services is implemented the demand for psychiatric services in the ED will remain high. While more study is needed to determine the generalizability of our findings, we believe that implementation of similar interventions would likely benefit other EDs struggling with delays in psychiatric evaluation and disposition.

7 Placebo/Active Controlled, Safety, Pharmaco-Kinetic/Dynamic Study of INP105 (POD® olanzapine) in Healthy Adults

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Introduction: A 2008 survey of emergency department staff (ED) found that 65% had witnessed physical attacks, 32% reported at least one verbal threat per day, and 18% had been assaulted at least once with a weapon. While many of the attacks were due to acute agitation, only 6% of the surveyed EDs had a protocol for medication selection and 40% provided training for staff. During acute agitation episodes – up to seven million/year in U.S. hospitals and EDs – olanzapine (OLZ) intramuscular (IM) is favoured due to a shorter Tmax over oral tablets or oral disintegrating tablets (ODT); however, IM administration requires cooperation, is invasive and can be painful. Uncooperative patients require restraint for the administration of OLZ IM that may be viewed as an assault, thereby reducing trust in medical personnel and increasing the likelihood of staff injuries. When possible, non-injectable forms are preferred during agitation; however, currently approved oral products have slower onset of effect, often requiring labour-intensive observation of the medicated patient until resolved.

INP105 is a drug-device combination product consisting of a powder form of OLZ delivered by a precision olfactory delivery (POD®) device to the vascular-rich, upper nasal space for rapid control of agitation in a cooperative or uncooperative patient (with a potentially caregiver administered dose). For this study a near-final formulation of OLZ was administered by the research embodiment of the POD (I231) device. For subsequent studies, INP105 will use the final commercial formulation adjustments and the commercial POD device. INP105 should provide faster onset of relief compared to oral therapy and be a more accessible dosage form compared to IM therapy without a needle. INP105 may also be suitable for early use by the patient who has insight into his or her condition and can recognize early symptoms of agitation before escalating, uncontrolled agitation leads to violence and injury to the patient, the caregiver and/or healthcare workers. The objectives of this

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.