THOR 201: A Proof-of-Concept Study Assessing Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of L-dopa delivered by Impel's Precision Olfactory Delivery (POD™) to Parkinson's Disease Patients in a Morning OFF Episode (in the presence of Dopa Decarboxylase Inhibitor)

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Introduction

- The progression of Parkinson's Disease (PD) can lead to fluctuations of motor symptoms even in treatment optimized patients resulting in OFF states.
- There is an unmet need for rescue therapy options that will rapidly and efficiently manage OFF periods in PD patients whenever and wherever they occur.
- Precision Olfactory Delivery (POD™) technology targets drugs to the vascular-rich upper nasal space consistently and efficiently (**Figure 1**).
- The upper nasal cavity allows for rapid absorption and is a desirable route of administration for drugs where time to onset of effect is critical.
- POD delivery to this upper region of the nasal cavity reduces overall variability and improves bioavailability by minimizing the amount of drug that drips out of the nose or runs into the posterior pharynx compared to traditional nasal spray.
- The INP103 drug-device combination product is designed for rapid delivery of L-dopa through the upper nasal space, to permit rapid and efficient resolution of OFF periods in PD patients treated chronically with L-dopa.
- This proof of concept study in PD patients experiencing OFF episodes evaluated the bioavailability and benefits of 3 single doses on INP103.
- Pharmaceutical development of a novel formulation of carbidopa/L-dopa (INP107) allowed a 4th cohort to be dosed with this formulation and without administration of an oral DCI.

Figure 1. Illustration of I231 (clinical research) POD Device and Target Delivery Area

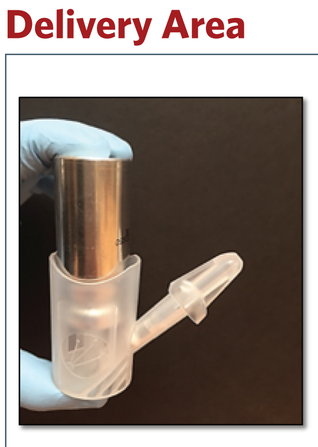


Figure 1a: Loaded research device (I231 POD device), ready for use.

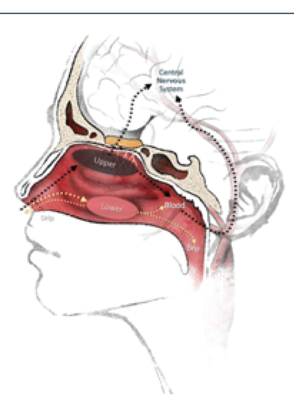


Figure 1b: Diagram of the nasal space (lower=target of most "nasal sprays"; upper=target for POD device)

Study Objectives

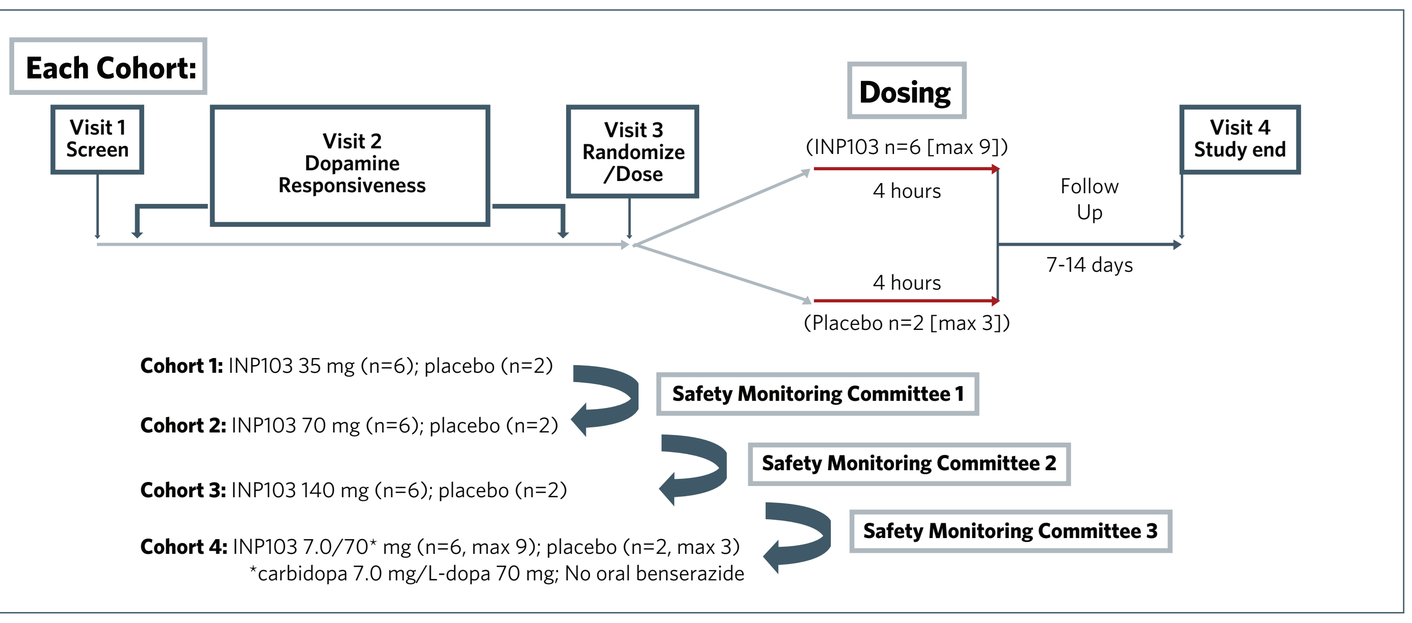
- This study assessed the effects of L-dopa administered with the INP103 drug-device combination product (after oral benserazide as the dopa decarboxylase inhibitor (DCI) in Cohorts 1, 2 and 3, and with co-formulated carbidopa in Cohort 4) on PD morning OFF episodes in terms of safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PDyn).

Methods

Study Design

- This ongoing Phase 2a randomized, double-blind, placebo-controlled, single ascending dose (SAD) study evaluated nasal administration of INP103 (POD L-dopa) or placebo in the presence of DCI in PD patients during a morning OFF episode. A fourth cohort is also evaluating INP107 (POD carbidopa/L-dopa) vs placebo in PD patients during a morning OFF episode without oral benserazide. (**Figure 2**).

Figure 2. Study Design



Patient Selection Criteria

Inclusion Criteria
Adult males and females, 40 to 80 years of age (inclusive) at the time of Screening
Diagnosed with Idiopathic PD (UK Brain Bank Criteria) with Modified Hoehn & Yahr Stage I-III during an ON period at Visit 1
Patients who are prone to (and recognize) OFF episodes (when their usual PD medication has worn off)
Shown to be responsive to L-dopa (≥30% improvement in MDS-UPDRS Part III Motor Examination score) as assessed during the Screening period
On a stable dose of L-dopa containing medication for at least 2 weeks prior to Visit 1 (up to 1200 mg/day) with no single dose exceeding 250 mg
All other anti-PD medication (e.g. dopamine agonists [DAs], monoamine oxidase-B inhibitor (MAOB-I) or catechol-O-methyl transferase (COMT) inhibitors ARE allowed if the subject has been on a stable dose for at least 30 days prior to Visit 1.
Willing to omit their (usual) PD drugs from 22:00 pm the evening prior to study dosing until 120 minutes post-study treatment dosing, but WILL take oral benserazide 25 mg at 60 ± 5 minutes before dosing with INP103 or placebo (in Cohorts 1, 2 and 3)

Exclusion Criteria
Severe dyskinesia (defined per MDS-UPDRS) during a 'normal day' that would significantly interfere with the subject's ability to perform study assessments
In receipt of L-dopa containing medication at >1200 mg/day

Study Treatments

- Eligible patients randomized to study treatment with the INP103 or placebo dose delivered via the I231 POD device to each nostril.

Cohort	Treatment
1	INP103 35 mg (1 puff) L-dopa (n=6); placebo (n=2)
2	INP103 70 mg (2 puffs) L-dopa (n=6); placebo (n=2)
3	INP103 140 mg (4 puffs) L-dopa (n=6); placebo (n=2)
4	INP103 7.0 mg carbidopa/70 mg L-dopa (2 puffs) (n=6, max 9); placebo (n=2, max 3)

- All Parkinson's medication dosing were stopped from 22:00 h the evening before.
- In the AM, when the OFF state was confirmed, oral benserazide 25 mg was administered 60 minutes prior to dosing with INP103 (Cohorts 1, 2 & 3 only).
- Patients were observed for 4 hours after receiving INP103 (POD L-dopa) or placebo and were observed for 4 hours.
- For Cohort 4, once OFF state confirmed on morning of dosing, combined carbidopa/L-dopa formulation was administered.
- At 120 minutes, patients received their missed morning dose of usual L-dopa-based medication and OFF medication if required.

Study Endpoints

Endpoints	
Pharmacokinetic	$AUC_{0-2'}$, C_{max}, T_{max} PK/PDyn relationship to MDS-UPDRS
Objective Response	Time to MDS-UPDRS response Duration of MDS-UPDRS response Maximum MDS-UPDRS response Change in MDS-UPDRS from baseline to 30 minutes Change in MDS-UPDRS AUC
Subjective Response	Time to ON by investigator and patient assessment
Safety Assessments	Physical examination, vital signs, 12-lead ECG, laboratory assessments, AEs, nasal examination

Study Analyses

- Safety and tolerability, and PK data, are summarized by descriptive statistics.
- Changes from baseline for the MDS-UPDRS Part III scores were estimated using a mixed model for repeated measures (MMRM) with treatment group, time point, and their interaction as fixed factors.
- The cumulative proportion of responders are summarized with descriptive statistics.
- Time of response, duration of response or time to ON is evaluated with Kaplan-Meier methods.
- AUC and maximum response are analyzed with an ANCOVA model with treatment group as a fixed factor and pre-dose MDS-UPDRS Part III score as a covariate.

Preliminary Results

- To date, 3 of the 4 treatment cohorts have completed dosing.
- Blinded, drug-related AE data were available from 12 active and 4 placebo dosed subjects from an interim analysis of Cohorts 1 and 2.

Safety/Tolerability

- Single episodes of: hypertension, sinus dryness, foggy head, mucus back of nose/throat, sneezing + coughing, drowsiness and nasal irritation occurred.
- Two episodes of headache were reported.
- All AEs were mild, self-limiting, and most lasted less than 1 hour.
- Three (blinded) events of slight post dosing dyskinesia were reported in Cohort 1 (but data has not been unblinded yet).
- No events of dyskinesia occurred in Cohorts 2 or 3.

Summary

- Nasal drug delivery is an underutilized route of administration for CNS therapeutics.
- Nasal delivery with POD device technology:
  - Is effective for delivering drugs to the upper nasal space
  - Provides rapid and consistent systemic uptake
  - Avoids first-pass hepatic metabolism
  - Is independent of GI absorption, useful during gastric stasis, and can be administered without regard to meal time
- While L-dopa is a standard of care for managing dopamine-related symptoms of PD, most patients develop motor complications related to fluctuations in the levels of plasma L-dopa over the course of their disease that may become debilitating and impact quality of life.
- An unmet need exists for novel approaches to managing the OFF episodes in PD patients that occur as the disease progresses.
- Satisfactory safety and tolerability results have allowed for 3 single escalating doses of INP103 to be administered to PD patients in morning OFF episodes.
- A further cohort is currently dosing with a novel formulation of combined carbidopa 7 mg/L-dopa 70 mg, and should report out in Q3 2019.
- Final results from THOR 201 should guide further clinical development of INP103 as a self- or care-giver administered, rapidly effective treatment proposed to abort OFF episodes in patients with PD.

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