A Phase IIa, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Safety and Pharmacokinetic/Pharmacodynamic (PK/PDyn) Study of INP103 (POD® L-dopa) Administered in the Presence of Benserazide, to L-dopa Responsive Parkinson's Disease (PD) Patients (THOR 201)

Shrewsbury SB,[1] Lehn A,[2] Satterly KH,[1] Swardstrom M,[1] Hoekman J[1]

[1]Impel NeuroPharma, Seattle, WA, USA; [2]Mater Hospital, Brisbane, Australia

Abstract

Objectives: Primary: Compare the safety and tolerability of intranasal INP103 to placebo in patients with PD during an OFF episode. Secondary: Characterize the PK of single ascending doses of INP103; Explore the effect of single ascending doses of INP103 versus placebo on motor function and PK/pharmacodynamic relationship of INP103 and motor function.

Background: PD is a degenerative disorder characterised by motor symptoms linked to depleted basal ganglia dopamine. Initial management of PD has been oral L-dopa since 1961, but 4 limitations persist: (1) An enzymatic blood-brain barrier; (2) Peripheral decarboxylation of dopamine requiring co-administration of a decarboxylase inhibitor (DDI: benserazide or carbidopa); (3) Progressive decline in L-dopa responsiveness leading to switches between mobility and immobility (ON and OFF periods, respectively) in >50% of patients; (4) Slow gastric transit. The Precision Olfactory Delivery (POD) device aims to deliver drugs to the vascular rich upper nasal space consistently and efficiently. PD patients suffering OFF episodes would benefit from rapid delivery of L-dopa.

Methods: Subjects must demonstrate 30% dopamine responsiveness by UPDRS Part III to their usual anti-OFF medication. All Parkinson medication from 22:00 hrs the evening before dosing will be stopped. The following morning OFF state confirmed, benserazide 25 mg will be given orally then 60 minutes later they will receive treatment by POD and observed for 4 hours. At 2 hours, subjects will receive their missed morning dose of L-dopa based medication and usual OFF medication if required. Dyskinesia rating and blood draws for PK of L-dopa and benserazide will be conducted and routine safety assessments for 7 days post dosing.

Conclusions: This study, administering L-dopa to the vascular-rich upper nasal space with the novel POD device should guide further clinical development for an easy self or care-giver administered, rapidly effective treatment to abort OFF episodes in PD.

Introduction

In PD, motor complications, namely motor fluctuations and dyskinesias, occur commonly with long-term exposure to L-dopa and complicate the management of PD.[1] Motor complications affect >50% of patients on L-dopa within 5 years of diagnosis, and up to 90% experience dyskinesias and 60% motor fluctuations within the first decade of treatment,[2] and the frequency of motor complications increases with age at onset of PD, duration of treatment with L-dopa, and dose of L-dopa.[2-4] Yet L-dopa remains the "platinum" treatment for PD.[5] Motor fluctuations and dyskinesias as a consequence of L-dopa use have a direct impact on patient quality of life[6,7] and anxiety about motor fluctuation occurrence may have a significant impact on patients. Thus, a need exists for treatment options that will prevent, reduce, or limit the occurrence of OFF episodes during long-term treatment and also address the dyskinesias that occur with L-dopa.

The Precision Olfactory Delivery (POD®) device technology (Impel NeuroPharma) targets delivery of drugs to the vascular rich upper nasal space consistently and efficiently (**Figure 1**). This region of the nasal cavity has many advantages for drug delivery including reduced overall variability and improved bioavailability by minimizing the amount of drug that drips out of the nose or runs into the posterior pharynx after nasal administration. In addition, the upper nasal cavity is highly vascularized for rapid drug absorption into the plasma. These factors make the upper nasal cavity a desirable route of administration for drugs where rapid absorption and onset of effect are beneficial.

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

Figure 1a: Loaded I231 research POD Device, ready for use.

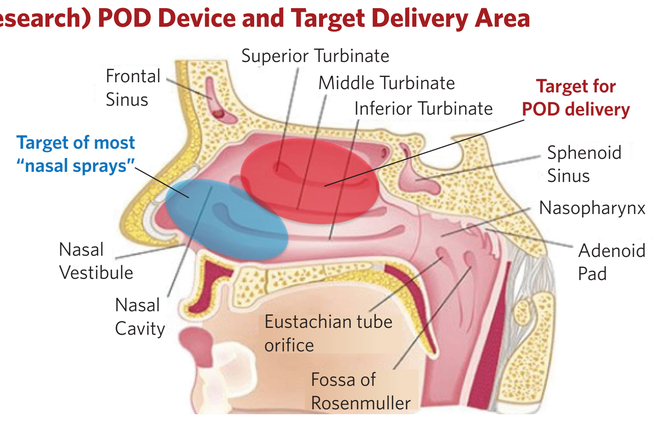


Figure 1b: Diagram of the nasal space (lower=blue, target of most "nasal sprays"; upper=red, target for POD delivery)

- The INP103 drug-device combination product is designed to rapidly deliver L-dopa, the dopamine precursor, to the brain via the richly vascularized upper nasal space, thereby permitting rapid and efficient resolution of OFF periods in patients treated with oral L-dopa.
- The present study is a proof of concept investigation of INP103 in PD patients suffering OFF episodes who would benefit from rapid delivery and onset of action of L-dopa.
- For this study, the novel spray dried L-dopa formulation is provided in capsules but the commercial product will have special disposable prefilled dosing tips.

Study Objectives

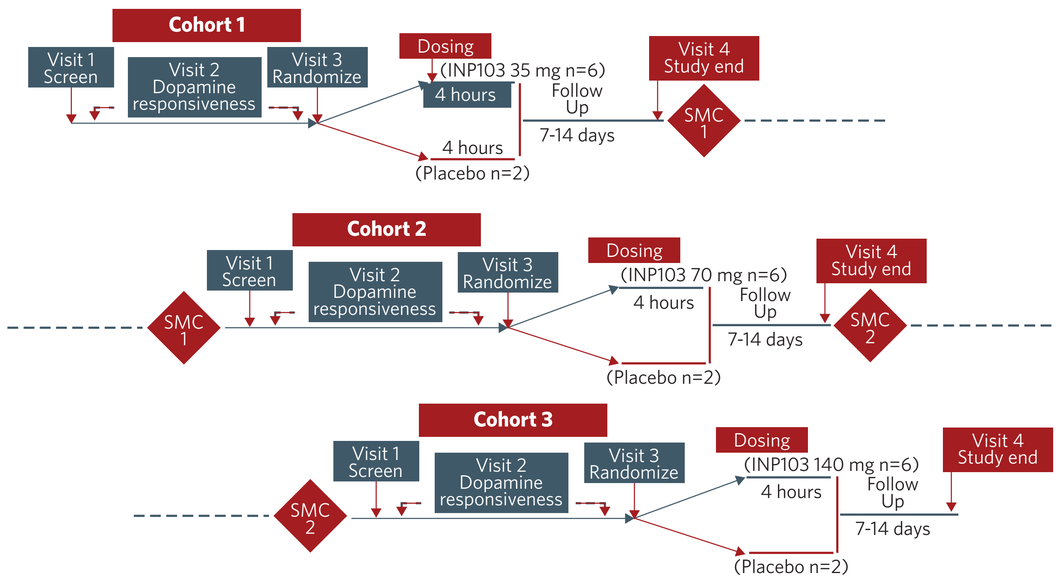
- Primary: Compare the safety and tolerability of single doses of intranasal INP103 and placebo in patients with PD during an OFF episode.
- Secondary:
  1. Characterize the pharmacokinetics (PK) of 3 single ascending doses of INP103.
  2. Explore the effect of single ascending doses of INP103 versus placebo on motor function and pharmacokinetic/pharmacodynamic (PKDyn) relationship of INP103 and motor function.

Methods

Study Design

- This is a Phase 2a randomized, double-blind, placebo-controlled, single ascending dose (SAD) study of intranasal administration of INP103 (POD L-dopa) or placebo in PD patients in the presence of benserazide during an OFF episode (**Figure 2**)

Figure 2. Study Design



- Patients must demonstrate 30% dopamine responsiveness by UPDRS Part III to their usual anti-OFF medication.
- All Parkinson's medication from 22:00 h the evening before dosing will be stopped.
- The following morning when the OFF state is confirmed, benserazide 25 mg orally will be administered.
- 60 minutes later, patients will receive treatment with INP103 (POD L-dopa) or placebo and will be observed for 4 hours.
- At 120 minutes, patients will receive their missed morning dose of L-dopa-based medication and usual OFF medication if required.
- Routine safety assessments will occur at screening, baseline, end of dosing, and 7 days post dosing:
  - Physical examination
  - Vital signs
  - 12-lead ECG
  - Laboratory assessments (hematology, serum chemistry, urinalysis)
  - Adverse events
  - Nasal examination
- Dyskinesia rating and blood draws for L-dopa PK assessments will be conducted (**Table 1**).

Table 1. Key Outcome Assessments

Assessments	Day 0									Day 7 (± 2)
Time (minutes)	pre-dose	0	15	30	45	60	90	120	240	
Rate Dyskinesia		X		X		X		X	X	X
Evaluation of ON/OFF	X		X	X	X	X	X	X	X	
MDS-UPDRS Full	X									X
MDS-UPDRS-III motor			X	X	X	X	X	X		
Blood for PK	X			X		X	X	X		

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

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
History of significant psychotic episode(s) within the previous 12 months in the opinion of the investigator, or currently receiving anti-psychotic medication at a moderate dose (quetiapine >50 mg/day, risperidone >1 mg/day or olanzapine >2.5 mg/day)
Mini Mental State Examination (MMSE) ≤25
History of suicidal ideation or attempted suicide within previous 12 months
Patients with any underlying physical condition that, in the opinion of the investigator, would make it unlikely that the subject will comply with or be able to complete the study requirements
Use of any medication likely to interact with benserazide or INP103
Clinically significant laboratory test abnormalities at Screening

Study Treatments

Eligible patients will be 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)
Safety Monitoring Committee (SMC) 1: (Safety + PDyn) + 7-14 days	
2	INP103 70 mg (2 puffs) L-dopa (n=6); placebo (n=2)
Safety Monitoring Committee (SMC) 2: (Safety + PDyn) + 7-14 days	
3	INP103 140 mg (4 puffs) L-dopa (n=6); placebo (n=2)

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

Study Analyses

- Safety and tolerability data will be summarized by descriptive statistics.
- PK assessments will be summarized by descriptive statistics.
- Changes from baseline for the MDS-UPDRS Part III scores will be 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 will be summarized with descriptive statistics.
- Time of response, duration of response or time to ON will be evaluated with Kaplan-Meier methods.
- AUC and maximum response will be analyzed with an Analysis of Covariance (ANCOVA) model with treatment group as a fixed factor and pre-dose MDS-UPDRS Part III score as a covariate.

Summary

- Intranasal drug delivery has been an underutilized route of administration focused primarily on local treatments with traditional nasal sprays.
- Intranasal delivery by the POD device technology will be effective for delivering drugs via the upper nasal space leading to rapid and consistent systemic levels.
  - Intranasal delivery avoids first-pass hepatic metabolism
  - Intranasal delivery 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 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 occurs as the disease progresses.
- This study administered L-dopa to the vascular-rich upper nasal space with the novel POD device – in a clinical research embodiment. The commercial POD embodiment is proposed for further studies.
- Results should guide further clinical development of INP103 as an easily self-administered, or care-giver administered, rapidly effective treatment to abort OFF episodes in patients with PD.

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