

## **Preclinical Development of a Novel Precision Olfactory Delivery (POD®) - L-dopa Drug-Device Combination Product for the Treatment of OFF Episodes in Parkinson's Disease**

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**Objective:** Impel NeuroPharma has developed the POD device to generate rapid, consistent systemic levels of drugs for neurological diseases. This work was to develop a L-dopa powder formulation delivered by the POD device that results in plasma exposure in rats and non-human primates (NHP), that when extrapolated to humans, will be sufficient to reverse OFF episodes in Parkinson's disease (PD) patients.

**Background:** L-dopa has been the "platinum" standard PD treatment for over 50 years<sup>1,2</sup>. As PD advances, patient response to pharmacotherapy decreases; the benefits of L-dopa become increasingly sensitive to change in systemic concentrations resulting in motor fluctuations (OFF episodes)<sup>3</sup>. Previous studies report the L-dopa plasma concentration threshold for switching from OFF to ON is approximately 400 ng/mL<sup>4</sup>. POD-L-dopa is a drug-device combination product consisting of a novel L-dopa powder formulation delivered to the upper nasal cavity by the POD device.

**Design/Methods:** Powder L-dopa formulations were designed and manufactured for POD device delivery and evaluated by analytical methods including assay, related substances, X-ray diffraction, differential scanning calorimetry, and device compatibility. Lead formulations were evaluated in rat and NHP using species specific POD devices.

**Results:** Over 50 formulations were manufactured, and 30 formulations were assessed in vivo. PK assessment focused on comparing time to achieve 400 ng/mL plasma levodopa,  $T_{max}$ , and  $C_{max}$ . Lead formulation candidates resulted in concentrations of 400 ng/mL within 5 - 12 min in NHP, a 3 to 5-fold improvement compared to unformulated L-dopa. Median  $T_{max}$  occurred between 30-60 min with  $C_{max}$  values exceeding 1 µg/mL.

**Conclusions:** Impel is developing POD-L-dopa, a powder formulation of L-dopa delivered to the vascular-rich upper nasal cavity with the POD device, allowing self- or care-giver administration, to achieve consistent and rapidly effective treatment to abort OFF episodes. This work has led to the selection and further evaluation of a novel formulation in a Phase 2A clinical study.