Design of Better Oral Levodopa Delivery: Formulation Strategy of IPX203, an Investigational Extended-Release Carbidopa-Levodopa

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Background

- Levodopa (LD) is the gold standard for the treatment of Parkinson's disease (PD). Because of its short half-life, oral LD provides pulsatile dopaminergic stimulation, which may lead to motor complications
- The ability to achieve steady LD exposure with current oral formulations is limited by erratic gastric emptying in patients with PD and a limited window of absorption for LD in the proximal small intestine
- IPX203 is a unique oral extended-release carbidopa-levodopa (ER CD-LD) developed to address the short half-life and the limited window of absorption for LD
- IPX203 contains immediate-release (IR) granules (CD and LD with a disintegrant polymer to allow for rapid dissolution) and ER beads (LD coated with a controlled-release polymer to allow for slow release of the drug, a mucoadhesive polymer to keep the granules anchored to the area of absorption longer, and an enteric coating to prevent the granules from disintegrating too early in the stomach). See **Figure 1**

Objective

- To present the formulation strategy of IPX203 and how it relates to the pharmacokinetic (PK) profile of this new ER CD-LD

Methods[1]

- Open-label, rater-blinded, multicenter, randomized crossover trial
- 28 patients with advanced PD who were experiencing motor fluctuations were randomly assigned in a 1:1 ratio to 15 days of treatment with IR CD-LD followed by IPX203 or IPX203 followed by IR CD-LD, with a 1-week washout period between treatments
- IPX203 was supplied as capsules in 2 dosage strengths: 45/180 or 67.5/270 mg CD-LD; IR CD-LD was supplied as a 25/100 mg capsule
- A dose-conversion algorithm was provided stating that for a 100 mg IR LD dose, the conversion should be 360 mg IPX203 for the first daily dose. For subsequent afternoon and evening doses of IR CD-LD, the most frequently used dose was determined, and 100 mg of IR LD was converted to 270 mg of IPX203 LD
- The dosing regimen for IPX203 was expected to be as infrequent as 3 times daily (at intervals of approximately 7 to 8 hours). During the first 9 days of each treatment period, investigators were permitted to adjust the dose regimens of IR CD-LD and IPX203 for optimal therapeutic effect. Thereafter, dosing regimens were unchanged

IPX203 provided steady LD concentrations for almost twice as long as IR CD-LD

Figure 1. IPX203 Schematic and Components

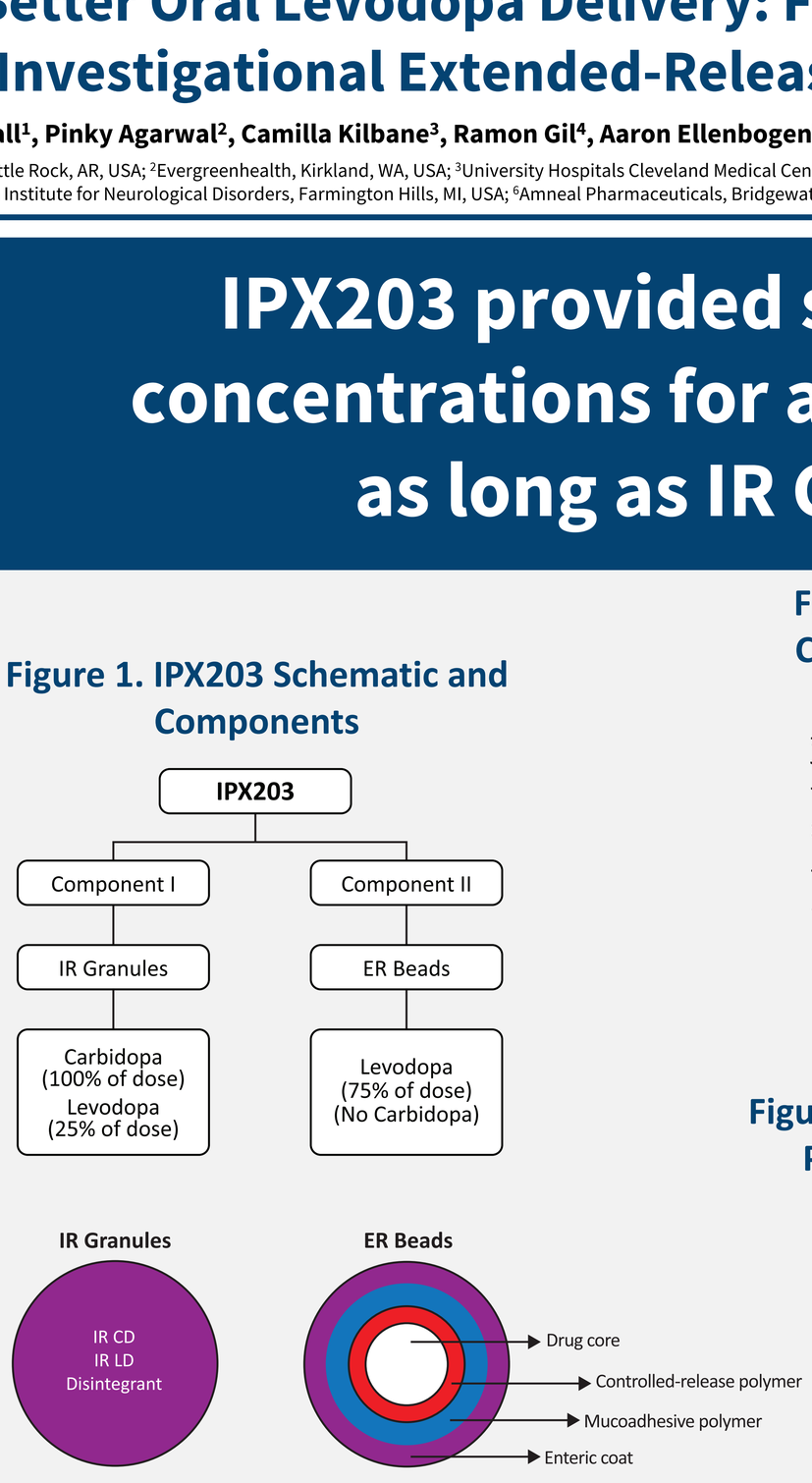


Figure 2. Mean Levodopa Plasma Concentration Profiles on Day 15

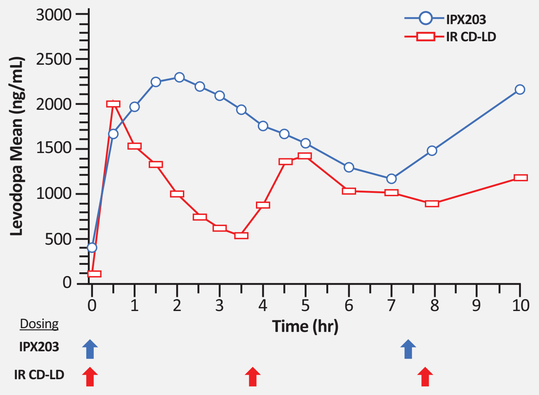
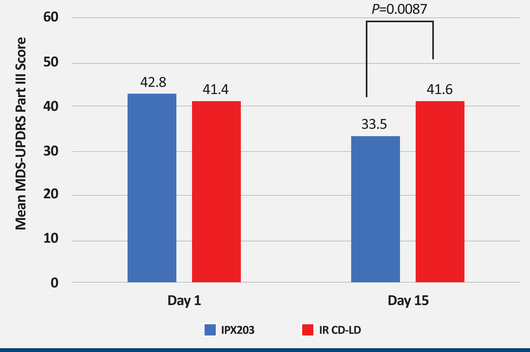


Figure 3. Mean Pre-dose MDS-UPDRS Part III Scores at Days 1 and 15



Results

- PK data from a Phase 2 study in patients with PD showed rapid absorption of LD followed by sustained LD plasma concentrations
- On day 15, LD concentration was sustained 50% above peak concentrations for 6.2 hours with IPX203 vs 3.9 hours with IR CD-LD (*P*=0.0002). See **Figure 2** and **Table**
- Pharmacodynamic analysis on day 15 demonstrated that mean MDS-UPDRS Part III scores prior to administration of the first daily dose were significantly lower among patients receiving IPX203 than IR CD-LD (LS means difference -8.1 [25.0], *P*=0.0255). See **Figure 3**

Table. Levodopa Primary PK Parameters Following First Dose on Day 15

Parameter*	IPX203	IR CD-LD
C_{max} (ng/mL)	2,768 ± 1,259	2,357 ± 1,179
T_{max} (h)*	1.5 (0.5-6.0)	0.5 (0.5-2.0)
AUC_{tau} (h·ng/mL)	11,214 ± 4,887	3,879 ± 1,744
Duration ≥50% C_{max} (h)†	6.2 ± 1.9	3.9 ± 2.2

*All values mean ± SD except T_{max}, which is reported as median (min-max). †Duration values are mean ± SD. Duration values were estimated over the entire concentration-time profile (10 h). AUC_{tau}, area under the concentration-time curve from Hour 0 to time of second dose, ie within a dosing interval; CD, carbidopa; C_{max}, maximum observed plasma concentration; IR, immediate-release; LD, levodopa; T_{max}, time to maximum concentration.

Conclusions

- PK and pharmacodynamic data appear to confirm that the unique design of the IPX203 formulation addresses some limitations of current oral LD delivery
- The design of IPX203 provides rapid absorption and prolonged, steady concentrations of LD which lead to sustained pharmacodynamic effect in patients with PD who exhibit motor fluctuations on conventional IR CD-LD formulations

Reference

1. Modi NB, Mittur A, Dinh P, Rubens R, Gupta S. Pharmacodynamics, efficacy, and safety of IPX203 in Parkinson disease patients with motor fluctuations. *Clin Neuropharmacol*. 2019;42(5):149-156. DOI:10.1097/WNF.0000000000000354

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