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Original Articles

Improving levodopa delivery: IPX203, a novel extended-release carbidopa-levodopa formulation

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ABSTRACT

Introduction: IPX203 is a novel oral extended-release (ER) formulation of carbidopa (CD) and levodopa (LD) developed to address the short half-life and limited area for absorption of LD in the gastrointestinal tract. This paper presents the formulation strategy of IPX203 and its relationship to the pharmacokinetics (PK) and pharmacodynamic profile of IPX203 in Parkinson's disease (PD) patients.

Methods: IPX203 was developed with an innovative technology containing immediate-release (IR) granules and ER beads that provides rapid LD absorption to achieve desired plasma concentration and maintaining it within the therapeutic range for longer than can be achieved with current oral LD formulations. The PK and pharmacodynamics of IPX203 were compared with IR CD-LD in a Phase 2, open-label, rater-blinded, multicenter, crossover study in patients with advanced PD.

Results: Pharmacokinetic data showed that on Day 15, LD concentrations were sustained above 50% of peak for 6.2 h with IPX203 vs. 3.9 h with IR CD-LD ($P = 0.0002$). Pharmacodynamic analysis 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 mean difference –8.1 [25.0], $P = 0.0255$). In a study conducted in healthy volunteers, a high-fat, high-calorie meal delayed plasma LD T_{max} by 2 h, and increased C_{max} and AUC_{tau} by approximately 20% compared with a fasted state. Sprinkling capsule contents on applesauce did not affect PK parameters.

Conclusion: These data confirm that the unique design of IPX203 addresses some of the limitations of oral LD delivery.

1. Introduction

The combination of levodopa (L-3,4-dihydroxyphenylalanine [LD]) and a peripherally acting aromatic amino acid decarboxylase (AADC) inhibitor (carbidopa [CD] or benserazide) has been the best treatment of Parkinson's disease (PD) for more than 5 decades [1]. Levodopa, a naturally occurring amino acid, is an intermediate in the dopamine synthesis pathway [2]. After oral administration, the majority of LD is absorbed in a short region of the upper small intestine via an active transport mechanism that is specific for large, neutral amino acids [3].

Abbreviations: CD, carbidopa; IR, immediate-release; LD, levodopa; MDS-UPDRS, Movement Disorder Society—Unified Parkinson's Disease Rating Scale.

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The coadministration of a peripherally acting AADC inhibitor greatly decreases the peripheral conversion of LD to dopamine, limiting the systemic side effects of treatment and increasing the fraction of an LD dose that reaches the brain. When administered in an immediate-release (IR) formulation combined with CD, LD has a plasma half-life of approximately 90 min [4].

As PD progresses, clinical responsiveness to oral LD becomes less predictable. Chronic LD treatment is associated with the development of motor fluctuations and dyskinesia, affecting up to 50% of patients after 5 years of treatment, and more than 80% of patients after 10 years [5]. In some advanced PD patients, these problems are the main sources of disability. Some patients can cycle between severe dyskinesias in the "on" state and prolonged periods of parkinsonism in the "off" state. Among patients with advanced PD, "off" time can occupy half or more of their awake time [3]. Not surprisingly, "off" time is often a frustrating clinical challenge for patients, who continue to respond to LD during those periods when sufficient plasma concentrations of the drug are achieved. The experience of "off" time is strongly correlated with worsened quality of life, increased disability, and increased caregiver burden [6–8].

Mechanisms underlying the development and brain circuitry of motor complications in patients with PD continue to generate controversy. However, underlying the clinical experience of both dyskinesias and "off" time is irregular and pulsatile delivery of LD to the brain [9]. Clinical investigations have shown that "off" time can be linked to subthreshold LD plasma concentration. The threshold needed to initiate anti-parkinsonian effect is approximately 1000 ng/mL [3]. Current limitations to achieving consistent brain LD exposure with available oral formulations is multifactorial, including variable dissolution of LD and CD products, erratic gastric emptying, irregular drug absorption in the duodenum and jejunum, and the short plasma half-life of the drug. In addition, dietary intake affects the absorption and clinical performance of LD formulations [10]. Simply increasing the dosage or decreasing inter-dose intervals of IR CD-LD formulations does not solve irregular drug absorption because it does not affect the underlying mechanisms of variability in gastrointestinal (GI) absorption. Furthermore, increased IR LD dosage is a risk factor for developing and exacerbating existing dyskinesia, in addition to other peak-dose adverse effects [11].

CD-LD formulations that maintain supra-threshold LD concentrations for longer periods of time with less dose-to-dose variability continue to be targets for improving management of PD. To date, clinical trials using sustained-release CD-LD formulations or enteral infusion of a CD-LD suspension have not successfully diminished "off" time. Rytary (IPX066; Numient in the European Union) is an extended-release (ER) formulation of CD-LD that consists of a capsule containing CD and LD in both IR and ER beads. Rytary was designed to provide an initial rapid absorption of LD comparable to that observed with IR CD-LD, followed by stable LD concentrations with reduced peak-to-trough variability in plasma concentrations [12]. The goal of Rytary's development was to reduce motor fluctuations associated with brief periods of pulsatile stimulation of dopamine receptors.

Recently, a new oral CD-LD formulation, IPX203, has been developed to address the short half-life and the limited area for absorption of LD in the proximal small intestine. While IPX203's formulation is distinctly different than Rytary, both achieve a rapid rise in LD plasma concentration that can be maintained within the therapeutic range for a longer duration than with IR CD-LD [13]. IPX203 is being developed in four dose-proportional strengths. The CD:LD ratio in IPX203 is 1:4 mg: mg, which is consistent with other approved CD-LD products, including IR Sinemet, Sinemet CR, and Rytary [14] . IPX203 contains IR granules and ER coated beads. IR granules contain 100% of the CD dose and 25% of the LD dose, and the ER beads contain the remaining 75% of the LD dose. Based on in vitro release data and a proof-of-concept PK study in healthy adults, it was determined that CD bioavailability would be greater if all its content is in IR form. This was confirmed in the Phase 2 studies. CD plasma concentrations were significantly greater than those from IR CD-LD and Rytary[Amneal; unpublished data]. Moreover, results from a single-dose IPX203 PK study in PD patients with motor fluctuations indicate that, following the initial increase in plasma LD concentration, this value was sustained for longer than with either IR CD-LD or Rytary [13]. In addition, IPX203 exerted a longer duration of pharmacodynamic effects compared with IR CD-LD and Rytary, consistent with its PK outcomes [13].

The IR granules consist of CD and LD, with a disintegrant polymer to allow for rapid dissolution. The ER beads consist of LD, coated with a sustained-release polymer to allow for slow release of the drug, a mucoadhesive polymer to keep the granules adhered to the area of absorption longer, and an enteric coating to prevent the granules from disintegrating too early in the stomach (Fig. 1).

This report focuses on how the formulation strategy of IPX203 relates to its PK. In addition, we discuss its pharmacodynamic profile and effects of food on the PK of IPX203. All studies reported here were conducted in accordance with ethical principles that are consistent with good clinical practice, and the protocols were approved by the institutional review boards of the participating institutions.

2. Methods

2.1. Pharmacokinetic evaluations

The methodology for the PK evaluation of IPX203 has been previously described [14]. This Phase 2, open-label, rater-blinded, multicenter, randomized crossover trial involved 28 patients with advanced PD who were experiencing motor fluctuations. Patients were randomly allocated (1:1) to 15 days of treatment with IR CD-LD followed by IPX203, or IPX203 followed by IR CD-LD. There was a 1-week washout period between treatment periods. IPX203, manufactured by Impax Laboratories, LLC (Bridgewater, NJ), was supplied as capsules in 2 dosage strengths containing 45–180 or 67.5–270 mg CD-LD. IR CD-LD (Merck & Company, Whitehouse Station, NJ) was supplied as a 25–100 mg capsule. During the IR CD-LD treatment period, the initial regimen of IR CD-LD was the same as the patient's stable prestudy regimen. Based on the results from a single dose study in patients with advanced PD [13], a dose conversion algorithm for the first morning dose of IPX203 was provided that converted a 100 mg IR LD dose, to 360 mg IPX203. 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. Based on product design considerations, dosing regimens for IPX203 among typical patients were anticipated to be as infrequent as 3 times daily (and at intervals of approximately 7 to 8 h). 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; the number of dose adjustment steps was not limited. Thereafter, dosing regimens were not changed [14].

In-clinic assessments by blinded raters occurred at Days 1 and 15 of each treatment period [14]. Subjects arrived for clinical ratings in the morning, having fasted for at least 8 h and having withheld drug ingestion since 10 PM the previous evening (for Day 1 assessments), or for at least 5 h (for Day 15 assessments).

The plasma concentration fluctuation index was calculated as $(C_{max}–C_{min})/C_{avg}$ over the 10-hour assessment period.

The effect of a standardized high-fat meal, which can delay gastric emptying, on the PK of single-dose IPX203 was evaluated in healthy volunteers. In a 3-period, randomized, crossover study, 27 subjects received 1 of 3 treatments per period including: (1) a single capsule of IPX203 (CD-LD: 87.5–350 mg) administered orally with 240 mL of water approximately 30 min after initiating a standardized high-fat, high-calorie breakfast; (2) the contents of one IPX203 capsule sprinkled on applesauce administered under fasting conditions; and (3) a single oral capsule of IPX203 administered under fasting conditions. Each treatment period was separated by a 6- to 7-day washout period.

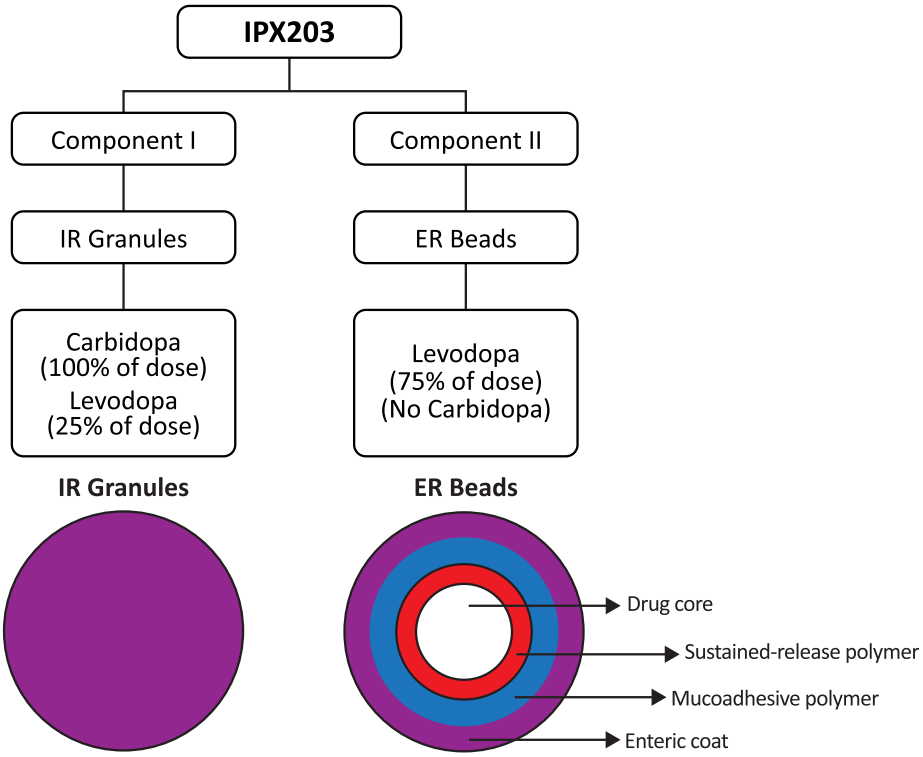

Fig. 1. IPX203 formulation schematic and components. The IPX203 formulation is composed of two components: Component I, containing immediate-release granules, and Component II, containing extended-release beads.

The efficacy of IPX203 was evaluated as part of the multiple-dose study described previously [14].

3. Results

3.1. Multiple-dose pharmacokinetics

The mean (±standard deviation [SD]) dose of LD administered in the clinic on Day 15 of the stable dosing regimen was 159 ± 46.1 mg for IR CD-LD and 560 ± 206.3 mg for IPX203. On Day 15, the median dosing intervals were 4 h in the IR CD-LD group and 7 h in the IPX203 group.

Prior to dosing on Day 15, median LD plasma concentrations in subjects treated with IR CD-LD and IPX203 were 34 ng/mL and 327 ng/mL, respectively. LD and CD PK profiles on Day 15 are shown in Fig. 2A and 2B. The initial increase in LD concentration from IPX203 was comparable to that of IR CD-LD. IPX203 provided relatively stable LD concentrations for an extended duration as compared to IR CD-LD.

Key LD and CD PK parameters at Day 15 are summarized in Table 1. Following the first dose of IPX203 on Day 15, LD was absorbed with a median T_{max} of 1.5 h (range: 0.5–6.0 h). Mean LD C_{max} following the first dose of IPX203 treatment was 2768 ng/mL, approximately 15% greater than that of IR CD-LD. Mean LD AUC_{tau} value following IPX203 treatment was 11 214 h · ng/mL, approximately 2.9-fold greater than that of IR CD-LD. Time to 50% C_{max} was comparable for IPX203 and IR CD-LD (0.54 and 0.41 h, respectively). LD plasma concentrations were maintained above 50% C_{max} for a longer duration with IPX203 than with IR CD-LD (6.2 h vs. 3.9 h; $P = 0.0002$).

On Day 15, when each subject was on a stable dosing regimen, the fluctuation index in the plasma concentration of LD over the 10-hour assessment period was lower with IPX203 than with IR CD-LD (1.7 vs. 2.7, respectively).

Following the first dose of IR CD-LD on Day 15, the median T_{max} of CD was noted at approximately 2.0 h (min, max 1.5, 4.0 h). The mean CD C_{max} and AUC_{tau} values following IR CD-LD treatment were 146 ng/mL and 416 h · ng/mL, respectively. Following the first dose of IPX203 on Day 15, CD was absorbed with a median T_{max} of 2.5 h (min, max 1.5, 4.0 h). The mean CD C_{max} and AUC_{tau} values following IPX203 treatment were 479 ng/mL and 1892 h · ng/mL, respectively. The mean CD AUC_{tau} value following IPX203 treatment was approximately 4.5-fold greater than that of IR CD-LD, which is consistent with the higher CD content and formulation characteristics.

3.2. Effect of food

After oral administration of IPX203 in the fasted state, LD concentrations increased rapidly, reaching T_{max} at a median of 2 h (Fig. 3, Table 2). A high-fat, high-calorie meal delayed LD median T_{max} by 2 h, and increased LD C_{max} and AUC_{tau} by approximately 20% compared with the fasted state. The C_{max} and AUC_{tau} values for CD were approximately 64% lower in the fed state vs. the fasted state. Sprinkling the capsule contents on applesauce did not affect PK parameters as compared to results in the fasted state.

3.3. Pharmacodynamic evaluations

As shown in Fig. 4, mean MDS-UPDRS Part III motor scores prior to administration of the first daily dose were similar for IPX203 and IR CD-LD on Day 1 (42.8 and 41.4, respectively). The motor exam data on Day 15 demonstrated that mean MDS-UPDRS Part III scores prior to administration of the first daily dose were significantly lower (indicating clinical improvement) among patients receiving IPX203 (33.5) than IR CD-LD (41.6; least square [LS] means difference –8.1 [25.0], $P = 0.0255$).

4. Discussion

Though LD is the most effective therapeutic option for the treatment of PD, its pharmacological imperfections have been recognized since its introduction in the late 1960s [1]. The pharmacodynamic response to LD often changes during long-term therapy. Disease progression, the

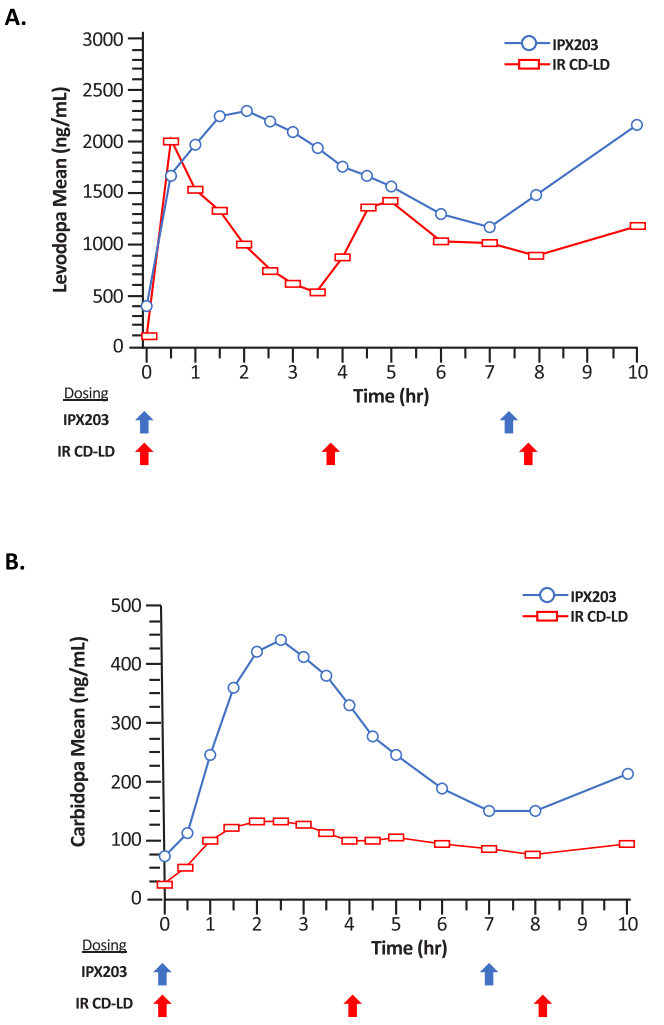

Fig. 2. Mean levodopa (A) and carbidopa (B) plasma concentration profiles on Day 15. (A) The initial increase in LD concentration from IPX203 was comparable to that of IR CD-LD, and provided relatively stable LD concentrations for an extended duration as compared to IR CD-LD. (B) IPX203 produced a higher C_{max} for carbidopa compared to IR CD-LD. Arrows indicate the median redosing interval for IPX203 and IR CD-LD.

Table 1
Levodopa and carbidopa primary PK parameters following first dose on Day 15.

Parameter*	IPX203	IR CD-LD
Levodopa		
C_{max} (ng/mL)	2768 ± 1259	2357 ± 1179
T_{max} (h)*	1.5 (0.5–6.0)	0.5 (0.5–2.0)
AUC_{tau} (h · ng/mL)	11 214 ± 4887	3879 ± 1744
Duration ≥ 50% C_{max} (h)†	6.2 ± 1.9	3.9 ± 2.2
Carbidopa		
C_{max} (ng/mL)	479 ± 291	146 ± 83
T_{max} (h)	2.5 (1.5–4.0)	2.0 (1.5–4.0)
AUC_{tau} (h · ng/mL)	1892 ± 1018	416 ± 279

*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).
Abbreviations: AUC_{tau}, area under the concentration–time curve from Hour 0 to time of second dose, i.e., within a dosing interval; CD, carbidopa; C_{max}, maximum observed plasma concentration; IR, immediate-release; LD, levodopa; T_{max}, time to maximum concentration.

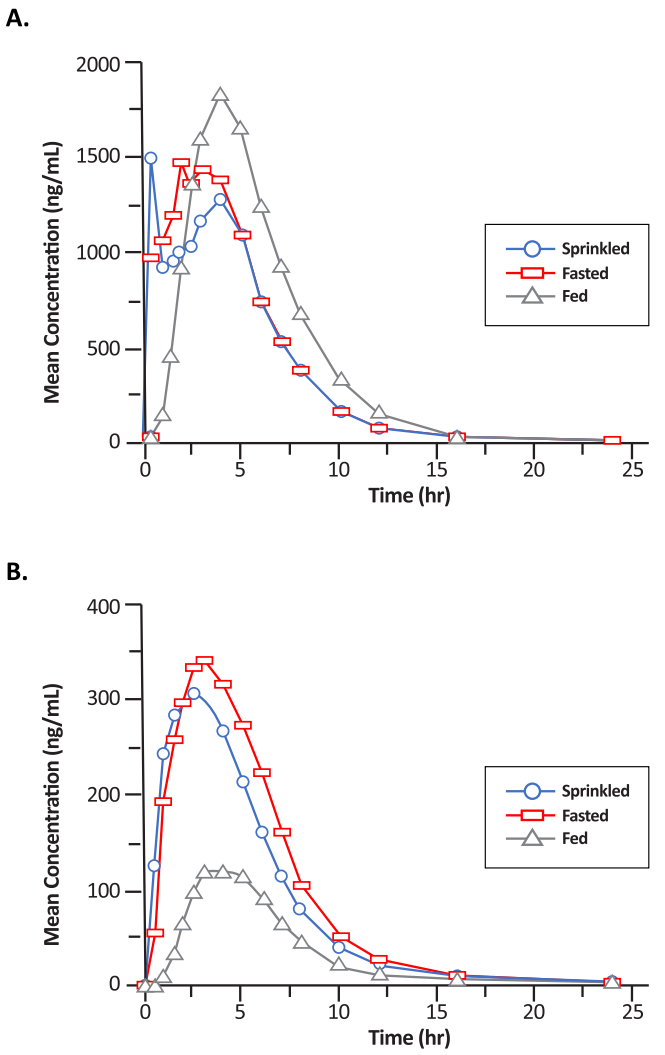

Fig. 3. Mean plasma concentration–time profiles for levodopa (A) and carbidopa (B) after single oral administration of IPX203 (CD-LD: 87.5–350 mg) in healthy subjects under fasted (intact and sprinkled on applesauce) and fed conditions. Fasted state: After oral administration of IPX203, LD concentrations increased rapidly, reaching T_{max} at a median of 2 h. Fed state: LD median T_{max} delayed by 2 h, and increased LD C_{max} and AUC_{tau} by approximately 20% compared with the fasted state. C_{max} and AUC_{tau} values for CD were approximately 64% lower in the fed state vs. the fasted state. Sprinkled: No effect on PK parameters as compared to results in the fasted state.

short plasma half-life of LD, and alterations in its absorption are important factors responsible for motor fluctuations. For many patients, LD must be titrated to optimal dosing for maintaining plasma concentrations within a therapeutic window. When patients have lost their long-duration response, sub-threshold plasma concentrations of LD (typically, less than 1000 ng/mL) lead to the reemergence of motor and non-motor symptoms of PD. LD concentrations that exceed patient-specific thresholds can lead to the emergence of dyskinesia and other peak-dose adverse effects.

The absorption of LD is mediated by a sodium-dependent L-neutral amino acid carrier system that is expressed only in duodenal and jejunal mucosa [3]. Hence, LD formulations need to target this relatively short region of the small intestine to optimize drug absorption. Unpredictable LD PK can be the result of variable gastric emptying, a long-term consequence of PD in majority of patients [21].

Various pharmacological strategies have been devised to reduce the inherent variability of LD absorption and delivery to the brain. Several orally administered CR formulations of LD (with CD or benserazide)

Table 2
Key IPX203 pharmacokinetic parameters for levodopa and carbidopa after administration following a high-fat meal, sprinkled on applesauce, and after an overnight fast (N = 27).

Parameter*	Fed	Sprinkled on Applesauce	Fasted
Levodopa			
C_{max} (ng/mL)	2185.6 ± 472.7	1634.2 ± 409.3	1826.9 ± 385.3
T_{max} (h)	4.0 (2.0–5.0)	0.5 (0.5–5.0)	2.0 (0.5–5.0)
$AUC_{0\text{-}t}$ (h · ng/mL)	10 552.8 ± 1425.6	8330.9 ± 1965.0	9125.0 ± 2149.8
$T_{1/2}$ (h)	1.79 ± 0.3	2.02 ± 0.31	2.00 ± 0.30
Carbidopa			
C_{max} (ng/mL)	140.8 ± 41.1	338.6 ± 91.8	403.6 ± 156.7
T_{max} (h)	4.0 (2.0–6.0)	2.5 (1.5–5.0)	3.0 (1.0–6.0)
$AUC_{0\text{-}t}$ (h · ng/mL)	751.0 ± 205.15	1909.2 ± 618.2	2175.0 ± 905.8
$T_{1/2}$ (h)	3.86 ± 0.78	3.95 ± 0.67	3.90 ± 0.56

*All values mean ± SD except T_{max}, which is reported as median (min–max).
Abbreviations: $AUC_{0\text{-}t}$, area under the concentration–time curve from Hour 0 to time of second dose, i.e., within a dosing interval; C_{max}, maximum observed plasma concentration; $T_{1/2}$, half-life; T_{max}, time to maximum concentration.

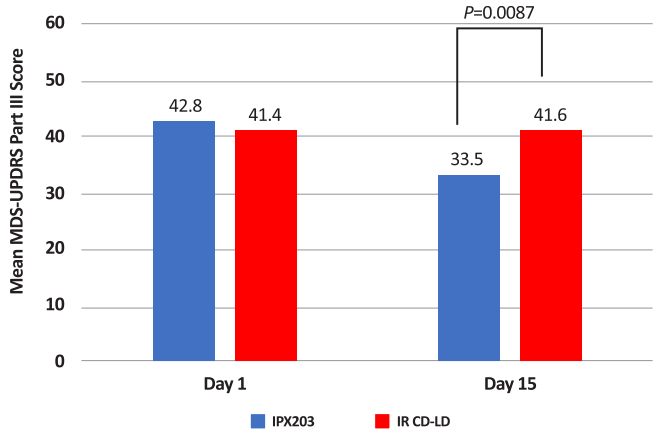

Fig. 4. Mean predose MDS-UPDRS Part III scores at Days 1 and 15. Mean MDS-UPDRS Part III motor scores prior to administration of the first daily dose were similar for IPX203 and IR CD-LD on Day 1. Mean MDS-UPDRS Part III scores prior to administration of the first daily dose were significantly lower (indicating clinical improvement) among patients receiving IPX203 than IR CD-LD on Day 15.

have been developed and are commercially available. However, CR CD-LD (Sinemet CR) is associated with erratic absorption and variable LD plasma concentrations [15]. To deal with the delayed rise in LD plasma concentration of CR formulations, IR CD-LD is often coadministered with the first morning dose [16]. Another strategy is to administer a continuous enteral infusion of CD-LD to achieve relatively stable plasma LD concentrations. Studies providing PK-pharmacodynamic correlations have shown that this approach is associated with reduced daily "off" time and dyskinesia compared with IR CD-LD formulations [17,18]. However, this delivery method is invasive, cumbersome, and therefore impractical for most PD patients. Rytary was designed to provide a rapid onset of effect that is then sustained for a longer duration than standard formulations of CD-LD [12]. Phase 3 studies of Rytary in PD patients showed a significant reduction in daily "off" time compared to both IR CD-LD and CD-LD plus entacapone [19,20].

IPX203 is an investigational ER CD-LD developed for rapid delivery of therapeutic LD plasma concentrations that are maintained for a longer duration than currently marketed products. Its design aims to minimize peak-to-trough fluctuations and reduce dose-to-dose variability. IPX203 is formulated to provide immediate delivery of 25% of the LD dose, followed by an extended release of the remaining 75% of the LD over a sustained period. The clinical impact is reduction in both LD fluctuations and dosing frequency. This unique product design avoids the limitation of slow initial release, and the consequent latency to improvement of motor symptoms seen with current CR formulations. Unlike Rytary, in which both IR and ER beads contain CD [12], the IR granules in IPX203 contain all of the CD dose. Initial release of the total CD dose is intended to maximize AADC inhibition during the interval when LD is most vulnerable to peripheral AADC conversion to dopamine.

Although multiple factors influence the uptake of LD, delayed and/or variable gastric emptying is a major contributing factor. GI dysfunction is seen across all stages of PD, and some degree of gastroparesis occurs eventually in most PD patients [21]. In patients experiencing gastroparesis, prolonged exposure of LD to the gastric environment may be the reason for reduced quantity of LD available for subsequent absorption in the upper small intestine [21]. The absorption and action of LD is influenced by impaired gastric emptying and contributes to motor fluctuations observed in patients receiving long-term LD therapy [21].

IPX203 contains IR granules and ER beads. The IR granules consist of CD and LD, with a disintegrant polymer to allow for rapid dissolution. The ER beads consist of LD, coated with a sustained-release polymer to allow for slow release of the drug, a mucoadhesive polymer to keep the granules adhered to the area of absorption longer, and an enteric coating to prevent the granules from disintegrating too early in the stomach. The result is a facilitated delivery of the drug to the proximal small intestine. The formulation of IPX203 ensures an initial rapid increase in LD plasma concentration, with a plateau around 2 to 3 h post-dose, followed by a slow decline through to the time of redosing, approximately 7 h later.

Food alters gastric emptying, gastric pH, and GI motility [22]. Dietary factors, including fat and L-neutral amino acids, have been shown to influence the absorption of LD [3]. In the food effect study, administration of IPX203 with a high-fat, high-calorie breakfast led to a delay in LD absorption, and the median T_{max} occurred 2 h later than in the fasted state. This study also found that a high-fat breakfast decreased absorption of CD. This finding is consistent with previously reported data that showed food intake decreased absorption of the CD component of Sinemet CR [23]. With IPX203, the food effect study also demonstrated that the capsule contents can be sprinkled on applesauce without affecting LD PK, as compared to results obtained with the intact capsule. The ability to sprinkle capsule contents allows for effective dosing, even in patients unable to swallow the intact capsules.

The clinical actions of IPX203 vs. IR CD-LD are consistent with its PK profile [14]. PD daily home diary data showed that, relative to IR CD-LD, IPX203 was associated with significantly less daily "off" time (19.3% of waking hours for IPX203 vs. 33.5% with IR CD-LD; $P < 0.0001$), a 2.3-hour greater reduction in "off" time, and a 1.9-hour increase in "good on" time ("on" without experience of troublesome dyskinesia), despite less frequent IPX203 dosing (mean inter-dosing intervals of 4 h for IR CD-LD vs. 7 h for IPX203) [14]. The present pharmacodynamic analysis showed that on Day 15, mean MDS-UPDRS Part III scores prior to administration of the first daily dose were significantly lower among patients who received IPX203 compared to IR CD-LD, suggesting that the clinical effects of IPX203 may extend into the following morning. IPX203 has been recently evaluated in PD patients who experience motor fluctuations on a stable dose of IR CD-LD in a large Phase 3 clinical program (NCT03670953) [24].

5. Conclusions

The goal of continuous anti-parkinsonian benefits from LD therapy can be undermined by interruptions and other irregularities in its delivery from the GI tract to the brain. With current LD formulations, inability to maintain continuous central nervous system (CNS) LD exposure is attributable to its short half-life, erratic gastric emptying, and a limited window of opportunity for LD absorption in the proximal small intestine. IPX203, a new oral ER CD-LD, was developed with an innovative formulation to address the short plasma half-life and the

limited window of absorption for LD. IPX203 contains IR granules, ER coated beads, and mucoadhesive polymers to provide rapid and maximized absorption of LD. PK analyses confirmed the rapid increase in the LD plasma level that was sustained for longer than current formulations of CD-LD, including those intended for a more constant delivery. Administration of IPX203 with a high-fat, high-calorie breakfast delayed the initial increase in LD concentration by approximately 2 h and increased C_{max} and AUC_{tau} by 20% compared with the fasted state. Sprinkling the IPX203 capsule contents on applesauce did not affect the PK compared to the fasted state.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: P. L. has served as a consultant or investigator in clinical trials sponsored by Acorda Therapeutics, Amneal, Appello, Axovant, Aptinyx, Biogen, Biotie, Bukwang Pharmaceutical, Cavion, Cerevel, Denali Therapeutics, F. Hoffmann-LaRoche, Impax Laboratories Inc., Impel Neuropharma, Ipsen, Kyowa Hakko Kirin, Lundbeck A/S, the Michael J. Fox Foundation for Parkinson's Research, Mitsubishi Tanabe Pharma, Neurocrine Biosciences, NeuroDerm Ltd, Noven, Parkinson Study Group, Pharma Two B, Prexton Therapeutics, Revance Therapeutics, Saccadous, Sun Pharma, and US WorldMeds. He has received speaking fees from Acorda Therapeutics, Britannia, the American Academy of Neurology, the International Parkinson and Movement Disorder Society, Kyowa Hakko Kirin, Neurocrine Biosciences, Paladin Labs, US WorldMeds, and the World Parkinson Congress. He is compensated for services as editor-in-chief of *Clinical Neuropharmacology* and serves without compensation on the editorial boards of *Journal of Neural Transmission, Translational Neurodegeneration*, and *Journal of Parkinson's Disease*. A.E. has received speaking and consulting fees from AbbVie/Allergan, Acadia, Acorda Therapeutics, Adamas, Affiris, Amneal, Biohaven, Cerevel, Ipsen, NeuroDerm, Teva, US WorldMeds, and XW Labs. D.B. has received research support for clinical trials from AbbVie, Amneal, Athira Pharma, Axial Biotherapeutics, Cerevel, Enterin, Jazz Pharmaceuticals, Merck, Neuraly, Pharma Two B, and Praxis. S.G. has received research funding from the NIH and has participated in clinical studies funded by Biogen, Amneal, Parkinson Foundation, and the Michael J. Fox Foundation. R.G. has received speaking and consulting fees, as well as payment for his participation in clinical research trials as principal investigator, from companies including, but not limited to: Allergan, Adamas, Teva, Ipsen, US WorldMeds, Impax, Sunovion, AbbVie, Kyowa, Cynapsus, Neurocrine, Pharma Two B, Lundbeck, Novartis, Boehringer Ingelheim, GlaxoSmithKline, Amneal, Merz, Acadia, Medtronic, Merz, Abbott, and NeuroDerm. R.D. has participated as a clinical trial investigator in clinical studies funded by Amneal, Pharma Two B, AbbVie, NeuroDerm, Cerevel, Neurocrine/HSG, Neuraly, Alexion, Global Kinetics, AEON Biopharma, Praxis, and Sage Therapeutics. He has received grants from UAMS Translational Research Institute. He has served as a consultant for Best Doctors Inc. and Synergic Medical Technologies. He owns stock in Biogen, Gilead Sciences, Imara, Atea Pharmaceuticals, and Compass Pathways. G.B. and R.D. are employees of Amneal Pharmaceuticals, LLC.

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Ethical Compliance Statement

This study was designed and conducted in accordance with the general ethical principles outlined in the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and the principles embodied in the Declaration of Helsinki and was compliant with all United States Food and Drug Administration requirements and local governmental regulations. The protocols were approved by institutional review boards (IRBs) for each site. Quorum Inc., now Advarra Inc. (Seattle, WA), a commercial independent review board, provided IRB services for 7 of the 11 sites included in this trial. Institutional IRBs for the remaining 4 sites were the Duke University Health System Institutional Review Board (Durham, NC), the Western Institutional Review Board (Puyallup, WA), the University Hospitals IRB (Cleveland, OH), and the University of Arkansas for Medical Sciences IRB (Little Rock, AR).

Research Data Availability

Data from this study will be shared according to regulatory guidelines and timelines (eg, on ClinicalTrials.gov), and as determined by Amneal Pharmaceuticals. De-identified patient data can only be shared by people other than Amneal Pharmaceuticals after written approval from Amneal Pharmaceuticals.

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