BRIEF REPORT

Safety and Efficacy of IPX203 in Parkinson's Disease: The RISE-PD Open-Label Extension Study

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ABSTRACT: Background: IPX203 is a novel oral extended-release formulation of carbidopa/levodopa (CD/LD) developed to address the short half-life of immediate-release CD/LD. In the phase 3 RISE-PD trial, IPX203 significantly improved "Good On" time in patients with Parkinson's disease compared with immediate-release CD/LD.

Objectives: To evaluate the safety and efficacy of IPX203 in an open-label extension of the pivotal phase 3 study.

Methods: This 9-month extension enrolled patients who completed the randomized, double-blind trial. Key efficacy endpoints included Movement Disorder Society-Unified Parkinson's Disease Rating Scale and Patient and Clinical Global Impression scores. Adverse events (AEs) were recorded.

Results: Improvements in efficacy were maintained and dosing frequency and total daily dose remained stable through the trial. A total of 52.7% of patients experienced ≥1 treatment-emergent AE, mostly mild or moderate and occurred within the first 90 days of treatment.

Conclusions: In this phase 3 open-label extension, IPX203 exhibited a favorable safety and tolerability profile and sustained efficacy of comparable magnitude to the end of the double-blind study.

Key Words: extended release; levodopa; motor fluctuations; parkinson's diseases

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Introduction

Levodopa/carbidopa (LD/CD) has been a standard for treating motor symptoms of Parkinson's disease (PD) for nearly 50 years.[1] However, immediate-release (IR) formulations of CD/LD have short half-lives, and long-term use of IR CD/LD is complicated by development of motor fluctuations.[2] IPX203 is an investigational oral extended-release (ER) CD/LD formulation that was designed to prolong plasma concentrations of LD. A double-blind, randomized, active-controlled phase 3 trial (RISE-PD) assessed the efficacy and safety of IPX203 versus IR CD/LD in patients with PD and motor fluctuations (ClinicalTrials.gov identifier: NCT03670953).[3] Compared with patients who received IR CD/LD, IPX203 when given three times per day, compared with five times per day for IR CD/LD, led to significant improvement in "Good On" time per dose (least squares [LS] mean difference [95% confidence interval (CI)], 1.55 [1.37–1.73] hours; $P < 0.001$)[3] and "Good On" time per day (LS mean difference [95% CI], 0.53 [0.09–0.97] hours; $P = 0.02$).[3] Treatment with IPX203 (mean standard deviation [SD], 1488.05 [592.78] mg LD per day) was well tolerated during the double-blind treatment period.[3] Here, we present the safety and efficacy of IPX203 during the open-label extension of the RISE-PD trial.

Methods

Study Design and Participants

This 9-month, multicenter, open-label extension trial was conducted at 94 sites in the United States, Italy, Spain, France, United Kingdom, Czech Republic, Poland, and Germany between April 2019 and March 2022 (ClinicalTrials.gov Identifier: NCT03877510). All patients who completed the RISE-PD trial could enroll in the open-label extension trial. The extension trial consisted of a baseline visit (visit 1) and three follow-up visits at ~3-month intervals (visits 2–4). The baseline visit of this study occurred at the same time as the end-of-study visit of the RISE-PD trial.

The trial was conducted in accordance with standards set out by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice. The study protocol and relevant documents were reviewed and approved by an institutional review board before the start of the study. All patients provided informed consent; patients enrolled in the United States also signed Health Insurance Portability and Accountability Act authorization.

Treatments and Dosing

Patients were started on the final IPX203 dosing regimen that was determined during the IPX203 dose-conversion period of RISE-PD, as previously described.[3] Investigators could adjust the dosing regimen of IPX203 to achieve the optimal balance of efficacy and safety. Patients were advised to take the dose approximately every 8 hours and no more frequently than every 6 hours.

Assessments

Efficacy was assessed at every visit and included the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part I to IV,[4] Patient (PGI-S) and Clinician (CGI-S) Global Impression of Severity.

Safety, including adverse event (AE) reporting, was assessed at each visit. Clinical laboratory tests, vital signs, electrocardiogram, and physical examinations were also performed. AEs were considered treatment emergent if the date of onset was on or after the date of the first open-label study drug administration and no later than 1 day after the last dose of study drug.

Study drug exposure was assessed as frequency of daily dose administration (ie, number of administrations per day), total daily dose (TDD) of IPX203 in mg, and most frequently used dose of IPX203 in mg, as well as changes from the dosage initiated at visit 1 at the start of the open-label extension.

Statistical Analysis

There was no prespecified sample size determination. All patients who successfully completed the randomized lead-in trial could enroll in the open-label extension. A total of 300 patients were estimated to enroll, but enrollment was not capped at 300.

Efficacy data were analyzed in the intent-to-treat (ITT) population, which included all patients who received open-label study drug and had ≥1 post-baseline efficacy assessment. Safety was analyzed in the safety analysis set, which included all patients who received open-label study drug. Missing data were not imputed, with the exception of missing MDS-UPDRS data.

Results

Study Participants

Between April 3, 2019, and March 21, 2022, 419 patients were enrolled and received treatment, and 352 (84.0%) completed the trial (Supplementary Fig. S1). A total of 67 patients (16.0%) discontinued; the most common reasons for discontinuation were withdrawal by patient (22 patients [32.8%]), AEs (20 [29.9%]), and lack of efficacy (14 [20.9%]). Among patients who received IPX203 in the double-blind trial, the rate of discontinuation was stable over the 9-month extension (4%–5%); among patients switching from IR CD/LD to IPX203, the rate of discontinuation was higher in the first 6 months after switching (8%–8.5% vs. 2.3% at month 9 [visit 4]). Overall, mean (SD) age was 66.9 (8.9) years and most patients (66.6%) were male (Supplementary Table S1).

Dosing Regimen

The daily dosing frequency was stable over the 9-month trial; mean daily dosing frequency was approximately three doses a day at each visit (Supplementary Table S2; Supplementary Fig. S2A). Over the 9-month trial, the mean (SD) TDD of LD in IPX203 was 1539.6 (630.8) mg (Supplementary Fig. S2B).

Efficacy

Efficacy and quality of life (QoL) measures were unchanged throughout the 9-month open-label extension (Table 1). No notable changes were observed in mean MDS-UPDRS total and parts I–IV from baseline to visit 4. Similarly, no changes were observed in PGI-S or CGI-S scores.

Mean 39-item Parkinson's Disease Questionnaire, Parkinson Anxiety Scale, Non-Motor Symptom Assessment Scale, Parkinson's Disease Sleep Scale-2, and Early Morning Symptoms Questionnaire scores were unchanged throughout the trial with no differences observed from baseline to visit 4 (Table 1). Overall,

TABLE 1 *Summary of efficacy endpoints (ITT analysis set)*

Endpoint Score	RISE-PD baseline*	Visit 1 (trial baseline†)	Visit 2 (month 3)	Visit 3 (month 6)	Visit 4 (month 9)	Change from baseline to visit 4
MDS-UPDRS Total, n	412	409	379	355	351	349
Mean (SD)	60.2 (27.0)	56.7 (28.6)	56.5 (30.1)	56.0 (28.9)	58.8 (29.6)	2.3 (16.7)
MDS-UPDRS Part I, n	412	410	390	362	351	350
Mean (SD)	9.9 (5.4)	9.9 (6.3)	10.6 (6.4)	10.7 (6.2)	11.0 (6.8)	1.2 (4.7)
MDS-UPDRS Part II, n	412	409	390	362	351	349
Mean (SD)	13.3 (7.3)	12.8 (7.8)	13.0 (8.0)	12.8 (7.7)	13.5 (8.1)	0.8 (4.9)
MDS-UPDRS Part III, n	412	410	379	357	351	350
Mean (SD)	29.6 (17.2)	27.5 (17.2)	26.8 (17.9)	26.6 (17.5)	27.9 (17.1)	0.4 (11.4)
MDS-UPDRS Part IV, n	412	410	382	358	351	350
Mean (SD)	7.5 (2.6)	6.6 (3.0)	6.0 (3.2)	6.0 (3.1)	6.3 (3.2)	−0.1 (2.6)
PGI-S, n	412	409	390	363	351	349
Mean (SD)	3.8 (0.9)	3.7 (1.0)	3.8 (1.0)	3.7 (1.0)	3.7 (1.1)	0 (1.1)
CGI-S, n	412	409	383	358	350	348
Mean (SD)	3.9 (0.8)	3.8 (0.9)	3.8 (0.9)	3.7 (0.9)	3.7 (1.0)	−0.1 (0.8)
PDQ-39 total, n	411	406	392	364	348	343
Mean (SD)	44.9 (26.9)	41.7 (27.7)	42.7 (27.7)	42.8 (28.2)	44.4 (28.7)	4.1 (18.8)
PAS total, n	410	408	390	365	350	347
Mean (SD)	10.7 (7.8)	10.4 (8.2)	10.3 (8.2)	10.3 (7.7)	10.9 (8.3)	0.8 (6.3)
NMSS total, n	412	407	388	362	349	346
Mean (SD)	34.9 (27.5)	32.0 (29.0)	32.5 (28.5)	33.4 (29.2)	35.0 (30.2)	3.9 (22.4)
PDSS-2, n	412	410	389	363	344	343
Mean (SD)	17.4 (9.4)	16.6 (9.7)	15.8 (9.2)	16.1 (9.3)	16.1 (9.2)	−0.1 (8.8)
TSA, n	N/A	N/A	392	365	350	N/A
Mean (SD)	N/A	N/A	5.2 (1.3)	5.4 (1.2)	5.4 (1.3)	N/A
ZBI-12 total, n	N/A	153	149	141	135	124
Mean (SD)	N/A	9.2 (7.8)	10.5 (8.4)	11.0 (9.0)	10.6 (8.9)	1.3 (7.6)
EMSQ total severity, n	411	406	388	362	349	345
Mean (SD)	9.5 (4.3)	8.4 (5.2)	8.1 (5.4)	8.0 (5.1)	8.4 (5.5)	0.4 (4.5)

Abbreviations: CGI-S, Clinical Global Impression of Severity; EMSQ, Early Morning Symptoms QuestionnaireITT, intent to treat; MDS-UPDRS, Movement Disorders Society–Unified Parkinson's Disease Rating Scale; N/A, not applicable; NMSS, Non-Motor Symptom Assessment Scale; PAS, Parkinson Anxiety Scale; PDQ-39, 39-item Parkinson's Disease Questionnaire; PDSS-2, Parkinson's Disease Sleep Scale-2; PGI-S, Patient Global Impression of Severity; SD, standard deviation; TSA, Treatment Satisfaction Assessment; ZBI-12, 12-Item Zarit Burden Interview.

*Defined as the last assessment before the first dose of study drug during the dose-adjustment period.

†Defined as the last assessment before the first dose of open-label drug.

80.4% of patients reported being at least somewhat satisfied with treatment (score of 5, 6, or 7 on the Treatment Satisfaction Assessment) at 3 months; 84.4% and 81.7% reported being at least somewhat satisfied with treatment at 6 and 9 months, respectively.

Safety

Among the 419 patients who entered the open-label extension, 221 (52.7%) patients experienced ≥1 treatment-emergent AE (TEAE), and 42 (10.0%) experienced ≥1 serious AE (Table 2). In general, TEAEs more commonly occurred within the first 90 days of the trial, with 17.7% of patients experiencing a TEAE within 30 days of trial start and 16.9% of patients experiencing a TEAE between 30 and 90 days (Supplementary Fig. S3). TEAEs were considered treatment related in 66 patients (15.8%); the most commonly reported treatment-related TEAEs (occurring in

TABLE 2 *Summary of TEAEs (safety analysis set)*

Patients, No. (%)	Overall N = 419
≥1 TEAE	221 (52.7)
≥1 treatment-related TEAE	66 (15.8)
≥1 serious TEAE	42 (10.0)
TEAE leading to study drug discontinuation	25 (6.0)
TEAE leading to death	6 (1.4)
TEAEs reported in ≥2% of patients	
Dyskinesia	21 (5.0)
Fall	21 (5.0)
Urinary tract infection	21 (5.0)
Back pain	15 (3.6)
Constipation	11 (2.6)
COVID-19	10 (2.4)

Abbreviations: COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

≥1% of patients) were dyskinesia (4.5%) and nausea (1.0%). A total of 25 patients (6.0%) discontinued the trial because of a TEAE. Six patients died during the trial. All serious AEs (SAEs) leading to death were deemed not related to study drug, with the exception of one patient who had a severe SAE of drowning that was considered by the investigator to be related to study drug.

No clinically meaningful changes from trial baseline (visit 1) to visit 4/early termination were observed in clinical laboratory parameters, vital signs, electrocardiogram parameters, and physical examination. As measured by the Columbia-Suicide Severity Rating Scale, a small percentage of patients had any suicidal ideation at baseline (0.5%) and at visit 4 (0.8%); no patient had any suicidal behavior at any visit. No clinically meaningful differences were seen from baseline to visit 4 in gastroparesis cardinal symptom index questionnaire scores.

Discussion

During 9 months of open-label treatment, IPX203 was associated with sustained efficacy and acceptable safety and tolerability profiles in patients with PD experiencing motor fluctuations. TEAEs were generally mild to moderate in intensity and mostly occurred within the first 90 days of treatment.

IR CD/LD formulations are limited by their short half-lives, and when motor fluctuations emerge, doses or dosing frequency are commonly increased to circumvent this limitation. However, increasing the amount of LD can lead to, or worsen, LD-induced dyskinesia.[2] ER CD/LD has shown a more stable pharmacokinetic profile with less fluctuations in plasma LD concentrations compared with IR CD/LD[5,6] and sustained efficacy; however, it must still be dosed at least four times a day in advanced PD. In the RISE-PD trial, patients taking IPX203 dosed an average of three times a day experienced 0.53 hours more "Good On" time per day than patients taking IR CD/LD dosed an average of five times a day.[3] IPX203 also increased the "Good On" time per dose by 1.55 hours compared to IR CD/LD.[3] At the end of the double-blind RISE-PD trial, mean (SD) MDS-UPDRS part III scores were 27.8 (17.7) and 28.0 (16.6) for patients in the IPX203 and IR CD/LD groups, respectively. Mean (SD) MDS-UPDRS part IV was 6.6 (3.3) for patients in the IPX203 group and 6.9 (2.8) for patients in the IR CD/LD group. In this extension trial, patients taking IPX203 dosed an average of three times a day experienced unchanged MDS-UPDRS part III and IV scores throughout the 9-month open-label trial, suggesting stable control of motor symptoms. MDS-UPDRS part III and IV scores were also similar between patients previously receiving IPX203 and patients switching from IR CD/LD to IPX203. All other efficacy outcomes were unchanged throughout the trial, providing further evidence for maintained efficacy with IPX203. In the double-blind trial, a significantly greater proportion of patients ($P = 0.002$) reported themselves "much improved" or "very much improved" with IPX203 treatment (29.7%) compared with IR CD-LD treatment (18.8%).[3] Patient-reported outcomes remained stable throughout the open-label extension.

Changes in dosing regimens were more likely to occur within the first 90 days of the trial, suggesting that dosing regimens can be relatively quickly stabilized.

The most commonly reported TEAEs in this open-label extension trial were dyskinesia and nausea, which are commonly associated with PD therapies. Dyskinesia was reported in 5.0% of patients during the open-label extension (Table 2) compared with 2.0% of patients receiving IPX203 in the double-blind period of the lead-in trial.[3] Nausea was reported in 1.9% of patients in the open-label extension, whereas 4.3% of patients receiving IPX203 in the double-blind period of the lead-in trial reported nausea. Rates of treatment-related AEs in the open-label extension were generally lower for patients continuing on IPX203 than for patients switching from IR CD/LD, and AEs were more common within the first 30 days of treatment, suggesting that AEs may improve over time as the dosing regimen is stabilized.

Overall, in this phase 3 open-label extension trial of IPX203, most patients achieved a stable dosing regimen within 3 months. Trial results suggest that treatment with IPX203 given an average of three times a day for 9 months provides maintained efficacy and is generally

safe and well tolerated in patients with PD and motor fluctuations.

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Data Availability Statement

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

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

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