How to dose extended-release carbidopa-levodopa capsules (IPX203) in patients with Parkinson's disease: Experience from the phase 3 clinical trial

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Objective

- To study dosing of IPX203 based on clinical trial experience from the phase 3 RISE-PD study in patients with Parkinson's disease (PD)

Background

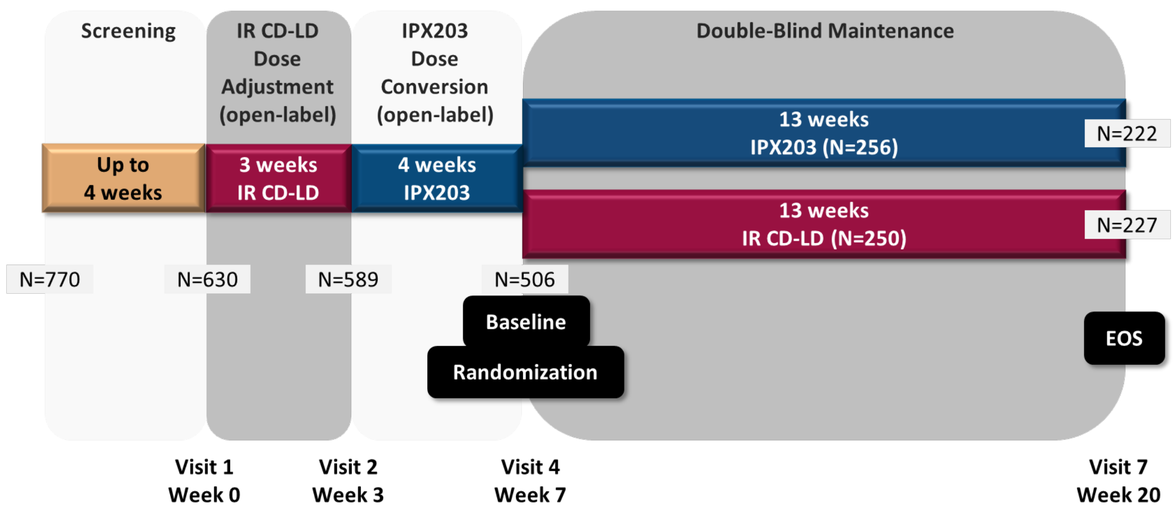
- IPX203 is an oral extended-release carbidopa-levodopa (CD-LD) formulation
- IPX203 is designed to rapidly achieve therapeutic LD plasma concentrations and maintain LD concentrations for a longer duration with less peak-to-trough variations than currently approved oral CD-LD products
- The formulation results in approximately 85% bioavailability of LD in terms of total exposure (area under the curve [AUC]) and 38% maximum plasma LD concentrations (C_{max}) compared to an equivalent dose of immediate-release (IR) CD-LD. Because of these differences, it is critically important to recognize that dosages of IPX203 are not interchangeable with IR CD-LD
- In the phase 3 RISE-PD study, IPX203 showed superior efficacy compared to IR CD-LD in PD patients with motor fluctuations

Methods

- RISE-PD was a multicenter, double-blind, double-dummy, randomized, active-controlled phase 3 study (**Figure 1**) conducted at 105 sites across the United States and Europe (NCT03670953)
- The initial dosing regimen of IPX203 was based on the most frequent individual dose of the subject's IR CD-LD at the end of the dose adjustment period
- The conversion ratio for IPX203 from IR CD-LD was 2.8
- IPX203 was dosed about every 8 hours; not more frequent than every 6 hours

Methods (cont'd)

Figure 1. RISE-PD Study Design



- Subjects on a total daily dose <125-500 mg IR CD-LD were advised to take IPX203 every 12 hours; could be reduced to every 8 hours if needed
- Individual dose could be increased if needed for optimal motor response
- All patients randomized to the IPX203 treatment arm during the double-blind period were examined for their dosing
- Dosing scenarios are based on the four available capsule strengths of IPX203 (**Figure 3**)

Identify the starting IPX203 individual dose based on the most frequent individual IR CD-LD dose

Table 1. Conversion From IR CD-LD to IPX203 Used in the Phase 3 Clinical Trial

Most frequent IR CD-LD single dose (LD mg)	Recommended IPX203 individual starting dose of levodopa (LD mg)	Recommended IPX203 starting dose frequency[a]
100 mg	280 mg	3 times daily
150 mg	420 mg	3 times daily
200 mg	560 mg	3 times daily
>200 mg	700 mg	3 times daily

IR CD-LD, immediate-release carbidopa-levodopa.

[a]Patients on a total daily dose of less than 125–500 mg IR CD-LD at the end of the dose-adjustment period were advised to initially take IPX203 every 12 hours. After starting treatment with IPX203, the dosage (mg) and dosing frequency could be reduced to approximately every 8 hours if the subject did not achieve an acceptable duration of effect.

Figure 2. IPX203 Distribution of Dosing Frequency During Randomized Double-Blind Period

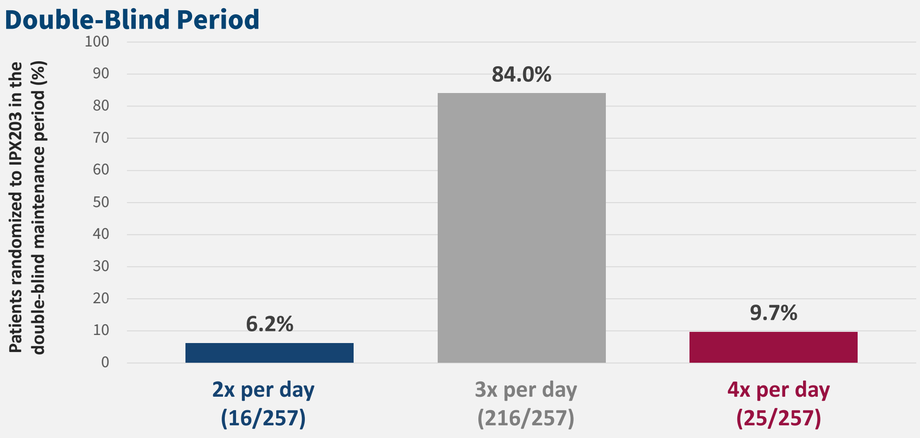


Figure 3. Dose Strengths of IPX203 Included in the NDA

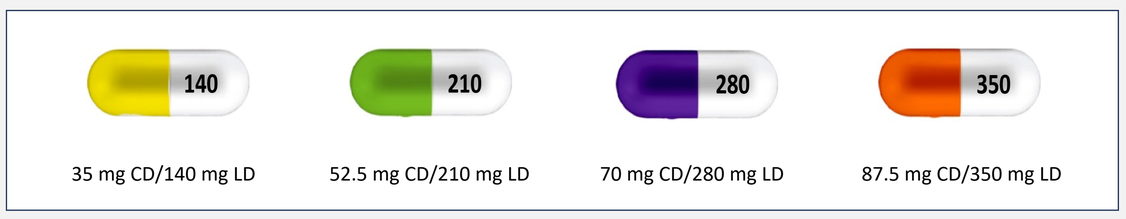


Table 2. Hypothetical Conversion Table From IR CD-LD to IPX203 Using 4 Dose Strengths

	Identify the starting IPX203 individual dose based on the most frequent individual IR CD-LD dose		
	Most frequent individual IR CD-LD dose	Conversion to IPX203 (x2.8)	Suggested individual IPX203 dose
1	25/**100** mg IR CD-LD	2x 140 or 1x 280	70/**280** mg CD-LD IPX203
	37.5/**150** mg IR CD-LD	3x 140 or 2x 210	105/**420** mg CD-LD IPX203
	50/**200** mg IR CD-LD	4x 140 or 2x 280	140/**560** mg CD-LD IPX203
	≥62.5/**250** mg IR CD-LD	2x 350 or 2x 140 plus 2x 210	175/**700** mg CD-LD IPX203
2	Initiate patients on the above individual IPX203 dose TID. For patients receiving a total daily dose of <125/500 mg IR CD-LD, initiate IPX203 BID		
3	Adjust the dosing regimen to achieve optimal balance of efficacy and tolerability by minimizing "Off" time without causing troublesome dyskinesia or other dopaminergic side effects		

Results

- The conversion of IR CD-LD to IPX203 was based on the most frequent individual IR LD dose (**Table 1**)
- Following the conversion and optimization phase of the study, patients with motor fluctuations required about 1.79 times the mean daily LD mg dose compared to IR CD-LD
  - On average, individual doses were about 2.9 times the mean most frequent stable individual dose of IR CD-LD
  - The higher daily dose was needed to avoid the troughs in plasma LD concentrations seen with IR CD-LD
  - The higher single dose was needed to obtain peak plasma concentrations close to those obtained from IR CD-LD
- During the randomized double-blind phase of the RISE-PD study, the mean daily dosing frequency of IPX203 at the end of the study was 3.04 times per day; 84.0% (216/257) of patients took it three times per day (**Figure 2**)
- Hypothetical dose conversion in **Table 2** is based on the four available capsule strengths of IPX203

Conclusions

- When converting patients from IR CD-LD to IPX203, it is important to try to match the C_{max} of IR CD-LD to provide the same level of expected benefit for the patient
- Patients experiencing motor fluctuations on IR CD-LD can be converted to IPX203 by multiplying the most frequent individual dose of IR CD-LD by 2.8 and initiating dosing three times daily, followed by titration according to clinical response
- Dose conversion based on most frequent individual LD dose may facilitate the conversion process in clinical practice; dosing frequency may be adjusted to address patient's motor fluctuations as needed

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