726

Dose Conversion from Immediate-Release Carbidopa-Levodopa to IPX203 (ER CD-LD) in Parkinson's Disease Patients with Motor Fluctuations

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Background

- IPX203 is an extended-release (ER), oral carbidopa-levodopa (CD-LD) formulation designed to rapidly achieve therapeutic LD plasma concentrations and to maintain LD concentrations for a longer duration, with less peak-to-trough variation than currently approved oral CD-LD products

Objective

- To analyze dosing regimen data from a Phase 3 study in order to identify an optimal dose conversion from immediate-release (IR) CD-LD to IPX203, for use in clinical practice

Methods

- RISE-PD was a randomized, double-blind, active-controlled Phase 3 study of the safety and efficacy of IPX203 vs IR CD-LD in Parkinson's disease (PD) patients with motor fluctuations **(Figure 1)**
- Following screening, patients entered a 3-week IR CD-LD dose-adjustment period, during which the IR CD-LD dosing regimen was adjusted to achieve an optimal balance of efficacy and tolerability
- Following completion of the IR CD-LD dose-adjustment period, subjects began a 4-week open-label dose-conversion period
- The initial IPX203 dosing regimen was based on the most frequent IR CD-LD dose of the subject's stable dosing regimen at the end of the dose adjustment period, selecting the most frequent dose according to **Table 1**
- IPX203 was administered every 8 hours for most patients. Dosing interval could vary, but could not be shorter than every 6 hours
- The conversion ratio from the most frequent IR CD-LD unit dose to the recommended starting IPX203 dose was 2.8 (except when individual IR LD dose above 250 mg). Each individual dose of IPX203 could be adjusted at the investigator's discretion

For IPX203, multiplying a patient's most frequent IR LD dose by 2.8 provides a simple starting point for most patients

Figure 1. RISE-PD Study Design

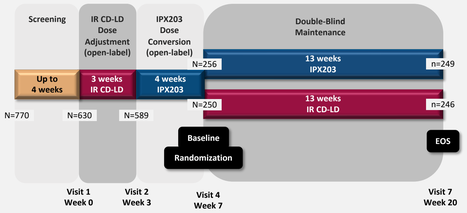

Table 1. Conversion from IR CD-LD to IPX203[a]

Most Frequent IR CD-LD Unit Dose (mg) at End of Dose Adjustment Period	Recommended Starting IPX203 Daily Dosing Regimen CD-LD (mg)[b]
25-100 mg	70-280 mg (2 x 35-140mg)
37.5-150 mg	105-420 mg (3 x 35-140mg)
50-200 mg	140-560 mg (4 x 35-140mg)
≥62.5-250mg	175-700 mg (5 x 35-140mg)

[a]Adjusted from the clinical trial protocol [b]Taken TID-QID. BID dosing recommended for total daily dose of less than 125-500 mg IR CD-LD.

Table 2. Study Drug Regimen in the IPX203 Conversion Period[a]

Characteristic	IPX203 in IPX203 Conversion Period	
	Start of Period (N=506)	End of Period (N=506)
Daily dosing frequency (times/day)		
Mean (SD)	2.9 (0.31)	3.0 (0.42)
Median (min, max)	3.0 (2, 3)	3.0 (2, 5)
Most frequent LD dose (mg)		
Mean (SD)	464 (168.21)	491 (187.15)
Median (Min, Max)	420 (140, 840)	420 (140, 1120)

[a]Randomized analysis set.

Table 3. Titration Steps from IR CD-LD to Stable IPX203 Dosing in the IPX203 Conversion Period[a]

Characteristic	IPX203 Conversion Period
Subjects who entered the period	589
Subjects who achieved stable dosing[b], n (%)	506 (85.9)
Subjects who did not achieve stable dosing[b], n (%)	83 (14.1)
Number of titration steps to stable dosing[c], n (%)	
N	506
Mean	1.6
SD	1.74
Median	1.0
Min	0
Max	11
0	175 (34.6%)
1 – 2	205 (40.5%)
3 – 4	93 (18.4%)
5 – 6	26 (5.1%)
> 6	7 (1.4%)

[a]Safety analysis set; [b]Percentages were based on the number of subjects who entered the study period; [c]Percentages were based on the number of subjects who achieved stable dosing.

Table 4. Conversion from Stable IR CD-LD Regimen to Starting and Stable IPX203 Regimens[a]

Stable (Visit 2) IR CD-LD Regimen Most Frequently Used LD dose (mg)	Starting IPX203 Regimen (LD dose, mg)	Stable IPX203 Regimen (LD dose, mg)	Number (%) of Subjects[b]
100 (N=152)	**280-280**	**280-280**	**29 (19.1)**
	280-280-280	**280-280-280**	**37 (24.3)**
		420-420-420	11 (7.2)
>100 – 150 (N=99)	**420-420-420**	280-280-280	5 (5.1)
		420-420-420	**25 (25.3)**
		560-420-420	5 (5.1)
		560-560-560	8 (8.1)
>150 – 200 (N=158)	**560-560-560**	420-420-420	10 (6.3)
		560-560-560	**50 (31.6)**
		700-700-700	10 (6.3)
	700-700-700	**700-700-700**	**8 (5.1)**
>200 (N=96)	**560-560-560**	**560-560-560**	**5 (5.2)**
	700-700-700	**700-700-700**	**30 (31.3)**
	840-700-700	**840-700-700**	**5 (5.2)**
	840-840-700	**840-840-700**	**5 (5.2)**

[a]Randomized analysis set; [b]Percentages (≥5%) are based on number of subjects with the given most frequently used LD dose in their stable IR CD-LD regimen at visit 2.

Table 5. The Stable Dose of IPX203 Was Similar to the Starting Dose

Most Frequent IR CD-LD Unit Dose at End of Dose-Adjustment Period (Visit 2)	Recommended Starting IPX203 Daily Dosing Regimen CD-LD (mg) Every 8 Hours	Most Frequent IPX203 Unit Dose (mg) of LD at the End of IPX203 Dose Conversion Period (Period 4)
25-100	70-280 mg (2 x 35-140 mg)	317 mg (range: 140-700 mg)
>25-100 – 37.5-150	105-420 mg (3 x 35-140 mg)	452 mg (range: 140-840 mg)
>37.5-150 – 50-200	140-560 mg (4 x 35-140 mg)	574 mg (range: 140-980 mg)
>50-200	175-700 mg (5 x 35-140 mg)	675 mg (range: 280-1120 mg)

Table 6. Conversion Ratio of IR CD-LD to IPX203 by Stable IR CD-LD Total Daily Dose[a]

Stable IR CD-LD Total Daily Dose (LD dose, mg)	<400 (N=0)	400-<800 (N=227)	800-<1200 (N=183)	1200-<1600 (N=63)	1600-2400 (N=33)	>2400 (N=0)	Total (N=506)
Ratio of Stable IPX203 Total Daily Dose to Stable IR CD-LD Total Daily Dose							
Mean (SD)	—	1.87 (0.532)	1.86 (0.436)	1.54 (0.345)	1.29 (0.223)	—	1.79 (0.492)
Median (min, max)	—	1.80 (0.7, 3.5)	1.87 (0.6, 3.5)	1.54 (0.8, 2.5)	1.32 (0.7, 1.9)	—	1.70 (0.6, 3.5)
Ratio of Stable IPX203 Most Frequent Dose to Stable IR CD-LD Most Frequent Dose							
Mean (SD)	—	2.97 (0.917)	2.95 (0.887)	2.88 (0.767)	2.53 (0.547)	—	2.92 (0.873)
Median (min, max)	—	2.80 (0.9,7.0)	2.80 (0.7, 7.0)	2.80 (1.4, 4.9)	2.40 (1.4, 3.7)	—	2.80 (0.7, 7.0)

[a]Randomized analysis set.

EOS, end of study; IR CD-LD, immediate release carbidopa-levodopa; max, maximum; min, minimum; SD, standard deviation.

Results

- 506/589 patients (85.9%) who entered the IPX203 dose conversion period achieved stable dosing
- 54/589 patients who entered the dose conversion period started on BID dosing, including 31 (57%) who remained on twice daily IPX203 through the end of dose conversion, 21 (39%) increased to TID dosing and 2 (4%) increased to QID dosing. Of the 425 patients who started on TID dosing, 12% increased to QID dose frequency
- Mean daily dosing frequency and most frequent LD dose were similar at the start and end of the conversion period (**Table 2**); stable dosing was achieved in 1.6 (1.74) titration steps (**Table 3**)
- In all cases, the starting IPX203 regimen was the most frequent regimen when dosing stability was achieved (**Table 4**)
- The stable dose of IPX203 was similar to the starting dose (**Table 5**)
- The stable IPX203 total daily dose was proportionally higher than the stable IR daily dose (mean 1.79 [0.492]) (**Table 6**)
- The ratio of the most frequent stable individual IPX203 dose to IR CD-LD dose was 2.92 (**Table 6**)

Conclusions

- For doses up to 250mg LD, a conversion ratio of 2.8 from the most frequent individual IR CD-LD dose is an appropriate starting dose of IPX203
- At the end of conversion, average individual IPX203 LD doses were close to doses at the start of dose conversion despite the dosing frequency restrictions in the study
- 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

Presented at the 2022 International Congress of Parkinson's Disease and Movement Disorders Annual Meeting, September 15-18, 2022, Madrid, Spain. Data from Amneal Pharmaceuticals LLC