Duration of Benefit Per Dose: Post Hoc Analysis of "Good On" Time Per Dose for IPX203 vs IR CD-LD in the RISE-PD Phase 3 Trial

Robert A. Hauser[1], Hubert H. Fernandez[2], Kevin Klos[3], Susan Criswell[4], Neepa Patel[5], Ghazal Banisadr[6], Stanley Fisher[6]

[1]USF Parkinson's Disease and Movement Disorders Center/Parkinson Foundation Center of Excellence, Tampa, FL, USA; [2]Cleveland Clinic, Cleveland, OH, USA; [3]The Movement Disorder Clinic of Oklahoma, Tulsa, OK, USA; [4]Washington University, St. Louis, MO, USA; [5]Rush University Medical Center, Chicago, IL, USA; [6]Amneal Pharmaceuticals, Bridgewater, NJ, USA

Background

- Approximately 50% of PD patients develop motor fluctuations within 5 years of treatment with levodopa[1, 2]
- Convenient, highly effective, and well tolerated therapies that maintain therapeutic levodopa levels throughout the day are needed[3]
- IPX203 is a long-acting, oral CD-LD formulation
- IPX203 was evaluated vs IR CD-LD in PD patients with motor fluctuations in a phase 3, double-blind, randomized study
- A key metric to characterize the potential benefit of a long-acting oral levodopa formulation is duration of "Good On" time per dose

Objective

- To determine the mean duration of "Good On" time per dose for IPX203 in comparison to IR CD-LD in PD patients with motor fluctuations

Methods

- RISE-PD study design is shown in **Figure 1**
- Primary endpoint was mean change from baseline in "Good On" time
- "Good On" was defined as "On" time without troublesome dyskinesia
- Post hoc analysis:
  - Least squares (LS) mean "Good On" time per dose was calculated at the end-of-study (EOS) visit for the modified intention-to-treat (mITT) population for IPX203 and IR CD-LD treatment groups using an MRMM model
  - "Good On" time per dose was defined as daily "Good On" time (hours) divided by daily dosing frequency in the subject's stable dosing regimen

References:

1. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord.* 2001;16(3):448-458. 2. Hauser RA, LeWitt PA, Comella CL. On demand therapy for Parkinson's disease patients: Opportunities and choices. *Postgrad Med.* 2021;133(7):721-727. 3. Stocchi F. The hypothesis of the genesis of motor complications and continuous dopaminergic stimulation in the treatment of Parkinson's disease. *Parkinsonism Relat Disord.* 2009;15(S1):S9-S15.

IPX203 increased "Good On" time per dose by 1.55 hours compared to IR CD-LD (*$P<0.0001$)

Figure 1. RISE-PD Study Design

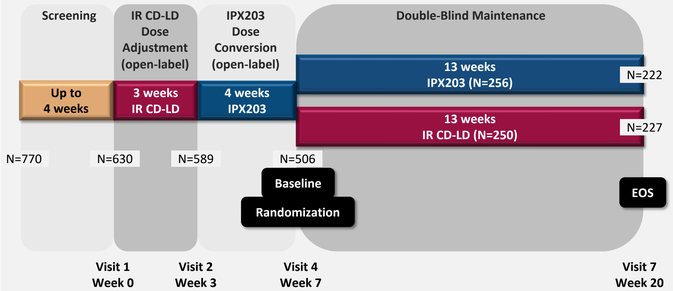


Table 1. RISE-PD Efficacy Results Summary

Endpoint	IPX203 (N=249)	IR CD-LD (N=246)	Difference IPX203 vs IR CD-LD	P-value
Primary Endpoint:				
Change from baseline to Visit 7/ET in "Good On" time (hr), LS Mean	-0.50	-1.03	0.53	0.0194[a]
Key Secondary Endpoints:				
Change from baseline to Visit 7/ET in "Off" time (hr), LS Mean	0.38	0.86	-0.48	0.0252[a]
Percentage of subjects with "much improved" or "very much improved" PGI-C scores at Visit 7/ET[c]	29.7	18.8	10.9	0.0015[b]
Change from baseline to Visit 7/ET in MDS-UPDRS Part III score, LS Mean[c]	0.8	0.8	0.0	0.9587[a]
Change from baseline to Visit 7/ET in the sum of MDS-UPDRS Part II and III scores, LS Mean[c]	1.7	1.8	0.0	0.9668[a]

IPX203 was dosed on average 3 times a day and IR CD-LD 5 times a day.

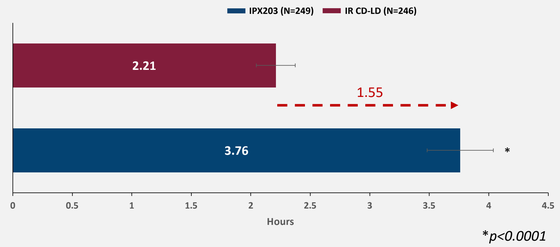
CMH = Cochran-Mantel-Haenszel; ET: early termination; MDS-UPDRS, Movement Disorders Society-Unified Parkinson's Disease Rating Scale; PGI-C, Patient Global Impression of Change.

[a]P-value for the hypothesis of equal LS means.

[b]P-value from the CMH test stratified by pooled center comparing the proportion of much or very much improved patients between the treatment groups.

[c]IPX203; N=256 and IR CD-LD; N=250.

Figure 2. "Good On" time per dose



*$p<0.0001$

Table 2. "Good On" time (hours) per dose at the end of study

"Good On" Time Per Dose	IPX203 (N=249)	IR CD-LD (N=246)	Difference IPX203-IR CD-LD
LS mean (hours)	3.76	2.21	1.55
Standard error	0.074	0.074	0.091
95% confidence interval	3.62, 3.91	2.07, 2.36	1.37, 1.73
P-value[a]			<0.0001

[a]p-value for the hypothesis of equal LS means.

LS means, standard errors, confidence intervals, and P-value from a mixed model for repeated measures with value in "Good On" time per dose as outcome, treatment and visit as fixed effects, pooled center as random effect and a treatment-by-visit interaction. The degree-of-freedom of the denominator was estimated using the Kenward-Roger method. Unstructured covariance structure was assumed. Data from Randomization Visit 4 and all the following scheduled visits were used in the model and estimates for Visit 7/end of study visit were summarized.

Results

- In the RISE-PD study, IPX203 treatment resulted in 0.53 more hours of "Good On" time than IR CD-LD, when dosed on average 3 times a day compared to 5 times a day for CD-LD IR (**Table 1**)
- Secondary endpoints:
  - IPX203 resulted in significantly less "Off" time vs IR CD-LD (-0.48 hr, p=0.0252)
  - PGI-C scores showed significantly more patients treated with IPX203 were "much improved" or "very much improved" compared with those treated with IR CD-LD (29.7% vs 18.8%; *P=0.0015*)
  - Change from baseline scores for MDS-UPDRS Part III and sum of MDS-UPDRS Part II and III were similar for the two treatment groups
- The current post hoc analysis found that IR CD-LD and IPX203 provided 2.21 hours and 3.76 hours of "Good On" time per dose respectively (*$p<0.0001$*) (**Figure 2**; **Table 2**)

Conclusions

- IPX203 provided 1.55 more hours of "Good On" time per dose vs IR CD-LD, representing a 70% increase
- Information from this post hoc analysis may help clinicians make better medication management decisions and anticipate the longer lasting duration of effect per dose when patients on IR CD-LD treatment are converted to IPX203

Disclosures:

Robert A. Hauser has received personal compensation serving as a consultant and on the Speakers Bureau for Amneal. Dr. Hauser has received personal compensation serving as a consultant for Abbvie, Acadia Pharmaceuticals, Acorda Therapeutics, Adamas Pharmaceuticals, Alterity, Aptinyx, BioMedical Insights, BRACKET/Signant, Britannia, Cerevance, Clarity Science, ClearView Healthcare Partners, Coleman Research, Curium Pharma, DDB Health, Deallus, Decision Resource Group (DRG), Efficient CME, Enterin, EPI-Q, FirstWord, Global Kinetics, Global Life Sciences, GuidePoint Global, Health Advances, Huron, Inhibikase, InSearch Consulting, Insignia Strategies, Jazz Pharmaceuticals, Kansas City Southwest Clinical Society, KeiferRX, KeyQuest, KX Advisors, Kyowa Kirin Pharmaceuticals, L.E.K. Consulting, LifeSciences Consultants, Lundbeck A/S, Merck, Merz, Neurocrine Biosciences, NeuroDerm, Novus, Orion, Ovid Therapeutics, Perception OpCo (Cerevel Therapeutics), Pharma Two B, Pharmather, Projects in Knowledge, Research Catalyst, Revance Therapeutics, Roche, Scion Neurostim, Sage Therapeutics, Sio Gene Therapies, Sunovion Pharmaceuticals, Supernus, Syneos, Tolmar, Triangle Insights, US World Meds, and Vivifi Biotech; Dr. Hauser has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Inhibikase and Vivifi Biotech; Dr. Hauser has received personal compensation for serving on a Speakers Bureau for Acorda Therapeutics, Adamas, Kyowa Kirin, Neurochallenge, Neurocrine, Sunovion, and Kansas City Southwest Clinical Society; Dr. Hauser has stock in Axial Therapeutics and Inhibikase; The institution of Dr. Hauser has received research support from AbbVie, Axovant Sciences, Bukwang Pharmaceuticals, Cavion, Centogene, Cerevance, Cerevel, Cynapsus Therapeutics, Enterin, Genentech, Global Kinetics Corporation, Impax Laboratory, Intec Pharma, Jazz Pharmaceuticals, Integrative Research Laboratories Sweden AB, MJFF, Neuraly, NeuroDerm, Northwestern University, Pfizer, Pharma Two B, Revance Therapeutics, Roche, Sanofi US Services, Sun Pharma Advanced Research, Sunovion, and UCB Biopharma; Dr. Hauser has received intellectual fees from his institution for licensing of a PD diary. **The institutions of Dr. Fernandez, Dr. Klos, Dr. Criswell, and Dr. Patel have received research support from Amneal. Ghazal Banisadr and Stanley Fisher have received personal compensation for serving as employees of Amneal.**

Presented at American Academy of Neurology 2022 Annual Meeting, April 2-7 2022, Seattle, Washington. Data from Amneal Pharmaceuticals LLC