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Extended-release carbidopa-levodopa: How is IPX203 different from IPX066?

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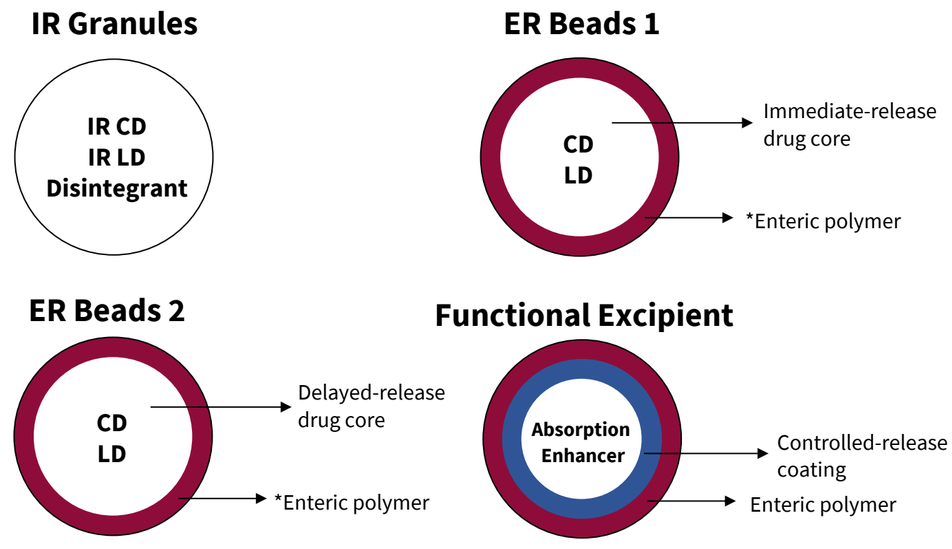
Objective

- To compare two oral extended-release (ER) carbidopa-levodopa (CD-LD) formulations, IPX203 and IPX066 (RYTARY®)

Background

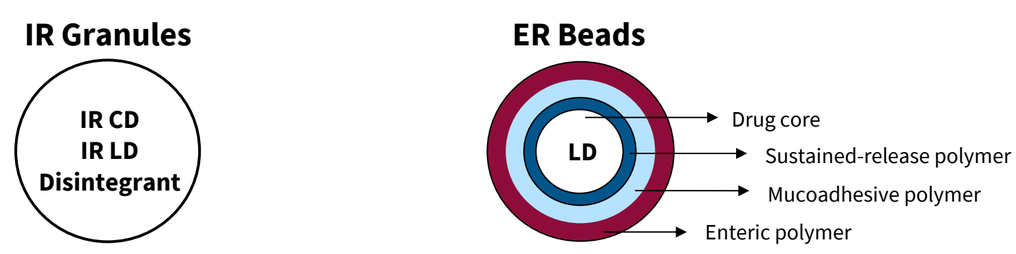
- Rytary is designed to provide fast-acting and long-lasting efficacy for up to 6 hours, containing four components[1]: (**Figure 1**)
  - Immediate-release (IR) granules consist of CD and LD with rapid drug release profile
  - Two types of ER beads having distinct release profiles, consist of CD and LD, coated with enteric polymers to allow for the delayed and slower release of CD-LD
  - A functional excipient designed to enhance the absorption of LD
- IPX203 is designed to provide fast-acting and long-lasting efficacy for approximately 8 hours and to address the short half-life and limited area of absorption for LD in the gastrointestinal tract; it contains two components[2]: (**Figure 2**)
  - IR granules consist of CD and LD with a disintegrant polymer to allow for rapid dissolution
  - 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 beads adhered to the area of absorption longer, and an enteric polymer to prevent the beads from disintegrating too early in the stomach

Figure 1. Rytary Formulation.



*Release-controlling polymer

Figure 2. IPX203 Formulation.



CD, carbidopa; ER, extended-release; IR, immediate-release; LD, levodopa.

Methods

- Phase 2a study: The pharmacokinetics (PK) and pharmacodynamics of IPX203 and Rytary were compared in a single-dose, open-label, rater-blinded, multicenter study in Parkinson's disease (PD) patients with motor fluctuations
- Phase 3 studies: "Good On" time per dose was analyzed from two separate phase 3, randomized, double-blind trials

The formulation designs of IPX203 and Rytary are distinctly different:
PK data shows a longer duration of LD plasma concentrations for IPX203 vs Rytary.
Pharmacodynamic data shows a longer duration of effect for IPX203 vs Rytary

PHASE 2A STUDY

Figure 3. Mean Levodopa Plasma Concentration Profiles After a Single Dose of IPX203, IR CD-LD, or Rytary.

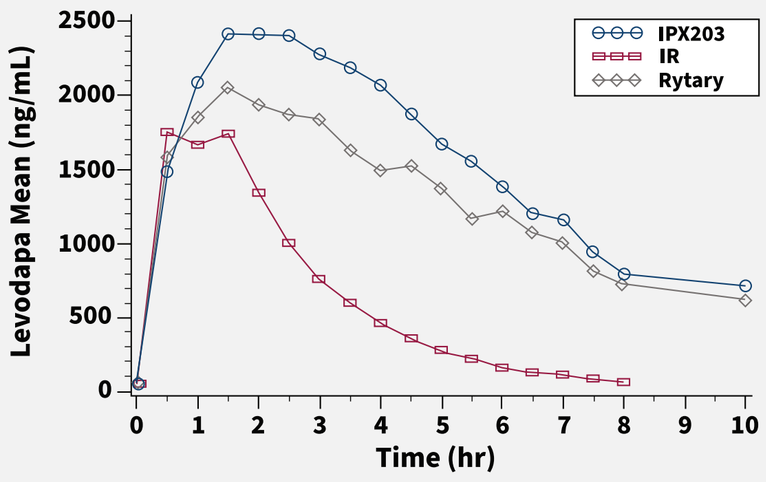
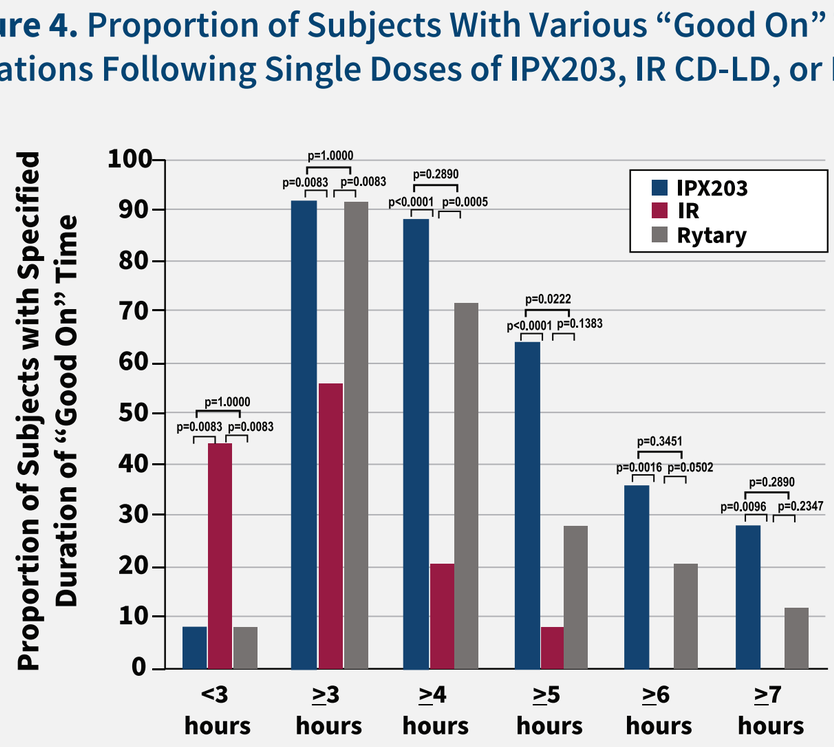
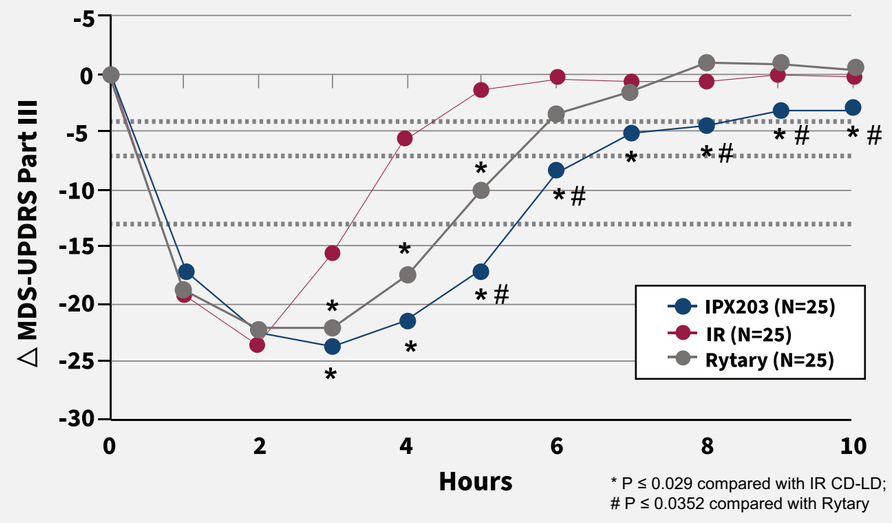


Figure 4. Proportion of Subjects With Various "Good On" Time Durations Following Single Doses of IPX203, IR CD-LD, or Rytary.



PHASE 2A STUDY

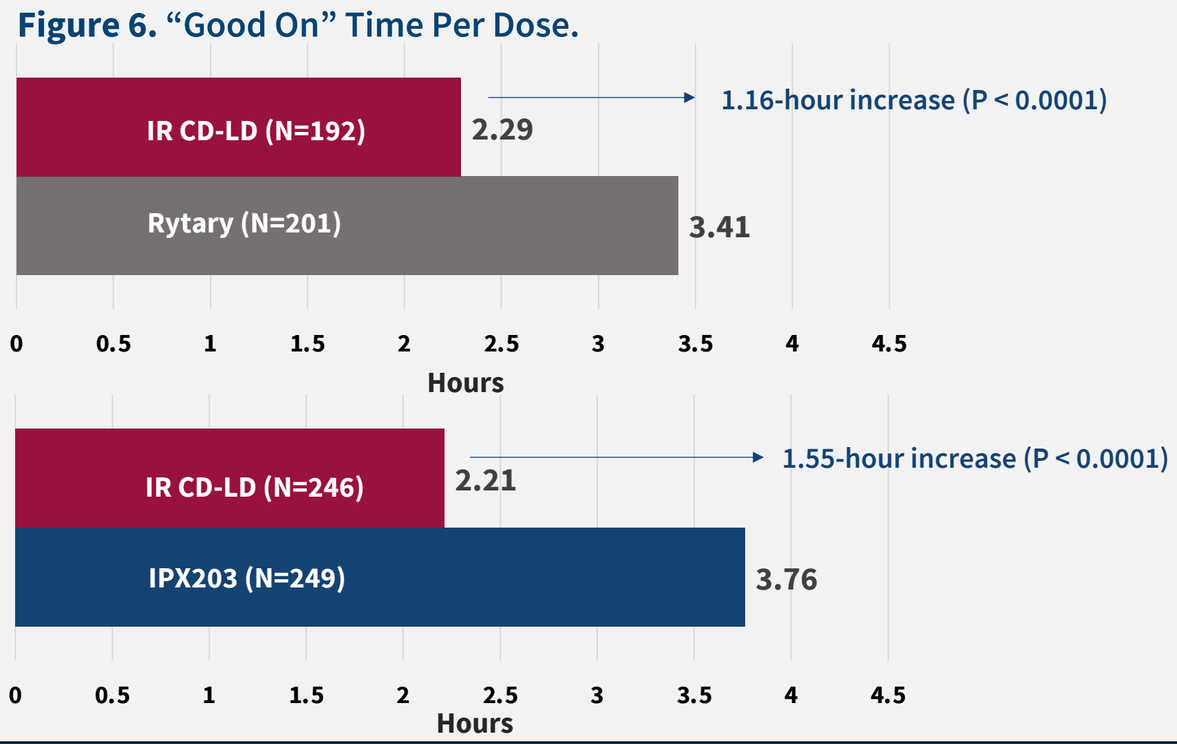
Figure 5. Mean Change From Average Predose MDS-UPDRS Part III Scores.



* P ≤ 0.029 compared with IR CD-LD;
# P ≤ 0.0352 compared with Rytary

POST HOC ANALYSIS OF TWO PHASE 3 STUDIES

Figure 6. "Good On" Time Per Dose.



Results

Phase 2a study:

- Results from a single-dose, open-label, phase 2a study in PD patients with motor fluctuations indicated that LD plasma concentrations were sustained >50% maximum concentration (C_{max}) for 4.6 and 3.9 hours for IPX203 and Rytary, respectively[3] (**Figure 3**)
- In the single-dose, phase 2 study, the mean "Off " time was 4.5 hours following IPX203 treatment and 5.4 hours following Rytary, demonstrating a 0.9-hour advantage for IPX203 over Rytary ($P = 0.023$)[3]
- The reduction in "Off " time with IPX203 was accompanied by a corresponding increase in "Good On" time, demonstrating 0.9 hours more "Good On" time vs Rytary ($P \leq 0.0259$). Following treatment with IPX203, a significantly larger proportion of subjects achieved at least 4, 5, 6, and 7 hours of "Good On" time compared with Rytary (**Figure 4**)[3]
- After IPX203 treatment, subjects experienced significantly greater improvement (decrease) from average predose Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III scores over 10 hours vs Rytary (−12.70 vs −9.33 units; $P = 0.0333$)[3] (**Figure 5**)
- Improvements in MDS-UPDRS part III scores were similar for IPX203 and Rytary treatments during the first 2 hours, consistent with the PK findings and suggestive of a similar onset of effect
- When examined hour by hour, IPX203 showed significant differences vs Rytary from 5-10 hours (all $P \leq 0.0352$), except at 7 hours where the improvement did not reach statistical significance ($P = 0.0601$) (**Figure 5**)

Results

Phase 3 studies:

- Post hoc analysis of "Good On" time per dose, derived from separate phase 3, randomized, double-blind trials, showed an increase of 1.16 hours for Rytary compared to IR CD-LD,[4] vs an increase of 1.55 hours for IPX203 vs IR CD-LD[5] (**Figure 6**)

Conclusions

- PK data indicated a longer duration of LD plasma concentrations for IPX203 vs Rytary
- Pharmacodynamic data indicated a longer duration of effect and improved MDS-UPDRS scores for IPX203 vs Rytary

References

1. Mittur A, et al. *Clin Pharmacokinet*. 2017;56(9):999-1014. 2. LeWitt P, et al. *Clinical Parkinsonism & Related Disorders* 2023; https://doi.org/10.1016/j.prdoa.2023.100197. 3. Modi NB, et al. *Clin Neuropharmacol*. 2019;42(1):4-8. 4. Hauser RA, et al. *Parkinsonism and Related Disorders*. 2021;82:133-137. 5. Hauser RA, et al. *JAMA Neurol*. 2023;80(10):1062-1069.

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