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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hopledo

International non-proprietary name: levodopa / carbidopa

Procedure No. EMEA/H/C/006629/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

3-OMD	3-O-Methyldopa
AADC	Amino Acid Decarboxylase
AdAM	Analysis Data Model
AE	Adverse Event
ak	Aphakia
ASMF	Active substance master file
AUC	Area under the curve
AUC _{0-t}	Area under the plasma concentration-time curve from time 0 to the last measurable concentration at time t
AUC _{0-∞}	Area under the concentration-time curve from time 0 extrapolated to infinity
AUEC	Area Under the Effect Curve
BBB	Blood-Brain Barrier
BCS	Biopharmaceutics Classification System
BMC	Butylated methacrylate copolymer
BMI	Body Mass Index
BP	Blood Pressure
BSE/TSE	Bovine spongiform encephalopathies/Transmissible spongiform encephalopathies
C _t	Concentration at time <i>t</i>
CA	Cellulose Acetate
cAMP	Cyclic Adenosine Monophosphate
CD	Carbidopa
CEP	Certificate of Suitability of the European Pharmacopeia
CGI-S	Clinical Global Impression of Severity
CHMP	Committee for Medicinal Products for Human Use
CKD	Chronic Kidney Disease
C _{max}	Maximum observed plasma concentration
CNS	Central Nervous System
COMTI	Catechol-O-methyltransferase inhibitors
CPPs	Critical process parameters
CQAs	Critical quality attributes
CR	Child resistant; Controlled-release
eCRF	electronic case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
D2R	Dopamine D2 Autoreceptor
DA	Dopamine
DAs	Dopamine Agonists

DAT	Device-Aided Therapy
DBS	Deep Brain Stimulation
DCP	Decentralised Procedure
DDC	Dopa Decarboxylase
DDCI	Dopa Decarboxylase Inhibitor
DDI	Drug-Drug Interaction
DHP	3,4-dihydroxyphenylacetone
DLP	Data Lock Point
DNA	Deoxyribonucleic Acid
DOPAC	Dihydroxyphenylacetic Acid
DRN	Dorsal Raphe Nucleus
DRNCHMP	Dorsal Raphe Nucleus Committee for Medicinal Products for Human Use
EC	European Commission
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
EMSQ	Early Morning Symptoms Questionnaire
EOS	End of Study (visit)
ER	Extended Release
ERA	Ecotoxicity/environmental risk assessment
EU	European Union
FDA	US Food and Drug Administration
FRCs	Functional related characteristics
GBD	Global Burden of Disease
GCP	Good clinical practice
GCSI	Gastroparesis Cardinal Symptom Index
GD	Gestation Day
GDEMA	Gestation Day European Medicines Agency
GDNF	Glial Cell Line-derived Neurotrophic Factor
GI	Gastrointestinal
GIPD	Gastrointestinal Pharmacodynamics
GLP	Good Laboratory Practice
GMP	Good manufacturing practice
GPI	Globus Pallidus Interna
GRAS	Generally Recognised as Safe
GRASPK	Generally Recognised as Safe Pharmacokinetics
HCP	Healthcare Professionals
HDPE	High-density polyethylene
HPLC	High-performance Liquid Chromatography
HVA	Homovanillic Acid

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IA	Intra-aortic
ICH	International Conference on Harmonisation
ICP/MS	Inductively Coupled Plasma/Mass Spectrometry
IIG	Inactive Ingredients Database
IM	Intramuscular
IPSmPC	Intraperitoneal Summary of product characteristics
IP	Intraperitoneal
IPA	Isopropyl alcohol
IPC	In-process control
IPX203	Hopledo
IR	Infrared; Immediate release
IV	Intravenous
k _e	Elimination constant
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LD	Levodopa
LD ₅₀	Lethal Dose 50
LID	Levodopa-induced dyskinesia
LLOQ	Lower limit of quantification
LNAA	Large neutral amino acid
LOD	Loss on drying
Max	Maximum
MAO	Monoamine Oxidase
MAOI	Monoamine Oxidase Inhibitor
MDS-UPDRS	Movement Disorders Society-Unified Parkinson's Disease Rating Scale
Min	Minimum
MMC	Methyl methacrylate copolymer
MoA	Mechanism of Action
MoCA	Montreal cognitive assessment
MPTP	1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine
MR	Modified-Release
MRI	Magnetic Resonance Imaging
MVTR	Moisture vapour transmission rate
NF	National Formulary
NMSS	Non-Motor Symptom Assessment Scale
6-OHDA	6-hydroxydopamine
OLE	Open-Label Extension
3-OMD	3-O-methyldopa
OOS	Out of specification
OP	Oscillatory Potentials

PADERS	Periodic Adverse Drug Experience Report
PARs	Process acceptable ranges
PAS	Parkinson Anxiety Scale
PD	Pharmacodynamics; Parkinson's disease
PDE9	Phosphodiesterase 9
PDQ 39	39-item Parkinson's Disease Questionnaire
PDSS-2	Parkinson's Disease Sleep Scale-2
PGI-C	Patient Global Impression of Change
PGI S	Patient Global Impression of Severity
Ph.Eu.	European Pharmacopeia
PK	Pharmacokinetics
popPK	Population PK
PP	Polypropylene; Per protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
QbD	Quality by design
QC	Quality control
QID	Four times a day
QP	Qualified person
QTPP	Quality target product profile
R	Resistant
RMP	Reference Medicinal Product; Risk Management Plan
RSD	Relative standard deviation
S	Susceptible
SAE	Sepsis-associated encephalopathy
SAS	Safety Analysis Set
SC	Subcutaneous
SD	Standard deviation
SmPC	Summary of product characteristics
SOC	System Organ Class
SR	Sustained-Release
STN	Subthalamic Nucleus
STZ	Streptozotocin
$t_{1/2}$	Terminal elimination half-life; Mean apparent half-life
TBM	To-be-marked
TDD	Total Daily Dose
TEC	Triethyl citrate
TID	Three times a day
t_{max}	Time to Reach Maximum Concentration After Drug Administration (or Time at Which the Maximum Plasma Concentration Occurred)

TSA	Treatment Satisfaction Assessment
TSB	Tryptic soy broth
US	United States
USP	United States Pharmacopeia
UV	Ultraviolet
V/F	Apparent volume of distribution
ZBI-12	12-Item Zarit Burden Interview

1. Regulatory information and recommendations on the procedure

1.1. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Eligibility to the centralised procedure

The applicant Zambon S.p.A. submitted on 31 May 2025 an application for marketing authorisation (MA) to the European Medicines Agency (EMA) for Hopledo (levodopa/carbidopa), through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2025.

The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication:

- Treatment of adult patients with Parkinson's disease and moderate to severe motor fluctuations who cannot be stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment and/or other available Parkinson oral medicinal products.

1.3. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is:

- Composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain test(s) or study(ies);
- A fixed-dose combination medicinal product.

1.4. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision (EMA/PE/0000258095) on the granting of a product-specific waiver on the grounds set out in Article 11(1)(c) of said Regulation for the above-mentioned medicinal product. The waiver applies to all subsets of the paediatric population from birth to less than 18 years of age.

1.5. Information on orphan market exclusivity

Not applicable.

1.5.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.6. Steps taken for the assessment of the product

The rapporteur and Co-Rapporteur appointed by the CHMP were:

rapporteur:	Fátima Ventura
Co-rapporteur:	Ewa Balkowiec Iskra

The application was received by the EMA on	31 May 2025
The procedure started on	17 July 2025
The CHMP rapporteur's first assessment report was received on	15 October 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	16 October 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	17 October 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	13 November 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 February 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs' joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	31 March 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 April 2026
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	23 April 2026
The applicant submitted the responses to the CHMP list of outstanding issues on	25 May 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs' Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	12 June 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Hopledo on	25 June 2026

During the assessment of the application for the marketing authorisation of Hopledo, the following non-EU authorities were allowed to participate as part of the OPEN framework and contribute to the scientific

discussions of the CHMP:

- Health Canada (1st round of assessment; CHMP plenary meeting held on 10-13 November 2025).

This authority did not participate in the overall benefit/risk determination, which was decided by the CHMP.

1.7. CHMP outcome

1.7.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this assessment report (AR).

1.7.2. Considerations related to orphan market exclusivity

Not applicable.

1.7.2.1. Similarity with authorised orphan medicinal products

Not applicable.

1.7.2.2. Derogation(s) from market exclusivity applicable to similar orphan products

Not applicable.

1.7.3. CHMP Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Hopledo is favourable in the following indication(s):

- Treatment of adult patients with Parkinson's disease and moderate to severe motor fluctuations who have not been sufficiently stabilised with oral levodopa/dopa decarboxylase (DDC) inhibitor-based treatment regimens.

1.7.4. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

1.7.5. Other conditions and requirements of the marketing authorisation

1.7.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines' web-portal.

Considering that (e.g., with regard to the therapeutic indication, posology, pharmaceutical form) Hopledo does not differ significantly from the already approved products containing carbidopa/levodopa, the CHMP is of the opinion that Hopledo should be added to the existing entry in the EURD list for carbidopa/levodopa (NAP). Therefore, Hopledo should follow a 3-year PSUR cycle. The next data lock point (DLP) will be 1 October 2028.

1.7.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.7.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.7.6.2. Additional risk minimisation measures

Not applicable.

1.7.6.3. Obligation to conduct post-authorisation measures

Not applicable.

1.7.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

1.7.8. Proposed list of recommendations

Not applicable.

2. Introduction

2.1. Therapeutic context

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterised by the loss of dopaminergic neurons. According to the Global Burden of Disease (GBD) 2021 study, the global prevalence of PD was estimated at 138.6/100,000 people and caused 388000 deaths in the world population. By 2035, age-standardised rates of incidence and prevalence will increase from

14.62/100,000 and 139.79/100,000 in 2021 to 20.20/100,000 and 165.05/100,000, respectively (Luo *et al* 2025). In Europe, in a projection between 2021 and 2050, the all-age prevalence of PD was estimated between 152/100,000 and 267/ 100,000, respectively (Su *et al* 2025).

Sinemet®, an immediate release (IR) formulation, was approved by the Food and Drug Administration (FDA) in 1975 as a fixed dose combination of levodopa and carbidopa (LD-CD). In Europe, Sinemet® and Madopar® (containing the fixed dose combination of levodopa and benserazide - LD-BZ), were also approved at the same time. The IR LD-CD formulation offers rapid absorption but is quickly degraded in the periphery. The elimination half-life of LD following Sinemet IR administration was approximately 1.5 hours. Controlled-Release (CR) Sinemet (Sinemet CR 2023), the first CR-LD formulation, was approved in the European Union (EU) in 1990 and in the United States (US) in 1991. CR LD-CD is a polymeric-based drug delivery that slowly erodes and releases LD-CD. Nowadays it is usually administered only for the night-time symptoms of PD to supplement IR LD-CD. After a single dose in healthy young and elderly adult subjects, the mean time to maximum LD concentration (T_{max}) was 1.8 to 2.1 hours for the CR LD-CD versus 0.5 to 0.8 hours for the IR LD-CD, with a maximum observed plasma concentration (C_{max}) approximately one-third of that noted following IR LD-CD (Yeh *et al* 1989). In clinical trials of Sinemet CR, patients with moderate to severe motor fluctuations did not experience significant reductions in “Off” time versus Sinemet IR (Sinemet CR 2023). CR LD-CD has less predictable symptom relief than IR LD-CD (LeWitt *et al* 2023; Sinemet CR 2023).

Levodopa, in combination with carbidopa, is considered an efficacious treatment for the motor symptoms of PD, and nearly all PD patients require LD treatment as the disease progresses (Jankovic and Poewe 2012). Despite the available treatment options, including adjunctive therapies and rescue medications, disease progression and LD exposure are the major factors in the development of motor complications, and most patients with PD experience motor complications, including wearing-off and peak-dose dyskinesias after several years of LD treatment (Fabbri *et al* 2023).

As PD progresses, the response to IR LD-CD and CR LD-CD becomes less reliable. To maintain symptom control, it is often necessary to increase the daily dose of levodopa, divide the LD-CD intake into smaller, more frequent doses, and use adjunctive therapies. As dopaminergic medications become less effective, many PD patients experience motor fluctuations, which they report as the most challenging aspect of the disease. These fluctuations typically emerge after several years of levodopa therapy and tend to increase in severity as the disease progresses, though the pattern can vary between patients.

In the 1990’s, two catechol-O-methyl transferase (COMT) inhibitors, entacapone (Comtan®) and tolcapone (Tasmar®) were approved by the European Medicines Agency (EMA) as adjunct medications to be combined with LD in patients with motor fluctuations (Comtan SPC 2024, Tasmar SPC 2022). In 2016, the COMT inhibitor opicapone (Ongentys®) was approved by the EMA.

As PD further progresses, motor fluctuations tend to intensify and lose predictability, resulting in a broader range of possible presentations:

- On-off phenomenon may arise: rapid switches between the “On” and “Off” states may appear along with sudden “Off”, seemingly without obvious relationship to levodopa dosing;
- Patients can notice an increased latency after LD intake for the beginning of the clinical benefit (delayed “On”), even after the first-day dose (“prolonged morning akinesia”);
- A complete failure to respond to a levodopa dose (No “On”) can happen (Fabbri *et al* 2023);

Moreover, motor fluctuations tend to worsen over time, even with optimised oral or transdermal therapies, eventually leading to a point where adequate symptom control can no longer be achieved with these treatment options. At this stage, patients usually become eligible for a device-aided therapy

(DAT) (Deuschl *et al.* 2022). DATs are invasive treatments that require permanent access to the patient's body via a catheter or stimulator and necessitate careful monitoring to ensure tolerability. DATs can be used when motor fluctuations cannot be adequately controlled with an oral medication. They aim to reduce dopaminergic sensitivity by delivering continuous (instead of a pulsatile) stimulation of the dopaminergic terminals. The ideal candidate for DAT should generally have shown good response to previous LD treatment, absence of cognitive impairment and an age threshold of 70 years (75 years old for deep brain stimulation).

The following DATs are available in EU:

- Duodopa® (approved in the EU in 2005) is a gel formulation of LD and CD for continuous intestinal administration for PD patients with severe motor fluctuations and hyperkinesia or dyskinesia. In 2022 the subcutaneous (SC) formulation of foslevodopa/foscarbidopa, was also approved in the EU as Produodopa® for the same indication as Duodopa®.
- APO-go® (SC apomorphine, a short-acting dopamine agonist) has been approved since 2014 for the treatment of motor-fluctuations in PD patients who are not sufficiently controlled by oral anti-PD medication.
- Onerji, approved in 2026, is a formulation of LD and CD administered as a continuous solution for SC infusion using a specialised portable delivery pump system (Yurway Delivery System or Crono Twin ND pump). It is indicated for the treatment of motor fluctuations in patients with advanced PD not sufficiently controlled by oral anti-Parkinson medicinal products. Onerji is administered with a levodopa oral morning dose. Additional oral LD can be prescribed as needed. If required, other classes of medicinal products for PD can be taken concomitantly with Onerji and adjusted as needed.
- Deep Brain Stimulation (DBS) (approved in the EU in 1998, Gardner, 2013) is based on the finding that high-frequency (100-200 Hz) electrical stimulation of specific brain targets can mimic the effect of a lesion without the need to destroy brain tissue. It requires the implantation of an electrode into the brain tissue.

Electrodes for DBS are implanted in the subthalamic nucleus (STN) and in the globus pallidus interna (GPI). Deep Brain Stimulation of the STN has demonstrated significant antiparkinsonian efficacy and is now an established, evidence-based treatment for managing motor fluctuations and dyskinesia in patients with advanced PD (Poewe 2017). Deep Brain Stimulation enables a continuous stimulation, where three main parameters can be adjusted to obtain the maximal benefit with least adverse events (AEs). Despite their efficacy, the effect of DBS remains symptomatic, and no disease-modifying effect has been proved. At the same time, not all patients with advanced PD will be willing to implement DBS and some of them will have a contraindication (e.g., older age, cognitive impairment). Once implanted, patients with deep brain stimulators should not undergo full-body magnetic resonance imaging scans (MRIs), transcranial magnetic stimulation, or diathermy (Pycroft *et al.* 2018).

- Kynmobi®, a sublingual apomorphine strip, was approved by the FDA in 2020 (and discontinued by the MAH for commercial reasons in 2023), by Health Canada (and in the EU via a decentralised procedure – DCP) in 2023 to treat "Off" episodes.
- Inbrija®, an inhaled LD, was approved by the EMA in 2019 for the treatment of individual "Off" episodes.

Currently, there is no curative or disease-modifying treatment available for PD. Fluctuating response to medication was identified as the top concern among patients with PD.

No long-acting preparation of LD is available in the EU that would combine the advantages of IR and ER components in a modified-release (MR) LD-CD oral combination. In 2015 Numient, the 1st generation MR oral formulation was registered through a centralised procedure in the EU and withdrawn in 2019 without being commercialised.

2.2. Aspects of development

IPX203 was developed by a company subsidiary of Amneal Pharmaceuticals LLC (with which Zambon has an agreement in place for Europe).

IPX203 is a second-generation MR LD-CD formulation proposed for the treatment of adult patients with PD and moderate to severe motor fluctuations who cannot be stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment and/or other available PD oral medicinal products.

The IPX203 program has been conducted in line with the principles of the relevant guidelines for drug development and with the "Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease" (EMA/CHMP/330418/2012, 2012 rev. 2). All biopharmaceutics and clinical pharmacology studies were conducted according to relevant regulatory guidelines. All safety and efficacy clinical studies were also conducted in accordance with applicable regulatory guidance, ensuring compliance with the current Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

No scientific advice has been requested to the CHMP for IPX203. Previous interactions between the applicant and the EMA/CHMP regarding IPX203 included written pre-submission interactions, in January 2025 and a (Co)-Rapporteurs' meeting held on 18 March 2025, upon EMA product team recommendation, as detailed in the pre-submission interactions response dated 31 January 2025. At the meeting, the legal basis initially proposed by Zambon [Article 10(3) of Directive 2001/83/EC], with a proposed Reference Medicinal Product (RMP), was challenged, because the PK/PD clinical study selected to be pivotal for bridging the RMP data was conducted using batches of a corresponding levodopa/carbidopa prolonged-release product authorised outside the EU instead of batches of a product authorised in the EU. In line with these recommendations, Zambon submitted a full mixed application in accordance with Article 8(3) of Directive 2001/83/EC (known Active substances).

The proposed indication for IPX203 is the treatment of adult patients with PD and moderate to severe motor fluctuations who cannot be stabilised on DDC inhibitor treatment and/or other available PD oral medicinal products. The IPX203 clinical development program includes:

- Three Phase 1 PK studies in healthy volunteers (Study **IPX203 B16 04**, Study **IPX203 B16 05**, and Study **IPX203-B16-06**);
- Two Phase 2 studies, a single-dose PK, pharmacodynamics/efficacy, and safety study in advanced PD patients (Study **IPX203-B14-02**), where both Rytary/Numient (MR LD-CD) and Sinemet (IR LD-CD) were used as references, and a single and multiple-dose PK, pharmacodynamics, efficacy, and safety study in advanced PD patients (Study **IPX203 B16 01**).
- Two Phase 3 studies, a randomised, double-blind, double-dummy, active-controlled, parallel-group, prospective study in PD patients with motor fluctuations (Study **IPX203-B16-02**), and an open-label 9-month extension study in PD patients with motor fluctuations (Study **IPX203 B16 03**).

2.3. Description of the product

Hopledo (IPX203) is a novel oral modified release (MR) LD-CD multi-particulate capsule formulation, with a proprietary innovative release system which allows a better targeting of the active ingredient and a more efficient therapeutic action. Hopledo has two components: an immediate-release (IR) component I in granules, and an extended-release (ER) component II, as coated beads. There are functional excipients designed / intended to:

- prevent pellets disintegration in the stomach;
- prolong residence within the gastrointestinal tract and support extended drug adsorption. The exact site and duration of absorption are unknown;
- provide sustained drug release.

The formulation was developed and designed to combine dual-release mechanism and thereby provide fast attainment of therapeutic LD plasma concentrations to ensure early onset of effect, and to maintain the desired concentrations for a longer duration with minimal peak-to trough-fluctuations than provided by the authorised oral administered LD-CD products. When administering IPX203, LD from IR granules produces an initial boost of LD exposure, with a rapid onset of effect followed by a continuous LD supply from the ER beads. With prolonged duration of stable therapeutic concentrations after each dose, IPX203 is designed to provide better control of PD symptoms, fewer motor fluctuations or unfavourable side effects such as dyskinesia, less frequent dosing, enhanced patient compliance, and possibly improved quality of life in PD patients. Additionally, IPX203 design would allow for dosing intervals of approximately 6-8 hours (3 times/day, range: 2 to 4 times/day) in patients with PD with motor fluctuations.

This product formulation was designed to avoid the limitation of slow initial release and the consequent latency to improvement of motor symptoms seen with CR formulations.

This product was authorised in the US on 7 August 2024, under the brand name Crexont™ and is marketed by Amneal. Subsequently, Zambon signed an agreement with Amneal to apply for IPX203 MA in the EU. The proposed legal basis for the IPX203 marketing authorization in EU is a full-mixed application under Article 8(3) of Directive 2001/83/EC.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

The CHMP agreed that no inspection was required.

2.4.2. Good laboratory practice (GLP) inspection(s)

Some nonclinical studies were conducted and published before 1980 due to the research timeline in this field. These studies were not conducted in accordance with Good Laboratory Practice (GLP) conditions. However, the review of these pre-GLP published studies outlined consistency in the reported findings in comparison to those studies performed post-GLP. Furthermore, the quality of these investigations corresponds to that of most studies conducted for other medicinal products during the same period of time. The CHMP agreed that, overall, these studies provided a clear overview of the properties of LD and CD, and additional studies adhering to the current GLP requirements did not reveal new information.

In summary, the CHMP agreed that no GLP inspection was required

2.4.3. Good clinical practice (GCP) inspection(s)

No ethical or clinical issues have been suspected from the assessment of the clinical trials presented in this initial MAA submission.

Therefore, the CHMP agreed that no inspection was required.

3. Quality aspects

3.1. Introduction

The finished product is presented as modified-release hard capsules containing 140 mg, 210 mg, 280 mg and 350 mg of levodopa and carbidopa monohydrate equivalent to 35 mg, 52.5 mg, 70 mg and 87.5 mg carbidopa as active substances.

Other ingredients are:

Capsule contents: microcrystalline cellulose, mannitol, sodium lauryl sulfate, povidone, cellulose acetate, copovidone, basic butylated methacrylate copolymer, talc (E553b), triethyl citrate (E1505), croscarmellose sodium, magnesium stearate, methacrylic acid and methyl methacrylate copolymer (1:1)

Capsule shell: gelatine, titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), quinoline yellow (E104), brilliant blue FCF (E133), and erythrosine (E127)

Printing ink: shellac glaze 45% (E904), ferrousferic oxide/iron oxide black (E172), propylene glycol (E1520), ammonium hydroxide 28% (E525), shellac NF (E904), sodium hydroxide (E524), povidone, and titanium dioxide (E171).

The product is available in opaque, white, high-density polyethylene (HDPE) bottle with a white polypropylene (PP) child resistant screw closure fitted with an induction inner-seal. Desiccant, silica gel in high-density polyethylene fibre packs, is included in the bottle as described in section 6.5 of the SmPC.

3.2. Active substance – Carbidopa

There is a monograph of carbidopa in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for carbidopa which has been provided within the current Marketing Authorisation Application.

3.2.1. General information

The chemical name of carbidopa is (2S)-3-(3, 4-dihydroxyphenyl)-2-hydrazino-2-methyl propanoic acid corresponding to the molecular formula $C_{10}H_{14}N_2O_4 \cdot H_2O$. It has a relative molecular weight of 244.24 and the following structure:

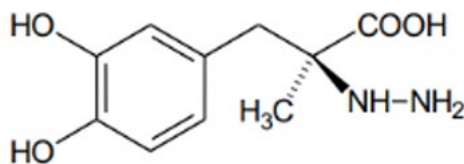


Figure 1: Carbidopa structure

Characterisation of the active substance is covered by the Certificate of Suitability, and the control of potential mutagenic impurities is considered adequately addressed.

Carbidopa is a slightly hygroscopic white or yellowish white powder slightly soluble in water, practically insoluble in methylene chloride, soluble in dilute solution of mineral acids.

Carbidopa exhibits stereoisomerism due to the presence of one chiral centre. The 2S laevorotatory form is used as therapeutic agent. Enantiomeric purity is controlled routinely.

Polymorphism has not been observed for carbidopa.

3.2.2. Manufacture, characterisation, and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability (CEP).

The active substance is manufactured at one manufacturing site. Satisfactory GMP documentation has been provided.

The packaging is described in the current CEP.

3.2.3. Control of active substance

Specifications

Carbidopa specification applied by the finished product manufacturer includes tests for appearance (visual), identification (IR), appearance of solution (Ph. Eur.), specific optical rotation (Ph. Eur.), hydrazine (Ph. Eur.), related substances (Ph. Eur.), loss on drying (Ph. Eur.) sulphated ash (Ph. Eur.), assay (HPLC), para toluene sulfonic acid (HPLC), residual solvents (GC), particle size analysis (Lasser). The specification is in line with the current version of Ph. Eur. monograph for carbidopa and with current CEP. The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for selected additional quality attribute. All additional methods have been adequately validated and described according to ICH Q2.

Batch analysis

Batch analysis data (three commercial scale batches) of carbidopa are provided. The results are within the specifications and consistent from batch to batch.

3.2.4. Stability

The proposed re-test period is covered by the current Certificate of Suitability.

3.3. Active substance – Levodopa

There is a monograph of levodopa in the European Pharmacopoeia (Ph.Eur.), the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for levodopa which has been provided within the current Marketing Authorisation Application.

3.3.1. General information

The chemical name of levodopa is (2S)-2-amino-3-(3,4 dihydroxyphenyl) propanoic acid corresponding to the molecular formula $C_9H_{11}NO_4$. It has a relative molecular weight of 197.2 and the following structure:

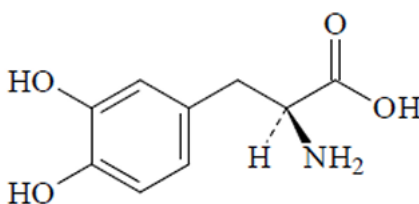


Figure 2: Levodopa structure

Levodopa is a non-hygroscopic white or almost white, crystalline powder freely soluble in 1M hydrochloric acid, sparingly soluble in 0.1 M hydrochloric acid, slightly soluble in water and practically insoluble in ethanol (96%)

Levodopa exhibits stereoisomerism due to the presence of one chiral centre. The asymmetric centre has the "S" absolute configuration. Enantiomeric purity is controlled routinely by chiral HPLC/specific optical rotation.

Polymorphism has not been observed for levodopa.

3.3.2. Manufacture, characterisation, and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The active substance is manufactured at one manufacturing site. Satisfactory GMP documentation has been provided.

The packaging is described in the current CEPs.

3.3.3. Control of active substance

Specifications

Levodopa specification applied by the finished product manufacturer includes tests for: appearance (visual), identity (IR), appearance of solution (Ph. Eur.), pH (Ph. Eur.), related substances (HPLC), enantiomeric purity (Ph. Eur.), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), assay (HPLC), residual solvents (GC), and particle size (Lasser). The specifications are in line with the current version of Ph. Eur. monograph for Levodopa and with current CEP. The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have

been set for residual solvents and particle size. All additional methods have been adequately validated and described according to ICH Q2.

Batch analysis

Batch analysis data (three commercial scale batches) of levodopa are provided. The results are within the specifications and consistent from batch to batch.

3.3.4. Stability

The proposed re-test period is covered by the current Certificate of Suitability.

3.4. Finished medicinal product

3.4.1. Description of the product and pharmaceutical development

Description of the product

The finished product is presented as follows:

140 mg levodopa and 35 mg carbidopa: hard capsules with white opaque body and yellow opaque cap. Body imprinted with "140" in black ink and cap imprinted with "IPX203" in white ink. Filled capsules are 18 mm x 6 mm in size and contain white to off-white granules and beads.

210 mg levodopa and 52.5 mg carbidopa: hard capsules with white opaque body and green opaque cap. Body imprinted with "210" in black ink and cap imprinted with "IPX203" in white ink. Filled capsules are 20 mm x 7 mm in size and contain white to off-white granules and beads.

280 mg levodopa and 70 mg carbidopa: hard capsules with white opaque body and purple opaque cap. Body imprinted with "280" in black ink and cap imprinted with "IPX203" in white ink. Filled capsules are 23 mm x 8 mm in size and contain white to off-white granules and beads.

350 mg levodopa and 87.5 mg carbidopa: hard capsules with white opaque body and medium orange opaque cap. Body imprinted with "350" in black ink and cap imprinted with "IPX203" in white ink. Filled capsules are 23 mm x 9 mm in size and contain white to off-white granules and beads.

Pharmaceutical development

The goal of the finished product development was to develop a modified-release levodopa (LD) and carbidopa (CD) formulation which attains therapeutic LD plasma concentrations rapidly and maintains a therapeutic concentration profile for the duration longer than the currently approved products.

The capsules contain two components: component I contains immediate release (IR) granules and component II contains extended release (ER)-coated beads.

The formulation development focused on the design of a multiparticulate modified-release dosage form combining immediate-release and prolonged-release characteristics. The selected formulation was developed to support rapid onset of action while maintaining levodopa plasma concentrations over an extended period, thereby achieving the intended therapeutic profile.

The different product strengths are proportional and are distinguishable by colour, imprinting and size of the capsules.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The formulation development started with the quality target product profile (QTPP) which defined the critical quality attributes (CQAs). A comprehensive finished product Quality Target Product Profile (QTPP) was established which enabled the appropriate identification of the finished product critical quality attributes (CQAs)

Pharmaceutical development activities included formulation optimisation, development of an appropriate dissolution methodology and confirmation of in vivo product performance. The overall development programme supported the selection of the final formulation, establishment of a suitable control strategy and demonstration of comparable performance of products manufactured at the relevant manufacturing sites.

Manufacturing process development

The selected manufacturing process of each component of the finished product was based on the manufacturer's prior experience with a similar finished products consisting of the same combination of active substances. The manufacturing process was developed to produce immediate-release and modified-release components that together provide the intended release characteristics and therapeutic performance of the finished product. The final dosage form consists of hard capsules containing both formulation components. The manufacturing process for each component was characterised in order to identify which parameters were important to process predictability and to identify process parameters which may impact the component's CQAs. Characterisation studies were conducted during manufacturing process development and the scale-up from pilot batch to registration batch for each component of the finished product. Parameters which were found to influence the component or product CQAs based on the risk assessment activity were identified as impacting process parameters.

3.4.2. Manufacture of the product and process controls

The finished product is manufactured in a dedicated manufacturing site

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

- The manufacturing process consists of three main stages. Component I, a granule formulation manufactured by a wet granulation process, followed by drying, milling, and blending.
- Component II, a multi-particulate bead formulation manufactured by wet granulation, extrusion, spherization, drying, and screening process, followed by Wurster coating, drying and screening.
- Encapsulation, filling of Components I and II into hard gelatine capsule shells

The process is considered to be a nonstandard manufacturing process.

The description of the manufacturing process has been presented with all necessary relevant details, including equipment and normal operating ranges (NORs) for process parameters.

The IPCs are defined and specifications and analytical procedures are described.

Satisfactory process validation protocols and reports are presented for three batches manufactured at commercial manufacturing scale. The results support the consistency of the manufacturing process in meeting the IPCs and finished product specifications. The product processing times and hold times were qualified for the maximum allowable times during manufacturing. The IPCs are adequate for this type of manufacturing process and contribute to the ensuring consistent product quality. The consistency of the manufacturing process and the quality of the finished product were demonstrated based on extensive IPC, release and stability results obtained from the process validation batches.

Major steps of the manufacturing process have been validated by a number of studies on three full-scale batches per strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. All the results generated during the process validation met the acceptance criteria and it can be concluded that the manufacturing process of the finished product is fully validated for all product strengths. The in-process controls are adequate for this type of manufacturing process.

3.4.3. Control of Finished Product

Specifications

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC, HPLC/UV), loss on drying (Ph. Eur.), uniformity of dosage units (Ph. Eur.), dissolution carbidopa (HPLC), dissolution levodopa (HPLC), related substances (HPLC), assay carbidopa (HPLC), assay levodopa (HPLC), hydrazine (LC/MS), residual solvents (GC), and microbial limits (Ph. Eur.).

During evaluation, two Major Objections (MO) were raised on the control of the product for purity profile. Following submission of additional justification and supporting evidence by the applicant for both clinical and commercial batches of the finished product, the CHMP considered the objections satisfactorily addressed and the Major Objections were resolved.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The risk assessment of elemental impurities in the finished product evaluated the different potential sources of elemental impurities, including, active substances, excipients, manufacturing, equipment, container closure systems and water. The results showed that the elemental impurities in the finished product of all the batches met the requirements and are below the established control limit of 30% PDE. Based on the assessment, risk of presence of elemental impurities in the finished product is low and no control has to be included in the finished product specification.

Analytical procedures and reference standards

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis

Batch analysis results are provided for three commercial scale batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Container Closure system

The container closure system is opaque, white, high-density polyethylene (HDPE) bottle with a white polypropylene (PP) child resistant screw closure fitted with an induction inner. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

3.4.4. Stability of the product

The shelf life of 3 years and store in the original package due to sensitivity to moisture in the proposed container, as stated in the SmPC, is justified by the available stability data. Use 100 days after first opening of the bottle.

Real time stability data from 3 commercial scale batches per strength of finished product stored under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, appearance of container, loss of drying, dissolution, related substances, assay levodopa, assay carbidopa, hydrazine, and microbial limits. The analytical procedures used are stability indicating.

Stability studies were designed in accordance with applicable regulatory guidance, also based on ICH Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substance and Product and included representative container closure systems and commercial presentations. The data generated were considered supportive of the proposed shelf life and storage conditions for the marketed product; the batches used in stability studies are representative to those proposed for marketing.

All results were within the specifications with no significant changes in the tested attributes under long term and accelerated conditions.

Appropriate photostability and in-use stability studies were conducted in accordance with relevant regulatory requirements. No significant changes affecting product quality were observed, and the data supported the proposed product presentation, storage conditions and in-use use of the finished product..

The stability results justify the proposed shelf-life of 3 years and store in the proposed container due to sensitivity to moisture as stated in the SmPC (section 6.3) are acceptable. Use 100 days after first opening of the bottle.

3.4.5. Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

3.5. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner.

During the evaluation, two MOs were raised on the control of the product for purity profile. Appropriate additional justification and supporting information were provided by the applicant for both MOs, and the CHMP considered both issues satisfactorily addressed.

The results of the quality assessment indicate consistency and adequate control of the critical quality attributes relevant to product performance.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

3.6. Recommendation(s) for future quality development

Not applicable.

4. Non-clinical aspects

4.1. Introduction

Zambon submitted a full-mixed MAA under Article 8(3) of Directive 2001/83/EC, for LD and CD MR hard capsules (oral use), relying on pharmacology, pharmacokinetics (PK) and toxicology studies from the published literature, considering that the constituents of IPX203 (levodopa and carbidopa) have a well-established medicinal use with recognised efficacy and an acceptable level of safety.

Levodopa/carbidopa modified hard capsules are intended to provide improved control of plasma LD levels compared with currently available LD-CD products for the treatment of PD. Considering the available published nonclinical information, the long history of LD-CD for PD treatment, and the clinical data generated in the IPX203 clinical development program, no new nonclinical pharmacology, pharmacokinetic and toxicology studies were conducted with IPX203 by the Applicant in support of this application.

Fixed combinations of LD and CD have been used extensively worldwide for the treatment of PD since the 1970s. The safety and efficacy of these combinations have been established through numerous non-clinical studies reported in the literature and many decades of clinical dosing experience. To support the well-established safety and efficacy of LD and CD and summarise the findings from published non-clinical studies that might have an impact on the product labelling, the following search strategy was applied to retrieve articles related to pharmacology, PK, and toxicology of LD, CD, and LD:CD between January 2012 and June 2022 using EMBASE (Elsevier B.V.). The following search terms were applied:

('carbidopa plus levodopa'/mj OR 'carbidopa'/mj OR 'levodopa'/mj) AND ('animal pharmacology' OR (('animal'/exp OR animal) AND ('pharmacology'/exp OR pharmacology)) OR pharmacokinetics OR 'acute toxicity'/exp OR 'acute toxicity' OR toxicity OR 'repeated dose toxicity' OR 'target organ toxicity' OR (('target'/exp OR target) AND ('organ'/exp OR organ) AND ('toxicity'/exp OR toxicity)) OR 'genotoxicity'/exp OR genotoxicity OR 'mutagen testing'/exp OR 'mutagen testing' OR 'mutagenicity'/exp OR mutagenicity OR 'reproduction toxicity' OR (('reproduction'/exp OR reproduction) AND ('toxicity'/exp OR toxicity)) OR 'fertility'/exp OR fertility OR 'embryofetal toxicity' OR (embryofetal AND ('toxicity'/exp OR toxicity)) OR 'embryofoetal toxicity' OR (embryofoetal AND ('toxicity'/exp OR toxicity)) OR 'teratogenicity'/exp OR teratogenicity OR 'teratogenesis'/exp OR teratogenesis OR 'local tolerance' OR (local AND ('tolerance'/exp OR tolerance)) OR 'occupational exposure'/exp OR 'toxicity'/exp OR toxic*:de,ab,ti OR pharmacotox*:de,ab,ti OR neurotox*:de,ab,ti

OR cardiotox*:de,ab,ti OR nephrotox*:de,ab,ti OR immunotox*:de,ab,ti OR hepatotox*:de,ab,ti OR cytotox*:de,ab,ti OR immunocytotox*:de,ab,ti OR 'intoxication'/exp OR 'congenital disorder'/exp OR 'no-observed-adverse-effect level'/exp OR 'no-observed-adverse-effect level' OR 'no-observed-effect level'/exp OR 'no-observed-effect level' OR 'embryotoxicity'/exp OR embryotoxicity OR 'fetotoxicity'/exp OR fetotoxicity OR foetotoxicity OR 'safety pharmacology'/exp OR 'safety pharmacology' OR 'vital system' OR (('vital'/exp OR vital) AND system) OR 'autonomic nervous system'/exp OR 'autonomic nervous system' OR 'cardiovascular system'/exp OR 'cardiovascular system' OR 'respiratory system'/exp OR 'respiratory system' OR 'renal system' OR (('renal'/exp OR renal) AND system) OR 'urinary system'/exp OR 'urinary system' OR (urinary AND system) OR 'safety'/exp OR safety OR 'risk assessment'/exp OR 'risk assessment' OR 'adverse event'/exp OR 'adverse event' OR 'drug interactions'/exp OR 'drug interaction'/exp) AND [animals]/lim AND [01-01-2012]/sd NOT [16-06-2022]/sd.

Published pharmacological and safety pharmacology studies detailed beneficial and adverse effects of modifying brain and peripheral dopamine (DA) levels in laboratory animals via LD administration. The PK characteristics of LD, CD, and LD:CD, including absorption, distribution, metabolism, and excretion, are well characterised. Published literature on general toxicology of LD, CD, and CD:LD includes acute- and repeat-dose studies in mice, rats, dogs, and monkeys, an assessment of genetic toxicity and carcinogenicity, reproductive and developmental toxicology studies, as well as other toxicity, immunotoxicity and neurotoxicity studies.

Safety considerations of excipients and degradants present in the drug product were based on information obtained from the FDA Inactive Ingredients Database (IIG), FDA Generally Recognised as Safe (GRAS) food ingredient listings and notices, the United States Pharmacopoeia (USP)-National Formulary (NF), and Drug Master Files.

Following the review of the published literature above mentioned, Zambon concluded that there were no new relevant non-clinical findings that would have an impact on the product labelling.

Analytical methods

The analytical methods used to quantify levodopa (LD), carbidopa (CD) and their metabolites are described in the historical literature. Early studies employed radiolabelling at various carbon positions of LD and CD, enabling tracking of metabolic fate and excretion patterns in multiple species. Classical chromatographic techniques (e.g., gas-liquid and thin-layer chromatography) were used initially, while later studies employed more sensitive and specific methods such as high-performance liquid chromatography (HPLC) with electrochemical or mass spectrometry detection. Available data indicate acceptable assay sensitivity and specificity for the intended pharmacokinetic evaluations. Overall, the methods described appear appropriate and consistent with the standards applied at the time the studies were conducted and are considered acceptable in the context of the long-standing clinical use of LD and CD.

4.2. Pharmacology

4.2.1. Pharmacodynamics

4.2.1.1. Primary pharmacodynamics

The primary pharmacodynamic properties of LD and its combination with CD are comprehensively described in the published literature and considered adequately addressed in the present MAA.

Levodopa, a precursor of dopamine (DA), restores dopaminergic neurotransmission in the striatum through decarboxylation by aromatic L-amino acid decarboxylase (AADC), thereby compensating for the loss of dopaminergic neurons characteristic of PD. Carbidopa, a peripheral AADC inhibitor, prevents premature metabolism of LD in peripheral tissues, enhancing its delivery to the central nervous system (CNS).

The pharmacodynamic effects of LD and LD:CD have been consistently demonstrated in several well-established and pharmacologically relevant PD animal models, including 6-hydroxydopamine (6-OHDA)-lesioned rats and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned non-human primates. These studies have shown that LD administration resulted in increased striatal DA levels and improved motor behaviour. In animals with dopaminergic denervation, LD led to more pronounced behavioural effects than in intact controls, consistent with the hypersensitivity of DA-depleted systems.

In vitro and *in vivo* studies confirm that LD increases DA release both in brain slices and in whole animals, and these effects are potentiated by CD or benserazide co-administration. The observed enhancement of DA and its metabolites (e.g., Dihydroxyphenylacetic Acid [DOPAC], Homovanillic Acid [HVA]) in the striatum following LD:CD treatment provided further evidence of central dopaminergic activation. Moreover, studies demonstrated that the behavioural efficacy of LD is closely associated with increases in extracellular, rather than tissue, DA levels, supporting the relevance of extracellular DA as a pharmacodynamic biomarker.

Additional pharmacodynamic (PD) insights include the involvement of serotonergic terminals in LD metabolism and DA release in DA-denervated striatum, which may contribute to levodopa-induced dyskinesias (LID). Experimental interventions targeting serotonergic neurons or their receptors (e.g., 5-HT₁ agonists, D₂ autoreceptor gene transfer) have been shown to modulate this phenomenon, further elucidating the mechanism of LD's action and its long-term effects.

Taken together, in the applicant's view, the primary PD data available in the literature outlined the mechanism of action of LD:CD in the treatment of PD and are considered adequate to support the indication and posology proposed for IPX203. The relevance of the animal models used was considered acceptable. Therefore, no additional primary pharmacodynamic studies were deemed necessary.

4.2.1.2. Secondary pharmacodynamics

The secondary pharmacodynamic profile of levodopa (LD) was addressed throughout a selection of published studies that explored the potential effects of LD beyond its primary action in the central dopaminergic system. While these effects are not directly related to the treatment of PD, they may provide additional insights into the pharmacological activity and safety of LD.

The applicant summarised evidence of LD's effects in several non-motor domains, including neuroinflammation, visual and cognitive function, gastrointestinal motility and pain modulation. In models of sepsis-associated encephalopathy, LD administration improved cognitive outcomes and reduced neuroinflammatory markers, in part via D₁ and D₂ receptor mechanisms. In diabetic rat models, LD preserved retinal function and prevented progression of visual dysfunction, an effect associated with increased retinal DA levels. These findings suggested a broader neuroprotective potential of LD in disease states involving dopaminergic pathways or oxidative stress.

Furthermore, LD was shown to exert antinociceptive effects in rats, increasing the threshold for colonic distension via D₂ receptor activation, and to enhance synaptic plasticity in the hippocampus following global cerebral ischemia. While these findings do not bear directly on the claimed indication, they contributed to the understanding of the compound's pharmacodynamic profile and may support aspects of tolerability or ancillary clinical benefits observed in patients.

Overall, the secondary pharmacodynamic data were consistent with the known pharmacology of LD and provided no evidence of off-target activities that would raise concern. Although these studies are not pivotal for the benefit–risk assessment of Hopleto, they were informative and reinforced the plausibility of DA-mediated effects outside the striatum. No issues requiring further clarification were identified in this context, and no additional studies are considered necessary.

4.2.1.3. Safety pharmacology

The safety pharmacology profile of LD and CD was characterised throughout a wide range of published studies covering the CNS, cardiovascular, respiratory, and gastrointestinal (GI) systems in several animal species. While most of these studies were conducted prior to the implementation of the current ICH S7A and ICH S7B guidelines, the data are consistent and reflected the extensive clinical experience with LD/CD fixed combinations.

Regarding CNS effects, LD/CD administration has been shown to induce dose-dependent behavioural responses across species, including hyperactivity in rodents and motor alterations in monkeys. These effects were attributable to central dopaminergic stimulation and were consistent with the intended pharmacological action. Emesis, commonly observed in dogs, is mediated by stimulation of dopamine receptors in the chemoreceptor trigger zone and is attenuated by peripheral AADC inhibition with CD.

In the respiratory system, LD alone had limited effects on ventilation under normoxic and hypoxic conditions; however, a modest stimulation of ventilatory response was observed in combination with CD. These findings suggested that the central control of respiration may be modulated through dopaminergic mechanisms but with limited clinical relevance.

Cardiovascular studies demonstrated that LD can increase blood pressure (BP) via peripheral conversion to catecholamines, with secondary hypotension observed thereafter. In dogs and rats, intravenous LD induced transient pressor responses and, at higher doses, arrhythmias. Importantly, these effects were significantly reduced or prevented when LD was co-administered with CD, supporting the rationale for peripheral decarboxylase inhibition in clinical use.

Gastrointestinal effects of LD and CD include reduced gastric acid secretion, delayed intestinal transit, and modulation of smooth muscle tone. These effects were generally observed at high doses and are likely to reflect dopaminergic influences on enteric nervous system activity.

Overall, the safety pharmacology findings did not raise concerns and are consistent with the known pharmacological profile of LD/CD. The effects observed in animals are largely reflective of the clinical safety profile and appear to be dose-related, reversible, and consistent with dopaminergic stimulation. Although dedicated safety pharmacology studies were not conducted under GLP, the historical data are considered sufficient in the context of the long-standing clinical use of these substances.

No new safety signals emerged from the literature review, and no additional safety pharmacology studies are considered necessary.

4.2.1.4. Pharmacodynamic drug interactions

The pharmacodynamic interactions of levodopa, particularly in combination with carbidopa, have been addressed throughout a review of relevant non-clinical studies evaluating co-administration with compounds that may influence dopaminergic transmission or modulate motor function. These interactions are of particular importance in the context of Parkinson's disease, where polypharmacy is common.

The available literature demonstrated that the antiparkinsonian effects of LD can be potentiated by agents acting via complementary mechanisms. For example, co-administration with glial cell line-derived neurotrophic factor (GDNF) in MPTP-lesioned non-human primates enhanced the therapeutic

efficacy while reducing LD-associated adverse effects such as dyskinesia and vomiting. This suggested that neuroprotective or neurorestorative agents may synergise with LD therapy in advanced disease stages.

Further non-clinical studies indicated that co-administration of LD with remacemide hydrochloride, a glutamate receptor antagonist, or with phosphodiesterase 9 (PDE9) inhibitors, resulted in enhanced motor performance in PD models. These findings supported potential synergistic effects when LD is combined with agents targeting excitatory neurotransmission or intracellular signalling cascades.

In addition, the combination of LD/CD with opicapone, a catechol-O-methyltransferase (COMT) inhibitor, significantly increased plasma LD exposure in non-human primates, consistent with clinical pharmacokinetics and current treatment strategies. Similar enhancement of LD effects was reported with celecoxib, a COX-2 inhibitor, suggesting potential interactions involving neuroinflammation.

Taken together, the pharmacodynamic interaction data support the rationale for co-treatment strategies commonly used in clinical practice. No unexpected or deleterious interactions were identified, and the studies are consistent with the known mechanisms of action of LD and CD. These interactions are relevant for the optimisation of clinical therapy but do not alter the safety profile of the fixed LD/CD combination as such.

In conclusion, the pharmacodynamic interaction profile of LD/CD is well described and adequately supported by the published data. No further non-clinical studies are required in this regard.

4.2.2. Pharmacokinetics

4.2.2.1. Absorption

The absorption of LD and CD was described based on published studies in both animals and humans. LD is consistently shown to be rapidly absorbed, with peak plasma concentrations typically occurring within one hour after oral administration. However, the oral bioavailability of LD is limited due to extensive presystemic metabolism, with reported values around 35% in rats and dogs, and 30–50% in humans. CD is absorbed more slowly and incompletely, with time to peak levels between 1–2 hours in animals and 3–5 hours in humans. The co-administration of CD with LD enhances LD systemic exposure and prolongs its half-life, confirming its role in inhibiting peripheral AADC activity. The data also indicated that chronic administration of LD and CD does not significantly alter the peripheral pharmacokinetics of LD. The findings are in line with the known pharmacological properties and support the expected absorption behaviour of the fixed-dose combination.

4.2.2.2. Distribution

Distribution data for LD and CD were drawn from published studies in both animals and humans. LD distribution across tissues, including the gastrointestinal tract and brain, is mediated by the large neutral amino acid (LNAA) transport system, which may be subject to competition by dietary amino acids. LD is not highly protein-bound in plasma (<30%) and is evenly distributed between plasma and erythrocytes. Tissue distribution studies in rodents indicated an uptake of radiolabelled LD in multiple organs, including the brain, kidney, liver, lung, skin, pancreas and muscle. CD shows high concentrations in peripheral tissues such as kidney, liver, lungs, and intestines, but does not appear to cross the blood-brain barrier. Both LD and CD have been shown to cross the placenta in animal studies, and LD also in humans. Overall, the distribution profiles were consistent with the established knowledge and did not raise any new safety concerns. Overall, the data presented were considered adequate to support the distribution characteristics of the fixed combination.

4.2.2.3. Metabolism

The metabolic pathways of LD and CD are well described in the literature and consistent across species. LD undergoes rapid decarboxylation by AADC to dopamine in the GI tract and liver, accounting for its limited oral bioavailability. This decarboxylation is saturable and can be inhibited by CD. LD is also metabolised by the COMT to 3-O-methyldopa (3-OMD), and subsequently to other metabolites such as DOPAC and HVA. CD metabolism involves loss of the hydrazine group and formation of α -methyl derivatives, with no indication of toxicologically relevant species-specific metabolites. Importantly, LD and CD metabolism does not involve cytochrome P450 enzymes, minimising the risk of metabolic drug-drug interactions. The metabolic profiles described support the known pharmacological activity and safety of the substances and are adequate for the purpose of this MA application.

4.2.2.4. Excretion

Excretion data from literature indicate that both LD and its metabolites are primarily eliminated via the renal route in all species studied, with the majority of the administered dose recovered in urine within 24 hours. Only a small fraction is excreted as unchanged LD, confirming extensive metabolic conversion. CD is also primarily excreted in urine, with variable amounts of unchanged drug depending on species. Faecal excretion reflects incomplete absorption rather than biliary elimination. Excretion of both compounds in milk has been reported in rats, and transplacental passage has also been demonstrated. The excretion profiles are consistent with historical data and support the lack of accumulation or retention concerns. The data are considered sufficient and relevant for the proposed clinical use of the fixed-dose combination of LD and CD under evaluation.

4.2.2.5. Pharmacokinetic drug interactions

Co-administration with magnesium oxide reduced the plasma levels of both LD and CD in rats, consistent with human findings and likely due to altered GI absorption. Other interactions include increased LD exposure when administered with catechin, benserazide, and opicapone, as expected from inhibition of LD metabolism. These interactions are well understood and aligned with the known pharmacology of these substances. The data supported the need to consider possible absorption or metabolic interactions in clinical use but did not raise any new safety issues.

4.2.2.6. Other pharmacokinetic studies

Additional studies, such as those in hepatectomised rats, further supported the role of the liver in first-pass metabolism of LD. These findings reinforced the conclusion that pre-systemic metabolism is a major determinant of LD bioavailability, and that formulation's approaches designed to modify release and absorption profiles are pharmacologically justified. No new concerns arose from these supplementary data.

4.3. Toxicology

4.3.1. Single-dose toxicity

Data on single dose toxicity for levodopa, carbidopa and the two active substances in combination were provided from published literature. Reported oral LD₅₀ of levodopa in rats ranged from 1780 up to >8000 mg/kg; oral LD₅₀ of carbidopa in mice was 1750 mg/kg and, in male and female rats, 5610

and 4080 mg/kg, respectively. In mice, the oral LD₅₀ of a 1:10 mixture of carbidopa and levodopa was 3440 mg/kg.

4.3.2. Repeat-dose toxicity

Data on repeated dose toxicity for levodopa, carbidopa and the two active substances in combination were provided from published literature.

Repeated dose toxicity of LD was tested in rats and monkeys with a treatment duration of approximately 12 weeks in both species. Toxicity of CD was tested in rats, dogs and monkeys, with treatment durations up to 96 weeks, 34 weeks and 1 year, respectively. Toxicity of levodopa/carbidopa combinations, employing the two active substances in different proportions, was tested in rats, monkeys and minipigs with treatment durations up to 2 years, 1 year and 13 weeks, respectively.

Levodopa

The 12-week studies with LD alone showed no treatment-related effects in monkeys (which received levodopa at doses up to 1000 mg/kg/day). Organs with histopathological changes identified in rats included salivary glands and adrenals, at all tested doses (i.e., 250 to 1000 mg/kg/day), kidneys, at ≥ 500 mg/kg/day, and stomach, at 1000 mg/kg/day.

Carbidopa

For CD alone, the longer-term study in rats, with administration of doses of up to 135 mg/kg/day, revealed no effects other than a slight degree of flaccidity during the first year of the treatment. No pathologic changes related to carbidopa were observed in a shorter-term study (14-day) that employed doses up to 400 mg/kg/day.

The longer-term study with CD alone in dogs, with administration of 5, 15, 45, 135 mg/kg/day, showed tremors, emesis, soft stools or diarrhoea sometimes with blood in the faeces, anorexia, and weight loss at >15 mg/kg/day. At 135 mg/kg/day all dogs were killed in the 4th week, at 45 mg/kg/day, all dogs were killed in the 6th week; all other dogs survived until termination of the experiment. Another study in dogs, a 43-day study, revealed that coadministration of pyridoxine hydrochloride markedly attenuated the development of lesions associated with carbidopa administration.

In the studies with carbidopa alone conducted in monkeys, the animals received doses of up to 400, 45 and 135 mg/kg/day for 14 days, 86 days and 1 year, respectively. No significant effects were observed.

Levodopa/carbidopa combination

In rats, administration of LD in combination with CD resulted in reduced activity, ptialism, irregular respiration, and weakness or flaccidity at all doses investigated across all studies. Organs with histopathological changes included the stomach, adrenal and salivary glands, which were observed at the maximum tested dose (500 mg/kg/day of levodopa in combination with carbidopa [25, 50 and 100 mg/kg/day], tested in a 30-day study). These histomorphologic changes were attributed to LD.

Effects observed in the longest-term study in monkeys (1 year, with administration of up to 100/10 mg/kg/day levodopa/carbidopa) were limited to transient increase in activity (at 50/10 and 100/10 mg/kg/day levodopa/carbidopa), muscular incoordination and weakness (at 100/10 mg/kg/day levodopa/carbidopa). Deaths were observed in a shorter-term study (85 days) with administration of doses of 120/30 mg/kg/day levodopa/carbidopa.

A study in minipigs employed a formulation of LD/CD administrated by subcutaneous infusion. This study did not reveal any systemic effects. Only local effects were noted at the infusion sites.

4.3.3. Genotoxicity

Data from studies on genotoxicity of dopamine, levodopa and carbidopa were provided from published literature. Studies on the genotoxic potential of dopamine included an Ames assay, mouse lymphoma assay, sister chromatid-exchange analysis in human lymphocytes *in vitro*, DNA single strand breaks in human skin fibroblast *in vitro* and an *in vivo* micronucleus assay. Studies with LD included an Ames assay, *in vitro* micronucleus and *in vivo* micronucleus and Comet assay. Additionally, data was also provided on a clinical study with levodopa that investigated a potential induction of chromosomal damage in peripheral blood lymphocytes. Regarding CD, data was provided on an *in vivo* micronucleus and Comet assay.

According to available data, dopamine was positive (genotoxic) in the mouse lymphoma assay and in the assay for single strand breaks in human fibroblasts *in vitro*; it was negative in the remaining conducted assays.

Levodopa was weakly positive in the Ames assay and *in vitro* micronucleus assay and was positive in the *in vivo* micronucleus and Comet assays. In a clinical study, it has not induced an increase in the frequency of micronuclei in peripheral blood lymphocytes.

Carbidopa was negative in both *in vivo* micronucleus and Comet assays.

The observed positive results for dopamine in two *in vitro* assays were suggested to be related to the oxidation of dopamine and generation of reactive oxygen radicals, semiquinones, and quinones. For the genotoxicity observed for levodopa, reference was made to oxidative damage.

4.3.4. Carcinogenicity

No data on carcinogenicity-specific studies were provided. However, the repeated dose toxicity studies in rats with administration of carbidopa and LD/CD combination (lasting 2 years) did not provide any evidence of a carcinogenic effect.

4.3.5. Developmental and reproductive toxicity

Fertility

Regarding studies on fertility, submitted data from public literature were limited to information from a study in mice with near-lifetime dietary administration of levodopa. No effects were observed at 10 and 20 mg/g diet, but only at the maximum tested dose of 40 mg/g diet, the maximum tolerated dose, which showed a reduction in the number of pregnancies and offsprings. Therefore, SmPC section 4.6 details that *there are no data on the effects of levodopa or carbidopa on human fertility. No effects on fertility were observed in animal studies.*

Embryo-foetal development

Data was provided on embryo-foetal development studies with LD, CD and the two substances in combination. Studies with levodopa alone were conducted in mice and rabbits; with carbidopa alone and the combination, in mice, rats and rabbits.

Embryo-foetal development studies revealed foetal (e.g., visceral and skeletal) malformations in rabbits upon administration of LD or LD/CD combination. This information is reflected in SmPC section 5.3.

Prenatal and postnatal development

No data on conventional prenatal and postnatal development studies have been provided. Instead, information from literature was submitted, specifically pertaining to one study in mice, describing administration of LD from gestation day 11 up to birth, and one study on milk excretion of CD conducted in rats. The publications describing studies focusing on mice given LD revealed persistent increases in dopamine content in the brain and behavioural changes in the progeny. The study where rats received CD showed its excretion in milk.

The above is reflected in SmPC section 4.6, where it is stated that *levodopa and possibly levodopa metabolites are excreted in human milk. There is evidence that lactation is suppressed during treatment with levodopa. It is unknown whether carbidopa or its metabolites are excreted in human milk. Animal studies have shown excretion of carbidopa in breast milk.*

4.3.6. Toxicokinetics and exposure margins

Only published data were provided by the applicant. Toxicokinetic data were limited to one LD/CD combination study in minipigs receiving the fixed-dose combination via SC infusion.

4.3.7. Local tolerance

No data on dedicated local tolerance studies were submitted. This was considered acceptable by the CHMP.

4.3.8. Other toxicity studies

Data from published literature was provided on immunotoxicity and neurotoxicity. Studies on immunotoxicity were conducted with both LD and LD/CD combination; those on neurotoxicity, with LD.

Levodopa and the combination were found to suppress immuno-inflammatory skin reactions in mice and rats. Both *in vitro* and an *in vivo* study with LD revealed a potential neurotoxic effect.

4.3.9. Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) report was prepared in accordance with the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMA/CHMP/SWP/4447/00 Rev.1, 2024)*.

The justification for the absence of a complete ERA for LD and CD was documented separately for each active substance.

Levodopa and CD are naturally occurring substances, and the exclusion of an ERA is in line with Question 1, related to the Phase I Decision tree (Figure 2) of the above noted guideline:

- *In the case of medicinal products comprised of naturally occurring substances (e.g., vitamins, electrolytes, amino acids, peptides, proteins, nucleotides, carbohydrates and lipids) as active substances, the ERA may consist of a justification for not submitting ERA studies, as they are unlikely to result in significant risk to the environment. Alternatively, given their environmental fate and/or common presence, these products are unlikely to alter the concentration or distribution of the substance.*

Due to the nature of LD and CD, a risk to the environment arising from their use is therefore not expected. Levodopa/Carbidopa finished products currently approved and marketed in the EU for the treatment of Parkinson's disease patients are most commonly formulated as oral tablets. Hopedo prescribed use is not expected to increase significantly environmental exposure to LD/CD. This supported and contributed to the applicant's justification for not performing ERA studies for CD

following the prescribed use of Hopledo 140 mg/35 mg, 210 mg/52.5 mg, 280 mg/70 mg, and 350 mg/87.5 mg modified-release hard capsules.

The applicant's justification for the absence of ERA studies was accepted by the CHMP. In addition, the applicant applied suitable precautionary and safety measures to inform patients and healthcare professionals (HCPs), mitigate environmental risks, and promote environmental protection, in accordance with guideline EMEA/CHMP/SWP/4447/00, 2024.

4.4. Overall discussion and conclusions on non-clinical aspects

The PK profile of LD and CD, based on extensive published data, is also considered well established. Information submitted by the applicant adequately supported the description of absorption, distribution, metabolism, and excretion characteristics of both active substances. No new PK concerns have been identified.

The PD profile of LD and CD is well established and sufficiently characterised in the non-clinical literature. Data presented by the applicant are consistent across species, models and study types, providing robust support for Hopledo proposed indication and posology. Observed PD effects are predictable, reproducible and aligned with extensive clinical experience. No additional pharmacology studies were considered necessary by the CHMP to support this MA application.

Regarding toxicological data, no new non-clinical studies have been provided. Instead, published literature on single and repeated dose toxicity, genotoxicity, carcinogenicity, reproductive toxicity and other toxicity studies was submitted.

This information was considered sufficient: and no further studies were considered necessary by the CHMP.

With regard to non-clinical safety data, the wording included in Hopledo SmPC is generally consistent with that encountered for already approved medicinal products containing LD and CD.

Levodopa and CD active substances are natural compounds, the utilisation of which is unlikely to modify the concentration or distribution of these substances within the environment. Consequently, the authorisation of Hopledo (levodopa/carbidopa) 140 mg/35 mg, 210 mg/52.5 mg, 280 mg/70 mg, and 350 mg/87.5 mg modified-release hard capsules is not anticipated to pose an environmental risk.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The applicant claimed that the clinical trials presented in this initial MAA were performed in accordance with GCP.

In addition, it was also confirmed that the clinical trials conducted outside the European community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Based on the review of clinical data, the CHMP did not identify the need for a GCP inspection of the clinical trials included in this MAA dossier.

5.1.2. Tabular overview of clinical trials

Table 1: Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 1					
IPX203-B16-04	Randomised, single-site, open-label, single-dose, 3-treatment, 3-period, crossover 16 days	IPX203 Fed: IPX203 MR LD-CD 350-87.5 mg, 1 capsule after initiating standardised high-fat, high-calorie breakfast IPX203 Sprinkled on applesauce: IPX203 MR LD-CD 350-87.5 mg, 1 capsule of IPX203 contents sprinkled on 1 tablespoon of applesauce and swallowed without chewing. IPX203 Fasted: IPX203 MR LD-CD 350-87.5 mg, 1 capsule under fasted conditions Oral administration	Healthy participants Male: 27 Age: 30.11 ± 6.94 years	To assess the effect of a standardized high-fat meal on the PK of IPX203 and to characterise the PK of IPX203 after sprinkling the capsule contents on applesauce as a representative soft food.	Enrolled: 27 Completed: 27
IPX203-B16-05	Randomised, single-site, open-label, single-dose, 3-treatment, 3-period, crossover. 15 days	IPX203 MR LD-CD 280-70 mg, 1 capsule IR LD-CD (Sinemet [LD-CD] 100-25 mg), 1 tablet CR LD-CD (Sinemet CR [LD-CD] SR 100-25 mg), 1 tablet Oral administration under fasted conditions	Healthy participants Male: 25 Age: 33.64 ± 6.58 years	To compare the single-dose PK of IPX203 (LD-CD MR capsules) with IR LD-CD (Sinemet) and controlled-release (CR) LD-CD (Sinemet CR).	Enrolled: 27 Completed: 25
IPX203-B16-06	Randomised (first 2-treatment periods only), single-site, open-label, single-dose, 5-treatment, 5-period, crossover bioequivalence (Treatments A and E) and dose proportionality (Treatments A through D) study.	A: IPX203 MR LD-CD 140-35 mg, 1 capsule B: IPX203 MR LD-CD 210-52.5 mg, 1 capsule C: IPX203 MR LD-CD 280-70 mg, 1 capsule D: IPX203 MR LD-CD 350-87.5 mg, 1 capsule E: IPX203 MR LD-CD 140-35 mg, 1 capsule Treatments A through D made in the US. Treatment E made in Taiwan.	Healthy participants Male: 36 Female: 4 Age: 32.70 ± 6.19 years	To assess the bioequivalence of IPX203 capsules manufactured at two sites (US, and Taiwan) and to assess the dose proportionality of IPX203 capsules (140-35 mg LD-CD, 210-52.5 mg LD-CD, 280-70 mg LD-CD, 350-87.5 mg LD-CD)	Enrolled: 40 Completed: 40

	23 days	Treatments A and E were given during the first 2 treatment periods (randomised sequence). Then, Treatments B, C, and D were given in Treatment Periods 3, 4, and 5. Oral under fasted conditions			
Phase 2					
Study IPX203-B14-02	Randomised, open-label, rater-blinded, multicentre, 3-treatment, 3-period, single-dose crossover	PX203 (LD-CD) capsules: 180 mg (180-45 mg) and 270 mg (270-67.5 mg) MR LD-CD (Rytary/Numient) capsules: 145 mg (145-36.25 mg) and 195 mg (195-48.75 mg) IR LD-CD (Sinemet) tablets: 100 mg (100-25 mg) Oral under fasted conditions Single doses of each study treatment, with washout periods of ~1 week between doses.	Participants diagnosed with idiopathic PD at age ≥ 40 years, Hoehn and Yahr Stages 2, 3, or 4, MoCA score ≥ 24 , responsive to LD-CD therapy, and currently being treated on a stable regimen of LD-CD for at least 4 weeks. Male: 13 Female: 12 Age: 66.2 ± 7.1 yea	To assess the pharmacodynamics and PK of single doses of IPX203 in subjects with advanced PD, using Rytary/Numient and IR LD-CD as the references, and to characterize the safety of single doses of IPX203 in these subjects.	Enrolled: 26 Completed: 25
Study IPX203-B16-01	Randomised, open-label, rater-blinded, 2 nd treatment, 2-period, multiple-dose crossover, multicentre 8 weeks	PX203 (LD-CD) capsules: 180 mg (180-45 mg) and 270 mg (270-67.5 mg) IR LD-CD (Sinemet) tablets: 100 mg (100-25 mg) Oral	Participants diagnosed with idiopathic PD at age ≥ 40 years, Hoehn and Yahr Stages 2, 3, or 4, MoCA score ≥ 24 in the "On" state, responsive to LD-CD therapy, and currently treated with a stable regimen of LD-CD for at least 4 weeks and experiencing motor complications. Male: 16 Female: 11 Age: 65.9 ± 9.8 years	To compare the PK and pharmacodynamics of single and multiple doses of IPX203 with IR LD-CD in subjects with advanced PD	Enrolled: 28 Completed: 27
Phase 3					
Study IPX203-B16-02	Randomised, double-blind, double-dummy, active-controlled, parallel-group,	IPX203 (LD-CD) 140-35 mg capsules IR LD-CD 100-25 mg tablets	Participants diagnosed with PD at age ≥ 40 years, Hoehn and Yahr Stages 1, 2, 3, or 4, MoCA score ≥ 24	To evaluate the safety and efficacy of IPX203 in comparison to IR LD-CD in the treatment of LD-CD experienced	Enrolled: 630 Randomised: 506 Completed: 449

	prospective, multicentre 24 weeks (4-week Screening period, a 3-week open-label IR LD-CD dose adjustment period, a 4-week open-label period for conversion to IPX203, and a 13-week double-blind, treatment period)	Matching IPX203 and IR LD-CD placebos Oral Individualised based on incoming IR LD-CD dose.	in the "On" state, responsive to LD-CD therapy and currently treated with a stable regimen of CD and LD for at least 4 weeks and experiencing motor complications. Male: 396 Female: 234 Age: 66.5 ± 8.95 years	subjects with PD who have motor fluctuations.	
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Abbreviations: CR = controlled-release; ER = extended-release; IR LD-CD = immediate-release levodopa-carbidopa; MoCA = Montreal Cognitive Assessment; MR = modified-release; PD = Parkinson's disease; PK = pharmacokinetic; SR = sustained-release; US = United States

Table 2: Clinical pharmacology studies

Study Protocol Number Batch/Lot number	Study Design	Number of Subjects (M/F) Age: Mean (range) years	Treatments (Dose, Dosage Form, Route)	Mean PK Parameters (%CV)				Mean Ratio ^a (90% CI)			
				C _{max} (ng/mL)	T _{max} ^b (h)	AUC _{0-t} (hr*ng/mL)	t _{1/2} (h)	C _{max}	AUC _{0-t}	AUC _{0-∞}	
Study IPX203-B16-04											
								IPX203 Fed versus Fasted			
BA08819C	Randomised, open-label, single-dose, 3-treatment, 3-period, crossover, single-site	27 patients (27 M) Age: 30.11 (18 to 48)	IPX203 Fed: IPX203 (LD-CD) MR 350-87.5 mg, capsules, oral	LD: 2185.564 (21.63)	LD: 4.000 (2.00-5.00)	LD: 10552.789 (13.51)	LD: 1.786 (17.56)	LD: 119.23 (110.43-128.74)	LD: 117.83 (111.56-124.46)	LD: 118.00 (111.76-124.58)	
				CD: 140.767 (29.21)	CD: 4.000 (2.00-6.00)	CD: 751.026 (27.32)	CD: 3.861 (20.15)	CD: 36.11 (32.34-40.33)	CD: 36.38 (32.68-40.50)	CD: 36.49 (32.79-40.61)	
							IPX203 Sprinkled on Applesauce versus Fasted				
BA08819C			IPX203 Sprinkled on Applesauce: IPX203 (LD-CD) MR 350-87.5 mg, capsules, oral	LD: 1634.170 (25.05)	LD: 0.500 (0.50-5.00)	LD: 8330.925 (23.59)	LD: 2.024 (15.21)	LD: 88.51 (81.97-95.56)	LD: 91.42 (86.56-96.57)	LD: 91.50 (86.67-96.61)	
				CD: 338.559 (27.10)	CD: 2.500 (1.50-5.00)	CD: 1909.196 (32.38)	CD: 3.948 (16.93)	CD: 86.88 (77.80-97.02)	CD: 90.91 (81.66-101.20)	CD: 90.91 (81.70-101.16)	
BA08819C			IPX203 Fasted: IPX203 (LD-CD) MR 350-87.5 mg, capsules, oral	LD: 1826.947 (21.09)	LD: 2.000 (0.50-5.00)	LD: 9124.960 (23.56)	LD: 1.988 (15.09)				
				CD: 403.573 (38.83)	CD: 3.000 (1.00-6.00)	CD: 2174.983 (41.65)	CD: 3.903 (14.36)				

Study Protocol Number Batch/Lot number	Study Design	Number of Subjects (M/F) Age: Mean (range) years	Treatments (Dose, Dosage Form, Route)	Mean PK Parameters (%CV)				Mean Ratio ^a (90% CI)			
				C _{max} (ng/mL)	T _{max} ^b (h)	AUC _{0-t} (hr*ng/mL)	t _{1/2} (h)	C _{max}	AUC _{0-t}	AUC _{0-∞}	
Study IPX203-B16-05											
BA11219C	Randomised, open-label, single-dose, 3-treatment, 3-period, crossover, single-centre	27 patients (27 M) Age: 33.93 (20 to 42)	IPX203 (LD-CD) MR 280-70 mg, capsules, oral	LD: 1621.360 (30.53)	LD: 2.000 (0.50-5.00)	LD: 7662.313 (26.62)	LD: 1.997 (13.12)				
				CD: 403.416 (35.86)	CD: 3.000 (1.50-6.00)	CD: 2228.936 (40.01)	CD: 3.886 (10.60)				
IPX203 versus IR LD-CD											
IR LD-CD (Sinemet 100-25 mg), tablets, oral			LD: 1600.146 (50.28)	LD: 0.500 (0.50-2.00)	LD: 2752.742 (22.09)	LD: 2.094 (15.47)	D: 105.93 (92.35-121.50)	LD: 273.18 (254.90-292.78)	LD: 272.05 (253.97-291.41)		
			CD: 120.441 (35.24)	CD: 2.500 (1.00-4.00)	CD: 648.964 (45.64)	CD: 3.956 (20.40)	CD: 331.86 (281.28-391.52)	CD: 342.50 (295.37-397.15)	CD: 342.12 (295.48-396.13)		
IPX203 versus CR LD-CD											
CR LD-CD (Sinemet CR 100-25 mg), tablets, oral			LD: 735.869 (30.13)	LD: 2.000 (0.50-2.50)	LD: 2459.708 (26.66)	LD: 2.021 (19.44)	D: 220.86 (192.54-253.33)	LD: 313.20 (292.24-335.67)	LD: 310.88 (290.22-333.00)		
			CD: 92.572 (48.10)	CD: 3.000 (1.50-6.00)	CD: 504.663 (60.07)	CD: 3.483 (22.79)	CD: 460.63 (390.43-543.45)	CD: 483.59 (417.05-560.76)	CD: 480.85 (415.29-556.75)		
R003551											
Study IPX203-B16-06											
US, Taiwan											
BA11319C	Open-label, single-dose, 5-treatment, 5-period, crossover, single-site	40 patients (36 M/4 F) Age: 32.70 (19 to 43)	IPX203 (LD-CD) MR 140-35 mg (Manufactured in US), capsules, oral	LD: 664.606 (26.88)	LD: 2.500 (0.50-5.00)	LD: 3225.528 (20.24)	LD: 1.665 (9.74)	LD: 103.14 (98.33-108.19)	LD: 103.15 (100.12-106.27)	LD: 103.20 (100.14-106.35)	
				CD: 153.484 (44.35)	CD: 2.500 (1.00-4.00)	CD: 824.626 (37.97)	CD: 3.680 (15.75)	CD: 100.55 (92.28-109.55)	CD: 105.47 (97.45-114.14)	CD: 105.29 (97.37-113.84)	
IPX203 (LD-CD) MR 140-35 mg (Manufactured in Taiwan), capsules, oral			LD: 636.216 (21.26)	LD: 2.750 (0.50-5.00)	LD: 3115.380 (18.61)	LD: 1.640 (10.80)					
			CD: 154.918 (40.69)	CD: 2.500 (1.00-5.00)	CD: 797.201 (39.35)	CD: 3.679 (16.51)					

Study Protocol Number Batch/Lot number	Study Design	Number of Subjects (M/F) Age: Mean (range) years	Treatments (Dose, Dosage Form, Route)	Mean PK Parameters (%CV)				Mean Ratio ^a (90% CI)				
				C _{max} (ng/mL)	T _{max} ^b (h)	AUC _{0-t} (hr*ng/mL)	t _{1/2} (h)	C _{max}	AUC _{0-t}	AUC _{0-∞}		
Study IPX203-B14-02												
								IPX203 versus IR LD-CD				
PB00115, PB00215	Randomised, open-label, rater-blinded, multicenter, 3-treatment, 3-period, single-dose crossover	25 patients (13 M/12 F) Age: Mean ± SD: 66.2 ± 7.1	IPX203: 180 mg (180 mg LD-45 mg CD) and 270 mg (270 mg LD-67.5 mg CD), capsules, oral	LD Mean ± SD: 3161 ± 1665	LD: 2.0 (0.5–7.0)	LD Mean ± SD: 13291 ± 7264	LD Mean ± SD: 2.3 ± 0.9	LD: 37.76 (32.59-43.75)	LD: 77.50 (71.25-84.31)	LD: 85.50 (77.89-93.85)		
				CD Mean ± SD: 571 ± 400	CD: 2.5 (1.5–6.0)	CD Mean ± SD: 2192 ± 1353	CD Mean ± SD: 2.3 ± 0.8	CD: 97.60 (83.59, 113.95)	CD: 118.51 (99.84, 140.67)	CD: 112.07 (92.40, 135.92)		
								Rytary versus IR LD-CD				
10010691 , 10010848			MR LD-CD (Rytary): 145 mg (145 mg LD-36.25 mg CD) and 195 mg (195 mg LD-48.75 mg CD), capsules, oral	LD Mean ± SD: 2839 ± 1909	LD: 2.0 (0.5–6.5)	LD Mean ± SD: 10467 ± 6771	LD Mean ± SD: 2.0 ± 0.7	LD: 34.03 (29.38-39.43)	LD: 62.81 (57.74-68.32)	LD: 71.79 (65.26-78.97)		
				CD Mean ± SD: 217 ± 130	CD: 2.5 (1.0–7.5)	CD Mean ± SD: 922 ± 602	CD Mean ± SD: 2.8 ± 0.9	CD: 40.09 (34.33, 46.80)	CD: 51.53 (43.41, 61.16)	CD: 55.37 (45.50, 67.38)		
L022921			IR LD-CD (Sinemet): 100 mg (100 mg LD-25 mg CD), tablets, oral	LD Mean ± SD: 2492 ± 1459	LD: 1.0 (0.5–2.5)	LD Mean ± SD: 4879 ± 2631	LD Mean ± SD: 1.4 ± 0.3					
				CD Mean ± SD: 180 ± 123	CD: 2.5 (1.5–3.5)	CD Mean ± SD: 593 ± 402	CD Mean ± SD: 2.1 ± 0.7					
Study IPX203-B16-01												
PB00116, PB00216	Randomised, open-label, rater-blinded, 2-treatment, 2-period, multiple-dose crossover, multicenter	27 patients (16 M/11 F) Age: Mean ± SD: 65.9 ± 9.8	IPX203: 180 mg (180 mg LD-45 mg CD) and 270 mg (270 mg LD-67.5 mg CD), capsules, oral	LD Mean ± SD: 2858 ± 1205	LD: 2.0 (0.5–5.0)	LD Mean ± SD: 12108 ± 5794	LD Mean ± SD: 1.7 ± 0.5			LD: 263.87 (194.59, 357.80) ^c		
				CD Mean ± SD: 500 ± 316	CD: 2.5 (1.5–4.0)	CD Mean ± SD: 1941 ± 1095	CD Mean ± SD: 2.0 ± 0.5, (n=26)					
PB00216			IR LD-CD (Sinemet): 100 mg (100 mg LD-25 mg CD), tablets, oral	LD Mean ± SD: 2173 ± 1241	LD: 0.5 (0.5–2.0)	LD Mean ± SD: 3748 ± 1819	LD Mean ± SD: 1.4 ± 0.3, (n=26)					
				CD Mean ± SD: 152 ± 103	CD: 2.0 (0.5–4.0)	CD Mean ± SD: 437 ± 286	CD Mean ± SD: 2.0 ± 0.7, (n=20)					
Source: Study IPX203-B16-04, Study IPX203-B16-05, Study IPX203-B16-06, Study IPX203-B14-02, Study IPX203-B16-01												
Abbreviations: AUC = area under the plasma concentration-time curve; AUC _{0-t} = AUC from time 0 hour to the last measurable concentration at time t; AUC _{0-∞} = AUC from time 0 hour extrapolated to infinity; CD = carbidopa; CI = confidence interval; CR = controlled-release; C _{max} = maximum observed plasma concentration; CV = coefficient of variance; MR = modified-release; IR = immediate-release; LD = levodopa; SD = standard deviation; t _{1/2} = apparent half-life; T _{max} = time to maximum plasma concentration.												
a. Ratios of geometric means are presented with 90% CI.												
b. Data are presented as median (minimum – maximum).												
c. AUC _{8-∞} = AUC extrapolated from 8 hours up to infinity. N=25 since value could not be estimated reliably in 1 subject following IR LD-CD, and in 1 subject following IPX203.												

Table 3: Clinical efficacy / safety studies

Number of Study Centres, Locations	Study Start Date Enrolment Status and Date Total Enrolment/Planned	Study Design Study Duration	Treatments (Dose, Route, Regimen)	Study Objective	Diagnosis Inclusion Criteria	Number of Subjects Entered/Completed Gender M/F Age: Mean $\pm$ SD	Primary Efficacy Endpoint Other Efficacy Assessments
Study IPX203-B14-02							
10 centres in the US	Started: 07 Dec 2015 Completed: 10 Aug 2016 26/51	Randomised, open-label, rater-blinded, multicentre, 3-treatment, 3-period, single-dose crossover 6 weeks	IPX203 (LD-CD) oral capsules: 180 mg (180-45 mg) and 270 mg (270-67.5 mg) MR LD-CD (Rytary/Numient) oral capsules: 145 mg (145-36.25 mg) and 195 mg (195-48.75 mg) IR LD-CD (Sinemet) oral tablets: 100 mg (100-25 mg) Single doses of each study treatment, with washout periods of ~1 week between doses.	To assess the pharmacodynamics and PK of single doses of IPX203 in subjects with advanced PD, using Rytary/Numient and IR LD-CD as the references, and to characterize the safety of single doses of IPX203 in these subjects.	Male or female subjects diagnosed with idiopathic PD at age ≥ 40 years, Hoehn and Yahr Stages 2, 3, or 4, MoCA score ≥ 24 , responsive to LD-CD therapy, and currently being treated on a stable regimen of LD-CD for at least 4 weeks.	Randomised / Enrolled: 26 Completed: 25 13 M/12 F ^a Age ^a : 66.2 $\pm$ 7.1 years	"Off" time based on the assessment of subject's motor state Assessment of subject's other motor states ("Asleep", "On" without dyskinesia, "On" with non-troublesome dyskinesia, "On" with troublesome dyskinesia, or "On" without troublesome dyskinesia) Duration of at least 4-, 7-, and 13-point improvements in MDS-UPDRS Part III scores from average pre-dose value
Study IPX203-B16-01							
10 centres in the US	Started: 08 Nov 2016 Completed: 01 Aug 2017 28/30	Randomised, open-label, rater-blinded, 2-treatment, 2-period, multiple-dose crossover, multicentre 8 weeks	IPX203 (LD-CD) oral capsules: 180 mg (180-45 mg) and 270 mg (270-67.5 mg) IR LD-CD (Sinemet) oral tablets: 100 mg (100-25 mg) Subjects Randomised to 1 of 2 dosing sequences: IR LD-CD followed by IPX203, and IPX203 followed by IR LD-CD. Variable dosing, 15 days per treatment period, separated by a 1-week washout period.	To compare the PK and pharmacodynamics of single and multiple doses of IPX203 with IR LD-CD in subjects with advanced PD	Male or female subjects diagnosed with idiopathic PD at age ≥ 40 years, Hoehn and Yahr Stages 2, 3, or 4, MoCA score ≥ 24 in the "On" state, responsive to LD-CD therapy, and currently treated with a stable regimen of LD-CD for at least 4 weeks and experiencing motor complications.	Randomised / Enrolled: 28 Completed: 27 16 M/11 F ^a Age ^a : 65.9 $\pm$ 9.8 years	Average percent "Off" time during waking hours, based on subject PD diaries. Averages of total "Off" time, total "Good On" time, total "On" without dyskinesia time, total "On" with non-troublesome dyskinesia time, total "On" with troublesome dyskinesia time, and total time asleep. MDS-UPDRS scores (Parts I to IV and total) at pre-dose on Day 15 of each treatment period. Mean absolute and change-from-Screening scores for each MDS-UPDRS Part IV question at pre-dose on Day 15 for each treatment. Kinesia 360 sensors: tremor, dyskinesia, and mobility measures.
Study IPX203-B16-02							
105 centres across US, Italy, Spain, France, United	Started: 06 Nov 2018 Completed: 15 Jun 2021 630/510	Randomised, double-blind, double-dummy, active-controlled,	IPX203 (LD-CD) oral capsules: 140 mg (140-35 mg)	To evaluate the safety and efficacy of IPX203 in comparison to IR LD-CD in the treatment	Male or female subjects diagnosed with PD at age ≥ 40 years,	Enrolled: 630 Randomised : 506 Completed: 449	Mean change from baseline (randomization visit) in "Good On" time in hours per day, averaged over the PD Diary days,

Number of Study Centres, Locations	Study Start Date Enrolment Status and Date Total Enrolment/Planned	Study Design Study Duration	Treatments (Dose, Route, Regimen)	Study Objective	Diagnosis Inclusion Criteria	Number of Subjects Entered/ Completed Gender M/F Age: Mean $\pm$ SD	Primary Efficacy Endpoint Other Efficacy Assessments
Kingdom, Czech Republic, Poland, and Germany		parallel group, prospective, multicentre 24 weeks (4-week Screening period, a 3-week open-label IR LD-CD dose adjustment period, a 4-week open-label period for conversion to IPX203, and a 13-week double-blind, double-dummy treatment period).	IR LD-CD oral tablets: 25 mg CD-100 mg LD Matching IPX203 and IR LD-CD placebos Individualized based on incoming IR LD-CD dose	of LD-CD experienced subjects with PD who have motor fluctuations.	Hoehn and Yahr Stages 1, 2, 3, or 4, MoCA score ≥ 24 in the "On" state, responsive to LD-CD therapy, and currently treated with a stable regimen of LD-CD for at least 4 weeks and experiencing motor complications.	396 M/234 F ^b Age ^b : 66.5 $\pm$ 8.95 years	Change from baseline in "Off" time in hours per day, averaged over the PD Diary days, "Good On" time per dose, Proportion of subjects with either "much improved" or "very much improved" in PGI-C scores, Change from baseline in the MDS-UPDRS Part III scores, sum of MDS-UPDRS Part II and Part III scores, Percent "Off" time during waking hours, Average duration of each continuous "Good On" and each continuous "On" per PD Diary, "On" time with no or non-troublesome dyskinesia per PD Diary, Proportion of subjects with an improvement in "Good On" time per PD Diary, Proportion of subjects with a reduction in "Off" time per PD Diary, Proportion of subjects who were "On" upon awakening and "Good On" upon awakening, Average time to "On" upon awakening per PD Diary, Average number of motor fluctuations per day per PD Diary, MDS-UPDRS total score and Parts I, II, and IV scores separately, MDS-UPDRS Part II Question 2.9, PDQ-39, NMSS, PDSS-2, PAS, PGI-S, CGI-C, and CGI-S.
Study IPX203-B16-03							
94 centres across US, Italy, Spain, France, United Kingdom, Czech Republic, Poland, and Germany	Started: 03 Apr 2019 Completed: 21 Mar 2022 419/300	Open-label safety extension, multicentre study 9 months	4 strengths of IPX203 (LD-CD) capsules; 140-35 mg, 210-52.5 mg, 280-70 mg, 350-87.5 mg Individualized based on the final IPX203 dosing regimen that was	To evaluate the long-term safety and clinical utility of IPX203 in the treatment of subjects with advanced PD who have motor fluctuations	Subjects who successfully completed Study IPX203-B16-02	Enrolled: 419 Completed: 352 279 M/140 F ^b Age ^b : 66.9 $\pm$ 8.86 years	Clinical Utility Measures: MDS-UPDRS Part I to IV, PGI-S, CGI-S, PDQ-39, PAS, NMSS, PDSS-2, TSA, ZBI-12, and EMSQ

Number of Study Centres, Locations	Study Start Date Enrolment Status and Date Total Enrolment/Planned	Study Design Study Duration	Treatments (Dose, Route, Regimen)	Study Objective	Diagnosis Inclusion Criteria	Number of Subjects Entered/ Completed Gender M/F Age: Mean $\pm$ SD	Primary Efficacy Endpoint Other Efficacy Assessments
			determined during the IPX203 dose conversion period of Study IPX203-B16-02				
Source: Clinical Study Reports (CSRs) of Study IPX203-B14-02, Study IPX203-B16-01, Study IPX203-B16-02, and Study IPX203-B16-03 Abbreviations: CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; EMSQ = Early Morning Symptoms Questionnaire; MR = modified-release; F = female; IR LD-CD = immediate-release levodopa-carbidopa; M = male; MDS-UPDRS = Movement Disorders Society- Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; NMSS = Non-Motor Symptom Assessment Scale; PAS = Parkinson Anxiety Scale; PD = Parkinson's disease; PDQ-39 = 39-Item Parkinson's Disease Questionnaire; PDSS-2 = Parkinson's Disease Sleep Scale-2; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impressions of Severity; PK = pharmacokinetic; SD = standard deviation; TSA = Treatment Satisfaction Assessment; ZBI-12 = 12-Item Zarit Burden Interview; US = United States Note: "Off" was defined as the typical functional state when the medication no longer provided benefit with regard to mobility, slowness, and stiffness in spite of taking medications. "On" was defined as the typical functional state when a subject's medication provided benefit with regard to mobility, slowness, and stiffness. Dyskinesia was defined as involuntary and irregular twisting and/or turning movements that were an effect of medication and occurred during "On" time. Non troublesome dyskinesias did not interfere with function or cause meaningful discomfort. Troublesome dyskinesias interfered with function or caused meaningful discomfort. a. Reported for Completers b. Reported for enrolled subjects							

5.2. Clinical pharmacology

5.2.1. Methods

Validated bioanalytical methods were used for the determination of LD and CD in human plasma samples collected during the clinical development programme, across IPX203 clinical protocols (IPX203-B16-04/-05/06; IPX203-B14-02; IPX203-B16-01). Method validation activities were conducted in accordance with applicable regulatory requirements to demonstrate that the analytical procedures were suitable for their intended use and capable of generating reliable data to support the clinical studies.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The (PK of IPX203 was studied in three Phase 1 studies in healthy volunteers (Studies **IPX203-B16-04**, **IPX203-B16-05**, and **IPX203-B16-06**). Pharmacokinetics and PD have been studied in two Phase 2 studies following a single dose (Study **IPX203-B14-02**) and multiple therapeutic doses (Study **IPX203-B16-01**) in subjects with advanced PD.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population pharmacokinetics

No PopPK models were used.

5.2.2.2.2. Physiology based pharmacokinetic model

No PBPK models were used.

5.2.2.3. Absorption

The PK of IPX203 was studied in three Phase 1 studies in healthy volunteers (Studies **IPX203-B16-04**, **IPX203-B16-05** and **IPX203-B16-06**). Pharmacokinetics and PD have been studied in two Phase 2 studies following a single dose (Study **IPX203-B14-02**) and multiple therapeutic doses (Study **IPX203-B16-01**) in subjects with advanced PD. Phase 2 studies were conducted between 2015 and 2017 and Phase 1 studies were conducted in 2019. A tabular summary of the conducted studies is provided below.

Table 4: Tabular summary of PK and PD studies conducted for IPX203

Study	IPX203-B14-02	IPX203-B16-01	
Description	3x3, phase 2 with PD patients, SD	2x2, phase 2 with PD patients, MD	
Clinical conduction	December 2015 to August 2016	August 2016 to January 2017	
Reference product 1	Rytary LD-CD 145-36.25 mg	Sinemet [LD-CD] tablets 100-25 mg	
Reference product 2	Rytary LD-CD 195-48.75 mg		
Reference product 3	Sinemet [LD-CD] tablets 100-25 mg		
Test product 1	IPX203 MR LD-CD 180-45 mg	IPX203 MR LD-CD 180-45 mg	
Test product 2	IPX203 MR LD-CD 270-67.5 mg	IPX203 MR LD-CD 270-67.5 mg	
Study	IPX203-B16-04	IPX203-B16-05	IPX203-B16-06
Description	3x3 Food effect, SD	3x3 BE study, SD	5x5, SD, dose proportional
Clinical conduction	Jun-19	May 2019 to June 2019	April 2019 to May 2019
Reference product 1		Sinemet [LD-CD] tablets 100-25 mg	
Reference product 2		Sinemet CR [LD-CD] tablets 100-25 mg	
Test product 1	IPX203 MR LD-CD 350-87.5 mg	IPX203 MR LD-CD 280-70 mg	IPX203 MR LD-CD 140-35 mg
Test product 2			IPX203 MR LD-CD 210-52.5 mg
Test product 3			IPX203 MR LD-CD 280-70 mg
Test product 4			IPX203 MR LD-CD 350-87.5 mg

Phase 1 studies

Study IPX203-B16-04

Levodopa

In comparison to the fasted state condition, when IPX203 is administered on fed state condition, all point estimates (C_{max} and AUC) for LD are >100%, indicating higher exposure with food. The geometric mean ratios (A/C) are ~119% for C_{max} and ~118% for both AUC metrics, showing a consistent ~18–19% increase of levodopa bioavailability under fed conditions. Intra-subject CVs are modest (~12–17%), not suggestive of a highly variable drug.

In the course of the procedure, the applicant provided partial AUC estimates for LD. These results showed a marked redistribution of LD exposure over time under fed conditions, with a very pronounced reduction in early exposure. Specifically, LD $pAUC_{0-1h}$ (fed/fasted) is 4.53% (90% CI 3.13–6.56), i.e., far outside the usual 80–125% range, while later exposure is increased, e.g., $pAUC_{5-10h}$ (fed/fasted) is 181.80% (90% CI 157.31–210.11).

Based on these study results, the applicant revised the wording of SmPC sections 4.2 and 5.2 to describe the food effect in PK terms only. Of note, following administration of IPX203 with high-fat, high-calorie meal, absorption of levodopa may be slower/delayed, as reflected by a delayed median T_{max} compared with the fasted state, while overall systemic exposure (AUC) remains unchanged. In addition, for patients in whom a rapid onset of IPX203 effect is considered important, such as at the first dose of the day, administration on an empty stomach may be considered.

In comparison to the fasted state condition, when IPX203 is administered sprinkled in applesauce, all point estimates ($C_{\max}$ and AUC) for levodopa were <100%, indicating slightly lower exposure when sprinkled. Intra-subject CVs were modest ($\approx 12\text{--}17\%$), and the analysis was highly powered ($\sim 100\%$).

Administration by sprinkling the contents of IPX203 on apple sauce was however considered bioequivalent to the administration in the fasted state, for both rate and extent of exposure. The $\sim 8\text{--}12\%$ decreases are unlikely to be clinically meaningful, and no dose adjustment is needed. These data supported inclusion of sprinkling on applesauce as an acceptable alternative administration method in the product labelling, with appropriate sprinkling instructions, as detailed in SmPC section 4.2 (and PL).

Carbidopa

In contrast to LD, a very large decrease in exposure with food was observed for CD, with point estimates $\sim 36\%$ of fasted for $C_{\max}$ and AUC (i.e., $\sim 64\%$ lower under fed conditions). Nevertheless, a modest decrease in exposure was observed for CD when sprinkled: $C_{\max}$ 86.9%, AUCs $\sim 90.9\%$. Of note, a “no food effect” claim cannot be made for carbidopa, as food reduces both rate and extent of exposure substantially. Sprinkling supports comparable extent of exposure (AUC) but a lower peak.

Study IPX203-B16-05

Levodopa

When comparing the new modified-release (MR) LD/CD 280/70 mg (IPX203 – treatment A) with Sinemet IR 100/25 mg (treatment B), and although the dose of IPX203 is 2.8-fold higher (280 mg vs 100 mg), levodopa $C_{\max}$ was essentially the same as IR, whereas AUCs were $\approx 2.7\times$ those of IR. However, in IPX203 MR capsules 25% of LD dose (corresponding to 70 mg) is contained in the immediate release granules. The attained $C_{\max}$ was probably mostly driven by such IR amount and partially from the ER beads, given the delayed $T_{\max}$ (the median LD $T_{\max}$ was 2.0 hours for IPX203 *versus* 0.5 hours for IR LD-CD). When dose-normalised (using the least square means), the IPX203 product yielded $\sim 38\%$ lower peak than IR.

Extent of exposure (AUC) scaled as expected with dose. When dose-normalised, represented $\sim 97\text{--}98\%$ of IR (based on the geometric least square means of $AUC_{0-\infty}$), indicating comparable bioavailability to IR on a per-mg basis.

These findings are consistent with a MR profile that reduces peak-to-trough fluctuation while maintaining (*versus* IR) an overall exposure.

As dose differ between treatments, this is not a bioequivalence assessment; dose-normalised metrics would provide the appropriate relative bioavailability context. In the course of the procedure, as requested, the applicant provided partial AUC analyses. Overall, the data supported that IPX203 maintains early LD exposure while providing substantially greater later exposure compared with IR, consistent with a comparable onset by about 2 hours and a more sustained LD profile thereafter. In particular, LD AUC_{0-2h} was broadly similar between IPX203 and IR, whereas LD exposure was markedly higher with IPX203 in the 2–6h and 6–12h intervals, supporting the prolonged duration of action and the proposed BID/TID dosing.

On the other hand, for LD, exposure in the first hour (AUC_{0-1h}) was lower with IPX203 than IR, even though AUC_{0-2h} is similar, suggesting that very early onset may differ while overall early exposure by 2 hours was comparable. In addition, the statement that early partial AUCs are “similar” for both IPX203 and IR does not apply to CD, for which early partial AUCs appear higher with IPX203. However, these observations did not change the main conclusion on LD onset and sustained exposure.

When comparing the new IPX203 MR LD/CD 280/70 mg (A) with Sinemet CR 100/25 mg (C), LD C_{max} was approximately 2.2-fold higher, whereas AUCs were ≈ 3.1 fold higher. On a per-mg basis the MR product yielded $\sim 21\%$ lower peak and $\sim 11\%$ higher total exposure than Sinemet CR 100/25 mg, indicating slight supra-bioavailability in the extent of LD absorption. In summary, it can be concluded that the new MR provided greater total exposure than CR but with a lower peak.

Carbidopa

When comparing the new IPX203 MR LD/CD 280/70 mg (A) with Sinemet IR 100/25 mg (B), CD C_{max} and AUC were approximately 3.2 and 3.4-fold higher, respectively, in line with the higher dose of the MR formulation, i.e., 2.8-fold higher (70 mg vs 25 mg). On a per-mg basis (using the least square means), the MR product yielded $\sim 18\%$ higher peak and $\sim 22\%$ higher total exposure than IR, indicating slight supra-bioavailability vs IR. In the new MR formulation, the IR granules contained 100% of CD dose.

When comparing the new IPX203 MR LD/CD 280/70 mg (A) with Sinemet CR 100/25 mg (C), CD C_{max} was approximately 4.6-fold higher, whereas AUCs are ≈ 4.8 fold higher. In a per mg analysis based on the least square means, the MR formulation delivered $\sim 65\text{--}73\%$ higher exposure and peak than CR, implying substantially greater bioavailability than the CR tablet.

Study IPX203-B16-06

For both levodopa and carbidopa, study results showed bioequivalence between the two IPX203 batches (IPX203 MR LD-CD 140-35 mg), one manufactured in the US and the other in Taiwan.

For both LD and CD, a dose proportionality was observed in the dose range of IPX203 MR LD-CD 140-35 mg to IPX203 MR LD-CD 350-87.5 mg. The elimination pattern of both drugs was not modified with an increased dose.

Phase 2 studies

Phase 2 studies (single and multiple dose) were conducted using IPX203 capsules 180 mg (LD-CD 180-45 mg) and 270 mg (LD-CD 270-67.5 mg), which are not the proposed to be marketed dose strengths. However the derived PK results were bridged to results from the to-be-marked (TBM) formulations (IPX203 MR capsules LD-CD 140-35 mg, LD-CD 210-52.5 mg, LD-CD 280-70 mg and LD-CD 350-87.5 mg) through the dose proportionality study **IPX203-B16-06**, as well as through the food effect study **IPX203-B16-04**, given that both LD and CD showed dose-normal linearity PKs (within the range of LD-CD 140-35 mg to LD-CD 350-87.5 mg), which assures a predictable exposure scaling across strengths. Moreover, no accumulation and time-invariant pPKs were observed with the multiple dose regimens tested in the Phase 2 study **IPX203-B16-01**. Of note, the Phase-3 pivotal trial was conducted using the TBM IPX203 MR capsules LD-CD 140-35 mg.

Study IPX203-B14-02

In this randomised, open-label, rater-blinded, three-period crossover conducted in fasted subjects with advanced PD, all treatments contained LD and CD at a fixed 4:1 ratio, with IPX203 and Rytary given at doses roughly three times higher than the comparator IR LD-CD.

Levodopa

Following IPX203, LD showed a median T_{max} of 2.0 h (range 0.5–7.0 h); as anticipated for modified/extended-release products, T_{max} for both IPX203 and Rytary exceeded that of IR LD-CD. Despite the higher doses, the early rise in LD concentration with IPX203 was similar to that seen with IR LD-CD and Rytary, indicating comparable performance of the IR fraction. The mean C_{max} (all doses)

after IPX203 was 3161 ng/mL with a mean half-life of about 2.3 h; on average, $C_{\max}$ was only ~27% higher with IPX203 and ~14% higher with Rytary than with IR LD-CD, whereas AUC_{0-t} was larger for both modified/extended-release regimens, consistent with the higher administered dose.

The bioavailability of LD based on dose-normalised natural-log-transformed AUC_{0-inf} following IPX203 administration was approximately 85.5% relative to IR CD-LD.

A useful indicator of profile “flatness” was the time for which plasma concentrations remained above 50% of $C_{\max}$. By this measure IPX203 sustained LD levels the longest—about 4.7 h above 50% $C_{\max}$ compared with 3.9 h for Rytary and 1.9 h for IR LD-CD—and this pattern was consistent across all IPX203 dose strengths studied. The time to reach 50% of $C_{\max}$ was broadly similar for IPX203 and Rytary and slightly shorter for IR LD-CD; importantly, the time to attain a clinically meaningful concentration (~430 ng/mL) was comparable across all three treatments. Overall, IPX203 delivered a smoother and more prolonged LD exposure than IR LD-CD and somewhat longer than Rytary, with only modest increases in peak concentrations despite higher doses—an exposure profile consistent with reduced peak–trough fluctuation while preserving prompt onset.

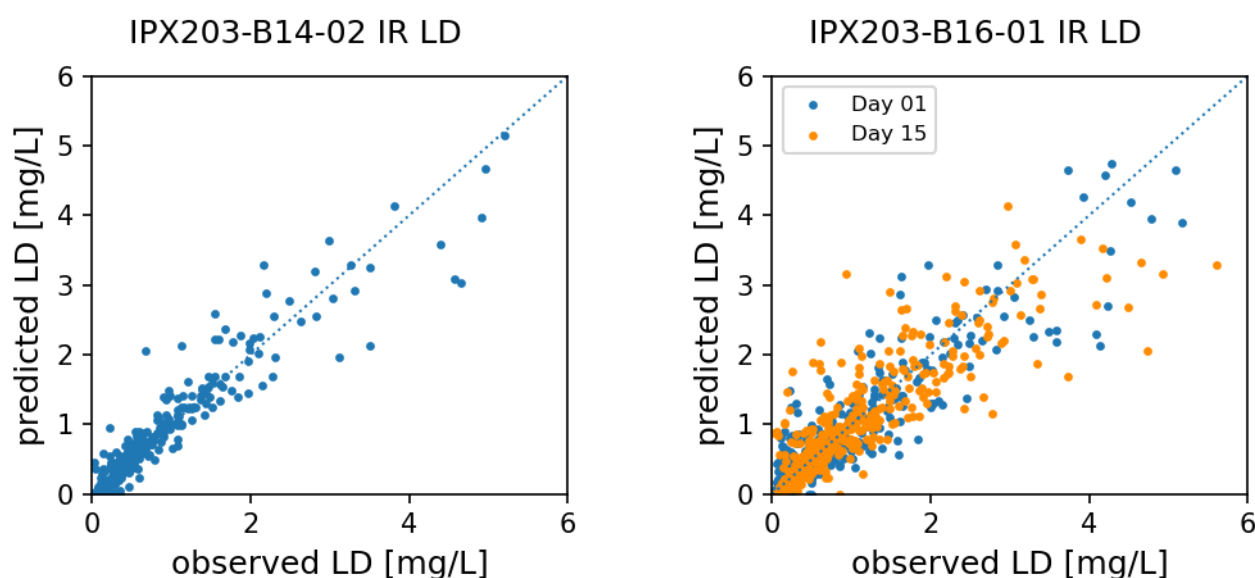
As requested in the course of the procedure, the applicant provided a model-based sensitivity analysis to check if the first sampling time at 0.5 h was sufficient to capture the true IR LD $C_{\max}$ in Studies IPX203-B14-02 and IPX203-B16-01.

This analysis used individual one-compartment PK fits and different absorption rate constants. The predicted $T_{\max}$ values were close to the first sampling time, mainly around 0.44–0.78 h, and predicted $C_{\max}$ values for plausible k_a values were within about $\pm 10\%$ of the reference estimate. Therefore, a clinically relevant underestimation of IR $C_{\max}$ due to the 0.5 h first sample is unlikely. The applicant also provided early exposure metrics, including $AUC_{0-0.5h}$, AUC_{0-1h} , and AUC_{0-2h} , dose-normalised to 100 mg LD. These results were broadly similar between studies IPX203-B14-02 and IPX203-B16-01 and supported the early exposure assessment, as detailed below.

A total of 51 subjects with PD (24 in study IPX203-B14-02 and 27 in study IPX203-B16-01), were considered for sensitivity analyses estimating the true IR $T_{\max}/C_{\max}$. Measured plasma LD exposure data were obtained from patients resulting from a single morning dose or multiple dosing uptake of 100-250 mg Sinemet IR.

In a first step, for all study individuals (one) compartment structural PK models were fitted to their LD exposure profiles (total $n = 24 + 2 \times 27 = 78$). Diagnostic plots of observed LD plasma exposure *versus* model predicted LD exposure were used to verify fit quality. Such plots are shown in the figure below for IPX203-B14-02 (left) and IPX203-B16-01 (right), with lines of identity plotted for guidance.

Figure 3: Diagnostic plots of observed versus predicted LD plasma exposure



Calculated LD exposure correlates well with measured LD exposure. Due to the higher complication of study IPX203-B16 (a multi-dose Phase 2 study) observed variability to model calculated exposure is higher but still in an acceptable range. In both studies, variability increases at higher plasma concentrations, i.e., at exposure levels at which C_{max} is located, and also observed plasma levels have a slight tendency to be higher than their predicted counterparts. Individual estimates of absorption rate (k_a), volume of distribution (V_d), and elimination (CL) were analysed by descriptive statistics. The table below lists ranges, mean, median, %CV, and 95% confidence intervals for those PK parameters:

Table 5: Descriptive statistics of modelled population PK parameters

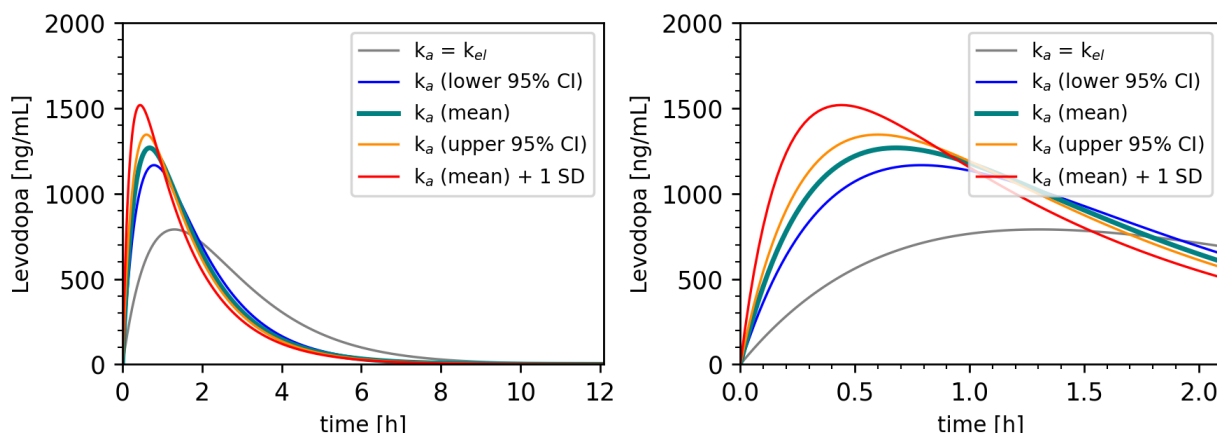
PK parameter	unit	range	mean (SD)	% CV	geometric mean	95% CI
k_a	h^{-1}	0.1 - 11.1	2.54 (2.53)	99.8%	1.67	1.97 - 3.11
V_d	L	23.3 - 58.0	47.8 (6.68)	14.0%	47.2	46.3 - 49.3
CL	L/h	19.0 - 56.3	36.9 (9.11)	24.7%	35.7	34.8 - 38.9
Abbreviations: SD – standard deviation, CV – coefficient of variability, CI – confidence interval						

Variability of V_d and CL is below 15% and 25%, respectively. Variability of k_a is high (100%) while k_a distribution is skewed as indicated by the location of the geometric mean within the observed range.

As requested, sensitivity analyses to estimate the true IR T_{max} and C_{max} were then run by estimating C_{max} and T_{max} using best-fit one compartment PK models individual by individual. This was performed by using a common dose of 100 mg LD, fixed population geometric mean V_d (47.8 L) and CL (36.9 L/h) values, and variable k_a values. As a lower boundary for k_a , $k_{el} = CL/V_d$ ($0.772 h^{-1}$) was selected, since individual LD plasma exposure analyses showed that $k_{el} > k_a$ in more than 80% of individual analyses, indicating that exposure is an elimination rate limited clearance. In addition, lower (1.97) and upper (3.11) k_a values of the 95% confidence interval (CI), population mean k_a (2.54), and the geometric mean k_a value + 1 SD (5.7) estimated in the subject population were used.

The plasma exposure as a function of this k_a value set is shown in the Figure below for a 12-hour range (left column) and the same data plotted in a 2 hours' time frame (right column).

Figure 4: Sensitivity Analysis of predicted LD plasma exposure as function of absorption rate (k_a) range



The lower boundary ($k_a=k_{el}$) clearly shows that at this k_a level >2h post-dose exposure would no longer be adequately predicted. In the remaining four other cases, small differences in T_{max} and C_{max} are observed in the 0–1-hour post-dose period. Importantly, T_{max} values range from 0.44–0.78 h and are thus close to the first sampling time point of 0.5 h. Observed plasma levels at 0.5 h should therefore capture the real C_{max} quite well.

The estimated T_{max} , C_{max} , and C_{max} ratios of these scenarios are listed in the Table below.

Table 6: T_{max} , C_{max} , and C_{max} ratios obtained by sensitivity analyses

k_a reference	value (h^{-1})	T_{max} (h)	C_{max} (ng/mL)	C_{max} ratio
k_{el}	0.7771	1.30	790	62.3%
95% CI lower	1.967	0.78	1166	92.0%
k_a mean	2.538	0.68	1268	100.0%
95% CI upper	3.110	0.60	1345	106.1%
k_a mean + 1 SD	5.072	0.44	1518	119.8%

C_{max} ratios for k_a values at the 95% CI lower and upper boundaries are within $\pm 10\%$ of C_{max} exposure predicted for the mean k_a value. Thus, as already discussed above, over- and underestimation of C_{max} due to missing early sampling time points should be of marginal concern.

Based on the compiled studies IPX203-B14-02 (n=24) and IPX203-B16-01 (day 1, n=27) individual best-fit PK models, early AUC exposure metrics were calculated for time periods: 0–0.5h, 0–1h, and 0–2h for a standard dose of 100 mg LD. Longer time periods were not analysed because rescue doses (IPX203-B14-02) or the second daily dose IPX203- (B16-01) occurred during 3–8 hours post-dosing. The two Tables below show descriptive statistics summaries of these compilations.

Table 7: IPX203-B14-02: Descriptive statistics of partial AUCs estimated from individual best-fit PK models (n=24, dose normalised to 100 mg LD IR)

Parameter	unit	range	mean	SD	Geo mean	% CV	95% CI
T_{max}	h	0.21 - 1.92	0.95	0.52	0.79	54.5	0.737 - 1.16
C_{max}	ng/mL	582 - 3126	1299	609	1173	46.9	1051 - 1546
AUC_{0-0.5h}	h ng/mL	98 - 1295	411	304	312	73.9	287 - 534
AUC_{0-1h}	h ng/mL	329 - 2123	963	514	825	53.3	755 - 1172
AUC_{0-2h}	h ng/mL	914 - 3120	1868	694	1737	37.1	1586 - 2150

Table 8: IPX203-B16-01: Descriptive statistics of partial AUCs estimated from individual best-fit PK models (day 1 n=27, dose normalised to 100 mg LD IR)

Parameter	unit	range	mean	SD	Geo mean	% CV	95% CI
T_{max}	h	0.25 - 2.4	0.92	0.60	0.74	65.8	0.679 - 1.16
C_{max}	ng/mL	290 - 2524	1227	594	1073	48.4	992 - 1461
AUC_{0-0.5h}	h ng/mL	38.9 - 1062	416	300	296	72.1	297 - 535
AUC_{0-1h}	h ng/mL	133 - 2084	937	533	760	56.9	726 - 1148
AUC_{0-2h}	h ng/mL	396 - 3370	1697	706	1529	41.6	1418 - 1976

Descriptive statistics results of individual profiles support the sensitivity analysis. Comparison of T_{max}, C_{max}, and partial AUCs from both Phase 2 studies shows a good congruity across these studies. Although having wide ranges, estimated geometric mean values of all analysed parameters are comparable from study to study. Geometric mean T_{max} is estimated at 0.75 hours again sustaining that sampling at 0.5 hours post-dosing is deemed acceptable for capturing C_{max} correctly.

In summary, the Applicant adequately justified that the 0.5 h first sampling time was acceptable for estimation of IR C_{max}, and any possible underestimation is unlikely to have a major impact on the 2.8× conversion factor.

Moreover, in the course of the procedure, the applicant confirmed that the proposed unit-dose conversion factor (x2.8) was derived using C_{max} matching approach.

A more complete justification of the proposed IR-to-IPX203 conversion algorithm was provided, including additional clinical evidence, quantitative PK simulations for the illustrative cases, and one additional example with the same IR total daily dose. The Applicant also proposed a targeted mitigation at the upper end of the conversion range, allowing initiation with the next lower available capsule strength for patients with a most frequent IR LD dose of 200 mg or higher.

Interim data from a Phase 4 real-world evidence (RWE) study conducted in the United States (ELEVATE-PD study interim analysis with 111 patients) were supplied. This study evaluated the performance of the current IR-to-IPX203 conversion algorithm in routine clinical practice.

These real-world data provided additional external validation that the proposed conversion approach is robust, predictable, and clinically workable across a heterogeneous patient population, and directly addressed concerns that the algorithm would result in unstable or disproportionate dosing in practice.

It was explained that the conversion algorithm is intended as an initial dosing recommendation, followed by individual titration based on efficacy and tolerability. This is clinically relevant, as dose adjustment is expected in advanced Parkinson's disease. The currently available Phase 4 data are

interim and supportive, but they provided useful reassurance that the 2.8× unit-dose conversion can be used in routine clinical practice, with a median of one titration step after conversion. The Phase 3 and Phase 4 data also support BID initiation in patients receiving <500 mg/day IR LD, with maintained clinical benefit and no new safety concern.

The simulations for the proposed cases showed that large nominal increases in total daily LD do not necessarily lead to excessive $C_{\max}$. They also suggest that IPX203 provides more sustained exposure above the proposed efficacy threshold and less fragmented exposure compared with IR. Importantly, in higher-dose scenarios, the proposed lower-dose starting option reduces $C_{\max}$ and total exposure, while maintaining predicted ON-time. This addressed the main concern that the algorithm could lead to excessive exposure in some patients after switch.

In addition, the Applicant proposed a revised SmPC wording for the conversion algorithm. This keeps the 2.8-fold conversion principle but allows starting with the next lower strength when the most frequent IR levodopa dose is 200 mg or higher. The recommendation for follow-up after 1 to 3 days and further dose or dosing-frequency adjustment based on individual response is also clinically relevant and supports safe use during conversion.

Some uncertainty remains because the simulations are model-based and the proposed efficacy threshold may vary between patients. In addition, patients with the same IR TDD but different IR dose patterns may still receive different nominal IPX203 TDD after conversion. However, the Applicant's explanation was considered acceptable in the context of the initial nature of the conversion algorithm, the need for later individual titration, supportive Phase 3/4 data, and the proposed mitigation option for the upper conversion range.

Carbidopa

In the same crossover study, CD was absorbed relatively rapidly after IPX203, with a median $T_{\max}$ of 2.5 h (range 1.5–6.0 h). The mean $C_{\max}$ (all doses) was 571 ng/mL and the mean half-life about 2.3 h. Both IPX203 and Rytary produced a more sustained CD profile than IR LD–CD, maintaining concentrations for longer and indicating extended-release behaviour. As expected from the higher CD dose in IPX203, systemic exposure was greater: $C_{\max}$ and AUC were approximately 3 to 3.5-fold higher than those observed with IR LD–CD. Overall, IPX203 achieved higher and more prolonged CD levels than IR LD–CD, with stability over time comparable to Rytary.

The bioavailability of CD based on dose-normalised natural-log-transformed $AUC_{0-\infty}$ following IPX203 administration was approximately 112% relative to IR CD-LD.

Study IPX203-B16-01

In this phase-2, randomised, open-label, rater-blinded, two-period crossover in advanced PD, IPX203 (LD:CD 4:1) was compared with IR LD–CD under steady dosing after individual titration. For LD, IPX203 delivered a smoother, longer-lasting profile than IR: on Day 15, concentrations were maintained above 50% of $C_{\max}$ for 6.2 h *versus* 3.9 h and above 430 ng/mL for 9.0 h *versus* 7.4 h (both statistically significant), with broadly similar time to 50% $C_{\max}$ and dose-normalised $C_{\max}$ across treatments; fluctuation over 10 h was lower with IPX203 (1.7 vs 2.7) and accumulation over 15 days was minimal and comparable (≈ 1.0 –1.1). The larger AUC with IPX203 reflected the higher LD dose used, and the IR fraction supported a similar onset to clinically meaningful concentrations. The applicant clarified, based on literature data, that the clinically relevant LD threshold for onset of effect is approximately 1000 ng/mL, and that 430 ng/mL was only an internal working reference.

The adequacy of the 0.5h hour as the first sampling timepoint in study IPX203-B16-01 was supported by the model-based sensitivity analysis discussed above for study IPX203-B14-02.

For CD, IPX203 produced higher and more sustained exposure than IR at both single and multiple doses. On Day 15, T_{max} was similar (2.5 h vs 2.0 h), while C_{max} averaged 479 vs 146 ng/mL and AUC_{τ} 1892 vs 416 ng·h/mL (≈ 4.5 -fold), consistent with the higher CD dose and modified-release design; fluctuation indices were comparable (1.7 vs 1.5) and accumulation was low (≈ 1.1) for both treatments. It is emphasised that the non-clinical margin based on the 1-year rhesus monkey NOAEL (≥ 135 mg/kg/day) corresponds to an estimated 4.4-fold margin over the proposed maximal daily CD dose (595 mg/day), which is considered acceptable in the context of the absence of toxicological findings at high chronic doses in primates and the lack of clinically relevant QTc effects at supratherapeutic CD exposure.

Overall, relative to IR LD-CD, IPX203 provided extended coverage with modest peaks for levodopa and substantially higher, sustained carbidopa exposure, without meaningful accumulation over 15 days.

IPX203 PK properties, as summarised above, are reflected in the SmPC.

5.2.2.4. Bioequivalence

No bioequivalence studies were conducted. This was considered acceptable by CHMP.

5.2.2.5. Distribution

The apparent volume of distribution (V/F) was not determined from the conducted phase 1 and phase 2 studies. No PopPK analysis, or *in vitro* and *ex vivo* protein binding studies of LD and CD were performed. However, in the context of a full-mixed application under Article 8(3) of Directive 2001/83/EC, the characterisation of LD and CD PK distribution (as outlined in SmPC section 5.2) was substantiated with literature references.

5.2.2.6. Metabolism

No dedicated *in vitro* metabolism studies were conducted. Instead, the Applicant substantiated with appropriate literature references the statements in SmPC section 5.2 regarding metabolism of both levodopa and carbidopa, including the PKs of its metabolites.

5.2.2.7. Elimination

No mass balance study was conducted.

The elimination half-life was estimated for both LD and CD in the conducted phase 1 and phase 2 studies. The estimates are summarised in the Table below ($t_{1/2}$ (h) (mean $\pm$ SD)):

Table 9: Elimination half-life of levodopa and carbidopa

Drug	IPX203-B16-04 (n=27)	IPX203-B16-05 (n=25)	IPX203-B16-06 (n=40)
Levodopa	1.988 $\pm$ 0.3000	1.997 $\pm$ 0.2620	1.668 $\pm$ 0.1629 to 2.113 $\pm$ 0.6700
Carbidopa	3.903 $\pm$ 0.5606	3.886 $\pm$ 0.4117	3.684 $\pm$ 0.5868 to 3.770 $\pm$ 0.3606

The applicant substantiated with literature references the statements in SmPC section 5.2 regarding the biotransformation and elimination of LD and CD. Levodopa and CD are primarily eliminated via non-renal routes. According to the population PK analysis done with extended-release LD/CD, creatinine clearance is unlikely to have a clinically meaningful effect, given the minor contribution of estimated creatinine clearance to the variability in levodopa exposures. The magnitude of the effect for creatinine clearance above 30 mL/min is not considered clinically meaningful.

Special consideration was given to CD and its metabolites, eliminated in the urine (with a notable fraction excreted unchanged), and possible accumulation in patients with advanced renal disease: during IPX203 administration the exposure to CD was about four times higher than with IR forms administration, thus additional accumulation is possible, and the applicant discussed accordingly the

possible clinical consequences of CD accumulation in patients with renal impairment. Even though in PD patients with renal impairment CD accumulation can cause neuropsychiatric, autonomic, gastrointestinal, metabolic, and motor complications, data from IPX203-B16-01 study confirmed that accumulation ratios for CD following 15 days of IPX203 or IR LD-CD treatment were low and comparable (1.1 for each). In patients with renal impairment, theoretical risks include enhanced peripheral LD exposure, potentially increasing dopaminergic adverse effects (e.g., nausea, orthostatic symptoms) and increased frequency of known LD-related ADR rather than new safety concerns. In the applicant's view, no evidence suggested nephrotoxicity or direct renal adverse effects from CD.

A phase I study to evaluate the effect of high-dose CD on LD PK (Hayashi *et al.*, 2025) brought additional data. In previous non-clinical studies using rats, more than 3-fold prolongation of the LD $t_{1/2}$ was achieved when combined with a high CD dose. This Phase I study aimed to evaluate the effects of high-dose CD on the PK of LD. The study was performed to examine the effects of a combination of LD, CD, and entacapone in healthy male volunteers. Levodopa and entacapone doses were set at approved dose levels. The CD dose ranged from the approved 10 mg–600 mg. In addition to plasma concentrations of LD, those of the metabolites were also determined to evaluate their inhibitory effects on LD-metabolising enzymes. The plasma concentrations of LD and its metabolites were monitored by LC/MS_MS up to 24 h after administration. The observed AEs were mild, and all participants completed the study. At higher CD doses, the area under the LD plasma concentration-time curve increased by approximately 2-fold, and the half-life of LD was slightly prolonged by < 1.4-fold. These changes were much smaller than those observed in rats. The ratios of LD metabolites suggested that dopa deoxy-carboxylase inhibition was saturated at a CD dose of 300 mg. In conclusion, higher CD doses were confirmed as tolerable, and the effect of CD on LD half-life limited.

While CD and its metabolites are eliminated renally and higher CD exposure is expected with IPX203, clinical data from Study IPX203-B16-01 showed low and comparable accumulation for CD after repeated dosing (accumulation ratio ~1.1 for both IPX203 and IR LD-CD), suggesting no meaningful build-up over 15 days in the studied population. The proposed SmPC approach (no dedicated data in renal impairment and recommendation for cautious use) was therefore considered acceptable by the CHMP. For transparency, it is stated that IPX203 has not been specifically studied in patients with renal impairment and that appropriate clinical monitoring during titration is recommended in patients with moderate to severe renal impairment (and severe hepatic impairment).

5.2.2.8. Dose proportionality and time dependency

A dose proportionality study (**IPX203-B16-06**) was conducted to assess the PK of LD and CD following single dose administration of IPX203 capsules (140-35 mg LD-CD, 210-52.5 mg LD-CD, 280-70 mg LD-CD, and 350-87.5 mg LD-CD). For both LD and CD, a dose proportionality was observed in the dose range of IPX203 MR LD-CD 140-35 mg to IPX203 MR LD-CD 350-87.5 mg. The elimination pattern of both drugs was not modified with an increased dose.

Time dependency PK of both LD and CD were assessed in the phase 2 **study IPX203-B16-01**. No time dependent PK were observed for both LD and CD following multiple dose administration of IPX203 in PD patients. Therefore, in SmPC section 5.2 "linearity", is reflected stating that *Hopledo shows dose proportional pharmacokinetics for both carbidopa and levodopa over the levodopa dosage strength range of 140 mg to 350 mg.*

5.2.2.9. Pharmacokinetics in the target population

As already summarised in section 5.2.2.3, the PKs of LD and CD were studied in two Phase 2 studies following IPX203 administration as a single dose (Study **IPX203-B14-02**) and multiple therapeutic doses (Study **IPX203-B16-01**), in subjects with advanced PD.

5.2.2.10. Special populations

No dedicated renal or hepatic impairment studies were conducted following administration of IPX203.

However, the applicant provided an literature-based justification, supported by the known disposition of LD and CD, together with available experience with other LD/CD containing medicinal products already in the EU market, and the individualised titration approach used for this therapeutic class.

With regard to Hopledo administration in patients with **hepatic impairment**, it was justified accordingly that a clinically relevant impact on LD/CD exposure is not expected in patients with mild to moderate hepatic impairment, considering that LD and CD are not primarily dependent on hepatic microsomal metabolism and that LD is mainly metabolised through aromatic AADC and COMT pathways in peripheral tissues. The absence of dedicated PK data is likewise appropriately reflected in SmPC section 5.2, and the recommendation for caution in patients with severe hepatic impairment is considered adequate. Moreover, the applicant revised SmPC section 4.2, recommending caution on dose adjustment in patients with severe hepatic impairment, with appropriate clinical monitoring.

Concerning Hopledo administration in patients with **renal impairment**, the applicant clarified that unchanged LD represents only a minor component of urinary excretion and that renal elimination mainly concerns metabolites rather than parent LD. Of note, the available literature describes that, following a single 50 mg oral dose of ¹⁴C-carbidopa in Parkinsonian patients, about 64% and 33% of the radioactivity were recovered in the urine and faeces, respectively, with a radioactivity amount of 32% in the 0–24-hour urine due to unchanged carbidopa. Three metabolites were identified in urine (2-methyl-3-methoxy-4-hydroxy-phenylpropionic acid, 2-methyl-3,4- dihydroxy-phenylpropionic acid, and 3-hydroxy- α -methylphenylpropionic acid), and each accounted for approximately 10% of the radioactivity excreted in the urine. Therefore, renal excretion is not a major elimination pathway for CD. The applicant amended SmPC section 4.2, recommending caution on dose adjustment in patients with moderate to severe renal impairment, with appropriate clinical monitoring. Supportive information was provided from a population PK analysis performed with an extended-release LD/CD capsule formulation that combined IR and ER beads. This analysis suggested that renal impairment is unlikely to have a clinically significant effect on ER carbidopa–levodopa PK, given the minor contribution of estimated creatinine clearance to the variability in LD exposures. This is appropriately reflected in SmPC section 5.2.

5.2.2.11. Pharmacokinetic interaction studies

5.2.2.11.1. Special populations

Regarding the potential effects of gender, ethnics, and body weight in the pharmacokinetics of levodopa and carbidopa, no dedicated study was performed. Instead, in response to CHMP request, the applicant reviewed literature data accordingly.

Effect of gender

Sex has been recognised as an intrinsic factor contributing to the substantial interindividual variability of LD PK. In clinical studies conducted with ER LD-CD formulation (Numient/Rytary), plasma concentrations of LD were higher in women compared with men, in both healthy subjects and patients with Parkinson's disease ([Mittur et al., 2017](#)). In healthy subjects, mean dose-normalised LD C_{max} values were approximately 25% greater and $AUC_{0-\infty}$ values approximately 38% higher in females than in males, while in patients with PD, mean dose-normalized C_{max} was 35% greater and $AUC_{0-\infty}$ was 37% higher in females than in males. Median t_{max} and $t_{1/2}$ of LD were comparable in men and women for both healthy subjects and patients with PD ([Mittur et al., 2017](#)).

Miyaue *et al.* concluded that sex influences LD PK but has little effect on CD ([Miyaue et al., 2025](#)). In the study by Zappia *et al.*, women were significantly lighter in terms of body weight and had significantly greater AUC than men ([Zappia et al., 2002](#)). Similar results were seen in other studies ([Conti et al., 2022](#)), irrespective of age ([Kumagai et al., 2014](#)). Among the underlying suggested mechanisms, sex-mediated differences in COMT activity and incorrectly normalizing body weight difference between men and women have been accounted for ([Martinelli et al., 2003](#); [Chen et al., 2012a](#); [Chen et al., 2012b](#)).

Effect of body weight

In the study by Mittur *et al.* (2017), dose-normalised C_{max} and $AUC_{0-\infty}$ of LD from ER LD-CD were negatively correlated with body weight in healthy subjects and patients with PD. No difference in t_{max} and $t_{1/2}$ was observed between the weight groups ([Mittur et al., 2017](#)). In the study by Adamiak-Giera *et al.*, body weight has been shown to impact T_{lag} ; very short times correspond to patients with motor complications and times of order of 20 minutes were observed in patients without that impairment. The authors concluded that the higher C_{max} , a large $AUC_{0-\infty}$ ($p < 0.01$), a smaller V/F, and CL/F ($p < 0.01$) seen in patients with motor fluctuations as compared to those without such fluctuations may be explained partly because the mean body weight of this group (68.2 ± 12.3 kg) was lower than that of patients without motor complications (88.7 ± 18.6 kg) ([Adamiak-Giera et al., 2021](#)). The automatic model selection procedure selected neither age nor body weight as statistically significant covariates of the population model for V/F. The patient's age but not the weight proved to be one of predictors of k_{10} and, consequently, of the C_{max} and AUC ([Adamiak-Giera et al., 2021](#)).

Effect of race

The majority of patients with PD in whom PK data were collected were white, therefore, very limited data are available regarding the LD PK across racial and ethnic groups. Studies on ER LD-CD (Rytary/Numient) found that in the healthy population, LD C_{max} and $AUC_{0-\infty}$ values were 10–17% higher in Black *versus* White subjects. Median t_{max} and $t_{1/2}$ were comparable in the two groups.

In summary, some literature data suggested LD bioavailability to be slightly higher in females than in males. However, there may be confounding factors such as body weight. No difference in t_{max} and $t_{1/2}$ were reported between genders and different weight groups. Comparison data regarding PK of LD across racial and ethnic groups are scarce. Nevertheless, individual studies (cited above) conducted in different populations did not indicate any meaningful differences between races.

In summary, IPX203 dosing is individually titrated for patients, and such individualisation considers the differences between gender, race, and body weight. Therefore, the following text, included in SmPC section 5.2. was considered duly justified by the CHMP:

- *There are no clinically significant differences in the pharmacokinetic of levodopa or carbidopa based on gender, race, or body weight.*

Effect of age

Elderly patients were well represented in the PK studies IPX203-B14-02 and IPX203-B16-01, with more than half of participants aged 65 years or older and approximately 20% aged 75 years or older (see also section 5.3.3 of this AR).

In addition, the applicant described the impact of elderly in the PKs of both LD and CD within a review of literature data.

It is well-known that the incidence of PD is closely related to ageing. Ageing may influence PK factors following IR LD-CD administration in the elderly, where the PK of LD-CD was characterised by lower systemic clearance and higher bioavailability, leading to an increased AUC and C_{max} (Robertson *et al.*, 1989). Other published studies demonstrated LD absorption to be consistent regardless of age. Increasing patient's age has been associated with a statistically significant, albeit clinically negligible, increase in LD $t_{1/2}$ and a decrease in apparent oral clearance (Contin *et al.*, 1991). In a population PK model, Othman *et al.* showed that age almost reached significance for inclusion as a covariate for LD clearance but was not included in the final model (Othman and Dutta, 2014).

Some differences in PK parameters between age groups were reported for the ER LD-CD formulation by Mittur *et al.* (2017). Dose-normalised LD $AUC_{0-\infty}$ increased with increasing age in healthy subjects and patients with PD. Age accounted for approximately 4% and 15% of the variability in LD $AUC_{0-\infty}$ in healthy volunteers and patients with PD, respectively, and mean dose-normalised C_{max} and $AUC_{0-\infty}$ were 27% and 52% higher, respectively, in PD patients older than 65 years of age compared with those younger than 50 years of age. However, the authors admitted that majority of patients with PD in whom PK data were available were significantly older than healthy subjects, whereas majority of healthy subjects were younger than 50 years of age.

For IPX203, C_{max} and $AUC_{0-\infty}$ exposure for LD and CD were plotted using data from all Phase 1 and Phase 2 studies (as per the Figures below). Results indicated that LD and CD exposure are not influenced by the age of the patients.

Figure 5: Dose-normalised C_{max} for LD and CD as a Function of Age

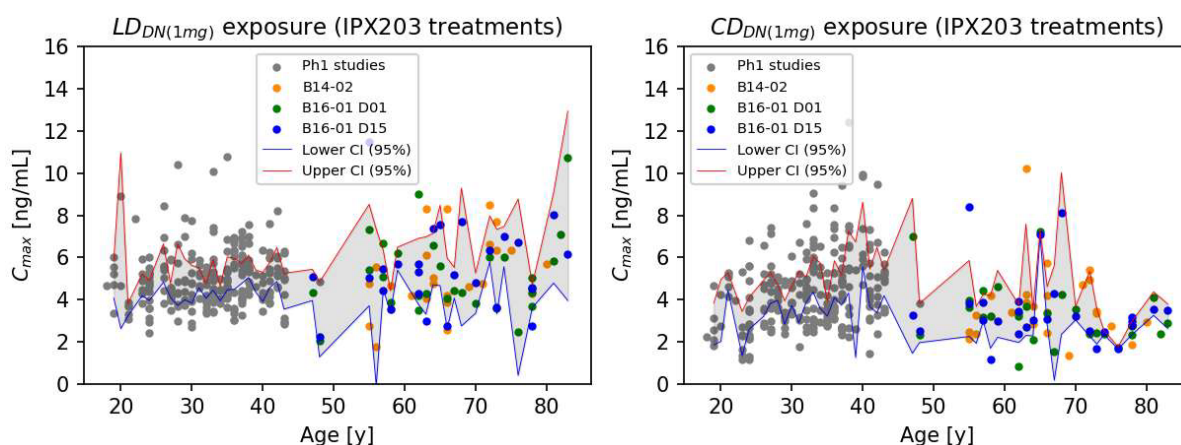
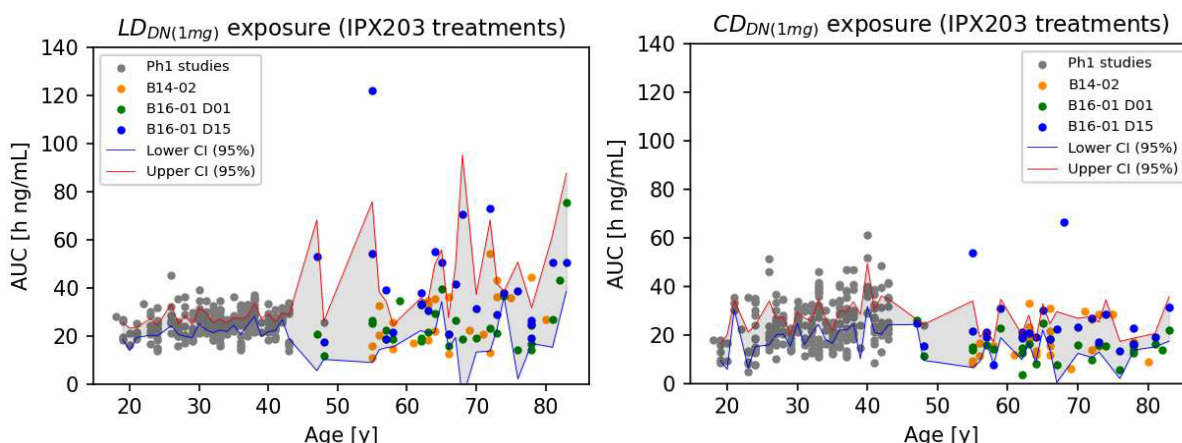


Figure 6: Dose-normalised $AUC_{0-\infty}$ for LD and CD as a Function of Age



In summary, the totality of evidence indicated no PK basis for dose adjustment of LD-CD products by age, particularly in the elderly. Therefore, as outlined in SmPC section 5.2, as the peak concentrations of LD and CD are generally similar between younger (45 to 60 years) and older (60 to 75 years) subjects, no dose adjustment is needed in the elderly. However, as discussed in the safety sections of this AR (and detailed in the SmPC), in patients aged 75 years and older experience serious AEs with IPX203. Consequently, these patients should be converted cautiously from IR LD/DDCI into IPX203. Close clinical monitoring is also recommended during the conversion period and subsequent dose optimisation, in line with standard clinical practice for older patients during dopaminergic therapy adjustments.

5.2.2.11.2. PK drug-drug interactions

No *in vivo* drug-drug interaction (DDI) studies were performed during the development of IPX203. However, in the absence of dedicated DDI studies literature data was supplied. Levodopa/Carbidopa derived from IPX203 is subjected to the same, known drug interactions that are common to other products containing LD/CD, as described in SmPC section 4.5.

5.2.2.11.3. Dose proportionality/time independence/accumulation

A dose proportionality study (**IPX203-B16-06**) was conducted to assess the PK of LD and CD following single dose administration of IPX203 capsules (140-35 mg LD-CD, 210-52.5 mg LD-CD, 280-70 mg LD-CD, and 350-87.5 mg LD-CD). For both LD and CD a dose proportionality was observed in the dose range of IPX203 MR LD-CD 140-35 mg to IPX203 MR LD-CD 350-87.5 mg. The elimination pattern of both drugs was not modified with an increased dose.

Time dependency PK of both LD and CD were assessed in the phase 2 study **IPX203-B16-01**. No time dependent PK were observed for both LD and CD following IPX203 multiple dose administration in PD patients.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

As already outlined in this assessment report (AR), LD is a precursor of dopamine (DA). When administered orally, it is rapidly decarboxylated to DA in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the CNS. Carbidopa is a peripheral dopa decarboxylase inhibitor that prevents metabolism of LD to DA in the peripheral circulation, ensuring that a higher proportion of the dose reaches the brain, where DA can act by restoring dopaminergic stimulation. This mechanism of action (MoA) is extensively documented in the literature.

5.2.3.2. Primary and secondary pharmacology

Primary pharmacodynamics

Primary PD was established throughout the measurement of effects on clinical scores of Parkinson's disease. Therefore, the PD endpoints used were concomitantly efficacy endpoints as well.

Study IPX203-B14-02

The subject motor state assessment results demonstrated a 2.7-hour advantage in total "OFF" time during IPX203 treatment compared with IR CD-LD treatment ($p < 0.0001$) and a 0.9-hour advantage compared with Rytary ($p = 0.023$). During IPX203 treatment, this reduction in "OFF" time was accompanied by increased in "ON time" without troublesome dyskinesia ("Good ON time"), on average, 2.6 hours more than IR CD-LD and 0.9 hours more than Rytary ($p < 0.0001$ and $p = 0.0259$, respectively).

The MDS-UPDRS Part III score results showed a similar pattern of effect in favour of IPX203. In the first 2 hours postdose, IPX203, Rytary, and IR CD-LD each exhibited rapid improvement in motor function. Starting at hour 3, both IPX203 and Rytary maintained significantly greater improvement in MDS-UPDRS Part III scores than did IR CD-LD, which lasted through Hour 5 with Rytary and through the last measurement at Hour 10 with IPX203. IPX203 had a longer duration of effect compared with IR CD-LD ($p < 0.0001$) and Rytary ($p \leq 0.0290$), respectively, based on 4, 7, and 13-point improvements in MDS-UPDRS Part III scores from average predose value.

Study IPX203-B16-01

With IPX203 treatment, subjects experienced less "OFF time" as a percentage of their waking hours (mean 19.3% compared with 33.5% with IR CD-LD). In addition, subjects had more total "Good ON Time" with IPX203 compared to IR CD-LD, whether measured out (of clinic) by the subject with a home diary or by the investigator in the clinic. The average durations of "Good ON" episodes or any "ON" episodes based on patient's diary entries were longer with IPX203 compared to IR CD-LD. Treatment with IPX203 was also associated with fewer motor fluctuations per day than IR CD-LD.

With IPX203, subjects were 73.3% less likely to receive rescue medication (Day 1) and 72.1% less likely to receive a re-dose (Day 15) than during IR CD-LD treatment.

Improvements in MDS-UPDRS Part III mean scores were greater for subjects receiving IPX203 than IR CD-LD from 3 to 8 hours postdose on Day 1, and from 2 to 4 hours post-dose on Day 15. On Day 15, when subjects had not had a study treatment for at least 5 hours, mean predose Part III scores were lower in IPX203-treated subjects.

Nevertheless, it should be noted that the results from the MDS-UPDRS Part III scores were much more relevant than for the MDS-UPDRS Part IV scores, both in terms of statistical and clinical significance.

It is unquestionable that MDS-UPDRS Part III remains the classical and well-established endpoint to demonstrate motor benefit, as stated in the EMA Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease (EMA/CHMP/330418/2012 rev. 2). It is also unquestionable that MDS-UPDRS Part IV is not relevant for the assessment of dyskinesias, as also stated in this EMA guideline. Nevertheless, the purpose of the guideline is to guide in the clinical development of investigational products for the treatment of PD, which implies the assessment of their efficacy in treating the motor symptoms, aspect in which MDS-UPDRS Part III is considered the best score.

However, in the specific development of Hopledo, the efficacy of LD-CD in treating motor symptoms in PD had been already thoroughly established, while the main objective of the clinical development was

to specifically demonstrate that this formulation shows improvements in motor fluctuations and treatment-related motor complications.

While it can be agreed that measurement of "OFF"-time or "On-time" is the main efficacy variable, an operational definition of what will be considered an "OFF" and "ON" period should be established. It should be also clear to what extent "On"-time with dyskinesia and "On"-time without dyskinesia is increased. Patients changing from "OFF" to "ON" with dyskinesia should be asked whether they consider this an improvement or not, as per the EMA guideline above mentioned.

Taking this into consideration, the assessment of MDS-UPDRS Part IV added value in these particular development goals.

While for Part III results were consistently improved with IPX203, in several questions of Part IV that was not the case. Of note, the only statistical difference obtained (in questions) from MDS-UPDRS Part IV was outlined for question 4.3: "Time spent in the OFF state". However, in the analysis of "change from baseline" the differences in the mean of change from baseline was 0.5 (+/-0.51). If considering the median, there was no difference. A reduction of approximately 1 hour/day of "OFF" time is generally regarded as the minimal clinically important improvement.

There was a lack of correlation of the MDS-UPDRS Part III positive results with the absence of results in Part IV, specifically given the limited clinical relevance of the results in the time spent in the "OFF state". The applicant provided a largely acceptable methodological explanation for the discordance between MDS-UPDRS Part III and Part IV. However, this response was generally descriptive and partially evasive of the main issue raised in this question: whether the observed Part III improvements translated into clinically meaningful benefit in a formulation specifically intended to modify levodopa exposure and, therefore, motor complications.

It can be acknowledged that the short-duration Phase 2 studies were not designed to capture Part IV changes and that the general design is broadly consistent with the EMA Guideline on clinical investigation of medicinal products in Parkinson's disease. Although the applicant's explanation is methodologically reasonable it is scientifically insufficient and the absence of correlation between Part III and Part IV remains a concern, not merely a design artefact. Overall, the response failed to address the central PD expectation that a modified-release levodopa formulation is specifically intended to smooth plasma concentrations and reduce motor complications, which in this case still lacks sufficient PK/PD translation. Nevertheless, the CHMP agreed not to pursue further this matter, as not impacting Hopledo overall benefit-risk profile.

Secondary pharmacodynamics

Hopledo intendeds to provide a peak LD plasma concentration (C_{max}) that does not exceed the exposures reached with other currently marketed formulations to treat PD. However, the CD C_{max} following maximum dosing was expected to exceed that (of other currently marketed preparations).

QT prolongation effects were assessed in a supratherapeutic study with moxifloxacin as positive control. No significant ECG changes were detected, and C-QT analysis did not show any statistically significant relationship between CD and QTc.

In the course of the procedure the applicant was asked to provide the empirical distribution of clinical C_{max} for CD (including the data from studies IPX203-B14-02, IPX203- B16-01 or pooled PK and fasting status) at the maximal per-dose 175 mg (per SmPC conversion), reported as the 50th and 95th percentile (the median), and overlaid against the TQT 400 mg C_{max} distribution.

In the TQT study with IPX203 (**study IPX203-102-23**), 35 healthy subjects received IPX203, placebo and moxifloxacin in separate treatment periods using a 3-way crossover design. The primary objective was to evaluate the effect of a single supratherapeutic dose of CD (400 mg) on cardiac repolarisation

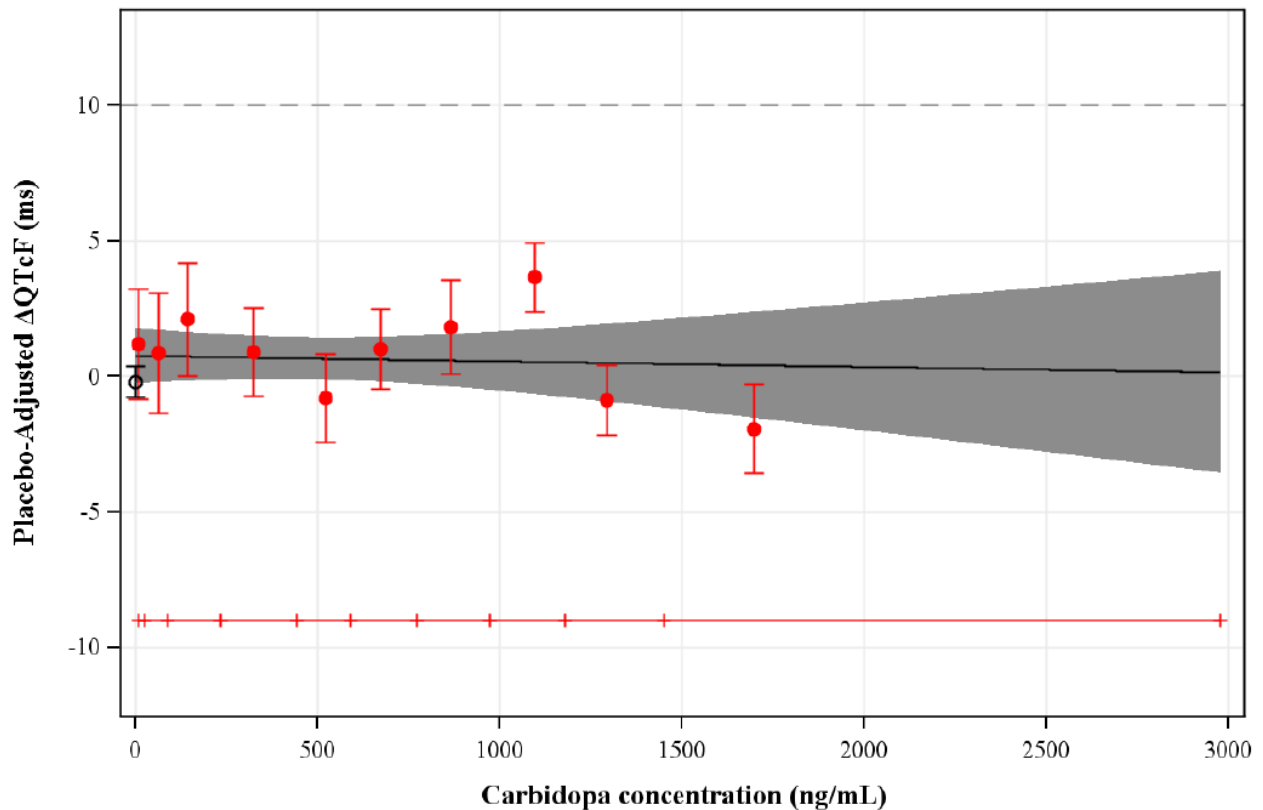
relative to placebo in healthy adult subjects. CD at the studied concentrations did not have a relevant effect on heart rate and therefore, change-from-baseline QTcF (ΔQTcF) was used as the primary endpoint. Carbidopa did not have an effect on the placebo-corrected, change-from-baseline QTc interval ($\Delta\Delta\text{QTcF}$) and an effect exceeding 10 ms could be excluded within the full range of observed range of plasma concentrations up to ~3000 ng/mL.

Based on data from healthy subjects in studies IPX203-B16-04, IPX203-B16-05, and IPX203-B16-06, in which the highest studied CD dose was 70 to 87.5 mg, mean C_{max} of a 175 mg dose could be estimated to levels between 740 and 1010 ng/mL, with a median value between 700 and 940 ng/mL and the 95th percentile between 1250 and 1710 ng/mL. It should be noted that these values were extrapolated from lower doses assuming PK linearity.

In the targeted patient population with advanced PD, PK data were available from 25 to 28 subjects in studies, IPX203-B14-02 and IPX203-B16-01. In these studies, the highest studied CD dose was 67.5 mg. In this patient's population, mean C_{max} of a 175 mg dose of CD could be estimated to levels between 570 to 650 ng/mL, with a median value between 540 and 595 ng/mL and 95th percentile between 990 and 1370 ng/mL (Day 15 in Study IPX203-B16-01, n= 27).

The Figure below displays the Goodness-of-fit plot of placebo-adjusted, change-from-baseline QTcF vs CD concentrations from the TQT study (Study IPX203-102-23).

Figure 7: Model-predicted $\Delta\Delta\text{QTcF}$ (Mean and 90% CI) and Estimated Placebo-adjusted ΔQTcF (Mean and 90% CI) Across Deciles of Carbidopa Plasma Concentrations (Concentration-QTc Analysis Set)



The solid black line with gray shaded area denotes the model-predicted mean $\Delta\Delta\text{QTcF}$ with 90% CI, which is calculated from the equation $\Delta\Delta\text{QTcF (ms)} = 0.75 \text{ (ms)} - 0.00020 \text{ (ms per ng/mL)} \times \text{carbidoopa plasma concentration (ng/mL)}$.

The red filled circles with vertical bars denote the estimated mean placebo-adjusted ΔQTcF with 90% CI displayed at the associated median plasma concentration within each decile for carbidoopa, among which the individually estimated placebo-adjusted $\Delta\text{QTcF}_{i,k}$ equals the individual $\Delta\text{QTcF}_{i,k}$ for subject i administered with carbidoopa at time point k minus the estimation of time effect at time point k . The black circle with vertical bars denotes the mean placebo-adjusted ΔQTcF with 90% CI for placebo at a concentration of 0.

The horizontal red line with notches shows the range of concentrations divided into deciles for carbidoopa. The area between each decile represents the point at which 10% of the data are present; the first notch to second notch denotes the first 10% of the data, the second notch to third notch denotes the 10-20% of the data and so on. The dashed line is a reference line at 10 ms.

The slope of the CD concentration- $\Delta\Delta\text{QTcF}$ relationship was very shallow and slightly negative, (-0.00020 ms per ng/mL) and not statistically significant (2-sided 90% CI: -0.001644 to 0.001237 ms per ng/mL). Using this model, the predicted effect on the QTc interval, at the most conservative concentration, estimated in the targeted patient population on a CD dose of 175 mg, is shown in the Table below. Mean, median, and 95th percentile values were calculated by standard statistical procedures. Mean expressed as the sum of all observations divided by their total number. Median (50th percentile) as the number separating the data set into two equal parts lower and higher than the median. The 95th percentile is the number that is greater than 95% of the numbers in the given data set.

Table 10: Predicted effect on the QTc interval ($\Delta\Delta\text{QTcF}$, ms) at estimated concentrations in patients with advanced Parkinson's disease dosed with IPX203 175 mg

Study	Concentration at steady state (Day 15) ng/mL		
	Mean C_{max}	Median	95 th percentile
IPX203-B16-01, Day 15	613	539	1371
Predicted $\Delta\Delta\text{QTcF}$, ms	0.63	0.64	0.48

The red vertical lines in the Goodness-of-fit plot above show the predicted effect at concentrations of ~600 ng/mL and ~1400 ng/mL. The grey shaded area corresponds to the 2-sided 90% CI of the predicted effect on the QTc interval, and it is evident that an effect exceeding the regulatory threshold of 10 ms can be excluded at these concentrations (i.e., the upper bound of the 90% CI is even below 5 ms).

Overall, the requested exposure-margin context for CD at the maximal per-dose level (175 mg), linked to the TQT exposure-QTc model provided by the applicant was considered adequate. The CHMP noted that, in the target PD population (Study IPX203-B16-01, Day 15), the estimated C_{max} distribution for a 175 mg CD dose (mean 613 ng/mL; median 539 ng/mL; 95th percentile 1371 ng/mL) falls within the concentration range covered by the TQT study, where an effect >10 ms was excluded across observed concentrations (up to 3000 ng/mL). Using the final concentration-QTc model, the predicted $\Delta\Delta\text{QTcF}$ at mean/median/P95 clinical C_{max} values is small (0.5–0.6 ms), and remains well below the regulatory threshold, supporting a low QT risk for CD.

While the 175 mg estimates were derived by extrapolation from lower CD doses assuming PK linearity, this was considered acceptable in the context of the clearly negative TQT results, the shallow (slightly negative) concentration-QTc slope, and the substantial exposure coverage provided by the TQT dataset.

However, because the achieved exposure margin *versus* the worst-case clinical C_{max} was below the ICH E14 preference, in the course of the procedure, the applicant was also requested to demonstrate, using the final concentration-QTc model, that the predicted $\Delta\Delta\text{QTcF}$ and its upper 90% CI remain <10 ms up to the clinical 95th percentile C_{max} from clinical studies. Thus, an exposure-QTc bridging assessment, using the final concentration-QTc model from study **IPX203-102-23** and the observed clinical C_{max} data from studies **IPX203-B14-02** and **IPX203-B16-01**, was submitted and it is summarised below.

In study IPX203-B14-02, where subjects with advanced PD were given a single dose of IPX203, mean C_{max} ($\pm$ SD) across all dose groups was 571 (400) ng/mL ($n = 24$). In the highest IPX203 dose group (202.5 mg; $n = 5$), mean C_{max} was 1022 (615) ng/mL.

At steady state on Day 15 in study IPX203-B16-01, mean C_{max} across all dose groups was 479 (291) ng/mL ($n = 27$) and in the highest dose group with a mean dose of 225 mg ($n = 2$), mean C_{max} was 862 (9.2) ng/mL.

The effect on the placebo-adjusted, change-from-baseline QTc ($\Delta\Delta\text{QTcF}$) at these concentrations could be estimated using data from Study IPX203-102-23, as above described.

Table 11: Predicted effect on mean QTc interval ($\Delta\Delta\text{QTcF}$) at selected concentrations in patients with advanced Parkinson's disease (Study IPX203-B14-02 and IPX203-B16-01)

Study		Mean C_{max} (SD), ng/mL	$\Delta\Delta\text{QTcF}$ mean, ms	95 th percentile ng/mL	$\Delta\Delta\text{QTcF}$ mean, ms
IPX203-B14-02	All doses n= 24	571 (400)	0.64	1229	0.50
	Highest IPX203 dose (202.5 mg) n= 5	1022 (615)	0.55	2034	0.34
IPX203-B16-01 Day 15	All doses n= 27	479 (291)	0.65	958	0.56
	Highest IPX203 dose (225 mg) n= 2	862 (9.2)	0.58	877	0.57

As can be seen from the Figure above, the upper bound of the 90% CI at the concentrations given in Table 18 is substantially below 10 ms, in fact below 5 ms. Predicted placebo-adjusted QTc effects ($\Delta\Delta\text{QTcF}$) at both the mean C_{max} and the clinical 95th percentile C_{max} values are small (0.3–0.7 ms), and the upper bound of the 90% CI at these concentrations remains below the regulatory threshold of 10 ms (reported as <5 ms). Therefore, the Applicant adequately demonstrated that a clinically relevant QTc effect can be excluded up to the clinical upper tail of exposure.

In addition, since CD is eliminated via renal route, the applicant provided an exposure-margin sensitivity showing predicted $\Delta\Delta\text{QTcF}$ (upper 90% CI) at the upper tail of C_{max} expected in low-eGFR subgroups (e.g., pooled PK stratified by eGFR categories), confirming that the upper bound remains <10 ms at those exposures, including a sensitivity cut stratified by age $\geq 65/\geq 75$ years to account for age-related decline in renal function.

The Table below shows CD concentration values from subjects in the Phase 2 program with concentrations above 900 ng/mL. Table 20 thereafter shows CD concentration values in subjects in the Phase 2 program with eGFR < 60 mL/1.73m² (KDIGO stage 3b). As can be seen, reduced renal function does not seem to result in substantially higher C_{max} levels and importantly, all observed peak concentrations are well below the threshold for a concerning QTc effect of 3000 ng/mL.

Table 12: Subjects in Phase 2 Studies with CD C_{max} >900 mg/mL

STUDY	SUBJID	DAY	AGE	CD dose (mg)	C_{max} (ng/mL)
IPX203-B14-02	IPX203-B14-02-103-003		66	180	1030
IPX203-B14-02	IPX203-B14-02-107-001	all	63	202.5	2070
IPX203-B14-02	IPX203-B14-02-107-002	Day 1	72	202.5	1000
IPX203-B14-02	IPX203-B14-02-110-004		64	180	661
IPX203-B16-01	IPX203-B14-02-110-004	Day 1	65	180	1300
IPX203-B16-01	IPX203-B14-02-110-004	Day 15	65	180	1280
IPX203-B16-01	IPX203-B16-01-101-006	Day 1	47	180	1260
IPX203-B16-01	IPX203-B16-01-101-006	Day 15	47	202.5	659
IPX203-B16-01	IPX203-B16-01-104-001	Day 1	68	135	571
IPX203-B16-01	IPX203-B16-01-104-001	Day 15	68	112.5	916
IPX203-B16-01	IPX203-B16-01-114-001	Day 1	57	225	1000
IPX203-B16-01	IPX203-B16-01-114-001	Day 15	57	225	868

Table 13: Subjects in Phase 2 Studies with eGFR <60 mL/1.73m² (KDIGO stage 3b)

STUDY	SUBJID	SEX	AGE	eGFR (mL/1.73m ²)	CD dose (mg)	C _{max} (ng/mL)
IPX203-B14-02	IPX203-B14-02-101-006	F	71	44	180	849
IPX203-B14-02	IPX203-B14-02-106-003	F	75	59	135	370
IPX203-B14-02	IPX203-B14-02-106-005	M	73	58	135	467
IPX203-B14-02	IPX203-B14-02-110-005	F	66	55	90	220
IPX203-B16-01	IPX203-B14-02-106-005	M	73	49	90	215
IPX203-B16-01	IPX203-B14-02-110-005	F	66	55	90	302

Supportive empirical data from the Phase 2 programme were also submitted, by listing subjects with CD C_{max} >900 ng/mL and subjects with eGFR <60 mL/min/1.73 m², including age and observed C_{max}. These data did not indicate a consistent increase in CD C_{max} in the low-eGFR subgroup, and the observed peak concentrations in this subgroup remained within the concentration range covered by the TQT exposure-QTc assessment, where a clinically relevant QTc effect was excluded.

Although the response did not present a formal model-based “exposure-margin sensitivity” by eGFR category (with predicted $\Delta\Delta\text{QTcF}$ and upper 90% CI) as originally requested, the provided patient-level listings adequately addressed the underlying concern by showing that reduced renal function (including older subjects) is not associated with materially higher peak CD exposure in the available clinical dataset.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

The Applicant included relevant interactions in the SmPC, which overlap with those of other currently approved LD/CD-containing medicinal products.

5.2.3.4. Genetic differences in PD response

No genetic difference that can affect Hopledo PD response in a clinically significant way was foreseen.

5.2.3.5. Immunological events

Not applicable.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Pharmacodynamics

Study **IPX203-B14-02** aimed to assess, amongst other objectives, the pharmacodynamics and pharmacokinetics of IPX203 single doses in subjects with advanced PD, using Rytary and IR CD-LD as references.

The initial rates of decrease in MDS-UPDRS Part III scores from average baseline (corresponding to an improvement in motor symptoms) were comparable for all three treatments. However, the MDS-UPDRS Part III score decrease(s) lasted for a longer duration following IPX203 treatment than following IR CD-LD or Rytary. Maximum decreases in MDS-UPDRS Part III scores from average baseline occurred at times that lagged behind the time of peak plasma concentrations of LD for the particular treatment.

Study **IPX203-B16-01** intended to assess also PK/PD correlations in both single and multiple doses. In the single dose setting the initial decreases in MDS-UPDRS Part III scores from average baseline (corresponding to an improvement in motor symptoms) were comparable between the two treatments. However, decrements in the MDS-UPDRS Part III scores lasted for a longer duration following IPX203 treatment than following IR CD-LD treatment. Maximum decreases in MDS-UPDRS Part III scores from average baseline occurred at times that lagged behind the time of peak plasma concentrations of LD for this particular treatment.

In the multiple dose setting, at predose on Day 15, treatment with IPX203 showed a greater mean decrement (-9.3) in MDS-UPDRS Part III scores than did treatment with IR CD-LD (+0.1). As observed following the first dose on Day 1, a qualitative concordance was noted between the LD plasma concentration profile and changes in MDS-UPDRS Part III scores. The initial rates of improvement in motor symptoms were comparable between the two treatments. However, improvements in the MDS-UPDRS Part III scores lasted for a longer duration following IPX203 treatment than IR CD-LD, which may be associated with less frequent dosing of IPX203 than IR CD-LD.

Given the uncertainties on whether the improved duration of motor benefit with IPX203 was driven by higher total levodopa exposure (dose/AUC) or by a true pharmacokinetic advantage (PK profile, longer time above effective concentration or other), the applicant was asked to provide further data. Specifically, it was requested to provide a simple exposure-matched comparison (IPX203 vs IR at comparable LD AUC_{0-τ} or comparable total daily LD dose), presenting key clinical outcomes (e.g., Area Under the Effect Curve [AUEC] of ΔMDS-UPDRS III, time in "Good ON" / time to rescue or second dose, and dyskinesia-related tolerability if available).

The applicant submitted accordingly an exposure-response analysis using data from Studies IPX203-B14-02 and IPX203-B16-01. Individual C_{max}, AUC, time above the proposed LD efficacy threshold of 750 ng/mL, and AUEC of ΔMDS-UPDRS Part III were assessed and presented by treatment. The applicant explained that a fully exposure-matched comparison is difficult, because IPX203-B14-02 was a single-dose study and IPX203-B16-01 included multiple-dose treatment with individual dose adjustments and limited PK/PD sampling. This limitation was acknowledged and considered acceptable by CHMP. Study IPX203-B16-01 was designed to compare plasma exposure and anti-parkinsonian efficacy following Sinemet IR or IPX203 administration. Efficacy data were only recorded during PK days after the first dose until rescue in study IPX203-B14-02. From the 24 PK completers, during IR treatment 11 subjects took rescue administration at less than 6 hours. To avoid exposure and efficacy readings due to unscheduled rescue dose administration, only IPX203-B14-02 PK-PD data were evaluated for data readings limited to the period post-dose until rescue. However, this data set was the cleanest available as all dose (exposure) responses were associated with a single dose administration.

The administration regimen on day 15 in study IPX203-B16-01 did, however, better reflect the typical clinical use. On day 15, PK sampling and MDS-UPDRS part III scores were performed over 10 hours during which dose amounts, frequency, and intervals were different from individual to individual.

Plasma exposure data compilation

For both studies, C_{max} and AUC values were extracted from the respective study analysis data model (AdAM) database. Time above threshold was calculated from each individual's LD exposure data. To assure better precision before evaluating the time above threshold periods, LD exposure profiles were enriched with additional time-concentration data. This was done by interpolating concentration at time *t* (C_t) levels for time points in-between measured values in a step size of 0.05 hours.

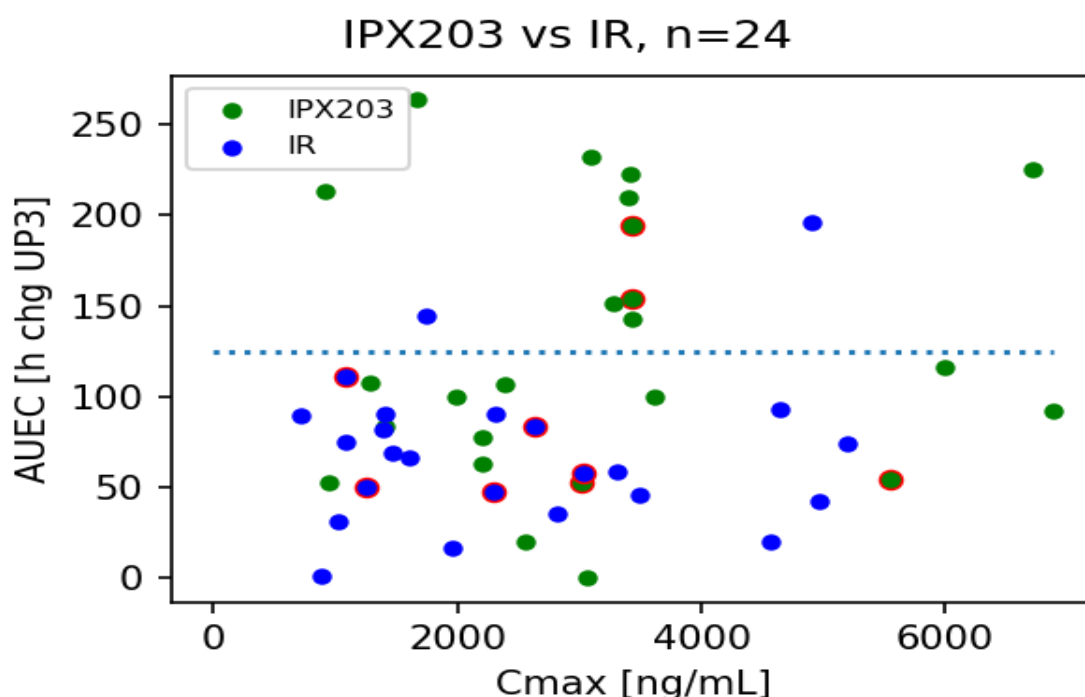
MDS-UPDRS part III data compilation

Data of Δ MDS-UPDRS part III scores were extracted from the AdAM data base of IPX203-B14-02 and IPX203-B16-01 recordings. Using these data, AUEC of Δ MDS-UPDRS part III scores were compiled for each individual over the period from dose administration until rescue medication for study IPX203-B14-02 and over 10 hours for study IPX203-B16-01.

PK-PD relations

All data sets (time above 750 ng/mL threshold, C_{max} , AUC, and AUEC of Δ MDS-UPDRS part III scores) were combined by subject and treatment and used for the evaluation of PK-PD relations. The Figure below shows the correlation of LD C_{max} with efficacy expressed as AUEC of Δ MDS-UPDRS part III scores. Treatment results with Sinemet IR plotted as orange and those with IPX203 as green dots.

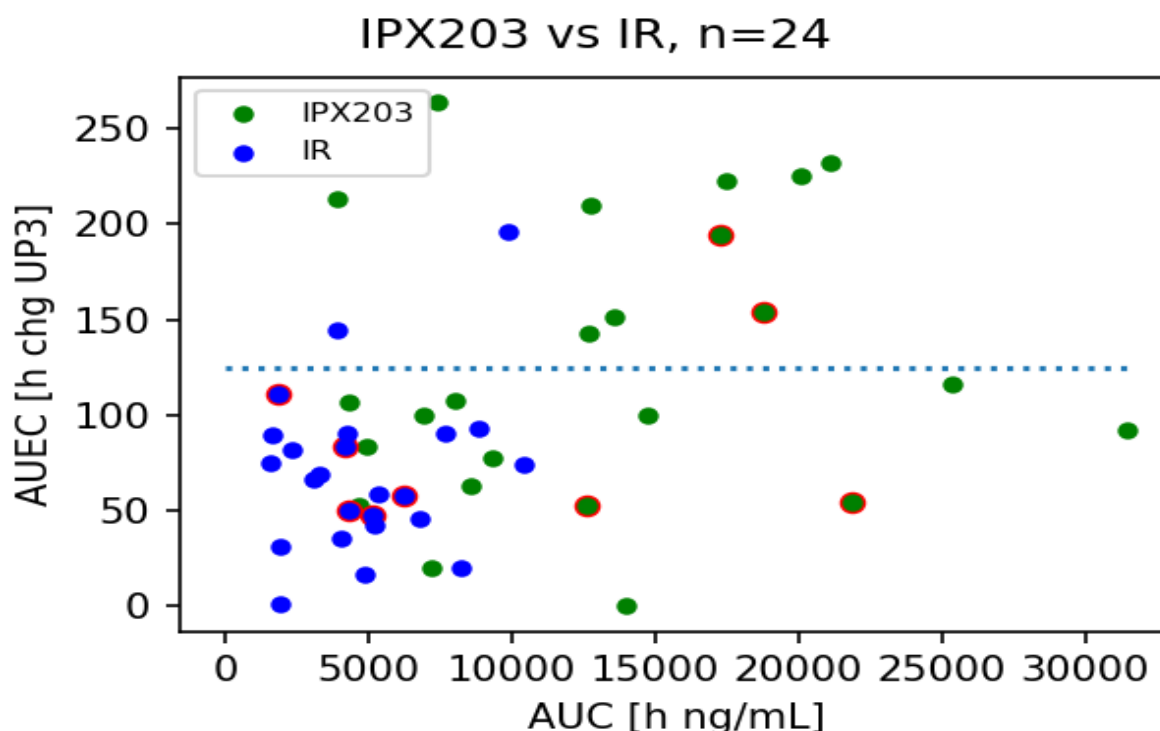
Figure 8: Correlation of C_{max} with AUEC of Δ MDS-UPDRS part III scores



IPX203 results are presented as green and Sinemet IR results as blue circles. Data points of those subjects in IPX203-B14-02, for whom a treatment emerging adverse event (TEAE) was recorded, are decorated by a red ring. The dotted line represents the half-maximal AUEC value observed in either study. Of note: AUEC scales are different in both plots. This due to the fact that AUEC was derived from a single dose administration (IPX203-B14-02) and multiple dose administrations (IPX203-B16-01, day 15), respectively.

C_{max} correlation shows that IPX203 was designed to align C_{max} levels of IR and IPX203 by conversion. Since doses of 100-250 mg LD (Sinemet IR) and 360-810 mg LD (IPX203) were administered in these Phase 2 studies, C_{max} is distributed over a wide range for both formulations with similar C_{max} exposure levels regardless which formulation was used. Although C_{max} exposure matching can be assumed, a tendency for IPX203 to result in better efficacy could already be postulated. TEAE in IPX203-B14-02 (dots decorated with red circles) occurred in similar number and type during both treatments and do not seem to be related to the observed C_{max} exposure level. The following Figure shows the correlation of AUEC Δ MDS-UPDRS part III scores with AUC with identical colour coding.

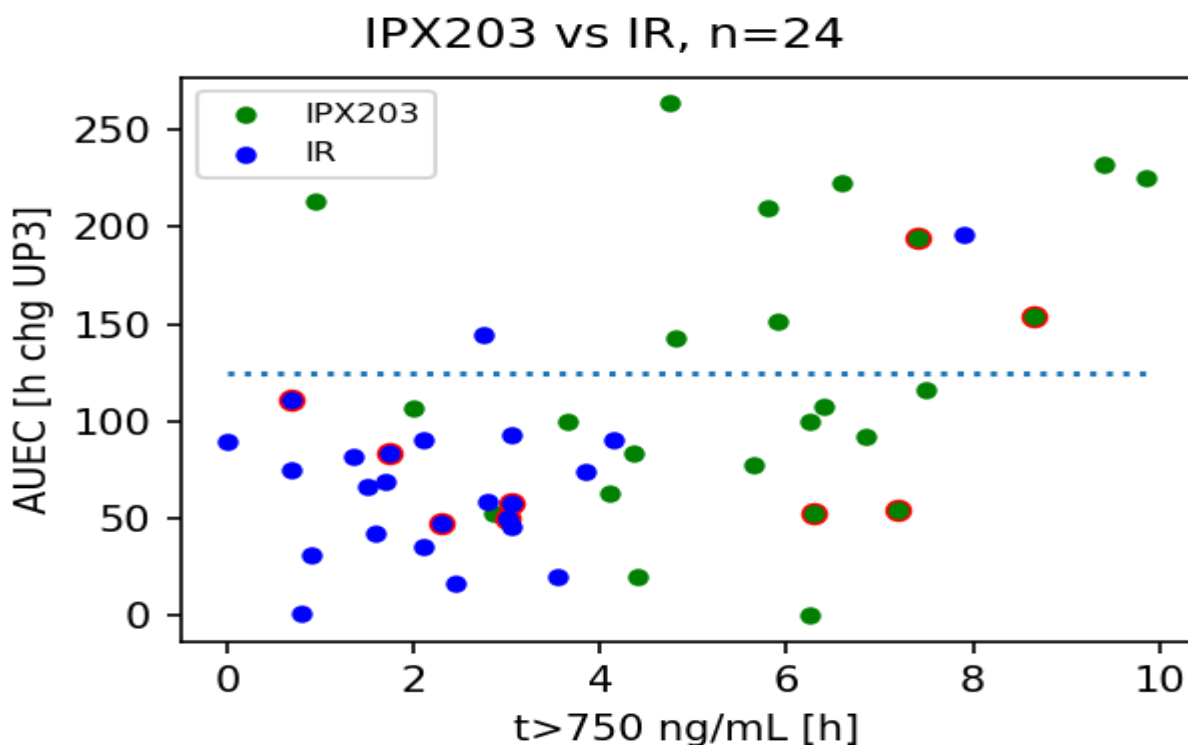
Figure 9: Correlation of AUC_{last} with AUEC of Δ MDS-UPDRS part III scores



In this representation, it is evident that Sinemet IR and IPX203 data sets separate. Most of Sinemet IR AUC exposure is located in the left lower quadrant of the plot (blue dots). Due to IPX203 formulation design and conversion requirements, there is limited overlap in AUC exposure (green dots in lower left quadrant). Nevertheless, for similar AUC exposure due to Sinemet IR or IPX203 administration also similar efficacy was recorded, likewise with a tendency to result in better efficacy when IPX203 is used. Otherwise, no AUC exposure matching of Sinemet IR with IPX203 is achieved due to dose conversion as per study design. For AUC exposure beyond 10000 h ng/mL there are no more or few equivalent Sinemet IR AUC levels upon single dosing. Due to multiple dosing in IPX203-B16-01, this separation is less remarkable. Notably, almost all higher AUEC Δ MDS-UPDRS part III values were achieved with IPX203 treatment. TEAEs can as well not clearly be related to AUC.

Finally, the Figure below shows the correlation of exposure above a putative threshold for the onset of anti-parkinsonian effects at 750 ng/mL.

Figure 10: Correlation of time>750 ng/mL with AUEC of Δ MDS-UPDRS part III scores



As derived from the AUC vs AUEC plots, also in this comparison Sinemet IR results reside in the lower left quadrant for study IPX203-B14-02 (single dose). All but one Sinemet IR administrations result in limited times above efficacy threshold (left lower quadrant, <4h). In both study reports it was already documented that Δ MDS-UPDRS part III changes from baseline had a significantly longer duration of effect (from 2 to up to 10 hours) compared with Sinemet IR ($p < 0.0001$).

Due to multiple dosing on day 15 in study IPX-B16-01, time above threshold following Sinemet IR or IPX203 administration is no longer clustered. However, these were achieved with mean periods between daily doses of 7 hours (IPX203) versus 4 hours (Sinemet IR), thus, with fewer LD plasma level fluctuations when using IPX203. Moreover, as in IPX203-B14-02 best efficacy linked to longer periods above threshold is nearly exclusively seen following IPX203 administration.

It is difficult to identify a clear driver of efficacy, AUC or time above efficacy threshold are however potential candidates. In particular this is challenging for time above efficacy threshold in the multiple dosing situation on day 15 in study IPX203-B16-01. What is obvious is that IPX203 administration results in higher efficacy whatever comparison is used. Only IPX203 reaches maximum efficacy levels (AUEC). In general, equivalent C_{max} and AUC exposures result in similar efficacy regardless of whether administered as Sinemet IR or IPX203. Thus, the concept of the new IPX203 design to provide sustained LD supply over a longer period of time was achieved by delivering more LD amount from an extended-release component. These higher LD amounts led to an augmented AUC ($=D/CL$) and similarly longer time above efficacy threshold while limiting peak dose levels efficiently.

As seen in IPX203-B14-02, TEAEs did not seem to be related to C_{max} or AUC exposure. These events were similar in number and type for both treatment arms and were basically observed over the entire C_{max} and AUC range determined.

In summary, the provided analyses suggested that C_{max} alone is not the main driver of the longer motor benefit with IPX203, as C_{max} values overlap between IPX203 and IR. Higher AUC and longer time above the efficacy threshold seemed to be more relevant for the sustained response. This is consistent

with the formulation concept of IPX203, where additional LD is delivered from the extended-release (ER) component, leading to higher overall exposure and longer time above an effective concentration.

The applicant also noted that, where similar $C_{\max}$ or AUC values were observed, clinical efficacy was generally similar between IR and IPX203. Higher AUEC values of Δ MDS-UPDRS Part III and longer duration of effect were mainly observed with IPX203, which is consistent with the longer time above threshold.

In conclusion, presented data supported the notion that the prolonged clinical benefit of IPX203 is driven mainly by higher total LD exposure and longer time above an effective LD concentration, rather than by higher $C_{\max}$.

5.2.5. Dose selection and therapeutic window

The selection of doses for IPX203 and Rytary (LD/CD formulated in an ER capsule) was primarily based on achieving peak LD plasma concentrations within $\pm 20\%$ of those resulting from the corresponding doses of IR LD-CD. This approach aimed to ensure comparable peak exposure while minimising potential side effects.

Studies **IPX203-B14-02** and **IPX203-B16-01** provided key PK insights:

- The mean $C_{\max}$ (maximum concentration) and AUC $_{0-\infty}$ (area under the curve from time zero to infinity) values of LD increased in an approximately dose-proportional manner with the LD dose following IPX203 and Rytary administration.
- For IPX203, doses of 270 to 360 mg were estimated to provide peak LD concentrations comparable to those of 100 mg LD from IR LD-CD, based on previous PK data.
- The dose-proportional increase in LD $C_{\max}$ and AUC $_{0-\infty}$ was consistent across the dose range of 360 mg to 900 mg studied in the trials, indicating predictable PK.

The typical IPX203 dosing regimen was three times a day, approximately every 7 to 8 hours, allowing for adjustments during the first 9 days of each treatment period to optimise efficacy, tolerability, and safety.

The ability to adjust dosing frequency and amount enabled personalised treatment regimens, aiming to minimise "OFF" time and dopaminergic side effects.

IPX203 demonstrated a lower degree of peak-to-trough fluctuation in plasma LD concentrations and was associated with less frequent dosing compared to IR LD-CD.

The PK profile of IPX203 showed low accumulation and predictable PK following multiple doses, supporting its use as a therapeutic option with potentially favorable dosing profile.

The estimated comparable doses of IPX203 to IR LD-CD (e.g., 280-370 mg IPX203 to 100-250 mg IR LD-CD) provided a preliminary basis to shift patients from IR LD-CD to IPX203, with the aim of maintaining therapeutic efficacy while potentially reducing side effects associated with peak-to-trough fluctuations.

The applicant proposed a conversion table from IR formulations to IPX203. Although, the general concept of such conversion table could be understandable, some clarifications were required in the course of the procedure. This table appeared to prioritise $C_{\max}$ matching (100 mg IR $\rightarrow$ 280 mg IPX203), which results in a ~ 2.7 -fold AUC increase at that dose level. In addition, the applicant proposed two split rules (< 500 mg/day vs ≥ 500 mg/day IR). Such calculation seemed to give a large difference in doses in patients which at the beginning used very similar LD IR doses. Based on

Study **IPX203-B16-05**, the dose-normalised exposure of levodopa with IPX203 was essentially equivalent to IR (GMR AUC about 1.0 per mg) with a lower C_{max} . Therefore, a systematic increase of total daily LD at switch seemed not fully supported pharmacokinetically. Such increases seemed also not fully justified by other PK results.

Two hypothetical cases illustrate that, according to the rules in the table, the total daily dose of LD would increase markedly in patients that at the beginning used very similar LD IR doses:

- Case 1: LD 100–200–200–100 mg (Total LD 600 mg). Table → LD 560 mg TID = 1680 mg/day (+180% LD), with CD 420 mg/day.
- Case 2: LD 100–200–100–100 mg (Total LD 500 mg). Table → LD 280 mg TID = 840 mg/day (+68% LD), with CD 210 mg/day.

The Applicant was asked to revise the conversion algorithm to better anchor on total daily IR LD ($\pm 10\%$) with explicit BID/TID splits and rounding rules to available strengths, and to provide PK/PD simulations comparing IR baseline vs proposed IPX203 regimens for AUC, C_{max} , time-above threshold, and expected "ON-time".

Therefore, it explained accurately the rationale for a conversion approach based on the most frequent single IR LD dose (using a $2.8\times$ factor aimed at LD C_{max} matching) and referred to supportive Phase 3 data from study IPX203-B16-02 (RISE-PD). The illustrative concentration–time plots (see below) for the two hypothetical cases were helpful to understand the intended concept.

The conversion from IR LD to IPX203 was based on the most frequent single daily IR LD dose rather than the total daily dose (TDD) because IPX203 is designed to extend the effect of each individual dose over a longer period, maintaining therapeutic plasma levels with fewer administrations. In other words, IPX203's PK are structured around how a single dose is absorbed and sustained, not how multiple IR doses accumulate across the day. IPX203 rapidly achieves therapeutic plasma concentrations and then maintains them for a longer duration compared to IR LD, with less peak-to-trough fluctuation. Because of this, each IPX203 dose is intended to replace multiple IR LD doses spread throughout the day.

At the end of the Phase 3 IPX203-B16-02 (RISE-PD) study, the mean ratio of TDD of IPX203 to IR LD was 1.79, and the mean ratio of the most frequently administered single dose of IPX203 to the most common single dose of IR LD was 2.8 (median).

These differences are attributable to two key factors:

- Slightly lower bioavailability of IPX203 vs. IR LD-CD, ranging from 88% to 99% based on AUC data
- The need for a higher amount of LD required to compensate for the PK troughs associated with IR LD-CD and thereby maintain a smoother clinical response

When converting patients with motor fluctuations from IR LD-CD to IPX203, the primary objective is to match the LD C_{max} to preserve anti-Parkinsonian efficacy during the "ON time" while avoiding an increase in dyskinesia. IPX203 was designed to match the peak of the most frequent IR dose, which is expected to be the dose with the optimal benefit–risk ratio for that patient. Less frequent adjustments with higher or lower doses are typically used to tailor daily LD administration to individual needs. For example, a higher dose in the morning may compensate for reduced levels after overnight fasting, while a lower dose in the evening can better match the naturally lower dopamine requirements during night-time.

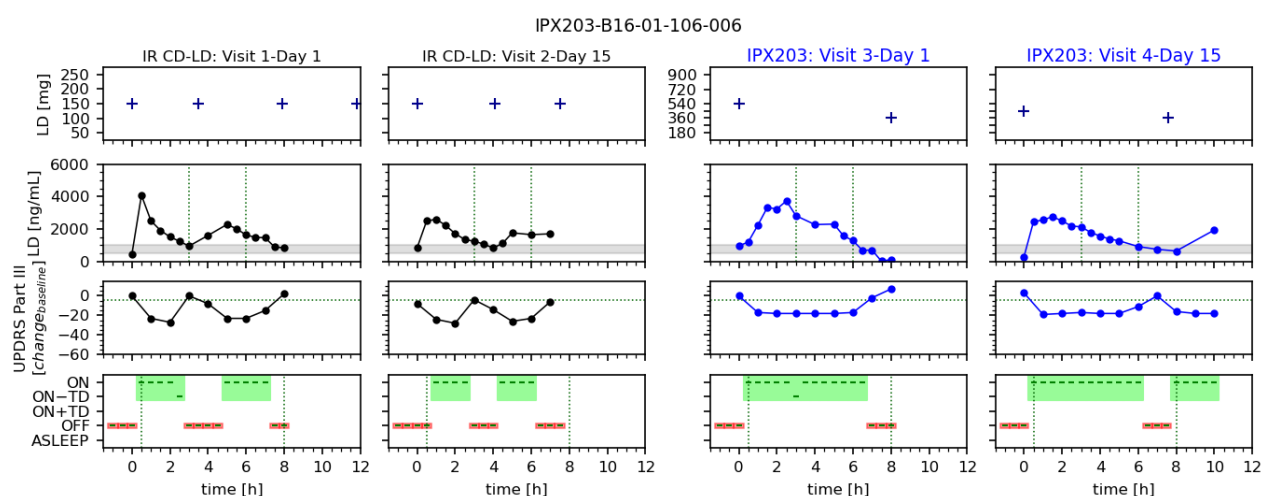
Since the C_{max} of IPX203 is approximately 38% of the C_{max} achieved with IR LD-CD, it is recommended that the LD content of IPX203 be increased by a factor of approximately 2.8 relative to the corresponding IR LD dose.

Clinical recommendations suggested multiplying the most frequent IR LD dose by 2.8 to determine the starting IPX203 dose. This strategy ensured that the MR capsule provides sufficient LD to cover the time interval during which the patient would typically require multiple IR doses.

Conversely, the total daily IR LD intake reflects multiple short-acting doses, each with its own absorption and wearing-off pattern. If conversion is based on the TDD, it could lead to overdosing or under-dosing because IPX203 does not mimic the cumulative peaks of IR LD—it smooths them out into a prolonged exposure. The most frequent single IR dose better represents the patient’s “effective unit” of therapy, which IPX203 is designed to extend.

The plot in the Figure below shows LD dosing, LD plasma exposure, MDS-UPDRS Part III response, and motor states for a typical IPX203-B16-01 study participant.

Figure 11: Dose-exposure Effect Relation of Sinemet IR and IPX203 Administration



Sinemet IR (left column) and IPX203 (right column) treatment are outlined. The horizontal line in row 3 depicts the minimum change in MDS-UPDRS Part III from baseline to produce clinically relevant effects.

Patients switched from IR LD to IPX203 experienced a longer “Good ON time” per dose, with fewer daily administrations. This was also confirmed based on Phase 3 data suggesting a conversion factor of 2.8 as the most appropriate.

This validated that matching IPX203 to the most frequent single IR LD dose provided consistent symptom control without requiring the same total daily milligram amount.

The primary concern might be the patient safety, specifically the risk of AEs associated with potentially excessive LD peak exposure, especially in patients who were previously controlled on lower doses of IR LD-CD, such as <500 mg.

Since the 2.8 conversion ratio for the individual IPX203 dose (100 mg IR LD converting to 280 mg IPX203) had been already established to ensure patients experienced an “ON time” comparable to their previous IR LD-CD regimen, the only remaining variable to control the total daily LD exposure was the dosing frequency, giving the drug less frequently.

In the applicant’s view, the twice-per-day dosing recommendation for patients on IR LD-CD doses <500 mg would provide a more controlled and gradual approach to dose titration, prioritising patient’s safety while still aiming for effective symptom control.

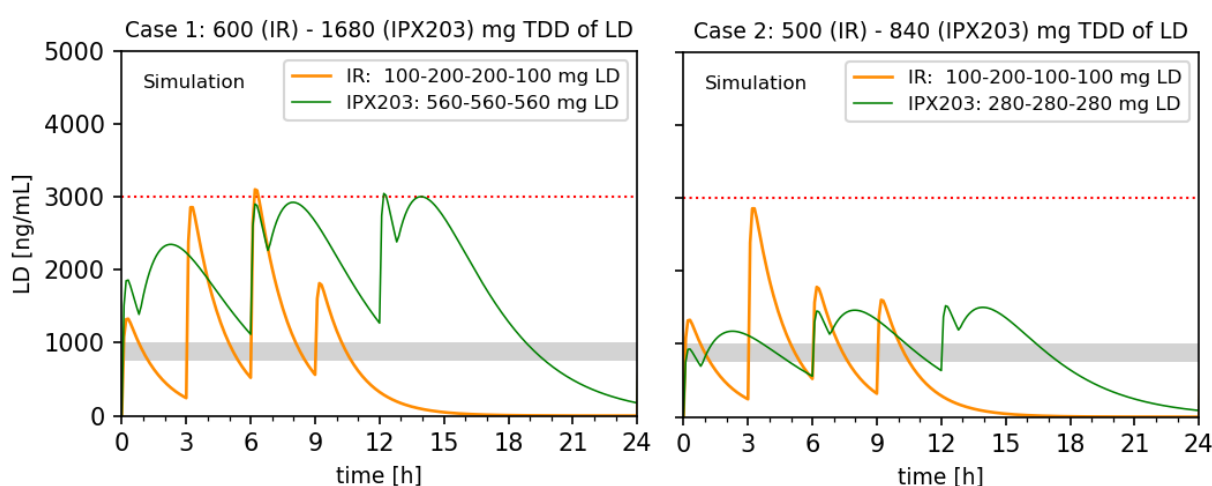
While it is important to recognise that the 2.8x conversion factor from study IPX203-B16-02 (RISE-PD) provides a useful **starting point**, in real-world practice, IPX203 conversion and dose optimisation would often require an individualised approach, including adjustments to dosing frequency and intervals. Clinicians may also consider a lower starting dose or reduced dosing frequency based on concomitant PD therapies and should ensure closer monitoring during titration. Finally, also important to note that in the RISE-PD study, more than half of the patients required no further dose adjustments as the 2.8x conversion factor immediately provided them with an optimal IPX203 dose.

To visualise the underlying rationale for conversion, the Figure below shows estimated LD plasma concentrations for the two cases above supplied by the assessor:

- Case 1: 100-200-200-100 mg Sinemet IR dosing, 600 mg LD TDD
- Case 2: 100-200-100-100 mg Sinemet IR dosing, 500 mg LD TDD

For the Sinemet IR to IPX203 conversion a mathematical prediction model was used. Relations of AUC, C_{max} , and time-above threshold were not calculated but can easily be compared in the plot.

Figure 12: Estimated LD Plasma Exposure of Two Sinemet IR and the Corresponding IPX203 Administration Schedules



The plot shows Sinemet IR LD profile (orange) with the proposed IPX203 LD profile (green), estimated for the two case scenarios. The grey area, representing the minimum LD plasma level, ranges above which anti-Parkinsonian effects are expected. The dotted red line is placed at the LD plasma level (3000 mg/L) above which TEAEs might occur.

Even when using the highest amount of IPX203 (Case 1, green line) also in case 2, peak LD concentrations are still in the same range as for both Cases of Sinemet IR doses used at study entry. Hence, peak-dose related side effects would have already been registered on Sinemet IR dosing. In addition, initial IPX203 doses determined by conversion are subject to optimisation (i.e., reduction and increase for case 1 and case 2, respectively). Furthermore, doubling of AUC when using IPX203 (case 2 vs case 1) was noted as rather advantageous because it leads to an augmented risk-benefit ratio by keeping LD plasma concentrations inside the therapeutic window for longer, even at reduced administration frequency.

The assessor considered the illustrative concentration–time plots for the two hypothetical case above discussed helpful to understand the intended concept.

However, the applicant's response did not resolve the concerns raised. In particular, the proposed split at 500 mg/day combined with a single-dose based algorithm could result in disproportionate differences in the starting IPX203 total daily dose for patients with similar baseline IR regimens (as illustrated by Case 1 *versus* Case 2). Moreover, patients receiving the same baseline IR total daily LD dose but using different IR dosing patterns may still be assigned materially different starting IPX203 doses, which indicates limited algorithm stability around the 500 mg/day cut-off. The statement that this is "only a starting dose", in the assessor's view, did not mitigate the clinical relevance during the switch period.

In addition, the applicant did not provide requested quantitative outputs to support the conversion approach. Thus, it was required to further revise and justify the proposed IR-to- IPX203 conversion algorithm, while retaining the 2.8× unit-dose conversion factor as a starting principle, it was needed to (re)assess the 500 mg/day cut-off and the associated BID/TID split to avoid disproportionate differences in starting total daily LD after switch.

Within a more complete justification of the proposed IR-to-IPX203 conversion algorithm, additional clinical evidence, quantitative PK simulations for the illustrative cases, and one additional example, with the same IR TDD, were supplied. The applicant also proposed a targeted mitigation at the upper end of the conversion range, allowing initiation with the next lower available capsule strength for patients with a most frequent IR LD dose of 200 mg or higher.

In addition, it explained that the conversion algorithm is intended as an initial dosing recommendation, followed by individual titration based on efficacy and tolerability. This is clinically relevant, as dose adjustment is expected in advanced PD.

Of note, since the initial submission, in the course of the procedure the applicant supplied new, relevant interim data from a Phase 4 RWE study conducted in the US, (ELEVATE-PD study interim analysis with 111 patients), evaluating the performance of the IR-to-IPX203 conversion algorithm in routine clinical practice. This provided useful reassurance that the 2.8× unit-dose conversion can be used in routine clinical practice, with a median of one titration step after conversion. The combined Phase 3 and 4 data supported BID initiation in patients receiving <500 mg/day IR LD, with maintained clinical benefit and no new safety concern.

The simulations for the proposed cases showed that large nominal increases in total daily LD do not necessarily lead to excessive C_{max} . They also suggest that IPX203 provides more sustained exposure above the proposed efficacy threshold and less fragmented exposure compared with IR. Importantly, in higher-dose scenarios, the proposed lower-dose starting option reduces C_{max} and total exposure, while maintaining predicted "ON time". This addressed the main concern that the original algorithm could lead to excessive exposure in some patients after switch.

The applicant also proposed a revised SmPC wording for the conversion algorithm, which keeps the 2.8-fold conversion principle, but it allows starting with the next lower strength when the most frequent IR LD dose is 200 mg or higher. The recommendation for FU after 1 to 3 days, and further dose or dosing-frequency adjustment, based on individual response, is also clinically relevant and supports safe use during conversion.

Overall, some uncertainty would remain because the simulations are model-based and the proposed efficacy threshold may vary between patients. In addition, patients with the same IR TDD but different IR dose patterns may still receive different nominal IPX203 TDD after conversion. However, the applicant's explanation was considered acceptable in the context of the initial nature of the conversion algorithm, the need for later individual titration, supportive Phase 3/4 data, and the proposed mitigation option proposed for the upper conversion range.

With regard to the apparent discrepancy between the maximum dose suggested by the conversion table, i.e., 700 mg LD three times daily corresponding to 2100 mg LD/day, and the previously proposed maximum daily dose of 2380/595 mg LD/CD, as mentioned above, the conversion algorithm is intended to define the initial conversion dose only, and that such (initial) conversion should not exceed 2100 mg LD/day, administered as 700 mg three times daily. Therefore, in SmPC section 4.2, the higher value of mg LD/CD is presented as a maximum daily dose not to be exceeded after subsequent individualised titration, based on clinical response and tolerability.

Table 14: Guidelines for initial conversion from immediate-release (IR) levodopa/DDC inhibitor medicinal to Hopledo in Parkinson's disease patients

Total daily IR levodopa dose	Most frequent* IR levodopa single dose (in mg)	Recommended initial dose of Hopledo (levodopa in mg)
<500 mg	100	280 two times daily
	150	420 two times daily
	200	560 two times daily
≥500 mg	100	280 three times daily
	150	420 three times daily
	200**	560 three times daily
	>200**	700 three times daily

The applicant acknowledged that, in the clinical programme, the exposure to doses at or above 2380/595 mg of LD/CD was limited, and that robust patient-level dose-history analyses, focused safety analyses and formal exposure–response assessments at this dose level would not provide reliable or clinically meaningful conclusions. This limitation is acceptable in the context of the agreed SmPC wording, where the dose of 2380/595 mg is presented only as an upper limit for selected patients after titration.

The agreed text in (SmPC) sections 4.2 and 4.4 likewise detailed the limited clinical experience with the total daily Hopledo doses above 2100 mg of levodopa, recommending that care should be exercised when considering further dose increases, and that patients receiving higher doses should be monitored closely for dopaminergic adverse reactions, including orthostatic hypotension, syncope, falls and dyskinesia. Also, of note, the total daily dose (TDD) can be divided up to four doses per day (QID).

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

The PK of IPX203 have been characterised in **three Phase 1** studies in healthy volunteers (Study **IPX203-B16-04**, **IPX203-B16-05** and **IPX203-B16-06**) and **two Phase 2** studies in patients with advanced PD receiving single (Study **IPX203-B14-02**) and multiple therapeutic doses (Study **IPX203-B16-01**). Although the Phase 2 studies used non-to-be-marketed (non-TBM) strengths of LD-CD (180-45 and 270-67.5 mg), the applicant bridged accordingly to the TBM LD-CD capsule strengths (140-35, 210-52.5, 280-70 and 350-87.5 mg) throughout a dedicated dose-proportionality study and food-effect data, demonstrating dose-normal linear PKs for both LD and CD across the commercial range and time-invariant PK under multiple dosing. Of note: the Phase 3 pivotal trial employed the TBM capsule strengths.

In terms of **absorption**, across studies, IPX203 achieved a profile consistent with a typical MR formulation: the median LD T_{max} was delayed relative to the IR comparator, and concentrations were sustained longer, while the initial rise attributable to the IR fraction was preserved. Collectively, the findings summarised in previous sections of this AR showed a smoother, longer-lasting LD exposure

with reduced peak-to-trough fluctuation. Furthermore, adequate CD bioavailability was also demonstrated with the proposed MR formulation. Greater CD bioavailability with the proposed MR formulation was also confirmed.

Study **IPX203-B16-04** assessed the **food effect** on IPX203 PK. In healthy volunteers, a high-fat meal delayed LD absorption and increased exposure. Sprinkling on apple sauce gave exposure close to fasted yet remained bioequivalent for LD under standard 80–125% bounds. Half-life was similar across arms. In contrast, CD exhibited a pronounced negative food effect (~64% lower exposure and a later T_{max}), whereas sprinkling yielded AUCs close to fasted with a modestly lower C_{max} (about 10–15% lower) with similar half-life. These data supported the proposed label statements about administration with or without food, recognising that a high-fat (or high-calorie) meal may delay/slow down LD absorption by ~2 h (as reflected by a substantially later T_{max} and marked reduction in early systemic exposure compared with the fasted state, while the overall exposure is not reduced and shifted to later time intervals), and acceptability of sprinkling on apple sauce, with appropriate instructions. The **distribution** of LD and CD was not studied. Instead, the applicant supplied literature data. Levodopa is bound to plasma proteins in the range of 10–30%, while CD at approximately 36%. Levodopa and CD distribution parameters were also not investigated, as well described in the literature.

Across the clinical programme study IPX203-B16-04, IPX203-B16-05, IPX203-B16-06), LD and CD **elimination** was consistent and similar to IR/CR comparators.

Metabolism was not investigated, as the pathways for LD and CD are well established in the literature. The PK of 3-OMD, the major metabolite of LD was likewise not investigated. Instead, literature data was supplied by the applicant. The to-be-marketed (TBM) LD-CD formulations range (LD-CD 140-35 to 350-87.5 mg) showed **dose proportionality**, with no change in elimination behaviour. Bioequivalence was demonstrated between US and Taiwan-manufactured batches (140-35 mg), supporting manufacturing flexibility and predictable dose-scaling. Across the tested strengths, IPX203 showed approximate **dose proportionality** under fasting conditions.

Study **IPX203-B16-01** demonstrated that results were consistent with a modified-release profile: later T_{max} , a flatter peak, and longer maintenance of LD within a dosing interval. Time above predefined concentrations and the fluctuation index favoured IPX203). However, some issues initially limited data interpretation and the proposed conversion scheme. In this study the first post-dose sample was at 0.5 h; therefore, for IR LD-CD T_{max} was censored at 0.5 h and IR C_{max} seemed likely underestimated.

Nevertheless, the applicant provided a model-based sensitivity analysis to confirm if the first sampling time at 0.5 h was sufficient to capture the true IR LD C_{max} in studies IPX203-B14-02 and IPX203-B16-01. The analysis used individual one-compartment PK fits and different absorption rate constants (k_a). The predicted T_{max} values were close to the first sampling time, mainly around 0.44–0.78 h, and predicted C_{max} values for plausible k_a values were within about $\pm 10\%$ of the reference estimate. Therefore, a clinically relevant underestimation of IR C_{max} due to the 0.5 h first sample was noted as unlikely. The applicant also provided early exposure metrics, including $AUC_{0-0.5h}$, AUC_{0-1h} , and AUC_{0-2h} , dose-normalised to 100 mg LD. These results were broadly similar between studies IPX203-B14-02 and IPX203-B16-01, supporting the exposure assessment.

In summary, the 0.5 h first sampling time is acceptable for estimation of IR C_{max} , and any possible underestimation is unlikely to have a major impact on the 2.8× conversion factor, confirmed as derived using C_{max} matching approach.

In addition, a plausible clinical rationale for the IR-only delivery of carbidopa in IPX203 was submitted, together with a demonstrated higher CD exposure versus IR LD-CD, consistent with the higher CD dose, and low accumulation after repeat dosing.

The non-clinical margin based on the 1-year rhesus monkey NOAEL (≥ 135 mg/kg/day), corresponding to an estimated 4.4-fold margin over the proposed maximal daily CD dose (595 mg/day), can likewise be considered acceptable in the context of absence of toxicological findings at high chronic doses in primates, and lack of clinically relevant QTc effects at supratherapeutic CD exposure.

Moreover, the applicant confirmed that the clinically relevant published levodopa threshold for onset of effect is approximately 1000 ng/mL.

The **pharmacokinetics** in the **target population** were investigated in IPX203-B14-02, a single-dose study in patients with advanced PD. The study results were generally consistent with what may be expected for a modified-release LD/CD: later T_{max} , a flatter peak, and longer maintenance of LD than IR. Time above 50% C_{max} was longer with IPX203 than IR (4.7 h vs 1.9 h) and numerically longer than Rytary, an ER LD-CD formulation (3.9 h). Carbidopa exposure with IPX203 was several-fold higher than IR, as anticipated from the higher CD dose. Across dose levels, the reported "bioavailability vs IR" for LD with IPX203 was roughly comparable to IR (about 80–109%), suggesting that per-mg exposure is similar.

Levodopa has an individual **therapeutic window**, and the dose must be titrated to clinical response (adequate motor control without troublesome dyskinesia). Carbidopa has no independent symptomatic effect: it is administered to ensure sufficient peripheral AADC inhibition. Within the IPX203 programme, differences between regimens were driven by absorption; elimination was unchanged. On this basis, plasma targets are not considered, and dosing is guided by effect and tolerability.

The concerns raised in the course of the procedure regarding IR LD/CD to Hopledo conversion algorithm were adequately addressed. The applicant clarified that the proposed conversion table defines only the initial conversion dose, which should not exceed 2100 mg levodopa per day, administered as 700 mg TID. The higher dose of 2380/595 mg LD/CD is not intended as a routine recommended conversion dose, but as a maximum daily dose not to be exceeded, after individualised titration according to clinical response and tolerability. Although clinical experience at doses at or above 2380/595 mg is limited and does not allow robust exposure–response or focused safety conclusions, this approach was considered acceptable, supported by detailed SmPC wording. Sections 4.2 and 4.4 clearly distinguish initial conversion from subsequent titration, state that experience above 2100 mg/day is limited, and recommend close monitoring for dopaminergic ADRs, including orthostatic hypotension, syncope, falls and dyskinesia. Also, of note, the TDD can be divided up to QID.

Concerning **multiple-dose behaviour** under steady dosing in patients, IPX203 reduced LD fluctuation over 10 h (≈ 1.7 vs 2.7 with IR), extended time above 50% C_{max} (6.2 h vs 3.9 h) and above 430 ng/mL (9.0 h vs 7.4 h), and showed minimal accumulation for both LD and CD (≈ 1.0 –1.1), confirming time-invariant PK at therapeutic use.

Looking at **special populations**, no dedicated renal or hepatic impairment studies have been conducted. Instead, the applicant's literature-based justification is considered generally acceptable from a PK perspective, given the known disposition of LD and CD, the clinical experience with other LD/CD-containing medicinal products, and the individualised titration approach to be used in clinical practice.

In addition, the applicant justified that a clinically relevant impact on LD/CD exposure is not expected in patients with mild to moderate **hepatic impairment**, since neither LD nor CD is primarily dependent on hepatic microsomal metabolism, and levodopa is mainly metabolised through peripheral

AADC and COMT pathways. The absence of dedicated PK data is adequately reflected in SmPC sections 4.2 and 5.2, where caution on dose adjustment and appropriate clinical monitoring is recommended.

In relation to **renal impairment**, unchanged levodopa represents only a minor component of urinary excretion and renal elimination mainly concerns metabolites rather than parent LD. In addition, available literature describes that, following a single 50 mg oral dose of ¹⁴C-carbidopa in Parkinsonian patients, about 64% and 33% of the radioactivity are recovered in urine and faeces, respectively, with a radioactivity amount of 32% in the 0–24-hour urine due to unchanged carbidopa. Three metabolites were identified in the urine, and each accounted for approximately 10% of the radioactivity excreted. Therefore, renal excretion is not a major elimination pathway for carbidopa.

The applicant revised adequately SmPC section 4.2 and 5.2, detailing that PK of Hopledo in subjects with renal impairment have not been established, and recommending caution on dose adjustment in patients with moderate to severe renal impairment, with appropriate clinical monitoring.

No **PK interaction studies** have been performed as LD/CD interactions are also well described in the literature.

Overall, for a full-mixed (Article 8(3) application, characterisation of distribution and elimination is limited. No **mass-balance study**, no **popPK**, no dedicated **protein-binding** or **in vitro** and **in vivo metabolite PK assessments** and no dedicated **DDI** and **renal** or **hepatic impairment studies** have been conducted. However, the Applicant presented adequate literature data supporting the proposed SmPC wording in sections 4.2, 4.5 and 5.2.

Primary pharmacodynamics were established through measurement of effects on clinical scores of Parkinson's disease. Therefore, the PD endpoints used were concomitantly efficacy endpoints. Levodopa **mechanism of action** is well known and sufficiently described in the literature. In study **IPX203-B14-02**, the subject **motor state assessment** results demonstrated a 2.7-hour advantage in total "OFF" time during IPX203 treatment compared with IR CD-LD treatment ($p < 0.0001$) and a 0.9-hour advantage compared with Rytary ($p = 0.023$). During IPX203 treatment, this reduction in "OFF" time was accompanied by increased "ON time" without troublesome dyskinesia ("Good ON time"), on average 2.6 hours more than IR CD-LD, and 0.9 hours more than Rytary ($p < 0.0001$ and $p = 0.0259$, respectively).

The **MDS-UPDRS Part III score** results showed a similar pattern of effect in favour of IPX203.

In study **IPX203-B16-01**, subjects receiving IPX203 experienced significantly less "OFF" time as a percentage of their waking hours (mean 19.3% compared with 33.5% with IR CD-LD). In addition, they had more total "Good ON time" with IPX203 compared with IR CD-LD, whether measured out of clinic by the subject himself (with a home diary) or by the investigator in the clinic. The average durations of "Good ON" episodes or any "ON" episodes based on patient's diary entries were longer with IPX203, in comparison to IR CD-LD. Treatment with IPX203 was also associated with fewer motor fluctuations per day than IR CD-LD.

Subjects on IPX203 treatment were 73.3% less likely to receive rescue medication (at Day 1), and 72.1% less likely to receive a re-dose (at Day 15) in comparison to those on IR CD-LD treatment.

Improvements in **MDS-UPDRS Part III mean scores** were greater for subjects receiving IPX203 than IR CD-LD, from 3 to 8 hours postdose on Day 1, and from 2 to 4 hours postdose on Day 15. On Day 15, when subjects had not had a study treatment for at least 5 hours, mean predose Part III scores were significantly lower in IPX203-treated subjects.

The results from the MDS-UPDRS Part III scores were more relevant than for the MDS-UPDRS Part IV scores, both in terms of statistical and clinical significance. It is unquestionable that MDS-UPDRS Part

III remains the classical and well-established endpoint to demonstrate motor benefit, as stated in the EMA "Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease".

However, in the specific development of Hopledo, the efficacy of LD-CD fixed-dose combination in treating motor symptoms in PD had been already thoroughly established, while the main objective was to specifically establish that this formulation shows improvements in motor fluctuations and treatment-related motor complications.

While it can be agreed that measurement of "OFF time" or "ON time" is the main efficacy variable, an operational definition of what will be considered an "OFF" and "ON" period should be established. It should be also clear to what extent "ON time" with dyskinesia and "ON time" without dyskinesia is increased. Patients changing from "OFF" to "ON" with dyskinesia should be asked whether they consider this an improvement or not, as per the EMA guideline already mentioned. Taking this into consideration, the assessment of MDS-UPDRS Part IV added value in these particular development goals.

While for Part III results were "consistently improved" with IPX203, in several questions of Part IV that was not the case. The only statistical difference obtained in (questions from) MDS-UPDRS Part IV was for question 4.3 "Time spent in the OFF state". However, in the analysis of "change from baseline" the differences in the mean of change from baseline was 0.5 (+/-0.51). If considering the median, there was no difference. A reduction of approximately 1 hour/day of "OFF time" is generally regarded as the minimal clinically important improvement.

Even though MDS-UPDRS Part III remains the classical and well-established endpoint to demonstrate motor benefit in assessing an effect on PD, while assessing new formulations of levodopa/carbidopa the measurement of Part IV gains an added usefulness by assessing therapy induced motor complications.

There was a lack of correlation of the MDS-UPDRS Part III positive results with the absence of results in Part IV, specifically given the limited clinical relevance of the results in the "time spent in the OFF state". The applicant provided a largely acceptable methodological explanation for the discordance between MDS-UPDRS Part III and Part IV. However, this response was generally descriptive and partially evasive of the main issue raised in this question: whether the observed Part III improvements translated into clinically meaningful benefit in a formulation specifically intended to modify levodopa exposure and, therefore, motor complications.

It can be acknowledged that the short-duration Phase 2 studies were not designed to capture Part IV changes and that the general design is broadly consistent with the EMA Guideline on clinical investigation of medicinal products in Parkinson's disease. Although the applicant's explanation is methodologically reasonable, it is scientifically insufficient, and the absence of correlation between Part III and Part IV remains a concern, not merely a design artefact. In summary the applicant's response failed to address the central pharmacodynamic expectation that a modified-release levodopa formulation is specifically intended to smooth plasma concentrations and reduce motor complications, which in this case still lacks sufficient PK/PD translation. Nevertheless, the CHMP agreed not to pursue this matter further, as it does not impact IPX203 overall benefit-risk profile. Looking at IPX203 **secondary pharmacodynamics**, attention was paid to the peak LD plasma concentration (C_{max}) and the effects of carbidopa (CD) on cardiac repolarization (QTc) and other ECG parameters.

Study IPX203-B16-01 was designed to assess the effects of supratherapeutic doses/exposures of CD on QTc and other ECG parameters, using moxifloxacin as a positive control. The results showed no significant ECG changes, and the concentration-QT (C-QT) analysis did not reveal any statistically significant relationship between carbidopa and QTc.

Due to the achieved exposure margin *versus* the worst-case clinical C_{max} being below the ICH E14 preference, an exposure-QTc bridging assessment was conducted using the final concentration-QTc model from Study IPX203-102-23, and the observed clinical C_{max} data from Studies IPX203-B14-02 and IPX203-B16-01. The predicted placebo-adjusted QTc effects ($\Delta\Delta QTcF$) at both the mean C_{max} and the clinical 95th percentile C_{max} values were small (0.3-0.7 ms), and the upper bound of the 90% CI at these concentrations remained below the regulatory threshold of 10 ms.

The applicant submitted the empirical distribution of clinical C_{max} for CD, including data from studies B14-02, B16-01, or pooled PK and fasting status, at the maximal per-dose 175 mg (per SmPC conversion). The distribution was reported as the 50th and 95th percentile (the median) and overlaid against the TQT 400 mg C_{max} distribution.

The requested exposure-margin context for CD, at the maximal per-dose level (175 mg), was linked to the TQT exposure-QTc model. The estimated C_{max} distribution for a 175 mg CD dose (mean 613 ng/mL; median 539 ng/mL; 95th percentile 1371 ng/mL) fell within the concentration range covered by the TQT study, where an effect >10 ms was excluded across observed concentrations (up to 3000 ng/mL).

Using the final concentration-QTc model, the predicted $\Delta\Delta QTcF$ at mean/median/P95 clinical C_{max} values was small (0.5-0.6 ms) and remained well below the regulatory threshold, supporting a low QT risk for CD. Although the 175 mg estimates were derived by extrapolation from lower CD doses assuming PK linearity, this was considered acceptable in the context of the clearly negative TQT results, the shallow (slightly negative) concentration-QTc slope, and the substantial exposure coverage provided by the TQT dataset.

Since CD is eliminated via renal route, the applicant also provided an exposure-margin sensitivity showing predicted $\Delta\Delta QTcF$ (upper 90% CI) at the upper tail of C_{max} expected in low-eGFR subgroups (e.g., pooled PK stratified by eGFR categories), confirming that the upper bound remains <10 ms at those exposures, including a sensitivity cut stratified by age $\geq 65/\geq 75$ years to account for age-related decline in renal function. Supportive empirical data from the Phase 2 programme were likewise submitted, by listing subjects with CD $C_{max} > 900$ ng/mL and subjects with eGFR <60 mL/min/1.73 m², including age and observed C_{max} . These data did not indicate a consistent increase in CD C_{max} in the low-eGFR subgroup, and the observed peak concentrations in this subgroup remain within the concentration range covered by the TQT exposure-QTc assessment, where a clinically relevant QTc effect was excluded. Although the response did not present a formal model-based “exposure-margin sensitivity” by eGFR category (with predicted $\Delta\Delta QTcF$ and upper 90% CI) as originally requested, the provided patient-level listings adequately addressed the underlying concern by showing that reduced renal function (including in older subjects) is not associated with materially higher peak CD exposure in the available clinical dataset. Relevant **pharmacodynamic interactions**, overlapping with those outlined for other currently approved levodopa/carbidopa-containing medicinal products, are accurately included in the PI.

No **genetic difference** that can affect the PD response in a clinically significant is foreseen.

With regard to the **relationship between plasma concentration and effect and safety** Study IPX203-B14-02 aimed to assess, amongst other objectives, PD and PK of single doses of IPX203 in subjects with advanced PD, using Rytary and IR CD-LD as the references.

The initial rates of decrease in MDS-UPDRS Part III scores from average baseline (corresponding to an improvement in motor symptoms) were comparable for all three treatments. However, the MDS-UPDRS Part III score decreases lasted for a longer duration following IPX203 treatment than following IR CD-LD or Rytary. Maximum decreases in MDS-UPDRS Part III scores from average baseline

occurred at times that lagged behind the time of peak plasma concentrations of LD for the particular treatment.

Study IPX203-B16-01 intended to assess also PK/PD correlations in both single and multiple doses.

In the single dose setting the initial decreases in MDS-UPDRS Part III scores from average baseline (corresponding to an improvement in motor symptoms) were comparable between the 2 treatments. However, decrements in the MDS-UPDRS Part III scores lasted for a longer duration following IPX203 treatment than following IR CD-LD treatment. Maximum decreases in MDS-UPDRS Part III scores from average baseline occurred at times that lagged behind the time of peak plasma concentrations of LD for the particular treatment.

In the multiple dose setting, at predose on Day 15, treatment with IPX203 showed a greater mean decrement (-9.3) in MDS-UPDRS Part III scores than did treatment with IR CD-LD (+0.1). As observed following the first dose on Day 1, a qualitative concordance was noted between the LD plasma concentration profile and changes in MDS-UPDRS Part III scores. The initial rates of improvement in motor symptoms were comparable between the two treatments. However, improvements in the MDS-UPDRS Part III scores lasted for a longer duration following IPX203 treatment than IR CD-LD, which may be associated with less frequent dosing of IPX203 than IR CD-LD.

The applicant was asked to prove whether the improved duration of motor benefit with IPX203 was driven by higher total LD exposure (dose/AUC) or by a true PK advantage (PK profile, longer time above effective concentration or other).

Across study IPX203-B14-02 (single dose, PD) and IPX203-B16-01 (single and multiple doses, PD), the time-course of clinical response was followed by the LD concentration-time profile. The onset of improvement (MDS-UPDRS III) was similar for IPX203 and IR LD-CD, but the duration of improvement was longer with IPX203, consistent with its sustained LD exposure. Peak clinical effect was behind LD C_{max} , which is expected for dopaminergic response.

Comparisons on Day 15 were confounded by higher total daily LD with IPX203 (2:1 vs IR) and lower dosing frequency (3.1 vs 4.7 doses/day); dose-normalised efficacy was not shown. Single-dose results used strengths not identical to the to-be-marketed strengths. Taken together the PK-PD data demonstrated a coherent exposure-response: similar onset but longer maintenance of effect with IPX203, fewer rescues, and longer time to redose. However, because Day-15 superiority coincided with higher LD exposure, the magnitude of benefit could be attributed solely to the release profile.

Therefore, the applicant provided dose-normalised PK-PD analyses (E_{max} and/or indirect-response) showing the relationship between LD exposure (C_{max} , $AUC_{0-\tau}$, and time above a clinically relevant concentration) and MDS-UPDRS III, adjusted for total daily LD dose and dosing frequency. Report C_{max}/D and $AUC_{0-\tau}/D$ for LD (and CD) by regimen and day.

A plausible mechanistic rationale for IPX203 (rapid IR component plus prolonged ER component) and an illustrative individual time-course plot linking LD concentrations with MDS-UPDRS III and motor states were also supplied.

In addition, the applicant provided an exposure-response analysis using data from studies IPX203-B14-02 and IPX203-B16-01. Individual C_{max} , AUC, time above the proposed LD efficacy threshold of 750 ng/mL, and AUEC of Δ MDS-UPDRS Part III were assessed and presented by treatment. It was also explained that a fully exposure-matched comparison is difficult, because IPX203-B14-02 was a single-dose study and IPX203-B16-01 included multiple-dose treatment with individual dose adjustments and limited PK/PD sampling. This limitation is acknowledged and considered acceptable by CHMP.

The provided analyses suggested that C_{max} alone is not the main driver of the longer motor benefit with IPX203, as C_{max} values overlap between IPX203 and IR. Higher AUC and longer time above the efficacy threshold seem to be more relevant for the sustained response. This is consistent with the formulation concept of IPX203, where additional LD is delivered from the extended-release component, leading to higher overall exposure and longer time above an effective concentration.

The applicant also noted that, where similar C_{max} or AUC values are observed, clinical efficacy is generally similar between IR and IPX203. Higher AUEC values of Δ MDS-UPDRS Part III and longer duration of effect were mainly observed with IPX203, which is consistent with the longer time above threshold. The presented data supported the notion that the prolonged clinical benefit of IPX203 is driven mainly by higher total LD exposure and longer time above an effective LD concentration, rather than by higher C_{max} .

The PK/PD correlation performed in the studies IPX203-B14-02 and IPX203-B16-01 was established by using only MDS-UPDRS Part III score as main endpoint. For a new LD/CD formulation, especially with the current claims, the clinically important PD question was not just whether Part III can be modelled against plasma LD, but whether the PK profile also translates into functionally meaningful benefit, such as reduced "OFF time", improved "ON time" without troublesome dyskinesia, or reduced motor complication burden. The applicant's response was partially acceptable as MDS-UPDRS Part III is the only component suitable for dense within-day PK/PD modelling in the cited studies. For a novel LD/CD formulation intended to improve motor response consistency and fluctuations, it would be expected the inclusion of longitudinal exposure-response analyses exploring clinically relevant outcomes beyond Part III, including MDS-UPDRS Part IV, patient diary-derived OFF time, ON time without troublesome dyskinesia, or related fluctuation endpoints. Therefore, although the explanation was methodologically reasonable it was however scientifically insufficient and the absence of correlation between Part III and Part IV remains a concern, not merely a design artefact. Nevertheless, the CHMP agreed that, in the absence of an impact on Hopledo overall benefit/risk profile, the matter would not be further pursued with follow-up questions.

Dose justification

In the (single dose, PD) study **IPX203-B14-02**, IPX203 and Rytary were dosed to target IR-like peaks ($\pm 20\%$). Mean C_{max} and $AUC_{0-\infty}$ increased "approximately dose-proportionally" across the tested doses. In study **IPX203-B16-01** (patients, Day 1 and multiple dose), IPX203 doses (≈ 270 –900 mg LD) were chosen from study **IPX203-B14-02** to target IR 100 mg peaks; redosing every ~ 7 –8 h was typical. Across Day-1 PK, peak-to-trough fluctuation was lower and dosing frequency reduced vs IR; accumulation was low.

The applicant proposed a conversion table from IR formulations to IPX203. Although, the general concept of such conversion table was understandable some clarifications were required in the course of the procedure.

Thereafter, the applicant explained accurately the rationale for a conversion approach based on the most frequent single IR LD dose (using a $2.8\times$ factor aimed at LD C_{max} matching) and referred to supportive Phase 3 information (RISE-PD study).

The applicant further provided a more complete justification of the proposed IR-to-IPX203 conversion algorithm. The response included additional clinical evidence, quantitative PK simulations for the illustrative cases, and one additional example with the same IR TDD. It was also proposed a targeted mitigation at the upper end of the conversion range, allowing initiation with the next lower available capsule strength for patients with a most frequent IR LD dose of 200 mg or higher.

Furthermore, the response explained that the conversion algorithm is intended only as an initial dosing recommendation, followed by individual titration based on efficacy and tolerability. This is clinically relevant, as dose adjustment is expected in advanced Parkinson's disease.

The Phase 3 and Phase 4 data also supported BID initiation in patients receiving <500 mg/day IR LD, with maintained clinical benefit and no new safety concern.

Furthermore, the Applicant proposed revised SmPC wording for the conversion algorithm. This text keeps the 2.8-fold conversion principle but allows starting with the next lower strength when the most frequent IR levodopa dose is 200 mg or higher. The recommendation for follow-up after 1 to 3 days and further dose or dosing-frequency adjustment based on individual response is also clinically relevant and supports safe use during conversion.

Some uncertainty would remain because the simulations are model-based and the proposed efficacy threshold may vary between patients. In addition, patients with the same IR TDD but different IR dose patterns may still receive different nominal IPX203 TDD after conversion. However, overall, the applicant's explanations are considered acceptable by the CHMP in the context of the initial nature of the conversion algorithm, the need for later individual titration, supportive Phase 3/4 data, and the proposed mitigation option for the upper conversion range.

5.2.6.2. Conclusions

In general, the PK/PD clinical programme can be considered acceptable.

IPX203 delivers the intended MR performance preserving onset, flattening LD peaks relative to IR, and extending coverage, while providing higher and more sustained CD exposure to support peripheral dopa-decarboxylase inhibition. The clinical programme demonstrated predictable, proportional PK across the TBM strengths range, bridging strengths used in phase 2 studies, confirms manufacturing site equivalence, and characterises relevant effects of food and alternative sprinkle IPX203 in applesauce. The CHMP agreed that the text detailed in SmPC section 4.2 and 5.2 is well supported by the submitted evidence.

The clinical PD section was also considered generally adequate.

5.3. Clinical efficacy

Table 15: Overview of clinical studies

Study ID	Study Start Date Enrolment Status and Date Total Enrolment / Planned	Study Design Study Duration	Treatments (Dose, Route, Regimen)	Diagnosis Inclusion Criteria	Number of Subjects Entered/ Completed Gender M/F Age: Mean $\pm$ SD
IPX203-B14-02 (Phase 2)	Started: 07 Dec 2015 Completed: 10 Aug 2016 26/51	Randomised, open-label, rater-blinded, multicentre, 3-treatment, 3-period, single-dose crossover 6 weeks	IPX203 (LD-CD) oral capsules: 180 mg (180-45 mg) and 270 mg (270-67.5 mg) MR LD-CD (Rytary/Numient) oral capsules: 145 mg (145-36.25 mg) and 195 mg (195-48.75 mg)	Male or female subjects diagnosed with idiopathic PD at age ≥ 40 years, Hoehn and Yahr Stages 2, 3, or 4, MoCA score ≥ 24 , responsive to LD-CD therapy, and currently being treated on a stable	Randomised/Enrolled: 26 Completed: 25 13 M/12 F ^a Age ^a : 66.2 $\pm$ 7.1 years

Study ID	Study Start Date Enrolment Status and Date Total Enrolment / Planned	Study Design Study Duration	Treatments (Dose, Route, Regimen)	Diagnosis Inclusion Criteria	Number of Subjects Entered/ Completed Gender M/F Age: Mean $\pm$ SD
			IR LD-CD (Sinemet) oral tablets: 100 mg (100 -25 mg) Single doses of each study treatment, with washout periods of ~1 week between doses.	regimen of LD-CD for at least 4 weeks.	
IPX203-B16-01 (Phase 2)	Started: 08 Nov 2016 Completed: 01 Aug 2017 28/30	Randomised, open-label, rater-blinded, 2-treatment, 2-period, multiple-dose crossover, multicentre 8 weeks	IPX203 (LD-CD) oral capsules: 180 mg (180-45 mg) and 270 mg (270-67.5 mg) IR LD-CD (Sinemet) oral tablets: 100 mg (100-25 mg) Subjects randomised to 1 of 2 dosing sequences: IR LD-CD followed by IPX203, and IPX203 followed by IR LD-CD. Variable dosing, 15 days per treatment period, separated by a 1-week washout period.	Male or female subjects diagnosed with idiopathic PD at age ≥ 40 years, Hoehn and Yahr Stages 2, 3, or 4, MoCA score ≥ 24 in the "On" state, responsive to LD-CD therapy, and currently treated with a stable regimen of LD-CD for at least 4 weeks and experiencing motor complications.	Randomised/ Enrolled: 28 Completed: 27 16 M/11 F ^a Age ^a : 65.9 $\pm$ 9.8 years
IPX203-B16-02 (Phase 3)	Started: 06 Nov 2018 Completed: 15 Jun 2021 630/510	Randomised, double-blind, double-dummy, active-controlled, parallel group, prospective, multicentre 24 weeks (4-week Screening period, a 3-week open-label IR LD-CD dose adjustment period, a 4-week open-label period for conversion to IPX203, and a 13-week double-blind, double-dummy treatment period).	IPX203 (LD-CD) oral capsules: 140 mg (140-35 mg) IR LD-CD oral tablets: 25 mg CD-100 mg LD Matching IPX203 and IR LD-CD placebos Individualized based on incoming IR LD-CD dose	Male or female subjects diagnosed with PD at age ≥ 40 years, Hoehn and Yahr Stages 1, 2, 3, or 4, MoCA score ≥ 24 in the "On" state, responsive to LD-CD therapy, and currently treated with a stable regimen of LD-CD for at least 4 weeks and experiencing motor complications.	Enrolled: 630 Randomised: 506 Completed: 449 396 M/234 F ^b Age ^b : 66.5 $\pm$ 8.95 years
IPX203-B16-03 (Phase 3)	Started: 03 Apr 2019	Open-label safety extension, multicentre study	4 strengths of IPX203 (LD-CD) capsules; 140-35 mg, 210-52.5 mg, 280-70 mg,	Subjects who successfully completed Study IPX203-B16-02	Enrolled: 419 Completed: 352 279 M/140 F ^b

Study ID	Study Start Date Enrolment Status and Date Total Enrolment / Planned	Study Design Study Duration	Treatments (Dose, Route, Regimen)	Diagnosis Inclusion Criteria	Number of Subjects Entered/ Completed Gender M/F Age: Mean $\pm$ SD
	Completed: 21 Mar 2022 419/300	9 months	350-87.5 mg Individualised based on the final IPX203 dosing regimen that was determined during the IPX203 dose conversion period of Study IPX203-B16-02.		Age ^b : 66.9 $\pm$ 8.86 years

5.4. Dose response studies

5.4.1.1. Phase 2 Study IPX203-B14-02

Study **IPX203-B14-02** was a **Phase 2** randomised, open-label, rater-blinded, multicentre, 3-treatment, 3-period, single-dose, crossover study that assessed the PK, PD/efficacy and safety of single doses of IPX203 in subjects with advanced PD, using Rytary/Numient (MR LD-CD) and Sinemet (IR LD-CD) as reference products, and characterised the safety of single doses of IPX203 in these subjects. Males or females diagnosed with idiopathic PD at age ≥ 40 years were enrolled. Idiopathic PD was defined by the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria. There were no known secondary causes (e.g., vascular, toxin or medication-induced, metabolic, or infectious) for subject's Parkinsonism nor did the subjects had another neurodegenerative disorder with Parkinsonism symptoms (e.g., progressive supranuclear palsy, corticobasal degeneration, multiple-system atrophy).

Subjects received a single oral dose of each of the three study treatments (IR LD-CD, Rytary/Numient and IPX203) in the fasted state in a randomised sequence.

Table 16: Randomised dosing sequences for study IPX-203-B14-02

	Period 1	Period 2	Period 3
Sequence 1	IPX203	IR CD-LD	Rytary
Sequence 2	IR CD-LD	Rytary	IPX203
Sequence 3	Rytary	IPX203	IR CD-LD

A crossover study design was selected to allow each subject to serve as his or her own control. IR LD-CD was the primary active comparator and Rytary/Numient was included as an additional active treatment. Subjects received single doses of each study treatment with washout periods of approximately 1 week between doses. Subjects continued taking IR LD-CD between study visits. During the IR LD-CD treatment period, the dosing regimen of IR LD-CD was expected to be the same as the subject's pre-study (stable) morning baseline dosing regimen. The dosing regimens for IPX203 and Rytary/Numient were selected based on the amount of LD in the subject's pre-study morning dose of IR LD-CD (as per Table below). All treatments were administered to subjects with 240 mL of room-temperature water in a fasted state. All study treatments contained LD and CD at a fixed ratio of 4:1.

Table 17: Levodopa dosage (Study IPX203-B14-02)

Pre-study morning dose of LD in IR LD-CD (mg)	LD dose in mg		
	IR LD-CD	Rytary/Numient	IPX203
100	100	340	360
150	150	485	540
200	200	630	720
250	250	780	810
IR LD-CD = immediate-release levodopa-carbidopa			
Note: CD and LD present at a fixed ratio of 1:4 in each strength and treatment.			

The subjects' motor state was assessed by a qualified blinded rater at -1 hour and -0.5-hour pre-dose, just before dosing (pre-dose), and every half hour following dosing through each 10-hour measurement period as one of the following states: "Asleep", "OFF", "ON" without dyskinesia, "ON" with non-troublesome dyskinesia, and "ON" with troublesome dyskinesia. "OFF" was defined as the typical functional state when the medication no longer provided benefit with regard to mobility, slowness, and stiffness despite taking medications. "ON" was defined as the typical functional state when a subject's medication provided benefit with regard to mobility, slowness, and stiffness. Dyskinesia was defined as involuntary and irregular twisting and/or turning movements that were an effect of medication and occurred during "ON" time. Non-troublesome dyskinesias did not interfere with function or cause meaningful discomfort. Troublesome dyskinesias interfered with function or caused meaningful discomfort. The Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (motor examination) was assessed pre-dose and hourly up to 10 hours post-dose by qualified site staff who were blinded to treatment. If rescue medication was required within 10 hours post-dose, no further PK or pharmacodynamic assessments were conducted following rescue at that visit.

The study endpoints were:

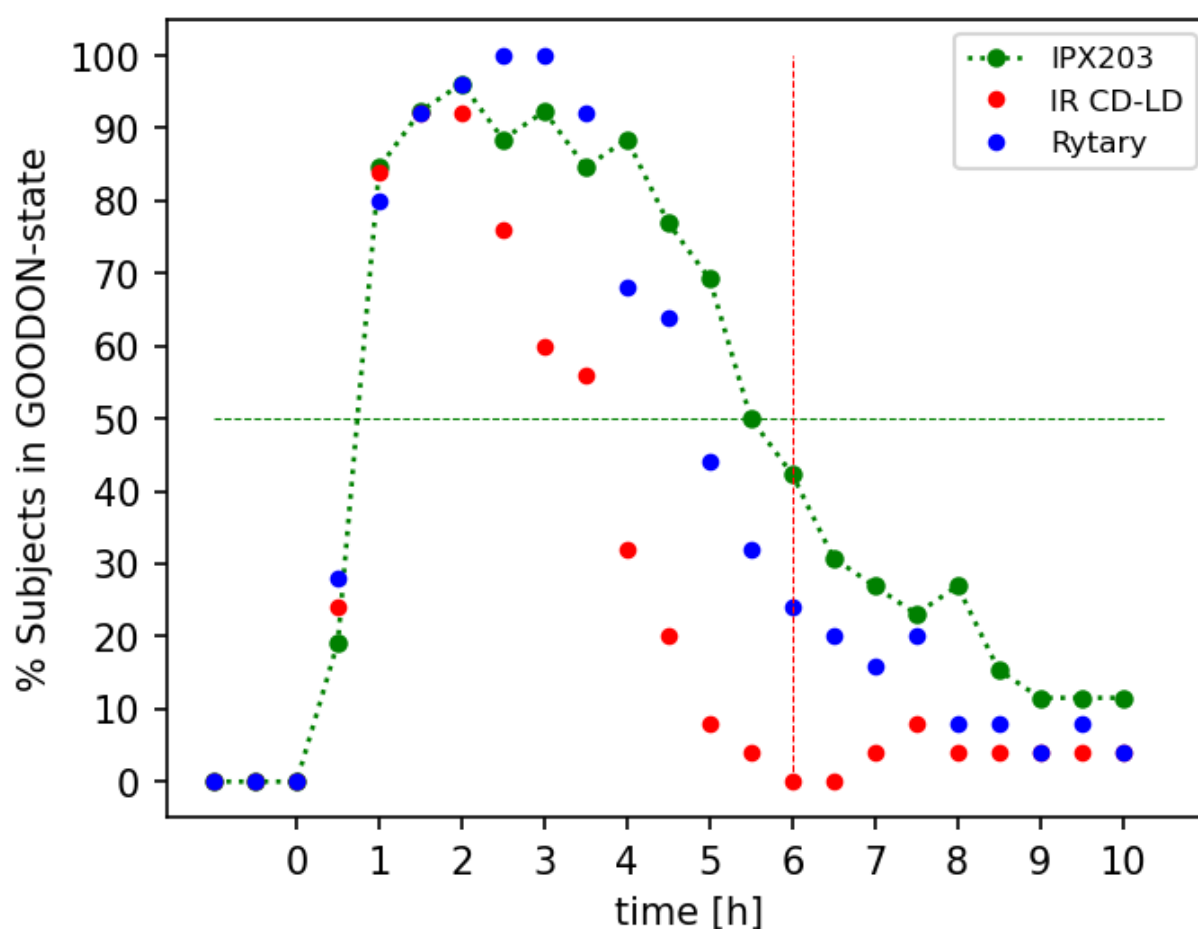
- "OFF" time based on the assessment of subject's motor state (primary endpoint);
- "ON" time without troublesome dyskinesia; also called "Good ON" time (the sum of "ON" time without dyskinesia plus "ON" time with non-troublesome dyskinesia), based on the assessment of subject's motor state;
- "ON" time without dyskinesia based on the assessment of subject's motor state;
- "ON" time with non-troublesome dyskinesia;
- "ON" time with troublesome dyskinesia based on the assessment of subject's motor state;
- "Asleep" time based on the assessment of subject's motor state;
- Change in MDS-UPDRS Part III score from pre-dose value at each time point;
- Duration of effect estimated from the time at which an improvement of at least 4 points in the MDS-UPDRS Part III score from pre-dose was first observed until the time at which the improvement was no longer observed (duration was also estimated for at least 7 and 13 points);
- Proportion of subjects with an improvement of at least 20%, 25%, 30%, and 35% in MDS-UPDRS Part III score from average pre-dose score;

- Proportion of subjects who required rescue provided by treatment group, along with a distribution by time point of rescue using the following categories: <2 hours, 2 to <4 hours, 4 to <6 hours, 6 to <8 hours, and ≥ 8 hours.

The primary PD endpoint was the mean total post-dose "OFF" time based on the assessment of the subject's motor state; the primary comparison was between IPX203 and IR LD-CD using a mixed-effect analysis of variance (ANOVA) model with treatment, period, and sequence as fixed effects and subject-within-sequence as a random effect. Mean times in each motor state were compared by treatment. The mean change from average pre-dose in MDS-UPDRS Part III scores was summarised and compared between treatments using mixed-effect ANOVA models. Duration of effect was examined by comparing improvement from average pre-dose MDS-UPDRS Part III scores for each treatment using prespecified thresholds (4-, 7-, and 13-point improvements). Percentages of subjects who required rescue medication and time to rescue were compared by treatment. If the subject withdrew prior to the 10-hour evaluation, the assessment of subject's motor state was imputed to be "OFF" for the remainder of the evaluation period, and the baseline observation (average pre-dose) was carried forward for the MDS-UPDRS Part III score.

The study results are outlined below.

Figure 13: Fraction of subjects in "Good ON" time as function of post-dose time in Study IPX203-B14-02



While there was no difference in onset, IPX203 apparently had a **one-hour** advantage over Rytary/Numient commencing at about 4 hours post-dose.

Deviations from study plan

Major protocol deviations occurred in study IPX203-B14-02: cases of incorrect dosing, dosing from a wrong bottle, continued PK samples collection after administration of a rescue medication, wrong sample volume collected and stabilizer solution volume that was not adjusted correctly, exit labs collected prior to study assessment completion all have occurred during the study. Considering the number and seriousness of such deviations, in the course of the procedure the applicant was requested to further justify why these did not impact the study results.

Among the 26 randomised subjects, 12 subjects (46.2%) had at least one major deviation. These deviations were isolated, infrequent, and managed according to prespecified procedures. Their nature and impact are described below.

1. Dosing Deviations.

Incorrect dosing occurred in 2 subjects (7.7%), and dosing from the wrong bottle occurred in 1 (3.8%). In all cases, the deviations involved minor differences in the administered dose (e.g., 250 mg instead of 200 mg, or 200 mg instead of 150 mg). Importantly, these deviations did not compromise the integrity of PK analyses because the actual dose received by each subject was used in all summaries and statistical analyses. This ensured accurate estimation of PK parameters and preserved the validity of efficacy assessments.

2. PK sampling after rescue medication

In cases of PK samples collected after administration of rescue medication (in 1 subject, 3.8%), these samples were excluded from the PK analysis, as prespecified in the Statistical Analysis Plan (SAP). This approach ensured that any potential confounding effect of rescue medication on PK parameters was avoided.

3. Sample handling and early lab collection

Deviations related to sample handling, such as incorrect sample volume or stabiliser solution errors, were observed in 1 subject (3.8%), while early collection of exit labs occurred in 4 subjects (15.4%). Additionally, 5 subjects (19.2%) had safety labs collected pre-dose at Visit 3. For these cases, laboratory summaries were analysed both including and excluding affected subjects, and no clinically meaningful differences were observed. These findings confirm that such deviations did not impact safety evaluations or overall study conclusions.

4. Severity Assessment and Data Handling

The applicant confirmed that all protocol deviations were documented, and their severity assessed before database lock, in accordance with the SAP. This process ensured that any potential impact of deviations could be identified and addressed prior to final data analysis, minimising the risk of bias and preserving the validity of the study results.

In spite of the high number of major protocol deviations, affecting 12 (46.2%) out of the 26 randomised subjects, it is agreed that none of them impacted the credibility of the study findings.

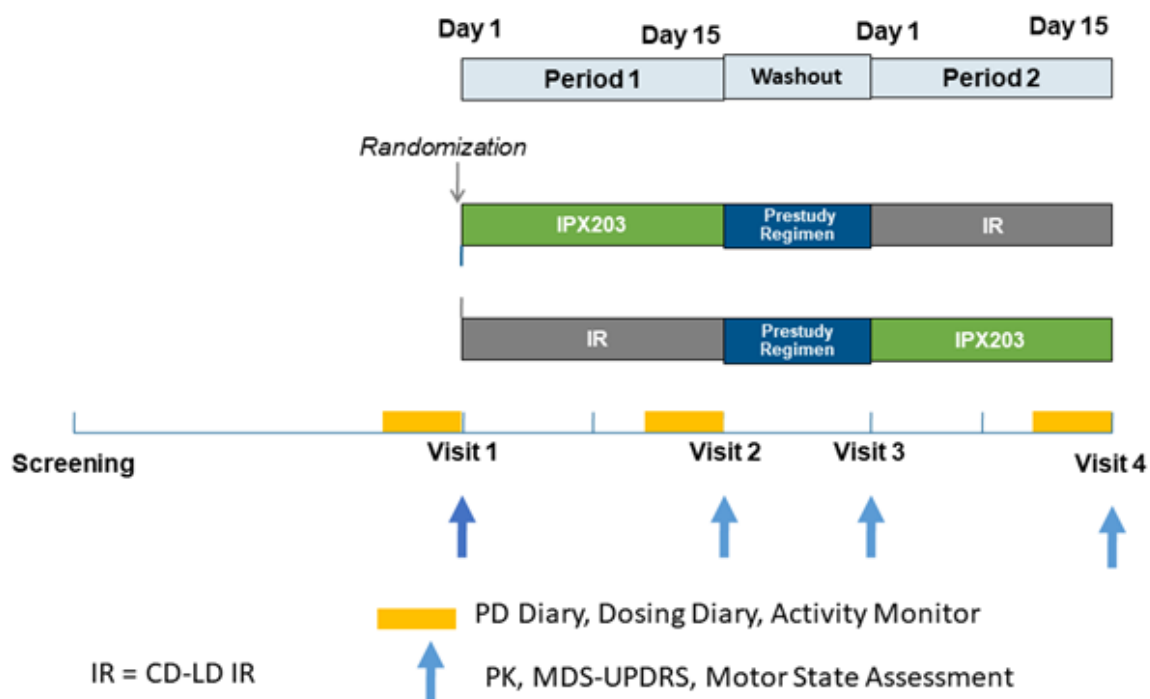
5.4.1.2. Phase 2 Study IPX203-B16-01

Study **IPX203-B16-01** was a **Phase 2** randomised, open-label, rater-blinded, 2-treatment, 2-period, multiple-dose, crossover, multicentre study that assessed the PK and PD of single and multiple doses of IPX203 and IR LD-CD in subjects with advanced PD.

Male or female subjects diagnosed with idiopathic PD at age ≥ 40 years who were being chronically treated with stable regimens of LD-CD but experiencing motor complications were enrolled. Motor complications were defined as the subject experiencing daily “wearing OFF” episodes with periods of bradykinesia and rigidity and experiencing an “OFF” state upon awakening on most mornings by history. The definition of idiopathic PD was the same as in Study IPX203-B14-02.

Eligible subjects were randomised 1:1 to one of two dosing sequences: IPX203 followed by IR LD-CD, or IR LD-CD followed by IPX203, according to their randomised sequence for Periods 1 and 2. A crossover study design was selected to allow each subject to serve as his or her own control thereby reducing confounding factors due to inter-subject variability. IR LD-CD was the primary active comparator. Subjects completed two 15-day treatment periods, one for each study treatment, with a washout period of approximately 1 week (± 2 days) between the 2 treatment periods. Given the expected short half-lives of IPX203 and IR LD-CD, a 1-week washout period was considered sufficient to minimise any carryover effects. The investigators could adjust each subject's IPX203 or IR LD-CD dose regimen for optimal efficacy, tolerability, and safety. The number of dose adjustment steps was not limited during the 9-day dose adjustment period. The study design of Study IPX203-B16-01 is presented below.

Figure 14: Study Design for IPX203-B16-01



Abbreviations: LD-CD = levodopa-carbidopa; IR = immediate-release; MDS-UPDRS = Movement Disorders Society- Unified Parkinson’s Disease Rating Scale, PD = Parkinson’s disease; PK = pharmacokinetic

On Day 1 of each treatment period (Visit 1 and Visit 3), subjects arrived at the study site and received a single dose of study medication. Subjects randomised to receive IR LD-CD started with a single dose of their usual pre-study first morning IR LD-CD dose. Subjects randomised to receive IPX203 started with a single dose of IPX203 based on their usual pre-study first morning IR LD-CD dose according to the guidance provided in Table below.

Table 18: Day 1 In-Clinic Dosing - First morning dose of study medication (Study IPX203-B16-01)

Pre-study Morning IR LD Dose (mg)	IR LD-CD LD (mg) (100 mg Tablets)	IPX203 LD (mg) (180 mg and 270 mg Capsules)
100	100	360
150	150	540
200	200	720
250	250	900
Abbreviations: CD = carbidopa; IR = immediate release; LD = levodopa		

Subjects were instructed to take their medications as whole capsule (not to be crushed or chewed) or tablet with approximately 240 mL of room-temperature water. The study treatments contained LD and CD at a fixed ratio of 4:1.

Table 19: Initial IPX203 LD dosing regimen subsequent to IPX203 morning dose based on pre-study regimen of LD (Study IPX203-B16-01)

Most Frequent Afternoon and Evening LD Unit Dose (mg)	IPX203 Regimen Post Morning Dose
100 – 125 mg	270 mg every 7 to 8 hours (270 mg × 1)
150 – 175 mg	450 mg every 7 to 8 hours (180 mg × 1 + 270 mg × 1)
200 – 225 mg	540 mg every 7 to 8 hours (270 mg × 2)
250 – 275 mg	720 mg every 7 to 8 hours (270 mg × 2 + 180 mg × 1)
300 mg	810 mg every 7 to 8 hours (270 mg × 3)
Abbreviation: IR = immediate release; LD = levodopa	
Note: A 100-mg unit dose of IR LD converts approximately to a 270-mg unit dose of IPX203.	

The study was open-label with specific PD assessments done by qualified raters who were blinded to treatment assignments (i.e., assessment of subject's motor state and MDS-UPDRS).

The efficacy and pharmacodynamic assessments in this study were intended to evaluate and quantify the treatment effect-time profile of the two different formulations of LD-CD on the motor symptoms of PD. The PD measures were typically responsive to LD.

The efficacy endpoints of the study were:

- Subject PD diaries (Days 12–14 of each treatment period):
 - Average percent "Off" time during waking hours, based on subject PD diaries (primary efficacy endpoint);
- MDS-UPDRS (Parts I–IV);
- Kinesia 360 sensors.

The PD endpoints were:

- Investigator Assessment of the Subject's Motor State;

- MDS-UPDRS, Part III.

All PD analyses (i.e., investigator's assessment of Subject Motor State and MDS-UPDRS Part III) were conducted using the Pharmacodynamic Completers analysis set. Pharmacodynamic Completers included all subjects who received both treatments and had at least 1 pre-dose and 4 post-dose motor state assessments at each visit.

The MDS-UPDRS Part III figures were plotted using all randomised subjects. randomised set included all subjects who were randomised into the study and received at least one dose of study drug.

Kinesia 360 data were analysed using the Kinesia 360 Completers analysis set. Kinesia 360 Completers included all subjects who received both treatments and had at least 2 hours of evaluable Kinesia 360 data during at least 1 of the 3 days prior to each of Visits 1, 2, and 4. Evaluable Kinesia 360 data was defined as at least 2 hours of Kinesia 360 data for the particular day.

Results

Twenty-eight subjects were randomised, and 27 (96.4%) completed both treatments. One withdrew, because of an AE while receiving IPX203, and did not receive IR CD-LD.

For the 28 randomised subjects, the mean (SD) age was 66.4 (10.1) years. Males slightly outnumbered females (16 *versus* 12, respectively). The majority (92.9%) of the subjects were white.

Pharmacokinetic results

Single-dose PK on Day 1 (Table A)

In the 27 subjects who received both treatments, the mean LD first dose taken in the clinic on Day 1 was 159 mg for IR CD-LD and 573 mg for IPX203. Following IPX203 treatment, LD was absorbed with a median T_{max} of 2.0 hours (range: 0.5–5.0 hours). As expected, T_{max} values were greater for IPX203 than for IR CD-LD due to continued drug release from the extended-release (ER) component.

The initial increase in LD concentration from IPX203 was comparable to that from IR CD-LD. The time to reach therapeutic or clinically meaningful plasma LD concentrations (e.g., 430 ng/mL) was similar for both treatments. After a single dose, LD plasma concentrations were sustained longer above 50% C_{max} after IPX203 treatment than after IR CD-LD (on average, 4.6 vs. 1.5 hours, respectively) and above 430 ng/mL (6.8 vs. 2.8 hours, respectively). Plasma exposure to LD (based on C_{max} and AUC_{∞} values) increased in an approximately dose-proportional manner following IPX203 treatment across the dose range of 360 mg to 900 mg studied in the trial.

Table 20: Table A: Levodopa single-dose pk parameters on Day 1 (PK Completers)

Parameter	IPX203 (N = 27)	IR CD-LD (N = 27)
	<i>All Doses</i>	<i>All Doses</i>
C _{max} (ng/mL)	2858 ± 1205	2173 ± 1241
T _{max} (h)	2.0 (0.5–5.0)	0.5 (0.5–2.0)
t _{1/2} (h)	1.7 ± 0.5	1.4 ± 0.3
AUC _t (ng·h/mL)	12108 ± 5794	3748 ± 1819
AUC _∞ (ng·h/mL)	13969 ± 7607	4308 ± 2123
Bioavailability (%) ^a	89 ± 22	–
Time to 430 ng/mL (h)	0.18 (0.0-1.1)	0.14 (0.0-1.6)
Duration > 50% C _{max} (h)	4.6 ± 1.2	1.5 ± 0.6
Duration > 430 ng/mL (h)	6.8 ± 0.9	2.8 ± 0.9

Note: All values are mean ± SD except T_{max} and time to 430 ng/mL, which are median (min–max). PK completers analysis set (N=27) comprises all subjects for whom at least one PK parameter (AUC_t or C_{max}) was calculable on Days 1 and 15 for both treatments.

^a Bioavailability relative to IR CD-LD

Carbidopa had a median T_{max} of 2.5 hours (min, max 1.5, 4.0) on Day 1 following the first dose of IPX203. Mean CD C_{max} following IPX203 was 500 ng/mL, and mean t_{1/2} was 2.0 hours. Values of AUC and C_{max} for CD following a single dose of IPX203 were higher than for the IR CD-LD treatment, as expected from the higher dose of CD in IPX203 and formulation characteristics. The bioavailability values for LD and CD in IPX203 relative to IR CD-LD, based on arithmetic mean AUC_∞ ratios, were 89% and 117%, respectively.

Multiple-dose PK on Day 15 (Table B)

The mean morning dose of LD administered in the clinic on Day 15 of a stable dosing regimen was 159 mg for IR CD-LD and 560 mg for IPX203. Following the first dose of IPX203 on Day 15, LD was absorbed with a median T_{max} of 1.5 hours (min, max 0.5, 6.0). The initial rate of increase in LD concentration from IPX203 was comparable to that of IR CD-LD. The mean LD C_{max} following IPX203 treatment was only 15% greater than that of IR CD-LD in spite of a 3.5-fold greater LD dose. The mean LD AUC_{tau} value following IPX203 treatment was approximately 2.9-fold greater than that of IR CD-LD, consistent with the higher dose of LD administered.

Table 21: Table B: Levodopa multiple-dose pk parameters on Day 15 (PK Completers)

Parameter	IPX203 N = 27	IR CD-LD N = 27
	<i>All Doses</i>	<i>All Doses</i>
C _{max} (ng/mL)	2768 ± 1259	2357 ± 1179
T _{max} (h)	1.5 (0.5–6.0)	0.5 (0.5–2.0)
AUC _{tau} (h·ng/mL)	11214 ± 4887	3879 ± 1744
Fluctuation index	1.7 ± 0.5	2.7 ± 1.0
Accumulation ratio	1.0 ± 0.3	1.1 ± 0.2 ^a

Note: All values are mean ± SD except T_{max}, which is median (min–max).

^a N=26

The duration that plasma LD concentrations remained above 430 ng/mL was significantly longer for IPX203 (on average 9.0 hours vs. 7.4 hours with IR CD-LD).

Following the first dose of IPX203 on Day 15, CD was absorbed with a median T_{max} of 2.5 hours (min, max 1.5, 4.0). The mean CD C_{max} following IPX203 treatment was 479 ng/mL. The mean CD AUC_{tau} value following IPX203 treatment was approximately 4.6-fold greater than that of IR CD-LD. The mean fluctuation index for LD over the 10-hour in-clinic assessment duration on Day 15 of a stable dosing regimen was lower with IPX203 than IR CD-LD (1.7 vs. 2.7, respectively) and comparable for CD (1.7 vs. 1.5, respectively). Accumulation ratios for LD and CD were low with both treatments.

In terms of efficacy, during IPX203 treatment, subjects had less "OFF" time as a percentage of their waking hours compared with IR CD-LD (mean 19.3% vs. 33.5%, respectively), based on PD diary data collected on Days 12 to 14 of each treatment period (primary efficacy measure). On average, treatment with IPX203 was associated with approximately 2.3 hours less "OFF" time than was IR CD-LD during waking hours; most of this improvement (1.9 hours) was "Good ON" time. The durations of "Good ON" episodes or any "ON" episodes were significantly longer with IPX203 (LS means differences 2.89 hours and 3.79 hours, respectively). Treatment with IPX203 was also associated with significantly fewer motor fluctuations per day than IR CD-LD. Significantly higher proportions of subjects experienced a reduction in "Off" time of at least 1.0, 1.5, and 2.0 hours during IPX203 treatment than during IR CD-LD treatment.

When predose mean MDS-UPDRS Parts I–IV scores were compared by treatment on Day 15, subjects had significantly lower scores for Parts III, II and III, and IV as well as the MDS-UPDRS total score during IPX203 treatment, indicating less PD impairment. Pre-dose on Day 15, when subjects had not had a study treatment for at least 5 hours, the mean MDS-UPDRS Part III score was significantly lower during IPX203 treatment (33.5 vs. 41.6), suggesting that the clinical effects of IPX203 may carry over to the next morning. Analysis of Part IV individual items demonstrated benefits of IPX203 *versus* IR CD-LD on time spent in "OFF state" and on functional impact of fluctuations.

On Day 1, subjects receiving IPX203 were 73.3% less likely to receive rescue medication (defined as the 2nd study drug dose of the day) than those receiving IR CD-LD. Similarly, on Day 15, subjects receiving IPX203 were 72.1% less likely to receive a predose than those receiving IR CD-LD.

With regards to PD, the investigator's assessment of the subject's motor state on Day 1 demonstrated significantly less "OFF" time and significantly more "Good ON" time with IPX203 compared with IR CD-LD (2.57 hours difference for each). On Day 15, significant treatment differences were again seen in "OFF" time and "Good ON" time, although the magnitude of the differences was smaller. During the 10-hour post-dose observation period, 63% of subjects experienced less than 2 hours of "OFF" time compared to 19% of subjects during the IPX203 and IR CD-LD treatment periods, respectively. Average times to first "ON" and first "Good ON" states after the first dose were not significantly different between treatments on Days 1 or 15.

MDS-UPDRS Part III mean scores on Day 1 were lower during IPX203 treatment than during IR CD-LD treatment from 3 to 8 hours post-dose; across the 8 hours post-dose, the mean scores were 23.6 during IPX203 treatment and 33.0 during IR CD-LD treatment ($p < 0.0001$). Subjects had longer total durations of pharmacodynamic effect during IPX203 treatment than during IR CD-LD treatment, based on minimal improvement thresholds of at least 4, 7, and 13 points on the MDS-UPDRS Part III scale. From 3 to 7 hours post-dose, greater proportions of subjects taking IPX203 than taking IR CD-LD met each of 3 minimal improvement thresholds. On Day 15, across the 10 hours post-dose, the mean MDS-UPDRS Part III scores were 18.2 for IPX203 and 22.0 for IR CD-LD ($p = 0.0226$).

The sum of scores from bradykinesia questions from Part III (sum of Questions 4-8, and 14) showed more reduction with IPX203 than IR CD-LD on Day 1 (overall and at Hours 3 through 7) but not on Day 15 (except at Hours 3 and 4).

Deviations from study plan

In total, 28.6% of patients experienced major protocol's deviations during study IPX203-B16-01: 14.3% (4 subjects) had incorrect dosing regimen used on Day 15 visit, 1 subject was given wrong drug at EOS, 1 subject missed IR dose before Day 1 visit, 1 subject used more IPX203 270-mg capsules than expected. Importantly, these protocol's deviations were reviewed and adjudicated prior to database lock to ensure appropriate handling and to confirm that they did not compromise the validity of efficacy or PK/pharmacodynamic analyses.

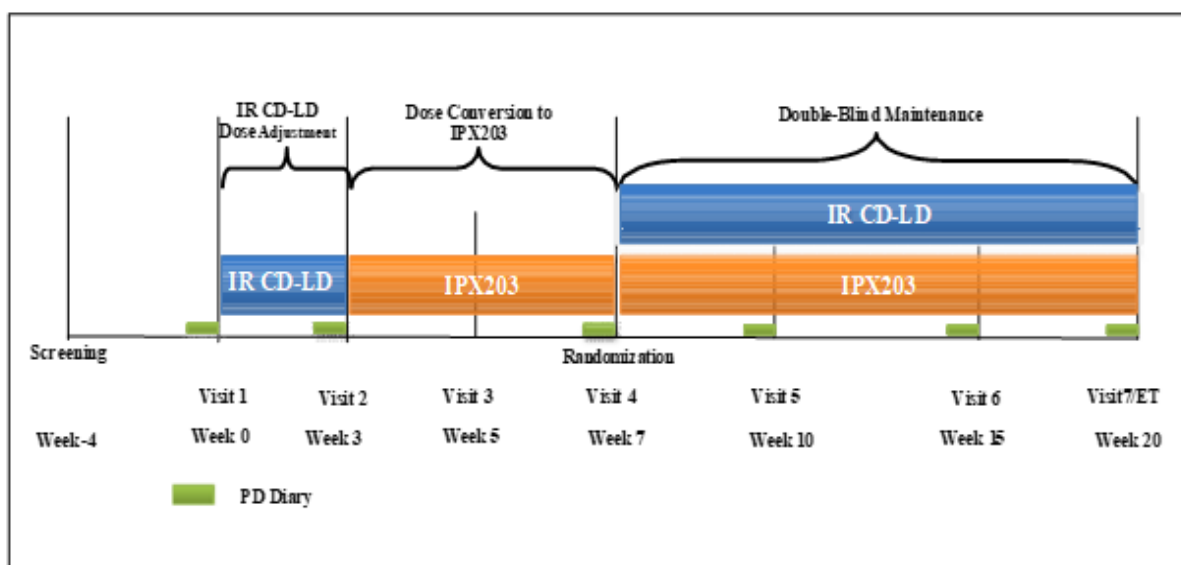
5.4.2. Main studies

5.4.2.1. IPX203-B16-02

Study objective

Study **IPX203-B16-02** was a **Phase 3** randomised, double-blind, double-dummy, active-controlled, parallel-group, prospective, multicentre study that evaluated the safety and efficacy of IPX203 in comparison to IR LD-CD in the treatment of LD-CD subjects with PD who had motor fluctuations, despite being treated with stable regimens of IR LD-CD.

Figure 15: Study IPX203-B16-02 scheme



Abbreviations: ET = early termination; IR CD-LD = immediate-release carbidopa-levodopa; PD = Parkinson's disease

Treatment

The study consisted of an up to 4-week screening period, a 3-week open-label IR CD-LD dose adjustment period, a 4-week open-label period for conversion to IPX203, and a 13-week double-blind, double-dummy treatment period. Subjects were randomised in a 1:1 ratio and stratified by centre to receive either IPX203 (with matching IR CD-LD placebo) or IR CD-LD (with matching IPX203 placebo).

Subjects continued to take permitted non-CD-LD-based PD medications throughout the study if documented in their pre-study regimen and if dosing regimens had been stable for at least 4 weeks prior to Visit 1. A "stable dosing regimen" meant no change in dose or in dosing frequency.

- Within 4 weeks following the screening visit, eligible subjects completed their PD diaries on each of the 3 consecutive days immediately prior to Visit 1 (study entry visit).
- Following Visit 1, qualified subjects entered a 3-week, open-label IR CD-LD treatment period allowing for dose adjustment. The dosing regimen of IR CD-LD could be adjusted during the dose adjustment period to achieve optimal balance of efficacy and tolerability (minimize "Off" time without causing troublesome dyskinesia or other dopaminergic side effects). The doses and regimens of the subject's other non-CD-LD PD medications (dopamine agonists, monoamine oxidase [MAO]-B inhibitors, amantadine, anticholinergics) had to remain stable throughout this study. Any adjustments to the IR CD-LD dosing regimen were to be done in consultation with the investigator or sub-investigator and were recorded. Regular phone calls (approximately every 1 to 3 days) to the subjects were made by the Investigator or sub-investigator while the IR CD-LD dose was being adjusted. The IR CD-LD dosing regimen had to be stable for at least 5 days prior to returning for Visit 2. Rescue with additional or modified doses of concomitant PD medications or with use of CD-LD products other than the dispensed study medications was not permitted and triggered discontinuation from the study. Subjects had to complete their 3-day PD Diaries on each of the 3 consecutive days immediately prior to Visit 2.
- Following completion of the IR CD-LD dose adjustment period, subjects began a 4-week open-label dose conversion period for conversion from IR CD-LD to IPX203. The initial dosing regimen of IPX203 was based on the most frequent dose of the subject's stable dosing regimen of IR CD-LD at the end of the dose adjustment period (Visit 2). A 25-100 mg dose of IR CD-LD was converted to a 70-280 mg CD-LD dose of IPX203 (2 capsules of 35-140 mg CD-LD IPX203), and a 12.5-50 mg (half-tablet) dose of IR CD-LD was converted to a 35-140 mg CD-LD dose of IPX203, but with a longer duration of effect. It was recommended that IPX203 be dosed approximately every 8 hours with the exception that subjects who were currently receiving a TDD of less than 125-500 mg from IR CD-LD at the end of the dose adjustment period had to be initially administered IPX203 every 12 hours. The dosing interval could be reduced to approximately every 8 hours if the subject did not achieve an acceptable duration of effect. The dosing regimen of IPX203 could be adjusted during the dose conversion period to achieve the optimal balance of efficacy and tolerability (minimize "Off" time without causing troublesome dyskinesia or other dopaminergic side effects). The dosing interval could vary but was not to be more frequent than every 6 hours. The doses and regimens of the subject's other non-CD-LD PD medications (dopamine agonists, MAO-B inhibitors, amantadine, anticholinergics) had to remain stable throughout this study. The subject had to be on a stable dosing regimen of IPX203 (no change in dose or in dosing frequency) for at least 5 days prior to returning for Visit 4 (randomization visit). Any adjustments to the IPX203 dosing regimen were to be done in consultation with the investigator or sub-investigator and were recorded. During the dose adjustment period, subjects were to be called by the investigator or sub-investigator to adjust the IPX203 dose further, as needed, and subjects returned to the clinic every 2 weeks for Visit 3 and Visit 4. Subjects were instructed to complete their 3-day PD diaries on each of the 3 consecutive days immediately prior to Visit 4 (randomization visit).
- At Visit 4, subjects who successfully completed the IPX203 dose conversion period were randomised in a 1:1 ratio, stratified by centre, to one of two parallel treatment arms of IPX203 (with matching IR CD-LD placebo) or IR CD-LD (with matching IPX203 placebo). Subjects underwent 13 weeks of double-blind, double-dummy maintenance therapy with the stable dosing regimen established at the end of Week 3 (Visit 2) for IR CD-LD and at the end of Week 7 (Visit 4) for IPX203. No new dose adjustments could be made in the double-blind maintenance period. Rescue with additional or modified doses of concomitant PD medications or with use of CD-LD products other than the dispensed study medications was not permitted and triggered

discontinuation from the study. During the 13-week maintenance therapy period, subjects returned to the clinic for visit 5 (3 weeks after Visit 4), visit 6 (5 weeks after visit 5), and visit 7 (end of study [EOS] visit, 5 weeks after Visit 6). Subjects completed their 3-day PD Diaries on each of the 3 consecutive days immediately prior to each of these visits.

Rescue with additional or modified doses of concomitant PD medications or with use of CD-LD products other than the dispensed study medications was not permitted and triggered discontinuation from the study.

Randomisation and blinding

On Week 7 at visit 4, subjects were randomised, stratified by centre, in a 1:1 ratio into one of two double blind parallel treatment arms of IPX203 (and matching IR CD-LD placebo) or IR CD-LD (and matching IPX203 placebo).

Patient population

Patients were enrolled from US, Italy, Spain, France, UK, Czech Republic, Poland and Germany.

Male or female subjects diagnosed at age ≥ 40 years with PD, consistent with the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria and who were being treated with stable regimens of LD-CD but experienced motor fluctuations, were enrolled.

Objectives and estimands

Primary objectives

1. To evaluate the efficacy of IPX203 in comparison to IR CD-LD in the treatment of CD-LD experienced subjects PD who have motor fluctuations with respect to the change from baseline in "Good ON" time in hours per day, averaged over the PD Diary days, at the end of double-blind treatment period (Visit 7 or early termination).
2. To evaluate the safety of IPX203 in comparison to IR CD-LD in the treatment of CD-LD experienced subjects with Parkinson's disease (PD) who have motor fluctuations.

Estimand for the primary objective

Table 22: Estimand for primary objective: change from baseline in "Good ON" time in hours per day, averaged over the PD Diary days, at the end of double-blind treatment period (Visit 7 or early termination)

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events
Endpoint (variable)	Mean change from baseline in "Good ON" time (hours/day), averaged over the 3-day PD Diary at Visit 7 or early termination. Baseline is defined as the average "Good ON" time from the PD Diary collected prior to randomization (Visit 4).
Population-level	Difference in least squares means (LS means) between treatment groups at Visit 7/ET,

summary	estimated using a Mixed Model for Repeated Measures (MMRM)
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death

Planned analyses

The primary endpoint and 4 key secondary endpoints were tested in a sequential hierarchical order as follows:

1. The primary endpoint, the mean change from baseline in "Good ON" time (hours per day), to be tested first at a 0.05 level of significance.
2. If statistical significance is demonstrated, then the first key secondary endpoint, the mean change from baseline in "OFF" time (hours per day), to be tested next at a 0.05 level of significance.
3. If statistical significance is demonstrated, then the second key secondary endpoint, the proportion of subjects with either "much improved" or "very much improved" on the PGI-C, to be tested next at a 0.05 level of significance.
4. If statistical significance is demonstrated, then the third key secondary endpoint, the mean change from baseline in the MDS-UPDRS Part III, to be tested at a 0.05 level of significance.
5. If statistical significance is demonstrated, then the fourth key secondary endpoint, the mean change from baseline in the sum of the MDS-UPDRS Parts II and III combined to be tested next at a 0.05 level of significance.

For the other efficacy endpoints, no adjustment to be made.

Statistical methods for estimation and sensitivity analysis on primary estimand

Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from baseline in "Good ON" time in hours per day, averaged over the PD Diary days, at the end of the double-blind therapy (Visit 7 or early termination). "Good ON" time is derived from the 3-day PD Diaries. For each day, "Good on" time is calculated by adding the number of half-hour intervals in which either an "ON without dyskinesia" or "ON with non-troublesome dyskinesia" is checked.

The primary efficacy endpoint was analysed using a mixed model for repeated measures (MMRM). The model included baseline (Visit 4) "Good ON" time as a covariate, treatment, visit, and pooled centre as fixed effects, and a treatment-by-visit interaction. The model employed an unstructured within subject covariance matrix and a restricted maximum likelihood (ReML) estimation method. The degree-of-freedom of the denominator was estimated using the Kenward-Roger method (30TKenward and Roger 199730T). The primary analysis population will be the modified intent-to-treat.

Secondary Objectives

To evaluate the efficacy of IPX203 in comparison to IR CD-LD in the treatment of CD-LD experienced subjects with PD who have motor fluctuations with respect to the following key secondary endpoints:

- Change from baseline in "OFF" time in hours per day, averaged over the PD Diary days at the end of double-blind treatment period (Visit 7 or early termination)
- Proportion of subjects with either "much improved" or "very much improved" in Patient Global Impression of Change (PGI-C) scores at the end of double-blind treatment period (Visit 7 or early termination)
- Change from baseline in the MDS-UPDRS Part III at the end of double-blind treatment period (Visit 7 or early termination)
- Change from baseline in the sum of MDS-UPDRS Parts II and III at the end of double-blind treatment period (Visit 7 or early termination).

Exploratory Objectives

To evaluate the efficacy of IPX203 in comparison to IR CD-LD in the treatment of CD-LD experienced subjects with Parkinson's disease (PD) who have motor fluctuations with respect to the following exploratory endpoints:

- Percent "OFF" time during waking hours derived from the 3-day PD Diaries
- Average duration of each continuous "Good on" and each continuous "ON"
- Hours of (1) "OFF" time (from Visit 1), (2) "Good ON" time (from Visit 1), (3) "ON" time with dyskinesia, (4) "ON" time with troublesome dyskinesia, and (5) "ON" time with non-troublesome dyskinesia, and (6) asleep time derived from the 3-day PD Diaries
- Proportion of subjects with an improvement in "Good ON" time of at least 1, 1.5, 2, 2.5, and 3 hours
- Proportion of subjects with a reduction in "OFF" time of at least 0.5, 1, 1.5, 2, 2.5, and 3 hours
- Proportions of subjects who are "ON" upon awakening and "Good on" upon awakening
- Average time to "ON" upon awakening
- Change from baseline in the average number of motor fluctuations per day averaged over the PD Diary days. A motor fluctuation is defined as a change from "Off" to "On" state or from "ON" to "OFF" state.
- MDS-UPDRS total score (sum of Parts I, II, III, and IV) and Parts I, II, and IV separately
- MDS-UPDRS Part III and Parts II + III combined (from Visit 1)
- MDS-UPDRS Part II Question 2.9
- PDQ-39 total score and individual domain scores
- NMSS total score and individual domains
- PDSS-2 total score and individual domains
- PDSS-2 items 9, 10, 11, 12, and 13 combined
- PAS total score and individual domains

- PGI-S
- Proportion of subjects with either “severely ill” or “extremely severely ill” on the PGI-S
- CGI-S
- Proportion of subjects with either “severely ill” or “among the most extremely ill of subjects” on the CGI-S
- PGI-C scores
- CGI-C scores
- Proportion of subjects with either “much improved” or “very much improved” on the CGI-C.

Estimands for the secondary objectives

Secondary Endpoints

Change from baseline in “OFF” time in hours per day, averaged over the PD Diary days at the end of double-blind treatment period (Visit 7 or early termination)

Population	Patients with Parkinson’s disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Mean change from baseline in “OFF” time (hours/day), averaged over the 3-day PD Diary at Visit 7 or early termination. baseline is defined as the average “off” time from the pd diary collected prior to randomisation (visit 4).
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

Proportion of subjects with either “much improved” or “very much improved” in Patient Global Impression of Change (PGI-C) scores at the end of double-blind treatment period (Visit 7 or early termination)

Population	Patients with Parkinson’s disease and motor fluctuations under any treatment assignment.
Treatment condition	Assignment to IPX203, regardless of discontinuation, compared to assignment to IR LD-CD, regardless of discontinuation.
Endpoint (variable)	PGI-C responder status at Visit 7 or early termination: defined as a score of “much improved” or “very much improved” on the 7-point PGI-C scale.
Population-level summary	Difference in responder proportions between treatment groups, tested using Cochran-Mantel-Haenszel (CMH) test stratified by pooled centre.

Population	Patients with Parkinson's disease and motor fluctuations under any treatment assignment.
Intercurrent events and strategy to handle them	
Treatment discontinuation	Composite: Subjects who discontinue treatment are not assessed at Visit 7/ET and are imputed as non-responders.
Use of prohibited medications	Composite: Use of prohibited medications leads to study withdrawal; subjects are imputed as non-responders.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	Composite: Subjects who die before Visit 7/ET are considered non-responders.

Change from baseline in the MDS-UPDRS Part III at the end of double-blind treatment period (Visit 7 or early termination)

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Mean change from baseline in MDS-UPDRS Part III total score at Visit 7 or early termination. Baseline is defined as the last assessment prior to randomization (Visit 4).
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

Change from baseline in the sum of MDS-UPDRS Parts II and III at the end of double-blind treatment period (Visit 7 or early termination).

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Mean change from baseline in the sum of MDS-UPDRS Parts II and III total scores at Visit 7 or early termination. Baseline is defined as the last assessment prior to randomization (Visit 4).
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

The first key secondary endpoint was the mean change from baseline in "OFF" time in hours per day, averaged over the PD Diary days, at the end of the double-blind therapy (Visit 7 or early termination). "OFF" time was derived from the 3-day PD Diaries. For each day, "OFF" time was calculated by adding the number of half-hour intervals in which an "OFF" is checked. This endpoint was analysed using a MMRM model with baseline (Visit 4) "OFF" time as a covariate, treatment, visit, and pooled centre as fixed effects, and a treatment-by-visit interaction. The model employed an unstructured within subject covariance matrix and a restricted maximum likelihood (ReML) estimation method. The degree-of-freedom of the denominator was estimated using the Kenward-Roger method (30TKenward and Roger 199730T).

The proportion of subjects with either "much improved" or "very much improved" in PGI-C scores at the end of the double-blind therapy (Visit 7 or early termination), the second key secondary endpoint, was analysed using a Cochran-Mantel-Haenszel test to compare the two treatment groups with pooled centre as a stratification factor.

Key secondary endpoints:

- Change from baseline in "OFF" time in hours per day, averaged over the PD Diary days at the end of double-blind treatment period (Visit 7 or early termination) – Proportion of subjects with either "much improved" or "very much improved" in Patient Global Impression of Change (PGI-C) scores at the end of double-blind treatment period (Visit 7 or early termination).
- Change from baseline in the MDS-UPDRS Part III at the end of double-blind treatment period (Visit 7 or early termination).
- Change from baseline in the sum of MDS-UPDRS Parts II and III at the end of double-blind treatment period (Visit 7 or early termination).

Tertiary objectives

The following endpoints were evaluated (at the post-randomization visits) as change from baseline (Visit 4) as well as change from the study entry (Visit 1), when applicable, by visits:

- Percent "OFF" time during waking hours derived from the 3-day PD Diaries
- Average duration of each continuous "Good ON" and each continuous "ON".

Estimands for the tertiary objectives

Exploratory endpoints

Percent "OFF" time during waking hours derived from the 3-day PD Diaries

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Percent of "OFF" time during waking hours, calculated as: [Total duration of all time periods in "OFF" state] / [Total duration of all periods in state other than "Asleep"] *100%, averaged over the 3-day PD Diary at Visit 7 or early termination.
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

Average duration of each continuous "Good ON" and each continuous "ON"

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Average duration of each continuous "Good ON" period (i.e., consecutive half-hour intervals marked as "ON without dyskinesia" or "ON with non-troublesome dyskinesia") Average duration of each continuous "ON" period (i.e., any "ON" state, including with or without dyskinesia), calculated from the 3-day PD Diary at Visit 7 or early termination.
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

Hours of (1) "OFF" time (from Visit 1), (2) "Good ON" time (from Visit 1), (3) "ON" time with dyskinesia, (4) "ON" time with troublesome dyskinesia, and (5) "ON" time with no troublesome dyskinesia, and (6) asleep time derived from the 3-day PD Diaries

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Average daily hours spent in each of the following PD Diary states, derived from the 3-day diary at Visit 7 or early termination: 1. "OFF" time 2. "Good ON" time (On without dyskinesia or with non-troublesome dyskinesia) 3. "ON" time with dyskinesia (troublesome or non-troublesome) 4. "ON" time with troublesome dyskinesia 5. "ON" time with no troublesome dyskinesia 6. Asleep time
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

Proportion of subjects with an improvement in "Good ON" time of at least 1, 1.5, 2, 2.5, and 3 hours

Population	Patients with Parkinson's disease and motor fluctuations under any treatment assignment.
Treatment condition	Assignment to IPX203, regardless of discontinuation, compared to assignment to IR LD-CD, regardless of discontinuation.
Endpoint (variable)	Proportion of subjects with an increase in average daily "Good ON" time from double-blind baseline (Visit 4) to Visit 7 or early termination of at least: 1 hour 1.5 hours 2 hours 2.5 hours 3 hours (based on 3-day PD Diary data)
Population-level summary	Difference in responder proportions between treatment groups, tested using CMH test stratified by pooled centre.
Intercurrent events and strategy to handle them	
Treatment discontinuation	Composite: Subjects who discontinue treatment are not assessed at Visit 7/ET and are imputed as non-responders.
Use of prohibited medications	Composite: Use of prohibited medications leads to study withdrawal; subjects are imputed as non-responders.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	Composite: Subjects who die before Visit 7/ET are considered non-responders.

Proportion of subjects with a reduction in "OFF" time of at least 0.5, 1, 1.5, 2, 2.5, and 3 hours

Population	Patients with Parkinson's disease and motor fluctuations under any treatment assignment.
Treatment condition	Assignment to IPX203, regardless of discontinuation, compared to assignment to IR LD-CD, regardless of discontinuation.
Endpoint (variable)	Proportion of subjects with a decrease in average daily "OFF" time from double-blind baseline (Visit 4) to Visit 7 or early termination of at least: 0.5 hour 1 hour 1.5 hours 2 hours 2.5 hours 3 hours (based on 3-day PD Diary data)
Population-level summary	Difference in responder proportions between treatment groups, tested using CMH test stratified by pooled centre.
Intercurrent events and strategy to handle them	
Treatment discontinuation	Composite: Subjects who discontinue treatment are not assessed at Visit 7/ET and are imputed as non-responders.
Use of prohibited medications	Composite: Use of prohibited medications leads to study withdrawal; subjects are imputed as non-responders.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	Composite: Subjects who die before Visit 7/ET are considered non-responders.

Proportions of subjects who are "ON" upon awakening and "Good ON" upon awakening

Population	Patients with Parkinson's disease and motor fluctuations under any treatment assignment.
Treatment condition	Assignment to IPX203, regardless of discontinuation, compared to assignment to IR LD-CD, regardless of discontinuation.
Endpoint (variable)	Proportion of subjects who are: 1. In an "ON" state (any "ON" with or without dyskinesia), and 2. In a "Good ON" state ("ON without dyskinesia" or "On with non-troublesome dyskinesia") during the first half-hour interval after awakening, on at least 1, 2, or 3 of the 3 diary days at Visit 7 or early termination (based on 3-day PD Diary data)
Population-level summary	Difference in responder proportions between treatment groups, tested using CMH test stratified by pooled centre.
Intercurrent events and strategy to handle them	
Treatment discontinuation	Composite: Subjects who discontinue treatment are not assessed at Visit 7/ET and are imputed as non-responders.
Use of prohibited medications	Composite: Use of prohibited medications leads to study withdrawal; subjects are imputed as non-responders.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	Composite: Subjects who die before Visit 7/ET are considered non-responders.

Average time to "On" upon awakening

Population	Patients with Parkinson's disease and motor fluctuations who, under either treatment assignment, would provide complete and classifiable PD Diary data for all 3 days at Visit 7 or early termination.
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Treatment condition<s>	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Average time (in hours) from awakening to the first "ON" state (with or without dyskinesia), calculated across valid diary days at Visit 7 or early termination.
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

Change from baseline in the average number of motor fluctuations per day averaged over the PD Diary days. A motor fluctuation is defined as a change from "OFF" to "ON" state or from "ON" to "off" state.

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition<s>	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Change from baseline in the average number of motor fluctuations per day, calculated from the 3-day PD Diaries at Visit 7 or early termination. A fluctuation is defined as a change from "Off" to "ON" or from "ON" to "OFF" state.
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

MDS-UPDRS total score (sum of Parts I, II, III, and IV) and Parts I, II, and IV separately

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition<s>	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Change from baseline (Visit 4) to Visit 7 or early termination in: 1. MDS-UPDRS total score (sum of Parts I, II, III, and IV) 2. MDS-UPDRS Part I score 3. MDS-UPDRS Part II score

	4. MDS-UPDRS Part IV score
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

MDS-UPDRS Part III and Parts II + III combined (from Visit 1)

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition<s>	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Change from study entry baseline (Visit 1) to Visit 7 or early termination in: 1. MDS-UPDRS Part III total score 2. MDS-UPDRS Parts II + III combined total score
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

MDS-UPDRS Part II Question 2.9

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition<s>	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Change from baseline (Visit 4) to Visit 7 or early termination in the score for MDS-UPDRS Part II, Question 2.9.
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.

Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

PDQ-39 total score and individual domain scores

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition<s>	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Change from baseline (Visit 4) to Visit 7 or early termination in: - PDQ-39 total score - PDQ-39 domain scores: 1. Mobility 2. Activities of Daily Living (ADL) 3. Emotional Well-being 4. Stigma 5. Social Support 6. Cognition 7. Communication 8. Bodily Discomfort
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

NMSS total score and individual domains

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition<s>	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Change from baseline (Visit 4) to Visit 7 or early termination in: - NMSS total score - NMSS domain scores: 1. Cardiovascular 2. Sleep/Fatigue 3. Mood/Cognition 4. Perceptual Problems 5. Attention/Memory

	6. Gastrointestinal 7. Urinary 8. Sexual Function 9. Miscellaneous
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

PDSS-2 total score and individual domains

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition<s>	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Change from baseline (Visit 4) to Visit 7 or early termination in: - PDSS-2 total score - PDSS-2 domain scores: 1. Disturbed Sleep (Questions 1-3, 8, 14) 2. Motor Symptoms at Night (Questions 4-6, 12, 13) 3. PD Symptoms at Night (Questions 7, 9-11, 15)
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

PDSS-2 items 9, 10, 11, 12, and 13 combined

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition<s>	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Change from baseline (Visit 4) to Visit 7 or early termination in the sum of Questions 9-13
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	

Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

PAS total score and individual domains

Population	Patients with Parkinson's disease and motor fluctuations who would encounter the intercurrent events of treatment discontinuation, use of prohibited medications, or death under any treatment assignment.
Treatment condition<s>	Assignment to IPX203 compared to assignment to IR LD-CD, considering only data collected prior to the occurrence of the intercurrent events.
Endpoint (variable)	Change from baseline (Visit 4) to Visit 7 or early termination in: - PAS total score - PAS domain scores: 1. Persistent Anxiety (Questions A.1-A.5) 2. Episodic Anxiety (Questions B.1-B.4) 3. Avoidance Anxiety (Questions C.1-C.3)
Population-level summary	Difference in LS means between treatment groups at Visit 7/ET, estimated using MMRM.
Intercurrent events and strategy to handle them	
Treatment discontinuation	While-on-Treatment: Data collected up to discontinuation are used; no further data are collected post-discontinuation.
Use of prohibited medications	While-on-Treatment: Use of prohibited medications leads to study withdrawal; data post-event are not collected.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	While-on-Treatment: Only data collected prior to death are used; no imputation beyond death.

Proportion of subjects with either "severely ill" or "extremely severely ill" on the PGI-S

Population	Patients with Parkinson's disease and motor fluctuations under any treatment assignment.
Treatment condition<s>	Assignment to IPX203, regardless of discontinuation, compared to assignment to IR LD-CD, regardless of discontinuation.
Endpoint (variable)	Proportion of subjects with PGI-S score of 6 ("severely ill") or 7 ("extremely severely ill") at Visit 7 or Early Termination.
Population-level summary	Difference in responder proportions between treatment groups, tested using CMH test stratified by pooled centre.
Intercurrent events and strategy to handle them	
Treatment discontinuation	Composite: Subjects who discontinue treatment are not assessed at Visit 7/ET and are imputed as non-responders.
Use of prohibited medications	Composite: Use of prohibited medications leads to study withdrawal; subjects are imputed as non-responders.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.

Death	Composite: Subjects who die before Visit 7/ET are considered non-responders.
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Proportion of subjects with either “severely ill” or “among the most extremely ill of subjects” on the CGI-S

Population	Patients with Parkinson’s disease and motor fluctuations under any treatment assignment.
Treatment condition<s>	Assignment to IPX203, regardless of discontinuation, compared to assignment to IR LD-CD, regardless of discontinuation.
Endpoint (variable)	Proportion of subjects with CGI-S score of 6 (“severely ill”) or 7 (“among the most extremely ill of subjects”) at Visit 7 or Early Termination.
Population-level summary	Difference in responder proportions between treatment groups, tested using CMH test stratified by pooled centre.
Intercurrent events and strategy to handle them	
Treatment discontinuation	Composite: Subjects who discontinue treatment are not assessed at Visit 7/ET and are imputed as non-responders.
Use of prohibited medications	Composite: Use of prohibited medications leads to study withdrawal; subjects are imputed as non-responders.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	Composite: Subjects who die before Visit 7/ET are considered non-responders.

Proportion of subjects with either “much improved” or “very much improved” on the CGI-C

Population	Patients with Parkinson’s disease and motor fluctuations under any treatment assignment.
Treatment condition<s>	Assignment to IPX203, regardless of discontinuation, compared to assignment to IR LD-CD, regardless of discontinuation.
Endpoint (variable)	CGI-C responder status at Visit 7 or early termination: defined as a score of “much improved” or “very much improved” on the 7-point CGI-C scale.
Population-level summary	Difference in responder proportions between treatment groups, tested using CMH test stratified by pooled centre
Intercurrent events and strategy to handle them	
Treatment discontinuation	Composite: Subjects who discontinue treatment are not assessed at Visit 7/ET and are imputed as non-responders.
Use of prohibited medications	Composite: Use of prohibited medications leads to study withdrawal; subjects are imputed as non-responders.
COVID-19 related restrictions	Treatment policy: data are analysed as collected, regardless of whether the visit was delayed, cancelled, or conducted remotely for COVID-19 related reasons.
Death	Composite: Subjects who die before Visit 7/ET are considered non-responders.

Statistical methods for estimation and sensitivity analysis on the tertiary estimands

Not applicable.

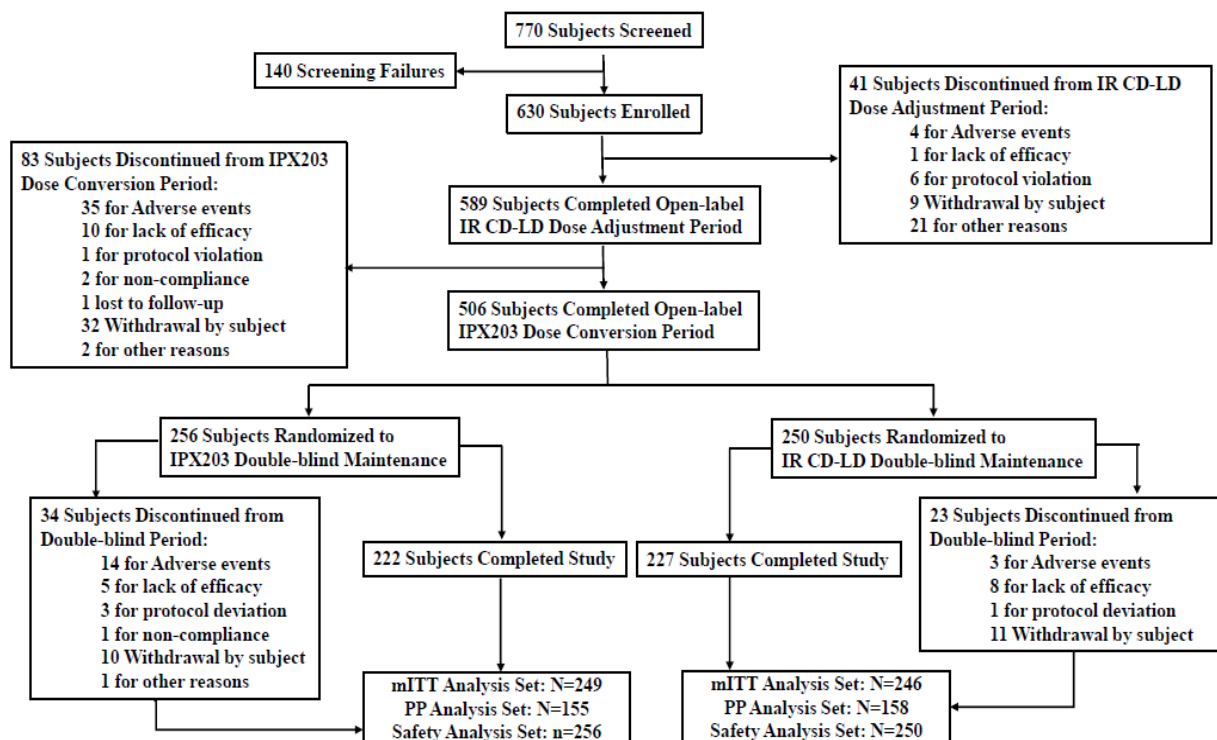
Results

Participant flow and numbers analysed

A total of 770 subjects were screened; 140 were screen failures and 630 were enrolled in the study. All 630 enrolled subjects entered the IR LD-CD dose adjustment period and there were 41 (6.5%) subject’s discontinuations. A total of 589 (93.5%) subjects entered the IPX203 conversion period and there were **83** (13.2%) discontinuations (discussed thereafter in this section). At the end of IPX203

dose conversion period, 506 subjects were randomly assigned; 256 subjects to IPX203 and 250 subjects to IR LD-CD. Of these, 449 (88.7%) subjects completed the study; 222 (86.7%) subjects in the IPX203 group and 227 (90.8%) subjects in the IR LD-CD group.

Figure 16: Participant flow



Deviations from study plan

As per study IPX206-B16-02 protocol, rescue(s) with additional or modified doses of concomitant non-LD-CD PD medications were not permitted and constituted a protocol deviation that could trigger discontinuation. While the clinical database did not include a data point specifically labelled as “discontinued due to rescue treatment” the applicant reviewed all documented reasons for discontinuation to identify subjects whose narratives indicated rescue with additional or modified doses of concomitant non-LD-CD PD medications. Based on this review, 6 subjects discontinued for reasons consistent with the administration of rescue treatment or prohibited medication use, including:

- Requests for ability to change dose (1 subject),
- Inadvertent regimen changes (1 subject),
- Use of PD medication not allowed by protocol (1 subject),
- Modification of study medication dose during maintenance phase (2 subjects),
- Combining study drug with former levodopa medication (1 subject).

These cases were categorised under protocol deviations or dosing non-compliance in the clinical study report. No additional subjects were identified as discontinued for rescue treatment beyond these cases.

Baseline data

The mean (SD) age of the subjects enrolled in the study was 66.5 (8.95) years with a mean (SD) body mass index (BMI) of 27.3 (4.9) kg/m².

Table 23: Summary of demographic characteristics (Mean $\pm$ SD)

Characteristic	Study IPX203-B16-02
Statistic	N=630
Age (years)	66.5 $\pm$ 8.95
Male	396 (62.9)
Female	234 (37.1)
American Indian or Alaska Native	3 (0.5)
Asian	10 (1.6)
Black or African American	6 (1.0)
White	606 (96.2)
Mixed	0
Other	0
Unknown or not reported	5 (0.8)
Height (cm)	169.6 $\pm$ 10.27
Weight (kg)	78.87 $\pm$ 17.646
Body mass index (kg/m ²)	27.285 $\pm$ 4.9235

Table 30 cont.

Characteristic	Study IPX203-B16-02
Statistic	N=630
Screening MDS-UPDRS Part I Total Score, "On" State	10.0 $\pm$ 5.34
Screening MDS-UPDRS Part II Total Score, "On" State	12.8 $\pm$ 7.39
Screening MDS-UPDRS Part III Total Score, "On" State	24.7 $\pm$ 15.66
Screening MDS-UPDRS Part IV Total Score, "On" State	7.2 $\pm$ 2.82
Screening MDS-UPDRS Part I Total Score, "Off" State	10.8 $\pm$ 5.55
Screening MDS-UPDRS Part II Total Score, "Off" State	15.1 $\pm$ 7.67
Screening MDS-UPDRS Part III Total Score, "Off" State	45.2 $\pm$ 14.33
Screening MDS-UPDRS Part IV Total Score, "Off" State	7.3 $\pm$ 2.73
Hoehn and Yahr Stage, "On" State, n (%)	

Characteristic	Study IPX203-B16-02
Statistic	N=630
0	0
1	60 (9.5)
2	432 (68.6)
3	122 (19.4)
4	16 (2.5)
5	0
Screening MoCA Score	27.1 ± 1.81
Age of onset of PD (years)	58.0 ± 9.42

Withdrawals

Out of the 660 subjects enrolled, **589** (93.5%) entered the IPX203 **conversion period** and **83** (13.2%) discontinued the study.

At the end of the IPX203 dose conversion period, **506** subjects were randomly assigned to IPX203 or IR LD-CD and **57** (11.3%) subjects discontinued early from the **double-blind (DB) maintenance period**. Out of these **57** subjects who discontinued early from the DB maintenance period **34** (13.3%) were from the IPX203 group and **23** (9.2%) from the IR LD-CD group.

The primary reasons of discontinuation ($\geq 5\%$ of subjects who discontinued) in the IPX203 group were AEs (**14** [**41.2%**] subjects), withdrawal by subject (**10** [29.4%]), lack of efficacy (**5** [14.7%]), and protocol deviations (**3** [8.8%]). The primary reasons of discontinuations ($\geq 5\%$ of subjects who discontinued) in the IR LD-CD group were withdrawal by subject (**11** [47.8%]), lack of efficacy (**8** [34.8%]), and AEs (**3** [**13.0%**]). The difference in the incidence of discontinuations in the DB maintenance period due to AEs was of concern (**14** AEs [**41.2%**] in the in the IPX203 group versus **3** AEs [**13%**] in the IR LD-CD).

The applicant provided information on the reason(s) for subjects' stepping out of the study, especially during the forced conversion period. It is understood that the design put particular stress on this period, and **32** out of the **83** subjects who discontinued while in the IPX203 **conversion period** had their reason described. The majority reported that the treatment had failed to meet their expectations in terms of efficacy or symptom control. In approximately **15** cases, participants described persistent or worsening symptoms, dissatisfaction with the study drug, or a preference to return to their previous medication (most often Sinemet). These individuals often reported issues such as troublesome dyskinesias, significant "OFF" periods, or unpredictable ON/OFF times, all of which contributed to their decision to discontinue.

Adverse events or side effects were also reported, with **6** subjects citing problems such as elevated blood pressure, nausea, anxiety, or other reactions that made continuation undesirable. For some, the challenge was not just the side effects themselves, but the inability to find a satisfactory or effective dose. In **4** cases, difficulty with dose optimisation was explicitly mentioned, sometimes in combination with unpredictable symptom control. Personal and logistical reasons were reported as well, accounting for at least **5** withdrawals. These included family or social stressors, a general unwillingness to continue, or personal circumstances unrelated to the drug's efficacy or safety.

Overall, the impact of the **83** subjects who discontinued during the dose-conversion period of study IPX203-B16-02 on the overall efficacy and safety should be interpreted in the context that IPX203 is a new MR formulation designed to replace IR LD-CD in patients with PD with motor fluctuations. Conversion to IPX203 involved dose titration, including transient lack of efficacy or dopaminergic AEs, which could lead to discontinuation. The initial suggested IPX203 doses in the protocol were based on average bioavailability relative to IR LD-CD. However, most subjects required individualised up-titration or down-titration to achieve an optimal balance of efficacy and tolerability. During the 4-week IPX203 dose-conversion period, these **83** subjects (14.1%) discontinued primarily due to AEs and lack of efficacy. These discontinuations largely reflected the process of establishing a clinically effective and tolerable IPX203 regimen rather than inherent lack of efficacy of IPX203.

These results are in line with Numient/Rytary IPX066-B09-02 study of Robert *et al* (2013), evaluating safety and efficacy of IPX066 in advanced PD patients, where the largest proportion of dropouts occurred during the 6-week IPX066 dose-conversion period. Specifically, **57** subjects (12.7% of the 450 who entered the period) discontinued early and the remaining **393** were randomised into the maintenance period. AEs were the most common reason for discontinuation during dose conversion (23 subjects). Lack of efficacy was the second most common reason for discontinuation during dose conversion (13 subjects, 2.9%), and a total of 12 subjects (2.7%) withdrew consent during dose conversion.

In study IPX203-B16-02, during the IPX203 conversion period, 229 (38.9%) subjects experienced at least one TEAE. The most frequently reported TEAEs ($\geq 2\%$) in subjects who received IPX203 were dyskinesia (40 [6.8%] subjects), nausea (29 [4.9%] subjects), dry mouth (25 [4.2%] subjects), dizziness (17 [2.9%] subjects), constipation (12 [2.0%] subjects), and vomiting, fall and insomnia (each 13 [2.2%] subjects). These patterns are consistent with the pharmacologic transition from IR LD-CD to an MR LD-CD formulation.

The impact of these pre-randomisation discontinuations on the overall efficacy and safety conclusions is considered limited because both primary and key secondary efficacy analyses were conducted based on the intention-to-treat principle, i.e., on the randomised population (modified ITT set, N=495), which excluded subjects who discontinued before randomisation.

In summary, the observed discontinuations during the IPX203 conversion period reflected the inherent complexity of transitioning PD patients from a well-established IR regimen to a novel MR formulation under blinded conditions. These discontinuations did not undermine robustness of efficacy and safety conclusions drawn from the randomised DB phase, which demonstrated benefit of IPX203 over IR LD-CD.

Outcomes and estimation

Initially all patients were optimised in their IR LD-CD treatment regimen (Sinemet), followed by the conversion of all patients to IPX203, which led to an increase in "ON" time compared to the end of IR optimisation (+1.46 h in mean "Good ON" time after conversion to IPX203) and reduction in "OFF" time (-1.46 h in mean "Off" time after conversion to IPX203). Subsequently patients were randomised 1:1 to either continue IPX203 or to be treated with the optimised IR dose. The primary efficacy endpoint of the study was the mean change from baseline (randomisation visit) in "Good ON" time in hours per day, averaged over the PD Diary days, at the end of the double-blind treatment period (Visit 7 or early termination [ET]). "Good ON" time was derived from the 3-day PD diaries and was defined as the sum of "ON time without dyskinesia" and "ON time with non-troublesome dyskinesia". Compared to patients treated with IR LD-CD, patients in the IPX203 arm showed maintenance of the previously achieved increase in "On" time (11.73 h/V4 to +11.35 h/V7), whereas patients randomised

to IR LD-CD declined towards their IR optimised “Good On” time (11.73 h/v4 to 10.77 h/V7).

In the **mITT analysis set**, subjects receiving IPX203 experienced a lesser decrease in the mean “Good ON” time from baseline to the end of double-blind therapy (Visit 7/ET) (LS mean: -0.50 hours) compared with those receiving IR LD-CD (LS mean: -1.03 hours). A statistically significant result in “Good ON” time was noted with IPX203 treatment compared with IR LD-CD treatment (**p=0.0194**), as outlined e.g., in the table below. A similar trend in “Good ON” time results was observed in the **PP Analysis Set**. However, it failed to reach statistical significance (**p=0.1718**), most likely due to the small size of this analysis set (n=155 for IPX203 group and n=158 for IR LD-CD group).

Figure 17: Change from baseline in “Good ON” Time in hours per day (mITT)

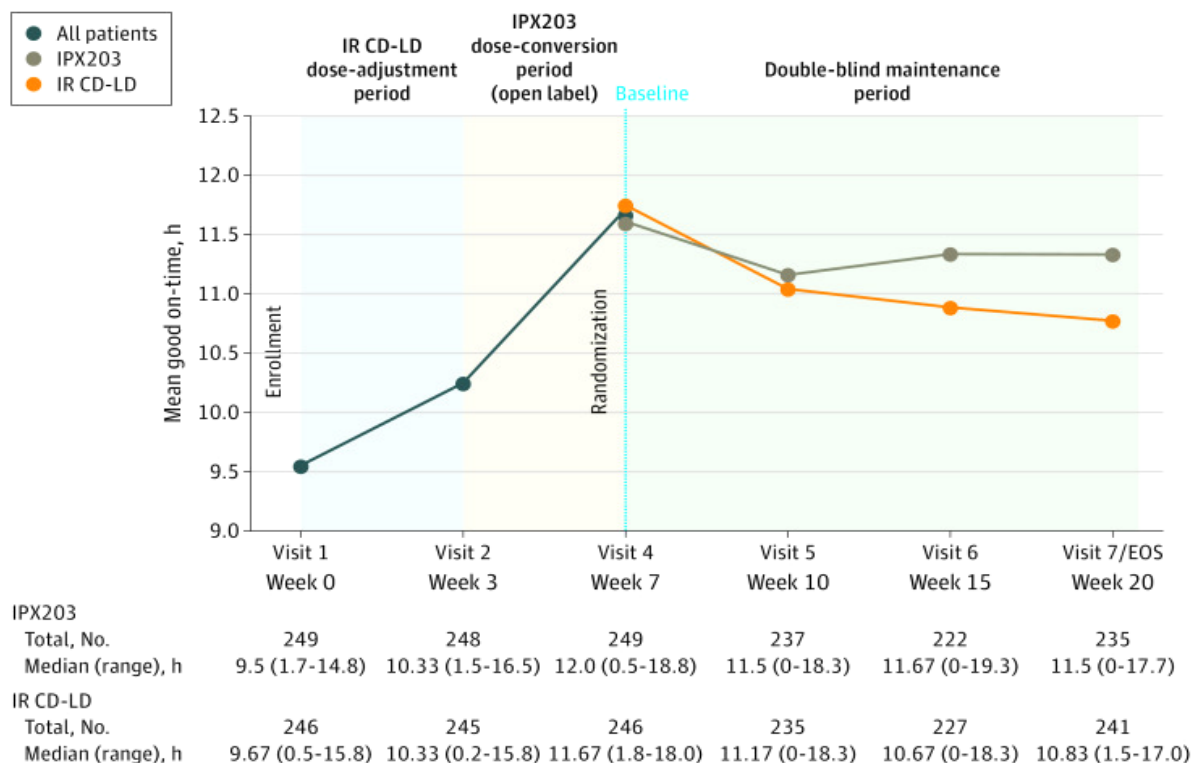


Table 24: Summary of efficacy endpoint results (Study IPX203-B16-02)

Endpoints	IPX203 (N=249)	IR LD- CD (N=246)	Difference (IPX203 vs. IR LD-CD)	p-value
Primary Endpoint				
Change from Baseline to Visit 7/ET in “Good On” Time (h), LS Mean	-0.50	-1.03	0.53	0.0194^a
Key Secondary Endpoints				
Change from Baseline to Visit 7/ET in “Off” Time (h), 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	0.8	0.8	0.0	0.9587^a

Endpoints	IPX203 (N=249)	IR LD- CD (N=246)	Difference (IPX203 vs. IR LD-CD)	p-value
MDS-UPDRS Part III Score, LS Mean ^c				
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
Subjects who were "On" Upon Awakening at Visit 7/ET				
0 days	46.9%	55.5%		0.0046^d
1 day	17.1%	20.8%		
2 days	11.4%	7.6%		
3 days	24.6%	16.1%		
Subjects who were "Good On" Upon Awakening at Visit 7/ET				
0 days	46.9%	55.5%		0.0060^d
1 day	18.4%	21.6%		
2 days	11.4%	7.2%		
3 days	23.2%	15.7%		
Abbreviations: CMH = Cochran-Mantel-Haenszel; ET: early termination; IR LD-CD = immediate-release levodopa-carbidopa; LS = least square; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale; PD = Parkinson's disease; PGI-C = Patient Global Impression of Change; PP = per-protocol ^{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 subjects between the treatment groups. ^{c.} IPX203; N=256 and IR LD-CD; N=250 ^{d.} p-values from the "row mean scores differ" CMH test stratified by pooled center comparing the proportions of subjects between the treatment groups at Visit 7/ET. ^{e.} Double-blind baseline was defined as data obtained from PD Diary collected over 3 days prior to Visit 4/Randomisation.				

Statistically significant results were also noted for the key secondary endpoint of change from baseline in "OFF" time (**p=0.0252**). In the mITT analysis set, subjects receiving IPX203 experienced almost maintenance of their previously achieved decrease in mean "OFF" time from baseline to Visit 7/ET (LS mean: 0.38) compared with the subjects receiving IR LD-CD, who experienced a meaningful increase in "Off" time (LS mean: 0.86). A similar trend in "OFF" time results was observed in the PP Analysis Set; however, it failed to reach statistical significance (**p=0.0670**).

With regard to the key secondary endpoint of Patient Global Impression of Change (PGI-C) scores in the ITT Analysis Set, 56.9% of subjects in the IPX203 group reported improvement in PGI-C scores (defined as "minimally improved", "much improved", or "very much improved") compared with 46.3% of subjects in the IR LD-CD group, at Visit 7/ET. A statistically significant proportion of subjects (**p=0.0015**) reported "much improved" or "very much improved" response with IPX203 treatment (29.7%) compared with IR LD-CD treatment (18.8%). Similar statistically significant results were observed in the PP Analysis Set (**p=0.0161**).

In terms of the key secondary endpoint of MDS-UPDRS-based endpoints in the ITT Analysis Set, subject scores in both groups increased to a similar degree from baseline to Visit 7/ET (LS mean 0.8 increase in Part III score in both groups; LS mean 1.7 and 1.8 increase, in sum of Parts II and III

score, in the IPX203 and IR LD-CD groups, respectively) with no statistically significant difference ($p=0.9587$ for Part III score and $p=0.9668$ for sum of Parts II and III score). A similar trend was observed in the PP Analysis Set with no statistically significant difference between the IPX203 and IR LD-CD groups in the MDS-UPDRS Part III results ($p=0.7265$) and sum of MDS-UPDRS Part II and III results ($p=0.6785$).

The primary endpoint and five key/important secondary endpoints were tested in a sequential hierarchical order (the "ON" upon awakening endpoint was considered an important secondary endpoint and was included in the sequential hierarchical testing of endpoints). As detailed above, since the endpoint of change from baseline to Visit 7/ET in the MDS-UPDRS Part III score failed to show statistical significance, no claims of superiority can be made on any endpoint further in the hierarchical testing list.

A statistically significant difference was noted in the percentage of subjects who were in the "ON" state upon awakening for at least 1 of the 3 recorded PD Diary days; IPX203 (53.1%) *versus* IR LD-CD treatment (44.5%) at Visit 7/ET ($p=0.0046$). Similar results were noted in the proportion of subjects who were in "Good ON" state upon awakening at Visit 7/ET (0 days, $p=0.0060$).

With regard to additional endpoints in the mITT Analysis Set, subjects on IPX203 showed greater improvement (lesser decrease) in average duration of continuous "Good ON" interval from Visit 4/baseline to Visit 7/ EOS when compared with those on IR LD-CD (mean change from Visit 4/baseline to Visit 7/EOS for continuous "Good ON" interval [hours] for IPX203: -0.07 and IR LD-CD: -0.98, $p=0.0002$).

Subjects on IPX203 showed a greater improvement (lesser increase) in the average number of motor fluctuations per day from baseline to Visit 7/EOS when compared with those on IR LD-CD (mean change from Visit 4/baseline to Visit 7/EOS; IPX203: 0.17 and IR LD-CD: 1.47). This difference was statistically significant favouring IPX203 ($p<0.0001$, difference in LS means: -1.35). Mean number of motor fluctuations per day was 3.75 for IPX203 and 5.14 for IR LD-CD at EOS.

This was a randomised withdrawal study, to assess whether the maintenance of IPX203 was better than the IR LD in keeping the previously optimised oral treatment. In fact, both arms worsened at the double-blind phase (DB). This is the expected placebo effect loss when both the patient and the investigator do not know which treatment the patient is having.

There was some attrition during the DB phase of the study, and several patients were lost for some visits including the EOS visit (up to 27 of 249 in IPX203 and 19 of 246 in IR LD). In the course of the procedure, as requested, the applicant reviewed the cases where patients missed any visit or the primary endpoint assessment. Overall, missed assessments were infrequent, evenly distributed across treatment arms, and primarily attributable to external circumstances rather than treatment-related factors. No missed assessments occurred at Visit 1 (Week 0) or Visit 4 (Week 7), which represented critical time points for study entry and randomisation during the DB, respectively. The missed assessments were observed mainly at Visit 6 (Week 15) which did not represent a primary timepoint for the analysis. At Week 15, 27 patients (10.8%) in the IPX203 group and 19 patients (7.7%) in the IR-LD-CD group missed the primary endpoint assessment. At Week 20, 14 patients (5.6%) in the IPX203 group and 5 patients (2%) in the IR-LD-CD group missed the assessment. Earlier visits (Weeks 3 and 10) had very few missed assessments ($\leq 1\%$ at Week 3 and approximately 4.5% at Week 10), and these were balanced between treatment arms, as noted in the Table below.

Table 25: Number of Patients with Missing Primary Endpoint per Visit- mITT

Visit	Treatment	
	IPX203 N=249	IR LD-CD N=246
Visit 1 (Week 0)	0 (0%)	0 (0%)
Visit 2 (Week 3)	1 (0,4%)	1 (0,4%)
Visit 4 (Week 7)	0 (0%)	0 (0%)
Visit 5 (Week 10)	12 (4,8%)	11 (4,5%)
Visit 6 (Week 15)	27 (10,8%)	19 (7,7%)
Visit 7/EOS (Week 20)	14 (5,6%)	5 (2%)

A review of the patient-level information available for a portion of the missed assessments indicated that the majority of missed assessments were due to logistical and external factors, most notably restrictions related to the COVID-19 pandemic. Several visits were conducted remotely during periods of site limitations, which prevented collection of PD diaries required for the primary endpoint. Other reasons included early termination due to lack of efficacy or AEs, patient non-compliance or refusal, and isolated cases such as diaries lost in transit or incomplete due to acute medical events. These reasons were unrelated to the treatment assignment and occurred sporadically across both arms.

Given the low frequency of missed assessments, their occurrence at non-critical time points, and the balanced distribution across treatment groups, in the applicant's view, these missing data had no meaningful impact on the study conclusions. Furthermore, the primary endpoint analysis employed a modified intent-to-treat (ITT) approach with appropriate statistical handling of missing data, ensuring robustness and validity of the results.

Th CHMP, having considered the above, noted that there were no missed assessments neither at visit 1 or 4, and most of those which occurred later were at the non-critical visits 5 and 6. It was nonetheless evident that from visit 5 onwards, there was more missingness in the IPX203 arm than in the IR LD arm. The applicant did not discuss such difference. However, since the end of study (EOS) visit 7 had much less missing data and the difference was only of nine patients, corresponding to 5.6% in IPX203 and 2% in IR LD, respectively, the applicant's response was considered satisfactory.

Pre-defined and post-hoc subgroup analyses

The sensitivity analysis on the primary endpoint (as noted below), with completers only, provided support to the primary endpoint. Of note, the sensitivity analysis on per-protocol (PP) population did not reach statistical significance.

Table 26: Sensitivity analysis on the primary endpoint

Sensitivity Analysis of Primary Endpoint	IPX203 (N=249)	IR LD- CD (N=246)	Difference (IPX203 vs. IR LD-CD)	p-value
Change from Baseline to Visit 7 in "Good On" Time (h): Completers Analysis Set (N=220, 226), LS Mean ^e	-0.38	-1.00	0.62	0.0072^a
Change from Baseline to Visit 7 in "Good On" Time (h): PP Analysis Set (N=155, 158), LS Mean	-0.43	-0.80	0.38	0.1718^a

Pre-defined and post-hoc sensitivity analyses

Not applicable.

Ancillary analyses

Post hoc analyses

Patients entering Phase 3 had in average 2.34 hours of "ON" time with dyskinesia of which 1.82 hours were categorised as non-troublesome and 0.51 hours were categorized as troublesome dyskinesia. To better understand the effect of IPX203 on patients with clinically meaningful duration of dyskinesia compared to advanced patients with non-relevant durations of dyskinesia the following post hoc analysis was performed.

Patients at study entry were stratified of having more or less than 1 h dyskinesia. In addition, a sensitivity analysis was performed, stratifying patients with more or less of 0.5 h of dyskinesia and patients with having at least 3.5 h "OFF" time combined with more than 1 h of dyskinesia. At baseline 237 patients had at least 1 h of dyskinesia (in average 4.4 h of dyskinesia, of which 1 h was with troublesome dyskinesia). A total of 267 patients had less than 1 h of dyskinesia (in average 0.5 h of dyskinesia, of which only 0.09 h was with troublesome dyskinesia). Subgroups discriminated well patients having motor fluctuations with or without dyskinesia.

Analysis of "ON" time with dyskinesia

During IR LD-CD optimisation phase, time with dyskinesia increased from 4.4 to 4.9 h per day. After conversion to IPX203, mean time with dyskinesia was reduced to 4.6 h per day. During the double-blind maintenance phase, the change of "ON" time with dyskinesia was 0.03 h in the IPX203 arm, whereas change in the IR arm was 0.24 h per day (slight increase). Figures for troublesome dyskinesia were similar, increasing from 1 h at baseline, to 1.06 h after optimisation of IR LD-CD. At the end of the conversion to IPX203 (V4), troublesome dyskinesia time was reduced to 0.87 h.

In the double-blind phase, patients in the IPX203 arm showed a further slight decrease of time with troublesome dyskinesia by 0.017 h, whereas patients randomised to IR showed an increase of 0.237 h.

Analysis of "Good ON" time

Results for the main efficacy endpoints showed that patients with or without >1 h dyskinesia per day had comparable "Good ON" time at Visit 1 (9.7 h or 9.5 h, respectively). After optimisations of IR LD-CD (Visit 2), "Good ON" time increased in both groups reaching 10.3 h per day. At the end of the double-blind treatment period (Visit 7), patients on IPX203 retained 1.0 additional hour "Good ON" time compared to Visit 2, whereas patients randomised to IR LD-CD retained 0.4 hours "Good ON" time. Overall results were nearly identical for patients with and without dyskinesia.

Major differences were observed in "Good ON" time with dyskinesia. At Visit 1, patients with dyskinesia had 4.43 h of "Good ON" time per day, whereas patients without dyskinesia had less 0.49 h per day. "Good ON" time in patients with dyskinesia increased by approximately half an hour (reaching 4.94 h) by Visit 2 (IR LD-CD optimisation) and subsequently decreased to 4.61 hours by Visit 4 (conversion to IPX203).

"Good ON" time without dyskinesia was virtually unchanged during IR LD-CD optimisation (6.24 hours at Visit 1 and 6.40 hours at Visit 2) but improved by 1.5 hours after conversion to IPX203 (7.92 hours at Visit 4). Thus, in patients with dyskinesia, conversion to from IR LD-CD to IPX203 resulted in an increase in "Good ON" time without dyskinesia but not in "Good ON" time with dyskinesia.

In patients having dyskinesia at Visit 2, more than 1 hour of "Good ON" time, time without dyskinesia was retained after the double-blind period in the IPX203 group, whereas patients re-exposed to IR LD-CD retained about 45 minutes (1.09 and 0.77 h, respectively).

Analysis of "OFF" time

During IR LD-CD optimisation period, "OFF" time was reduced by approximately 0.7 hours, reaching 4.74 h for patients with dyskinesia and 6.06 hours for patients without dyskinesia. At Visit 4, "OFF" time was further reduced to 3.65 h (1.1 h reduction) for patients with dyskinesia and 4.26 h (1.8 h reduction) for patients without dyskinesia. At the end of the double-blind period (Visit 7), patients with >1 h dyskinesia at Visit 2 retained 0.68 and 0.67 h time reduction of "OFF" time on IPX203 and IR LD-CD group, respectively. Patients without dyskinesia or ≤1 hours dyskinesia at Visit 2 showed an increase of 0.91 h in "OFF" time versus Visit 4 when re-exposed to IR LD-CD and an increase of 0.28 h when receiving IPX203.

In summary, IPX203 had equally comparable benefits in patients with motor fluctuations with more than 1 hour and with no or less than 1 hour of dyskinesia. Importantly, the gain in "Good ON" time in patients with more than 1 hour dyskinesia under IPX203 treatment was not associated with an increase in overall time with dyskinesia or time with troublesome dyskinesia. The conversion from IR LD-CD to IPX203 led also to a minor reduction in time with dyskinesia and troublesome dyskinesia.

Treatment effects were overall comparable in patients with more than 1 hour and with no or less than 1 hour of dyskinesia and always favoured IPX203 over IR LD-CD. The only exception was the amount of "OFF" time in patients with more than 1 hour dyskinesia, which was comparable for both treatments after the end of the double-blind randomisation phase. It is noteworthy that patients on IR LD-CD had a slight increase of dyskinesia and troublesome dyskinesia time compared to IPX203, indicating that the reduction in "OFF" time was resulting in more dyskinesia in the IR LD-CD group.

Results of the sensitivity analysis in patients with at least 0.5 hours of dyskinesia per day and patients with more than 3.5 hours "OFF" time and more than 1 hour dyskinesia per day supported the robustness of the findings.

Table 27: Post-Hoc Analysis of "Good ON" Time (h) (Study IPX203-B16-02)

Post-Hoc Analysis	IPX203 (N=249)	IR LD-CD (N=246)	Difference (IPX203 vs. IR LD-CD)	p-value
"Good On" Time (h) per Dose at Visit 7/ET, LS Mean	3.76	2.21	1.55	<0.0001^a

Table 28: Post-hoc Analysis of Data from Patients with or without >1 h dyskinesia (Study IPX203-B16-02)

	Total ITT population		Subpopulation >1h dyskinesia (Visit 2)			
	Total N=506		Yes N=237		No N=267	
'Good On' Time Per Day (Hours) - Mean (SD)						
Visit 1	9.559	(2.220)	9.666	(2.305)	9.466	(2.140)
Visit 2	10.270	(2.418)	10.280	(2.571)	10.261	(2.279)

	Total ITT population		Subpopulation >1h dyskinesia (Visit 2)			
	Total N=506		Yes N=237		No N=267	
Visit 4	11.731	(2.879)	11.660	(2.892)	11.796	(2.875)
Visit 4 - Change from Visit 2	1.462	(2.727)	1.379	(2.606)	1.535	(2.833)
Visit 7- IPX203 group	11.349	(3.065)	11.270	(3.160)	11.411	(2.994)
Visit 7- IPX203 group - Change from Visit 2	1.018	(2.855)	1.033	(2.593)	1.003	(3.095)
Visit 7- IPX203 group - Change from Visit 4	-0.385	(2.706)	-0.247	(2.813)	-0.510	(2.616)
Visit 7- IR LD-CD group	10.773	(2.775)	10.796	(2.814)	10.825	(2.635)
Visit 7- IR LD-CD group - Change from Visit 2	0.506	(2.832)	0.440	(2.883)	0.565	(2.796)
Visit 7- IR LD-CD group - Change from Visit 4	-0.968	(3.081)	-0.990	(2.941)	-0.897	(3.170)
'On without dyskinesia' Time Per Day (Hours) - Mean (SD)						
Visit 1	7.732	(2.910)	6.240	(2.855)	9.060	(2.256)
Visit 2	8.404	(3.277)	6.405	(3.080)	10.178	(2.274)
Visit 4	9.628	(3.866)	7.917	(3.921)	11.149	(3.132)
Visit 4 - Change from Visit 2	1.226	(3.199)	1.512	(3.300)	0.971	(3.090)
Visit 7- IPX203 group	9.158	(4.079)	7.454	(4.174)	10.796	(3.262)
Visit 7- IPX203 group - Change from Visit 2	0.778	(3.641)	1.089	(3.861)	0.482	(3.408)
Visit 7- IPX203 group - Change from Visit 4	-0.431	(3.071)	-0.297	(3.437)	-0.538	(2.692)
Visit 7- IR LD-CD group	8.734	(3.565)	7.233	(3.584)	10.126	(2.898)
Visit 7- IR LD-CD group - Change from Visit 2	0.331	(3.087)	0.772	(3.010)	-0.062	(3.113)
Visit 7- IR LD-CD group - Change from Visit 4	-0.972	(3.352)	-0.995	(3.432)	-0.901	(3.253)
'On with dyskinesia' Time Per Day (Hours) - Mean (SD)						
Visit 1	2.342	(2.893)	4.428	(2.792)	0.491	(1.272)
Visit 2	2.367	(3.079)	4.936	(2.763)	0.087	(0.238)
Visit 4	2.538	(3.355)	4.611	(3.521)	0.699	(1.761)
Visit 4 - Change from Visit 2	0.172	(2.551)	-0.325	(3.172)	0.612	(1.721)
Visit 7- IPX203 group	2.790	(3.671)	4.877	(3.924)	0.781	(1.882)
Visit 7- IPX203 group - Change from Visit 2	0.226	(3.206)	-0.255	(4.143)	0.683	(1.841)
Visit 7- IPX203 group - Change from Visit 4	0.095	(2.527)	0.033	(3.201)	0.142	(1.673)
Visit 7- IR LD-CD group	2.499	(3.297)	4.505	(3.489)	0.734	(1.758)
Visit 7- IR LD-CD group - Change from Visit 2	0.219	(2.568)	-0.275	(3.194)	0.658	(1.740)

	Total ITT population		Subpopulation >1h dyskinesia (Visit 2)			
	Total N=506		Yes N=237		No N=267	
Visit 7- IR LD-CD group - Change from Visit 4	0.108	(2.592)	0.243	(3.231)	-0.010	(1.869)
'On with troublesome dyskinesia' Time Per Day (Hours) - Mean (SD)						
Visit 1	0.515	(1.187)	1.003	(1.553)	0.086	(0.372)
Visit 2	0.501	(1.220)	1.062	(1.606)	0.004	(0.038)
Visit 4	0.435	(1.091)	0.869	(1.444)	0.052	(0.305)
Visit 4 - Change from Visit 2	-0.065	(1.058)	-0.192	(1.501)	0.049	(0.303)
Visit 7- IPX203 group	0.599	(1.413)	1.061	(1.748)	0.165	(0.793)
Visit 7- IPX203 group - Change from Visit 2	-0.015	(1.483)	-0.200	(1.950)	0.161	(0.794)
Visit 7- IPX203 group - Change from Visit 4	0.049	(1.200)	-0.017	(1.566)	0.114	(0.701)
Visit 7- IR LD-CD group	0.460	(1.186)	0.942	(1.590)	0.035	(0.193)
Visit 7- IR LD-CD group - Change from Visit 2	0.043	(1.094)	0.057	(1.585)	0.031	(0.189)
Visit 7- IR LD-CD group - Change from Visit 4	0.104	(0.861)	0.237	(1.175)	-0.014	(0.395)
'On with nontroublesome dyskinesia' Time Per Day (Hours) - Mean (SD)						
Visit 1	1.827	(2.286)	3.425	(2.257)	0.405	(1.028)
Visit 2	1.866	(2.496)	3.875	(2.360)	0.083	(0.234)
Visit 4	2.102	(2.852)	3.742	(3.051)	0.647	(1.622)
Visit 4 - Change from Visit 2	0.236	(2.250)	-0.133	(2.778)	0.564	(1.581)
Visit 7- IPX203 group	2.191	(2.935)	3.816	(3.153)	0.615	(1.533)
Visit 7- IPX203 group - Change from Visit 2	0.240	(2.625)	-0.056	(3.419)	0.522	(1.492)
Visit 7- IPX203 group - Change from Visit 4	0.046	(2.375)	0.050	(2.956)	0.028	(1.664)
Visit 7- IR LD-CD group	2.039	(2.683)	3.563	(2.776)	0.699	(1.714)
Visit 7- IR LD-CD group - Change from Visit 2	0.175	(2.210)	-0.332	(2.587)	0.627	(1.698)
Visit 7- IR LD-CD group - Change from Visit 4	0.004	(2.330)	0.005	(2.892)	0.004	(1.705)
'Off' Time Per Day (Hours) - Mean (SD)						
Visit 1	6.102	(2.169)	5.452	(1.933)	6.686	(2.211)
Visit 2	5.440	(2.173)	4.739	(1.878)	6.061	(2.231)
Visit 4	3.976	(2.501)	3.648	(2.252)	4.260	(2.671)
Visit 4 - Change from Visit 2	-1.468	(2.606)	-1.091	(2.271)	-1.802	(2.833)
Visit 7- IPX203 group	4.177	(2.833)	3.901	(2.783)	4.443	(2.878)

	Total ITT population		Subpopulation >1h dyskinesia (Visit 2)			
	Total N=506		Yes N=237		No N=267	
Visit 7- IPX203 group - Change from Visit 2	-1.154	(2.803)	-0.678	(2.616)	-1.606	(2.910)
Visit 7- IPX203 group - Change from Visit 4	0.292	(2.235)	0.295	(2.224)	0.278	(2.260)
Visit 7- IR LD-CD group	4.748	(2.884)	4.178	(2.759)	5.183	(2.813)
Visit 7- IR LD-CD group - Change from Visit 2	-0.730	(2.564)	-0.673	(2.484)	-0.780	(2.643)
Visit 7- IR LD-CD group - Change from Visit 4	0.758	(2.901)	0.538	(2.518)	0.911	(3.176)
Bad Time Per Day (Hours) - Mean (SD)						
Visit 1	6.617	(2.292)	6.455	(2.405)	6.772	(2.186)
Visit 2	5.941	(2.293)	5.801	(2.360)	6.065	(2.229)
Visit 4	4.411	(2.689)	4.517	(2.713)	4.312	(2.669)
Visit 4 - Change from Visit 2	-1.532	(2.698)	-1.284	(2.513)	-1.753	(2.839)
Visit 7- IPX203 group	4.776	(3.084)	4.963	(3.250)	4.608	(2.932)
Visit 7- IPX203 group - Change from Visit 2	-1.169	(2.780)	-0.878	(2.557)	-1.445	(2.960)
Visit 7- IPX203 group - Change from Visit 4	0.340	(2.609)	0.279	(2.824)	0.392	(2.408)
Visit 7- IR LD-CD group	5.209	(2.926)	5.119	(2.953)	5.219	(2.817)
Visit 7- IR LD-CD group - Change from Visit 2	-0.686	(2.711)	-0.617	(2.797)	-0.748	(2.641)
Visit 7- IR LD-CD group - Change from Visit 4	0.862	(2.933)	0.775	(2.626)	0.896	(3.165)

Abbreviations: ITT = intention-to-treat; SD = standard deviation.

Note: Observed data only, no imputation.

Note: Results were analysed for Visit 1 (study entry), Visit 2 (end of IR LD-CD optimization period), Visit 4 (end of IPX203 conversion period and randomization visit), Visit 7 (end of double-blind period). Patients were stratified by having dyskinesia for >1 h versus ≤1h per day at Visit 2.

The applicant discussed several post-hoc analyses to support robustness and relevance of the primary endpoint but did not discuss the variation regarding overall time with dyskinesia and variation in time with troublesome dyskinesias as a group. Furthermore, since IPX203 may prevent or delay the use of advanced medical therapies for PD, such as duodopa or foslevodopa, to increase robustness of the study data, the applicant was invited to compare study IPX203-B16-02 results with those for these advanced medical therapies for PD.

In the response, the applicant pointed out that, unlike the pivotal studies for LD-CD intestinal gel (LCIG, Duodopa) and foslevodopa/foscarbidopa, IPX203-B16-02 (RISE-PD) employed a withdrawal design, where randomisation took place only after the whole patient population was converted to IPX203. Therefore, a direct comparison of results was not straightforward. To make it meaningful, the applicant focused on the improvements observed during the IPX203 dose conversion period, which most closely corresponds to the double-blind treatment phase of the LCIG and foslevodopa/foscarbidopa Phase 3 trials. This allowed to compare the incremental benefit of the therapy on top of the optimised IR LD-CD. This approach was justified because the study populations

were advanced and comparable across all studies, and IPX203 efficacy was maintained during the DB phase following conversion. It was also important to note that the DB phase for device-aided therapies (DATs) may not have been fully blinded, as dose optimisation and adjustments occurred after blinding. These post-blinding modifications could have revealed to both patients and investigators whether the treatment was active drug or placebo.

During the IPX203 conversion period, patients already optimised on IR LD-CD experienced an improvement in "Good ON time" of 1.45 h and in "OFF time" of 1.46 h. In comparison, the foslevodopa/foscarbidopa pivotal trial of [Soileau *et al.*, \(2022\)](#) reported an improvement in "Good ON" time of 1.75 h and a reduction in "OFF time" of 1.79 h vs IR LD-CD, while the LCIG pivotal trial of [Olanow *et al.*, \(2014\)](#) demonstrated an increase in "Good ON" time of 1.86 h and a reduction in "OFF time" of 1.91 h vs IR LD-CD.

In this context it would also be flagged that, regarding safety, IPX203 demonstrated a TEAE rate of 42.2%, serious TEAE rate of 3.1%, and a total discontinuation rate of 27.4% (14.1% during dose conversion and 13.3% during the DB period). Foslevodopa/foscarbidopa reported a TEAE rate of 85%, serious TEAE rate of 8%, and discontinuation rate of 35.1%, while LCIG reported a TEAE rate of 95%, serious TEAE rate of 14%, and discontinuation rate of 8.8%.

In summary, the applicant's analysis compared accordingly the gains in "ON time" and reduction in "OFF time" at the end of the period of forced conversion to IPX203 in the randomised withdrawal study of IPX203, to the results obtained with duodopa or foslevodopa, all *versus* optimised IR LD-CD. However, since duodopa and foslevodopa studies were conducted longitudinally on a classical prospective parallel study, the shorter forced IPX203 period suffered less placebo effect waning. Furthermore, and in spite of the longer duration of the comparative studies as compared to the forced adjustment to IPX203, the assessors noted that the numerical improvement was higher with the non-oral alternatives than with IPX203. Nevertheless, it could be admitted that the improvement observed was within the same magnitude of effect, although probably less efficacious.

Concomitant use of dopamine agonists (DA)

In study IPX203-B16-02 concomitant use of dopamine agonists (DA) was allowed. Therefore, available data supporting the use of Hopledo with DA came primarily from the inclusion of DA-treated patients in this trial population.

Clinical and demographic differences between DA-treated and non-DA treated populations are detailed in the Tables below.

DA-treated patients tended to have an earlier age of diagnosis (mean 56.22 vs. 59.99 years), a longer duration of PD (mean 8.84 vs. 7.69 years), and were more frequently from Europe, while non-DA patients were mostly from North America. When comparing the overall IPX203-B16-02 population to the DA-treated subgroup, the treatment effect of IPX203 on "Good On" time was noted as consistent.

In the overall population who entered the conversion period (N=589), an improvement in "Good On" time of 1.44 h (95% CI: 1.19 to 1.68; $p < 0.0001$), compared to Visit 2, was observed. Among patients receiving concomitant DA (N=296), the improvement was 1.30 h (95% CI: 0.94 to 1.65; $p < 0.0001$), comparable to the overall population. In the double-blind period (modified ITT), the change in "Good On" Time were -0.50 h (95% CI: -0.86 to -0.14) and -1.03 h (95% CI: -1.39 to -0.67) for IPX203 and IR LD-CD, respectively, with a least squares mean difference of 0.53 h (95% CI: 0.09 to 0.97; $p = 0.0194$), favouring IPX203. Similarly, among patients using DA, the difference was 0.56 h (95% CI: -0.06 to 1.17; **$p = 0.0766$**). Although the p-value in the DA subgroup did not reach conventional statistical significance, the magnitude of benefit was comparable to the overall population, and the two CIs overlap.

Table 29: Baseline characteristics by use of concomitant dopamine agonists - ITT analysis set

	Statistics	Use of dopamine agonists	
		Yes (N=264)	No (N=242)
Geographic Region	Europe	173 (65.5%)	77 (31.8%)
	North America	91 (34.5%)	165 (68.2%)
	N	264	242
	Mean	56.220	59.992
	SD	8.676	9.694
	Median	56.000	60.000
Sex	Female	90 (34.1%)	80 (33.1%)
	Male	174 (65.9%)	162 (66.9%)
Race	American Indian Or Alaska native	1 (0.4%)	2 (0.8%)
	Asian	3 (1.1%)	5 (2.1%)
	Black or African American	2 (0.8%)	3 (1.2%)
	Unknown	0	4 (1.7%)
	White	258 (97.7%)	228 (94.2%)
Baseline BMI (Kg/m2)	N	263	242
	Mean	27.435	27.270
	SD	4.898	4.863
	Median	26.770	26.997
Good On Time at Study Entry (avg. h/day)	N	264	242
	Mean	9.805	9.291
	SD	2.206	2.207
	Median	10.000	9.292
Off Time at Study Entry (avg. h/day)	N	264	242
	Mean	6.045	6.165
	SD	2.090	2.254
	Median	5.833	6.000
Duration of PD (Years)	N	264	242
	Mean	8.837	7.690
	SD	4.744	4.819
	Median	8.000	7.000
MoCA Score at Screening (On State)	N	264	242
	Mean	27.375	27.021
	SD	1.731	1.837

	Statistics	Use of dopamine agonists	
		Yes (N=264)	No (N=242)
	Median	28.000	27.000
Screening Hoehn-Yahr Stage	1	29 (11.0%)	19 (7.9%)
	2	172 (65.2%)	174 (71.9%)
	3	56 (21.2%)	43 (17.8%)
	4	7 (2.7%)	6 (2.5%)

Table 30: Analysis of Change from Visit 2 to Visit 4 in "Good ON" Time (h)

Change from Visit 2 to Visit 4 (Conversion Period)			IPX203 (N=589)
LS Mean			1.44
Standard Error			0.123
95% Confidence Interval			1.19; 1.68
p-value [a]			<0.0001
Change from Baseline to Visit 7/ET (mITT Analysis Set)	IPX203 (N=249)	IR LD-CD (N=246)	Difference (IPX203 - IR LD-CD)
LS Mean	-0.50	-1.03	0.53
Standard Error	0.183	0.183	0.226
95% Confidence Interval	-0.86; -0.14	-1.39; -0.67	0.09; 0.97
p-value [b]			0.0194

[a] p-value for the hypothesis of LS Means equal to zero.

LS means, standard errors, confidence intervals and p-value from a mixed model for repeated measures with change from baseline in "Good on" time as outcome, baseline "Good on" time as a covariate, visit as fixed effects, and pooled center as random effect. The degree-of-freedom of the denominator is estimated using the Kenward-Roger method. Unstructured covariance structure is assumed.

[b] p-value for the hypothesis of equal LS Means between treatments.

LS means, standard errors, confidence intervals and p-value from a mixed model for repeated measures with change from baseline in "Good on" time as outcome, baseline "Good on" time as a covariate, treatment and visit as fixed effects, pooled center as random effect and a treatment-by-visit interaction. The degree-of-freedom of the denominator is estimated using the Kenward-Roger method. Unstructured covariance structure is assumed.

Table 31: Analysis of Change from Baseline to Visit 7/ET in "Good ON" Time (h) in patients using concomitant dopamine agonists

Change from Visit 2 to Visit 4 (Conversion Period)			IPX203 (N=296)
LS Mean			1.30
Standard Error			0.175
95% Confidence Interval			0.94; 1.65
p-value [a]			<.0001
Change from Baseline to Visit 7/ET (mITT Analysis)	IPX203 (N=142)	IR LD-CD (N=116)	Difference (IPX203 - IR LD-CD)

LS Mean	-0.45	-1.01	0.56
Standard Error	0.256	0.277	0.313
95% Confidence Interval	-0.96; 0.05	-1.56; -0.46	-0.06; 1.17
p-value [b]			0.0766

[a] p-value for the hypothesis of LS Means equal to zero.

LS means, standard errors, confidence intervals and p-value from a mixed model for repeated measures with change from baseline in "Good on" time as outcome, baseline "Good on" time as a covariate, visit as fixed effects, and pooled center as random effect. The degree-of-freedom of the denominator is estimated using the Kenward-Roger method. Unstructured covariance structure is assumed.

[b] p-value for the hypothesis of equal LS Means between treatments.

LS means, standard errors, confidence intervals and p-value from a mixed model for repeated measures with change from baseline in "Good on" time as outcome, baseline "Good on" time as a covariate, treatment and visit as fixed effects, pooled center as random effect and a treatment-by-visit interaction. The degree-of-freedom of the denominator is estimated using the Kenward-Roger method. Unstructured covariance structure is assumed.

These findings indicated that concomitant use of DA does not attenuate the efficacy of IPX203. On the contrary, data suggested that patients receiving DA therapy experienced similar improvements in "Good ON" time compared to those not on DA therapy. In the course of the procedure the applicant provided further reassurance, comparing baseline characteristics of concomitantly treated LD+DA agonists vs. LD alone. Both populations were similar, although DA treated population came mostly from EU and were younger than those on LD alone, which were mostly based in the US and 3 years older. The use of Hopledo yielded similar results. The applicant did not provide the comparison of LD alone vs. LD+DA, but the comparison between the overall population (LD alone + LD and DA agonists). Notwithstanding, the results of the DA treated population had similar difference between use of IPX203 and IRLD: -0.56h in the DA+LD treated vs. -0.50h in those LD alone.

Gender differences on "Good ON time"

A statistically significant treatment difference in change from baseline in "Good ON" time was demonstrated in males in favour of IPX203 vs IR LD-CD ($p=0.0208$, difference in LS means: 0.67 h [95% CI: 0.10, 1.24]), whereas in females the numerical difference favoured IPX203 but did not reach statistical significance ($p=0.3934$; difference in LS means: 0.33 h [95% CI: -0.43, 1.08]).

These observed difference between males and females in study IPX203-B16-02 should be perceived as resulting from the exploratory nature of subgroup analyses, differences in LD exposure, and underlying sex-related heterogeneity in Parkinson's disease biology and clinical management. There was a difference in average daily LD dose between males and females throughout the study: females received a lower mean daily dose of LD compared to males in both treatment arms during the DB period.

Literature data indicated several factors that may be responsible for sex differences in PD. Cattaneo, C., Pagonabarraga, J. (2025) stated that sex differences in PD are multifactorial, involving neurobiological, hormonal, PK and clinical factors. Women tend to have lower body weight, higher LD bioavailability, and a higher risk of LD-induced motor complications and non-motor fluctuations, leading clinicians to preferentially use lower LD equivalent doses to mitigate dyskinesia risk. Oestrogen and other sex hormones exert neuroprotective and dopaminergic modulatory effects, and women often display a different motor and non-motor phenotype, including later onset of motor symptoms and higher prevalence of treatment-related complications compared with men.

Overall, the applicant considered that the sex-subgroup findings in Study IPX203-B16-02 were best explained by the exploratory and underpowered nature of the subgroup analyses, lower LD doses in female participants across study phases, and known biological and clinical sex differences in PD that influence dosing decisions and variability of response. The directionally consistent, albeit

non-significant, treatment difference in females, coupled with significant benefit in males and in the overall population, supported a treatment effect of IPX203 in both sexes. Therefore, the lack of statistical significance in women should not be interpreted as lack of efficacy, but as a reflection of multifactorial influences on observed effect size within this subgroup.

These factors provided biological plausibility for sex-related differences in optimal dosing and clinical response patterns without implying a fundamentally different efficacy of IPX203 per se. In summary, no dose optimisation in females was considered justified.

Race - Caucasian vs. Non-Caucasian

The primary study endpoint was met in Caucasians but not in non-Caucasians.

In study IPX203-B16-02 the LS mean difference among non-Caucasian participants was -0.09 h (5.4 minutes), numerically favouring IR LD-CD with no statistical significance ($p=0.9473$). The non-Caucasian subgroup was notably small ($n=19$), and the 95% CIs of the LS means were wide and totally overlapping, limiting the interpretability and reliability of this comparison.

Despite the lack of statistical significance and the direction of the primary endpoint in this subgroup, several other efficacy parameters, including "OFF" time, PGI-C, and motor function assessments, showed numerical trends favouring IPX203 in non-Caucasian subjects. The consistency of these findings across multiple endpoints suggested a potential clinical benefit that may not have been detectable due to the limited sample size and variability within the subgroup.

Importantly, subgroup analyses were exploratory and not powered for formal statistical comparisons. Therefore, the absence of statistical significance should be interpreted cautiously and cannot be taken as evidence of absence of treatment effect. The observed difference in "Good ON" time among non-Caucasian participants should be viewed in the context of these limitations. The small sample size and large CIs constrain the ability to draw conclusions regarding treatment effect in this subgroup.

Region / Geography - American vs. European

The North American and European cohorts were balanced in terms of age (mean 58.8 and 57.4 years, respectively), "Good ON" and "OFF" time at study entry ("Good ON": 9.44 and 9.63 h/day; OFF: 6.04 and 6.17 h/day), and racial composition (94.0% and 98.4% White/Caucasian, respectively). There were some differences in sex distribution (30.1% female in North America, 38.2% in Europe), duration of PD (7.72 years in North America, 8.84 years in Europe), and Hoehn & Yahr stage (14.9% and 29.3% in HY stage 3-4).

With regard to the primary endpoint of study IPX203-B16-02, measured in hours per day, in the cohort of North American subjects ($N=249$), IPX203 demonstrated a statistically significant benefit over IR LD-CD, with LS mean difference of +0.79 h (95% CI: 0.19, 1.38; $p=0.0096$). In the cohort of European subjects ($N=246$), the difference was +0.28 h (95% CI: -0.39, 0.94; $p=0.4135$), which, while numerically favouring IPX203, did not reach statistical significance. To be noted that, when focusing on patients with "OFF time" ≥ 6 h at study entry, the treatment effect of IPX203 was confirmed in North America but it was more pronounced also in Europe: the LS mean difference in "Good ON" time was +0.67 h (95% CI: -0.18, 1.52; $p=0.1213$), reinforcing that IPX203 provided benefit even in European patients.

When analysing "Good ON" time normalised per LD dose at the end of the treatment period (as outlined in the Table below) the treatment effect of IPX203 vs IR LD-CD was consistent and statistically significant in both EU and North American subjects. IPX203 treatment significantly increased "Good

ON" time per dose compared with IR LD-CD treatment (LS means difference 1.38 h [95% CI: 1.11, 1.65] in Europe, 1.73 h [95% CI: 1.49, 1.96] in North America; $p < 0.0001$ in both regions).

No statistically significant difference was noted between the two treatments in MDS-UPDRS Part III and sum of MDS-UPDRS Part II and III scores, both in North America and Europe.

A similar pattern like in "Good ON" time was observed for PGI-C. In North America, 37.7% of IPX203-treated subjects were rated as "much improved" or "very much improved," compared to 21.6% for IR LD-CD ($p=0.0023$). In Europe, the rates were 22.4% for IPX203 and 15.5% for IR LD-CD ($p=0.1786$).

In summary, while the magnitude of the treatment effect for IPX203 was numerically smaller in Europe, the direction of benefit was consistent with North America and the overall study population. The lack of statistical significance in the European subgroup can be explained by demographic and disease-related factors, rather than any difference in drug response. Considering the safety profiles reported in North America and Europe, the benefit-risk profile for IPX203 was noted as favourable and consistent across regions.

The percentage of females was higher in the EU group compared to North America. All the differences outlined above between the two groups may have contributed to the lower "Good ON" time observed in the European population.

Table 32: Analysis of Good on Time (h) per Dose at Visit 7/ET by Region – mITT

	Treatment		
	IPX203 N=249	IR LD-CD N=246	Difference IPX203 - IR LD-CD
Daily Good On time (Hours) per LD dose			
Overall			
n	249	246	
LS Mean	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]	-	-	<.0001
Europe			
n	132	114	
LS Mean	3.61	2.23	1.38
Standard Error	0.096	0.104	0.137
95% Confidence Interval	3.41, 3.80	2.02, 2.43	1.11, 1.65
p-value [a]	-	-	<.0001
North America			
n	117	132	
LS Mean	3.92	2.19	1.73
Standard Error	0.105	0.099	0.119
95% Confidence Interval	3.71, 4.13	2.00, 2.39	1.49, 1.96
p-value [a]	-	-	<.0001

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

Note: Estimates from a mixed model for repeated measures with baseline as a covariate, treatment and visit as fixed effects, pooled centre as random effect and a treatment-by-visit interaction.

Unstructured covariance structure is assumed. Estimates for Visit 7/ET are summarised.

Other subgroup analysis

Based on the results of the performed analyses of the primary endpoint per subgroups, the applicant was requested to justify the efficacy and safety (discussed in section 5.4.12 of this AR) of IPX203 in subjects (with):

- ≥ 65 years
- body weight of < 75 kg
- PD duration of ≥ 8 years
- PD onset at ≥ 65 years
- "Off" time of < 6 hours

In the applicant's view, IPX203 overall efficacy (and safety) was preserved across these patient's populations, and no consistent signal of reduced benefit (or excess risk) was identified that would warrant excluding these patients from treatment.

As detailed above, in the overall modified ITT population, IPX203 showed superiority over IR LD-CD in change from baseline to Visit 7/ET in "Good ON time" (least squares [LS] mean difference 0.53 h, $p=0.0194$), "OFF time" (LS mean difference -0.48 h, $p=0.0252$), and in the proportion of subjects reporting "much improved" or "very much improved" PGI-C (29.7% vs 18.8%, $p=0.0015$). These effects were accompanied by improvements in several diary-based additional endpoints (e.g., percent "OFF time", duration of continuous "Good ON") without worsening of MDS-UPDRS motor scores (or emergence of new safety concerns).

For the primary endpoint, **subjects < 65 years** showed a statistically significant IPX203 benefit in "Good ON Time" (LS mean -0.40 h vs -1.75 h, $p=0.0004$), whereas in subjects ≥ 65 years "Good ON time" had a LS mean of -0.61 h vs -0.57 h, $p=0.8852$). For the secondary endpoint "OFF time", in **subjects ≥ 65 years** the LS mean was 0.44 h vs 0.57 h with IR CD-LD, ($p=0.6423$). In this older group, neither the primary endpoint nor the "OFF" time and PGI-C secondary endpoints reached statistical significance. These results have been reflected accordingly in the PI, where it is outlined that, particularly in patients aged 75 years and older, *the available clinical data do not allow a definitive assessment of potential differences in the clinical response of Hopledo compared with IR levodopa/carbidopa. In this age group, a higher rate of dopaminergic adverse events was observed. Those adverse events were generally mild to moderate in severity and transient. For these reasons, cautious dose conversion with close clinical monitoring is recommended.*

In the **primary analysis by weight** (< 75 vs ≥ 75 kg), "Good ON" time was significantly improved with IPX203 only in subjects with weight ≥ 75 kg; in subjects < 75 kg, the LS mean changes in "Good ON" time were similar between treatments with no statistically significant difference (IPX203 -0.55 h vs IR CD-LD -0.82 h; $p=0.4523$). Importantly, primary and secondary endpoints were numerically in favour of IPX203 in the < 75 kg subgroup, and there was no evidence of reduced tolerability or excess AEs in lower-weight subjects that would contraindicate IPX203. Given that the trial was not powered for weight-based subgroup hypotheses, the absence of a statistically significant difference in the < 75 kg subgroup should be interpreted as a limitation of the sample size and multiplicity rather than a clinically meaningful lack of efficacy.

IPX203 showed an advantage in "Good ON" time in subjects with **PD duration < 8 years** (LS mean -0.41 h vs -1.18 h; difference 0.77 h; $p=0.0207$), whereas in subjects with **PD duration ≥ 8 years** "Good ON" time changes were similar between treatments (-0.55 h vs -0.88 h; $p=0.2996$). However, when examining "OFF time" in the PD duration ≥ 8 years subgroup, this result is non-significant and near zero (0.58 h versus 0.59 h, respectively; $p=0.9595$).

In this longer-duration subgroup, a higher proportion of subjects on IPX203 were “much” or “very much” improved on PGI-C compared with IR CD-LD ($p=0.0489$), with no deterioration in MDS-UPDRS motor scores.

It is important to also flag in this context a safety aspect: it is well-known that LD PK may be altered by gastrointestinal dysfunctions such as dysphagia, delayed gastric emptying, constipation, bacterial infection, gut dysbiosis, diet, comorbidities and concomitant medication intake ([Leta et al, 2023](#)). These factors may contribute to non-optimal LD response, symptoms fluctuations and unpredictable dyskinesia, and are more common in older patients and those with a PD onset in advanced age. Due to these “confounding” factors, the results of these post-hoc analyses should be interpreted cautiously.

Subgroup **analyses by age at PD** onset showed that, in subjects with onset <65 years, “Good ON” time decreased less with IPX203 (LS mean -0.45 h) than with IR LD-CD (LS mean -1.29 h), with a statistically significant treatment difference of 0.84 h (95% CI: 0.33, 1.34; $p=0.0013$). In subjects with PD onset **≥65 years**, the LS mean change in “Good ON” time was -0.74 h with IPX203 vs -0.27 h with IR LD-CD (treatment difference -0.47 h [95% CI: -1.43, 0.49]; $p=0.3351$); non-significant patterns were also seen for “OFF time” (treatment difference 0.13 h [95% CI: -0.72, 0.98]; $p=0.7646$), PGI-C (% much/very much improved: 19.4% vs 25.8%; difference -6.4% [95% CI: -20.8, 8.0]; $p=0.8984$), and MDS-UPDRS Part III/Part II+III scores. These results should be interpreted cautiously given the exploratory nature of the subgroup analyses, smaller sample size, and wide CIs indicating no clear signals. Of note that, as discussed in section 5.4.6 of this AR, safety profiles were comparable across subgroups. Hence, in the applicant’s view, no evidence-based reason could be identified to exclude subjects with PD onset ≥65 years from IPX203 treatment.

In subjects with **baseline “OFF time” ≥6 hours**, IPX203 increased “Good ON” time (LS mean -0.64 h vs -1.66 h; difference 1.02 h; $p=0.0010$) and attenuated “OFF time” increase *versus* IR LD-CD (LS mean 0.15 h vs 0.98 h; difference -0.83 h; $p=0.0202$), with a higher proportion of subjects reporting “much” or “very much” improved PGI-C. In the complementary subgroup with baseline “OFF time” <6 h, treatment differences were smaller and non-significant for “Good ON” time (LS mean -0.30 h vs -0.41 h; difference 0.10 h; $p=0.7539$) and “OFF time” (LS mean 0.27 h vs 0.31 h; difference -0.04 h; $p=0.9015$). Importantly, there was no indication of deterioration with IPX203; “Good ON”, “OFF time”, and PGI-C remained comparable between treatments.

In addition to the exploratory nature of the subgroup analyses, one further known limitation, especially relevant for this subgroup of patients, was that the study did not allow IPX203 administration more frequently than every 6 hours. Some participants might have experienced a greater increase in “Good ON” time and reduction in “OFF time” with more frequent dose than every 6 h or if dosing frequency could have been titrated to clinical response. When analysing “Good ON” time per LD dose at the end of the treatment period (as outlined in the Table below), IPX203 consistently showed a statistically significant benefit over IR LD-CD in both groups: those with less than 6 h and those with 6 h or more of “OFF time”. Specifically, IPX203 led to significantly more “Good ON” time per dose compared to IR LD-CD treatment ($p<0.0001$, LS mean difference: 1.65 h [95% CI: 1.38, 1.92] for “OFF time” <6 h; and 1.48 h [95% CI: 1.25, 1.71] for “OFF time” ≥6 h).

In conclusion, while subgroup analyses suggest attenuation of the primary “Good ON” effect in certain highly overlapping subgroups (older age, lower weight, longer disease duration, later onset, lower baseline OFF), these analyses were exploratory, underpowered, and affected by strong correlations between covariates. Within these subgroups, IPX203 generally maintained favourable effects on “Good ON time”, “OFF time”, and PGI-C (and did not exhibit new safety concerns – as discussed in the dedicated safety section of this AR), even when formal statistical superiority *versus* IR CD-LD was not demonstrated.

Table 33: Analysis of Good on Time (h) per Dose at Visit 7/ET by Baseline "Off time" - mITT

	Treatment		
	IPX203 N=249	IR LD-CD N=246	Difference IPX203 - IR LD-CD
Daily Good On time (Hours) per LD dose			
Overall			
LS Mean	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]	-	-	<.0001
Off time <6 hours			
LS Mean	4.03	2.37	1.65
Standard Error	0.109	0.106	0.137
95% Confidence Interval	3.81, 4.24	2.16, 2.58	1.38, 1.92
p-value [a]	-	-	<.0001
Off time ≥6 hours			
LS Mean	3.52	2.04	1.48
Standard Error	0.081	0.084	0.117
95% Confidence Interval	3.36, 3.68	1.88, 2.21	1.25, 1.71
p-value [a]	-	-	<.0001

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

Note: Estimates from a mixed model for repeated measures with baseline as a covariate, treatment and visit as fixed effects, pooled center as random effect and a treatment-by-visit interaction. Unstructured covariance structure is assumed. Estimates for Visit 7/ET are summarised.

5.4.2.2. Study IPX203-B16-03

Study objective

IPX203-B16-03 was a Phase 3, 9-month, multicenter, **open-label safety extension study** to evaluate the long-term safety and clinical utility of IPX203 in the treatment of subjects with advanced PD who had motor fluctuations.

. Subjects who had successfully completed the randomised controlled trial IPX203-B16-02 had the opportunity to enrol in this open-label study.

The study consisted of a baseline visit (no 1) followed by 3 visits (no 2 to 4) spaced at approximately 3-month intervals. For subjects who had successfully completed Study IPX203-B16-02, the baseline visit (of this study coincided with the EOS Visit 7 of the preceding study (with an allowed window of + 7 days). Subjects were initially started on the final IPX203 dosing regimen determined during the IPX203 dose conversion period of study IPX203-B16-02. Investigators were permitted to adjust the dosing regimen of IPX203 during this study to achieve the optimal balance of efficacy and safety and any changes were recorded. Subjects continued to take their non-LD containing PD concomitant medications (including dopamine agonists, amantadine, selective monoamine oxidase [MAO]-B inhibitors [safinamide, rasagiline, and selegiline]) during study IPX203-B16-03. Changes in doses or in dosing regimens of all non-CD-LD PD medications and/or the addition of new non-CD-LD PD medications were also captured. Supplemental CD and benserazide, apomorphine, and the addition of COMT inhibitors (e.g., entacapone, opicapone, and tolcapone) could likewise be initiated during this study.

Adverse events, supine and standing orthostatic vital signs, and concomitant medications were evaluated throughout the course of the study. Electrocardiograms (ECGs), clinical laboratory tests, physical examinations, the Columbia-Suicide Severity Rating Scale (C-SSRS) and Gastroparesis Cardinal Symptom Index (GCSI), were also considered.

The following clinical utility measures were assessed: Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I to IV, Patient Global Impression of Severity (PGI-S), Clinician Global Impression of Severity (CGI-S), the 39-item Parkinson's Disease Questionnaire (PDQ-39), Parkinson Anxiety Scale (PAS), Non-Motor Symptom assessment scale (NMSS) for Parkinson's disease, Parkinson's Disease Sleep Scale 2 (PDSS-2), Treatment Satisfaction Assessment (TSA), 12-Item Zarit Burden Interview (ZBI-12), and Early Morning Symptoms Questionnaire (EMSQ). Visit 4 was the EOS visit.

Diagnosis and Main Criteria for Inclusion

Inclusion Criteria:

1. Successfully completed Study IPX203-B16-02;
2. Able to provide written informed consent prior to the conduct of any study-specific procedures;
3. Female subjects of childbearing potential were to have a negative urine pregnancy test at the Baseline visit (Visit 1);
4. Agreed to use a medically acceptable method of contraception throughout the study and for 6 weeks after completing the study.

Exclusion Criteria:

1. Intended to use any doses of Rytary® or Duopa™ during this study;
2. Planned to use an investigational treatment other than IPX203 during the course of this study;
3. Neurosurgical ablation treatment for PD planned or anticipated during the study period. Implantation of a deep brain stimulator (DBS) for the treatment of PD was permitted during this study;
5. Subjects who, in the opinion of the clinical investigator, were not to participate in the study.

Clinical Utility Measures:

MDS-UPDRS Part I to IV, PGI-S, CGI-S, PDQ-39, PAS, NMSS, PDSS-2, TSA, ZBI-12, and EMSQ were assessed at every visit.

Statistics

Subjects were assigned to treatment group defined by the treatment received in the DB phase of the previous IPX203-B16-02 study (IPX203 or IR CD-LD). Data were summarised using descriptive statistics for continuous variables. Unless otherwise specified, statistics included number of subjects, mean, standard deviation (SD), minimum, median, and maximum. Tables of categorical variables, counts and percentages were displayed accordingly by the applicant. Baseline was defined as the last assessment obtained prior to the first dose of the open-label drug in this IPX203-B16-03 study.

The study electronic case report form (eCRF) did not explicitly capture when the subject took the first open-label study drug dose. Therefore, it was assumed that this dose had been taken on the day of Visit 1, after all study assessments.

The analysis' populations used in this study were:

- Safety Analysis Set (SAS): it included all subjects treated with the open-label study drug in the study.

The study eCRF did not explicitly capture if a subject took the open-label study drug. Thus, it was assumed that a subject took the open-label study drug if (and only if) the study drug was dispensed to the subject at one of the study visits.

- Intent-to-Treat (ITT) Analysis Set: it included all subjects treated with the open-label study drug in the study and had at least one post-baseline clinical utility assessment.

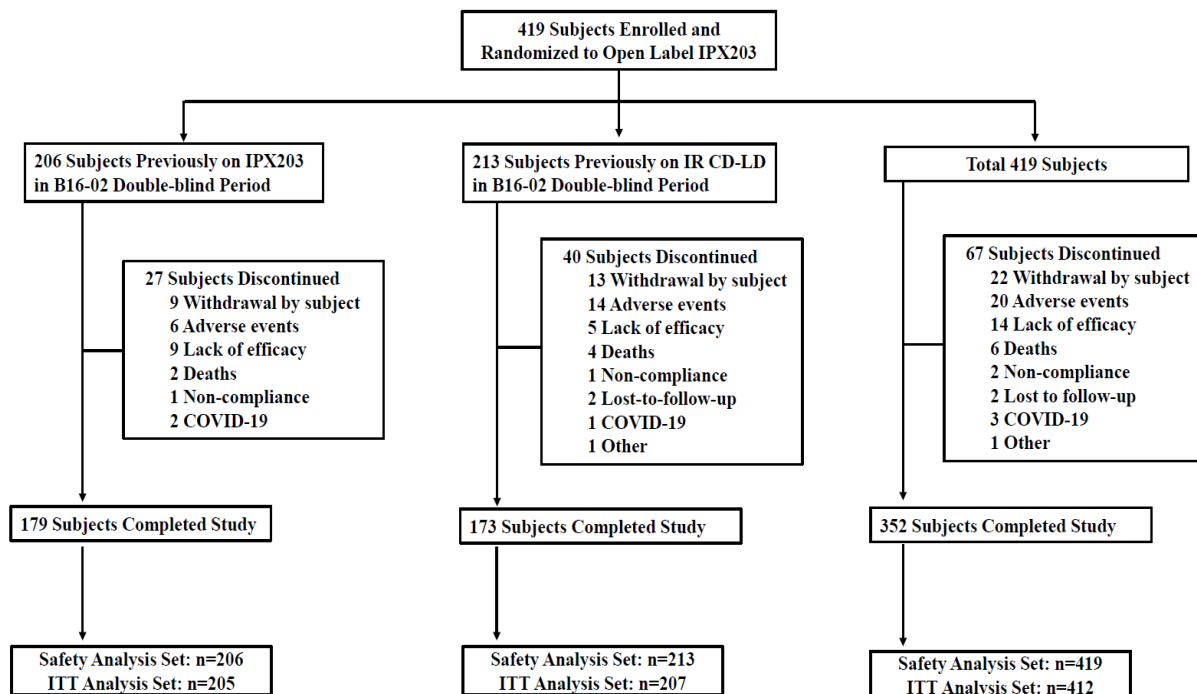
Clinical Utility Analysis

Analysis of the clinical utility endpoints was performed on the ITT population.

The Total MDS-UPDRS and each of its components (Parts I through IV), and Parts II and III combined, PGI-S, CGI-S, PDQ-39, PAS, NMSS, PDSS-2, TSA, ZBI-12, and EMSQ scores, as well as the changes from baseline in these scores, were summarised by visit and treatment group, as well as for both treatment groups combined. A summary of the study entry baseline of Study IPX203-B16-02 was also included.

A total of 419 subjects were enrolled: 206 from the previous IPX203 randomised group and 213 from the previous IR LD-CD randomised group (in the double-blind period of Study IPX203-B16-02). A total of 352 (84%) subjects completed the study: 179 (86.9%) from the previous IPX203 group and 173 (81.2%) from the previous IR LD-CD group, respectively. Overall, 67 (16.0%) subjects discontinued the study: 27 (13.1%) from the previous IPX203 group and 40 (18.8%) from the previous IR LD-CD group, respectively. The primary reasons of study discontinuations ($\geq 20\%$ of total subjects who discontinued) were subject withdrawal (22 [32.8%] subjects), AEs (20 [29.9%] subjects), and lack of efficacy (14 [20.9%] subjects).

Figure 18: Subject Disposition Flowchart (Study IPX203-B16-03)



The demographic and baseline characteristics were comparable among the subjects from the previous IPX203 IR CD-LD groups. Overall, the mean (SD) age of subjects was 66.9 (8.86) years, majority were male (279 [66.6%]) and white (406 [96.9%]) The mean (SD) BMI of the subjects was 27.472

(5.0074) kg/m². The mean (SD) age of onset of PD was 58.0 (9.32) years, and the mean (SD) duration of PD was 8.8 (4.84) years.

All clinical utility measures were stable, and efficacy was maintained for the full duration of the study, (throughout the 9 months). Overall, there were minor changes in mean (SD) TDD of LD or in dosing frequency over the 9 months of treatment. After 3 months, most subjects had found a stable dosing regimen and maintained that regimen for the remainder of the study. This was an indication that the efficacy/safety profile of IPX203 was acceptable and could be maintained over a long period of time. No notable difference was observed in any of the clinical utility measures scores from baseline to EOS (Visit 4/Month 9). The scores were also comparable over the 9-month treatment period between the subjects previously randomised to IPX203 compared to those previously randomised to IR LD-CD (in the DB period of Study IPX203-B16-02) as detailed below.

Table 34: Summary of Change from Baseline to Visit 4 in Clinical Utility Endpoint Results (Study IPX203-B16-03)

Endpoints	Total IPX203, Mean Values					
	Study IPX203-B16-02 Baseline ^a	Baseline ^b	Visit 2 (Month 3)	Visit 3 (Month 6)	Visit 4 (Month 9)	Change from Baseline ^b to Visit 4
MDS-UPDRS Total Score	60.2	56.7	56.5	56.0	58.8	2.3
MDS-UPDRS Part I Score	9.9	9.9	10.6	10.7	11.0	1.2
MDS-UPDRS Part II Score	13.3	12.8	13.0	12.8	13.5	0.8
MDS-UPDRS Part III Score	29.6	27.5	26.8	26.6	27.9	0.4
MDS-UPDRS Part IV Score	7.5	6.6	6.0	6.0	6.3	-0.1
Sum of MDS-UPDRS Part II and III Score	42.8	40.3	39.8	39.4	41.5	1.2
PGI-S Score	3.8	3.7	3.8	3.7	3.7	0
CGI-S Score	3.9	3.8	3.8	3.7	3.7	-0.1
PDQ-39 Total Scores	44.9	41.7	42.7	42.8	44.4	4.1
PAS Total Scores	10.7	10.4	10.3	10.3	10.9	0.8
NMSS Total Scores	34.9	32.0	32.5	33.4	35.0	3.9
PDSS-2 Scores	17.4	16.6	15.8	16.1	16.1	-0.1
TSA Scores	NA	NA	5.2	5.4	5.4	NA
ZBI-12 Total Scores	NA	9.2	10.5	11.0	10.6	1.3
EMSQ Total Severity Scores	9.5	8.4	8.1	8.0	8.4	0.4
Abbreviations: EMSQ = Early Morning Symptoms Questionnaire; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's						

Endpoints	Total IPX203, Mean Values					
	Study IPX203- B16-02 Baseline ^a	Baseline ^b	Visit 2 (Month 3)	Visit 3 (Month 6)	Visit 4 (Month 9)	Change from Baseline ^b to Visit 4
Disease Rating Scale; NA = 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; CGI-S = Clinical Global Impression of Severity; TSA = Treatment Satisfaction Assessment; ZBI-12 = 12-Item Zarit Burden Interview ^{a.} Study IPX203-B16-02 study baseline was defined as the last assessment obtained prior to the first dose of the study drug (IR LD-CD) in the Dose Adjustment period ^{b.} This study baseline was defined as the last assessment obtained prior to the first dose of the open-label study drug.						

At baseline, the two groups were well balanced in demographic and clinical characteristics and demonstrated comparable efficacy profiles throughout the extension.

Age distribution was similar across groups. The mean age was 66.7 years in the prior IPX203 group and 67.1 years in the prior IR LD-CD group, while the median age was identical, at 68 years in both cohorts. Gender distribution was also aligned: the IPX203 group included 131 males (63.6%) and 75 females (36.4%), whereas the IR LD-CD group comprised 148 males (69.5%) and 65 females (30.5%). Most participants were white (97.1% in the IPX203 group and 96.7% in the IR LD-CD group). Anthropometric measures were closely matched, with mean BMI of 27.6 kg/m² for IPX203 and 27.4 kg/m² for IR LD-CD, respectively.

Disease history was comparable between groups. The mean time since diagnosis was 8.9 years for IPX203 and 8.8 years for IR LD-CD, and the mean age at PD onset was 57.7 years for IPX203 and 58.3 years for IR LD-CD respectively.

Baseline disease severity was also similar across multiple measures: the mean MDS-UPDRS total score was 57.3 for IPX203 and 56.7 for IR LD-CD. Sub-scores were nearly identical, with Part I averaging 10.0 in both groups; Part II at 13.1 for IPX203 and 12.6 for IR LD-CD; Part III at 27.8 and 27.3; and Part IV at 6.5 and 6.8, respectively. Hoehn and Yahr stage averaged 2.2 in both groups, and most subjects were classified as stage 2 (69.4% for IPX203 and 73.9% for IR LD-CD).

Subjects initiated IPX203 at the regimen determined at the end of the double-blind phase, and the dosing remained stable throughout the 9-month extension. The mean TDD at baseline was 1477.1 mg for prior IPX203 subjects and 1483.5 mg for prior IR LD-CD subjects, with minimal increases by month 9 (+100.8 mg and +64.3 mg, respectively). Dose adjustments occurred but returned to baseline levels in 10.2% and 8.2% of subjects, respectively.

Study completion rates were slightly higher in the prior IPX203 group (86.9%) compared to the prior IR LD-CD group (81.2%). Discontinuations were more frequent among prior IR LD-CD subjects (18.8% versus 13.1%), primarily due to AEs (14 subjects, 35.0% vs 6 subjects, 22.2%). Conversely, discontinuations due to lack of efficacy were more common in the prior IPX203 group (9 subjects, 33.3% vs 5 subjects, 12.5%). Subjects' withdrawals accounted for approximately one-third of discontinuations in both groups.

Efficacy was assessed primarily through changes in MDS-UPDRS scores and other patient-reported outcomes. MDS-UPDRS total scores increased slightly from baseline to Month 9 (+2.5 points for prior IPX203; +2.0 points for prior IR LD-CD). Scores remained comparable throughout the study: Month 3 (57.0 vs 55.9), Month 6 (56.5 vs 55.6), and Month 9 (58.9 vs 58.6). Part I and II scores were stable, with no clinically meaningful changes. For Part I, baseline scores were 9.9 vs 9.8, rising to 11.1 vs

10.9 at Month 9 (mean change: +1.4 vs +1.0; overall +1.2). Part II started at 13.0 vs 12.6 and ended at 13.6 vs 13.5 (mean change: +0.8 vs +0.7; overall +0.8). Part III remained unchanged, moving from 27.8 vs 27.1 at baseline to 28.1 vs 27.8 at Month 9 (mean change: +0.4 both). Motor complications (Part IV) decreased slightly, from 6.4 vs 6.8 at baseline to 6.2 vs 6.4 at Month 9 (mean change: -0.1 vs -0.2).

Non-motor symptoms and quality-of-life measures were similarly stable:

- Patient Global Impression of Severity (PGI-S) remained at around 3.7 in both groups by Month 9 (mean change: 0 vs -0.1).
- Clinical Global Impression of Severity (CGI-S) decreased marginally (baseline 3.8 vs 3.9; Month 9: 3.8 vs 3.7; overall -0.1).
- 39-item Parkinson's Disease Questionnaire (PDQ-39) total score increased by 4.1 points overall (IPX203 +5.3; IR LD-CD +2.9).
- Parkinson Anxiety Scale (PAS) total rose by 0.8 (IPX203 +0.7; IR LD-CD +0.8).
- Non-Motor Symptom Assessment Scale (NMSS) increased by 3.9 points (IPX203 +4.0; IR LD-CD +3.8).
- Sleep quality, assessed by PD Sleep Scale-2 (PDSS-2), showed negligible change (-0.1 overall, IPX203 0; IR LD-CD -0.2). Domain changes: Disturbed Sleep +0.3 both; Motor Symptoms at Night -0.2 total (-0.1 IPX203; -0.4 IR LD-CD); PD Symptoms at Night -0.2 both.

Overall, the open-label extension of study IPX203-B16-02 did not show any critical issues in efficacy, as it would be expected after a randomised withdrawal study to similar active components and return to the expected best treatment. Notwithstanding, it would have been expected that the subgroup of patients who had previously been in IR-LD would improve slightly under IPX203 again.

The pivotal IPX203-B16-02 (RISE-PD) study employed the Hauser diary to capture daily fluctuations in motor state, specifically "Good On time" and "OFF time", highly sensitive indicators of treatment benefit in PD. In contrast, the OLE (IPX203-B16-03) did not include Hauser diary assessments, relying instead on clinic-based scales such as the MDS-UPDRS. This approach was not optimal.

At the end of RISE-PD, the difference between groups in "Good On time" and "OFF time" was only approximately 30 minutes, as the IR LD-CD group unexpectedly did not return to its pre-conversion level, suggesting a carryover effect. All patients entering the OLE had been previously optimised on both IR LD-CD and IPX203 during the parent study, which further minimised baseline differences. Given this minimal difference at OLE entry, any incremental improvement in the prior IR LD-CD group after switching to IPX203 was expected to be small and clinically subtle and unlikely to be detected by clinic-based instruments such as the MDS-UPDRS.

These scales, while appropriate for global severity assessment, are less sensitive to short-term changes in motor fluctuations compared to the Hauser diary. Therefore, the absence of measurable differences between subgroups in the OLE reflects both the small difference in disease control at baseline and the limited responsiveness of the scales used. Importantly, the OLE was not designed to compare efficacy between prior IR LD-CD and IPX203 groups, so differences were not expected. Rather its purpose was to evaluate long-term safety, tolerability, and stability of IPX203.

The results confirmed that IPX203 maintained stable efficacy and tolerability over 9 months, regardless of prior treatment assignment. Switching between formulations did not harm patients, supporting treatment flexibility in clinical practice.

5.4.3. Clinical studies in special populations

Table 35: Clinical studies in special populations

	Controlled Trials N=684	Non-controlled trials N=419
Clinical trials		
IPX203-B14-02 (Randomised Set)	26 (3.8%)	0
IPX203 B16-01 (Randomised Set)	28 (4.1%)	0
IPX203-B16-02 (Safety Set)	630 (92.1%)	0
IPX203 B16-03 (Safety Set)	0	419 (100%)
	n / T (%)	n / T (%)
Related TEAEs		
Renal impairment* patients	1/8 (12.5%)	2 / 6 (33.3%)
Hepatic impairment** patients	4 / 12 (33.3%)	2 / 5 (40%)
Paediatric patients <18 years	0/ 0	0/ 0
Age 18-64	81 / 261 (31.0%)	25 / 152 (16.4%)
Age 65-74	88 / 301 (29.2%)	33 / 191 (17.3%)
Age 75-84	33 / 116 (20.5%)	8 / 73 (11.0%)
Age 85+	0 / 6 (0%)	0 / 3 (0%)
Related Serious TEAEs		
Renal impairment* patients	0/8 (0%)	0 / 6 (0%)
Hepatic impairment** patients	0 / 12 (0%)	0 / 5
Paediatric patients <18 years	0/ 0	0/ 0 (0%)
Age 18-64	1 / 261 (0.4%)	4 / 152 (2.6%)
Age 65-74	1 / 301 (0.3%)	3 / 191 (1.6%)
Age 75-84	0 / 116 (0%)	0 / 73 (0%)
Age 85+	0 / 6 (0%)	0 / 3 (0%)

Abbreviation:- n=number of subjects with at least one event, T = total number of subjects in each subgroup, Percentage (%) calculated as number of subjects (n) /total number (T)*100.

Adverse Events considered related include Related, Possibly Related, and Unlikely Related

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)

** Hepatic impairment is defined as having Child-Pugh score B or C

Overall, the number of subjects with renal or hepatic impairment was limited. No paediatric patients (<18 years) were enrolled in the clinical program. Age-based subgroup analyses indicate that the majority of subjects were adults aged ≥65 years.

Data for age-related special populations enrolled in the PK studies IPX203-B14-02 and IPX203-B16-01 was also submitted upon request. Although no patients above 85 years were enrolled, CHMP noted that elderly subjects were well represented in both studies. More than half of participants were aged 65 years or older and more than 20% were above the age of 75.

Table 36: Distribution of Patients by Age Class – IPX203-B14-02 and IPX203-B16-01 PK Completers Set

Study	Age 65-74 n(%)	Age 75-84 n(%)	Age 85+ n(%)	Overall n(%)
IPX203-B14-02 (N=24)	10 (41.7)	3 (12.5)	0	13 (54.2)
IPX203-B16-01 (N=27)	8 (29.6)	6 (22.2)	0	14 (51.9)
Total (N=51)	18 (35.3)	9 (17.6)	0	27 (52.9)

Study	Age 65-74 n(%)	Age 75-84 n(%)	Age 85+ n(%)	Overall n(%)
The total number of subjects reflects participants from both studies. Some individuals took part in both studies and are counted separately in each.				

5.4.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

5.4.5. Supportive studies

Not applicable.

5.4.6. Analysis performed across trials (pooled analyses and meta-analysis)

Detailed, as relevant, thought this AR.

5.4.7. Observational data/data from registries

Not applicable.

5.4.8. Patient experience data (PED)

No data was gathered by the CHMP on early dialogue with patients' organisations.

5.4.9. Healthcare professional engagement

No data was gathered by the CHMP on early dialogue with HCPs organisations.

5.4.10. Overall discussion and conclusions on clinical efficacy

5.4.10.1. Discussion

Key information on IPX203 efficacy is outlined below. This should be read in conjunction with section 5.2.6.

The applicant conducted **two Phase 2** (Studies **IPX203-B14-02** and **IPX203-B16-01**) and **two Phase 3** (Studies **IPX203-B16-02** and **IPX203-B16-03**) studies to support this initial MAA. The primary objective of the Phase 2 study **IPX203-B16-01** was to compare the PK of single and multiple doses of IPX203 with immediate-release (IR) CD-LD in subjects with advanced PD. Levodopa and CD were administered at a fixed ratio of 4:1.

Idiopathic PD patients, aged ≥ 40 years, chronically treated with stable regimens of LD-CD but experiencing motor complications, were randomised to one of two dosing sequences: IPX203 followed by IR CD-LD or vice versa. Each treatment period lasted 15 days, separated by a 1-week washout when subjects received their usual stable pre-study PD medications. The study consisted of four visits

after screening: at Day 1 (visits 1 and 3) and 15 (visits 2 and 4) of each treatment period.

Twenty-eight subjects were randomised; 27 (96.4%) completed the study. One withdrew because of an AE while on IPX203, and did not receive IR CD-LD. The subjects mean (SD) age was 66.4 (10.1) years. Males slightly outnumbered females (16 versus 12). The majority (92.9%) of subjects were white.

Initial IPX203 doses were chosen based on previous PK data with IPX203 and IR CD-LD in advanced PD patients: a LD dose of approximately 270 to 360 mg from IPX203 was expected to provide peak LD concentrations comparable to those of 100 mg LD from IR CD-LD. This approach was considered acceptable.

During IPX203 treatment, on average, IPX203 treatment was associated with approximately 2.3 hours less "OFF time" than IR CD-LD. Most of this improvement (1.9 hours) was on "Good ON" time. Durations of "Good ON" episodes or any "ON" episodes were longer with IPX203 (LS means differences: 2.89 h and 3.79 h, respectively). IPX203 treatment was also associated with fewer motor fluctuations per day. A higher proportion of subjects experienced a reduction in "OFF" time of at least 1.0, 1.5, and 2.0 hours during IPX203 than during IR CD-LD treatment.

When predose mean MDS-UPDRS Parts I–IV scores were compared by treatment on Day 15, subjects had lower scores for Parts III, II and III, and IV as well as the MDS-UPDRS total score with IPX203, indicating less PD impairment.

At predose on Day 15, when subjects had not had a study treatment for at least 5 hours, the mean MDS-UPDRS Part III score was lower during IPX203 than IR CD-LD treatment (33.5 versus 41.6), suggesting that IPX203 clinical effects may carry over to the next morning.

Analysis of Part IV individual items also demonstrated benefits of IPX203 *versus* IR CD-LD, both in terms of time spent in "OFF" state and functional impact of fluctuations.

On Day 1, subjects receiving IPX203 were 73.3% less likely to receive rescue medication; on Day 15, these subjects were 72.1% less likely to receive a predose than those receiving IR CD-LD.

The investigator's assessment of the subject's motor state on Day 1 demonstrated less "OFF" time and significantly more "Good ON" time with IPX203 compared with IR CD-LD (2.57 h difference for each). On Day 15, treatment differences were again seen in "OFF" time and "Good ON" time, although the magnitude of these differences was smaller.

During the 10-hour postdose observation period, 63% of subjects on IPX203 treatment period experienced less than 2 hours of "OFF" time compared to 19% during IR CD-LD treatment period. Average times to first "ON" and first "Good ON" states after the first dose were not significantly different between treatments on Days 1 or 15.

MDS-UPDRS Part III mean scores on Day 1 were lower during IPX203 treatment than during IR CD-LD treatment from 3 to 8 hours postdose; across the 8 hours post-dose, the mean scores were 23.6 during IPX203 and 33.0 during IR CD-LD treatment ($p < 0.0001$). Subjects had longer total durations of PD effect during IPX203 than during IR CD-LD treatment, based on minimal improvement thresholds of at least 4, 7, and 13 points on the MDS-UPDRS Part III scale. From 3 to 7 hours postdose, greater proportions of subjects taking IPX203 than taking IR CD-LD met each of 3 minimal improvement thresholds. On Day 15, across the 10 hours postdose, the mean MDS-UPDRS Part III scores were 18.2 for IPX203 and 22.0 for IR CD-LD ($p = 0.0226$), respectively.

The sum of scores from bradykinesia questions from Part III (sum of Questions 4-8, and 14) showed more reduction with IPX203 than IR CD-LD on Day 1 (overall and at hours 3 through 7) but not on Day 15 (except at hours 3 and 4).

The pivotal Phase 3 study **IPX203-B16-02** evaluated safety and efficacy of IPX203 (in comparison to IR LD-CD) in the treatment of LD-CD-experienced subjects with PD, with motor fluctuations aged $\geq$ 40 years.

The study population accurately reflected IPX203 the proposed target population and indication for use (revised in the course of the procedure, as detailed in section 8.1.1.). This trial consisted of an up to 4-week screening period, a 3-week open-label (OL) IR CD-LD dose adjustment period, followed by a 4-week OL period for conversion to IPX203, and a 13-week double-blind (DB), double-dummy treatment period. Subjects were randomised in a 1:1 ratio, stratified by center, to receive either IPX203 (with matching IR CD-LD placebo) or IR CD-LD (with matching IPX203 placebo).

The study primary endpoint (PEP) was a mean change from baseline in "Good ON" time in hours per day, averaged over the PD diary days, at the end of the DB treatment period (Visit 7 or early termination). "Good ON" time was derived from the 3-day PD diaries and defined as the sum of "ON time without dyskinesia" and "ON time with non-troublesome dyskinesia". No medication adjustments were allowed after randomisation and during the study DB phase. This approach was considered acceptable.

The study design, the choice of endpoints and hierarchy were also considered adequate.

Usually, improving "ON time" is frequently done at the cost of increased sleep time or increased dyskinesias. The effect on sleep and the harmonised "ON time" deals with the first aspect. However, the details regarding frequency and severity were not provided. No dedicated tool to measure dyskinesias were used.

Six-hundred and thirty subjects were enrolled and entered the IR CD-LD dose adjustment period.

Forty-one (6.5%) dropped out. Thereafter, of the 589 who entered the IPX203 conversion period, **83** (13.2%) withdrew from the study. The primary reasons for discontinuation were AEs (**35 [42.2%]** subjects), withdrawal by subject (**32 [38.6%]**), and lack of efficacy (**10 [12.0%]**). The applicant clarified the reasons behind "withdrawals by subject": most were due to the stabilisation falling behind the patients' expectations. This may be related to the rigid drug scheme required.

Further, 506 subjects were randomised to IPX203 (256) and IR CD-LD (250); 449 completed the study: 222 (86.7%) in IPX203 group and 227 (90.8%) in IR CD-LD group.

Fifty-seven (11.3%) subjects discontinued early from the DB maintenance period: 34 (13.3%) from IPX203 and 23 (9.2%) from IR CD-LD group, respectively. The primary reasons for discontinuations in IPX203 group were AEs (14 [41.2%] subjects), withdrawal by subject (10 [29.4%]), lack of efficacy (5 [14.7%]) and protocol deviations (3 [8.8%]). The primary reasons for discontinuations in IR CD-LD group were withdrawal by subject (11 [47.8%]), lack of efficacy (8 [34.8%]), and AEs (3 [13.0%]). The number of subjects, who discontinued IPX203 in study **IPX203-B16-02**, considered very high, raised concerns (especially, the **83** during dose conversion period, of whom 10 due to lack efficacy, also looking at the overall higher number of subjects who discontinued from the DB maintenance period). Particularly, the difference in an incidence of discontinuations due to AEs (41.2% vs 13%) was flagged to the applicant for further analysis.

It was agreed that the impact on the overall efficacy and safety of the **83** subjects who discontinued during the dose-conversion period of study IPX203-B16-02 should be interpreted in the context of IPX203 as new MR formulation designed to replace IR LD-CD in patients with PD with motor fluctuations. Conversion to IPX203 involved dose titration, including transient lack of efficacy or dopaminergic AEs, which could lead to discontinuation. The initial suggested IPX203 doses in the protocol were based on average bioavailability relative to IR LD-CD. However, most subjects required individualised up-titration or down-titration to achieve an optimal balance of efficacy and tolerability.

During the 4-week IPX203 dose-conversion period, **83** subjects (14.1%) discontinued primarily due to AEs and lack of efficacy. These discontinuations largely reflected the process of establishing a clinically effective and tolerable IPX203 regimen rather than inherent lack of efficacy of IPX203.

In addition, the applicant provided information on AEs during IPX203 conversion period: 229 (38.9%) subjects experienced at least one TEAE. The most frequently reported TEAEs ($\geq 2\%$) in subjects who received IPX203 were dyskinesia (40 [6.8%]), nausea (29 [4.9%]), dry mouth (25 [4.2%]), dizziness (17 [2.9%]), constipation (12 [2.0%]), vomiting, fall and insomnia (each 13 [2.2%]). Overall, the above is consistent with what expected upon transitioning from IR to MR LD.

Subjects receiving IPX203 showed a greater improvement in the mean "Good ON" time from baseline to the end of DB therapy (Visit 7/ET) when compared with those receiving IR CD-LD (mean change from baseline to Visit 7/ET; IPX203: -0.39 h and IR CD-LD: -0.97 h). "Good ON" time decreased less in the IPX203 group (LS mean: -0.50 h) when compared with IR CD-LD group (LS mean: -1.03 h). IPX203 treatment resulted in significantly more hours of "Good ON" time compared with IR CD-LD treatment ($p=0.0194$, difference in LS means: 0.53 h [95% CI: 0.09, 0.97]). However, in the per-protocol (PP) analysis set, no statistical significance was observed in "Good ON" results.

Subjects receiving IPX203 showed a greater improvement in the mean "OFF" time from baseline to Visit 7/ET when compared with those receiving IR CD-LD (IPX203: 0.29 h and IR CD-LD: 0.76 h). "OFF" time increased less in the IPX203 group (LS mean: 0.38 h) when compared with IR CD-LD group (LS mean: 0.86 h). IPX203 treatment resulted in significantly less "OFF" time compared with IR CD-LD treatment ($p=0.0252$, difference in LS means: -0.48 h [95% CI: -0.90, -0.06]). However, in the PP analysis set statistical significance was not reached.

At Visit 7/ET, higher number of subjects in IPX203 group reported improvement in PGI-C scores (56.9%) compared with IR CD-LD group (46.3%). Moreover, a statistically significant proportion of subjects ($p=0.0015$) reported "much improved" or "very much improved" response with IPX203 treatment (29.7%) compared to IR CD-LD treatment (18.8%). Similar statistically significant results were observed in the PP analysis set ($p=0.0161$): 32.9% of subjects reported "much improved" or "very much improved" response with IPX203 treatment compared to 22.2% of those with IR CD-LD treatment. However, no statistically significant difference in MDS-UPDRS Part III scores from baseline to Visit 7/ET was reached with IPX203 *versus* IR CD-LD ($p=0.9587$). Also, no statistically significant difference in sum of MDS-UPDRS Part II and III scores was reported with IPX203 *versus* IR CD-LD ($p=0.9668$).

A lesser increase in the mean percent "OFF time" during waking hours from baseline to Visit 7/ET was observed in subjects receiving IPX203 *versus* those receiving IR CD-LD (mean change from baseline to Visit 7/ET; IPX203: 1.75 and IR CD-LD: 4.55).

Likewise, a lesser decrease from double-blind baseline to Visit 7/ET was reported in the mean "ON time" without dyskinesia in subjects on IPX203 compared with those on IR CD-LD (mean change from double-blind baseline to Visit 7/ET; IPX203: -0.43 h and IR CD-LD: -0.97 h).

There were no significant differences between IPX203 and IR CD-LD groups from the DB baseline to Visit 7/ET in the mean "ON time" with troublesome dyskinesia, in the mean "asleep" time and in proportion of subjects with an improvement in "Good On" time as per PD Diary.

A 36.2% of subjects in the IPX203 group had a reduction of at least 0.5 hours in "OFF time" at Visit 7/ET compared with 33.6% in the IR CD-LD group. Significantly fewer subjects in IPX203 group (11.9%) compared to IR CD-LD group (18.7%) had a reduction of ≥ 2 hours ($p=0.0309$) at Visit 7/ET.

The percentage of subjects in the “ON” state upon awakening for at least 1 of the 3 recorded PD diary days at Visit 7/ET was statistically significantly higher in IPX203 group (53.1%) compared to IR CD-LD group (44.5%) ($p=0.0046$). Moreover, the proportion of those in “Good ON” state upon awakening at Visit 7/ET was also higher in IPX203 group compared to IR CD-LD group ($p=0.0060$).

Subjects receiving IPX203 showed a lesser increase in the average number of motor fluctuations per day from baseline to Visit 7/ET when compared with those receiving IR CD-LD ($p<0.0001$, difference in LS means: -1.35 [95% CI: -1.72 , -0.97]).

No statistically significant difference was noted with IPX203 *versus* IR CD-LD treatment in MDS-UPDRS total score ($p=0.9639$), Part I ($p=0.5549$), Part II ($p=0.9186$), or Part IV scores ($p=0.8735$): subjects in both groups had a similar degree of change.

No differences were noted with IPX203 compared to IR CD-LD in the PDQ-39 total score. However, a statistically significant difference was reported in favour of IPX203 for the emotional well-being score.

There were no differences in IPX203 *versus* IR CD-LD treatment in the NMSS total score, except for a statistically significant difference in perceptual problems/hallucinations score ($p=0.0094$, difference in LS means: 0.6 [95% CI: 0.1 , 1.0]).

To increase robustness of data, the applicant compared study IPX203-B16-02 results with those of advanced medical therapies for PD, namely Duodopa and Foslevodopa. Since a direct comparison was not possible due to different study design (IPX203-B16-02 was a randomised withdrawal while the others were prospective), the applicant focused on the improvements observed during IPX203 dose conversion period, which most closely corresponds to the DB treatment phase of the LCIG and Foslevodopa/Foscarbidopa Phase 3 trials. This allowed to compare the incremental benefit of the therapy on top of the optimised IR LD-CD.

There are several strategies to improve motor control. Of these, the use of dopamine agonists (DA) is very common in patients with motor fluctuations / dyskinesias, concomitantly being treated with LD. Available data supporting the concomitant use of IPX203 with DA, and whether the use of oral or transdermic formulations showed a different response pattern, was also sufficiently presented.

During IPX203 conversion period, patients already optimised on IR LD-CD experienced an improvement in “Good ON time” of 1.45 h and in OFF time of 1.46 h. In comparison, the Foslevodopa/Foscarbidopa pivotal trial of [Soileau et al \(2022\)](#) reported an improvement in “Good ON time” of 1.75 h and a reduction in “OFF time” of 1.79 h vs IR LD-CD, while the LCIG pivotal trial of [Olanow n. \(2014\)](#) demonstrated an increase in “Good On time” of 1.86 h and a reduction in “OFF time” of 1.91 h vs IR LD-CD. The IPX203 forced conversion period, however, was much shorter than the FU provided in Duodopa and Foslevodopa studies, making them probably more effective. Therefore, it can only be admitted that the observed improvement is in the same magnitude of effect as the non-oral alternatives.

A statistically significant result in “Good ON” time was achieved in IPX203 group compared with IR CD-LD group only in subjects <65 years ($p=0.0004$, difference in LS means: 1.35 h [95% CI: 0.62 , 2.08]). In subjects ≥ 65 years no statistically significant difference was noted between groups. The CHMP could agree that, although in subjects ≥ 65 years “Good ON time” was comparable between treatments and statistical significance was not reached, benefits of treatment in this population can be expected based on results of other endpoints (e.g., “OFF time” and PGI-C).

Statistically significant result in “Good ON” time was achieved in males treated with IPX203 compared with those treated with IR CD-LD but not in females. However, these differences should be perceived as resulting from the exploratory nature of the subgroup analyses, differences in LD exposure, and underlying sex-related heterogeneity in PD biology and clinical management. There was a difference in

average daily levodopa dose between males and females throughout study IPX203-B16-02: females received a lower mean daily dose of LD compared to males in both treatment arms during the DB period. Literature data also indicated several factors that may be responsible for sex differences in PD. Based on these aspects, no dose optimisation in females was considered justified.

Similarly, the primary endpoint was met in Caucasians but not in non-Caucasians. However, the non-Caucasian subgroup was very small (n=19), which largely limits interpretability of the comparison to Caucasians. Nevertheless, several efficacy parameters ("OFF time", PGI-C and motor function assessments), showed numerical trends favouring IPX203 in non-Caucasians.

The primary endpoint was not met in EU subjects. In North American subjects, "Good ON" time decreased less in IPX203 (LS mean: -0.39 h) when compared with IR CD-LD group (LS mean: -1.18 h). A statistically significant result in "Good ON" time was achieved in IPX203 group when compared with IR CD-LD group (p=0.0096). Looking at the identified differences between North American and EU subjects, the more pronounced benefit in US patients seemed related to the more widespread use of concomitant medications such as dopamine agonists (DAs) and monoamine oxidase inhibitor (MAOI), and to the fact that in the EU population, although with the disease for longer time and with higher H&Y score than those in US, but the duration of "OFF time", was lower. When comparing those with more severity, there was a similar magnitude of improvement, even favouring EU patients.

Body weight was also shown to affect the study results. A statistically significant result in "Good ON" time was achieved only in subjects with a **body weight of ≥ 75 kg** treated with IPX203 *versus* those treated with IR CD-LD. The applicant justified that most intrinsic patient's factors (identified as being possible discriminators between treatment responses) have been thoroughly discussed in the literature (gender, BMI, disease severity and age), and none justifies a reappraisal of the B/R or a recommendation for different posology. The CHMP could agree that, although in subjects <75 kg no statistically significant difference was shown in the LS mean changes in "Good ON time", numerical difference was observed. Moreover, no signs of worse tolerability or higher incidence of AEs in this group of patients was observed.

In subjects with a **PD duration of <8 years**, a statistically significant difference in "Good ON" time was achieved with IPX203 rather than IR CD-LD treatment (p=0.0207, difference in LS means: 0.77 h [95% CI: 0.12, 1.42]). In subjects with a **PD duration of ≥ 8 years**, although "Good ON time" changes were not statistically significant, a smaller increase in "OFF time" was observed with IPX203 (LS mean 0.11 h) vs IR CD-LD (1.07 h).

Similarly, a statistically significant difference was shown in subjects with a **PD onset at <65 years**. In subjects with PD onset **≥ 65 years**, the LS mean change in "Good ON" time was -0.74 h with IPX203 vs -0.27 h with IR LD-CD (treatment difference -0.47 h [95% CI: -1.43, 0.49]; p=0.3351). Non-significant patterns were also seen for "OFF time" (treatment difference 0.13 h [95% CI: -0.72, 0.98]; p=0.7646), PGI-C (% much/very much improved: 19.4% vs 25.8%; difference -6.4% [95% CI: -20.8, 8.0]; p=0.8984), and MDS-UPDRS Part III/Part II+III scores. However, the results should be interpreted cautiously given the exploratory nature of the subgroup analyses, smaller sample size, and wide CIs indicating no clear signals. Of note, as discussed in section 5.4.6 of this AR, safety profiles were comparable across subgroups. Hence, in the applicant's view, no evidence-based reason could be identified to exclude subjects with PD onset ≥ 65 years from IPX203 treatment. A statistically significant difference in "Good ON" time was shown in IPX203 subjects with a **"OFF" time of ≥ 6 hours** *versus* IR CD-LD subjects) and no statistically significant difference was reported in subjects with a "OFF time" of ≥ 6 hours at study entry.

Importantly, there was no indication of deterioration with IPX203; "Good ON time," "OFF time", and PGI-C remained comparable between treatments. In addition to the exploratory nature of the subgroup analyses, one further known limitation, especially relevant for this subgroup of patients, was

that the study did not allow IPX203 administration more frequently than every 6 hours. Some participants might have experienced a greater increase in "Good ON" time and reduction in "OFF time" with more frequent dose than every 6 hours or if dosing frequency could have been titrated to clinical response. When analysing "Good ON" time per LD dose at the end of the treatment period, IPX203 consistently showed a statistically significant benefit over IR LD-CD in both groups: those with less than 6 h and those with 6 h or more of "OFF time".

In conclusion, while these subgroup analyses suggest attenuation of the primary "Good ON" effect in certain highly overlapping subgroups (older age, lower weight, longer disease duration, later onset, lower baseline "OFF"), these analyses were exploratory, underpowered, and affected by strong correlations between covariates. Within these subgroups, IPX203 generally maintained favourable effects on "Good ON time", "OFF time", and PGI-C and did not exhibit new safety concerns, even when formal statistical superiority versus IR CD-LD was not demonstrated.

Overall, the observed magnitude of effect of IPX203 was small (0.53 hour) as compared to IR-LD, but IPX203 was administered three times a day while IR-LD was to be taken five times a day. The fact that the 3 oral formulations of IPX203 performed better than the 5 of IR-LD suggested that the time of intake is less critical for IPX203 than with IR-LD, representing an inherent advantage in the target patient's population.

IPX203-B16-03 was a Phase 3, 9-month, OLE study evaluating long-term safety and clinical utility of IPX203 in patients who had successfully completed the pivotal study IPX203-B16-02. It consisted of a baseline visit (no 1) followed by 3 others (no 2 to 4) approximately every 3-months.

A total of 419 subjects (of which 71.7% had a baseline Hoehn and Yahr Stage 2) were enrolled: 206 from previous IPX203 and 213 from previous IR CD-LD group. Of those enrolled, 352 (84%) completed the study: 179 (86.9%) from previous IPX203 and 173 (81.2%) from previous IR CD-LD group.

Sixty-seven (16.0%) subjects withdrew: 27 (13.1%) from previous IPX203 and 40 (18.8%) from previous IR CD-LD group.

Overall, the **mean MDS-UPDRS total scores** were stable throughout the treatment period. No notable difference was observed in the mean MDS-UPDRS total score from baseline to EOS (Visit 4/Month 9) (mean change from baseline to Visit 4; total: 2.3, previous IPX203 group: 2.5, and previous IR CD-LD: 2.0). The total scores were also comparable between previous IPX203 and IR CD-LD subjects over the treatment period.

The **mean MDS-UPDRS Part I, Part II, Part III and Part IV scores** were also stable and comparable between groups. Moreover, no differences in PGI-S, CGI-S, PD Questionnaire-39, Parkinson Anxiety Scale, PD Sleep Scale-2 and Early Morning Symptoms Questionnaire scores were observed from baseline to EOS (Visit 4/ET), and between previous IPX203 and IR CD-LD subjects over the treatment period.

The indication was revised accordingly.

5.4.10.2. Conclusions on the clinical efficacy

Overall, the clinical development programme is considered acceptable.

It can be agreed that efficacy of IPX203 has been demonstrated, in terms of a benefit over IR LD-CD, expressed on longer duration of "Good ON time", without significant worsening of sleep time or time with troublesome dyskinesias. The smaller number of intakes per day may also be an inherent advantage in the target patient's population.

5.5. Clinical safety

Please refer to the Table(s) of studies in section 5.1.2 of this AR.

For the purpose of this document, the following definitions apply:

- 'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment.
- 'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.
- 'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.5.1. Safety data collection

The safety of IPX203 has been evaluated in the clinical development program comprising seven studies: three Phase 1 pharmacokinetics (PK) studies in healthy volunteers (Studies **IPX203-B16-04**, **IPX203-B16-05** and **IPX203-B16-06**), a Phase 2 single-dose PK, pharmacodynamics/efficacy and safety study in advanced PD patients (Study **IPX203-B14-02**), a Phase 2 study to evaluate the PK, PD, efficacy, and safety of single and multiple doses of IPX203 in advanced PD patients (Study **IPX203-B16-01**), a Phase 3, randomised, controlled trial to evaluate safety and efficacy in PD patients who have motor fluctuations (Study **IPX203-B16-02**) and its open-label, 9-month extension (Study **IPX203-B16-03**).

Additionally, two Phase 1 studies have been conducted to assess the safety and tolerability of carbidopa, with focus on safety of its high doses. However, as only CD was used, these were not added to the pooled safety analyses.

Furthermore, in the course of this initial MAA procedure, the applicant supplied new interim data from a Phase 4 RWE study conducted in the US (ELEVATE-PD study interim analysis with 111 patients), evaluating the performance of the IR-to-IPX203 conversion algorithm in routine clinical practice.

The seven clinical studies were pooled into the following analyses pools. The grouping of studies was based on the subject population characteristics and study duration:

- **P1HLT**: Phase 1 studies in healthy volunteers, 1 day dosing (Study IPX203-B16-04, Study IPX203-B16-05, Study IPX203-B16-06)
- **P2APD**: Phase 2 studies in advanced PD Patients, 1 to 14 days of dosing
- **P3PDMF**: Phase 3 studies in PD patients with motor fluctuations, long-term dosing (Study IPX203-B16-02, Study IPX203-B16-03)
- **P123ALL**: All the studies in the pools defined above

An overview of the safety assessments for each study pool is presented in the Table below.

Table 37: Overview of the safety assessment

Type of Summary	Phase 1 Studies in Healthy Volunteers	Phase 2 Studies in Advanced PD Patients	Phase 3 Studies in PD Patients with Motor Fluctuations	All Studies Pool
Enumeration of subjects	X	X	X	X
Listing of unique subjects				X
Subject disposition	X	X	X	
Demographics and baseline characteristics	X	X	X	
Medical history ^a		X	X	
Prior medications ^b		X	X	
Concomitant medications ^c		X	X	
Study drug exposure	X	X	X	X
Overview of AEs	X	X ^d	X ^d	
AEs by SOC/PT	X	X ^d	X ^d	
AEs by TDD at onset of event			X	
AEs by daily dosing frequency at onset of event			X	
AEs by average TDD			X	
AEs by duration of continuous exposure at onset			X	
AEs by total duration of exposure			X	
AEs by maximum severity	X	X	X	
AEs by relationship to study drug	X	X	X	
AEs leading to study drug withdrawal	X	X	X	
AEs leading to study discontinuation			X	
Listing of AEs leading to study drug withdrawal				X
SAEs	X	X	X	
Listing of SAEs				X
AEs leading to death	X	X	X	
Listing of AEs leading to death				X
AEs by occurrence rate in IPX203-treated subjects	X	X	X	
Exposure-adjusted incidence of AEs			X	
Clinical laboratory data (actual values and change from baseline)	X	X	X	
Clinical laboratory data (shift from baseline)	X	X	X	

Type of Summary	Phase 1 Studies in Healthy Volunteers	Phase 2 Studies in Advanced PD Patients	Phase 3 Studies in PD Patients with Motor Fluctuations	All Studies Pool
Clinical laboratory data (markedly abnormal values)	X	X	X	
Clinical laboratory data (Hy's law)	X	X	X	
ECG (actual values and change from baseline)		X	X	
ECG (categorical summary)		X	X	
ECG (overall interpretation)	X	X	X	
ECG (markedly abnormal values)	X	X	X	
Vital signs (actual values and change from baseline)	X	X	X	
Vital signs (categorical summary)	X	X	X	
Vital signs (orthostatic hypotension)		X	X	
C-SSRS		X	X	
GCSI			X	

Source: IPX203 ISS Statistical Analysis Plan, Table 5

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale;

ECG = electrocardiogram; GCSI = Gastroparesis Cardinal Symptom Index; PD = Parkinson's disease;

PT = preferred term; SAE = serious adverse event; SOC = system organ class; TDD = total daily dose

- While in all Phase 1 studies collection of medical history was planned, in Studies IPX203-B16-04 and IPX203-B16-05 none was reported and only a few history events were reported in Study IPX203-B16-06.
- In Phase 1 studies, medications were to be recorded starting from the date of informed consent, but none were reported.
- In Phase 1 studies, no concomitant medications were reported.
- Summaries were also presented by subgroups

5.5.2. Patient exposure

The following three tables show the number of participants in each treatment group across all studies. A total of 731 subjects were exposed to IPX203: 94 in Phase 1 studies in healthy volunteers, 48 in Phase 2 studies in advanced PD patients, and 589 in Phase 3 studies in PD patients with motor fluctuations.

The Phase 1 studies in healthy volunteers and the Phase 2 Study IPX203-B1402 used a single dose of IPX203. Conversely, Phase 2 Study IPX203-B16-01 included both single and multiple doses, while the Phase 3 studies IPX203-B16-02 and IPX203-B16-03 utilised individualised, multiple-dose regimens over time.

Table 38: Subjects by study and treatment: Phase 1 studies in healthy volunteers (Safety Population)

Phase 1 Studies in Healthy Volunteers	All IPX203 n	IR LD-CD n	CR LD-CD n	All Comparators n	Total n
IPX203-B16-04	27	0	0	0	27
IPX203-B16-05	27	25	27	27	27
IPX203-B16-06	40	0	0	0	40
Total	94	25	27	27	94

Source: Study IPX203-B16-04 CSR, Table 15; Study IPX203-B16-05 CSR, Table 19; Study IPX203-B16-06, Table 24
Abbreviation: LD-CD = levodopa-carbidopa; CR = controlled-release; IR = immediate-release
Note: Subjects were counted once under "Total" column and "Total" row.

Table 39: Subjects by study and treatment: Phase 2 studies in advanced PD patients (Safety Population)

Phase 2 Studies in Advanced PD Patients	All IPX203 n	IR LD-CD n	Rytary n	All Comparators n	Total n
IPX203-B14-02	26	25	25	25	26
IPX203-B16-01	28	27	0	27	28
Total	48	46	25	46	48

Source: Study IPX203-B14-02 CSR, Table 14.1.1-2; Study IPX203-B16-01, Table 14.1.1-1
Abbreviation: IR LD-CD = immediate-release levodopa-carbidopa; PD = Parkinson's disease
Note: Subjects received multiple treatments in each study and were counted once in the "Total" column.
Six subjects enrolled in study IPX203-B16-01 were previously enrolled in Study IPX203-B14-02, and were counted once in the "Total" row

Table 40: Subjects by study and treatment: Phase 3 studies in PD patients with motor fluctuations (Safety Population)

Phase 3 Studies in PD Patients with Motor Fluctuations	IPX203 Open-Label n	IPX203 Double-Blind n	All IPX203 n	IR LD-CD Open-Label n	IR LD-CD Double-Blind n	All IR LD-CD n	Total n
IPX203-B16-02	589	256	589	630	250	630	630
IPX203-B16-03	419	0	419	0	0	0	419
Total	589	256	589	630	250	630	630

Table 41: Patient exposure (cut off)

Study	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
Blinded studies (placebo-controlled)	NA			
Blinded studies (active -controlled)	630	589	Described below	Described below
Open label studies	54	54	-	-
Compassionate use	Not applicable			

* Received at least 1 dose of active treatment

** In general, this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

A summary of the study drug exposure across IPX203 studies (three analysis pools) for the Safety Population is presented in the Table below.

Table 42: Summary of safety drug exposure across IPX203 studies (Safety Population)

Characteristic, Statistic Studies	All IPX203	Comparators ^a
Average Total Daily Dose of Levodopa (mg), Mean (SD)		
Phase 1 Studies in healthy volunteers	275.63 (53.523), n=94	100.00 (0.000), n=27
Phase 2 Studies in advanced PD patients	1074.05 (571.322), n=48	548.73 (236.715), n=46
Phase 3 Studies in PD patients with motor fluctuations	1520.97 (587.777), n=585	857.67 (363.221), n=626
Treatment Duration (days), Mean (SD)		
Phase 1 Studies in healthy volunteers	3.3 (1.67), n=94	1.9 (0.27), n=27
Phase 2 Studies in advanced PD patients	9.2 (7.19), n=48	9.9 (6.74), n=46
Phase 3 Studies in PD patients with motor fluctuations	242.9 (146.80), n=584	56.8 (44.48), n=626
Average Daily Dosing Frequency (times/day), Mean (SD)		
Phase 1 Studies in healthy volunteers	-	-
Phase 2 Studies in advanced PD patients	2.14 (0.993), n=48	3.04 (1.923), n=46
Phase 3 Studies in PD patients with motor fluctuations	3.08 (0.391), n=588	5.02 (1.184), n=626
Person-Years of Exposure^b		
Phase 1 Studies in healthy volunteers	0.84	0.14
Phase 2 Studies in advanced PD patients	1.21	1.25
Phase 3 Studies in PD patients with motor fluctuations	388.34	97.37
Source: ISS Table 4.1.1.1; Table 4.1.1.2; Table 4.1.1.3		
Abbreviations: LD-CD = levodopa-carbidopa; CR = controlled-release; IR = immediate-release;		
PD = Parkinson's disease; SD = standard deviation		
Note: Percentages were based on the number of subjects with non-missing value. Subjects were counted under each treatment they received.		
Comparators for the Phase 1 Studies were all subjects on IR LD-CD or CR LD-CD treatment from Study IPX203-B16-05.		
Comparators for the Phase 2 Studies were all subjects on IR LD-CD or Rytary treatment from Study IPX203-B14-02 and all subjects on IR LD-CD treatment from Study IPX203-B16-01.		
^a All IR LD-CD for the Phase 3 Studies		
^b Person-Years of Exposure = (total treatment duration days)/365.25		

For the Phase 3 studies pool in PD patients with motor fluctuations, the distribution of the average total daily dose (TDD) and treatment duration of IPX203 is presented in the Table below. A total of 97 subjects were exposed for ≥ 12 months with an average TDD of < 1600 mg LD, 82 subjects were exposed for ≥ 12 months with an average TDD of ≥ 1600 mg LD, and 43 subjects were exposed for ≥ 12 months with an average TDD of ≥ 2000 mg LD.

Table 43: Distribution of average TDD and treatment duration of IPX203 - Phase 3 studies in PD patients with motor fluctuations (Safety Population) based on levodopa dose

	IPX203 Treatment Duration ^a				
	<3 months	3 - <6 months	6 - <9 months	9 - <12 months	≥12 months
Number of subjects	155	44	22	184	179
IPX203 mean average total daily dose (mg)	1598.98	1424.29	1621.61	1482.70	1503.27
IPX203 average total daily dose category, n (%)					
<400	1 (0.6)	0	0	0	0
400 - <800	11 (7.1)	6 (13.6)	4 (18.2)	19 (10.3)	22 (12.3)
800 - <1200	23 (14.8)	14 (31.8)	2 (9.1)	45 (24.5)	39 (21.8)
1200 - <1600	33 (21.3)	6 (13.6)	1 (4.5)	45 (24.5)	36 (20.1)
1600 - <2000	42 (27.1)	7 (15.9)	9 (40.9)	35 (19.0)	39 (21.8)
2000 - <2400	37 (23.9)	9 (20.5)	4 (18.2)	30 (16.3)	32 (17.9)
2400 - <2800	7 (4.5)	2 (4.5)	2 (9.1)	8 (4.3)	9 (5.0)
2800 - <3200	1 (0.6)	0	0	1 (0.5)	0
≥3200	0	0	0	1 (0.5)	2 (1.1)

Source: ISS Table 4.1.2.1
Abbreviation: PD = Parkinson's disease
Note: Percentages were based on the number of subjects with the given IPX203 treatment duration category.
^a For this summary month was defined as 30 days.

Overall, the demographic and baseline characteristics were comparable among IPX203 and IR CD-LD groups. For the IPX203 group, the mean (SD) age of subjects was 66.3 (8.90) years, and majority were males (372 [63.2%] subjects). Their mean (SD) BMI was 27.31 (4.948) kg/m². The majority of subjects (69.4%) had Hoehn and Yahr Stage 2, and a mean (SD) screening Montreal cognitive assessment (MoCA) score of 27.2 (1.80). The mean (SD) age of onset of PD was 58.0 (9.29) years, and the mean (SD) duration of PD was 8.4 (4.82) years.

5.5.3. Adverse events

An overall summary of AEs is presented in the Tables below for the pooled IPX203 studies and the open-label and double-blind periods in Phase 3 studies, respectively.

Table 44: Overall summary of adverse events across the IPX203 studies (Safety Population)

Category	Phase 1 Studies in Healthy Volunteers		Phase 2 Studies in Advanced PD Patients		Phase 3 Studies in PD Patients with Motor Fluctuations	
	All IPX203 N=94	All Comparators N=27	IPX203 N=48	All Comparators N=46	All IPX203 N=589	All IR LD-CD N=630
	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m
Subjects with any TEAE	3 (3.2) 3	0	14 (29.2) 32	8 (17.4) 15	397 (67.4) 1355	176 (27.9) 328
Subjects with treatment-related TEAE	3 (3.2) 3	0	10 (20.8) 25	4 (8.7) 8	205 (34.8) 471	47 (7.5) 66
Subjects with treatment-related serious TEAE	0	0	0	0	9 (1.5) 11	0
Subjects with serious TEAE	0	0	1 (2.1) 1	0	60 (10.2) 102	10 (1.6) 17
Subjects with TEAE leading to study drug discontinuation	1 (1.1) 1	0	1 (2.1) 1	0	80 (13.6) 139	10 (1.6) 15
Subjects with TEAE leading to death	0	0	0	0	6 (1.0) 9	0
Subjects with TEAEs by maximum severity						
Mild	3 (3.2) 3	0	5 (10.4) 15	6 (13.0) 13	163 (27.7) 837	109 (17.3) 230
Moderate	0	0	9 (18.8) 17	2 (4.3) 2	174 (29.5) 419	54 (8.6) 82
Severe	0	0	0	0	60 (10.2) 99	13 (2.1) 16

Source: ISS Table 5.1.1.1, Table 5.1.1.2, Table 5.1.1.3
Abbreviations: AE = adverse event; LD-CD = levodopa-carbidopa; CR = controlled-release; eCRF = electronic case report form; IR = immediate-release;
PD = Parkinson's disease; TEAE = treatment-emergent adverse event
Note: n = number of subjects with events, m = number of events.
Percentages were based on the total number of subjects in the treatment group and population. An AE was defined as treatment-related if its relationship to the study drug was recorded as possibly related or related on the eCRF. Adverse events were counted under the last treatment prior to the onset of the event. Comparators for the Phase 1 Studies were all subjects on IR LD-CD or CR LD-CD treatment from Study IPX203-B16-05. Comparators for the Phase 2 Studies were all subjects on IR LD-CD or Rytary treatment from Study IPX203-B14-02 and all subjects on IR LD-CD treatment from Study IPX203-B16-01.

In the Phase 1 studies pool in healthy volunteers, three (3.2%) IPX203 subjects experienced three treatment-emergent adverse events (TEAEs) that were mild and treatment-related. One (1.1%) IPX203 subject experienced TEAE that led to discontinuation of the study drug. No serious TEAEs or deaths were reported.

In the Phase 2 studies pool in advanced PD patients, 14 (29.2%) IPX203 subjects experienced 32 TEAEs (15 mild, 17 moderate). Of these, 10 (20.8%) IPX203 subjects experienced 25 TEAEs that were treatment related. One (2.1%) IPX203 subject each experienced a serious TEAE and a TEAE that led to discontinuation of the study drug. No deaths were reported.

In the Phase 3 studies pool in PD patients with motor fluctuations, 397 (67.4%) of All-IPX203 subjects experienced 1355 TEAEs (837 mild, 419 moderate, 99 severe). Of these, 205 (34.8%) All-IPX203 subjects experienced 471 TEAEs that were treatment-related. Sixty (10.2%) All-IPX203 subjects experienced 102 serious TEAEs, of which 11 treatment-related. Eighty (13.6%) All-IPX203 subjects experienced 139 TEAEs that led to discontinuation of the study drug. Six (1.0%) subjects died during Phase 3 studies.

Table 45: Overall summary of adverse events in Phase 3 studies in PD patients with motor fluctuations (safety Population)

	IPX203 Open-label N=589 n (%) m	IPX203 Double-blind N=256 n (%) m	IR LD-CD Open-label N=630 n (%) m	IR LD-CD Double-blind N=250 n (%) m
Subjects with any TEAE	366 (62.1) 1110	107 (41.8) 245	118 (18.7) 188	77 (30.8) 140
Subjects with treatment-related TEAE	184 (31.2) 394	41 (16.0) 77	31 (4.9) 44	16 (6.4) 22
Subjects with treatment-related serious TEAE	7 (1.2) 9	2 (0.8) 2	0	0
Subjects with serious TEAE	52 (8.8) 93	8 (3.1) 9	7 (1.1) 12	4 (1.6) 5
Subjects with TEAE leading to study drug discontinuation	67 (11.4) 116	14 (5.5) 23	6 (1.0) 10	4 (1.6) 5
Subjects with TEAE leading to death	6 (1.0) 9	0	0	0
Subjects with TEAEs by maximum severity				
Mild	164 (27.8) 686	53 (20.7) 151	78 (12.4) 132	47 (18.8) 98
Moderate	147 (25.0) 334	46 (18.0) 85	34 (5.4) 48	23 (9.2) 34
Severe	55 (9.3) 90	8 (3.1) 9	6 (1.0) 8	7 (2.8) 8

Source: ISS Table 5.1.1.3
Abbreviations: IR LD-CD = immediate-release levodopa-carbidopa; PD = Parkinson's disease; TEAE = treatment-emergent adverse event
Note: n = number of subjects with events, m = number of events.

The TEAEs reported by System Organ Class (SOC) and Preferred Term (PT) for at least 2% of subjects in any treatment group are presented in the following Tables, for the pooled IPX203 studies and the open-label and double-blind periods in Phase 3 studies, respectively.

In the Phase 1 studies pool, 3 (3.2%) IPX203 subjects experienced three TEAEs, mild and treatment related. These TEAEs included vomiting, blood cholesterol increased (, and dizziness (1 [1.1%] subject each).

In the Phase 2 studies pool, 14 (29.2%) IPX203 subjects experienced 32 TEAEs. The most commonly reported TEAEs (≥5% subjects) in these subjects were dyskinesia (6 [12.5%]), dizziness and hypertension (3 [6.3%] subjects each).

In the Phase 3 studies pool, 397 (67.4%) of All-IPX203 subjects experienced 1355 TEAEs. The most commonly reported TEAEs (≥5% subjects) in these subjects were dyskinesia (63 [10.7%] subjects), nausea (44 [7.5%]), fall (35 [5.9%]), and urinary tract infection (31 [5.3%]).

Table 46: Common treatment-emerging adverse events (TEAEs) reported for at least 2% of subjects in either treatment group by SOC and PT across the IPX203 studies (Safety Population)

System Organ Class Preferred Term	Phase 1 Studies in Healthy Volunteers ^a		Phase 2 Studies in Advanced PD Patients		Phase 3 Studies in PD Patients with Motor Fluctuations	
	All IPX203 N=94	All Comparators N=27	IPX203 N=48	All Comparators N=46	All IPX203 N=589	All IR LD-CD N=630
	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m
Number of subjects with no events	91 (96.8)	27 (100.0)	34 (70.8)	38 (82.6)	192 (32.6)	454 (72.1)
Number of subjects with any event	3 (3.2) 3	0	14 (29.2) 32	8 (17.4) 15	397 (67.4) 1355	176 (27.9) 328
Gastrointestinal disorders	1 (1.1) 1	0	3 (6.3) 4	3 (6.5) 4	122 (20.7) 193	35 (5.6) 38
Nausea	0	0	2 (4.2) 2	2 (4.3) 2	44 (7.5) 51	9 (1.4) 9
Dry mouth	0	0	1 (2.1) 1	0	28 (4.8) 31	4 (0.6) 4
Constipation	0	0	0	0	25 (4.2) 27	8 (1.3) 8
Vomiting	1 (1.1) 1	0	1 (2.1) 1	0	20 (3.4) 23	3 (0.5) 3
Diarrhoea	0	0	0	1 (2.2) 1	8 (1.4) 9	4 (0.6) 4
Abdominal pain	0	0	0	1 (2.2) 1	4 (0.7) 4	0
Infections and infestations	0	0	2 (4.2) 2	2 (4.3) 2	91 (15.4) 118	32 (5.1) 35
Urinary tract infection	0	0	1 (2.1) 1	0	31 (5.3) 35	8 (1.3) 9
Bronchitis	0	0	1 (2.1) 1	0	2 (0.3) 2	2 (0.3) 2
Tinea pedis	0	0	0	1 (2.2) 1	0	0
Upper respiratory tract infection	0	0	0	1 (2.2) 1	4 (0.7) 4	5 (0.8) 5
Injury, poisoning and procedural complications	0	0	0	0	63 (10.7) 105	22 (3.5) 37
Fall	0	0	0	0	35 (5.9) 51	15 (2.4) 18
Investigations	1 (1.1) 1	0	0	0	38 (6.5) 53	6 (1.0) 8
Blood cholesterol increased	1 (1.1) 1	0	0	0	-	-

Table 53 continued

System Organ Class Preferred Term	Phase 1 Studies in Healthy Volunteers ^a		Phase 2 Studies in Advanced PD Patients		Phase 3 Studies in PD Patients with Motor Fluctuations	
	All IPX203 N=94	All Comparators N=27	IPX203 N=48	All Comparators N=46	All IPX203 N=589	All IR LD-CD N=630
	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m
Musculoskeletal and connective tissue disorders	0	0	1 (2.1) 1	0	72 (12.2) 93	25 (4.0) 28
Back pain	0	0	0	0	22 (3.7) 24	10 (1.6) 10
Musculoskeletal stiffness	0	0	1 (2.1) 1	0	1 (0.2) 1	0
Nervous system disorders	1 (1.1) 1	0	10 (20.8) 15	3 (6.5) 6	184 (31.2) 298	54 (8.6) 67
Dyskinesia	0	0	6 (12.5) 6	1 (2.2) 2	63 (10.7) 72	12 (1.9) 12
Dizziness	1 (1.1) 1	0	3 (6.3) 3	3 (6.5) 4	29 (4.9) 30	5 (0.8) 7
Headache	0	0	0	0	15 (2.5) 19	8 (1.3) 8
Somnolence	0	0	0	0	12 (2.0) 12	3 (0.5) 3
Balance disorder	0	0	1 (2.1) 2	0	8 (1.4) 8	1 (0.2) 1
Dystonia	0	0	1 (2.1) 1	0	7 (1.2) 9	2 (0.3) 2
Tremor	0	0	1 (2.1) 1	0	6 (1.0) 8	4 (0.6) 4
Hypersomnia	0	0	1 (2.1) 1	0	2 (0.3) 2	2 (0.3) 2
Occipital neuralgia	0	0	1 (2.1) 1	0	0	0
Psychiatric disorders	0	0	1 (2.1) 2	0	122 (20.7) 183	23 (3.7) 27
Confusional state	0	0	1 (2.1) 1	0	10 (1.7) 11	1 (0.2) 1
Insomnia	0	0	1 (2.1) 1	0	19 (3.2) 22	7 (1.1) 7
Anxiety	0	0	0	0	19 (3.2) 21	1 (0.2) 1
Depression	0	0	0	0	19 (3.2) 20	2 (0.3) 2
Hallucination	0	0	0	0	15 (2.5) 16	1 (0.2) 1
Renal and urinary disorders	0	0	1 (2.1) 1	0	29 (4.9) 40	9 (1.4) 10
Nephrolithiasis	0	0	1 (2.1) 1	0	8 (1.4) 11	0
Vascular disorders	0	0	6 (12.5) 7	2 (4.3) 3	44 (7.5) 51	14 (2.2) 15

System Organ Class Preferred Term	Phase 1 Studies in Healthy Volunteers ^a		Phase 2 Studies in Advanced PD Patients		Phase 3 Studies in PD Patients with Motor Fluctuations	
	All IPX203 N=94	All Comparators N=27	IPX203 N=48	All Comparators N=46	All IPX203 N=589	All IR LD-CD N=630
	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m
Orthostatic hypotension	0	0	1 (2.1) 1	0	16 (2.7) 17	5 (0.8) 5
Orthostatic hypertension	0	0	1 (2.1) 2	0	1 (0.2) 1	0
Hypertension	0	0	3 (6.3) 3	2 (4.3) 3	12 (2.0) 13	9 (1.4) 9
Hypotension	0	0	1 (2.1) 1	0	7 (1.2) 8	0

Source: ISS Table 5.1.2.1, Table 5.1.2.2, Table 5.1.2.3
Abbreviations: LD-CD = levodopa-carbidopa; CR = controlled-release; IR = immediate-release; MedDRA = Medical Dictionary for Regulatory Activities; PD= Parkinson's disease
Note: n = number of subjects with events, m = number of events.
Percentages were based on the total number of subjects in the treatment group and population. All reported terms coded with MedDRA Version 22.0.
Subjects were counted only once within each system organ class and preferred term. Adverse events were counted under the last treatment prior to the onset of the event.
Comparators for the Phase 1 Studies were all subjects on IR LD-CD or CR LD-CD treatment from Study IPX203-B16-05.
Comparators for the Phase 2 Studies were all subjects on IR LD-CD or Ryтары treatment from Study IPX203-B14-02 and all subjects on IR LD-CD treatment from Study IPX203-B16-01.
^a Treatment-Emergent Adverse Events (TEAEs) reported in at least 1% of subjects.

Table 47: Summary of TEAEs reported for at least 2% of subjects in either treatment group by SOC and PT in Phase 3 studies (Safety Population)

System Organ Class Preferred Term	IPX203 Open-label N=589 n (%) m	IPX203 Double-blind N=256 n (%) m	IR LD-CD Open-label N=630 n (%) m	IR LD-CD Double-blind N=250 n (%) m
Number of subjects with no events	223 (37.9)	149 (58.2)	512 (81.3)	173 (69.2)
Number of subjects with any event	366 (62.1) 1110	107 (41.8) 245	118 (18.7) 188	77 (30.8) 140
Gastrointestinal disorders	109 (18.5) 163	22 (8.6) 30	28 (4.4) 30	8 (3.2) 8
Nausea	36 (6.1) 39	11 (4.3) 12	7 (1.1) 7	2 (0.8) 2
Dry mouth	26 (4.4) 28	3 (1.2) 3	2 (0.3) 2	2 (0.8) 2
Constipation	22 (3.7) 23	4 (1.6) 4	7 (1.1) 7	1 (0.4) 1
Vomiting	18 (3.1) 20	3 (1.2) 3	3 (0.5) 3	0
General disorders and administration site conditions	38 (6.5) 42	11 (4.3) 16	9 (1.4) 9	12 (4.8) 13
Fatigue	6 (1.0) 6	5 (2.0) 5	1 (0.2) 1	3 (1.2) 3
Infections and infestations	79 (13.4) 96	18 (7.0) 22	15 (2.4) 15	17 (6.8) 20
Urinary tract infection	28 (4.8) 31	4 (1.6) 4	1 (0.2) 1	7 (2.8) 8
Injury, poisoning and procedural complications	54 (9.2) 90	12 (4.7) 15	11 (1.7) 20	11 (4.4) 17
Fall	32 (5.4) 45	5 (2.0) 6	6 (1.0) 7	9 (3.6) 11
Investigations	1 (1.1) 1	0	0	0
Blood cholesterol increased	1 (1.1) 1	0	0	0
Musculoskeletal and connective tissue disorders	57 (9.7) 73	16 (6.3) 20	13 (2.1) 14	12 (4.8) 14
Back pain	21 (3.6) 22	2 (0.8) 2	3 (0.5) 3	7 (2.8) 7
Nervous system disorders	162 (27.5) 245	38 (14.8) 53	37 (5.9) 43	17 (6.8) 24
Dyskinesia	58 (9.8) 67	5 (2.0) 5	11 (1.7) 11	1 (0.4) 1
Dizziness	23 (3.9) 24	6 (2.3) 6	3 (0.5) 3	2 (0.8) 4
Headache	13 (2.2) 15	3 (1.2) 4	8 (1.3) 8	0

System Organ Class Preferred Term	IPX203 Open-label N=589 n (%) m	IPX203 Double-blind N=256 n (%) m	IR LD-CD Open-label N=630 n (%) m	IR LD-CD Double-blind N=250 n (%) m
Somnolence	8 (1.4) 8	4 (1.6) 4	1 (0.2) 1	2 (0.8) 2
Psychiatric disorders	106 (18.0) 151	26 (10.2) 32	14 (2.2) 16	9 (3.6) 11
Anxiety	13 (2.2) 14	7 (2.7) 7	1 (0.2) 1	0
Depression	14 (2.4) 15	5 (2.0) 5	0	2 (0.8) 2
Insomnia	17 (2.9) 20	2 (0.8) 2	6 (1.0) 6	1 (0.4) 1
Hallucination	13 (2.2) 14	2 (0.8) 2	1 (0.2) 1	0
Vascular disorders	38 (6.5) 42	7 (2.7) 9	13 (2.1) 13	2 (0.8) 2
Orthostatic hypotension	14 (2.4) 15	2 (0.8) 2	5 (0.8) 5	0
Hypertension	9 (1.5) 10	3 (1.2) 3	7 (1.1) 7	2 (0.8) 2

Source: ISS Table 5.1.2.3
Abbreviations: IR LD-CD = immediate-release levodopa-carbidopa
Note: n = number of subjects with events, m = number of events.

All the three TEAEs reported in Phase 1 studies pool were mild in severity. No severe TEAEs were reported in Phase 2 studies pool, mild TEAEs were reported in five (10.4%) IPX203 subjects, and moderate TEAEs were reported in nine (18.8%) IPX203 subjects. In the Phase 3 studies pool, in All-IPX203 subjects, most of them experienced TEAEs that were either mild (163 [27.7%]) or moderate (174 [29.5%]) in severity; 60 (10.2%) subjects experienced severe TEAEs. The severe TEAEs reported by at least two IPX203 subjects were dyskinesia and nausea (4 [0.7%] subjects each), dry mouth (3 [0.5%]), and vomiting, volvulus, sepsis, fall, dizziness, syncope, sciatica, tremor, seizure, anxiety, depression, insomnia, nephrolithiasis, and hypertensive crisis (2 [0.3%] subjects each).

Study IPX203-B16-02

An overall summary of AEs is presented for the Safety Analysis Set (SAS) of the Phase 3 trial IPX203-B16-02 in the Table below.

Table 48: Overall summary of AEs – Safety analysis set of the Phase 3 trial IPX203-B16-02

Category	Double-Blind Period													
	Dose Adjustment Period		IPX203 Conversion Period											
	IR CD-LD (N=630)	n (%)	IPX203 (N=589)	n (%)	IPX203 (N=256)	n (%)	IR CD-LD (N=250)	n (%)	IPX203 Total (N=589)	n (%)	IR CD-LD Total (N=630)	n (%)	Total (N=630)	n (%)
Subjects with any TEAE	118	(18.7%)	229	(38.9%)	108	(42.2%)	79	(31.6%)	289	(49.1%)	178	(28.3%)	365	(57.9%)
Subjects with treatment-related TEAE	31	(4.9%)	140	(23.8%)	42	(16.4%)	17	(6.8%)	165	(28.0%)	47	(7.5%)	188	(29.8%)
Subjects with serious TEAE	7	(1.1%)	12	(2.0%)	8	(3.1%)	4	(1.6%)	20	(3.4%)	10	(1.6%)	30	(4.8%)
Subjects with TEAE leading to study drug discontinuation	6	(1.0%)	42	(7.1%)	14	(5.5%)	3	(1.2%)	55	(9.3%)	9	(1.4%)	62	(9.8%)
Subjects with TEAE leading to death	0		0		0		0		0		0		0	

Of the 630 enrolled subjects, 365 (57.9%) experienced TEAEs: 289 (49.1%) who received IPX203 in total (i.e., IPX203 dose conversion period and IPX203 double-blind period combined) and 178 (28.3%) who received IR CD-LD in total (i.e., IR CD-LD dose adjustment period and IR CD-LD double-blind period combined). Thirty (4.8%) subjects experienced SAEs and 62 (9.8%) discontinued the study drug due to TEAEs. There were no deaths during this study.

Study IPX203-B16-03

An overall summary of the AEs for the SAS is presented SAS in the Table below, and by subject in the Listing thereafter.

Table 49: Overall summary of AEs (SAS)

Category	Previous IPX203 N=206 n (%)	Previous IR CD-LD N=213 n (%)	Total N=419 n (%)
Number of subjects who had			
Any TEAE	106 (51.5)	115 (54.0)	221 (52.7)
Treatment-related TEAE	24 (11.7)	42 (19.7)	66 (15.8)
Serious TEAE	24 (11.7)	18 (8.5)	42 (10.0)
TEAE leading to study drug discontinuation	7 (3.4)	18 (8.5)	25 (6.0)
TEAE leading to death	2 (1.0)	4 (1.9)	6 (1.4)

Source: [Table 14.3.1.1](#)

Abbreviations: AE = adverse event; eCRF = electronic case report form;
IR CD-LD = immediate-release carbidopa-levodopa; TEAE = treatment-emergent adverse event

Note: Percentages were based on the total number of subjects in the treatment group and analysis set.
An AE was defined as treatment-related if its relationship to the study drug was recorded as possibly related or related on the eCRF.

Overall, 221 (52.7%) subjects experienced TEAEs: 106 (51.5%) subjects from the previous IPX203 group and 115 (54.0%) from the previous IR CD-LD group. A total of 66 (15.8%) subjects experienced treatment-related TEAEs; 25 (6.0%) experienced TEAEs that led to discontinuation of the study drug, and 42 (10.0%) experienced serious TEAEs. Six (1.4%) subjects died during this study.

5.5.3.1. Adverse Drug Reactions

In the Phase 1 studies pool, all three TEAEs reported in IPX203 subjects (i.e., vomiting, blood cholesterol increased, and dizziness) were considered treatment related.

In the Phase 2 studies pool, 10 (20.8%) IPX203 subjects experienced TEAEs considered treatment related. The most commonly reported ($\geq 5\%$ subjects) treatment-related TEAEs in the IPX203 group were dyskinesia (six [12.5%] subjects) and dizziness (three [6.3%] subjects).

In the Phase 3 studies pool, 205 (34.8%) All-IPX203 subjects experienced TEAEs considered treatment related. The most commonly reported ($\geq 5\%$ subjects) treatment-related TEAEs in the All-IPX203 group were dyskinesia (60 [10.2%] subjects) and nausea (32 [5.4%] subjects).

Table 50: Summary of TEAEs by maximum relationship - Phase 3 studies in PD patients with motor fluctuations (Safety Population)

System Organ Class Preferred Term	IPX203 Open-Label N=589 n (%)	IPX203 Double-Blind N=256 n (%)	All IPX203 N=589 n (%)	IR CD-LD Open-Label N=630 n (%)	IR CD-LD Double-Blind N=250 n (%)	All IR CD-LD N=630 n (%)	Total N=630 n (%)
Number of subjects with no TEAEs	223 (37.9)	149 (58.2)	192 (32.6)	512 (81.3)	173 (69.2)	454 (72.1)	194 (30.8)
Number of subjects with any TEAE	366 (62.1)	107 (41.8)	397 (67.4)	118 (18.7)	77 (30.8)	176 (27.9)	436 (69.2)
Related	184 (31.2)	41 (16.0)	205 (34.8)	31 (4.9)	16 (6.4)	47 (7.5)	226 (35.9)
Not Related	182 (30.9)	66 (25.8)	192 (32.6)	87 (13.8)	61 (24.4)	129 (20.5)	210 (33.3)
Treatment-Related TEAEs (Incidence ≥1% in any Treatment Group)							
Gastrointestinal disorders	109 (18.5)	22 (8.6)	122 (20.7)	28 (4.4)	8 (3.2)	35 (5.6)	142 (22.5)
Nausea	25 (4.2)	7 (2.7)	32 (5.4)	2 (0.3)	0	2 (0.3)	34 (5.4)
Dry mouth	17 (2.9)	3 (1.2)	19 (3.2)	2 (0.3)	0	2 (0.3)	21 (3.3)
Constipation	9 (1.5)	2 (0.8)	10 (1.7)	5 (0.8)	0	5 (0.8)	13 (2.1)
Vomiting	10 (1.7)	1 (0.4)	11 (1.9)	0	0	0	11 (1.7)
General disorders and administration site conditions	38 (6.5)	11 (4.3)	47 (8.0)	9 (1.4)	12 (4.8)	21 (3.3)	66 (10.5)
Fatigue	3 (0.5)	2 (0.8)	5 (0.8)	0	1 (0.4)	1 (0.2)	6 (1.0)
Feeling abnormal	2 (0.3)	3 (1.2)	4 (0.7)	0	0	0	4 (0.6)
Injury, poisoning and procedural complications	54 (9.2)	12 (4.7)	63 (10.7)	11 (1.7)	11 (4.4)	22 (3.5)	76 (12.1)
Fall	4 (0.7)	3 (1.2)	6 (1.0)	1 (0.2)	1 (0.4)	2 (0.3)	7 (1.1)
Metabolism and nutrition disorders	21 (3.6)	0	21 (3.6)	4 (0.6)	0	4 (0.6)	25 (4.0)
Decreased appetite	6 (1.0)	0	6 (1.0)	2 (0.3)	0	2 (0.3)	8 (1.3)
Nervous system disorders	162 (27.5)	38 (14.8)	184 (31.2)	37 (5.9)	17 (6.8)	54 (8.6)	212 (33.7)
Dyskinesia	55 (9.3)	5 (2.0)	60 (10.2)	8 (1.3)	1 (0.4)	9 (1.4)	65 (10.3)
Dizziness	18 (3.1)	2 (0.8)	20 (3.4)	2 (0.3)	1 (0.4)	3 (0.5)	23 (3.7)
Headache	6 (1.0)	1 (0.4)	7 (1.2)	1 (0.2)	0	1 (0.2)	8 (1.3)

System Organ Class Preferred Term	IPX203 Open-Label N=589 n (%)	IPX203 Double-Blind N=256 n (%)	All IPX203 N=589 n (%)	IR CD-LD Open-Label N=630 n (%)	IR CD-LD Double-Blind N=250 n (%)	All IR CD-LD N=630 n (%)	Total N=630 n (%)
Somnolence	6 (1.0)	2 (0.8)	8 (1.4)	1 (0.2)	1 (0.4)	2 (0.3)	9 (1.4)
On and off phenomenon	3 (0.5)	2 (0.8)	5 (0.8)	0	1 (0.4)	1 (0.2)	6 (1.0)
Balance disorder	4 (0.7)	2 (0.8)	6 (1.0)	0	0	0	6 (1.0)
Psychiatric disorders	106 (18.0)	26 (10.2)	122 (20.7)	14 (2.2)	9 (3.6)	23 (3.7)	137 (21.7)
Anxiety	5 (0.8)	2 (0.8)	7 (1.2)	1 (0.2)	0	1 (0.2)	8 (1.3)
Insomnia	9 (1.5)	2 (0.8)	11 (1.9)	2 (0.3)	0	2 (0.3)	13 (2.1)
Hallucination	8 (1.4)	2 (0.8)	10 (1.7)	0	0	0	10 (1.6)
Hallucination, visual	4 (0.7)	1 (0.4)	5 (0.8)	0	1 (0.4)	1 (0.2)	6 (1.0)
Abnormal dreams	6 (1.0)	0	6 (1.0)	1 (0.2)	0	1 (0.2)	7 (1.1)
Vascular disorders	38 (6.5)	7 (2.7)	44 (7.5)	13 (2.1)	2 (0.8)	14 (2.2)	56 (8.9)
Orthostatic hypotension	8 (1.4)	1 (0.4)	9 (1.5)	3 (0.5)	0	3 (0.5)	12 (1.9)

Source: Excerpt from ISS Table 5.1.4.3

Abbreviations: AE = adverse event; eCRF = electronic case report form; IR CD-LD = immediate-release carbidopa-levodopa; MedDRA = Medical Dictionary for Regulatory Activities; PD = Parkinson's disease; TEAE = treatment-emergent adverse event

Note: Percentages were based on the total number of subjects in the treatment group and population.

Subjects were counted only once within each system organ class and preferred term with the highest applicable relationship.

An AE was defined as treatment-related if its relationship to the study drug was recorded as possibly related or related on the eCRF. The AEs were counted under the last treatment prior to the onset of the event.

All reported terms coded with MedDRA Version 23.0.

A comprehensive assessment of all AE PTs reported in the IPX203 Phase 2/3 studies was performed. The following factors were applied to determine which AEs would be considered ADRs:

- Frequency of the reported AE
- Whether or not the event was an ADR in the prescribing information for a similar product
- Whether or not the event was reported in the bibliographic reference studies
- Known pharmacologic class effects of dopaminergic drugs
- Severity and seriousness of the event
- Clinical importance of the event
- Whether or not the event could be considered a part of the natural history of PD
- Whether the event was considered secondary to another event (e.g., fractures secondary to a fall)
- Whether the event represented a subset of another AE or ADR term

The process was iterative, and the adjudicated designations reviewed to ensure consistency. Preferred Terms for AEs (e.g., acute psychosis, psychotic disorder, etc.) were grouped under a descriptive ADR term (e.g., psychotic episodes), and the ADR term assigned to an appropriate MedDRA SOC.

The incidence of each ADR was summarised by AE PT, ADR term and SOC, with each subject represented only once at each level.

In the proposed SmPC, each ADR has been categorised by frequency using standard categories: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), or uncommon ($\geq 1/1,000$ to $< 1/100$). Because fewer than 1000 subjects were included, no IPX203 ADRs have been categorised as rare ($\geq 1/10,000$ to $< 1/1,000$) or very rare ($< 1/10,000$).

In line with the recommendations outlined in the Guideline on SmPC, September 2009, only the Phase 3 controlled clinical trial IPX203-B16-02 has been considered to determine ADRs frequency, as considered sufficiently large to be informative.

Sixty-one ADRs were identified and summarised in the following Table.

Of note, the latest two Table's columns present:

- AE MedDRA PTs grouped and included in ADR term, collected during the controlled clinical study IPX203-B16-02 and considered to determine ADR frequency;
- Additional AEs PTs - covered by the same ADR term- collected from the remaining Phase 2 and 3 clinical trials and not considered for ADR frequency calculation.

The most frequently reported ADRs were dyskinesia (7.6%), nausea (6.6%), dry mouth (4.6%) and dizziness (4.2%).

Table 51: Frequency of IPX203 ADRs in the Phase 3 controlled clinical trial IPX203-B16-02

SYSTEM ORGAN CLASS ADR Term ^a	Frequency of ADR in Phase 3 controlled Study (N = 589) Number (%) of Subjects			AE PTs included in ADR collected in the controlled clinical study IPX203-B16-02 and considered for determining ADR frequency	Additional AE PTs included in ADR - collected in the remaining phase 2 and 3 clinical studies- and NOT considered for determining ADR frequency
	Very common ≥10%	Common 1% to <10%	Uncommon 0.1% to <1%		
BLOOD AND LYMPHATIC SYSTEM DISORDERS					
Anaemia			3 (0.5%)	Anaemia	Normochromic, normocytic anaemia, microcytic anaemia
METABOLISM AND NUTRITION DISORDERS					
Decreased appetite		7 (1.2%)		Decreased appetite, appetite disorder	
Weight increased				None	Overweight
Weight decreased			2 (0.3%)	Weight decreased	
PSYCHIATRIC DISORDERS					
Insomnia		16 (2.7%)		Insomnia, initial insomnia	
Sleep Disorders		7 (1.2%)		Sleep disorder, rapid eye movement sleep behaviour disorder, rapid eye movements sleep abnormal	

SYSTEM ORGAN CLASS ADR Term ^a	Frequency of ADR in Phase 3 controlled Study (N = 589) Number (%) of Subjects			AE PTs included in ADR collected in the controlled clinical study IPX203-B16-02 and considered for determining ADR frequency	Additional AE PTs included in ADR - collected in the remaining phase 2 and 3 clinical studies- and NOT considered for determining ADR frequency
	Very common ≥10%	Common 1% to <10%	Uncommon 0.1% to <1%		
Hallucination		16 (2.7%)		Hallucination, hallucination visual, hallucination auditory, hallucination mixed	
Illusion			1 (0.2%)	Illusion	
Anxiety		19 (3.2%)		Anxiety, nervousness, panic attack, panic disorder, tearfulness	
Abnormal dreams			5 (0.8%)	Abnormal dreams	
Depression		13 (2.2%)		Depression, depressed mood	Depressive symptom, suicidal ideation
Confusional state		6 (1.0%)		Confusional state, behaviour disorder	
Agitation			5 (0.8%)	Agitation, restlessness	
Impulse control disorder			4 (0.7%)	Affect lability, impulse-control disorder	Compulsions, hypersexuality
Psychotic episode			2 (0.3%)	Mania	Psychotic disorder, delusion, delirium, acute psychosis
Bruxism			1 (0.2%)	Bruxism	
NERVOUS SYSTEM DISORDERS					
Cognitive impairment		6 (1.0%)		Thinking abnormal, memory impairment, cognitive disorder, depressed level of consciousness, judgment impaired	Mental status changes
Dizziness		25 (4.2%)		Dizziness, vertigo, dizziness postural	
Dyskinesia		45 (7.6%)		Dyskinesia	
Extrapyramidal disorder			3 (0.5%)	Hyperkinesia, movement disorder	
Muscle contraction involuntary			1 (0.2%)	Muscle contraction involuntary	
Headache		12 (2.0%)		Headache	
Worsening of Parkinson's disease		13 (2.2%)		Parkinsonian rest tremor, freezing phenomenon, Parkinson's disease, musculoskeletal stiffness, muscle rigidity	Bradykinesia, hypokinesia
Tremor			4 (0.7%)	Tremor	

SYSTEM ORGAN CLASS ADR Term ^a	Frequency of ADR in Phase 3 controlled Study (N = 589) Number (%) of Subjects			AE PTs included in ADR collected in the controlled clinical study IPX203-B16-02 and considered for determining ADR frequency	Additional AE PTs included in ADR - collected in the remaining phase 2 and 3 clinical studies- and NOT considered for determining ADR frequency
	Very common ≥10%	Common 1% to <10%	Uncommon 0.1% to <1%		
On and off phenomenon			4 (0.7%)	On and off phenomenon	
Somnolence		11 (1.9%)		Somnolence, hypersomnia	
Gait disturbance		9 (1.5%)		Balance disorder, gait disturbance	
Paraesthesia			2 (0.3%)	Paraesthesia	
Dystonia			5 (0.8%)	Dystonia	
Restless legs syndrome			1 (0.2%)	Restless legs syndrome	
Convulsion			1 (0.2%)	Epilepsy	Seizure
Trismus			1 (0.2%)	Trismus	
Syncope			4 (0.7%)	Syncope	
EYE DISORDERS					
Vision blurred		6 (1.0%)		Vision blurred, visual impairment	
CARDIAC DISORDERS					
Cardiac rhythm disorders			3 (0.5%)	Atrial fibrillation, bradycardia	Atrioventricular block first degree, bundle branch block left, tachycardia, tachyarrhythmia
Palpitations			1 (0.2%)	Palpitations	
IMMUNE SYSTEM DISORDERS					
Hypersensitivity				None	Hypersensitivity
VASCULAR DISORDERS					
Orthostatic hypotension		14 (2.4%)		Orthostatic hypotension, hypotension	
Hypertension		17 (2.9%)		Blood pressure increased, hypertension, labile hypertension, , hypertensive crisis, hypertensive urgency	Orthostatic hypertension
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS					
Dyspnoea			4 (0.7%)	Dyspnoea	
GASTROINTESTINAL DISORDERS					
Nausea		39 (6.6%)		Nausea	
Constipation		15 (2.5%)		Constipation	
Dry mouth		27 (4.6%)		Dry mouth	

SYSTEM ORGAN CLASS ADR Term ^a	Frequency of ADR in Phase 3 controlled Study (N = 589) Number (%) of Subjects			AE PTs included in ADR collected in the controlled clinical study IPX203-B16-02 and considered for determining ADR frequency	Additional AE PTs included in ADR - collected in the remaining phase 2 and 3 clinical studies- and NOT considered for determining ADR frequency
	Very common ≥10%	Common 1% to <10%	Uncommon 0.1% to <1%		
Abdominal pain		9 (1.5%)		Abdominal discomfort, abdominal pain, abdominal pain upper	
Vomiting		16 (2.7%)		Retching, vomiting	
Diarrhoea			5 (0.8%)	Diarrhoea	
Dyspepsia			4 (0.7%)	Dyspepsia	
Flatulence			2 (0.3%)	Flatulence	
Dysphagia			1 (0.2%)	Dysphagia	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS					
Rash		6 (1.0%)		Erythema, rash, rash generalised	Dermatitis
Hot flush			2 (0.3%)	Flushing	
Hyperhidrosis			3 (0.5%)	Cold sweat, hyperhidrosis	
Pruritus			1 (0.2%)	Pruritus	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS					
Muscle spasms		6 (1.0%)		Muscle spasms	
RENAL AND URINARY DISORDERS					
Urinary retention			2 (0.3%)	Urinary retention	Bladder dysfunction, hypertonic bladder
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
Fall		17 (2.9%)		Fall	
Peripheral oedema			3 (0.5%)	Oedema peripheral	
Asthenia			4 (0.7%)	Asthenia, lethargy	
Non-cardiac chest pain			4 (0.7%)	Chest discomfort, chest pain, musculoskeletal chest pain, non-cardiac chest pain	
Fatigue		9 (1.5%)		Fatigue	
Malaise				None	Malaise

Note: Adverse drug reactions (ADRs) in this table are the subset of adverse events (AEs) reported in IPX203 studies that were designated as having at least a reasonable possibility of a causal relationship with IPX203. AE preferred terms were assigned to descriptive ADR terms by the Sponsor.

^aADRs (and their associated AE preferred terms) were assigned to a MedDRA SOC by the Sponsor.

Table 52: Summary of serious TEAEs by SOC and PT - Phase 3 studies in PD patients with motor fluctuations (Safety Population)

System Organ Class Preferred Term	Open-Label N=589 n (%) m	Double-Blind N=256 n (%) m	All IPX203 N=589 n (%) m	Open-Label N=630 n (%) m	Double-Blind N=250 n (%) m	All IR LD-CD N=630 n (%) m	Total N=630 n (%) m
Number of subjects with no events	537 (91.2)	248 (96.9)	529 (89.8)	623 (98.9)	246 (98.4)	620 (98.4)	560 (88.9)
Number of subjects with any event	52 (8.8) 93	8 (3.1) 9	60 (10.2) 102	7 (1.1) 12	4 (1.6) 5	10 (1.6) 17	70 (11.1) 119
Blood and lymphatic system disorders	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Anaemia	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Cardiac disorders	4 (0.7) 5	1 (0.4) 1	5 (0.8) 6	0	2 (0.8) 2	2 (0.3) 2	7 (1.1) 8
Atrial fibrillation	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Acute myocardial infarction	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Bradycardia	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Cardiac failure	1 (0.2) 1	0	1 (0.2) 1	0	1 (0.4) 1	1 (0.2) 1	2 (0.3) 2
Cardiogenic shock	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Atrioventricular block complete	0	0	0	0	1 (0.4) 1	1 (0.2) 1	1 (0.2) 1
Ear and labyrinth disorders	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Vertigo	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Gastrointestinal disorders	5 (0.8) 5	0	5 (0.8) 5	2 (0.3) 2	0	2 (0.3) 2	7 (1.1) 7
Volvulus	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Abdominal distension	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Colitis	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Vomiting	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Duodenitis	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1

System Organ Class Preferred Term	IPX203 Open-Label N=589 n (%) m	IPX203 Double-Blind N=256 n (%) m	All IPX203 N=589 n (%) m	IR LD-CD Open-Label N=630 n (%) m	IR LD-CD Double-Blind N=250 n (%) m	All IR LD-CD N=630 n (%) m	Total N=630 n (%) m
General disorders and administration site conditions	6 (1.0) 6	1 (0.4) 2	7 (1.2) 8	0	0	0	7 (1.1) 8
Asthenia	1 (0.2) 1	1 (0.4) 1	2 (0.3) 2	0	0	0	2 (0.3) 2
Chest pain	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Drowning	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Fatigue	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Non-cardiac chest pain	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Pyrexia	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Immune system disorders	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Hypersensitivity	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Infections and infestations	11 (1.9) 17	1 (0.4) 1	12 (2.0) 18	1 (0.2) 1	1 (0.4) 1	2 (0.3) 2	14 (2.2) 20
COVID-19	3 (0.5) 3	0	3 (0.5) 3	0	0	0	3 (0.5) 3
Pneumonia	2 (0.3) 3	0	2 (0.3) 3	0	0	0	2 (0.3) 3
Sepsis	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
COVID-19 pneumonia	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Cystitis	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Encephalitis	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Gastroenteritis viral	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Gastrointestinal infection	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Herpes zoster	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Influenza	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Post procedural infection	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Pyelonephritis	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Urinary tract infection	1 (0.2) 1	0	1 (0.2) 1	0	1 (0.4) 1	1 (0.2) 1	2 (0.3) 2
Furunculitis	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1

System Organ Class Preferred Term	IPX203 Open-Label N=589 n (%) m	IPX203 Double-Blind N=256 n (%) m	All IPX203 N=589 n (%) m	IR LD-CD Open-Label N=630 n (%) m	IR LD-CD Double-Blind N=250 n (%) m	All IR LD-CD N=630 n (%) m	Total N=630 n (%) m
Injury, poisoning and procedural complications	9 (1.5) 12	0	9 (1.5) 12	1 (0.2) 1	0	1 (0.2) 1	10 (1.6) 13
Femur fracture	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Concussion	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Contusion	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Fall	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Head injury	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Hip fracture	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Joint dislocation	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Overdose	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Skin laceration	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Spinal cord injury cervical	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Subdural haematoma	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Radiation neuropathy	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
Investigations	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Ejection fraction decreased	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Metabolism and nutrition disorders	3 (0.5) 3	0	3 (0.5) 3	1 (0.2) 1	0	1 (0.2) 1	4 (0.6) 4
Hypokalaemia	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Dehydration	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Hyponatraemia	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
Musculoskeletal and connective tissue disorders	2 (0.3) 2	0	2 (0.3) 2	1 (0.2) 1	1 (0.4) 1	2 (0.3) 2	4 (0.6) 4
Lumbar spinal stenosis	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Scoliosis	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Back pain	0	0	0	0	1 (0.4) 1	1 (0.2) 1	1 (0.2) 1

System Organ Class Preferred Term	IPX203 Open-Label N=589 n (%) m	IPX203 Double-Blind N=256 n (%) m	All IPX203 N=589 n (%) m	IR LD-CD Open-Label N=630 n (%) m	IR LD-CD Double-Blind N=250 n (%) m	All IR LD-CD N=630 n (%) m	Total N=630 n (%) m
Osteoarthritis	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Bladder transitional cell carcinoma	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Lung neoplasm malignant	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Nervous system disorders	15 (2.5) 16	3 (1.2) 3	18 (3.1) 19	2 (0.3) 4	0	2 (0.3) 4	20 (3.2) 23
Seizure	3 (0.5) 3	0	3 (0.5) 3	0	0	0	3 (0.5) 3
Syncope	2 (0.3) 2	1 (0.4) 1	3 (0.5) 3	0	0	0	3 (0.5) 3
Epilepsy	1 (0.2) 1	1 (0.4) 1	2 (0.3) 2	0	0	0	2 (0.3) 2
Transient ischaemic attack	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Cauda equina syndrome	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Cerebrovascular accident	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Freezing phenomenon	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Parkinson's disease	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Peripheral sensory neuropathy	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Polyneuropathy	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Subarachnoid haemorrhage	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Vertebral artery aneurysm	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Cognitive disorder	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
Dyskinesia	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
Neuralgia	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
On and off phenomenon	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
Psychiatric disorders	8 (1.4) 9	1 (0.4) 1	9 (1.5) 10	0	0	0	9 (1.4) 10
Confusional state	3 (0.5) 3	0	3 (0.5) 3	0	0	0	3 (0.5) 3

System Organ Class Preferred Term	IPX203 Open-Label N=589 n (%) m	IPX203 Double-Blind N=256 n (%) m	All IPX203 N=589 n (%) m	IR LD-CD Open-Label N=630 n (%) m	IR LD-CD Double-Blind N=250 n (%) m	All IR LD-CD N=630 n (%) m	Total N=630 n (%) m
Psychotic disorder	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Delirium	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Depression	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Hallucinations, mixed	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Hypersexuality	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Mental status changes	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Renal and urinary disorders	4 (0.7) 4	0	4 (0.7) 4	1 (0.2) 2	0	1 (0.2) 2	5 (0.8) 6
Nephrolithiasis	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Neurogenic bladder	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Urinary retention	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Acute kidney injury	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
Urinary tract obstruction	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
Reproductive system and breast disorders	0	0	0	0	1 (0.4) 1	1 (0.2) 1	1 (0.2) 1
Benign prostatic hyperplasia	0	0	0	0	1 (0.4) 1	1 (0.2) 1	1 (0.2) 1
Respiratory, thoracic and mediastinal disorders	4 (0.7) 7	0	4 (0.7) 7	0	0	0	4 (0.6) 7
COPD	2 (0.3) 3	0	2 (0.3) 3	0	0	0	2 (0.3) 3
Pulmonary embolism	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Aspiration	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Hypoxia	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Surgical and medical procedures	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Inguinal hernia repair	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1

Source: Table 14.3.1.3 in both study reports.

Abbreviations: AE = adverse event; COPD = Chronic obstructive pulmonary disease; COVID-19 = Coronavirus disease-2019; IR LD-CD = immediate-release levodopa-carbidopa; MedDRA = Medical Dictionary for Regulatory Activities; PD = Parkinson's disease; TEAE = treatment-emergent adverse event

Adverse Events at Supratherapeutic Dose of carbidopa

In Study IPX203-101-23, no AEs were reported for any enrolled subject, and no clinically significant abnormal laboratory values were observed. Overall, 10 out of 35 (28.6%) subjects experienced at least one TEAE. Four (11.8%), 3 (9.1%), and one (2.9%) subject experienced at least one TEAE considered related to carbidopa, moxifloxacin hydrochloride, and placebo, respectively. The majority of TEAEs were mild in severity; no severe TEAE were reported. No TEAE led to discontinuation of the study drug, and no subject died or experienced other serious AEs. There were no clinically meaningful trends observed in haematology and chemistry parameters.

Adverse Events by Average Total Daily Dose (TDD) and Total Cumulative Duration of Exposure

There was a higher systemic exposure of CD from IPX203. Therefore, this subsection discusses reported AEs according to CD exposure and total cumulative duration, determined based on the available IPX203 formulations with a 4:1 ratio of LD:CD at each IPX203 dosage strength. The TDD refers to the daily mg exposure to LD.

The most common TEAEs (defined as occurring in $\geq 5\%$ subjects and in at least $n=5$ patients) were reported in the SOC of *Gastrointestinal, Infections and infestations, Injury, and Nervous System disorders*. In each of the categories over time, <1600 mg (CD <400 mg) versus ≥ 1600 mg (CD ≥ 400 mg), the percentage of IPX203 subjects who experienced the most common TEAEs appeared stable over time. When comparing between dose categories over time (<1600 mg versus ≥ 1600 mg), the percentage of IPX203 subjects who experienced the most common TEAEs were similar in ≥ 1600 mg versus <1600 mg. Of note: = dyskinesia was generally lower in the higher dose category (≥ 1600 mg versus <1600 mg); this was observed consistently over time. Overall, the percentage of subjects with most common TEAEs was not unexpected and relatively stable over time and dose categories.

5.5.4. Discontinuation due to adverse events

A summary of TEAEs leading to study drug withdrawal in the Phase 3 studies pool in PD patients with motor fluctuations for the Safety Population) is presented in the Table below.

Table 53: Summary of TEAEs leading to study drug withdrawal by SOC and PT - Phase 3 study in PD patients with motor fluctuations (Safety Population)

System Organ Class Preferred Term	IPX203 Open-Label N=589 n (%) m	IPX203 Double-Blind N=256 n (%) m	All IPX203 N=589 n (%) m	IR LD-CD Open-Label N=630 n (%) m	IR LD-CD Double-Blind N=250 n (%) m	All IR LD-CD N=630 n (%) m	Total N=630 n (%) m
Number of subjects with no events	522 (88.6)	242 (94.5)	509 (86.4)	624 (99.0)	246 (98.4)	620 (98.4)	543 (86.2)
Number of subjects with any event	67 (11.4) 116	14 (5.5) 23	80 (13.6) 139	6 (1.0) 10	4 (1.6) 5	10 (1.6) 15	87 (13.8) 154
Cardiac disorders	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Cardiogenic shock	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Ear and labyrinth disorders	1 (0.2) 1	1 (0.4) 1	2 (0.3) 2	0	0	0	2 (0.3) 2
Vertigo	1 (0.2) 1	1 (0.4) 1	2 (0.3) 2	0	0	0	2 (0.3) 2
Gastrointestinal disorders	10 (1.7) 15	2 (0.8) 2	12 (2.0) 17	2 (0.3) 2	0	2 (0.3) 2	14 (2.2) 19
Nausea	7 (1.2) 7	2 (0.8) 2	9 (1.5) 9	0	0	0	9 (1.4) 9
Vomiting	4 (0.7) 4	0	4 (0.7) 4	0	0	0	4 (0.6) 4
Dry mouth	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Chapped lips	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Dysphagia	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Duodenitis	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
Dyspepsia	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
General disorders and administration site conditions	3 (0.5) 3	5 (2.0) 6	8 (1.4) 9	1 (0.2) 1	2 (0.8) 2	3 (0.5) 3	11 (1.7) 12
Asthenia	1 (0.2) 1	1 (0.4) 1	2 (0.3) 2	0	1 (0.4) 1	1 (0.2) 1	3 (0.5) 3
Fatigue	0	2 (0.8) 2	2 (0.3) 2	0	0	0	2 (0.3) 2
Feeling abnormal	0	2 (0.8) 2	2 (0.3) 2	0	0	0	2 (0.3) 2
Drowning	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Gait disturbance	0	1 (0.4) 1	1 (0.2) 1	1 (0.2) 1	0	1 (0.2) 1	2 (0.3) 2

System Organ Class Preferred Term	IPX203 Open-Label N=589 n (%) m	IPX203 Double-Blind N=256 n (%) m	All IPX203 N=589 n (%) m	IR LD-CD Open-Label N=630 n (%) m	IR LD-CD Double-Blind N=250 n (%) m	All IR LD-CD N=630 n (%) m	Total N=630 n (%) m
Pyrexia	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Balance disorder	0	0	0	0	1 (0.4) 1	1 (0.2) 1	1 (0.2) 1
Infections and infestations	4 (0.7) 6	0	4 (0.7) 6	0	0	0	4 (0.6) 6
COVID-19	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Corona virus infection	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Encephalitis	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Gastrointestinal infection	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Urinary tract infection	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Injury, poisoning and procedural complications	4 (0.7) 6	0	4 (0.7) 6	1 (0.2) 1	0	1 (0.2) 1	5 (0.8) 7
Fall	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Facial bones fracture	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Head injury	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Overdose	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Spinal cord injury cervical	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Radiation neuropathy	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
Investigations	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Blood pressure increased	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Metabolism and nutrition disorders	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Decreased appetite	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Musculoskeletal and connective tissue disorders	3 (0.5) 4	0	3 (0.5) 4	0	0	0	3 (0.5) 4
Back pain	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Muscle spasms	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Musculoskeletal stiffness	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1

System Organ Class Preferred Term	IPX203 Open-Label N=589	IPX203 Double-Blind N=256	All IPX203 N=589	IR LD-CD Open-Label N=630	IR LD-CD Double-Blind N=250	All IR LD-CD N=630	Total N=630
	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m
Neck pain	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Bladder transitional cell carcinoma	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Lung neoplasm malignant	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Nervous system disorders	32 (5.4) 41	8 (3.1) 11	40 (6.8) 52	3 (0.5) 5	3 (1.2) 3	6 (1.0) 8	46 (7.3) 60
Dyskinesia	8 (1.4) 8	2 (0.8) 2	10 (1.7) 10	1 (0.2) 1	0	1 (0.2) 1	11 (1.7) 11
Dizziness	8 (1.4) 8	0	8 (1.4) 8	1 (0.2) 1	0	1 (0.2) 1	9 (1.4) 9
On and off phenomenon	3 (0.5) 3	2 (0.8) 2	5 (0.8) 5	1 (0.2) 1	0	1 (0.2) 1	6 (1.0) 6
Parkinson's disease	3 (0.5) 3	1 (0.4) 1	4 (0.7) 4	0	2 (0.8) 2	2 (0.3) 2	6 (1.0) 6
Balance disorder	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Epilepsy	1 (0.2) 1	1 (0.4) 2	2 (0.3) 3	0	0	0	2 (0.3) 3
Freezing phenomenon	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Tremor	2 (0.3) 3	0	2 (0.3) 3	0	0	0	2 (0.3) 3
Anosognosia	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Brachial plexopathy	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Dysaesthesia	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Dysarthria	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Dystonia	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Hyperkinesia	1 (0.2) 1	0	1 (0.2) 1	0	1 (0.4) 1	1 (0.2) 1	2 (0.3) 2
Hypoaesthesia	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Judgement impaired	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Memory impairment	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Movement disorder	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1

System Organ Class Preferred Term	IPX203 Open-Label N=589	IPX203 Double-Blind N=256	All IPX203 N=589	IR LD-CD Open-Label N=630	IR LD-CD Double-Blind N=250	All IR LD-CD N=630	Total N=630
	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m
Paraesthesia	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Peripheral sensorimotor neuropathy	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Peripheral sensory neuropathy	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Seizure	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Transient ischaemic attack	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Cognitive disorder	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
Neuralgia	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
Psychiatric disorders	22 (3.7) 26	2 (0.8) 3	23 (3.9) 29	1 (0.2) 1	0	1 (0.2) 1	24 (3.8) 30
Insomnia	5 (0.8) 5	0	5 (0.8) 5	0	0	0	5 (0.8) 5
Anxiety	2 (0.3) 2	1 (0.4) 1	3 (0.5) 3	0	0	0	3 (0.5) 3
Depression	3 (0.5) 3	0	3 (0.5) 3	0	0	0	3 (0.5) 3
Abnormal dreams	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Confusional state	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Hallucination	2 (0.3) 2	0	2 (0.3) 2	0	0	0	2 (0.3) 2
Agitation	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Delirium	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Depressed mood	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Hallucinations, mixed	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Hypersexuality	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Impulse-control disorder	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Irritability	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Mania	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Mood altered	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Mood swings	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1

System Organ Class Preferred Term	IPX203 Open-Label N=589	IPX203 Double-Blind N=256	All IPX203 N=589	IR LD-CD Open-Label N=630	IR LD-CD Double-Blind N=250	All IR LD-CD N=630	Total N=630
	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m
Nervousness	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Psychotic disorder	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Nightmare	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1
Respiratory, thoracic and mediastinal disorders	2 (0.3) 3	0	2 (0.3) 3	0	0	0	2 (0.3) 3
COPD	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Dyspnoea	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Pulmonary embolism	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Skin and subcutaneous tissue disorders	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Hyperhidrosis	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Vascular disorders	4 (0.7) 4	0	4 (0.7) 4	0	0	0	4 (0.6) 4
Hypertension	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Hypertensive urgency	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Hypotension	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Orthostatic hypotension	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1

Source: ISS Table 5.1.5.3

Abbreviations: AE = adverse event; COPD = Chronic obstructive pulmonary disease; IR LD-CD = immediate-release carbidopa-levodopa; MedDRA = Medical Dictionary for Regulatory Activities; m = number of events; n = number of subjects; PD = Parkinson's disease; TEAE = treatment-emergent adverse event

Note: n = number of subjects with events, m = number of events.

Percentages were based on the total number of subjects in the treatment group and population.

All reported terms coded with MedDRA Version 22.0.

Subjects were counted only once within each system organ class and preferred term. The AEs were counted under the last treatment prior to the onset of the

In the course of the procedure, the applicant was asked to discuss possible reasons for the higher incidence of TEAEs (including TEAEs related to study treatment) noted in subjects treated with IPX203 group compared to IR CD-LD in studies IPX203-B16-01 and IPX203-B16-02.

In the applicant's view, the higher incidence of TEAEs in study **IPX203-B16-01** was as expected. In fact, the vast majority of TEAEs were dopaminergic side effects commonly associated with the use of LD. In this study patients had used levodopa therapy for years. They entered the study on the IR dose they had been stable on for long periods of time. IPX203 bioavailability was higher than originally anticipated by the applicant, and higher than often seen in MR preparations. Since the IR dose was usually established in patients by titrating until side effects emerged, it was expected that dopaminergic side effects would occur much more often in the IPX203 group, due to the study design. All TEAEs were considered mild or moderate. Six patients reported TEAEs during IPX203 treatment that were considered dopaminergic; most of these events resolved with a dose reduction.

In the **IPX203-B16-02** study, patients were typically converted to IPX203-based on their current most frequent individual IR dose but with doses administered TID. Investigators rarely increased the dose frequency of IPX203 beyond TID; therefore, to increase the TDD individual doses were increased. The expected result of this increase in LD per administration event was an increase in dopaminergic side effects. One would expect this to increase the TEAE responses for IPX203 in both the dose titration and double-blind periods of the study.

Ultimately, it could be agreed that:

- In study IPX203-B16-01, the higher incidence of TEAEs in subjects treated with IPX203 group compared to IR CD-LD should be expected, since the study population had been using LD therapy for years. Thus, the higher incidence of TEAEs was most probably caused by IPX203 higher bioavailability. Nevertheless, it was reassuring that no severe TEAEs were observed.
- In study IPX203-B16-02, an increase in dopaminergic side effects was caused by increase in LD per administration.

5.5.5. Safety in special populations

The influence of the following intrinsic factors/subgroups on the AE profile of IPX203 was examined in the Phase 2 studies pool in advanced PD patients and in the Phase 3 studies pool in PD patients with motor fluctuations:

- Age: <65, ≥65 years old at study entry
- Gender: Males, Females
- Race: Caucasians, non-Caucasians
- Region: North America, Europe
- Concomitant medications (please see section 5.4.8) - the following non-exclusive subgroups were defined for subjects taking concomitant medications of the following categories:
 - Amantadine
 - Selective MAO-B inhibitors
 - Anticholinergic PD medications
 - Dopamine agonists
 - Others
- Weight: <75 kg, ≥75 kg
- BMI: <25 kg/m², ≥25 kg/m²
- PD duration at screening: <8 years, ≥8 years
- Age of PD onset: <65 years, ≥65 years

Adverse Events by Age

In the Phase 2 studies pool, a higher percentage of ≥65 years-old IPX203 subjects experienced TEAEs (50.0%) compared with <65 years-old subjects (8.3%). In the Phase 3 studies pool, the TEAEs were comparable in <65 years (67.7%) *versus* ≥65 years-old IPX203 subjects (67.2%). A higher percentage of ≥65 years IPX203 subjects experienced serious TEAEs (12.1%) *versus* <65 years-old (7.1%), and a higher percentage of <65 years IPX203 subjects experienced TEAEs that led to discontinuation of the study drug (15.0%) *versus* ≥65 years-old (12.7%).

The exact number of subjects included in the studies IPX203-B14-02, IPX203-B16-01, IPX203-B16-02, and IPX203-B16-03 have been stratified for the following age groups ≥65<75, ≥75<85, ≥85 years old in the Table below.

Table 54: Distribution of Patients by Age Group (Safety Population)

Study	IPX203 ≥65<75 years old	IPX203 ≥75<85 years old	IPX203 ≥85 years old	Tot (including all ages)
IPX203-B14-02	11	3	0	26
IPX203-B16-01	8	7	0	28
IPX203-B16-02	282	106	6	630
IPX203-B16-03	191	73	3	419

An overall summary of AEs by age (<65 years vs ≥65 years) for the Phase 3 studies pool in PD patients with motor fluctuations is presented (for the Safety Population) in the Table below.

Table 55: Overall summary of AEs by age - Phase 3 studies in PD patients with motor fluctuations (Safety Population)

	IPX203 Open-Label		IPX203 Double-Blind		All IPX203		IR CD-LD Open-Label		IR CD-LD Double-Blind		All IR CD-LD		Total	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Age: <65 years	N=226		N=100		N=226		N=236		N=92		N=236		N=236	
Number of subjects who had														
TEAE	140 (61.9)	404	42 (42.0)	101	153 (67.7)	505	44 (18.6)	57	27 (29.3)	53	63 (26.7)	110	169 (71.6)	615
Treatment-related TEAE	79 (35.0)	168	13 (13.0)	30	84 (37.2)	198	10 (4.2)	13	8 (8.7)	13	18 (7.6)	26	95 (40.3)	224
Serious TEAE	15 (6.6)	22	1 (1.0)	1	16 (7.1)	23	1 (0.4)	1	1 (1.1)	1	2 (0.8)	2	18 (7.6)	25
Treatment-related serious TEAE	5 (2.2)	6	1 (1.0)	1	6 (2.7)	7	0		0		0		6 (2.5)	7
TEAE leading to study drug discontinuation	31 (13.7)	54	4 (4.0)	8	34 (15.0)	62	1 (0.4)	1	1 (1.1)	1	2 (0.8)	2	35 (14.8)	64
TEAE leading to death	1 (0.4)	1	0		1 (0.4)	1	0		0		0		1 (0.4)	1
TEAEs by maximum severity														
Mild	59 (26.1)	245	20 (20.0)	58	59 (26.1)	303	25 (10.6)	33	18 (19.6)	37	36 (15.3)	70	62 (26.3)	373
Moderate	61 (27.0)	124	20 (20.0)	40	73 (32.3)	164	16 (6.8)	21	6 (6.5)	12	21 (8.9)	33	83 (35.2)	197
Severe	20 (8.8)	35	2 (2.0)	3	21 (9.3)	38	3 (1.3)	3	3 (3.3)	4	6 (2.5)	7	24 (10.2)	

	IPX203 Open-Label n (%) m	IPX203 Double-Blind n (%) m	All IPX203 n (%) m	IR CD-LD Open-Label n (%) m	IR CD-LD Double- Blind n (%) m	All IR CD-LD n (%) m	Total n (%) m
							45
Age: ≥65 years	N=363	N=156	N=363	N=394	N=158	N=394	N=394
TEAE	226 (62.3) 706	65 (41.7) 144	244 (67.2) 850	74 (18.8) 131	50 (31.6) 87	113 (28.7) 218	267 (67.8) 1068
Treatment-related TEAE	105 (28.9) 226	28 (17.9) 47	121 (33.3) 273	21 (5.3) 31	8 (5.1) 9	29 (7.4) 40	131 (33.2) 313
Serious TEAE	37 (10.2) 71	7 (4.5) 8	44 (12.1) 79	6 (1.5) 11	3 (1.9) 4	8 (2.0) 15	52 (13.2) 94
Treatment-related serious TEAE	2 (0.6) 3	1 (0.6) 1	3 (0.8) 4	0	0	0	3 (0.8) 4
TEAE leading to study drug discontinuation	36 (9.9) 62	10 (6.4) 15	46 (12.7) 77	5 (1.3) 9	3 (1.9) 4	8 (2.0) 13	52 (13.2) 90
TEAE leading to death	5 (1.4) 8	0	5 (1.4) 8	0	0	0	5 (1.3) 8
TEAEs by maximum severity							
Mild	105 (28.9) 441	33 (21.2) 93	104 (28.7) 534	53 (13.5) 99	29 (18.4) 61	73 (18.5) 160	107 (27.2) 694
Moderate	86 (23.7) 210	26 (16.7) 45	101 (27.8) 255	18 (4.6) 27	17 (10.8) 22	33 (8.4) 49	114 (28.9) 304
Severe	35 (9.6) 55	6 (3.8) 6	39 (10.7) 61	3 (0.8) 5	4 (2.5) 4	7 (1.8) 9	46 (11.7) 70

Source: [ISS Table 5.2.1.2](#)

Abbreviations: AE = adverse event; eCRF = electronic case report form;
IR CD-LD = immediate-release carbidopa-levodopa; PD = Parkinson's disease; TEAE = treatment-emergent adverse event

Note: n = number of subjects with events, m = number of events.

Percentages were based on the total number of subjects in the age group, treatment group and population.

An AE was defined as treatment-related if its relationship to the study drug was recorded as possibly related or related on the eCRF. The AEs were counted under the last treatment prior to the onset of the event.

An overall summary of AEs by age groups, for the Phase 2 studies in advanced PD patients and for the Phase 3 Studies in PD Patients with motor fluctuations is presented (for the Safety Population) in the two Tables below.

In Phase 2 studies, a numerically higher proportion of IPX203 subjects aged ≥75 to <85 years experienced TEAEs (50.0%) compared with those aged ≥65 to <75 years (36.8%). Similar trends were observed also in the groups IR LD-CD, and Rytary. No subjects ≥85 years old were enrolled in these studies.

One IPX203 subject ≥75<85 (10.0%) experienced a serious TEAE (Hypertension) and one a TEAE leading to discontinuation (10.0%) (Orthostatic hypertension).

In IPX203 ≥65<75 years-old IPX203 subjects, the most commonly reported TEAE (≥5% and occurring in at least two subjects) was dyskinesia (21.1%).

In IPX203 ≥75<85 years-old IPX203 subjects, the most commonly reported TEAE (≥5% and occurring in at least two subjects) was hypertension (20.0%).

A similar percentage of ≥75<85 years-old IPX203 subjects experienced TEAEs (68.4%) compared with ≥65<75 years-old subjects (66.9%). Serious TEAEs were experienced by 12.6% of ≥75<85-year-old IPX203 subjects and 11.8% of ≥65<75 years-olds. The percentage of TEAEs leading to discontinuation of study drug was 14.7% and 12.2%, respectively.

In $\geq 65 < 75$ years-old IPX203 subjects, the most commonly reported TEAEs ($\geq 5\%$ and occurring in at least two subjects) were dyskinesia (10.3%), nausea (7.2%) and fall (5.3%).

In $\geq 75 < 85$ years-old IPX203 subjects, the most commonly reported TEAEs ($\geq 5\%$ and occurring in at least two subjects) were dyskinesia (9.5%), nausea (8.4%), constipation (5.3%), depression (5.3%), insomnia (5.3%), and fall (10.5%).

Overall, exposure in patients above 75 years is uncharacterised: no popPK analysis was conducted, and no PK was assessed in the Phase 3 studies. As experience with IPX203 in patients aged 75 years and older is limited (e.g. no patients above 85 have been enrolled in any IPX203 clinical trial), the SmPC (section 4.2, 4.4, 5.2) details that these patients should be converted cautiously from IR levodopa/DDCI into IPX203. Close clinical monitoring is recommended during the conversion period and subsequent dose optimisation, in line with standard clinical practice for older patients during dopaminergic therapy adjustments. Also of note, the dopaminergic adverse reactions these patients might be more susceptible to (outlined in SmPC section 4.4) include dyskinesia, hallucinations, confusion, somnolence, orthostatic hypotension, syncope and falls.

Table 56: Phase 2 Studies in Advanced PD Patients (Safety Population)

	IPX203			IR LD-CD			Rytary			All Comparators		
	≥65<75 (N=19)	≥75<85 (N=10)	≥85 (N=0)	≥65<75 (N=19)	≥75<85 (N=9)	≥85 (N=0)	≥65<75 (N=11)	≥75<85 (N=3)	≥85 (N=0)	≥65<75 (N=19)	≥75<85 (N=9)	≥85 (N=0)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
TEAE	7 (36.8)	5 (50.0)	-	3 (15.8)	2 (22.2)	-	1 (9.1)	1 (33.3)	-	3 (15.8)	2 (22.2)	-
Treatment-related TEAE	5 (26.3)	3 (30.0)	-	2 (10.5)	1 (11.1)	-	1 (9.1)	0 (0.0)	-	2 (10.5)	1 (11.1)	-
Serious TEAE	0 (0.0)	1 (10.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Treatment-related Serious TEAE	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
TEAE leading to discontinuation	0 (0.0)	1 (10.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
TEAE leading to death	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-

Table 57: Phase 3 Studies in PD Patients with Motor Fluctuations (Safety Population)

	IPX203 OL			IPX203 DB			All IPX203			IR LD-CD OL			IR LD-CD DB			All IR LD-CD		
	≥65<7 5	≥75<8 5	≥85	≥65<7 5	≥75<8 5	≥85	≥65<7 5	≥75<8 5	≥85	≥65<7 5	≥75<8 5	≥85	≥65<7 5	≥75<8 5	≥85	≥65<7 5	≥75<8 5	≥85
	N=263	N=95	N=5	N=118	N=35	N=3	N=263	N=95	N=5	N=282	N=106	N=6	N=112	N=45	N=1	N=282	N=106	N=6
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
TEAE	167 (63.5)	56 (58.9)	3 (60)	43 (36.4)	20 (57.1)	2 (66.7)	176 (66.9)	65 (68.4)	3 (60)	56 (19.9)	18 (17)	0 (0.0)	35 (31.3)	15 (33.3)	0 (0.0)	86 (30.5)	27 (25.5)	0 (0.0)
Treatment- related TEAE	82 (31.2)	23 (24.2)	0 (0.0)	20 (16.9)	8 (22.9)	0 (0.0)	93 (35.4)	28 (29.5)	0 (0.0)	14 (5)	7 (6.6)	0 (0.0)	5 (4.5)	3 (6.7)	0 (0.0)	19 (6.7)	10 (9.4)	0 (0.0)
Serious TEAE	28 (10.6)	8 (8.4)	1 (20.0)	3 (2.5)	4 (11.4)	0 (0.0)	31 (11.8)	12 (12.6)	1 (20.0)	5 (1.8)	1 (0.9)	0 (0.0)	2 (1.8)	1 (2.2)	0 (0.0)	6 (2.1)	2 (1.9)	0 (0.0)
Treatment- related Serious TEAE	2 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to discontinuation	26 (9.9)	10 (10.5)	0 (0.0)	6 (5.1)	4 (11.4)	0 (0.0)	32 (12.2)	14 (14.7)	0 (0.0)	3 (1.1)	2 (1.9)	0 (0.0)	1 (0.9)	2 (4.4)	0 (0.0)	4 (1.4)	4 (3.8)	0 (0.0)
TEAE leading to death	3 (1.1)	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 58: Common Treatment-emergent Adverse Events by MedDRA PT

TEAE MedDRA PT	Phase 2 Studies in Advanced PD Patients (Safety Population) %			Phase 3 Studies in PD Patients with Motor Fluctuations (Safety Population) %		
	≥65<75	≥75<85	≥85	≥65<75	≥75<85	≥85
Dyskinesia	21.1	10.0	-	10.3	9.5	0.0
Hypertension	5.3	20.0	-	3.4	1.1	0.0
Nausea	0.0	10.0	-	7.2	8.4	20.0
Constipation	0.0	0.0		3.0	5.3	0.0
Fall	0.0	0.0	-	5.3	10.5	0.0
Depression	0.0	0.0	-	4.6	5.3	0.0
Insomnia	5.3	0.0	-	2.3	5.3	0.0

In the course of the procedure, based on the primary endpoint subgroup analysis (as discussed in Section 5.3.2.1), and with a close eye on safety-related matters, a careful evaluation of IPX203 treatment led to the following considerations in subjects (with):

- **≥65 years** – The safety profiles were comparable across subgroups (TEAEs in ≥1 subject: 59.1% for onset <65 years [n=470] *versus* 54.4% for onset ≥65 years [n=160]).
- **body weight of <75 kg** - No evidence of reduced tolerability or excess AEs (that would contraindicate IPX203 in lower-weight subjects) was noted.
- **PD duration of ≥8 years** - It is known that LD PK may be altered by gastrointestinal dysfunctions such as dysphagia, delayed gastric emptying, constipation, bacterial infection, gut dysbiosis, diet, comorbidities and concomitant medication intake ([Leta et al, 2023](#)). These factors may contribute to non-optimal LD response, symptoms fluctuations and unpredictable dyskinesia, and are more common in older patients and those with a PD onset in advanced age.
- **PD onset at ≥65 years** – The safety profiles were comparable across subgroups (TEAEs in ≥1 subject: 59.1% for onset <65 years [n=470] vs 54.4% for onset ≥65 years [n=160]).
- **“Off” time of <6 hours** - The proportion of subjects with at least one TEAE was higher in subjects who reported “OFF” time of ≥6 h (199 subjects out of 320, 62.2%) *versus* those who reported <6 h at study entry (166 subjects out of 310; 53.5%). Thus, these data support the use of IPX203 in the overall population, without excluding patients with shorter baseline “OFF” time.

In summary, the applicant adequately justified that safety was preserved across these patient’s populations and no consistent signal of excess risk (that would warrant excluding these subgroups of patients from IPX203 treatment) was identified.

Furthermore, the safety profile of IPX203 was also confirmed as consistent across **European and North America regions**. The incidence of TEAEs was in favour of European subjects: in North America, 49.2% of IPX203 subjects and 32.8% of IR LD-CD subjects experienced a TEAE; in Europe, the rates were 35.8% and 30.2%, respectively. SAEs and discontinuations due to AEs were also

comparable, and no deaths were reported in either region.

There were some differences between the two regions in terms of:

- Severity of illness (14.9% of patients in North America and 29.3% in Europe were in HY stage 3–4),
- Duration of PD (7.72 years in North America, 8.84 years in Europe),
- Sex distribution (30.1% female in North America, 38.2% in Europe).

The applicant pointed out the article of Athulya *et al* (2020) reporting that age, disease duration, disease severity (Hoehn & Yahr stage), duration of treatment with LD, TDD of LDD, and total LD equivalent dose were determinants of LD-induced dyskinesia. In the RISE-PD study, two of these predictors, i.e. higher severity and longer duration of PD, were more prevalent in the EU group. Another risk factor for developing dyskinesia is gender: the risk of dyskinesias is approximately three times higher in women compared to men (Cattaneo C., Pagonabarraga J. [2025]). The percentage of females was higher in the EU group compared to North America. Of note, all these differences between the two groups may have contributed to the lower “Good ON” time observed in the European population.

Renal disease

There are no published studies evaluating the PK of LD-CD in renally impaired patients. However, there is extensive clinical experience with LD-CD and review of the published literature has not highlighted or identified any significant safety concerns associated with use in renally impaired patients or those on haemodialysis. (Janzen *et al* 1999; Molnar *et al* 2006). In clinical practice, the dose of LD, generally, does not have to be adjusted in patients with renal failure.

The exact numbers of participants with mild and moderate renal impairment included in IPX203 clinical trials, and a summary of TEAEs and SAEs in these groups is detailed below.

Mild and moderate renal impairment

In the two Tables below it is presented, by study phase, the number of enrolled subjects showing abnormal baseline serum creatinine (but within studies inclusion criteria), categorised according to estimated glomerular filtration rate (eGFR) strata calculated using the CKD-EPI (2021) equation.

Table 59: Number of Patients with Renal Impairment in Phase 2 Studies (Safety Population)

CKD	eGFR (mL/min/1.73 m ²)*	IPX203	IR LD-CD	Rytary	All Comparators
Stage 2	60-89	1	1	0	1
Stage 3a	45-59	1	1	0	1
Stage 3b	30-44	1	1	1	1
Stage 4	15-29	0	0	0	0

Table 60: Number of Patients with Renal Impairment in Phase 3 Studies (Safety Population)

CKD	eGFR (mL/min/1.73 m ²)*	IPX203 OL	IPX203 DB	All IPX203	IR LD-CD OL	IR LD-CD DB	All IR LD- CD
Stage 2	60-89	21	10	21	24	11	24
Stage 3a	45-59	30	12	30	32	12	32
Stage 3b	30-44	10	6	10	11	1	11
Stage 4	15-29	0	0	0	0	0	0

An overall summary of AEs, by chronic kidney disease (CKD) stage, for both Phase 2 (in advanced PD patients) and Phase 3 studies (in PD patients with motor fluctuations) is presented below for the safety population.

Phase 2 Studies

Overall, one subject in IPX2023 group (Stage 3a) experienced a non-serious related TEAE of dyskinesia.

Phase 3 Studies – Stage 2 CKD

A higher percentage of IPX203 subjects experienced TEAEs (61.9%) as compared with those receiving IR LD-CD (41.7%). A higher percentage of IPX203 subjects experienced related TEAEs (47.6%) as compared with those receiving IR LD-CD (16.7%). A lower percentage of IPX203 subjects experienced serious TEAEs (4.8%) as compared with those receiving IR LD-CD (8.3%) (see Table above).

One subject in the IPX203 group experienced serious TEAEs (dehydration, syncope, depression).

One subject in IPX203 group experienced a TEAE (Parkinson's disease) leading to drug discontinuation.

No TEAEs leading to death were reported.

In IPX203 subjects, the most commonly reported TEAE ($\geq 5\%$ and occurring in at least two subjects) were: dyskinesia (23.8%), dizziness (9.5%), neck pain (9.5%), nasopharyngitis (9.5%), restlessness (9.5%), dry mouth (9.5%), nausea (9.5%), and fall (9.5%).

Phase 3 Studies – Stage 3a CKD

A higher percentage of IPX203 subjects experienced TEAEs (63.3%) as compared with those receiving IR LD-CD (21.9%). A higher percentage of IPX203 subjects experienced related TEAEs (36.7%) as compared with those receiving IR LD-CD (6.3%). A higher percentage of IPX203 subjects experienced serious TEAEs (6.7%) as compared with those receiving IR LD-CD (3.1%).

Two subjects in the IPX203 group experienced serious TEAEs (colitis, gastroenteritis viral, head injury, seizure, mental status changes). Five subjects in the IPX203 group experienced TEAEs leading to discontinuation (dyskinesia, freezing phenomenon, Parkinson's disease, seizure, nausea, head injury).

No TEAEs leading to death were reported.

In IPX203 subjects, the most commonly reported TEAE ($\geq 5\%$ and occurring in at least two subjects) were: dyskinesia (16.7%), nausea (10.0%), depression (10.0%), hallucination (6.7%), urinary tract infection (6.7%), fall (6.7%) (as outlined in the Tables below).

Phase 3 Studies – Stage 3b CKD

A higher percentage of IPX203 subjects experienced TEAEs (80.0%) as compared with IR LD-CD (45.5%) subjects. A higher percentage of IPX203 subjects experienced treatment-related TEAEs

(40.0%) as compared with IR LD-CD (18.2%) subjects. A higher percentage of IPX203 subjects experienced serious TEAEs (20.0%) as compared with IR LD-CD (0.0%) subjects.

Two subjects in the IPX203 group experienced serious TEAEs (acute myocardial infarction, cardiac failure, concussion, confusional state). One subject in the IPX203 group experienced TEAEs (nausea, vomiting) leading to drug discontinuation. No TEAEs leading to death were reported.

In IPX203 subjects, the most commonly reported TEAEs ($\geq 5\%$ and occurring in at least two subjects) were: blood creatinine increased (20.0%), dyskinesia (30.0%), hypertension (20.0%), musculoskeletal pain (20.0%).

Table 61: Summary of Adverse Events in Phase 3 Studies in PD Patients with Motor Fluctuations and Abnormal Renal Function (Safety Population)

	IPX203 OL	IPX203 DB	All IPX203	IR LD-CD OL	IR LD-CD DB	All IR LD-CD
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Stage 2 Chronic Kidney Disease						
N	N=21	N=10	N=21	N=24	N=11	N=24
TEAE	12 (57.1)	3 (30.0)	13 (61.9)	8 (33.3)	4 (36.4)	10 (41.7)
Treatment-related TEAE	9 (42.9)	2 (20.0)	10 (47.6)	3 (12.5)	1 (9.1)	4 (16.7)
Serious TEAE	1 (4.8)	0 (0.0)	1 (4.8)	1 (4.2)	1 (9.1)	2 (8.3)
Treatment-related Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to discontinuation	0 (0.0)	1 (10.0)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3a Chronic Kidney Disease						
N	N=30	N=12	N=30	N=32	N=12	N=32
TEAE	17 (56.7)	8 (66.7)	19 (63.3)	5 (15.6)	2 (16.7)	7 (21.9)
Treatment-related TEAE	9 (30.0)	3 (25.0)	11 (36.7)	2 (6.3)	0 (0.0)	2 (6.3)
Serious TEAE	2 (6.7)	0 (0.0)	2 (6.7)	1 (3.1)	0 (0.0)	1 (3.1)
Treatment-related Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to discontinuation	5 (16.7)	0 (0.0)	5 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3b Chronic Kidney Disease						
N	N=10	N=6	N=10	N=11	N=1	N=11
TEAE	8 (80.0)	2 (33.3)	8 (80.0)	4 (36.4)	1 (100)	5 (45.5)
Treatment-related TEAE	4 (40.0)	1 (16.7)	4 (40.0)	2 (18.2)	0 (0.0)	2 (18.2)
Serious TEAE	2 (20.0)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to discontinuation	1 (10.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 62: Most Common TEAEs by MedDRA PT Reported in Phase 3 Studies

TEAE MedDRA PTs	Stage 2 CKD %	Stage 3a CKD %	Stage 3b CKD %
Dyskinesia	23.8	16.7	30.0
Dizziness	9.5	3.3	0.0
Neck pain	9.5	0.0	0.0
Nasopharyngitis	9.5	0.0	0.0
Restlessness	9.5	0.0	0.0
Dry mouth	9.5	3.3	10.0
Nausea	9.5	10.0	10.0
Fall	9.5	6.7	10.0
Depression	4.8	10.0	0.0
Hallucination	0.0	6.7	10.0
Urinary tract infection	4.8	6.7	10.0
Blood creatinine increased	0.0	0.0	20.0
Hypertension	0.0	3.3	20.0
Musculoskeletal pain	0.0	3.3	20.0

The numbers of participants with CKD enrolled in the Phase 3 studies are low, which limits the conclusions that can be drawn. Nevertheless, in the DB period of Study IPX203-B16-02, IPX203-treated subjects with Stage 3a CKD showed higher rates of TEAEs (66.7% *versus* 16.7%) and treatment-related TEAEs (25.0% *vs* 0.0%) compared with IR LD-CD. Additionally, serious TEAEs and TEAEs leading to discontinuation reported in IPX203-treated subjects with Stage 3a and Stage 3b CKD across the study warranted further attention. These findings were of concern also in the context of carbidopa notably excreted unchanged in urine and likewise considering that IPX203 produces approximately four-fold higher CD systemic exposure than IR LD-CD, providing a plausible mechanistic basis for excess toxicity in patients with impaired renal clearance.

Consequently, the applicant identified the specific TEAEs driving the higher rates of treatment-related TEAEs in Stage 3a/b CKD subjects during the DB period of Study IPX203-B16-02, and all serious TEAEs and TEAEs leading to discontinuation across IPX203-treated subjects with Stage 3a/b CKD throughout the study.

Table 63: Treatment-related TEAE in Stage 3a/b CKD subjects during the double-blind period of Study IPX203-B16-02

Any Treatment-related TEAE	IPX203 double blind period N=18 n (%)		Immediate-release CD-LD double blind period N=13 n (%)	
	Safety set - CKD stage 3A/3B (KDIGO definition)		safety set - CKD stage 3A/3B (KDIGO definition)	
No of TEAE	4	(22.2%)	0	(0.0%)
Nervous system disorders	3	(16.7%)	0	(0.0%)
Dyskinesia	1	(5.6%)	0	(0.0%)
Headache	1	(5.6%)	0	(0.0%)
Somnolence	1	(5.6%)	0	(0.0%)
General disorders and administration site conditions	1	(5.6%)	0	(0.0%)
Fatigue	1	(5.6%)	0	(0.0%)

The higher rate of treatment-related TEAEs (22.2% in IPX203 versus 0.0% in IR CD-LD) was driven by 4 patients each, reporting dyskinesia, headache, somnolence and fatigue.

Table 64: Summary of Serious TEAEs in Study IPX203-B16-02

SAFETY SET - CKD STAGE 3A/3B (KDIGO DEFINITION)										
	Treatments									
	IPX203 Dose Conv. N=40 n (%) [E]	IPX203 DB N=18 n (%) [E]	IPX203 All N=40 n (%) [E]	IR CD-LD Dose Adj. N=43 n (%) [E]	IR CD-LD DB N=13 n (%) [E]	IR CD-LD All N=43 n (%) [E]				
Any Serious TEAE	4 (10.0%) [9]	0 (0.0%) [0]	4 (10.0%) [9]	1 (2.3%) [1]	0 (0.0%) [0]	1 (2.3%) [1]				
Gastrointestinal disorders	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	1 (2.3%) [1]	0 (0.0%) [0]	1 (2.3%) [1]				
Colitis	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Inguinal hernia	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]	1 (2.3%) [1]	0 (0.0%) [0]	1 (2.3%) [1]				
Injury, poisoning and procedural complications	2 (5.0%) [2]	0 (0.0%) [0]	2 (5.0%) [2]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Concussion	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Head injury	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Psychiatric disorders	2 (5.0%) [2]	0 (0.0%) [0]	2 (5.0%) [2]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Confusional state	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Mental status changes	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Cardiac disorders	1 (2.5%) [2]	0 (0.0%) [0]	1 (2.5%) [2]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Acute myocardial infarction	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Cardiac failure	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Infections and infestations	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Gastroenteritis viral	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Nervous system disorders	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Seizure	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				

N = patients in analysis set; n = number of patients with events; % = percentage based on N as denominator; E = number of events.
NOTE: Terms are sorted by frequency (overall).

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Table 65: Summary of TEAEs leading to treatment discontinuations in Study IPX203-B16-02

SAFETY SET - CKD STAGE 3A/3B (KDIGO DEFINITION)										
	Treatments									
	IPX203 Dose Conv. N=40 n (%) [E]	IPX203 DB N=18 n (%) [E]	IPX203 All N=40 n (%) [E]	IR CD-LD Dose Adj. N=43 n (%) [E]	IR CD-LD DB N=13 n (%) [E]	IR CD-LD All N=43 n (%) [E]				
Any TEAE leading to treatment discontinuation	6 (15.0%) [8]	0 (0.0%) [0]	6 (15.0%) [8]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Nervous system disorders	3 (7.5%) [4]	0 (0.0%) [0]	3 (7.5%) [4]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Dyskinesia	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Freezing phenomenon	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Parkinson's disease	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Seizure	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Gastrointestinal disorders	2 (5.0%) [3]	0 (0.0%) [0]	2 (5.0%) [3]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Nausea	2 (5.0%) [2]	0 (0.0%) [0]	2 (5.0%) [2]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Vomiting	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Injury, poisoning and procedural complications	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				
Head injury	1 (2.5%) [1]	0 (0.0%) [0]	1 (2.5%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]				

N = patients in analysis set; n = number of patients with events; % = percentage based on N as denominator; E = number of events.
NOTE: Terms are sorted by frequency (overall).

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For IPX203, all Serious TEAEs and TEAEs leading to drug discontinuation were registered only during the dose conversion phase.

The serious TEAEs reported in the IPX203 group, in a total of four patients, were: colitis, concussion, head injury, confusional state, mental status changes, acute myocardial infarction, cardiac failure, gastroenteritis viral and seizure.

The TEAEs leading to drug discontinuation reported in the IPX203 group, in a total of six patients, were: dyskinesia, freezing phenomenon, Parkinson's disease, seizure, nausea, vomiting, head injury.

The serious events reported in Stage 3a/3b subjects include seizure, confusional state, mental status changes, acute myocardial infarction, cardiac failure, and bradycardia, which overlap with the profile the applicant attributed to high carbidopa exposure.

Carbidopa systemic exposure with IPX203 is approximately 4.5-fold that of IR LD-CD, and approximately 30% of carbidopa is excreted unchanged in urine with a further fraction eliminated

renally as metabolites. In patients with reduced renal clearance, higher carbidopa exposure and the potential for accumulation are expected.

All serious TEAEs and TEAEs leading to discontinuation IPX203 subjects with stage 3a/3b (moderate) renal impairment occurred during the dose-conversion phase. The clustering of these events during such phase, before a stable dose is reached, indicates that the conversion step itself is the period of greatest risk in this population and that dose adjustment after conversion does not mitigate it. While the small number of stage 3a/3b subjects limits definitive conclusions, a relevant risk cannot be ruled out given the plausible mechanism. The potential effects of renal impairment on levodopa and carbidopa exposure are indirectly accounted for in dose titration. Nevertheless, dose adjustment should be conducted with caution in these special populations. Therefore, given the safety findings in stage 3a/3b subjects, higher carbidopa exposure, and its known renal excretion (as unchanged CD), the recommendations for appropriate clinical monitoring and caution on dose adjustment in the PI were extended from patients with severe renal impairment to those with moderate (renal) impairment (SmPC sections 4.2, 4.4, 5.2).

Hepatic insufficiency

There are no published data to suggest that LD use in patients with hepatic disease is associated with significant safety concerns. Levodopa has been used in the treatment of hepatic encephalopathy (Als-Nielsen *et al* 2004).

Mild and moderate hepatic impairment

The number of enrolled subjects, by study phase, showing abnormal baseline AST and/or ALT values (but within studies inclusion criteria) is summarised in the Tables below. Of note, stratification by Child-Pugh score was not possible due to the absence of data on hepatic encephalopathy, ascites, and INR.

Table 66: Number of Patients with Hepatic Impairment in Phase 2 Studies (Safety Population)

AST/ALT	IPX203	IR LD-CD	Rytary	All Comparators
Abnormal AST	1	1	1	1
Abnormal ALT	0	0	0	0

Table 67: Number of Patients with Hepatic Impairment in Phase 3 Studies (Safety Population)

AST/ALT	IPX203 OL	IPX203 DB	All IPX203	IR LD-CD OL	IR LD-CD DB	All IR LD-CD
Abnormal AST	5	3	5	5	2	5
Abnormal ALT	4	3	4	4	1	4

No TEAEs were reported in Phase 2 studies.

Phase 3 Studies – Abnormal AST

A higher percentage of IPX203 subjects experienced TEAEs (60.0%) as compared with those receiving IR LD-CD (40.0%). A higher percentage of IPX203 subjects experienced related TEAEs (20.0%) as compared with those receiving IR LD-CD (0.0%). A higher percentage of IPX203 subjects experienced serious TEAEs (20.0%) as compared with those receiving IR LD-CD (0.0%).

One subject in the IPX203 group experienced serious TEAEs (dehydration, syncope, depression). No TEAEs leading to discontinuation or death were reported.

In IPX203 subjects, the most commonly reported TEAE ($\geq 5\%$ and occurring in at least two subjects) was depression (40.0%).

Phase 3 Studies – Abnormal ALT

A lower percentage of IPX203 subjects experienced TEAEs (25.0%) as compared with those receiving IR LD-CD (50.0%).

No treatment related TEAEs, serious TEAEs or TEAEs leading to discontinuation or death were reported. No TEAEs were experienced by at least two subjects.

Table 68: Summary of Adverse Events in Phase 3 Studies in PD Patients with Motor Fluctuations and Abnormal Hepatic Function (Safety Population)

	IPX203 OL	IPX203 DB	All IPX203	IR LD-CD OL	IR LD-CD DB	All IR LD-CD
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abnormal Aspartate Aminotransferase						
N	N=5	N=3	N=5	N=5	N=2	N=5
TEAE	3 (60.0)	1 (33.3)	3 (60.0)	1 (20.0)	1 (50.0)	2 (40.0)
Treatment-related TEAE	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAE	1 (20.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal Alanine Aminotransferase						
N	N=4	N=3	N=4	N=4	N=1	N=4
TEAE	1 (25.0)	0 (0.0)	1 (25.0)	2 (50.0)	0 (0.0)	2 (50.0)
Treatment-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Overall, regarding hepatic impairment, the available sample is too small to draw meaningful conclusions. The applicant's proposed SmPC wording details that the potential effects of hepatic impairment on levodopa and carbidopa exposure are indirectly accounted for in dose titration (as referred to in sections 4.2, 4.4 and 5.2). Nevertheless, dose adjustment should be conducted with caution in patients with severe hepatic impairment, with appropriate clinical monitoring.

5.5.6. Immunological events

Not applicable.

5.5.7. Safety related to drug-drug interactions and other interactions

No drug-drug interaction (DDI) studies with IPX203 (LD-CD) have been performed. As with other LD-CD-containing products, the use of nonselective MAO inhibitors with IPX203 is contraindicated. The use of selective MAO-B inhibitors (e.g., rasagiline and selegiline) with IPX203 may be associated with orthostatic hypotension. Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone, metoclopramide) and isoniazid may reduce LD effectiveness. Iron salts or multi-vitamins containing iron salts can form chelates with LD and CD and cause a reduction in LD bioavailability from IPX203 (Sinemet SmPC 2023). The combination of different dopaminergic drugs may increase an

overall exposure to dopaminergic stimulation, some directly such as MAO-B inhibitors and some indirectly such as dopamine agonists.

Adverse Events by use of concomitant medications

In the Phase 3 studies pool, the proportion of IPX203 subjects who experienced TEAEs were comparable with the concomitant use of dopamine agonists (67.3%, n=202), selective MAO-B inhibitors (65.8%, n=129), amantadine (65.9%, n=83), anticholinergic PD medications (62.5% n=15), and other medications (74.6%, n=85). Similar comparable results were reported for serious TEAEs with the concomitant use of dopamine agonists (10.0%, n=30), selective MAO-B inhibitors (10.7%, n=21), amantadine (7.9%, n=10), anticholinergic PD medications (12.5%, n=3), and other medications (11.4%, n=13).

Overall, TEAE rates, were broadly comparable across the available co-medication subgroups, and no clinically meaningful safety signal attributable to any specific co-medication class was identified.

5.5.8. Vital signs and laboratory findings

Haematology

For the Phase 3 studies pool, a summary of haematological laboratory-related TEAEs is presented in the Table below.

Table 69: Haematological laboratory-related TEAEs: Phase 3 studies in PD patients with motor fluctuations (Safety Population)

Preferred Term	IPX203 Open-Label N=589		IPX203 Double-Blind N=256		All IPX203 N=589		IR LD-CD Open-Label N=630		IR LD-CD Double-Blind N=250		All IR LD-CD N=630		Total N=630	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Anaemia	6 (1.0)	8	2 (0.8)	2	8 (1.4)	10	0		2 (0.8)	2	2 (0.3)	2	10 (1.6)	12
Microcytic anaemia	1 (0.2)	1	0		1 (0.2)	1	0		1 (0.4)	1	1 (0.2)	1	2 (0.3)	2
Normochromic normocytic anaemia	1 (0.2)	1	0		1 (0.2)	1	0		0		0		1 (0.2)	1
Lymphocyte count decreased	2 (0.3)	2	1 (0.4)	1	3 (0.5)	3	0		0		0		3 (0.5)	3
Neutrophil count increased	2 (0.3)	2	0		2 (0.3)	2	0		0		0		2 (0.3)	2
Red blood cell count decreased	1 (0.2)	1	0		1 (0.2)	1	0		0		0		1 (0.2)	1
White blood cell count increased	1 (0.2)	1	0		1 (0.2)	1	0		0		0		1 (0.2)	1
Coronavirus test positive	1 (0.2)	1	0		1 (0.2)	1	0		0		0		1 (0.2)	1
Viral test negative	1 (0.2)	1	0		1 (0.2)	1	0		0		0		1 (0.2)	1

Source: ISS Table 5.1.2.3
Abbreviations: AE = adverse event; IR LD-CD = immediate-release levodopa-carbidopa; MedDRA = Medical Dictionary for Regulatory Activities; PD = Parkinson's disease
Note: n = number of subjects with events, m = number of events.
Percentages were based on the total number of subjects in the treatment group and population.
All reported terms coded with MedDRA Version 22.0.
Subjects were counted only once within each system organ class and preferred term.
The AEs were counted under the last treatment prior to the onset of the event.

Clinical Chemistry

For the Phase 3 studies pool, a summary of clinical chemistry laboratory-related TEAEs is presented in the Table below. None of the subjects across IPX203 studies (three analysis pools) met the Hy's Law criteria.

Table 70: Clinical chemistry laboratory-related TEAEs - Phase 3 studies in PD patients with motor fluctuations (Safety Population)

	IPX203 Open-Label N=589	IPX203 Double-Blind N=256	All IPX203 N=589	IR LD-CD Open-Label N=630	IR LD-CD Double-Blind N=250	All IR LD-CD N=630	Total N=630
Preferred Term	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m
Blood creatine phosphokinase increased	3 (0.5) 3	0	3 (0.5) 3	0	0	0	3 (0.5) 3
Blood alkaline phosphatase increased	1 (0.2) 1	1 (0.4) 1	2 (0.3) 2	0	0	0	2 (0.3) 2
Blood creatinine increased	2 (0.3) 2	0	2 (0.3) 2	1 (0.2) 1	1 (0.4) 1	2 (0.3) 2	3 (0.5) 4
Blood bilirubin increased	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Blood glucose increased	1 (0.2) 1	0	1 (0.2) 1	0	1 (0.4) 1	1 (0.2) 1	2 (0.3) 2
Blood potassium increased	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Blood sodium decreased	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Blood urea increased	1 (0.2) 1	0	1 (0.2) 1	0	1 (0.4) 1	1 (0.2) 1	1 (0.2) 2
Coronavirus test positive	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Viral test negative	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Hypokalaemia	3 (0.5) 3	0	3 (0.5) 3	0	0	0	3 (0.5) 3
Diabetes mellitus	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Hyperglycaemia	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Hyperuricaemia	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Vitamin D deficiency	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Hypercholesterolaemia	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2%) 1
Hyponatraemia	0	0	0	1 (0.2) 1	0	1 (0.2) 1	1 (0.2) 1

Source: ISS Table 5.1.2.3
Abbreviations: AE = adverse event; IR LD-CD = immediate-release levodopa-carbidopa; MedDRA = Medical Dictionary for Regulatory Activities; PD = Parkinson's disease
Note: n = number of subjects with events, m = number of events.
Percentages were based on the total number of subjects in the treatment group and population.
All reported terms coded with MedDRA Version 22.0.
Subjects were counted only once within each system organ class and preferred term.
The AEs were counted under the last treatment prior to the onset of the event

Urinalysis

A summary of urinalysis laboratory-related TEAEs reported in the Phase 3 studies pool is presented in the Table below.

Table 71: Urinalysis laboratory-related TEAEs - Phase 3 studies in PD patients with motor fluctuations (Safety Population)

	IPX203 Open-Label N=589	IPX203 Double-Blind N=256	All IPX203 N=589	IR LD-CD Open-Label N=630	IR LD-CD Double-Blind N=250	All IR LD-CD N=630	Total N=630
Preferred Term	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m
Urine uric acid increased	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
White blood cells urine positive	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Haematuria	2 (0.3) 2	0	2 (0.3) 2	1 (0.2) 1	0	1 (0.2) 1	3 (0.5) 3
Ketonuria	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1

Source: ISS Table 5.1.2.3
Abbreviations: AE = adverse event; IR LD-CD = immediate-release levodopa-carbidopa; MedDRA = Medical Dictionary for Regulatory Activities; PD = Parkinson's disease
Note: n = number of subjects with events, m = number of events.
Percentages were based on the total number of subjects in the treatment group and population.
All reported terms coded with MedDRA Version 22.0.
Subjects were counted only once within each system organ class and preferred term.
The AEs were counted under the last treatment prior to the onset of the event

Vital Signs

No clinically meaningful abnormal changes were noted from baseline to last post-baseline value in vital sign parameters across the IPX203 studies.

Electrocardiogram Evaluations

A summary of markedly abnormal ECG values in the Phase 3 studies pool is provided in the Table below and a summary of ECG-related TEAEs reported in Phase 3 studies pool is presented thereafter.

Table 72: Summaries of marketed abnormal ECGs values - Phase 3 studies in PD patients with motor fluctuations (Safety Population)

	IPX203 Open-Label N=589	IPX203 Double-Blind N=256	All IPX203 N=589	IR LD-CD Open-Label N=630	IR LD-CD Double-Blind N=250	All IR LD-CD N=630
Parameter (unit)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Criterion						
ECG Mean Ventricular Rate (beats/min)	479	253	521	22	250	264
Low: ≤ 50	26 (5.4)	14 (5.5)	36 (6.9)	2 (9.1)	12 (4.8)	13 (4.9)
High: ≥ 120	4 (0.8)	1 (0.4)	5 (1.0)	0	0	0
PR Interval, Aggregate (msec)	474	251	516	20	248	261
Low: ≤ 100	11 (2.3)	7 (2.8)	16 (3.1)	0	6 (2.4)	6 (2.3)
High: ≥ 220	30 (6.3)	9 (3.6)	34 (6.6)	1 (5.0)	19 (7.7)	19 (7.3)
QRS Duration, Aggregate (msec)	479	253	521	21	250	263
High: ≥ 120	50 (10.4)	20 (7.9)	60 (11.5)	1 (4.8)	36 (14.4)	33 (12.5)
QTcF Interval, Aggregate (msec)	478	253	520	21	250	263
High: ≥ 500	10 (2.1)	5 (2.0)	12 (2.3)	0	3 (1.2)	3 (1.1)
Increase >30 to 60 from baseline	48 (10.0)	18 (7.1)	57 (11.0)	0	18 (7.2)	17 (6.5)
Increase >60 from baseline	19 (4.0)	11 (4.3)	26 (5.0)	0	9 (3.6)	9 (3.4)

Source: Excerpt from ISS Table 8.1.4.2
Abbreviation: ECG = electrocardiogram; IR LD-CD = immediate-release levodopa-carbidopa, PD = Parkinson's disease
n = number of subjects meeting the criterion at least once post-baseline regardless of the baseline value.
Percentages were based on the total number of subjects in the treatment group in the safety population with a non-missing value at least once post-baseline.
Baseline was defined as the last assessment prior to the first administration of any study treatment in the pool

Table 73: Electrocardiogram-related TEAEs - Phase 3 studies in PD patients with motor fluctuations (Safety Population)

System Organ Class Preferred Term	IPX203 Open-Label N=589	IPX203 Double-Blind N=256	All IPX203 N=589	IR LD-CD Open-Label N=630	IR LD-CD Double-Blind N=250	All IR LD-CD N=630	Total N=630
	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m
Electrocardiogram QRS complex prolonged	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Electrocardiogram QT prolonged	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Electrocardiogram abnormal	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Electrocardiogram low voltage	1 (0.2) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Electrocardiogram repolarisation abnormality	0	1 (0.4) 1	1 (0.2) 1	0	0	0	1 (0.2) 1

Source: ISS Table 5.1.2.3
Abbreviations: IR LD-CD = immediate-release levodopa-carbidopa; MedDRA = Medical Dictionary for Regulatory Activities; PD = Parkinson's disease
Note: n = number of subjects with events, m = number of events.
Percentages were based on the total number of subjects in the treatment group and population.
All reported terms coded with MedDRA Version 22.0.
Subjects were counted only once within each system organ class and preferred term.
The AEs were counted under the last treatment prior to the onset of the event

In Study IPX203-102-23, the estimated slope of carbidopa plasma concentration in the concentration-QTc relationship was extremely shallow and not statistically significant: -0.00020 ms per ng/mL (90% CI: -0.001644 to 0.001237; P = 0.8141) with a very small and not statistically significant treatment effect-specific intercept of 0.75 ms. The effect on $\Delta\Delta\text{QTcF}$ can be predicted to 0.48 ms (90% CI: -1.00 to 1.97) at the geometric mean peak concentration for the carbidopa 400 mg dose (1333.8 ng/mL). Based on this concentration-QTc analysis, a QTcF effect ($\Delta\Delta\text{QTcF}$) exceeding 10 ms could be excluded within the full observed plasma concentrations of CD up to approximately 3000 ng/mL.

5.5.9. Post-marketing experience

IPX203 was approved in the US [via the 505(b)(2) pathway] on 7 August 2024 and launched in September 2024 under the brand name Crexont. In accordance with information available in the Periodic Adverse Drug Experience Report(s) (PADERs) no new safety concerns has been observed for IPX203.

5.5.10. In vitro biomarker test for patient selection for safety

Not applicable.

5.5.11. Overall discussion and conclusions on clinical safety

5.5.11.1. Discussion

5.5.11.1.1. Overall assessment of available safety data

The clinical safety evaluation of IPX203 is based on **seven clinical studies**: two early phase PK and bioavailability trials in healthy volunteers, two supportive Phase 2 studies (Study IPX203-B14-02 and Study IPX203-B16-01) in patients with Parkinson's disease, and the pivotal randomised, double-blind, active-controlled Phase 3 trial with its 9-month open-label extension 3 (Study IPX203-B16-02 and Study IPX203-B16-03, respectively). Additionally, two Phase 1 studies were conducted with carbidopa alone to further assess the safety and tolerability of its high doses, considering the higher systemic exposure observed with IPX203 compared with immediate-release LD/CD.

The safety database is of sufficient size, and the FU adequate for IPX203 intended use, and considering the long clinical experience with levodopa/carbidopa fixed-dose combination medicinal products in the (EU) market. In total, 731 participants received IPX203, 589 of which in the pivotal Phase 3 trial and its open-label extension in PD patients with motor fluctuations, which provided the main body of safety data.

In Study **IPX203-B14-02**, out of the 26 enrolled subjects, nine (34.6%) reported at least one TEAE. However, there were no deaths, SAEs or AEs that led to premature discontinuation. TEAEs were reported by more subjects during IR CD-LD (7/25; 28.0%) and IPX203 (5/26; 19.2%) treatments than during Rytary (2/25; 8.0%) treatment. The majority of TEAEs were mild, and none classified as severe. TEAEs reported by two or more subjects included dizziness (3 subjects), nausea (2), and hypertension (2).

In Study **IPX203-B16-01**, out of the 28 enrolled subjects, 11 (39.3%) reported TEAEs. A higher percentage reported TEAE(s) while taking IPX203 (10; 35.7%) than IR CD-LD (2; 7.4%). The incidence of reported TEAEs considered related to the study treatment was also higher in subjects receiving IPX203 than IR CD-LD (8 versus 1, respectively).

All reported TEAEs were assessed as mild or moderate. No severe TEAEs were reported. However, in IPX203 group seven subjects (25%) had one or more TEAEs with a maximal severity of mild and seven (25%) with a maximal severity of moderate. In IR CD-LD group, the number of subjects was much lower: two subjects (7.4%) had one or more TEAEs with maximal severity of mild, and one (3.7%) had one or more TEAEs with maximal severity of moderate.

One IPX203 subject experienced a treatment-emergent SAE (increased hypertension), assessed as not related to the treatment. Moreover, one subject experienced three SAEs (moderate dehydration, severe diarrhoea, and moderate atrial fibrillation) during the washout period, starting seven days after completing IPX203 treatment. One subject was withdrawn from the study due to intermittent moderate orthostatic hypertension. TEAEs reported by two or more subjects included dyskinesia (5 subjects), dizziness (2), and nausea (2); all these TEAEs occurred during IPX203 treatment. All other TEAEs occurred in a single subject each. Six subjects reported dopaminergic TEAEs during IPX203 treatment period; most of these events resolved with a dose reduction.

The applicant discussed possible reasons for the higher incidence of TEAEs (including those related to study treatment) in subjects receiving IPX203. Such higher incidence would be expected in a study population which had been using LD therapy for years and most probably caused by IPX203 higher bioavailability. This justification was considered acceptable.

In the pivotal **Study IPX203-B16-02**, 506 subjects were included in the Safety Analysis Set (SAS).

Overall, of the 630 enrolled, 57.9% experienced TEAEs: 49.1% who received IPX203 and 28.3% who received IR CD-LD. Thirty (4.8%) subjects experienced SAEs and 62 (9.8%) discontinued the study drug due to TEAEs. No deaths occurred during this study. During the dose adjustment period, higher number of subjects reported TEAEs in IPX203 group compared to IR CD-LD group. In IR CD-LD group, 118 (18.7%) subjects experienced TEAEs, including 31 (4.9%) treatment-related TEAEs. Six (1.0%) experienced TEAEs that led to discontinuation of the study drug and 7 (1.1%) experienced serious TEAEs. In IPX203 group 229 (38.9%) subjects experienced TEAEs, including 140 (23.8%) treatment-related TEAEs. Forty-two (7.1%) subjects experienced TEAEs that led to discontinuation of the study drug and 12 (2.0%) experienced serious TEAEs.

During the double-blind (DB) period, the number of TEAEs was higher in subjects receiving IPX203 (108 [42.2%]) compared with those receiving IR CD-LD (79 [31.6%]). Forty-two (16.4%) subjects who received IPX203 and 17 (6.8%) who received IR CD-LD experienced treatment-related TEAEs. Fourteen (5.5%) IPX203 subjects and 3 (1.2%) IR CD-LD ones experienced TEAEs that led to discontinuation of the study drug. Eight (3.1%) IPX203 subjects and 4 (1.6%) IR CD-LD subjects experienced serious TEAEs. Of note, during the DB period, 11 (4.3%) subjects in IPX203 group reported nausea, compared to 2 (0.8%) in IR CD-LD group. Moreover, dizziness was reported by six (2.3%) subjects in IPX203 group, compared to two (0.8%) in IR CD-LD group. Furthermore, seven subjects (2.7%) in IPX203 group reported anxiety, compared to zero subjects in IR CD-LD group.

The overall proportion of subjects who experienced at least one TEAE was higher in <65-year-old subjects (61.4%, n=236) *versus* those ≥65-year-old (55.8%, n=394). However, during the DB period there were no relevant differences in these percentages in both treatment groups in terms of TEAEs (IPX203: 44.0% *versus* 41.0% and IR CD-LD: 30.4% *versus* 32.3%, respectively). Similarly, there were no obvious differences in percentages of males and females who experienced TEAEs (57.8% *versus* 58.1%, respectively).

A higher proportion of subjects in North America (60.9%, n=327) experienced at least one TEAEs compared to European subjects (54.8%, n=303). However, the difference during the DB period was more pronounced in IPX203 group (49.2% *versus* 35.8%) compared to IR CD-LD group (32.8% *versus* 30.2%).

During the DB period, there were small differences in the percentage of subjects who experienced TEAEs between those with PD onset at ≥65 years and the ones with PD onset at <65 years (46.8% *versus* 40.7%, respectively in the IPX203 group and 32.6% *versus* 28.8%, respectively in the IR CD-LD group).

The most frequently reported TEAEs (≥2%) in subjects from IPX203 group were dyskinesia (45 [7.6%]), nausea (39 [6.6%]), dry mouth (27 [4.6%]), dizziness (23 [3.9%]), fall (17 [2.9%]), vomiting (16 [2.7%]), constipation, anxiety, insomnia (15 [2.5%]) subjects each, and headache (12 [2.0%]).

The most frequently reported TEAE (≥2%) in subjects who received IR CD-LD was fall (15 [2.4%]).

During the DB period, TEAEs were reported in 108 (42.2%) subjects who received IPX203 and in 79 (31.6%) who received IR CD-LD. The most frequently reported TEAEs (≥2%) in subjects who received IPX203 were nausea (11 [4.3%]), anxiety (7 [2.7%]), dizziness (6 [2.3%]), and dyskinesia and fall (each 5 [2.0%]). The most frequently reported TEAEs (≥2%) in subjects who received IR CD-LD were fall (9 [3.6%]), urinary tract infection (8 [3.2%]).

The majority of subjects experienced TEAEs that were either mild (171 [27.1%]) or moderate (156 [24.8%]) in severity; 38 (6.0%) subjects experienced severe TEAEs (4.4% on IPX203 total and 2.1% on IR CD-LD total).

During the DB period, eight (3.1%) subjects in IPX203 group and seven (2.8%) in IR CD-LD experienced severe TEAEs. The severe TEAEs in the IPX203 group were anxiety, feeling abnormal, nausea, dizziness,

dysesthesia, mixed hallucinations, and sciatica (each in one [0.4%] subject), and hypoesthesia and pain in extremity (in one [0.4%] subject). In those receiving IPX203, the time to resolution varied depending on the event type. Nevertheless, overall, the duration of events is not considered different from what would be expected.

The severe TEAEs experienced by subjects in IR CD-LD group were: atrioventricular block complete, asthenia, PD, mass, fatigue, back pain (each in one [0.4%] subject), and sciatica and limb injury (in one [0.4%] subject).

A total of 188 (29.8%) subjects experienced TEAEs considered treatment-related: 165 (28.0%) who received IPX203 in total (i.e., IPX203 dose conversion period and IPX203 DB period combined) and 47 (7.5%) who received IR CD-LD in total (i.e., IR CD-LD dose adjustment period and IR CD-LD DB period combined). Compared to IR CD-LD group, a higher number of subjects with treatment-related TEAEs was noted in IPX203 group.

During the DB period, 42 (16.4%) subjects in IPX203 group and 17 (6.8%) in IR CD-LD group experienced treatment-related TEAEs. The most frequently reported ones ($\geq 1\%$) experienced by IPX203 group subjects were nausea (7 [2.7%]), dyskinesia (5 [2.0%]), and feeling abnormal and fall (3 [1.2%] subjects each). The treatment-related TEAEs in the IR CD-LD group were noted in less than 1% of subjects.

Thirty (4.8%) subjects experienced serious TEAEs; 20 (3.4%) who received IPX203 and 10 (1.6%) who received IR CD-LD. Moreover, 62 (9.8%) experienced TEAEs that led to study drug discontinuation; 55 (9.3%) receiving IPX203 and 9 (1.4%) receiving IR CD-LD.

It can be agreed that no new, emerging safety issues have been reported in IPX203 – exposed subjects. Nevertheless, higher incidence of TEAEs (including treatment-related TEAEs) was noted. In this study, patients were typically converted to IPX203-based on their current most frequent individual IR dose, but with doses administered three times a day (TID). Investigators rarely increased the dose frequency of IPX203 beyond TID. Therefore, to increase the TDD, individual doses were increased. The expected result of this increase in LD per administration was an increase in dopaminergic side effects. One would expect this to increase the TEAE responses for IPX203 in both the dose titration and DB periods of the study. This justification (that an increase in dopaminergic side effects had been caused by increase in LD per administration) was endorsed.

Furthermore, based on the primary endpoint subgroup analysis (as discussed in Section 5.3.2.1), and with a close eye on safety-related matters, the applicant evaluated accurately IPX203 treatment in subjects (with):

- **≥ 65 years**

Safety profiles were comparable across subgroups (TEAEs in ≥ 1 subject: 59.1% for onset <65 years [n=470] *versus* 54.4% for onset ≥ 65 years [n=160]).

- **body weight of <75 kg**

No evidence of reduced tolerability or excess AEs (that would contraindicate IPX203 in lower weight subjects) was confirmed.

- **PD duration of ≥ 8 years**

It is known that LD PK may be altered by gastrointestinal dysfunctions such as dysphagia, delayed gastric emptying, constipation, bacterial infection, gut dysbiosis, diet, comorbidities and concomitant medication intake ([Leta et al, 2023](#)). These factors may contribute to non-optimal LD response, symptoms

fluctuations and unpredictable dyskinesia, and are more common in older patients and those with a PD onset in advanced age.

- **PD onset at ≥65 years**

Safety profiles were comparable across subgroups (TEAEs in ≥1 subject: 59.1% for onset <65 years [n=470] vs 54.4% for onset ≥65 years [n=160]).

- **“Off” time of <6 hours**

The proportion of subjects with at least one TEAE was higher in subjects who reported “OFF time” of ≥6 h (199 subjects out of 320, 62.2%) *versus* those who reported <6 h at study entry (166 subjects out of 310; 53.5%). Thus, these data support the use of IPX203 in the overall population, without excluding patients with shorter baseline “OFF time”.

In summary, it was adequately justified that safety was preserved across the patient populations above listed and no consistent signal of excess risk was identified that would warrant excluding these subgroups of patients from IPX203 treatment.

In the OLE Study **IPX203-B16-03** a total of 419 enrolled subjects were included in the SAS. Overall, the 52.7% experienced TEAEs: 51.5% from the previous IPX203 group and 54.0% from the previous IR CD-LD group. A total of 66 (15.8%) subjects experienced treatment-related TEAEs; 25 (6.0%) TEAEs led to discontinuation of the study drug and 42 (10.0%) were serious TEAEs. Six subjects died during this study. The most frequently reported TEAEs in both groups were dyskinesia, fall and urinary tract infection (21 [5.0%]), back pain (15 [3.6%]) and constipation (11 [2.6%]). These TEAE can be considered well-known safety issues of CD-LD. The majority of subjects experienced TEAEs that were either mild (107 [25.5%]) or moderate (77 [18.4%]) in severity; 37 (8.8%) experienced severe TEAEs. In total, three severe TEAEs of volvulus, fall, and seizure were reported in two (0.5%) subjects each, while the remaining severe TEAEs were reported in one (0.2%) subject each.

Sixty-six (15.8%) subjects experienced treatment-related TEAEs and the most frequently reported ones were dyskinesia (19 [4.5%] subjects) and nausea (4 [1.0%]).

Subjects **aged ≥65 years** experienced higher rates of both **TEAEs** (55.8% vs 47.4%) and **SAEs** (12.0% vs 6.6%) compared to those **under 65**. Urinary tract infections (6.7% vs 2.0%), falls (6.4% vs 2.6%), and hallucinations (3.0% vs 0%) were more frequently reported by subjects **aged ≥65 years** than by **those under 65**.

The incidence of TEAEs and SAEs was comparable between subjects with a PD duration of **<8 years** (55.4% and 10.2%, respectively) and those with a duration of **≥8 years** (50.6% and 9.9%, respectively).

The incidence of dyskinesia was higher in subjects with a PD duration of **≥8 years** than in those with **<8 years** (6.4% vs 3.2%). The AEs experienced by 32 (7.6%) subjects enrolled in Study IPX203-B16-02 were resolved only after entering the OLE Study IPX203-B16-03: 20 (4.8%) of the resolved TEAEs included constipation [3 subjects]; radius fracture, weight decreased, decreased appetite, back pain, insomnia [2 subjects each] and the remaining were in 1 subject each.

However, in 112 (26.7%) subjects the AEs were not resolved. These included dry mouth (14 subjects); dyskinesia (9); orthostatic hypotension (7); fatigue, somnolence, depression, hypertension (6 subjects each); constipation, back pain (5 subjects each); dyspepsia, hallucination, visual (4 subjects each); blood pressure increased, arthralgia, pain in extremity, anxiety, insomnia, headache (3 subjects each); atrial fibrillation, vision blurred, pain, decreased appetite, arthritis, muscle spasms, musculoskeletal pain, neck pain, balance disorder, carpal tunnel syndrome, cognitive disorder, freezing phenomenon, hypoaesthesia,

affect lability, asthma, hypotension (2 subjects each) and the remaining were in one subject each.

Six subjects died during the OLE study. Five of these deaths were unrelated to the study drug; the remaining case was a severe SAE of drowning considered related to IPX20. Other deaths were caused by subarachnoid haemorrhage, cardiogenic shock, pulmonary embolism, volvulus and sepsis.

Forty-two (10.0%) subjects experienced serious TEAEs. The most commonly reported TEAEs were COVID-19, seizure, and confusional state (each in three subjects), and atrial fibrillation, volvulus, pneumonia, femur fracture, syncope, psychotic disorder, chronic obstructive pulmonary disease, and pulmonary embolism (each in two subjects).

All of these serious TEAEs were assessed as not related to the study drug, except for fall, polyneuropathy, hypersensitivity, psychotic disorder, overdose, drowning, and pyrexia and delirium. Six serious TEAEs were fatal. Four serious TEAEs were not recovered/not resolved prior to study end: scoliosis, colitis, delirium, and cauda equina syndrome.

Overall, the AE profile observed across IPX203 development programme is largely consistent with the known safety profile from other LD/CD formulations. The most common ADRs were dyskinesia, nausea, dry mouth and dizziness. The distribution of events between treatment groups was broadly comparable. Analyses of SAEs and AEs leading to drug discontinuation did not raise new or unexpected safety concerns compared to other LD/CD products.

Furthermore, the subgroup analyses did not reveal new, emerging safety concerns. Special attention was paid to IPX203 administration in case of renal impairment.

Subjects with stage 3a/3b chronic kidney disease (CKD) had higher rates of treatment-related TEAEs with IPX203 than with IR LD-CD. All serious TEAEs and TEAEs leading to discontinuation in IPX203-treated Stage 3a/3b subjects occurred during the dose-conversion phase. Carbidopa systemic exposure with IPX203 is approximately 4.5-fold that of IR LD-CD, and approximately 30% of CD is excreted unchanged in urine, with a further fraction eliminated renally as metabolites. Therefore, higher exposure and accumulation are expected with reduced renal clearance. The SAEs reported in these subjects including seizure, confusional state, mental status changes, acute myocardial infarction, cardiac failure, and bradycardia, overlap with the profile the applicant itself attributes to high carbidopa exposure.

All serious TEAEs and TEAEs leading to discontinuation of IPX203 in subjects with stage 3a/3b (moderate) renal impairment occurred during the dose-conversion phase. The clustering of these events in this phase, before a stable dose is reached, indicates that the conversion step itself is the period of greatest risk in this special population and that dose adjustment after conversion does not mitigate it. While the small number of stage 3a/3b subjects limits definitive conclusions, a relevant risk cannot be ruled out, given the plausible mechanism. The potential effects of renal impairment on levodopa and carbidopa exposure are indirectly accounted for in dose titration. Nevertheless, dose adjustment should be conducted with caution in 3a/3b CKD subjects. Thus, given these safety findings, recommendations for appropriate clinical monitoring and caution on dose adjustment for patients with moderate to severe renal impairment are outlined in the PI. With regard to the elderly population, in the DB period of study IPX203-B16-02, older subjects, particularly those aged ≥ 75 to < 85 years treated with IPX203 showed higher rates of treatment-related TEAEs (22.9% *versus* 6.7%), serious TEAEs (11.4% *versus* 2.2%), and TEAEs leading to discontinuation (11.4% *versus* 4.4%) as compared with IR LD-CD. The applicant identified the contributing events, which were predominantly dopaminergic, along with serious cases of epilepsy and bradycardia. Exposure above 75 years is uncharacterised: no popPK analysis was conducted, and no PK was assessed in the Phase 3 studies. Therefore, as experience with IPX203 in patients aged 75 years and older is limited (e.g., no patients above 85 have been enrolled in any IPX203 clinical trial), the SmPC (section 4.2, 4.4, 5.2) details that these patients should be converted cautiously from IR levodopa/DDCI into IPX203. Close clinical monitoring is recommended during the conversion period and subsequent dose optimisation, in line with

standard clinical practice for older patients during dopaminergic therapy adjustments. Also of note, the dopaminergic ADRs these patients might be more susceptible to (outlined in SmPC section 4.4) include dyskinesia, hallucinations, confusion, somnolence, orthostatic hypotension, syncope and falls. In addition, the safety profile of IPX203 was consistent across both European and North American regions. Concerning TEAEs incidence: in North America 49.2% of IPX203 and 32.8% of IR LD-CD subjects experienced a TEAE, respectively; in Europe, the rates were 35.8% and 30.2%, respectively. SAEs and discontinuations due to AEs were also comparable. No deaths were reported in either region. There were some differences between the two regions in terms of:

- Severity of illness (14.9% of patients in North America and 29.3% in Europe were in HY stage 3–4),
- Duration of PD (7.72 years in North America, 8.84 years in Europe),
- Sex distribution (30.1% female in North America, 38.2% in Europe).

Athulya *et al* (2020) reported that age, disease duration and severity (Hoehn & Yahr stage), duration of treatment with LD, TDD of LDD, and total LD equivalent dose were determinants of LD-induced dyskinesia. In the pivotal trial, two of these predictors, i.e., higher severity and longer duration of PD, were more prevalent in the EU group. Another risk factor for developing dyskinesia is gender: the risk is approximately three times higher in women compared to men (Cattaneo C., Pagonabarraga J. [2025]). The percentage of females was higher in the EU group compared to the North American one. All these differences may have contributed to the lower “Good ON” time observed in the European population.

No relevant safety signals were seen in laboratory tests or vital signs. Abnormal ECG values and ECG-related TEAEs were low and similar to IR LD/CD overall. In the TQT study, AEs were infrequent and mostly mild and carbidopa showed no exposure-response effect on QTc, supporting no meaningful QT prolongation at therapeutic and high CD exposures.

The overall methodology used to define ADRs in the SmPC is also acceptable.

5.5.11.1.2. Adverse drug reactions (ADRs) in the SmPC

The ADRs proposed by the applicant for inclusion in the SmPC, as described above, are overall acceptable.

Furthermore, as triggered by the PRAC recommendation for CMDh attention pertaining to EMA/PSUR/0000327864 for carbidopa / levodopa (NAP), also applicable to Hopledo, the following ADR should be included in the SmPC (and PL, accordingly).

Table 74: ADRs proposed for inclusion in the SmPC by the PRAC

SOC: Metabolism and nutrition disorders	
PT: Vitamin B6 deficiency	Frequency: ‘common’

In addition, the CHMP agreed that the text below, also recommended by PRAC to CMDh in the framework of procedure EMA/PSUR/0000327864, should be included in SmPC section 4.4 (and PL, accordingly), to complement the update of SmPC section 4.8, as noted above:

- ‘Treatment with carbidopa/levodopa can lead to vitamin B6 deficiency, which may increase the risk of seizures, particularly in patients receiving higher doses, and/or those with poor nutritional status. Monitoring of pyridoxine (vitamin B6) levels and vitamin B6 supplementation should be considered in patients receiving high-dose carbidopa/levodopa and those presenting with clinical manifestations suggestive of vitamin B6 deficiency’.

5.5.11.2. Conclusions on clinical safety

The safety profile of IPX203 is acceptable and consistent with the long-standing clinical experience with levodopa/carbidopa. The PI reflects accordingly the need for dose adjustment and/or careful clinical monitoring in patients with (moderate to severe) renal or (severe) hepatic impairment. Furthermore, it details that elderly patients should be converted cautiously from immediate-release levodopa/DDCI. Close clinical monitoring is also recommended during the conversion period and subsequent dose optimisation, in line with standard clinical practice for older patients during dopaminergic therapy adjustments, as they would be more susceptible to dopaminergic adverse reactions.

6. Risk management plan

6.1. Safety specification

Table 75: Summary of safety concerns in the Risk Management Plan

Important identified risks	None
Important potential risks	None
Missing information	None

The safety concerns listed by the applicant in the proposed RMP are consistent with the known safety profile of levodopa/carbidopa-containing medicinal product already placed in the (European) market. No additional important risks or missing information have been identified. No resulting considerations are therefore raised. The safety specification is considered acceptable by PRAC and CHMP.

6.2. Pharmacovigilance plan

No routine pharmacovigilance (PhV) activities beyond adverse reactions reporting and signal detection are proposed by the applicant. Furthermore, no additional PhV activities are considered required.

The safety profile of carbidopa/levodopa fixed-dose combination is considered well characterised. Therefore, the applicant's proposals are endorsed by PRAC and CHMP.

6.3. Plans for post-authorisation efficacy studies

Not applicable.

6.4. Risk minimisation measures

No routine or additional risk minimisation measures (RMMs) have been proposed by the applicant, which is endorsed by PRAC and CHMP.

6.5. RMP summary and RMP annexes overall conclusion

The summary of the RMP and the RMP Annexes are in line with other sections of the document. Therefore,

they are endorsed by PRAC and CHMP.

6.6. Overall conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines' web-portal.

The CHMP considered that (e.g. regarding therapeutic indication, posology, pharmaceutical form) Hopledo does not differ significantly from the already approved medicinal products containing carbidopa/levodopa. Therefore, it should be added to the existing entry in the EURD list for carbidopa/levodopa (NAP) fixed-dose combination and follow a 3-year PSUR cycle. Hopledo first PSUR data lock point (DLP) will be 1 October 2028.

8. Product information

8.1. Summary of product characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The wording of the indication has been agreed to be as follows:

- *Hopledo is indicated for the treatment of adult patients with Parkinson's disease and moderate to severe motor fluctuations **who have not been sufficiently stabilised** with oral levodopa/dopa decarboxylase (DDC) inhibitor based treatment regimens.*

The applicant's initially proposed text (detailed below) was not considered adequate by CHMP:

- *Hopledo® is indicated for the treatment of adult patients with Parkinson's disease and moderate to severe motor fluctuations **who cannot be stabilised** on levodopa/dopa decarboxylase (DDC) inhibitor treatment and/or other available Parkinson oral medicinal products.*

It appeared contradictory to state that Hopledo, with its mix of oral IR and PR levodopa/carbidopa, should be indicated for PD patients "*who cannot be stabilised*" on oral medications (i.e., in line with the approved products for continuous infusions via the duodenal or subcutaneous routes) since this medicinal product indeed is an[other] oral Parkinson's disease medication.

The CHMP expressed that the modest improvement of “Good on time” and “OFF time” could not be considered to make the difference between “stabilisation” and “non-stabilisation” of PD for the proposed target population.

Thereafter, the applicant justified the modest statistical effect of IPX203 over the MR / IR levodopa with the complex study design and strict titration rules and timings, which were acknowledged by CHMP. Notwithstanding, the benefit, as shown in the study conditions, is considered scarce in clinical terms. While this population mean benefit is small, it may, nonetheless, be relevant to the individual patients, along with the better convenience of three intakes per day. The latter was considered an advantage by CHMP, especially for elderly patients with moderate-severe motor fluctuations and/or those who cannot handle infusion pumps or are not eligible for deep brain stimulation (DBS) treatment.

Also, of note: in the course of the procedure, the applicant provided analyses in various subpopulations, looking at different stages of disease severity (e.g., less or more than 6 hours “OFF time” at baseline), with long “OFF time” duration, observing that the effect size is preserved in all disease’s states.

8.2. Labelling

8.2.1. User consultation

The user test for Hopledo was performed by “Knowhownow”. The key outcomes of this test are listed below:

- Overall, the test methodology was considered acceptable;
- The inclusion and exclusion criteria for the recruitment were well described;
- The key safety issues were appropriately targeted through the questionnaire, reflecting the safe and correct use of the medicinal product:
- An appropriate number of subjects was enrolled: the test consisted of two rounds of testing with ten participants each;
 - The most important aspects of the leaflet were covered by the test and the results adequately presented;
- The overall impression of the leaflet (content, layout, font size, language, etc.) was considered generally positive by the users and “Knowhownow” did not recommend any changes to the leaflet based on the comments made in this context.

Overall, the PL user testing for Hopledo was well performed and executed. It contained all the necessary information in a way that is accessible and understandable to those who participated in this test.

8.2.1.1. Conclusion from the checklist for the review of user consultation

The results of the user consultation with target patient groups on the PL submitted by the applicant showed that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

Parkinson's disease (PD) is a common neurodegenerative disorder. The prevalence is increasing, both due to ageing of the population and other non-identified causes. According to the Global Burden of Disease (GBD) 2021 study, the global prevalence of PD was estimated at 138.6/100,000 people and caused 388,000 deaths in the world population. By 2035, age-standardised rates of incidence and prevalence will increase from 14.62/100,000 and 139.79/100,000, noted in 2021, to 20.20/100,000 and 165.05/100,000, respectively (Luo *et al* 2025). In Europe, in a projection between 2021 and 2050, the all-age prevalence of PD was estimated between 152/100,000 and 267/100,000, respectively (Su *et al* 2025).

The early stages of the disease are mostly well controlled with the available medications, but when the patient develops motor fluctuations, the control of the disease becomes a challenge.

Hopledo is proposed for the treatment of adult PD patients with moderate to severe motor fluctuations who have not been sufficiently stabilised with oral levodopa/dopa decarboxylase (DDC) inhibitor-based treatment regimens.

9.1.2. Available therapies and unmet medical need

Levodopa (LD), in combination with carbidopa (CD), is considered an efficacious treatment for the motor symptoms of PD, and nearly all PD patients require LD treatment as the disease progresses (Jankovic and Poewe 2012). Despite the available treatment options, including adjunctive therapies and rescue medications, disease progression and LD exposure are the major factors in the development of motor complications, and most patients with PD experience motor complications, including wearing-OFF and peak-dose dyskinesias, after several years of LD treatment (Fabbri *et al* 2023). Currently, there is no curative or disease-modifying treatment available for PD. A fluctuating response to medication(s) has been identified as the main concern among PD patients.

Most approved anti-PD medicinal products may be used either in Parkinson's early or advanced (with motor fluctuations) disease: immediate-release (IR) levodopa (LD) + dopa decarboxylase inhibitors (DDCI), anticholinergics, dopamine agonists (DAs), amantadine, monoamine oxidase inhibitors (MAOI). The exceptions are controlled release forms of LD+DDI and catechol-o-methyltransferase inhibitors (COMTI), which are reserved in Parkinson's advanced disease.

No long-acting preparation of LD combining the advantages of IR and ER components in a modified-release (MR) LD-CD oral combination is currently available in the EU market. In 2015, Numient, the first-generation MR oral formulation, was registered through the centralised procedure and withdrawn in 2019 without being commercialised.

Hopledo (IPX203) is a novel oral MR levodopa-carbidopa multi-particulate capsule formulation, with a proprietary innovative release system to allow better targeting of the active ingredient(s) and a more efficient therapeutic action. The IPX203 capsule has two components: component I contains IR granules and component II ER-coated beads. The IR granules contain 100% of CD dose and 25% of LD dose. The ER part of IPX203 is structured as follows:

- An enteric polymer that prevents the pellets from disintegrating too early in the stomach;

- A mucoadhesive polymer designed to keep the ER beads adhered to the area of absorption longer to sustain LD plasma levels. The exact site and duration of absorption are unknown;
- A sustained-release polymer which releases LD slowly;
- A drug core that contains 75% of the total LD dose in a IPX203 capsule. The ER beads do not contain carbidopa.

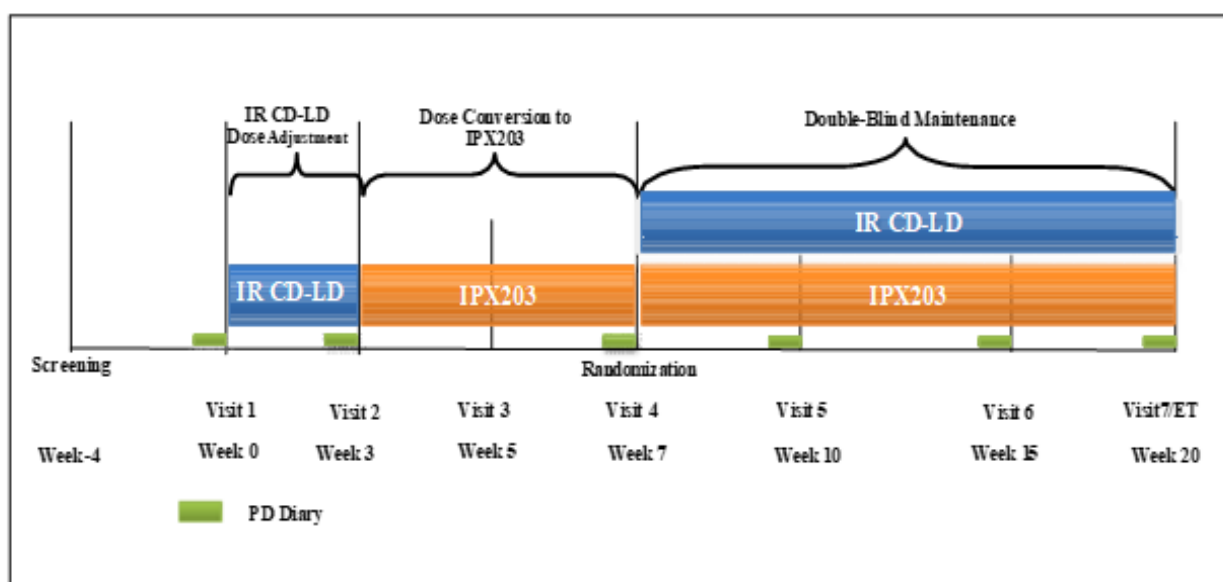
This formulation was developed and designed to combine a dual-release mechanism and thereby provide fast attainment of therapeutic LD plasma concentrations to ensure early onset of effect and maintain the desired concentrations for a longer duration with minimal peak-to-trough-fluctuations than what would be provided by other authorised oral LD-CD products. When administering IPX203, LD from IR granules produces an initial boost of LD exposure, with a rapid onset of effect, followed by continuous LD supply from the ER beads. With a prolonged duration of stable therapeutic concentrations after each dose, IPX203 is designed to achieve better control PD symptoms, fewer motor fluctuations or unfavourable side effects such as dyskinesia, less frequent dosing, enhanced patient's compliance, and possibly improved quality of life in PD patients. Additionally, IPX203 design would allow for dosing intervals of approximately 6-8 hours (TID; range: 2 to 4 times/day) in PD patients with motor fluctuations.

In summary, Hopledo would avoid the limitation of slow initial release and the consequent latency to improvement of motor symptoms seen with controlled-release (CR) formulations.

9.2. Main clinical studies

IPX203-B16-02 is a Phase 3, randomised, double-blind, double-dummy, active-controlled, parallel-group, prospective, multicentre study that evaluated safety and efficacy of IPX203 in comparison to IR LD-CD in the treatment of LD-CD experienced subjects with PD who had motor fluctuations, (despite being) treated with stable regimens of IR LD-CD.

Figure 19: Study IPX203-B16-02 scheme



The study had up to 4-week screening period, a 3-week open-label IR CD-LD dose adjustment period, a 4-week open-label period for conversion to IPX203, and a 13-week DB, double-dummy treatment period.

Subjects were randomised in a 1:1 ratio, and stratified by centre, to receive either IPX203 (with matching IR CD-LD placebo) or IR CD-LD (with matching IPX203 placebo). They continued to take permitted non-CD-LD-based PD medications throughout the study, if documented in their pre-study regimen, and if dosing regimens had been stable for at least 4 weeks prior to Visit 1. A “stable dosing regimen” meant no change in dose or dosing frequency.

On Week 7 at visit four subjects were randomised in 1:1 ratio into one of two DB parallel treatment arms of IPX203 (and matching IR CD-LD placebo) or IR CD-LD (and matching IPX203 placebo).

This pivotal study, with a formulation to be given TID for the treatment of fluctuating PD patients, had an acceptable study design to assess motor control in PD patients.

9.3. Favourable effects

IPX203 provided maintenance of effect of the optimised scheduled TID treatment (every 8 hours of daytime) with minimal loss (0.5 h), as compared to IR LD (loss of 1.03 h), in the randomised withdrawal study described above, after previous treatment optimisation. The maintenance of “Good ON time” was not at the expense of increased “OFF time” (0.38h, compared to 0.86h with IR LD), nor sleep time. It was further supported by the Patient Global Impression of Change (PGI-C) score where 29.7% of patients felt “much” or “very much improved”, as compared to 18.8% of patients on IR LD.

9.3.1. Uncertainties and limitations about favourable effects

From an efficacy perspective, uncertainties remain regarding the observed 0.53-hour difference between IR-LD and IPX203 in patients already benefiting from over 10 hours of “Good ON” quality on distribution of dyskinesias, among the patients with different levels of improvement in motor fluctuations, and on the results of the performed PEP analysis per subgroups. Notably, the favourable effects are driven by subjects aged <65 years.

The pivotal study IPX203-B16-02 applied sequential open-label run-in phases (IR LD/CD dose adjustment and IPX203 conversion/stabilisation) before randomisation. Consequently, only subjects who tolerated and responded to IPX203 were randomised. This potentially introduced selection bias and impacted validity of the estimated treatment effect. Furthermore, the high dropout rate, particularly the 83 subjects who withdrew during the dose conversion period, might have impacted the efficacy results. However, these discontinuations were mostly due to the transition to IPX203 falling below the patients’ expectations (32 out of the 83 subjects who discontinued, while in the IPX203 conversion period, had their reason described). The majority reported that the treatment had failed to meet their expectations in terms of efficacy or symptom control or lack of efficacy (10 subjects) rather than due to AEs.

In general, the impact of these 83 dropouts on the overall efficacy and safety should be interpreted in the context that IPX203 is a new MR formulation designed to replace IR LD-CD in PD patients with motor fluctuations. Conversion to IPX203 involved dose titration, including transient lack of efficacy or dopaminergic AEs, which could lead to discontinuation. The initial suggested IPX203 doses in the protocol were based on average bioavailability relative to IR LD-CD. However, most subjects required individualised up-titration or down-titration to achieve an optimal balance of efficacy and tolerability. During the 4-week IPX203 dose-conversion period, 83 subjects (14.1%) discontinued primarily due to AEs and lack of efficacy. It is agreed that these discontinuations largely reflected the process of establishing a clinically effective and tolerable IPX203 regimen rather than inherent lack of efficacy of IPX203.

Overall, the observed magnitude of effect of IPX203 was small (0.53 hour) as compared to IR-LD, but IPX203 was administered three times a day while IR-LD was to be taken five times a day. The fact that the three oral formulations of IPX203 performed better than the five of IR-LD suggested that the time of intake is less critical for IPX203 than with IR-LD, representing an inherent advantage in the target patient’s population, especially elderly patients with moderate-severe motor fluctuations and/or those who cannot handle infusion pumps or are not eligible for deep brain stimulation (DBS) treatment.

9.4. Unfavourable effects

In total, 731 participants received IPX203: 589 were enrolled in the pivotal Phase 3 trial and its 9-month open-label extension (Study IPX203-B16-03) in PD patients with motor fluctuations, providing the main body of safety data. The adverse event (AE) profile is largely consistent with the known safety profile from other LD/CD formulations. The most common adverse drug reactions (ADRs) were dyskinesia, nausea, dry mouth and dizziness. Most events were mild in severity and their distribution between treatment groups was broadly comparable. In line with the established LD/CD safety profile, the principal identified risks remain dyskinesia, psychosis-related events, impulse control disorders, orthostatic hypotension, somnolence/sudden sleep onset, and neuroleptic malignant syndrome. These are recognised class risks, already addressed through routine SmPC warnings, and do not appear to be increased in frequency or severity with IPX203 compared with other formulations. Melanoma is also retained, in accordance with the class labelling.

9.4.1. Uncertainties and limitations about unfavourable effects

Overall, there were no new and unknown safety issues reported during the clinical development programme. However, higher incidence of TEAEs, including serious TEAEs and TEAEs that led to study discontinuation, were observed in subjects receiving IPX203 compared to IR CD-LD, particularly in older participants. The main uncertainties relate to subgroup characterisation of elderly and patients with renal impairment. Exposure in older patients, especially those above 75 years, remains uncharacterised, as no population PK analysis was conducted, no PK data were assessed in the Phase 3 studies, and no patient above 85 years was enrolled in IPX203 clinical trials. In addition, a treatment-related TEAE signal was observed in subjects with stage 3a/3b chronic kidney disease (CKD). However, the numbers of Stage 3a/3b subjects CKD were small, which limits, but does not exclude, a relevant risk, given the plausible mechanism. These uncertainties and limitations have been carefully reflected in the product information (PI).

9.5. Effects table

Table 76: Effects Table

Effect (short description)	Treatment	Control	Uncertainties/Strength of evidence	Reference
Favourable effects				

Effect (short description)	Treatment	Control	Uncertainties/Strength of evidence	Reference
Change from baseline in "Good ON" time at the end of the double-blind period	-0.50h (-0.86; -0.14)	-1.03h (-1.39; -0.67)	SoE: randomised withdrawal study comparing return to immediate release vs. IPX203 after treatment optimisation Unc: moderate population, with >10h good on time overall; relevance of a difference of 0.53 h per day	Study IPX203-B16-02
Change from baseline in "OFF" time at the end of the double-blind period (LS-mean)	0.38h (0.04; 0.71)	0.86 (0.52; 1.19)	SoE: randomised withdrawal study comparing return to immediate release vs. IPX203 after treatment optimisation Unc: relevance of a difference in 0.48 h in off time	Study IPX203-B16-02
PGI-C Scores (%): Difference between groups ("much" or "very much improved")	29.7	18.8	SoE: Patient global impression of change is a relevant endpoint in PD Unc: Relevance of 10.9% difference in those who show a much improvement in advanced disease population	Study IPX203-B16-02
Unfavourable effects				
Dyskinesia (participants affected during the conversion period in the Phase 3 study)	40/589 (6.8%)	-	Most cases were mild to moderate. Class effect.	Study IPX203-B16-02
Other motor and non-motor ADRs consistent with LD/CD class profile: (participants affected during the conversion period in the Phase 3 study) Nausea dry mouth dizziness	29 / 589 (4.9%) 25 / 589 (4.2%) 17 / 589 (2.9%)	- - -	Notable differences observed in treatment-related TEAEs within the Nervous System Disorders SOC in subjects aged ≥75 to <85 years, during the double-blind study period	Study IPX203-B16-02
Higher incidence of adverse events in older patients (particularly ≥75 years)	Serious TEAE 11.4%	Serious TEAE 2.2%	Higher rates in serious TEAEs, treatment related TEAEs and TEAEs leading to discontinuation, proportionally larger with age and most evident at 75 years and over. Uncharacterised relation to dose-conversion scheme and resulting drug exposure. No demonstrated efficacy benefit for ≥65 years.	Study IPX203-B16-02

Effect (short description)	Treatment	Control	Uncertainties/Strength of evidence	Reference
Higher incidence of adverse events in older patients (particularly ≥75 years)	Treatment-related TEAE 22.9%	Treatment - related TEAE 6.7%	Higher rates in serious TEAEs, treatment related TEAEs and TEAEs leading to discontinuation, proportionally larger with age and most evident at 75 years and over. Uncharacterised relation to dose-conversion scheme and resulting drug exposure. No demonstrated efficacy benefit for ≥65 years.	Study IPX203-B16-02
Higher incidence of adverse events in older patients (particularly ≥75 years)	TEAEs leading to discontinuation 11.4%	TEAEs leading to discontinuation 4.4%	Higher rates in serious TEAEs, treatment related TEAEs and TEAEs leading to discontinuation, proportionally larger with age and most evident at 75 years and over. Uncharacterised relation to dose-conversion scheme and resulting drug exposure. No demonstrated efficacy benefit for ≥65 years.	Study IPX203-B16-02
Higher incidence of adverse events in Stage 3a/3b CKD	6/40 (15%)	0/43 (0%)	Higher rates in serious TEAEs and TEAEs leading to discontinuations. Small sample size.	Study IPX203-B16-02

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; CKD: chronic kidney disease

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

Motor fluctuations and dyskinesias are the most relevant drawbacks in patients with advanced PD. Treatment options may mitigate fluctuations, usually at the cost of less optimal "Good ON" time, increased "OFF" time or dyskinesias or added AEs (impulse control disorders with DA, hallucinations, diarrhoea and weight loss with COMTI).

The primary endpoint (PEP) of the pivotal Study IPX203-B16-02 was met. Subjects receiving IPX203 showed an improvement in the mean "Good ON" time from baseline to the end of the double-blind therapy when compared with those receiving IR CD-LD (IPX203: -0.39 h and IR CD-LD: -0.97 h). IPX203 resulted in more hours of "Good ON" time compared with IR CD-LD.

Subjects receiving IPX203 showed an improvement in the mean "OFF" time from baseline to Visit 7/ET when compared with those receiving IR CD-LD (IPX203: 0.29 h and IR CD-LD: 0.76 h).

"OFF" time increased less in the IPX203 group (LS mean: 0.38 h) when compared with IR CD-LD group (LS mean: 0.86 h).

IPX203 treatment resulted in less "OFF time" compared with IR CD-LD treatment (p=0.0252, difference in LS means: -0.48 h [95% CI: -0.90, -0.06]).

However, in the PP Analysis Set, statistical significance was not reached in the "Good ON" results. In addition, the pivotal study IPX203-B16-02 applied sequential open-label run-in phases (IR LD/CD dose adjustment and IPX203 conversion/stabilisation) before randomisation. Consequently, only

subjects who tolerated and responded to IPX203 were randomised, potentially introducing selection bias and limiting the validity of the estimated treatment effect. The high number of dropouts in study IPX203-B16-02 (especially, the 83 during the dose conversion period of whom 10 due to lack efficacy), might have had a potential impact on efficacy.

In conclusion, the benefit has been presented with the maintenance of improvement in an optimised fluctuating PD population, with a difference of better "Good ON" time of 0.53 h in the IPX203 arm as opposed to the IR LD arm, with a smaller but relevant impact in "OFF" time, given the fact that the "good ON" time was increased.

Overall, the observed magnitude of effect of IPX203 was small (0.53 hour) as compared to IR-LD, but IPX203 was administered three times a day while IR-LD was to be taken five times a day. The fact that the three oral formulations of IPX203 performed better than the five of IR-LD suggested that the time of intake is less critical for IPX203 than with IR-LD, representing an inherent advantage in the target patient's population, especially for elderly patients with moderate-severe motor fluctuations and/or those who cannot handle infusion pumps or are not eligible for deep brain stimulation (DBS) treatment.

From a safety perspective, the higher incidence of TEAEs, including serious TEAEs and TEAEs leading to study discontinuation in IPX203 compared to IR CD-LD group is concentrated in elderly and renally impaired patients. These findings have been carefully addressed throughout the PI.

9.6.2. Balance of Benefits and Risks

Levodopa, in a fixed dose combination with a dopa decarboxylase inhibitor (DDI), has been the gold standard for the treatment of PD for over 50 years.

IPX203 is a MR formulation for the treatment of adult patients with Parkinson's disease and moderate to severe motor fluctuations who have not been sufficiently stabilised with oral levodopa/dopa decarboxylase (DDC) inhibitor-based treatment regimens.

The AEs profile of IPX203 is largely consistent with the known safety profile from other levodopa/carbidopa formulations. The most commonly identified ADR were dyskinesia, nausea, dry mouth and dizziness.

9.6.3. Additional considerations on the benefit-risk balance

Not applicable.

9.7. Benefit-risk conclusions

9.7.1. CHMP conclusions

The benefit/risk profile of Hopledo is positive.