Amsterdam, 26 February 2026
EMA/CHMP/61327/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Onerji

International non-proprietary name: Levodopa / Carbidopa

Procedure No. EMEA/H/C/006429/0000

Note

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

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List of abbreviations

µg	Microgram
3-OMD	3-O-methyldopa
6-OHDA	6-hydroxydopamine
Adj	Adjusted
ADR	Adverse Drug Reaction
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
AIMS	Abnormal involuntary movement scale
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR FUQs	Adverse reaction follow-up questionnaires
API	Active pharmaceutical ingredient
aq	Aqueous solution
AR	Assessment Report
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}16}$	Area under the plasma concentration-time curve from time of dosing to sixteen hours after dosing
$AUC_{0\text{-}24}$	Area under the plasma concentration-time curve from time of dosing to twenty-four hours after dosing
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity
$AUC_{0\text{-}last}$	Area under the plasma concentration-time curve from time zero to last measurable concentration
$AUC_{0\text{-}t}$	Area under the plasma concentration-time curve from time zero until the time of the last measurable concentration
BA	Bioavailability
BBB	Blood brain barrier
BE	Bioequivalence
BL	Baseline
BLQ	Below the limit of quantification
BMI	Body mass index
C	Centigrade
C_{avg}	Average observed plasma concentration
CCIT	Container closure integrity test
CCS	Container closure system
CD	Carbidopa
CECP	Clinical Evaluation Consultation Panel
CEP	Certificate of suitability
CFB	Change from Baseline

CFU	Colony forming unit
CGI	Clinical Global Impression
CGI-C	Clinical global impression of change
CGI-I	Clinical Global Impression of Improvement
cGMP	Current good manufacturing practices
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIP	Cleaning in place
CL	Clearance
CL/F	Apparent total body clearance of the drug from plasma after extravascular administration
CL_{COMT}/F	Apparent catechol-O-methyl transferase-mediated clearance
CL_{DDC}/F	Apparent dopa decarboxylase-mediated clearance
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
CMO	Contract Manufacturing Organization
CMQ	Sponsor Customized MedDRA Queries
CNS	Central nervous system
COMT	Catechol-O-methyl transferase
COMTi	Catechol-O-methyl transferase inhibitor
cP	Centipois
CPP	Critical process parameter
CQA	Critical quality attribute
CR	Controlled release
CRCL	Creatinine clearance
CRO	Contract Research Organisation
CRT	Controlled room temperature (USP <659>)
CSR	Clinical study report
Css	Concentration of drug in plasma at steady state
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
D	Day(s) of study
DBDD	Double-blind, double-dummy
DBP	Diastolic blood pressure
DBS	Deep-Brain Stimulation
DBW12	Week 12 of double-blind, double-dummy period
DDC	Dopa decarboxylase
DDI	Dopa decarboxylase inhibitor
DDS	Drug Development Solutions
DF	Dilution factor

DMF	Drug master file
DO	Dissolved oxygen
DP	Drug product
DS	Drug substance
EAC	Enrolment Authorization Committee
EAIR	Exposure-adjusted incidence rate
EC50	Half maximal effect concentration
ECG	Electrocardiogram
EDC	Electronic Data Capture
EE	Eastern Europe
EMA	European Medicines Agency
E_{max}	Estimated Maximum effect
EQ-5D-5L	EuroQol 5-Dimension 5-level Questionnaire
EQ-VAS	EuroQol-Visual Analogue Scale
ER	Extended release
ESI+	Electrospray positive ionization mode
ESS	Epworth Sleepiness Scale
ET	Early termination
EU	Endotoxin units
EU	European Union
FDA	Food and Drug Administration
FI	Fluctuation index
FMQ	FDA MedDRA Queries
F_{rel}	Relative bioavailability
FTIR	Fourier transform infrared
FU	Follow-up
GC/MS	Gas chromatography mass spectrometry
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastrointestinal
GLIMMIX	Generalised Linear Mixed Models
GLP	Good laboratory practice
gMean	Geometric mean
GMR	Geometric mean ratio
GOF	Goodness of fit
h/H	Hour(s)
HI	High impurities
HPLC	High-performance liquid chromatography

HPLC-MS/MS	High-performance liquid chromatography tandem mass spectrometry
HVLD	High voltage leak detection
HVs	Healthy volunteers
IC50	Half maximal inhibitory concentration
ICD	Impulse-control disorder
ICE	Intercurrent event
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IIV	Interindividual variability
IOV	Interoccasion variability
IP	Intraperitoneal
IPC	In-process control
IPSP	Initial paediatric study plan
IR	Immediate release
IR-LD/CD	Immediate release levodopa/carbidopa
IIR	Integrated Inspection Report
IS	Internal standard
ISR	Infusion site reaction
ISS	Integrated Summary of Safety
ITT	Intention-to-treat
IV	Intravenous
JP	Japanese pharmacopeia
ka	Absorption rate constant
ka, oral	First-order absorption rate constant from oral compartment
ka, SC	First-order absorption rate constant from subcutaneous compartment
KM	Kaplan-Meier
L	Litre
L-arg	L-arginine
LC/MS/MS	Liquid chromatography coupled with tandem mass spectrometry
LCE	Levodopa/carbidopa/entacapone
LCIG	Levodopa/carbidopa intestinal gel
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LD	Levodopa
LD/CD	Levodopa/carbidopa
LD50	Median lethal dose
LEDD	Levodopa equivalent daily dose
$LEDD_{LD+COMTi}$	Levodopa equivalent daily dose coming from levodopa and Catechol-O-methyl transferase inhibitors
LH	luteinizing hormone

LI	Low impurities
LLE	Liquid-liquid extraction
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LOQ	Limit of quantitation
LS	Least-squares
LSM	Least squares mean
LTS	Long-term safety
m	Month(s)
M/D	Multiple dose
m/z	Mass to charge ratio
MAA	Marketing Authorization Application
MAO	Monoamine oxidase
MAO-B	Monoamine oxidase B
MAR	Missing at random
MD	Main degradant or 3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid
M-Dopa	Methyldopa
MDS-UPDRS	Movement Disorder Society-sponsored Revision of the Unified Parkinson's Disease Rating Scale
MedDRA	Medical dictionary for regulatory activities
M-EDL	Motor aspects of experiences of daily living
mg	Milligram
MI	Multiple imputation
Min	Minimum
mITT	Modified intention-to-treat
mL	Millilitre
MMRM	Mixed model repeated measures
MMSE	Mini-Mental State Examination
MNAR	Missing not at random
MOS	Margin of safety
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRHDD	Maximum recommended human daily dose
MRM	Multiple reaction monitoring
ms	Millisecond
MSE	Mean square estimate
N or n	Number of subjects studied
N/A	Not applicable
NA	North America
NAC	N-acetylcysteine
NCA	Non-compartmental analysis

ND0612	Levodopa/carbidopa solution for subcutaneous injection (investigational drug product)
NF	National formulary
ng	Nanogram
NLT	Not less than
NMLS	Neuroleptic malignant-like syndrome
NMSS	Non-motor Symptoms Scale
NMT	Not more than
OFV	Objective function value
OH	Orthostatic hypotension
OL	Open-label
OLE	Open-label extension
OR	Odds ratio
P	Period
PD	Parkinson's disease
PD	Pharmacodynamics
PDE	Permitted daily exposure
PDQ-39	39-Item Parkinson's Disease Quality of Life Questionnaire
PDSS	Parkinson's Disease Sleep Scale
PES	Polyethersulfone
PGIC	Patient Global Impression of Change
PGI-I	Patient global impression of improvement
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PMM	Pattern mixture model
popPK	Population pharmacokinetics
PP	Per-Protocol
PPQ	Process performance qualification
PRA	Plasma renin activity
PRAC	Pharmacovigilance Risk Assessment Committee
PS80	Polysorbate 80
PT	Preferred term
PT	Prothrombin time
PTT	Partial thromboplastin time
PtT	Peak-to-trough
PVDF	Polyvinylidene fluoride
PY	Person-years
q.s.	*Quantum satis* (sufficient quantity)

Q/F	Apparent inter-compartmental clearance
QID	Four times a day
QSAR	Quantitative structure-activity relationship
QTcF	QT corrected by the Fridericia formula
QTPP	Quality target product profile
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale
R	Release
RL	Reporting limit
RMP	Risk management plan
RP-HPLC-MS/MS	Reversed-phase high-performance liquid chromatography-tandem mass spectroscopy
RPM	Revolutions per minute
RP-UPLC-MS/MS	Reversed-phase ultra-performance liquid chromatography-tandem mass spectrometry
RRT	Relative retention time
RUV	Residual unexplained variability
S	Stability
SC	Subcutaneous or subcutaneously
S&E ADL	Schwab and England activities of daily living
S/D	Single dose
S/N	Signal-to-noise ratio
SAE	Serious adverse event
SAWP	Scientific Advice Working Party
SC	Subcutaneous
SC	Systolic blood pressure
SCM	Stepwise covariate model
SCS	Summary of clinical safety
SD	Standard deviation
SE	Standard error
SGI-I	Subject Global Impression of Improvement
SIL	Stable isotope label
SIP	Sterilization in place
SISPQ	Safety, identity, strength, purity and quality
SmPC	Summary of product characteristics
SMQ	Standardized MedDRA Queries
SoC	Standard of care
$T½_{abs}$	Absorption half-life
$t_{1/2}$	Apparent elimination half-life
TAMC	Total aerobic microbial count
TD	Treatment difference

TDI	Total daily intake
TDS	Twiko Delivery System
TE	Total error
TEAE	Treatment-emergent adverse event
TFA	Trifluoroacetic acid
TFL	Tables, figures and listings
TID	Three times a day
TK	Toxicokinetic(s)
Tlag, oral	Lag time for oral absorption
Tlag, SC	Lag time for subcutaneous absorption
t_{max}	Time to maximum observed plasma concentration
TQT	Thorough QT/QTc
TRS	Treatment Response Scale
TRT	Treatment
TYMC	Total combined yeasts/moulds count
UK	United Kingdom
ULOQ	Upper limits of quantification
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
USA	United States of America
USP	United States pharmacopeia
V	Visit
VAS	Visual Analogue Scale
V/F	Apparent volume of distribution
VAS	Visual analogue pain scale
Vc/F	Apparent central volume of distribution
VDC	Voltage direct current
Vp/F	Apparent peripheral volume of distribution
VPCs	Visual predictive checks
Vss	Volume of distribution at steady state
Vz/F	Apparent volume of distribution at terminal phase
W, w	Week(s)
WEI	Western Europe + Israel
WFI	Water for injection
WO	Washout

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Onerji
Active substance	levodopa / carbidopa
INN or common name	levodopa / carbidopa
Applicant	Tanabe Pharma GmbH Schiessstrasse 47 Heerdt 40549 Duesseldorf GERMANY
EMA Product Number	EMEA/H/C/006429
ATC code and Pharmacotherapeutic group	N04BA02 - levodopa and decarboxylase inhibitor
Pharmaceutical form(s) and strength (s)	Solution for infusion 60 mg/ml (levodopa) + 7.5 mg/ml (carbidopa)
Packaging	vial (glass)
Package size(s)	30 vials
Route of administration	Subcutaneous use
Orphan designation	No
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 8.3 of Directive 2001/83/EC (full-mixed MAA)
Final indication	Onerji is indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medicinal products.
New active substance status	Not applied

1.2. Scientific advice

Table 1. Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
23 October 2014	*Quality / non-clinical / clinical*	EMEA/H/SA/2859/1 /2014/SME/III	The Scientific advice pertained to the following quality, non-clinical, and clinical aspects: - Questions on chemical, pharmaceutical and biological development - Questions on toxico-pharmacological development - Questions on clinical development
26 January 2017	*Non-clinical / clinical*	EMEA/H/SA/2859/1/ FU/1/2016/SME/II	This request is a follow-up to the advice provided by CHMP in October 2014. The Scientific advice pertained to the following non-clinical, and clinical aspects: - Questions on toxico-pharmacological development - Questions on clinical development
18 May 2017	*Clinical*	EMEA/H/SA/2859/1/ FU/2/2017/SME/I	This request is a follow-up to the advice provided by CHMP in January 2017. The Scientific advice pertained to the following clinical aspects: - Questions on clinical development
28 March 2019	*clinical*	EMEA/H/SA/2859/1/ FU/3/2019/II	This request is a follow-up to the advice provided by CHMP in October 2014. The Scientific advice pertained to the following clinical aspects: - Questions on clinical development
14 November 2019	*clinical*	EMEA/H/SA/2859/1/ FU/4/2019/II	This request is a follow-up to the advice provided by CHMP in October 2014. The Scientific advice pertained to the following clinical aspects: - Questions on clinical development

1.3. Eligibility to the centralised procedure

The applicant Tanabe Pharma GmbH submitted on 29 January 2025 an application for Marketing Authorisation (MA) to the European Medicines Agency (EMA) for Onerji (levodopa / carbidopa), through the centralised procedure under Article 3 (2) (b) - Therapeutic innovation of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 October 2023.

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

The applicant applied for the following indication: treatment of motor fluctuations in patients with Parkinson's disease.

1.4. 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.

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision (EMEA-002687-PIP01-19; PIP decision, P/0068/2020, confirmed on 18 March 2020 on the granting of a product-specific waiver.

1.6. Information on orphan market exclusivity

Not applicable.

1.6.1. 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 procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. Steps taken for the assessment of the product

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

Rapporteur:	Fátima Ventura
Co-Rapporteur:	Grzegorz Cessak

The application was received by the EMA on	29 January 2025
The procedure started on	20 February 2025
The CHMP Rapporteur's first Assessment Report was received on	21 May 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	21 May 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	27 May 2025
The CHMP agreed on the consolidated List of Questions to be sent to the	19 June 2025

applicant during the meeting on	
The applicant submitted the responses to the CHMP consolidated List of Questions on	9 October 2025
A routine GCP inspection was requested by the CHMP for clinical trial ND0612-317 and the outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: The sites inspected were the below: - - Site A , Portugal - Site B, Poland - CRO Syneos Health France S.A.R.L., 25 Boulevard Romain Rolland, 75004 Paris, France	25 April 2025
The outcome of the inspection carried out was issued on	3 October 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	17 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	11 December 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 January 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	11 February 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 Onerji on	26 February 2026

1.8. CHMP outcome

1.8.1. 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).

1.8.2. Considerations related to orphan market exclusivity

Not applicable.

1.8.2.1. Similarity with authorised orphan medicinal products

Not applicable.

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

Not applicable.

1.8.3. 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 Onerji in the treatment of motor fluctuations in patients with advanced Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medicinal products is favourable.

1.8.4. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

1.8.5. Other conditions and requirements of the marketing authorisation

1.8.5.1. 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

1.8.6.1. 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.

1.8.6.2. Additional Risk Minimisation Measures

Prior to the launch of Onerji® in each Member State, Tanabe Pharma GmbH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The educational programme is aimed at minimising the risk of infusion site reactions associated to Onerji® treatment, enhancing awareness and educating patients (and/or their caregivers) on measures they should take to mitigate this risk.

Tanabe Pharma GmbH will ensure that in each Member State where Onerji® is marketed, all healthcare professionals who are expected to prescribe Onerji® have access to and provide their patients with the following educational package containing:

- Patient information pack

The patient information pack consists of the patient information leaflet, the user manual provided with

the drug delivery system that details the instructions for use and appropriate management of the infusion pump device (Yurway Delivery System or Crono Twin ND pump), and a patient/carer guide.

The patient guide will include the following key elements:

- Description of infusion site reactions, including symptoms, that could be signs of inflammation or infection.
- Details on how to minimise the safety concern of infusion site reactions, also ensuring that the subcutaneous infusion site location is changed daily and systematically rotated to avoid reusing an infusion site for at least 2 weeks.
- Measures to follow in case a patient experiences an infusion site reaction.
- Reference to the package leaflet and/or the user manual.

1.8.6.3. Obligation to conduct Post-Authorisation Measures

Not applicable.

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

Not applicable.

1.8.8. Proposed list of recommendations

Not applicable.

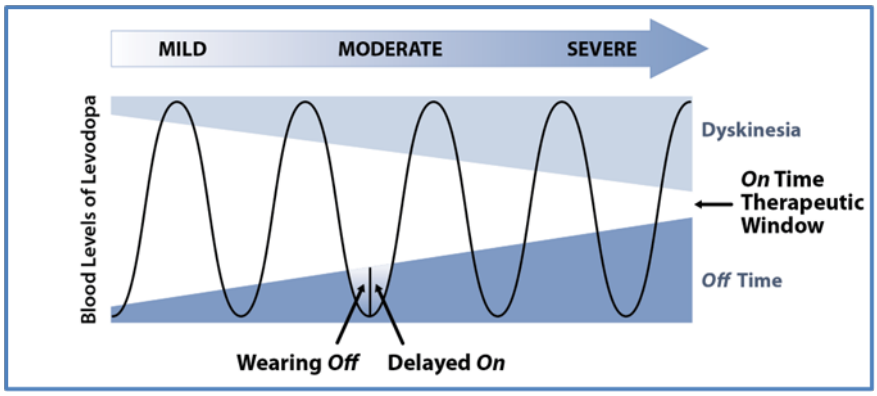
2. Introduction

2.1. Therapeutic Context

Parkinson's Disease (PD) is a progressive neurodegenerative movement disorder clinically characterised by the presence of cardinal motor features (including bradykinesia and, at least, tremor or rigidity), and pathologically characterised by the degeneration of dopaminergic neurons in the substantia nigra pars compacta, resulting in striatal dopamine deficiency. PD is the second most common neurodegenerative disorder after Alzheimer's disease and a major, increasing burden on patients, families, carers and healthcare systems. The prevalence of PD is approximately 1 million people in the United States (US) and 6 million people worldwide. It is estimated to affect 1% of people over the age of 60 and 3% over the age of 80 years.

Between 1990 and 2015, the global prevalence of PD doubled, a trend primarily attributed to an aging population. Data from the Global Burden of Disease Study projected that the number of individuals living with PD will increase to approximately 13 million by 2040.The administration of levodopa (LD) in combination with the peripheral dopa-decarboxylase (DDC) inhibitor carbidopa (CD) remains the gold standard of care for Parkinson's Disease. To date, this combination continues to be the most potent pharmacological intervention to manage the cardinal motor symptoms of the disease. Most PD patients experience satisfactory control with intermittent doses of oral LD/DDC inhibitor therapy, particularly during the early stages of the disease. At these early stages, patients typically experience a long-lasting response following each LD dose despite its relatively short half-life of only 45-90 minutes. However, chronic LD treatment and disease progression are associated with the development of motor complications in the form of motor fluctuations (wearing OFF, ON-OFF phenomenon) and dyskinesia (as illustrated in Figure 1 below), which can be severe and disabling.

Figure 1. Motor Fluctuations and Dyskinesias over time in Parkinson's Disease



There are several options to treat motor fluctuations in PD, but no drug yet has been able to manage them satisfactorily in the long-term. Oral therapies fail to provide sufficient control of motor fluctuations in many patients with advancing PD. One option is adjusting LD dose or frequency; however, increasing the dose can lead to worsening of dyskinesia, while lowering the dose can increase "OFF" time. Extended-release formulations have not proven to be more effective.

Different adjunct therapies have been developed to try to reduce "OFF" time. These include dopamine agonists, Monoamine Oxidase type B (MAO-B) inhibitors, Catechol-O-Methyltransferase (COMT) inhibitors, and/or the adenosine antagonist istradefylline. None of these options provides benefits superior to levodopa. In addition, each option has its own set of potentially serious side effects such as sleep disturbances, psychosis, impulse-control disorders, etc. Surgical therapies such as deep-brain stimulation (DBS) can also be used for the treatment of motor complications not adequately controlled by oral therapies. Indeed, they may provide benefit for both "OFF" time and dyskinesia. Nevertheless, they require a brain operation that can be associated with potentially serious complications related to the surgery, such as haemorrhage, infection, or seizure). In addition, complications related to the stimulation system or the stimulation itself, such as dysarthria, may also develop. Furthermore, frequent adjustments are necessary and, occasionally, repeated surgical procedures may be required (e.g. related to the stimulation system or for battery replacement). Importantly, no procedure has been shown to provide superior anti-parkinsonian benefits in comparison to levodopa (perhaps except for tremor).

The mechanism by which LD causes motor fluctuations and dyskinesia has been the source of intense investigation over the past two decades. Evidence indicates that motor complications are related to the non-physiologic (i.e., pulsatile) restoration of brain dopamine following intermittent doses of standard LD/CD. Under physiological conditions, brain dopamine is maintained at relatively constant levels, with continuous activation of (brain dopamine) receptors, even following administration of LD dose. In PD, where dopaminergic nigrostriatal projection neurons' dopamine terminals have degenerated, striatal dopamine levels are dependent on the peripheral availability of LD. Levodopa has a short half-life, and its absorption varies with the speed of gastric emptying and the presence of dietary protein competing for uptake in the small intestine. Thus, intermittent dosing with standard oral LD (even when co-administered with DDC inhibitor) is associated with prominent fluctuations in its plasma levels, which translates into oscillations of striatal dopamine levels and pulsatile stimulation of striatal dopamine receptors. This, in turn, has been shown to result in post-receptor molecular changes in striatal neurons, neurophysiologic changes in pallidal output neurons, and the development of motor complications. These observations led to the hypothesis that continuous delivery of levodopa would reduce the variability in its plasma concentration, and restore brain dopamine in a more physiologic manner, leading to a reduced risk of motor complications. Studies in both animal models and PD patients have demonstrated that continuous delivery of a dopaminergic agent is associated with a reduction of motor complications in

comparison to intermittent doses of the same agent. These findings were confirmed in a prospective, double-blind, double-dummy (DBDD) clinical study of continuous intrajejunal levodopa infusion (Olanow et al., 2014) showing a benefit on primary and secondary outcome measures ("OFF" time and "ON" time without troublesome dyskinesia) of a greater magnitude than, to date, has not been seen with any of the approved LD oral therapies. Based on these findings, Duopa® (CD/LD enteral suspension) was approved by FDA and Duodopa) in the European Union (EU) / European Economic Area (EEA).

However, LD/CD intestinal gel treatment is associated with potentially serious side effects, linked with the surgical procedure (e.g., peritonitis, pancreatitis, pain, infection, as detailed in Duodopa® SmPC) and the need of a permanent intrajejunal tube (e.g., potentially subjected to blockage, dislocation, infection) which may require periodic, invasive procedures. Additionally, it does not solve the issue of competitive absorption of LD in the jejunum.

Consequently, an unmet medical need remains for an alternate treatment method that could provide continuous LD delivery without the risks associated with surgical procedure or an indwelling jejunal catheter.

Foslevodopa/foscarbidopa, a pro-drug of LD/CD administered continuously subcutaneously (SC) over 24 h through a single infusion site, was approved in some European countries (as Produodopa®), in Canada, Japan and more recently in the US (as Vyalev®), for the "Treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results". It had been developed as a full replacement therapy, providing a maximum recommended daily dosage of levodopa equivalent to 2,500 mg as per Vyalev® USPI, or 4,260 mg as specified in Produodopa® SmPC.

Unlike Produodopa®, ND0612 DP 24 h SC infusion was developed as a partial replacement therapy, providing up to 720 mg levodopa daily. This treatment was designed to be complemented with an oral LD formulation to meet patients' individual needs. The approach was intended to provide the foundational levodopa concentrations enabling the benefits of continuous LD delivery, while minimizing the risk of excessive dopaminergic load, as discussed further below. Moreover, it would avoid the need to infuse large solution volumes, necessary to fully substitute oral levodopa intake, while compromising skin tolerability. Additionally, ND0612 treatment was designed to allow drug delivery through two infusion sites, rather than just one, to further dilute the volume burden at each infusion site.

2.2. Aspects of development

The clinical development program of ND0612 DP included 12 clinical studies:

- **Six Phase I studies in healthy volunteers** (HVs) (ND0612/001, ND0612/001b, ND0612/005, ND0612-114, ND0612-115 and ND0612-J01; all completed).
- **Six studies in PD patients**: four Phase I/IIa (ND0612/002, ND0612/003, ND0612/004, ND0612H-006; all completed); one Phase IIb long term safety study (ND0612H-012; 1-year core study completed; open-label extension ongoing); and one efficacy and safety pivotal Phase III study (ND0612-317; core study completed; open-label extension ongoing).

In addition, a thorough QT/QTc (TQT) study in healthy subjects to assess the potential effects of a supratherapeutic dose of CD on the QTc interval, conducted upon FDA request. All ND0612 DP clinical studies were performed in accordance with Good Clinical Practice (GCP).

The efficacy of ND0612 DP 24-hour infusion was primarily demonstrated in the **pivotal Study ND0612-317**. Exploratory efficacy results obtained from studies **ND0612/003, ND0612H-006** and **ND0612H-012** provided supportive evidence.

The pivotal study ND0612-317 enrolled 381 subjects with PD and motor fluctuations. Of them, 259 were randomised to receive either immediate release (IR)-LD/CD (n=131), or ND0612 DP 24-hour regimen (n=128), at the optimised doses (determined during previous adjustment and conversion open-label periods). The randomised, DBDD, parallel-group, active-comparator study design ensured a reliable and relevant efficacy comparison between a continuous 24-hour SC ND0612 infusion versus oral IR-LD/CD. Moreover, this study evaluated the ND0612 DP to-be-marketed formulation (60/7.5 mg/mL of LD/CD) and the dose range (370 mg/day to 720 mg/day of LD).

The main trials providing safety information in subjects with PD were study ND0612 317 and the Phase IIb (one-year) study ND0612H-012. The latter enrolled 214 subjects with PD and motor fluctuations, of which 120 completed the first-year core treatment period. This study evaluated both a 24-hour and a 16-hour infusion of ND0612 DP. The ND0612 DP formulation and the 24-dosing scheme were the same as in the pivotal trial ND0612 317.

Pooled analyses of data gathered from all studies conducted with ND0612 DP in PD subjects (including studies' extensions) and healthy volunteers, provided additional safety information.

At the cut-off date for this initial MAA, a total of 134 (22.4%) subjects were still under treatment in the **open label extensions** of **studies ND0612H-012** and **ND0612-317**.

To date, ND0612 DP has not yet received regulatory approval in any jurisdiction. Consequently, the clinical safety profile is characterised exclusively by data derived from the twelve studies above listed.

Product development rational

ND0612 DP was developed as a 24-hour SC infusion to deliver up to 720/90 mg of LD/CD per day (via two infusion sites, up to 6 mL each), complemented with oral LD treatment to meet the needs of individual subjects. This approach was designed to provide foundational concentrations to ensure the benefits of continuous LD delivery while minimising the risk of excessive dopaminergic load. In addition, by avoiding the high infusion volumes required for total LD oral substitution, this strategy also aimed at optimising local skin tolerability

ND0612 DP pharmacokinetic (PK) studies showed that 24-hour infusion of ND0612 LD/CD (720/90 mg/day) allowed both amelioration of LD troughs and reduction of fluctuation index (study **ND0612-005**). This reduction in LD plasma levels fluctuations was correlated with preliminary efficacy data in PD patients obtained in study **ND0612/003**. In this study, although a low dose of ND0612 was investigated (LD/CD 270/63 mg/day), the continuous ND0612 SC administration over 24 hours resulted in the elimination of LD plasma trough levels and in a reduced fluctuation index as compared to placebo. This was also translated into a reduction of "OFF" time (as documented in home diaries) at endpoint (Days 7-14) versus a baseline of 2.1 hours for ND0612, compared to 1.4 hours in the placebo control arm.

The Phase II study **ND0612H-006** compared two regimens: a 24-hour regimen (LD/CD dose up to 720/90 mg/day) and a 14-hour regimen (LD/CD dose up to 537.6/67.2 mg/day derived from ND0612 DP + a morning oral dose of 150/15 mg of LD/CD). The 24-hour regimen consisted of an 18 h daytime flow rate providing up to 690 mg LD and a fixed 6-h night-time flow rate providing 30 mg LD. Although the study was not designed for a formal statistical comparison between the two dosing regimens, benefits were numerically superior with the 24-hour dosing regimen. Reduction in early morning akinesia and improved sleep quality were only observed with the 24-hour dosing regimen.

Based on these data, the 24-hour regimen was selected for the pivotal study ND0612-317.

This was further supported by the findings of the Phase IIb study **ND0612H-012**, which evaluated this 24-hour regimen and a 16-hour regimen of ND0612 DP. The efficacy and safety data of these two regimens were overall comparable throughout the 1-year treatment period. However, the 24-hour regimen had a higher effect on morning akinesia, corroborated by the results of **ND0612H 012** PK sub-

study, showing higher LD plasma concentrations and higher treatment response scale (TRS) scores during the morning hours in subjects under the 24-hour regimen compared to those under the 16-hour regimen.

The ND0612 DP daytime/night-time dosing scheme (18 h daytime flow rate providing up to 690 mg LD and a fixed 6-h night-time flow rate providing 30 mg LD) was designed to allow for the larger portion of LD (up to 690 mg) to remain available for administration during the day, when subjects need higher LD levels to maintain "ON" state. The night-time LD dose was set as a low fixed dose (30 mg), to minimise the risk for nocturnal dopaminergic adverse events (AEs) (Olanow et al., 2006) and maintain continuity of delivery so that clinically relevant LD levels could be reached faster in the morning as daytime flow rate starts and therefore aiding in reducing morning akinesia.

The infusion pump used in most of the clinical studies, including ND0612-317 and ND0612H-012, was the Crono Twin ND, a CE marked (Notified Body 0476) ambulatory pump intended for SC infusion of drugs for PD therapy.

Scientific advice from EMA/CHMP was initially provided on 23 October 2014 (**EMEA/H/SA/2859/1/2014/SME/III**), with regard to Onerji quality (proposed drug product release and stability specifications; and arginine as an appropriate excipient for the subcutaneous route of administration), and (non) clinical development, in the proposed indications of:

- "Patients with advanced levodopa-responsive PD who do not have satisfactory control of severe, debilitating motor fluctuations and hyper/dyskinesias despite optimised treatment with commercially available combinations of Parkinson's medicinal products",
- "Patients with moderate to severe levodopa-responsive PD with motor fluctuations, who have not reached the stage requiring more invasive procedures/treatments such as DUODOPA® and deep brain stimulation (DBS)".

Thereafter, four scientific advice follow-ups were provided:

1. On **26 January 2017**, (**EMEA/H/SA/2859/1/FU/1/2016/SME/II**) regarding the:
    - re-clinical and clinical development (demonstration of comparable bioavailability of levodopa via the proposed pilot and pivotal pharmacokinetic studies ND6012-005 and -009) adequate to establish efficacy
    - Comparable bioavailability of carbidopa required to support a hybrid MAA
    - Safety of carbidopa exposure reached under administration of ND0612 up to the highest recommended dose of 12.0 mL i.e. LD/CD 720/90 mg/mL per day (based on literature and clinical experience with other approved medicinal products containing CD)
    - Safety concern related to high arginine concentrations in the ND0612 solution being adequately addressed in the completed non-clinical/planned pivotal clinical study (discussed in the previous SA procedure);
    - Safety database, expected to be available at the time of filing a hybrid MAA.
2. On **18 May 2017** (**EMEA/H/SA/2859/1/FU/2/2017/SME/I**) regarding the:
    - Clinical development (study population in ND0612-007), to support the proposed label claim of "ND0612 indicated for the treatment of PD patients on L-DOPA with motor fluctuations"
    - Selection of the primary and secondary endpoints chosen for study ND0612-007 to deliver efficacy and safety data supporting the proposed label claim of "ND0612 indicated for the treatment of PD patients on L-DOPA with motor fluctuations"

- Blinding scheme for trial ND0612-007, being open-label regarding the allocation to the high or low dose group but blinded for allocation to either the active treatment (ND0612) or placebo
- Adjunct oral dose and the dose adjustment during the "adjustment period"; 40 subjects in each of the placebo low dose and high dose groups proposed to be grouped together (n = 80) for the purpose of statistical analyses
- Matched parallel gatekeeping procedure for maintenance of overall Type I error rate
- Safety database
- Overall clinical program supporting the MAA for "ND0612 indicated in the treatment of PD patients on L-DOPA with motor fluctuations".

3. On **28 March 2019** (**EMEA/H/SA/2859/1/FU/3/2019/II**) regarding the clinical development, specifically on:
    - Sinemet (LD/CD) to be used as active control
    - In case of Sinemet supply shortages in US, an FDA approved generic version of IR Sinemet being acceptable as the comparator drug.
4. On **14 November 2019** (**EMEA/H/SA/2859/1/FU/4/2019/II**) with regard to the clinical development. Specifically, on the:
    - Proposed study design of ND0612-317 pivotal trial
    - Measures to maintain the study blinding
    - Primary and key secondary endpoints of the study
    - Definition of baseline for the proposed study
    - Sample size calculation and underlying assumptions
    - Blinded sample size reassessment procedure.

2.3. Description of the product

LD is an aromatic amino acid and a precursor to dopamine. CD is an inhibitor of the aromatic L-amino acid decarboxylase (or DOPA decarboxylase, DDC).

ND0612 Drug Product (DP) is a sterile preservative-free solution of levodopa (LD) (60 mg/mL) and carbidopa (CD) (7.5 mg/mL) for continuous 24 hours subcutaneous (SC) administration which includes an 18-hour day flow rate and a 6-hour night flow rate and that was developed by NeuroDerm for the treatment of motor fluctuations in patients with Parkinson's disease (PD). It will be administered using either one of the two referenced delivery pumps: the Crono Twin ND pump or the Twiko Delivery System (TDS) providing a total daily dose of up to 720 mg LD and 90 mg CD.

The day flow rate starts about 3 hours before the anticipated patient's wake-up time. The night flow rate is fixed at 0.08 mL/h (0.04 mL/h/infusion site) while the maximal day flow rate is 0.64 mL/h (0.32 mL/h/infusion site). The maximum recommended human daily dose (MRHDD) of ND0612 DP is 12 mL corresponding to 720/90 mg LD/CD. ND0612 DP will be administered concomitantly with a morning oral LD dose and, if needed, additional daily oral LD doses.

2.4. Inspection issues

2.4.1. GMP inspection(s)

No GMP inspection was initially required by CHMP. However, on 20 November 2025, the Food and Drug Administration (FDA) issued a warning letter to one of the two drug product contract manufacturing organization (CMOs) identified in the original MAA.

This site was proposed for the following activities related to Onerji drug product:

- Manufacturing, quality control testing, primary packaging, secondary packaging.

Consequently, to clarify the GMP status of the proposed manufacturing site, a major objection was raised by CHMP.

Since the applicant was unable to provide a confirmation of GMP compliance for this site timely for CHMP Opinion, this drug product CMO and its associated testing site were removed from the list of manufacturers. Only one commercial manufacturer of the drug product is now proposed, with valid GMP certification.

2.4.2. GLP inspection(s)

No inspection required.

2.4.3. GCP inspection(s)

A routine GCP inspection was requested and adopted for clinical trial ND0612-317 at the CHMP plenary meeting held in April 2025. The sites inspected were the below:

- Site A, Portugal
- Site B, Poland
- CRO Syneos Health France S.A.R.L., 25 Boulevard Romain Rolland, 75004 Paris, France.

The Integrated Inspection Report (IIR), timely issued on 3 October 2025, confirmed that the trial was conducted in accordance with GCP. The resulting data were therefore deemed acceptable for this MAA assessment process.

3. Quality aspects

3.1. Introduction

The finished product is presented as solution for infusion containing 60 mg of levodopa and 7.5 mg of carbidopa (as monohydrate) per mL as active substances.

Other ingredients are arginine, ascorbic acid (E 300), acetylcysteine, polysorbate 80 (E 433), and water for injections.

The product is available in clear Type I glass vial with a chlorobutyl rubber stopper and a royal blue flip-off plastic cap with aluminium seal as described in section 6.5 of the SmPC.

Onerji is subcutaneously administered and may only be used with one of the following delivery systems:

- Twiko / Yurway Delivery System, which includes a rechargeable Pump, a sterile single-use, Medication Cartridge (reservoir) for the solution with attached vial adapters. It is used with sterile, single-use infusion sets.
- Crono Twin ND pump, which uses sterile single-use syringes (reservoirs), vial adapters and single-use infusion sets.

These delivery systems will be provided to the patients separately from the finished product (not co-packed).

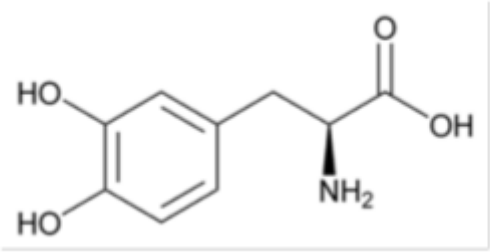
3.2. Active substance

Levodopa

General information

The chemical name of levodopa is (2*S*)-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 197.19 and the following structure:

Figure 2. Lévodopa structure



Information on the elucidation of structure and other characteristics of the active substance is covered by a CEP.

Levodopa is a white or almost white, crystalline powder freely soluble in 3M and 1M hydrochloric acid, sparingly soluble in 0.1M hydrochloric acid, slightly soluble in water and practically insoluble in ethanol (96 per cent).

Levodopa exhibits stereoisomerism due to the presence of one chiral centre. The active substance is the L-form. Enantiomeric purity is controlled routinely in the specifications.

Polymorphism has not been observed for levodopa.

As there is a monograph of levodopa in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability to the monograph of the European Pharmacopoeia (CEP) for levodopa which has been provided within the current marketing authorisation application.

Manufacture, characterisation and process controls

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

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

Specification

The active substance Levodopa used for the manufacture of the finished product complies with the requirements of monograph No 38 of the Ph. Eur. The active substance specification used by the finished product manufacturer includes tests for identification (Ph. Eur.), appearance of solution (Ph. Eur.), pH (Ph. Eur.), enantiomeric purity ((Ph. Eur.), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), assay (Ph. Eur.), related substances (Ph. Eur.), bioburden (Ph. Eur.), and endotoxins. (Ph. Eur.).

The analytical methods used by the finished product manufacturer are compendial. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data (12 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph.

Stability

A retest date of four years is proposed for levodopa. The retest period and storage conditions are not described in the CEP.

Stability data were provided for 3 commercial scale batches from the proposed manufacturer stored in the intended commercial package for up to 4 years under long term conditions (25 °C ± 2 °C, 60%RH ± 5%RH) and 6-months under accelerated conditions (40 °C ± 2 °C, 75% RH ± 5% RH) in line to with guideline CPMP/QWP/122/02, rev 1 corr. In addition, supportive data from three commercial scale batches tested annually were provided.

Samples were tested for specific optical rotation, appearance, related substances, enantiomeric purity, loss on drying, assay, and pH.

All results were within the specifications at all time-points under long term and accelerated conditions.

Forced degradation studies showed that levodopa is stable to heat, acid, and light but degraded under harsh alkaline conditions, thereby demonstrating that the analytical method is stability indicating.

In accordance with post approval stability protocol and stability commitment by the levodopa manufacturer, one lot of levodopa is placed on stability per year and tested annually under long-term conditions to confirm its stability.

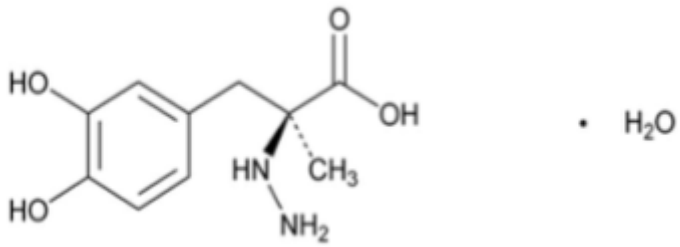
The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 4 years without specific storage conditions in the proposed container.

Carbidopa

General information

The chemical name of carbidopa is (2*S*)-3-(3,4-dihydroxyphenyl)-2-hydrazinyl-2-methylpropanoic acid monohydrate corresponding to the molecular formula $C_{10}H_{14}N_2O_4 \cdot H_2O$. It has a relative molecular weight of 244.2 and the following structure:

Figure 3. Carbidopa structure



Information on the elucidation of structure and other characteristics of the active substance is provided in the CEP(s).

The active substance is a non-hygroscopic white or yellowish-white powder, freely soluble in acidic media and slightly soluble in water.

Carbidopa exhibits stereoisomerism due to the presence of 1 chiral centre. The active substance is the L form. Enantiomeric purity is controlled routinely in the active substance specifications.

Based on a detailed bibliographic search no polymorphism of carbidopa was reported in the literature. The monohydrate form is routinely produced.

As there is a monograph of carbidopa in the European Pharmacopoeia, the manufacturers of the active substance have been granted Certificates of Suitability to the monographs of the European Pharmacopoeia (CEP) which have been provided within the current marketing authorisation application.

Manufacture, characterisation and process controls

Carbidopa is manufactured by two manufacturing sites. Satisfactory GMP documentation has been provided.

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

Specification

Carbidopa used for the manufacture of the finished product complies with the requirements of monograph No 755 of the Ph. Eur.

The active substance specification used by the finished product manufacturer includes tests for identification (Ph. Eur.), appearance of solution (Ph. Eur.), specific optical rotation (Ph. Eur.), hydrazine (Ph. Eur.), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.) , assay (Ph. Eur.) , related substances (Ph. Eur.), bioburden (Ph. Eur.), and endotoxins (Ph. Eur.).

The analytical methods used by the finished product manufacturer are compendial. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data (11 commercial scale batches) of the active substance are provided. The results were within the specifications and consistent from batch to batch.

Stability

The proposed re-test period for both manufacturers of 5 years is covered by the Certificates of Suitability.

3.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is presented as a clear, yellowish solution. The pH is 9.3 to 9.7 and the osmolality is approximately 900 to 1100 mOsm/kg.

The finished product development studies focused on achieving a stable aqueous solution, pharmaceutically acceptable for subcutaneous administration, formulated with sufficient active substance concentration to achieve the desired therapeutic effect.

The development strategy for the finished product was based on ICH guidelines Q8 (R2) for pharmaceutical development and Q9 for quality risk management. A comprehensive finished product Quality Target Product Profile (QTPP) was established which enabled the identification of the finished product critical quality attributes (CQAs).

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.

Compatibility of the active substances with the excipients was demonstrated in the stability studies.

Sterility of the finished product is achieved through sterile filtration and aseptic processing, instead of terminal sterilization, as carbidopa is unstable to standard heat sterilization conditions (121 ºC, 8 min).

The choice of the sterile filter, its chemical compatibility and microbiological suitability has been demonstrated. The filtration parameters were validated under conditions that reflect the intended manufacturing process parameters.

The order of addition of formulation materials during compounding was evaluated and optimised.

The active substance(s) are susceptible to oxidative degradation. Dissolved oxygen is reduced by nitrogen sparging and an IPC to limit headspace oxygen was established. Light protection controls are in place to avoid photodegradation. Extractables and leachables studies conducted on the manufacturing components and on the finished product did not reveal a toxicological concern.

The finished product is stored frozen and thawed before use.

The primary packaging is type I single-dose clear vials. The vials are sealed with chlorobutyl rubber stoppers and sealed with flip-off plastic cap with aluminium seal. The materials comply with Ph. Eur. and EC requirements.

The suitability of chosen container closure system was demonstrated by relevant compatibility studies with the finished product, including delamination as well as extractable and leachables studies.

Regarding the microbiological attributes, no preservatives are used in the formulation, thus, no testing is necessary. Sterility is ensured by the manufacturing process controls. Furthermore, sterility tests are performed as part of finished product release and stability testing.

The drug delivery system used to administer the finished product is a referenced medical device (two options: Crono Twin ND or Yurway), which will be provided to the patients separately from the finished product (not co-packed). Yurway Delivery System includes a rechargeable pump, a sterile single-use medication cartridge (reservoir) with attached vial adapters. It is used with sterile, single-use infusion sets and Crono Twin ND pump uses sterile single-use syringes (reservoirs), vial adapters and infusion sets. The finished product is delivered via two infusion sets and is used for simultaneous continuous administration of two finished product vials needed for daily treatment via two independent infusion

sites. The compatibility of the two proposed drug delivery systems with the finished product was demonstrated based on the results of in-use stability, microbial challenge and extractables and leachables studies. The Crono Twin ND device is CE marked. A notified body opinion (NBOp), required for the Yurway delivery system (YDS) was not available at the start of the procedure, resulting in a major objection. The notified body assessed the YDS device during the procedure, and the applicant provided the resultant CE mark. The MO was thus considered resolved.

Manufacture of the product and process controls

The finished product was initially proposed to be manufactured by two manufacturing sites: Following a major objection the applicant removed the site associated with the major objection from the marketing authorization application (MAA), and the MO was considered resolved.

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 6 main steps: it is considered non-standard.

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

There are no intermediates in the manufacture of the finished product.

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

At the time of assessment, before the first finished product manufacturer was withdrawn, it was proposed that for the bioburden IPCs at this manufacturer, only routine testing of TAMC would be carried out. This was not accepted by the CHMP, and it was requested in a MO requesting routine testing of bioburden by TAMC and TYMC at both manufacturing sites. The applicant complied with the request; therefore, the MO was considered resolved.

In the initial submission, the applicant proposed to use the rabbit pyrogenicity test as an IPC on the final bulk solution before sterile filtration. However, the test has been removed from Ph. Eur. in line with 3Rs principles. Therefore, CHMP raised a MO requiring the replacement of this test with a suitable validated method without use of animals. The applicant duly replaced the pyrogen IPC with a bacterial endotoxin test, and the MO was considered resolved.

Satisfactory process validation protocols and reports are presented for three consecutive 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 assurance of sterility.

The overall comparability between the finished product manufactured was demonstrated based on extensive IPC, release and stability results from the three PPQ batches.

Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (Ph. Eur.), pH (Ph. Eur.), particle matter (ph. Eur.), extractable volume (Ph. Eur.), identification (UV, HPLC), assay carbidopa (HPLC), assay levodopa (HPLC), assay of N-acetylcysteine (HPLC), assay of ascorbic acid (HPLC), impurities/degradation products (HPLC), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), visual inspection 45 days post-thawing (Ph. Eur.), container closure integrity test (HVLD) and hydrazine (GC/MS).

The omission of control for residual solvents and enantiomeric purity in the specifications of the finished product are duly justified, supported by relevant data and/or risk assessments.

The specified impurities and unspecified impurities are listed, and their source and mechanism of formation were explained. Details of characterisation studies and structural assignment of the impurities were provided.

The applicant was requested by the CHMP to develop a suitable validated *in vitro* test to control pyrogenicity in the finished product release specifications, avoiding use of the rabbit pyrogen testing (RPT) in line with 3Rs principles and the recent removal of the test from the Ph. Eur. pyrogen testing strategy, as MO. In response, the applicant submitted a risk assessment which rules out the presence of non-endotoxin pyrogenic substances in the finished product. Absence of pyrogenicity has already been tested and demonstrated for several batches of the finished product manufactured by the proposed manufacturer at commercial scale. The bacterial endotoxin IPC on the bulk pre-sterile filtration is considered sufficient and no additional testing using the monocyte-activation test, as recommended in newly published monograph, is needed. The MO is considered 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. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was submitted in the initial dossier.

However, the assessment did not rule out the risk of nitrosamine impurities in the finished product. The CHMP raised a major objection. The applicant responded to each MO Test data using a suitably sensitive method on 6 batches of the finished product stored under long term conditions for up to 28 months, and for 12-month-old batches used for a 45-day stability study on thawed samples at 25 ^{o}C. No nitrosamines were detected. Thus, the major objections were considered resolved.

Thus, it is agreed that there is no risk of formation of nitrosamine impurities and no controls are needed in the specifications.

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 results are provided for a number of batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 10 commercial scale batches of the finished product stored for up to 36 months under long term conditions (-20±5 ºC) according to ICH Q1A were provided. In addition, stability at elevated temperatures was investigated to evaluate the impact of short-term temperature excursions during distribution and at a patient's home following thawing. Samples were stored for up to 3 months at 25 ± 2 °C for up 3 months according to ICH Q1A to evaluate the impact of short-term excursions outside the proposed long-term storage conditions and for up to 2 weeks at 30 ± 2 °C to evaluate potential storage excursions at the patient's home. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, pH, particulate matter, assay of levodopa, assay of carbidopa, assay of N-acetylcysteine, assay of ascorbic acid, impurities and degradation products, volume in container, hydrazine, pyrogens, sterility and container closure integrity test.

All attributes analyzed were well within the proposed shelf-life acceptance criteria under all conditions.

Based satisfactory study results obtained with each of the two proposed drug delivery systems with unopened vials stored at 25 ± 2 °C for 45 days, at the unopened vials should be used within 45 days of thawing. This information is to be provided in the space provided on the carton when stored at this temperature.

A photostability study was conducted in accordance with ICH Q1B. Light exposure resulted in one impurity exceeding the specification limit. The intended commercial secondary package was shown to provide adequate protection from light exposure. Thus, a recommendation is added to the label indicating that the drug product vials should be stored in the original package until administration.

In-use stability studies were conducted with both delivery systems on batches stored under long term conditions for various lengths of time up to end of shelf-life. Samples were thawed and stored at 25 °C for a period covering the proposed in-use period, at which point, the vial contents were transferred to the delivery systems. Both delivery systems were programmed for the slowest rate with the longest duration as a worst-case scenario. Infusion was conducted for up to 27 hours (with a safety margin above the standard 24 hr infusion time) at 37 ± 2 ºC, i.e. body temperature to mimic the continuous wearing of the infusion pump externally against the body during administration. The remaining volume in the reservoir at the end of the 27 hours infusion period was used for analysis. A decrease in the content of the antioxidant N-Acetylcysteine was observed during the in-use period. This decrease was expected since NAC interacts with the available oxygen introduced during the preparation and infusion of the daily infusion, preventing the oxidative degradation of the active substances.

In addition, the impact of daylight exposure on finished product was assessed in the in-use stability studies with proposed drug delivery systems over the expected day time period. The results revealed no adverse impact on quality and no issue with light exposure during infusion.

Microbial challenge studies were conducted at 25 °C and 37 °C. No microorganism growth was observed at a period exceeding the infusion period, thus supporting the safety of the administered product over the daily infusion period.

Furthermore, vials of the finished product were exposed to repeated freeze/thaw cycles. While the study results revealed no impact on product quality by freezing and thawing, as an additional precaution considering the risk of levodopa precipitation, the applicant proposes to indicate in the label instructions that re-freezing of vials is not allowed. In case the product is accidentally re-frozen it should be discarded. As a precautionary measure, this is endorsed.

In conclusion, the reported stability and statistical evaluation performed support the claimed shelf life and storage conditions for the finished product. The applicant has confirmed that NfG on start of shelf-life of the finished dosage form, CPMP/QWP/072/96 is applied.

The post-stability commitments were acceptable. However, the CHMP raised an MO requesting the applicant to amend the post-approval stability protocol to remove the rabbit pyrogen test which is no longer acceptable for pyrogenicity testing. The post-approval stability protocol was amended as requested. Also, in accordance with EMA's Q&A on Quality Part 2, it is declared that endotoxins are not tested during stability studies. Therefore, the MO is resolved.

Based on available stability data, the proposed shelf-life of 3 years is acceptable with the following additional instructions as stated in the SmPC (section 6.3): store in a freezer (-25 °C to -15 °C). Store in

the original package in order to protect from light. After thawing, do not store above 25 °C. Do not refrigerate or refreeze. Use within 45 days (use-by date on the original package). The daily dose for infusion should be prepared immediately prior to administration to ensure that the period between initiation of preparation to end of daily administration will not exceed 25 hours.

Adventitious agents

No excipients derived from animal or human origin have been used.

3.3.1. Medical device issues

The finished product can be administered by either one of the following referenced delivery systems:

- Crono Twin ND

- Yurway delivery system (YDS)

To assess the usability of the Yurway Delivery System, a Human Factors Validation Testing study was conducted, evaluating its use in three user groups: the defined intended user groups.

These groups are intended to represent the two real-life modes of use described in the SmPC: either the patient uses the pump alone, or the pump is managed with the support of a caregiver (partner or healthcare professional). "Independent patients" generally had less advanced Parkinson's (shorter disease duration, lower total levodopa dose, OFF (time with troublesome dyskinesia) not always every day), while the "patient + caregiver" users were clinically more advanced (longer disease duration, higher levodopa daily dose, OFF every day). This reflects typical disease progression in advanced PD, where more severe patients often require caregiver support.

The results indicate that all patient groups were able to successfully use the YDS. Based on some issues observed in this study, clearer instructions and strengthened training protocols were implemented.

The SmPC text appropriately addresses (i) pre-initiation assessment by the physician, (ii) the requirement for a trained caregiver in patients unable to perform critical tasks safely, and (iii) the requirement for prior training and competence assessment, including provision for refresher training when difficulties are identified.

Information about the comparability of the Yurway Delivery System and the Crono Twin ND pump was provided. The devices were assessed by the Notified Body, and the Clinical Evaluation Consultation Panel (CECP) reviewed the clinical evaluation with no specific objections. This means that the pumps are considered compliant with safety and performance requirements for its intended use, that is continuous subcutaneous delivery of Onerji at home. In addition, the applicant explained that Yurway was designed to match the main technical characteristics of Crono Twin ND. This supports that both pumps can deliver the same dose regimen that is described in section 4.2 of the SmPC.

A bridging package, including a step-by-step comparison of both systems (Crono Twin ND and Yurway) covering all the administration steps (loading, priming, infusion initiation, etc.) has been provided. For each step, it has been indicated whether the process is the same or different. The comparison confirms that the Crono Twin ND pump, which was used in the clinical studies, involves a more manual preparation process, whereas the Yurway system automates several preparation steps. This simplification is not expected to negatively impact clinical outcomes. On the contrary, the reduced manual requirements may lower the demand for fine motor skills and the need for caregiver support in advanced Parkinson's disease patients. Differences in alarm handling, battery management, and end-of-day procedures are procedural in nature and do not affect the ability to maintain uninterrupted infusion.

Furthermore, pump switching, where applicable, will be performed under healthcare professional supervision, with programming and training of the patient and/or caregiver prior to home use, which mitigates potential usability or safety concerns.

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

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. MOs were raised during the procedure for the finished product, relating to the request for performance of routine testing of bioburden as an in-process control, replacement of the rabbit pyrogenicity test as an IPC, to develop a suitable validated *in vitro* test to control the pyrogenicity in the finished product specifications, to perform screening tests to investigate the levels of nitrosamines, to provide stability data under long term and in-use conditions to evaluate the levels of nitrosamines in representative batches of finished product, to amend the footnote in the post-approval stability protocol to replace the rabbit pyrogenicity test, to provide a CE certificate as granted by a notified confirming full compliance with requirements set out in Annex I of the MDR for the Yurway delivery system, and to provide confirmation of GMP compliance of one finished product manufacturing site. The applicant replaced the pyrogenicity test with a non-animal alternative and it was agreed that this is sufficient and there is no need for a further test at batch release. It was also demonstrated that there is no risk of nitrosamines in the finished product. The CE certificate for YDS was provided, but one of the drug product manufacturing sites was removed from the dossier due to GMP compliance issues. Satisfactory responses were provided for all the issues, and the MOs were considered resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

No applicable

4. Non-clinical aspects

4.1. Introduction

The current application relies on the well-established safety and efficacy of levodopa (LD) and carbidopa (CD) in both animals and humans. As such, most of the non-clinical data derived from publications. In line with the 3Rs principles the decision of not performing additional unnecessary animal studies is endorsed by the CHMP.

Due to the new (SC) route of administration of ND0612 DP, the non-clinical development program focused on the local toxicity at the infusion sites. Supported by Scientific Advice (SA) requested to EMA and a follow-up to such advice, a 90-day repeat-dose toxicity study in the minipig (reference: Report

95070) was conducted as the pivotal non-clinical study supporting the clinical development and MAA for ND0612 DP. This approach is acceptable.

4.2. Analytical methods

A bioanalytical method for determination of LD and CD in minipig plasma from GLP toxicology studies was developed and validated in accordance with EMA guideline on bioanalytical method validation, effective at the time of validations (reference: Report 2013-009, SOP 09.509.00). The samples were analysed by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) in the electrospray positive ionization mode (ESI+). To cover for higher LD plasma concentrations encountered in the TK analysis performed in the 90-day local toxicity study (reference: Report 95070, Addendum 4, bioanalytical phase report 2013-058), partial validation was conducted to evaluate the capability of dilution for LD in minipig plasma (reference: Report 2014-013). A later version (reference: SOP 09.509.03) with minor editorial changes added for clarification was effective at the time of analysis of samples obtained from a subsequent GLP 28-day toxicokinetic study (reference: Report A2369, Addendum 7, bioanalytical phase report 2017 001). To conclude, the method met the acceptance criteria for selectivity, sensitivity, precision, accuracy and stability over the range of concentrations found in samples from the toxicology studies. Therefore, this validated method was deemed suitable for the quantitative determination of LD and CD in Göttingen minipig plasma samples from the toxicology studies.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

No new non-clinical primary pharmacodynamic studies were conducted with ND0612 DP. The advantage of giving LD is its ability to pass through the blood-brain barrier (BBB) and be available at the site of need without exposing the patient to excessive peripheral dopaminergic activity. To increase the brain bioavailability of LD and minimise the systemic side effects of dopamine in the periphery, carbidopa (CD), a peripheral DDC inhibitor, was added to the formulation. CD prevents the premature conversion of LD to dopamine outside the central nervous system (CNS), allowing more LD to reach the brain.

4.3.1.2. Secondary pharmacodynamics

No new non-clinical secondary pharmacodynamic studies were conducted with ND0612 DP.

The beneficial effects of LD are limited by the dyskinesias that occur at higher doses. As the disease progresses, the threshold dose that produces undesirable dyskinesias decreases, narrowing the therapeutic window, making it progressively more difficult to obtain beneficial effects with the drug, and approaching the point at which intolerable dyskinesias are experienced at doses below the minimum effective dose (Mouradian et al., 1989).

Oral LD/CD given to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism monkey model relieved the parkinsonian symptoms, but after 2 weeks of treatment the animals developed prominent lingual dyskinesia which remained visible after each dose until the end of the experiment (Bedard et al. 1986). Similarly, dopamine-depleted rats given high doses of LD/CD developed severe dyskinesias (Lindner et al., 1996).

Intermittent administration of high-dose LD (25 mg/kg once daily) to 6-hydroxydopamine (6-OHDA)-lesioned rats induced dyskinesia more strongly than divided dose (6.25 mg/kg four times daily) or low-

dose administration (6.25 mg/kg once daily) (Tsironis et al., 2008). It has also been shown, clinically, that continuous LD administration reduced the development of dyskinesia compared to intermittent administration (Olanow et al.,2006; Stocchi et al., 2008), which aligns with the continuous SC infusion of ND0612 DP.

4.3.1.3. Safety pharmacology

No new non-clinical secondary pharmacodynamic studies were conducted with ND0612 DP.

A review of the literature revealed a few investigations reporting the effects of LD, mediated by its metabolite dopamine, on cardiovascular, central nervous, respiratory, gastrointestinal and renal/urinary systems. These findings are well-known and do not attribute any new information to the known safety profile of marketed LD/CD products. The studies reported in the literature are briefly summarised below.

CD alone at therapeutic doses has low intrinsic pharmacological activity, and has no notable effects on cardiovascular, central nervous, gastrointestinal, or renal systems (Yamori et al., 1972; Johansson et al., 1983; Scriabine et al., 1976).

Central Nervous System

LD produced an increase in locomotor activity and irritability in various species (Hornykiewicz, 1966). These actions have been correlated with the increase in brain dopamine which occurs because of its decarboxylation (reviewed in Everett et al., 1963). These effects are considered mediated by its chief metabolite, dopamine. While LD central effects (mediated by dopamine) appear to be excitatory, dopamine formed in the periphery (in the absence of DDC inhibitor) induces depressant effects on behaviour (Butcher et al., 1969).

Cardiovascular System

Electrocardiogram evaluations performed as part of a 4-week SC toxicity study in minipigs(reference: report A2369) demonstrated no arrhythmias at LD systemic exposures (C_{max} of 6623 ng/mL) that are considerably higher than the exposures following administration of ND0612 DP in humans.

LD demonstrated dose- and species-dependent haemodynamic effects mainly due to the peripheral conversion of LD to dopamine.

Intravenous (IV) infusion of LD, after blockade of extracerebral DDC by IV administration of CD, decreased both blood pressure and plasma renin activity (PRA) in the dog; the same dose of LD without CD treatment, caused a large but transient increase in blood pressure and a sustained increase in PRA. These data suggest that the increases in blood pressure after administration of LD alone can be attributed to the direct stimulatory effects on the vasculature of catecholamines formed in peripheral tissues. The decrease in blood pressure observed in CD-treated animals, however, appears to be a consequence of the action of catecholamines formed within the CNS from the infused LD (Blair et al., 1977). It has been shown that, when both cerebral and extracerebral DDC are inhibited in dogs by benserazide, subsequent IV administration of LD causes no change in blood pressure (Ganong, 1977). In the intact dog, the most prominent effects of LD given IV were an increase in myocardial contractile force and heart rate over time, and a decrease in venous return while contractile force was still enhanced. Comparative studies were performed in dogs with two decarboxylase inhibitors, CD and benserazide, which differ from each other in their peripheral and central activity. The results obtained indicate that the positive inotropic and chronotropic effects induced by LD are mediated mainly through peripheral mechanisms (Osborne et al., 1971).

Respiratory System

LD, when combined with CD, stimulates hypoxic and hypercapnic ventilation in the unanaesthetised mouse, whereas LD alone, in comparable dosage, has no effect on ventilation. In contrast, very high doses of dopamine alone (240 mg/kg) and LD alone (300 mg/kg) administered intraperitoneally (IP) depressed hypoxic but not hypercapnic ventilation. CD alone had no effect on ventilation. These findings indicate that central dopamine receptors stimulate ventilation in this species (Olson et al., 1985).

Gastrointestinal System

Nausea, anorexia, and vomiting are frequent side effects in the initial phases of therapy with LD in parkinsonism. Similar effects were observed in animals. These effects of LD are suggested to be mediated by its metabolite, dopamine. Both IV and intracerebroventricularly administered LD and dopamine to dogs were reported as emetic agents. Systemically administered CD did not affect the emetic action of systemically administered dopamine but attenuated the emetic response to LD administered both IV and intracerebroventricularly (Lotti et al., 1974). In view of the limited penetration of CD into the brain, the attenuating effect of CD upon LD-induced emesis would at first suggest that this LD action is mediated extra-cerebrally and CD acts by preventing its peripheral conversion to dopamine. However, since dopamine given systemically does not penetrate the BBB, the site must lie outside the BBB. It was reported that dopamine activated the chemoreceptor trigger zone, a CNS site which lies outside the BBB thus is readily accessible to substances from the blood stream, and induced nausea and vomiting (Lotti et al., 1974, Peng, 1963).

LD depressed motility of the small intestine in mice and such effect was blocked by benserazide (DDC inhibitor), indicating that motility depression of the small intestine might be induced by the LD metabolite dopamine ((Shuto et al., 1980).

Renal/Urinary System

The effect of endogenous dopamine on renal phosphate excretion was investigated by intrarenal infusion of the precursor LD to dogs. LD was phosphaturic both in the presence and absence of parathyroid hormone and calcitonin. In dogs pretreated with CD, LD was no longer phosphaturic, although the kidney remained responsive to dopamine. Thus, the phosphaturia associated with LD was not due to LD itself. Since the kidney can efficiently decarboxylate LD to dopamine, it is likely that the phosphaturic effect of LD is due to an increased renal content of endogenous dopamine. CD was not anti-phosphaturic when given alone. It is therefore suggested that dopamine may play a role in the intrarenal regulation of phosphate excretion (Cuche et al., 1976).

4.3.1.4. Pharmacodynamic drug interactions

No drug interaction studies were performed during the development of ND0612 DP. Regardless its route of administration, LD derived from ND0612 DP is subjective to the same, known drug interactions that are common to other LD/CD products.

4.3.2. Pharmacokinetics

Besides absorption, the disposition pattern of LD and CD is considered to be unaffected by the route of administration. Hence, distribution, metabolism, excretion or drug-drug interaction studies have not been conducted with ND0612 DP. The essence of these pharmacokinetic (PK) properties was taken from published literature references and is briefly summarised below. Furthermore, the TK of LD and CD were evaluated in the ND0612 DP-treated animals during the toxicology studies to confirm exposure. The results of these TK analyses are presented in the toxicology section thereafter.

4.3.2.1. Absorption

Each of the two local toxicity studies (reference: Report 95070 and A2369) included blood collection at specified timepoints to determine plasma concentrations of CD and LD, and TK analysis. Additional PK parameters were calculated by an external expert based on the original data from the pivotal toxicity study (reference: Report 95070) and were reported in an expert report(reference: Report DS-ND-2105). The TK evaluations established the PK proof of concept, demonstrating the potential of the suggested maximal dosing regimen (720/90 mg LD/CD infused over 24 hours) to provide relevant LD concentrations with minimal fluctuations across the desired time of active treatment.

ND0612 DP was developed as a continuous SC infusion of LD/CD to provide stable and sustained LD plasma levels by elimination of the trough concentrations and reduction of the plasma fluctuations associated with oral LD formulations. The published literature contained a comprehensive account of the PK of both LD, CD and of their combination, mostly when administered orally, which is not relevant for the absorption of ND0612 DP.

4.3.2.2. Distribution

No new distribution studies were conducted with ND0612 DP. LD is rapidly decarboxylated to dopamine by DDC in extracerebral tissues in the absence of peripheral decarboxylase inhibitor such as CD. Therefore, only a small portion of a given LD dose is transported across the BBB to the CNS. LD crosses the BBB by a stereospecific, saturable, facilitated process via the neutral amino acid transport carrier system (Khor et al., 2007). SC administration of 20 mg/kg 14C-LD to rats resulted in 0.1% of the radioactivity in the brain; most of the radioactivity was found in urine, skin, whole skeletal muscle, intestine, and liver (Gey et al., 1964). Following IV administration of 14C-CD (20 mg/kg) to rats, radioactivity was shown to be concentrated in the kidney, lungs, small intestine, and liver. Radioactivity was not detected in the rat brain, confirming that CD does not cross the BBB (Vickers et al., 1974). The free unbound fraction of LD in human plasma was found to be 68 ± 2%, 76 ± 8% and 94 ± 4% at concentrations of 100 ng/mL, 500 ng/mL and 5000 ng/mL, respectively (Rizzo et al., 1996). Like LD, CD has a low capacity for binding to plasma proteins. The free unbound fraction in human plasma was approximately 64% (Vickers et al., 1974).

Very limited information is available regarding the transplacental transfer of LD in pregnancy. Examination of aborted tissues from a foetus from a woman with PD who was receiving LD/CD doses of 800/200 mg/day showed that LD crosses the placental barrier and was found in foetal tissues, including brain and spinal cord (Merchant et al., 1995). The transplacental transport of 14C-CD was examined in pregnant rats following IV dose of 20 mg/kg on gestation Day 19. The drug and/or metabolites did cross the placental membrane, with highest levels observed in the placenta. Low levels of CD were detected in the foetus (Vickers et al., 1974).

4.3.2.3. Metabolism

No new metabolism studies were conducted with ND0612 DP. LD undergoes metabolism via four pathways: The two major ones are the decarboxylation by aromatic amino acid decarboxylase (AAAD, also known as DDC) to dopamine, which may be further metabolised to form 3,4-dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA) and, to a lesser extent, the 3-O-methylation by catechol-O-methyltransferase (COMT) to form 3-O-methyldopa (3-OMD). The other metabolic pathways are transamination by tyrosine aminotransferase, and oxidation by tyrosinase or other oxidants. The metabolism of LD by DDC is inhibited by the coadministration of carbidopa. Inhibition of DDC by CD in the periphery makes more LD available for transport to the brain, where it is then metabolised to dopamine. When the DDC is inhibited, the majority of LD is converted to 3-OMD in the peripheral tissues (Khor et al., 2007). CD is metabolised to three main metabolites: 2-methyl-3-methoxy-4-hydroxy-

phenylpropionic acid (10 and 16% of the radioactivity excreted in the urine of monkey and dog, respectively), 2-methyl-3,4-dihydroxy-phenylpropionic acid (17 and 19% of the radioactivity excreted in the urine of monkey and dog, respectively), and 3-hydroxy-α-methyl-phenylpropionic acid (10 and 20% of the radioactivity excreted in the urine of monkey and rat, respectively) (Vickers et al., 1975). The loss of the hydrazine functional group represented the major metabolic pathway for CD (Khor et al., 2007).

4.3.2.4. Excretion

No new excretion studies were conducted with ND0612 DP. LD is predominantly eliminated by decarboxylation to dopamine and only insignificant amounts are excreted as the unchanged drug (Khor et al., 2007). Metabolites of dopamine (DOPAC and HVA) are eventually excreted in the urine. LD and possibly LD metabolites are excreted in human milk (Thulin et al., 1998). Following oral administration of ^{14}C-labeled CD, urinary excretion accounted for approximately 16%, 66%, and 40%, of the related radioactivity, and faecal excretion was determined to be 52%, 11%, and 32% in the rat, dog, and rhesus monkey, respectively. The urine contained both unchanged drug and metabolites. Unchanged CD in dog urine represented 65% of the urinary radioactivity, whereas in the monkey and rat, the drug represented only 20% and 38%, respectively. CD was detected in the milk of lactating rats (15 days postpartum) following an IV dose of 20 mg/kg 14C-CD (Vickers et al., 1974). Co-administration of LD and CD reduced urinary excretion of dopamine and its metabolites because the majority of LD dose is converted to the long half-life 3-OMD during coadministration with CD (Bianchine et al., 1972; Khor et al., 2007).

4.3.2.5. Pharmacokinetic drug interactions

No new pharmacokinetic interaction studies were conducted with ND0612 DP. There are no drug interactions specific for ND0612 DP. ND0612 DP, when administered via SC route, and bypasses the first pass effect that medications administered orally undergo. Therefore, some interactions that apply for oral but not SC route (e.g., delayed gastric emptying, chelate formation in the gut) are not relevant for ND0612 DP. Additionally, the metabolism of LD/CD has not been shown to involve the CYP450 superfamily of enzymes and therefore CYP450-derived drug-drug interactions are not expected.

4.3.2.6. Other pharmacokinetic studies

Not applicable.

4.4. Toxicology

A 90-day repeated dose toxicity study in minipigs (reference: study no. 95070) was conducted as the pivotal non-clinical safety study to support the safety of the clinical SC route of administration. This was a GLP-compliant study with TK analysis, using the ND0612 to-be-marketed formulation.

In addition, the applicant completed a 28-day repeated dose toxicity study (reference: study No. A2369) that evaluated the tolerability of several dosing regimens, type of infusion pump and impurity profile. In addition, studies on impurities (reference: study no. A4093), in silico evaluation for genotoxicity and on excipients (reference: studies no. A3574, A4608 and ND 2-20-093) were also conducted.

Furthermore, toxicological data supporting this application were also obtained from published literature references.

4.4.1. Single-dose toxicity

No single-dose toxicity studies were conducted by the applicant. Instead, data from published literature was provided. This approach is acceptable.

4.4.2. Repeat-dose toxicity

The applicant conducted two repeated dose toxicity studies in minipigs.

- In the pivotal 90-day study with a 30-day recovery period the control group (group 1) received saline solution; two other groups (no. 2 and 3) received ND0612 DP at 60/7.5 mg/mL LD/CD concentration, and a fourth group (no. 4), ND0612 DP at 60/14 mg/mL LD/CD concentration. In all groups, the Crono ND pump delivered the SC infusion. For the infusion sites located on the right side of the body in animals from group 4, the volume administered per site, per administration, was 4.5 mL; for all the others, the volume was 6 mL. Treatment of the different groups also varied in terms of rate of infusion, frequency of site reuse and on whether single or dual infusion was used, as detailed below:
- Group 1 (saline): simultaneous dual daily infusions. The infusion sites were reused every 10 days, and the rates of infusion were the following: 0.32 mL/h x 16 h + 0.1 mL/h x 8 h, for sites on the left, and 0.72 mL/h x 8 h, for sites on the right.
- Group 2: single daily infusion. The infusion sites were reused every 5 days, up to Study Day 30 and, afterwards, every 15 days. The rate of infusion was the following: 0.32 mL/h x 16 h + 0.1 mL/h x 8 h.
- Group 3: simultaneous dual daily infusions. The infusion sites were reused every 10 days, and the rates of infusion were the following: 0.32 mL/h x 16 h + 0.1 mL/h x 8 h, for sites on the left, and 0.72 mL/h x 8 hr, for sites in the right.
- Group 4: single daily infusion on sites on the right or left. Sites on the left were reused every 10 days, and the rate of infusion was 0.32 mL/h x 16 h + 0.1 mL/h x 8 h. Sites on the right were reused every 20 days and the rate of infusion was 0.24 mL/h x 16 h + 0.08 ml/h x 8 h.

The study revealed no systemic toxicity but only infusion site reactions. Of note, at the maximum tested dose, systemic exposures to levodopa and carbidopa were nearly 6-8- and 1.5-fold higher, respectively, than exposures in humans at the maximum recommended dose. Information on this pivotal repeated dose toxicity study is outlined in Onerji SmPC section 5.3.

Toxicokinetic data, generally, revealed no gender differences in exposure to LD and CD. AUC0-t and C_{max} of LD and CD increased in a dose proportional manner and there was no accumulation of either LD or CD.

No systemic adverse effects were observed up the maximum tested dose of LD/CD, which was 720 mg/90 mg (group 3). At this dose, which equates the maximum recommended dose to be administered to patients, systemic exposures to LD and CD in the animals, based on plasma C_{max} and AUC_{0-t} values, were ~6-8- and 1.5-fold higher (LD and CD, respectively) than those measured in healthy volunteers during the ND0612-005 clinical study who were treated with the MRHDD of ND0612 DP (720/90 mg/day LD/CD).

At the microscopic examination of the infusion sites of all ND0612 DP-treated groups, sub-chronic or chronic inflammation, and/or necrosis, with or without cavity formation were observed. A few sites also showed mineralisation in the subcutis and/or panniculus muscle, and brown pigment-laden macrophages, indicative of a normal phagocytic response to previously present haemorrhage. Abscesses were seen sporadically at sites administered highest tested infusion rate (0.72 mL/h) of ND0612 DP (LD/CD 720/90 mg/day group 3 right sites). In general, the incidence and severity of findings increased

with higher rate of infusion and higher frequency of administration to the same site. The severity of observed chronic inflammation and necrosis in the different groups is summarised in the Table below.

Table 2. Severity of observed chronic inflammation and necrosis in the different groups

Group	**Dosing regimen**	**Frequency of site reuse**	**Chronic subcutaneous inflammation**	**Necrosis**
Group 2	Single daily infusion 0.32 mL/h x 16 h + 0.1 mL/h x 8 h	Every 5 days, until Study Day 30, and every 15 days, afterwards	Mild 54% Moderate 38%	None 19% Minimal 13% Mild 39% Moderate 26%
Group 3	Dual daily infusion - Left side: 0.32 mL/h X 16 h + 0.1 mL/h x 8 h - Right side: 0.72 mL/h x8 h	Every 10 days	Mild 11%, Moderate 84%	None 8%, Minimal 8% Mild 25% Moderate 55% Marked 4%
Group 4 (Note: Formulation with 60/14 mg/ml LD/CD) 4.5 ml/site on sites on the right)	Single daily infusion - Left side: 0.32 mL/h x16 h + 0.1 mL/h x 8 h - Right side: 0.24 mL/h x16 h + 0.08 mL/h x 8 h	Every 10 days Every 20 days	Mild 31% Moderate 69% Minimal 6% Mild 58% Moderate 38%	None 10% Mild 52%, Moderate 38% None 16% Minimal 8% Mild 61% Moderate 14%

After the recovery period, the reactions at the infusion sites showed evidence of reversibility.

In terms of extrapolation to humans of the observed infusion site reactions (ISR), the medicinal product under evaluation is to be administered via two infusion sites, at a fixed rate of 0.08 mL/hour during the night (6 hours) and at an individualised rate ranging between 0.32 to 0.64 mL/hour during the day (18 hours), for a total duration of 24 hours per day and a total daily dose of levodopa /carbidopa from 370 mg/46 mg up to 720mg/90 mg. Similarly, as that intended for patients, in animals from group 3, ND0612 DP was also administered via two infusion sites, and the daily dose was 720 mg LD/90 CD. Additionally, for most infusion sites, the volume of administration was 6 mL per site per administration (as the maximum intended for humans). Although not equal, the rates of infusion were close to those intended for humans and the same applied to the frequency of site reuse.

No additional findings were observed in the subsequent 28-day repeated dose toxicity study in minipigs. This study, conducted in males only, used two different infusion pumps, Crono ND pump and t:flex™ pump, respectively, and tested two formulations of ND0612 DP.

No chronic toxicity studies were conducted by the applicant. Instead, data from published literature were provided, including studies evaluating oral administration of LD/CD combination. This approach is acceptable.

Ultimately, the information on repeated dose toxicity detailed in Onerji SmPC section 5.3 is consistent with information in the SmPC of already approved medicinal products containing levodopa and carbidopa.

4.4.3. Genotoxicity

No genotoxicity studies were conducted by the applicant. Instead, data from published literature was presented. This approach is acceptable.

According to the published data, both levodopa and carbidopa appeared genotoxic in some assays. However, no genotoxicity was observed in other essays. Thus, the relevance of such positive findings was questioned.

Ultimately, the information on genotoxicity detailed in section 5.3 of Onerji SmPC is consistent with information in the SmPC of already approved medicinal products containing levodopa and carbidopa.

4.4.4. Carcinogenicity

No carcinogenicity studies were conducted by the applicant. Instead, data from published literature was presented. This approach is acceptable.

According to available data, no carcinogenicity was observed in a long-term carcinogenicity study in rats following oral administration of LD/CD combination.

Ultimately, information on carcinogenicity detailed in section 5.3 of Onerji SmPC is consistent with information in the SmPC of already approved medicinal products containing levodopa and carbidopa.

4.4.5. Developmental and reproductive toxicity

No reproductive toxicity studies were conducted by the applicant. Instead, data from published literature was presented.

The data from published literature covered studies on fertility, embryo-fetal development and pre-postnatal development, mostly conducted with levodopa. The lack of juvenile animal studies was justified as these are not required in the patient population who should receive Onerji treatment.

According to available information, levodopa showed adverse effects on fertility and induced fetal malformations in a study in rabbits (but not in rats). In a pre-postnatal study, the administration of LD/CD led to an increase in the length of gestation. Levodopa inhibited prolactin release and produced a dose-related inhibition of milk ejection.

Ultimately, information on reproductive toxicity detailed in Onerji SmPC is generally consistent with information in the SmPC of already approved medicinal products containing levodopa and carbidopa.

4.4.6. Toxicokinetics and exposure margins

The two repeated dose toxicity studies conducted by the applicant included toxicokinetic evaluation.

In general, in the pivotal repeated dose toxicity study, there were no gender differences in exposure to LD and CD. AUC_{0-t} and C_{max} of LD and CD increased in a dose proportional manner and there was no accumulation of either LD or CD. At the maximum tested dose, systemic exposures to LD and CD in the animals, based on plasma C_{max} and AUC_{0-t} values, were ~6-8- and 1.5-fold higher (LD and CD,

respectively) than those measured in healthy volunteers during the ND0612-005 clinical study who were treated with the MRHDD of ND0612 DP (720/90 mg/day LD/CD).

4.4.7. Local tolerance

Local tolerance was assessed in the repeated dose toxicity studies and in the studies that evaluated the safety of excipients (as detailed below). No additional dedicated studies on local tolerance were conducted by the applicant. This approach is acceptable.

4.4.8. Other toxicity studies

Studies on impurities

The specifications for the ND0612 DP include two substance-related impurities (both carbidopa-related) at maximum limits above the ICH Q3B(R2) qualification threshold. These are methyldopa and 3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid (also named "main degradant").

To qualify these impurities, the applicant conducted an additional 90-day repeated dose toxicity study in minipigs with administration of ND0612 DP at different levels of the impurities to be qualified, performed a QSAR evaluation (software CASE Ultra, version 1.7.0.5) of the mutagenic potential of 3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid and conducted a safety evaluation of both impurities, also based on published literature data.

The 90-day repeated dose toxicity study, GLP-compliant, in addition to saline and vehicle control groups, included three other animal groups which received ND0612 DP with different concentrations of the impurities to be qualified: ND0612 low impurities, ND0612 mid impurities, and ND0612 high impurities. In all groups, the respective solutions were administered by single daily subcutaneous infusions, at a same volume of 6 mL/site/administration and rate of infusion, which was 0.32 mL/h x 18hr + 0.05 mL x 6 h.

The study revealed no risks related to the impurities. The infusion site reactions to the formulation with the highest levels of impurities were similar to those observed after administration of the vehicle. These are relatively higher than the respective maximum exposures in humans.

The QSAR evaluation of 3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid for mutagenicity revealed no structural alerts for genotoxicity that were not also present in carbidopa, a substance shown to lack mutagenic potential. The impurity was classified into ICH M7(R2) class 4.

Also considering data from published literature, the impurities methyldopa and 3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid may be considered qualified, based on the following:

- Methyldopa is common to all LD/CD containing products at a specification limit of NMT 0.7%, as published in the USP monograph for CD and LD tablets. The specification set by the applicant of 0.5% for M-Dopa is noted as below the USP monograph for CD and LD tablets. The impurity qualification 90-day repeated dose toxicity study with administration by subcutaneous infusion revealed no risks attributed to the impurity.
- 3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid is a major metabolite of CD in humans, monkeys, and dogs, as detailed by Vickers et al., 1974; Vickers et al., 1975. These publications indicate that more than 5% of CD given to human subjects is transformed and excreted into the urine as 3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid. The QSAR evaluation (software CASE Ultra, Version 1.7.0.5), in accordance with the ICH M7 (R2) guideline, revealed no structural alerts that were not also present in carbidopa, a substance shown to lack mutagenic potential. The impurity qualification

90-day repeated dose toxicity study with administration by subcutaneous infusion revealed no risks attributed to the impurity.

A QSAR evaluation for mutagenicity in accordance with the ICH M7(R2) guideline was also conducted for three other impurities, all at levels below the ICH Q3B(R2) qualification threshold. The used software was CASE Ultra. For two impurities, no structural alerts were identified; both impurities were classified into class 5. For the third impurity, no structural alerts were identified that were not also present in levodopa, a substance shown to lack mutagenic potential; the impurity was classified into class 4.

No other studies on impurities or assessment reports were submitted. However, reports on the toxicological evaluation of different extractables and leachables were included in the submitted dossier for this initial MAA. Ultimately, the toxicological evaluation of extractables and leachables from the container closure system and delivery systems did not reveal compounds of toxicological concern. This evaluation was based, namely, on the TTC concept, values already established in available guidelines, published toxicological data and QSAR evaluations. No new experimental studies were conducted.

Excipient studies

The ND0612 formulation contains the following pharmaceutical excipients: L-arginine, ascorbic acid, N-acetylcysteine, and polysorbate 80 (3 mg/mL).

To specifically address the safety of ND0612 DP excipients, the applicant conducted two *in vivo* studies, one *in vivo/ex vivo* study and an evaluation based on published literature. The two *in vivo* studies were conducted in minipigs. The *in vivo/ex vivo* study used domestic pigs.

The first *in vivo* study was a 90-day repeated dose toxicity study, with daily administration by subcutaneous infusion using a CRONO ND pump. The study comprised three animal groups, one given saline solution (9 mL/site/administration) and the other two, ND0612 DP's vehicle (6 or 9 mL/site/administration). The study was intended to complement the pivotal 90-day repeated dose toxicity study which had not included a vehicle control group.

The study revealed infusion site reactions in animals treated with the vehicle, with relatively higher severity in those administered 9 mL. The reactions were similar to those observed in other studies in animals treated with ND0612 DP.

The second *in vivo* study was of shorter duration (six days of treatment). It tested, for infusion site reactions, different variations of the ND0612 DP vehicle, with changes in pH, osmolality and presence or absence of the excipient L-arginine, as well as solutions of L-arginine with different pH and osmolalities.

Results from this study indicated that the L-arginine was the component responsible for induction of inflammatory reactions observed at the infusion sites.

The *in vivo/ex vivo* study had two parts. In the *in vivo* part, domestic pigs were given a 24-hour subcutaneous infusion of ND0612 DP and were evaluated for blood coagulation at baseline, end of the infusion and 24 hours after the end of the infusion. In the *ex vivo* part, fresh blood samples from the domestic pigs were incubated with 12 different solutions, at different ratios. The 12 solutions comprised saline, sodium citrate, variations of ND0612 DP and ND0612 DP vehicle, ascorbic acid, N-acetylcysteine, Polysorbate 80, L-arginine and meglumine.

The *in vivo* part of the study showed no effect on blood coagulation.

The *ex vivo* part showed inhibition of clotting time when fresh blood samples were incubated with ND0612 formulations containing L-arginine or with isolated L-arginine solutions at the concentrations present in ND0612 DP. ND0612 formulations with either LD/CD 60/7.5 mg/mL or LD/CD 60/14 mg/mL inhibited coagulation when mixed at a ratio of 1:13, but not when mixed at 1:40 ratio.

Results from this study indicate, therefore, a lack of systemic effects on blood of coagulation. However, the possibility of a local effect on blood coagulation is not excluded. The potential effects of ND0612 DP on blood coagulation were attributed to L-arginine.

Regarding the safety evaluations of the excipients based on published literature, these mostly focused on potential systemic effects upon chronic administration. For all the four excipients, it was considered that these did not pose a systemic safety concern.

In addition to safety data obtained from the conducted non-clinical and clinical studies, both L-arginine and ascorbic acid are present in food. Moreover, albeit for short-term administration, L-arginine is used as an excipient or API at higher doses. N-acetylcysteine (NAC) is a precursor of L-cysteine and used as a dietary supplement. There are published clinical safety databases with long term administration and, albeit for short-term administration, NAC is used as a DP given at higher doses. Polysorbate 80 is used as a direct food additive, there are, likewise, published clinical safety databases with long term administration, and, albeit for short-term administration, it is used as an excipient at higher doses.

Altogether, the available data do not indicate a risk of systemic toxicity but a risk of infusion site reactions due to the presence of the excipient L-arginine. Ultimately, the observed effects are noted as reversible, not considered adverse and can be easily monitored in the clinical setting.

4.4.9. 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* (EMEA/CHMP/SWP/4447/00 Rev.1, 2024). The justification for the absence of a complete ERA for levodopa and carbidopa was documented separately for each active substance.

Levodopa and carbidopa are naturally occurring substances, and the exclusion of an environmental risk assessment is in line with Question 1, related to the Phase I Decision tree (Figure 2) of the Guideline EMEA/CHMP/SWP/4447/00 Rev.1, 2024:

- *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 levodopa and carbidopa, a risk to the environment arising from their use is therefore not expected.

Furthermore, the new ND0612 DP will reduce the dose of oral drug products currently prescribed to patients with Parkinson’s disease.

In conclusion, the ND0612 DP formulation comprising levodopa/carbidopa does not pose any environmental concerns when used as prescribed. Therefore, the Applicant's justification for the absence of ERA studies was accepted. In addition, the applicant applied suitable precautionary and safety measures to inform patients and healthcare professionals, mitigate environmental risks, and promote environmental protection, in accordance with Guideline EMEA/CHMP/SWP/4447/00,2024.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

The overall non-clinical development programme is partially supported by literature data, which is justified by LD and CD well-established safety and efficacy profile. This is acceptable from a regulatory perspective.

Pharmacology

The pharmacology of LD, CD and their combination has been extensively investigated and reported in the literature. Hence, non-clinical pharmacology studies were not conducted with ND0612 DP, which is acceptable.

Review of available pharmacology data identified no new information which could extend the well-known pharmacological profile of LD and CD in both animals and humans.

Levodopa's effectiveness is limited by dose-dependent dyskinesias, which worsen as Parkinson’s disease progresses, narrowing the therapeutic window. In animal models, high or intermittent LD dosing led to prominent dyskinesias, while continuous or low-dose regimens reduced this effect. Clinical studies also support that continuous LD administration lowers the risk of dyskinesia, consistent with the benefits observed with continuous SC infusion of ND0612 DP.

The systemic effects of levodopa, primarily mediated by its metabolite dopamine, are well known and aligned with the established safety profile of marketed LD/CD products. LD affects the central nervous, cardiovascular, respiratory, gastrointestinal, and renal systems, while CD alone shows minimal pharmacological activity at therapeutic doses.

In the CNS LD increases locomotor activity and irritability through central dopamine action, while peripheral dopamine may have depressant effects.

In the cardiovascular system LD has dose- and species-dependent haemodynamic effects, influenced by peripheral and central dopamine formation. CD mitigates peripheral effects, and no arrhythmias were observed in relevant animal studies at high LD exposures.

In the respiratory system LD/CD stimulates ventilation, whereas LD alone can depress hypoxic ventilation at high doses. CD alone has no respiratory effect.

In the gastrointestinal system LD causes nausea and vomiting, effects attributed to dopamine acting at the chemoreceptor trigger zone. CD reduces LD-induced emesis by preventing peripheral dopamine formation. LD also depresses intestinal motility via dopamine.

In the renal / urinary system LD increases renal phosphate excretion via local conversion to dopamine; this effect is blocked by CD, indicating a dopamine-mediated mechanism.

These findings reinforce the known pharmacological profile of LD/CD without identifying new safety concerns. Regardless of its route of administration, LD derived from ND0612 DP is subject to the same known drug interactions that are common to other LD/CD products.

In conclusion, the extensive literature on LD/CD ultimately supports their well-characterised pharmacological profile across systems, with no new safety signals identified. The absence of additional non-clinical pharmacology studies for ND0612 DP is justified. Continuous SC delivery aligns with known advantages of sustained LD exposure, particularly in reducing the risk of dyskinesia, and is subject to the same established drug interaction profile as existing LD/CD products.

Pharmacokinetics

The disposition of LD, CD and their combination were extensively investigated and reported in the literature. Besides absorption, the disposition pattern of LD and CD is considered unaffected by the route of administration. Hence, distribution, metabolism, excretion or drug-drug interaction studies were not conducted with ND0612 DP. The essence of these PK properties was taken from published literature.

A bioanalytical method for determination of LD and CD in minipig plasma from GLP toxicology studies was developed and validated in accordance with EMA guideline. The samples were analysed by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) in the electrospray positive ionization mode (ESI+). The method meets the acceptance criteria for selectivity, sensitivity, precision, accuracy and stability over the range of concentrations found in samples from the toxicology studies. Therefore, this validated method was deemed suitable for the quantitative determination of LD and CD in Göttingen minipig plasma samples from the toxicology studies.

Toxicokinetic data from two local toxicity studies confirmed the PK proof of concept for ND0612 DP, supporting its ability to deliver stable LD plasma levels with minimal fluctuations using the proposed 24-hour SC infusion regimen. Additional PK analysis by an external expert reinforced these findings.

While oral LD/CD data are not directly relevant to ND0612 DP, the literature highlights the limitations of oral administration and the benefits of continuous delivery. LD is extensively metabolized by peripheral DDC, limiting its availability to the CNS unless co-administered with CD, which does not cross the BBB. LD enters the brain via a stereospecific, saturable transporter. Animal studies show minimal brain distribution of LD and no brain penetration of CD. Both compounds exhibit low plasma protein binding. Limited data indicate that LD crosses the placenta and reaches foetal tissues, including the brain, while CD shows minimal foetal exposure. LD is primarily metabolised via decarboxylation by DDC to dopamine and by 3-O-methylation via COMT to 3-OMD. CD inhibits peripheral DDC, enhancing LD availability to the brain and shifting peripheral metabolism toward 3-OMD formation. Minor LD pathways include transamination and oxidation. CD is metabolised through loss of its hydrazine group, yielding three main urinary metabolites across species. LD is primarily eliminated through decarboxylation to dopamine, with minimal excretion of unchanged drug. Dopamine metabolites (DOPAC and HVA) are excreted in urine, and LD or its metabolites may be present in human milk. CD is eliminated via both urine and faeces, with species-specific differences in the proportion of unchanged drug excreted. CD has also been detected in rat milk. Co-administration of CD with LD reduces urinary excretion of dopamine and its metabolites by shifting LD metabolism toward 3-OMD formation.

There are no drug interactions specific for ND0612 DP. Its SC administration bypasses first-pass metabolism, making certain oral-specific interactions (e.g., delayed gastric emptying, chelation) irrelevant. As LD/CD metabolism does not involve CYP450 enzymes, CYP450-mediated drug interactions are not expected.

In conclusion, the pharmacokinetics of LD and CD are well established and consistent across routes of administration, supporting the use of existing data for ND0612 DP. Toxicokinetic studies confirmed stable systemic exposure with SC infusion. The validated bioanalytical method ensured reliable measurement in toxicology studies. ND0612 DP shares the known metabolic and interaction profile of oral LD/CD products, with no CYP450 involvement and no route-specific interactions expected.

Toxicology

LD/CD is a known combination of active substances. To support this MAA the following toxicological data were provided:

- A 90-day repeated dose toxicity study in minipigs (reference: study no. 95070) was conducted as the pivotal non-clinical safety study to support safety of SC route of administration. This was a GLP-compliant study with TK analysis, using the ND0612 to-be-marketed formulation.

  As justified, the Göttingen minipig was selected as the species of choice for this program because it is a large animal which allows continuous SC administration of the LD/CD formulation via a portable infusion pump system similar to the clinical setting and evaluation of TK profiles of the administered drugs. Furthermore, the swine's skin showed anatomic and physiologic characteristics similar to human skin (Swindle et al., 2012).

- A 28-day repeated dose toxicity study (Study No. A2369) evaluating the tolerability of several dosing regimens, type of infusion pump and impurity profile, together with studies on impurities, in silico evaluation for genotoxicity, and on excipients.

- Other toxicological data were obtained from published literature.

Single dose toxicity

No single-dose toxicity studies were conducted by the applicant. Instead, data from published literature was provided. This approach is acceptable.

Repeated dose toxicity

Two repeated dose toxicity studies, both conducted in minipigs, GLP-compliant and with daily administration by SC infusion, were submitted.

The pivotal study was a 90-day study with a 30-day recovery period, evaluating the toxicity of ND0612 DP following continuous SC infusion (with the Crono ND pump) at varying rates, different doses, two different CD concentrations, and different frequencies of infusions to the same site. This study did not reveal systemic toxicity but only infusion site reactions. No mortality was reported.

Toxicokinetic data, generally, revealed no gender differences in exposure to LD and CD. $AUC_{0\text{-}t}$ and C_{max} of LD and CD increased in a dose proportional manner and there was no accumulation of either LD or CD.

No systemic adverse effects were observed up the maximum tested dose of LD/CD.

In general, the incidence and severity of findings increased with higher rate of infusion and with higher frequency of administration to the same site. After the recovery period, the reactions at the infusion sites showed evidence of reversibility.

In terms of extrapolation to humans of the observed ISRs, for comparison, according to the SmPC, Onerji should be administered via two infusion sites, at a fixed rate of 0.08 mL/hour during the night (6 hours) and at an individualised rate ranging between 0.32 to 0.64 mL/hour during the day (18 hours), for a total duration of 24 hours per day and a total daily dose of levodopa /carbidopa from 370 mg/46 mg up to 720mg/90 mg. Similarly, as that intended for patients, in animals from group 3, ND0612 DP was also administered via two infusion sites, and the daily dose was 720 mg LD/90 CD. Additionally, for most infusion sites, the volume of administration was 6 mL per site per administration (as the maximum intended for humans). Although not equal, the rates of infusion were close to those intended for humans and the same applies to the frequency of site reuse.

Altogether, results from the 90-day repeated dose toxicity study suggested a risk of reversible infusion site reactions.

No additional findings were observed in the subsequent 28-day repeated dose toxicity study in male minipigs, using two different infusion pumps (Crono ND pump and t:flex™ pump), and testing two formulations of ND0612 DP, where one had higher concentrations of impurities than the other. The study

showed no systemic adverse effects or mortality. However, local infusion site reactions were seen in all animals treated with ND0612 DP. In the histopathological examination sub-chronic and chronic inflammatory reactions associated with moderate to marked necrosis and/or haemorrhage and/or cavitation and/or sporadic yellow/brown pigmentation were noted. The TK assessment showed that exposure to CD and LD increased with dose.

No chronic toxicity studies were presented. Instead, only data from published literature was provided, including studies investigating oral administration of LD/CD combination. Of note, studies investigating LD/CD administration via SC route were not considered needed given available knowledge on infusion site reactions, lack of systemic effects in the studies conducted by the applicant and based on clinical experience with LD / CD combination.

Overall, regarding repeated dose toxicity, the content in section 5.3 of Onerji SmPC is consistent with information in the SmPCs of already approved medicinal products containing levodopa and carbidopa, namely, Stalevo (EMEA/H/C/511), Duodopa (SE/H/0415/001): preclinical data revealed no special hazards for humans based on, among others, also studies on repeated dose toxicity. Moreover, section 5.3 of SmPC also includes adequate information on the pivotal repeated dose toxicity study conducted with Onerji.

No genotoxicity, carcinogenicity, reproductive toxicity studies were conducted by the applicant. Instead, data from published literature was provided, which is acceptable for the known active substance levodopa and carbidopa.

Information on genotoxicity and carcinogenicity, as detailed in section 5.3 of Onerji SmPC, is consistent with the content in the SmPCs of other already approved medicinal products containing levodopa and carbidopa. With reference to reproductive toxicity, data from published literature covered studies on fertility, embryo-fetal and pre-postnatal development, mostly conducted with levodopa. The lack of juvenile animal studies was justified: these are not required in the aging population to receive Onerji treatment, and in accordance with the agreed PIP.

Levodopa showed adverse effects on fertility and induced fetal malformations in a study in rabbits (but not in rats). In a pre-postnatal study, administration of LD/CD led to an increase in the length of gestation. Levodopa inhibited prolactin release and produced a dose-related inhibition of milk ejection.

According to the SmPC of other approved medicinal products containing levodopa and carbidopa, namely Stalevo (EMEA/H/C/511), Duodopa (SE/H/0415/001) and Doporio (FI/H/1142/002/E/01), studies in animals have shown reproductive toxicity. Overall, on this matter, the contents in Onerji SmPC are generally aligned with information in the SmPC of already approved medicinal products containing LD and CD.

Local tolerance was assessed upon the repeated dose toxicity studies and those evaluating safety of excipients. No additional dedicated studies on local tolerance were submitted by the applicant This approach is accepted.

No studies or published data on antigenicity, immunotoxicity, dependence, studies on metabolites or other toxicity studies were deemed necessary by CHMP.

No studies or published data on phototoxicity were likewise submitted. Although the applicant did not justify this absence of data, as levodopa/carbidopa is a known active substances combination, no request for clarifications in this respect was considered needed by CHMP.

Studies on impurities

The proposed specifications for the ND0612 DP include two substance-related impurities (both carbidopa-related) at maximum limits above the ICH Q3B(R2) qualification threshold. These are methyldopa and 3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid (also named "main degradant").

To qualify these impurities, the applicant conducted an additional 90-day repeated dose toxicity study in minipigs with administration of ND0612 DP at different levels of the impurities to be qualified, performed a QSAR evaluation (software CASE Ultra, version 1.7.0.5) of the mutagenic potential of 3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid and conducted a safety evaluation of both impurities also based on published literature data.

The 90-day repeated dose toxicity study, in addition to saline and vehicle control groups, included three other animal groups which received ND0612 DP with different concentrations of the impurities to be qualified: ND0612 Low Impurities, ND0612 Mid Impurities, and ND0612 High Impurities. In all groups, the respective solutions were administered by single daily subcutaneous infusions, at a same volume of 6 mL/site/administration and rate of infusion, which was 0.32 mL/h x 18hr + 0.05 mL x 6 h.

This study revealed no risks related to the impurities. The infusion site reactions to the formulation with the highest levels of impurities were similar to those observed after administration of the vehicle. These are relatively higher than the respective maximum exposures in humans.

The QSAR evaluation of 3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid for mutagenicity revealed no structural alerts for genotoxicity that were not also present in carbidopa, a substance shown to lack mutagenic potential. The impurity was classified into ICH M7(R2) class 4.

Also considering data from published literature, the impurities methyldopa and 3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid may be considered qualified:

- The impurity qualification 90-day repeated dose toxicity study with administration by subcutaneous infusion revealed no risks attributed to these impurities.

A QSAR evaluation for mutagenicity in accordance with the ICH M7(R2) guideline was also conducted for three other impurities, all at levels below the ICH Q3B(R2) qualification threshold. The used software was CASE Ultra. For two impurities, no structural alerts were identified; both impurities were classified into class 5. For the third impurity, no structural alerts were identified that were not also present in levodopa, a substance shown to lack mutagenic potential; the impurity was classified into class 4.

No other studies on impurities or assessment reports were provided. However, toxicological evaluation of extractables and leachables from the container closure system, and delivery systems did not reveal compounds of toxicological concern. This evaluation on based, namely, on the TTC concept, values already established in available guidelines, published toxicological data and QSAR evaluations. No new experimental studies were conducted.

Excipient studies

The ND0612 formulation contains the following pharmaceutical excipients: L-arginine, ascorbic acid, N-acetylcysteine, and polysorbate 80 (3 mg/mL).

To specifically address the safety of ND0612 DP excipients, the applicant conducted two *in vivo* studies, one *in vivo/ex vivo* study and an evaluation also based on published literature. The two *in vivo* studies were conducted in minipigs; the *in vivo/ex vivo* study used domestic pigs.

The first *in vivo* study was a 90-day repeated dose toxicity study, with daily administration by subcutaneous infusion using a CRONO ND pump. The study comprised three animal groups, one given saline solution (9 mL/site/administration) and the other two, ND0612 DP's vehicle (6 or 9 mL/site/administration). The study

was intended to complement the pivotal 90-day repeated dose toxicity study which had not included a vehicle control group. This study revealed infusion site reactions in animals treated with vehicle, with relatively higher severity in those administered 9 mL. The reactions were similar to those observed in other studies in animals treated with ND0612 DP.

The second *in vivo* study was a shorter duration study (6 days of treatment). This study tested, for infusion site reactions, different variations of the ND0612 DP vehicle, with changes in pH, osmolality and presence or absence of the excipient L-arginine, as well as solutions of L-arginine with different pH and osmolalities. Results from this study indicated that the L-arginine was the component responsible for the induction of the inflammatory reactions observed at the infusion sites.

The *in vivo/ex vivo* study had two parts. In the *in vivo* part, domestic pigs were given a 24-hour subcutaneous infusion of ND0612 DP and were evaluated for blood coagulation at baseline, end of the infusion and 24 hours after the end of the infusion. In the *ex vivo* part, fresh blood samples from the domestic pigs were incubated with 12 different solutions, at different ratios. The 12 solutions comprised saline, sodium citrate, variations of ND0612 DP and ND0612 DP vehicle, ascorbic acid, N-acetylcysteine, Polysorbate 80, L-arginine and meglumine.

The *in vivo* part of the study showed no effect on blood coagulation.

The *ex vivo* part showed inhibition of clotting time when fresh blood samples were incubated with ND0612 formulations containing L-arginine or with isolated L-arginine solutions at the concentrations present in ND0612 DP. ND0612 formulations with either LD/CD 60/7.5 mg/mL or LD/CD 60/14 mg/mL inhibited coagulation when mixed at a ratio of 1:13, but not when mixed at 1:40 ratio. Meglumine, that was a possible candidate for use in the formulation as an alternative solubilizing agent, also inhibited blood coagulation.

Results from this study indicate, therefore, a lack of systemic effects on blood of coagulation. The possibility of a local effect on blood coagulation is not excluded. The potential effects of ND0612 DP on blood coagulation were attributed to L-arginine.

Regarding the safety evaluations of the excipients based on published literature, these have mostly focused on potential systemic effects upon chronic administration. For all the 4 excipients, it was considered that these did not pose a systemic safety concern.

In addition to safety data obtained from the non-clinical and clinical studies, both L-arginine and ascorbic acid are present in food. Moreover, albeit for short-term administration, L-arginine is used as an excipient or API at higher doses. N-acetylcysteine (NAC) is a precursor of L-cysteine and used as a dietary supplement. There are published clinical safety databases with long term administration and, albeit for short-term administration, NAC is used as a DP given at higher doses. Polysorbate 80 is used as a direct food additive, likewise there are published clinical safety databases with long term administration, and, albeit for short-term administration, it is used as an excipient at higher doses.

Altogether, the available data do not indicate a risk of systemic toxicity but i a risk of infusion site reactions due to the presence of the excipient L-arginine. The observed effects are reversible, not considered adverse and can be easily monitored in the clinical setting.

Ecotoxicity/environmental risk assessment (ERA)

ND0612 DP formulation comprising levodopa/carbidopa does not pose any environmental concerns following the prescribed use. Therefore, the applicant's justification for the absence of ERA studies is accepted.

The precautionary and safety measures taken to inform patients and healthcare professionals, mitigate environmental risks, and promote environmental protection were applied, in accordance with the *Guideline*

on the Environmental Risk Assessment of Medicinal Products for Human Use EMEA/CHMP/SWP/4447/00 Rev.1, 2024.

4.5.2. Conclusions

Pharmacology

The extensive literature on LD/CD supports their well-characterised pharmacological profile across systems, with no new safety signals identified. The absence of additional non-clinical pharmacology studies for ND0612 DP is justified. Continuous SC delivery aligns with known advantages of sustained LD exposure, particularly in reducing the risk of dyskinesia, and is subject to the same established drug interaction profile as existing LD/CD products.

Pharmacokinetics

The pharmacokinetics of LD and CD are well established and consistent across routes of administration, supporting the use of existing data for ND0612 DP. Toxicokinetic studies confirmed a stable systemic exposure with SC infusion. The validated bioanalytical method ensured reliable measurement in the toxicology studies. ND0612 DP shares the known metabolic and interaction profile of oral LD/CD products, with no CYP450 involvement and no route-specific interactions expected.

Toxicology

The provided toxicological data, as well as information on non-clinical safety data in the SmPC, are considered adequate. Toxicological studies conducted with Onerji revealed no risks, other than local reactions at the infusion sites. The justification for the absence of ERA studies is also accepted. Furthermore, the applicant applied suitable precautionary and safety measures to inform patients and healthcare professionals, mitigate environmental risks, and promote environmental protection, in accordance with guideline EMEA/CHMP/SWP/4447/00, 2024.

5. Clinical aspects

5.1. Introduction

5.1.1. GCP aspects

A routine GCP inspection was requested and adopted for clinical trial ND0612-317 at the CHMP plenary meeting held in April 2025. The sites inspected were the below:

- Site A, Portugal

- Site B, Poland

- CRO Syneos Health France S.A.R.L., 25 Boulevard Romain Rolland, 75004 Paris, France.

The Integrated Inspection Report (IIR), timely issued on 3 October 2025, confirmed that the trial was conducted in accordance with GCP. The resulting data were therefore deemed acceptable for this MAA assessment process.

5.1.2. Tabular overview of clinical trials

Table 3. Tabular overview of main clinical studies

Study identifier	Study design	Population (incl. number of subjects, healthy *vs* patient and gender ratio)	Dosing regimen ND0612 LD/CD daily dose (mg) (infusion rate) + oral LD/CD	Main PK parameters
ND0612/001 NCT01486628	A phase I, single dose, single-center, randomised, double-blind, placebo-controlled dose escalation study evaluating safety, tolerability and levodopa plasma concentration following administration of subcutaneous continuously delivered levodopa/ carbidopa solution (ND0612) in healthy volunteers	Healthy male subjects N=36 (36 M/0 F)	115/27 (0.080 mL/h during 24h; formulation LD/CD 60/14 mg/mL) 173/40 (0.120 mL/h during 24h; formulation LD/CD 60/14 mg/mL)) 230/54 (0.230 mL/h during 24h; formulation LD/CD 60/14 mg/mL) 288/67 (0.200 mL/h during 24h; formulation LD/CD 60/14 mg/mL) 346/81 (0.240 mL/h during 24h; formulation LD/CD 60/14 mg/mL)	C_{max}, C_{avg}, AUCs, $t_{1/2}$
ND0612/001b NCT01486628 **Phase 1b**	A phase Ib, single dose, single-center, randomised, double- blind, placebo-controlled dose escalation study evaluating safety, tolerability and levodopa plasma concentration following administration of subcutaneous continuously- delivered levodopa/carbidopa solution (ND0612) in healthy volunteers	Healthy male subjects N=18 (18 M/0 F)	288/67 (0.240 mL/h during 24h; formulation LD/CD 50/11.7 mg/mL) 269/63 (0.080 mL/h during 8h and 0.240 mL/h during 16h; formulation LD/CD 60/14 mg/mL) 346/81 (0.240 mL/h during 24h; formulation LD/CD 60/14 mg/mL) + entacapone	C_{max}, C_{avg}, AUCs, $t_{1/2}$
ND0612/002 NCT01725802 **Phase 1/2a**	A phase I/IIa, single dose, single-centre, randomised, crossover, double-blind, placebo- controlled study evaluating safety, tolerability, and levodopa plasma concentration following administration of SC continuously delivered	PD patients N=8 (4 M/4 F)	269/63 (0.080 mL/h during 8h and 0.240 mL/h during 16h; formulation LD/CD 60/14 mg/mL) + Stalevo[1] 100 mg x2 Saline (0.080 mL/h during 8h and 0.240 mL/h during 16h) + Stalevo[1] 100 mg x2	C_{max}, C_{avg}, AUCs, $t_{1/2}$

	levodopa/carbidopa solution (ND0612) in pd patients			
ND0612/003 NCT01883505 **Phase 2a**	A phase IIa multicenter randomized double-blind, placebo-controlled study followed by an open-label period to evaluate the safety, tolerability and levodopa pharmacokinetics in levodopa-treated Parkinson's disease patients with motor fluctuations, administered with repeated continuous subcutaneous ND0612	PD patients N=30 (21 M/9 F)	269/63 (0.080 mL/h during 8h and 0.240 mL/h during 16h; formulation LD/CD 60/14 mg/mL) + Oral LD/CD SOC, for 14 days Placebo (0.080 mL/h during 8h and 0.240 mL/h during 16h) + Oral LD/CD SOC, for 14 days 269/63 (0.080 mL/h during 8h and 0.240 mL/h during 16h; formulation LD/CD 60/14 mg/mL) + Oral LD/CD SOC + Entacapone, for 7 days 269/63 (0.080 mL/h during 8h and 0.240 mL/h during 16h; formulation LD/CD 60/14 mg/mL) + Oral LD/CD SOC, for 7 days	C_{max}, C_{avg}, AUCs, $t_{1/2}$
ND0612/004 NCT02096601 **Phase 1/2a**	A multicenter, open-label, randomised, dose-finding study testing the safety, tolerability, and pharmacokinetics (PK) of ND0612, a liquid formulation of levodopa/carbidopa (LD/CD) delivered as a continuous subcutaneous infusion (SC) in Parkinson's disease (PD) patients treated with LD	PD patients: N=16 (12 M/4 F)	*Low treatment group:* D3: 115/14 (0.240 mL/h during 8h; formulation LD/CD 60/7.5 mg/mL) D4: 115/27 (0.240 mL/h during 8h; formulation LD/CD 60/14 mg/mL) D5: 115/27 (0.240 mL/h during 8h; formulation LD/CD 60/14 mg/mL) + Entacapone *High treatment group:* D3: 307/38 (0.640 mL/h during 8h; formulation LD/CD 60/7.5 mg/mL) D4: 307/72 (0.640 mL/h during 8h; formulation LD/CD 60/14 mg/mL) D5: 307/72 (0.640 mL/h during 8h; formulation LD/CD 60/14 mg/mL) + Entacapone	C_{max}, C_{avg}, AUCs, $t_{1/2}$
ND0612-005 NCT02604914 **Phase 1**	A sequential two- part, open-label study in	Healthy subjects N=36 (*Part 1:* 17 M/4 F	**Part 1** *Low treatment group:*	C_{max}, C_{avg}, AUCs, $t_{1/2}$

	healthy male and female subjects: part 1 (ND0612-005a) to identify the concentration of carbidopa that provides optimal bioavailability of a concomitant fixed concentration of levodopa infused subcutaneously via a pump system; part 2 (ND0612-005b) to assess the bioavailability of a selected levodopa/carbidopa solution relative to Duodopa®, a levodopa/carbidopa intestinal gel infused via a naso-jejunal tube [part 1: non-randomized, parallel arm; part 2: 3-treatment, 3-period, cross-over]	*Part 2:* 14 M/1 F)	269/34 (0.080 mL/h during 8h and 0.240 mL/h during 16h; formulation LD/CD 60/7.5 mg/mL) 269/27 (0.080 mL/h during 8h and 0.240 mL/h during 16h; formulation LD/CD 60/6 mg/mL) 269/18 (0.080 mL/h during 8h and 0.240 mL/h during 16h; formulation LD/CD 60/4 mg/mL) *High treatment group:* 720/90 (0.080 mL/h during 6h, 0.640 mL/h during 18h and 0.080 mL/h during 6h; formulation LD/CD 60/7.5 mg/mL) 720/72 (0.080 mL/h during 6h, 0.640 mL/h during 18h and 0.080 mL/h during 6h; formulation LD/CD 60/6 mg/mL) 720/48 (0.080 mL/h during 6h, 0.640 mL/h during 18h and 0.080 mL/h during 6h; formulation LD/CD 60/4 mg/mL) **Part 2** *Treatment group 1:* Period 1: Duodopa LD/CD 720/180 Period 2: Duodopa LD/CD 875/219 Period 3 (D5): 720/90 (0.080 mL/h during 6h and 0.640 mL/h during 18h; formulation LD/CD 60/7.5 mg/mL) *Treatment group 2:* Period 1: Duodopa LD/CD 875/219 Period 2: Duodopa LD/CD 999/250 Period 3 (D5): 720/90 (0.080 mL/h during 6h and 0.640 mL/h during 18h; formulation LD/CD 60/7.5 mg/mL) *Treatment group 3:*	

			Period 1: Duodopa LD/CD 720/180 Period 2: Duodopa LD/CD 999/250 Period 3 (D5): 720/90 (0.080 mL/h during 6h and 0.640 mL/h during 18h; formulation LD/CD 60/7.5 mg/mL)	
ND0612H-006 NCT02577523 EudraCT Number: 2015-005078-39 **Phase 2a**	A multicenter, parallel-Group, Rater-Blinded, Randomised clinical study investigating the efficacy, safety, tolerability and pharmacokinetics of 2 dosing regimens of ND0612h, a solution of levodopa/carbidopa delivered via a pump system as a continuous subcutaneous infusion in subjects with advanced Parkinson's disease	PD patients N=38 (26M/12 F)	*Treatment group 1:* 720/90 (0.080 mL/h during 6h and 0.640 mL/h during 18h; formulation LD/CD 60/7.5 mg/mL) + Oral LD/CD SOC *Treatment group 2:* 538/67 (0.640 mL/h during 14h; formulation LD/CD 60/7.5 mg/mL) + 150/15 IR-LD/CD (morning) + Oral LD/CD SOC	C_{max}, C_{avg}, AUCs, $t_{1/2}$
ND0612H-012 (BeyoND) NCT02726386 EU CT Number: 2024-513548-27-00 **Phase 2b**	A multicenter, international, open-label, safety study of ND0612, a solution of levodopa/carbidopa delivered via a pump system as a continuous subcutaneous infusion in subjects with advanced Parkinson's disease	PD patients rollover from ND0612-006 N=214 (142 M/72 F)	*Treatment group R1:* 720/90 (0.080 mL/h during 6h and 0.640 mL/h during 18h; formulation LD/CD 60/7.5 mg/mL) + Oral LD/DDI SOC *Treatment group R2:* 538/67 (0.640 mL/h during 14h; formulation LD/CD 60/7.5 mg/mL) + 150/15 IR-LD/CD (morning) + Oral LD/DDI SOC *Treatment group R3:* 720/90 (0.750 mL/h during 16h; formulation LD/CD 60/7.5 mg/mL) + Oral LD/DDI SOC	C_{max}, C_{avg}, AUCs, $t_{1/2}$
ND0612-114 **Phase 1**	An open-label, randomised, single-dose, 4-period, crossover study to compare the pharmacokinetics of subcutaneous ND0612 administered at different	Healthy subjects N=24 (16 M/8 F)	*Treatment groups 1-4:* 360/45 (0.375 mL/h during 16h; formulation LD/CD 60/7.5 mg/mL)	C_{max}, C_{avg}, AUCs, $t_{1/2}$

	infusion sites and two different cannula lengths in healthy male and female subjects			
ND0612-115 **Phase 1**	An open-label, single-dose, sequence-randomised, 3 period, crossover study to determine the relative bioavailability of levodopa and carbidopa in healthy male and female subjects, when administered as ND0612 subcutaneous infusion compared to oral immediate release levodopa/carbidopa	Healthy subjects N=16 (11 M/5 F)	*Treatment group A:* 360/45 (0.375 mL/h during 16h; formulation LD/CD 60/7.5 mg/mL) *Treatment group B:* 100/25 x4 IR-LD/CD *Treatment group C*	C_{max}, C_{avg}, AUCs, $t_{1/2}$
ND0612-317 (BouNDless) NCT04006210 EU CT Number: 2024-511940-20-00 **Phase 3**	A multicenter, randomised, active-controlled, double-blind, double-dummy, parallel-group clinical trial, investigating the efficacy, safety, and tolerability of continuous subcutaneous ND0612 infusion in comparison to oral IR-LD/CD in subjects with Parkinson's disease experiencing motor fluctuations (BouNDless)	PD patients Enrolled: N=381 Converted: N=322 (199 M/123 F) Randomised: N=259 (165 M/94 F)	*Treatment group 1:* ≤ 720 / 90 (0.080 mL/h during 6h and ≤ 0.640 mL/h during 18h; formulation LD/CD 60/7.5 mg/mL) + IR-LD/CD AND Placebo + IR-LD/CD *Treatment group 2:* IR-LD/CD AND Placebo infusion (0.080 mL/h during 6h and ≤ 0.640 mL/h during 18h) + Placebo IR-LD/CD	Sparse concentrations
ND0612-J01 **Phase 1**	Clinical Pharmacology Study of ND0612 in Healthy Japanese Adult Males (Single Dose Study)	Healthy male subjects N=16 (16 M/0 F)	*Treatment group 1:* 720 / 90 (0.080 mL/h during 6h and 0.640 mL/h during 18h; formulation LD/CD 60/7.5 mg/mL) *Treatment group 2:* 720 / 90 (0.750 mL/h during 16h; formulation LD/CD 60/7.5 mg/mL)	C_{max}, C_{avg}, AUCs, $t_{1/2}$

LD = levodopa; CD = carbidopa; PK = Pharmacokinetics; C_{max} = Maximum observed plasma concentration; C_{avg} = Average observed plasma concentration; AUCs = Area under the curve; $t_{1/2}$ = Apparent elimination half-life; M = male; F = female; SOC = standard of care; D = day; SC = subcutaneous; PD = Parkison's disease

5.2. Clinical pharmacology

5.2.1. Methods

Three validated bioanalytical methods supported the clinical development program. The methods employing reversed-phase high/ultra-performance liquid chromatography-tandem mass spectrometry (RP-HPLC-MS/MS or RP UPLC MS/MS) were used for determination of LD, CD, and 3-ortho-methyldopa, the principal metabolite of LD, in human plasma samples derived from ND0612 clinical trials. All three methods are based on the same principles of sample preparation and essentially the same analytical technique. These methods were validated in accordance with the FDA guidance for industry (May 2001/May 2018) and/or European Medicines Agency (EMA) guideline (July 2011) on bioanalytical method validation, effective at the time of validations.

Incurred sample reanalysis was assessed for LD, CD and 3-OMD. All these sample reanalysis assessments demonstrated method reproducibility and verified the reliability of the reported study sample analyte concentrations.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

As part of the clinical development, **ten studies** were completed to evaluate the PK, safety, tolerability and efficacy (where applicable) of ND0612 drug product (DP), using formulations with different ratios of levodopa /carbidopa (LD/CD), and a variety of dosing regimens.

Six clinical studies were conducted in **healthy subjects** (**ND0612/001, ND0612/001b, ND0612-005, ND0612-114, ND0612-115**, and **ND0612-J01**) and **four clinical studies** were conducted **in subjects with Parkinson Disease** (**ND0612/002, ND0612/003, ND0612-004,** and **ND0612H-006**).

In addition, **two main clinical studies completed their core periods**: **ND0612H-012**, a **long-term safety study** with 214 PD subjects enrolled and **ND0612-317**, a **pivotal efficacy study**, with 381 PD subjects enrolled.

In the early stages of the development program, an LD/CD ratio of 4:1 had been chosen based upon the ratio of commonly available LD/CD oral products. Four early-stage clinical trials, two in healthy subjects (ND0612/001 and ND0612/001b) and two in subjects with PD (ND0612/002 and ND0612/003). were conducted using this 4:1 ratio.

Following these studies, the development program included the assessment of LD/CD ratio in the formulation, with the aim to assure the proper dopa decarboxylase (DDC) inhibition by CD to maximise LD exposure, and the assessment of different infusion rates, as objectives for studies ND0612/004 and ND0612-005a.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population Pharmacokinetics

Population PK (popPK) models were developed to characterise the pharmacokinetics of CD and LD following SC administration of ND0612 DP with or without oral LD/CD therapy in healthy subjects and subjects with PD. The popPK model evaluated the impact of multiple covariates on LD and CD PK parameters.

The final popPK model for LD was a one-compartment disposition model with sequential zero and first-order SC absorption and first-order oral absorption with parallel elimination pathways involving DDC and COMT enzymes. The model accounts for both pre-systemic (via the oral route) and systemic DDC inhibition, which is almost completely saturated at the highest CD concentrations achieved in the studies.

The final popPK model for CD was a two-compartment disposition model with sequential zero and first-order SC absorption and first-order oral absorption with linear elimination from the central compartment.

For both CD and LD, the absorption rate constants ka oral and ka SC were similar, and body weight was included as a mechanistic covariate on the disposition parameters based on allometric scaling.

Overall, the developed levodopa and carbidopa population pharmacokinetic models were robust and replicated the features of the data from which it was built in simulations (VPCs). Thus, the models are considered well validated.

5.2.2.2.2. Physiology based pharmacokinetic model

No physiologically based PK models were developed. This is acceptable.

5.2.2.3. Absorption

Study ND0612/004

This was a multicenter, open-label, randomised, dose-finding study testing the safety, tolerability, and pharmacokinetics of ND0612, a liquid formulation of levodopa/carbidopa (LD/CD) delivered as a continuous SC infusion in Parkinson's disease patients treated with LD.

In this study the PK profiles demonstrated that therapeutically relevant LD plasma concentrations were achieved in the high dose (ND0612H) arm. The marked fluctuations in LD plasma concentrations observed with LD/CD oral therapy were significantly reduced with ND0612 DP SC treatment (as evidenced by a reduced model's root MSE of fluctuation = modified FI).

Comparable LD plasma concentrations were achieved within each LD dose, irrespective of the CD concentration in the formulation [7.5 mg/mL (LD/CD ratio of 8:1) or 14 mg/mL (LD/CD ratio of 4:1)]. As no meaningful differences in LD bioavailability were observed between the two CD concentrations, the effect of further reduction of CD concentration in the formulation on LD levels was further assessed in study ND0612-005a (part 1), detailed below.

The reduction of fluctuations in LD plasma concentration compared to baseline (Standard of care) was maintained following ND0612 DP administration irrespective of the ND0612 dosing regimen (LD/CD 60/7.5 mg/mL and 60/14 mg/mL). Concomitant COMT inhibition with oral entacapone (in addition to ND0612) increased LD levels and AUCs (17-20% increase) in both LD dose groups, as expected.

Moreover, LD plasma concentrations and AUC values were dose proportional between (high dose) ND0612H and (low dose) ND0612L.

Study ND0612/005a

This was a sequential two-part, open-label study in healthy male and female subjects. In Part 1 (ND0612-005a) the aim was to identify the concentration of CD that provides optimal bioavailability of a concomitant fixed concentration of LD infused subcutaneously via a pump system. In Part 2 (ND0612-005b) the aim was to assess the bioavailability of a selected LD/CD solution relative to Duodopa®, a LD/CD intestinal gel infused via a naso-jejunal tube.

The primary objectives of study Part 1 were:

• To identify the minimal concentration of CD that provides maximal bioavailability of a concomitant fixed concentration of LD (60 mg/mL) administered SC for **a total LD dose of 269 mg** (**ND0612L**)

• To identify the minimal concentration of CD that provides maximal bioavailability of a concomitant fixed concentration of LD (60 mg/mL) administered subcutaneously for **a total LD dose of 749 mg** (**ND0612H**).

The secondary objective of study Part 1 was:

• To characterise the safety and tolerability of ND0612L and ND0612H administered SC to healthy subjects.

In the initial phases of ND0612 development, the main objective was to develop a single LD solution with a minimal optimal CD concentration that would deliver a CD dose to sufficiently inhibit DDC when a minimal dose of 269 mg of LD would be administered or when a maximal dose of 720 mg would be needed.

Following SC administration of a combination of LD/CD formulations at a fixed LD concentration (60 mg/mL) and varying CD concentrations (4.0, 6.0 and 7.5 mg/mL) according to the ND0612L dosing regimen, exposure to LD in terms of C_{max}, $AUC_{8\text{-}24h}$ and $AUC_{0\text{-}inf}$ was unaffected by the CD dose level.

However, exploratory analyses indicated a statistically significant trend between CD dose levels used in the ND0612L regimen with respect to LD exposure, with LD AUC observed to increase as CD dose increased. As a result, it could not be ruled out that lower concentrations of CD than 7.5 mg/mL could potentially compromise LD bioavailability for the ND0612L regimen.

The trend for increased LD exposure with increasing CD dose level that was observed for ND0612L was not apparent for the entire range of CD doses when given with the ND0612H regimen, indicating that increased CD concentration did not affect the LD bioavailability for this regimen.

Based on these results, and to ensure optimal exposure of LD in the full range of 270-720 mg LD doses, the applicant decided to further continue the clinical development program with the 60/7.5 mg/mL (8:1 ratio) formulation. This formulation was tested in subsequent Phase I studies in healthy subjects (**ND0612-114**, **ND0612 115** and **ND0612-J01**) and in Phase II-III studies in subjects with PD (**ND0612H-006**, **ND0612H-012** and **ND0612-317**) and constituted the to-be-marketed formulation of ND0612 DP.

A dose proportionality was observed for CD exposure (C_{max} and AUC) with increasing CD dose.

The general mean for the elimination half-life ($t_{1/2}$) of levodopa was 2.08 h following administration of ND0612L and 3.33 h following administration of ND0612H. Apparently, there was a slight increase on the elimination $t_{1/2}$ of LD with LD dose increase.

The general mean for the elimination $t_{1/2}$ of carbidopa was 2.57 h following administration of ND0612L and 4.09 h following administration of ND0612H. Apparently, there was a slight increase in the elimination $t_{1/2}$ of CD with LD dose increase.

Bioavailability

Onerji should be administered as a continuous SC infusion, 24 hours per day, with a medicinal product delivery pump. There is no pre-systemic metabolism.

Two relative bioavailability studies were conducted with marketed products: study **ND0612-005b** and study **ND0612-115**.

In line with the modified regulatory strategy, and to support the 505 (b)(2) regulatory path in the US, relying on Sinemet® (oral IR-LD/CD) as the reference listed drug, study **ND0612-115** was conducted to evaluate the relative bioavailability of ND0612 DP versus an oral IR-LD/CD.

Study **ND0612-005b** assessed the comparative bioavailability of ND0612 DP versus an intestinal gel of LD/CD (Duodopa®). This study was also conducted due to the regulatory strategy pursued at that time, based on a comparative bioavailability (BA) approach using Duodopa® as the reference drug (Reference: EMEA/H/SA/2859/1/2014/SME/III). This approach was later modified to base the clinical development program in both EU and US on the pivotal efficacy and safety study of ND0612 DP versus oral immediate release (IR) LD/CD.

Both ND0612-005b and ND0612-115 studies were conducted with the final to be marketed formulation that was used in the LTS study **ND0612H-012** and in the pivotal efficacy and safety study **ND0612-317**.

Study ND0612-005b

The primary objectives of Part 2 of this study were:

- To assess the PK of 3 doses of Duodopa®, LD/CD intestinal gel (LCIG) infused via a naso-jejunal tube.
- To assess the BA of a dose of ND0612H LD/CD 60/7.5 mg/mL relative to Duodopa® LCIG infused via a naso-jejunal tube.

The secondary objective of Part 2 ND0612-005b of the study was:

- To monitor the safety and tolerability of study treatments.

In study ND0612-005b, the PK and safety of ND0612 60/7.5 mg/mL (LD:CD 8:1) were assessed following its administration as SC infusion via two infusion sites (with Crono Twin ND pump) over 24 hours (i.e. 0.04 mL/h [0.08 mL/h total] for 6 hours, followed by 0.32 mL/h [0.64 mL/h total] for 18 hours. A total dose of 720 mg LD and 90 mg CD were administered.

The relative BA comparisons representing clinically relevant hours (day rate: 10-26 h for ND0612H relative to the 0-16 h for Duodopa®) illustrated plasma concentrations of LD following ND0612H (720 mg LD/90 mg CD) that were considered similar to Duodopa® Dose 2 (875 mg LD/219 mg CD, with comparable peak to trough ratios and percent fluctuations.

LD C_{max} (at steady state) and AUC values were within the bioequivalence acceptance criteria when ND0612 DP (LD/CD 720/90 mg) was compared to Duodopa® Dose 2 (LD/CD 875/219 mg). Comparing LD exposure derived from ND0612 DP to that from Duodopa® suggested that ND0612 DP has 1.4-fold higher LD bioavailability than Duodopa®.

ND0612 DP demonstrated relatively low inter-subject and intra-subject PK variability and comparable fluctuation values to Duodopa®.

These data supported further assessment of ND0612 DP for the treatment of motor fluctuations in patients with PD.

Study ND0612-115

Study ND0612-115 was performed to assess the relative bioavailability of levodopa and carbidopa when administered as ND0612 SC infusion versus oral IR-LD/CD (100/25 mg) in healthy subjects.

SC infusion of ND0612 DP (LD/CD 60/7.5 mg/mL, infused as 0.375 mL/h for 16 hours [total daily dose of 360/45 mg]), resulted in a steady increase in levodopa plasma concentrations over time, reaching steady-state concentrations within 5 to 10 h from the start of the infusion, whereas the PK profile of LD, following four dose administrations of oral IR-LD/CD over the same period, comprised multiple peaks and trough LD concentrations and a higher degree of PK variability.

In this study, the dose-normalised AUC_s of LD and CD following SC ND0612 DP infusion (LD/CD 60/7.5 mg), compared to oral IR-LD/CD, were approximately 1.3- and 7- to 8-fold higher, respectively. However, no safety concerns on higher CD exposure were raised, as treatment with LD/CD given as SC infusion, or as SC infusion in combination with oral LD/CD, was generally safe and well tolerated. Local reactions (ISRs) were similar to those reported in previous ND0612 studies. The reported systemic adverse reactions were expected, as these are known side effects of LD/CD-containing products.

Final popPK model

Based on the final popPK model for LD, the bioavailability of LD from ND0612 DP was estimated to be 1.3 times the bioavailability of oral LD, which is consistent with the findings from study ND0612-115, where the ratio of the dose normalised LD AUC between SC and oral was approximately 1.3.

Based on the final popPK model for CD, the bioavailability of CD derived from ND0612 was 5.68 times the bioavailability of oral CD (F_{rel} =17.6%).

5.2.2.4. Bioequivalence

Study **ND0612-114** had the objective to compare the PK and local safety and tolerability of SC ND0612 DP, administered through a Crono Twin ND pump system and Accu-Chek® infusion set at a single infusion site per treatment, at different infusion sites, and with two different cannula lengths. The selected infusion site areas were the abdomen, outer thigh and back/flank, which are reported to have different thicknesses of subcutaneous fat tissue (Störchle et al., 2018; Gibney et al., 2010).

Study ND0612-114 demonstrated bioequivalence of ND0612 DP when administered using different infusion sites (abdomen, outer thigh, and back) and different cannula lengths (6 or 10 mm). SC infusion at different sites with a 10 mm cannula is therefore not expected to affect the efficacy of ND0612, thereby offering alternative SC infusion locations for long-term use of ND0612 DP. However, based on the safety results from this study, the short cannula (6 mm) was not recommended for use. Of note, the rationale to use a short cannula was to potentially reduce pain (especially in patients with lower BMIs). Nevertheless, this study showed that a short cannula treatment was associated with more TEAEs (eschar events) and rated higher on the VAS pain scale (visual analogue scale) compared to the long cannula.

5.2.2.5. Distribution

Information regarding protein binding of levodopa and carbidopa is based on literature. Specifically, LD is approximately 10-30% bound to plasma proteins (Rizzo et al., 1996), while CD is approximately 36% bound to plasma proteins (Vickers et al., 1974).

From the final popPK models, the V_c/F for levodopa was estimated as 144 L and for carbidopa 10.6 L. This estimate for LD is concordant with the literature (Br J Clin Pharmacol. 2014 Jul;78(1):94-105). Moreover, the popPK model estimated Vc/F in a subject with PD is noted to be 21.2% higher than that in a healthy volunteer of equivalent body weight.

5.2.2.6. Metabolism

Information regarding metabolism of levodopa and carbidopa is also based on literature.

LD undergoes metabolism via four pathways. The two major pathways are the decarboxylation by dopa decarboxylase (DDC) to dopamine, which may be further metabolised to form 3,4 dihydroxyphenyl acetic acid and homovanillic acid, and, to a lesser extent, the 3 O-methylation by COMT to form 3-O-methyldopa (3-OMD). Other metabolic pathways are transamination by tyrosine aminotransferase, and oxidation by tyrosinase or other oxidants (reviewed in Khor et al., 2007).

The 3-OMD plasma levels were determined (together with LD and CD levels) in all ND0612 DP studies where PK samples were drawn. Its exposure in ND0612 DP studies was consistent with the relevant LD exposure and within the known levels of oral IR-LD/CD and other LD treatments.

The three main metabolites of carbidopa are: 2-methyl-3-methoxy-4-hydroxy-phenylpropionic acid, 2 methyl-3,4- dihydroxy-phenylpropionic acid, and 3-hydroxy-methylphenylpropionic acid, each of which accounts for approximately 10% of the total urinary excretion. These metabolites are excreted as glucuronides and unconjugated compounds. Unchanged CD accounts for about 30% of the total urinary excretion (Vickers et al., 1974).

5.2.2.7. Elimination

Regarding elimination of LD and CD, the derived elimination half-life estimates are concordant between phase I studies. The SmPC (section 5.2) describes an estimate of 2.3 hours for the plasma elimination half-life of levodopa and 2.7 hours for carbidopa following administration of Onerji, based on results from ND0612-005 study.

The impact of possible genetic polymorphism in the pharmacokinetics of levodopa and carbidopa was also addressed via literature's review The variability in the PK of LD has been associated with genetic polymorphisms in several key enzymes and transporters involved in LD metabolism and distribution. No major polymorphisms affecting CD metabolism directly have been reported. A summary of available evidence provided by the applicant is presented below.

1. Levodopa pharmacokinetics and genetic polymorphisms

- *Catechol-O-methyltransferase (COMT): COMT catalyses the O-methylation of LD, particularly in the periphery.*

Genetic variants and possible clinical impact: the Val158Met (rs4680) polymorphism reduces COMT enzyme activity in individuals with the Met/Met genotype.

Low-activity COMT genotypes (rs4680, rs6269, rs4633, rs4818) were reported to be associated with higher LD plasma exposure (AUC) and an increased incidence of LD-induced dyskinesia in a cohort of PD patients (Fatima et al., 2023). However, in other studies, no significant differences in LD PK or motor responses across COMT genotypes were found (Contin et al., 2005; Lin et al., 2009).

- Aromatic L-amino acid decarboxylase (AADC/DDC): The DDC gene encodes AADC, which catalyses the conversion of LD to dopamine.

Genetic variants and possible clinical impact: in a population PK study using levodopa-carbidopa intestinal gel (LCIG) and levodopa-entacapone-carbidopa intestinal gel (LECIG), DDC polymorphisms (rs921451, rs3837091) were associated with higher CL/F of LD in individuals predicted to have higher AADC activity (Senek et al., 2020). However, due to CD pharmacologic inhibition of peripheral AADC, the functional impact of DDC polymorphism on systemic LD PK is limited under therapeutic conditions.

- *Monoamine Oxidase B (MAO-B): MAO-B metabolizes dopamine within the central nervous system.*

Genetic variants and possible clinical impact: the rs1799836 polymorphism was reported to be associated with differences in LD dose requirements and risk of dyskinesia in Brazilian PD patients (Sampaio et al.,

2018). However, its influence on LD PK per se appears indirect and can't be quantitatively characterised in PK studies.

- *Dopamine Transporter (SLC6A3/DAT1): SLC6A3 encodes the dopamine transporter.*

Genetic variants and possible clinical impact: Patients with the 10/10 genotype of the 40-bp VNTR in SLC6A3 were reported to have significantly higher LD AUC than 9/9 carriers, possibly due to altered dopamine reuptake kinetics (Fatima et al., 2020). Nevertheless, as LD itself is not a direct substrate of DAT, this likely reflects secondary effects on dopamine handling.

2. Carbidopa Pharmacokinetics and Genetic Polymorphisms

Metabolism and Excretion: CD undergoes minimal metabolism. To date, no significant impact of genetic polymorphisms on CD PK has been reported. While variability in AADC (DDC gene) may modulate CD pharmacodynamic inhibition efficiency, this does not affect its own PK profile.

3. Ethnic and Population Considerations

Ethnic variation in allele frequencies (e.g., COMT rs4680 Met/Met genotype being less frequent in Asian populations) may influence population-level variability, but findings remain inconsistent (Lin et al., 2009). Broad reviews of LD pharmacogenomics support that COMT polymorphisms represent the most studied and reproducible associations with LD PK, but that clinical implementation remains limited (Gilgun-Sherki et al., 2004).

In summary, although genetic polymorphisms may contribute to the interpatient variability in LD PK, the magnitude of PK changes was generally shown to be modest and does not warrant any genotyping or specific dosing recommendations, as the therapeutic regimen is adjusted according to individual response.

5.2.2.8. Dose proportionality and time dependency

Based on results from studies ND0612-001, ND0612-004 and ND0612-005a, a dose proportionality for levodopa and carbidopa was concluded until a maximum daily dose of LD/CD 720/90 mg.

Based on popPK analysis, it was also confirmed that the treatment duration has a negligible effect on the PK parameters of LD and CD.

5.2.2.9. Pharmacokinetics in the target population

The pharmacokinetics of LD and CD following ND0612 DP infusion was assessed in the phase II studies **ND0612-003**, **ND0612H-006** and **ND0612H-012**. Additionally, sparse PK sampling was done in the Phase III pivotal study **ND0612-317** to evaluate the exposure levels of LD, CD, and 3-OMD in the target population following administration of ND0612 DP.

In studies ND0612H-012 and ND0612-317, the to-be-marketed formulation of ND0612 DP (LD/CD 60/7.5 mg/mL) and the 24-hour treatment regimen, composed of a night-time infusion rate of 0.08 mL/h for 6 hours and a daytime infusion rate of 0.64 mL/h for 18 hours, was administered.

Based on results from study ND0612H-012, the arithmetic mean for LD CL/F was estimated as 25.4 L/h (14.5 and 35.8 L/h). Based on popPK model, CL/F of LD in a patient with Parkinson's disease tends to be approximately 31.7% lower than that in a healthy volunteer of equivalent body weight, while Vc/F in a patient with PD tends to be 21.2% higher than that in healthy volunteer of equivalent body weight.

The clinical overview submitted by the applicant described an absence of a fixed plasma concentration–effect relationship for levodopa, which, with the high inter- and intra-individual variability, precluded the definition of absolute "no-effect boundaries" based on exposure metrics. This reasoning aligns with the

current regulatory understanding that the therapeutic response to levodopa is clinically, not concentration, driven. Given that dose titration in PD is individualised and guided by clinical response, rather than LD plasma concentration targets, modest variations in systemic exposure do not generally necessitate LD dose adjustment nor raise safety concerns.

5.2.2.10. Special populations

Renal and Hepatic Impairment

No dedicated studies to assess the impact of renal and hepatic impairment on LD and CD pharmacokinetics following SC administration of ND0612 DP were conducted by the applicant as no difference in the known elimination patterns of either LD or CD following different routes of administration, including SC, were anticipated. In addition, as LD and CD are eliminated via non-renal and non-hepatic routes, such studies were not considered necessary.

In the presence of DDC inhibitors, majority of a LD dose is cleared by non-renal elimination mechanisms, and renal excretion of intact levodopa accounts for 10% or less of LD clearance (Yeh et al., 1989). Therefore, while impaired renal function in patients treated with ND0612 DP may contribute to some increased LD exposure, a clinically significant effect is considered unlikely.

About 30% of a carbidopa dose is excreted unchanged in the urine (Vickers et al., 1974). As such, a renal impairment study to evaluate the PK of CD would have had little value with respect to dosing of LD/CD.

However, during SC administration of ND0612 DP at the proposed daily dose of 720 mg LD and 90 mg CD, a significantly higher systemic exposure to carbidopa was observed in comparison to conventional oral LD/CD formulations. Although no carbidopa-related safety signals were observed in the clinical studies (e.g. ND0612-003, ND0612-004, ND0612-317, ND0612H-012), the overall exposure (AUC) to CD may exceed those reported for oral formulations. Therefore, as requested, the applicant discussed the potential safety consequences of this elevated carbidopa exposure, particularly in the context of long-term administration. In addition, it evaluated how carbidopa pharmacokinetics may be affected by renal impairment, as reduced renal clearance could further increase systemic CD levels.

The overall safety profile was noted as consistent with known effects of standard oral LD/CD. Of note, subgroup analyses did not show differences in safety between patients on lower vs higher oral LD/CD, which could suggest higher total CD exposure. In addition, the applicant considered the known theoretical risk of vitamin B6 (pyridoxine) depletion and a TQT study performed with a supratherapeutic oral carbidopa dose, where no effect on QT prolongation or ECG parameters was observed.

Furthermore, although ND0612 DP had not been directly studied in patients with chronic kidney disease, renal function (creatinine clearance, CrCl) was included as a covariate in a population PK model for carbidopa. This model included subjects down to CrCl of about 33 mL/min, and only a small effect of CrCl on CD clearance was reported. Furthermore, sparse PK data from ND0612H-012 and ND0612-317 showed only a slight increase in CD exposure (Cmax and Cavg) with decreasing renal function in patients with CrCl ≥30 mL/min. Further details are outlined in the Tables below.

Table 4. ND0612H-012 PK sub-study. Individual CD C_{max} values listed by CrCl. ND0612 24h treatment regimen (n=10)

CrCl subgroup	Subject #	CrCl, mL/min	CD C_{max}, ng/mL	CD C_{avg}, ng/mL*
Moderately impaired (≥30 <60 mL/min)		39.1	1040	800
Mildly impaired		68.6	580	519

(≥60 <90 mL/min)		74.4	1120	969
		75.7	768	698
		78.4	673	595
		89.6	671	598
Normal (≥ 90 mL/min)		116.7	878	752
		121.1	456	385
		127.2	440	375
		133.6	772	648

*CD C_{avg} is calculated for 1-14 hours post start of the ND0612 infusion (daytime hours) - Source: ND0612H-012 PK CSR, Table 16.2.3-29

Table 5. ND0612-317 study. Sparse C_{max} values by CrCl

CrCl subgroup	N pts with 1-6 sparse PK samples (all subjects dosed with ND0612)					N pts with 5-6 sparse PK samples (ND0612 arm only)				
	N	gMean	%CV	Min	Max	N	gMean	%CV	Min	Max
Moderately decreased (≥30…<60 mL/min)	29	855	28%	516	1480	12	898	19%	647	1220
Mildly decreased (≥60…<90 mL/min)	98	639	28%	256	1160	33	679	25%	395	1120
Normal (≥ 90 mL/min)	105	510	35%	56	1010	37	552	23%	333	848

In light of all the above, in agreement with the applicant, it was concluded that carbidopa increase is not clinically meaningful for patients with CrCl above 30 mL/min. However, in section 5.2 of the SmPC it is detailed that *dose adjustment should be conducted with caution in patients with severe renal (or hepatic) impairment.*

With regard to hepatic impairment, literature data indicate that levodopa is largely metabolised by enzymes widely distributed in the body. Levodopa is mainly eliminated via metabolism by DDC (69%) and COMT enzymes (10%) (Nutt et al., 1984). Thus, hepatic functional impairment is not likely to alter the exposure levels of LD, especially in the presence of CD which has a more profound effect on LD apparent clearance than the liver. Both LD and CD have minimal hepatic metabolism and lack of hepatotoxicity.

Overall, ND0612 DP administration to renal and hepatic impairment patients has no restrictions. As clarified in the SmPC, the "dosing is individualised by titration to optimal effect (which corresponds to individually optimised levodopa and carbidopa plasma exposures). Therefore, as stated in section 4.2, "*potential effects of hepatic or renal impairment on levodopa and carbidopa exposure are indirectly accounted for in dose titration (see sections 4.4 and 5.2).*"

Gender, Body Weight, Age, Ethnic, Paediatric

Gender was included in the final popPK model for LD as a covariate on the apparent total body clearance of the drug from plasma after extravascular administration (CL/F). CL/F in females was 13% lower than

in males. However, such difference is considered not clinically significant, as dosing with Onerji is individualised by titration to the optimal effect.

For both CD and LD, body weight was included in the final PopPK models as a mechanistic covariate on the disposition parameters based on allometric scaling. Clinical studies data included in the popPK models related to 426 subjects (healthy subjects and PD patients), with a body weight ranging between 43.1 and 136 kg (mean 74.9 kg). The estimated effects of ND0612 duration on the PK parameters in the popPK models for both compounds were negligible and uncertain, and therefore it was removed from the final models.

Population PK modelling also tested age as covariate in the popPK analysis, after accounting for patient effect on PK parameters of both compounds, and no trends with age were observed for CD and LD. The Table below summarises the age distribution within the elderly population included in the analysis.

Table 6. Elderly population included in the PopPK analysis

PK Trials*	Age 65-74 (Older subjects No /total No **)	Age 75-84 (Older subjects No /total No **)	Age 85+ ((Older subjects No /total No **)
ND0612-001	0 /16	0 /16	0 /16
ND0612-004	7 /16	0 /16	0 /16
ND0612-005	1 /36	0 /36	0 /36
ND0612H-012 PK sub-study	7 /17	2 /17	0 /17
ND0612-114	0 /24	0 /24	0 /24
ND0612-115	0 /16	0 /16	0 /16
ND0612-317	121 /301	30 /301	0 /301
Total	136 /426	32 /426	0 /426

* Data from these trials is included in the PopPK models for LD and CD

**Total number of subjects included in the PopPK model for LD and CD

The pharmacokinetics of levodopa and carbidopa following administration of ND0612 DP in healthy Japanese male subjects was evaluated in Study **ND0612-J01**. The results (including the PK parameters and plasma concentration profiles) of LD and CD in healthy Japanese adults were similar to those in healthy non-Japanese adults treated in study ND0612-005b (Part 2), as described in the SmPC. Moreover, no trends were observed between the different race groups in popPK analysis.

A product-specific waiver for studies in paediatric populations was granted by EMA on 18 March 2020 (EMEA-002687-PIP01-19).

5.2.2.11. Pharmacokinetic interaction studies

No drug-drug interaction studies were performed during the development of ND0612 DP. Literature provided information on drug-drug interactions for levodopa. Regardless its route of administration, LD/CD derived from ND0612 DP is subject to the same, known drug interactions that are common to other (already marketed) LD/CD products, as described in Onerji SmPC.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

The mechanism of action of the levodopa / carbidopa combination is extensively well known.

5.2.3.2. Primary and secondary pharmacology

5.2.3.2.1. ND0612H-012 PK sub-study

In the **ND0612H-012** PK sub-study pharmacodynamics were exploratorily assessed over the course of 24 hours: the plasma levels of LD, CD and 3-OMD were determined following SC infusion of ND0612 DP, at doses of 720 mg LD and 90 mg CD, in 17 subjects with advanced PD experiencing motor fluctuations and treated for more than a year.

The overall aims of this analysis were to characterise the PK of LD, CD and 3-OMD by means of non-compartmental analysis (NCA) and explore the pharmacodynamic and PK-pharmacodynamic relationships. The study design is summarised in the Figure below.

A 16-hour or a 24-hour dosing regimen of ND0612 administration was applied. The total infusion volume during the infusion period (of either 16 or 24 hour) was equivalent to 720 mg LD and 90 mg CD. Altogether 24 blood samples (3 ml) were drawn over a 24-h period.

Each subject enrolled in this sub-study had completed at least 12 months of treatment in the core clinical ND0612H-012 study and adhered to the same regimen as he/she had been allocated to for at least six months in that study, without any wash-out period before the entry into the PK sub-study. A duration of 24 h for the PK evaluation was chosen to assess concentration versus time profiles over a dosing interval at steady state. Adjunct anti-PD oral medications including LD/DDI-containing drugs, as well as other medications according to clinical routine use and per investigator judgment, were optionally co-administered with ND0612 DP.

Figure 4. Diagram of the design of ND0612H-012 PK sub-study

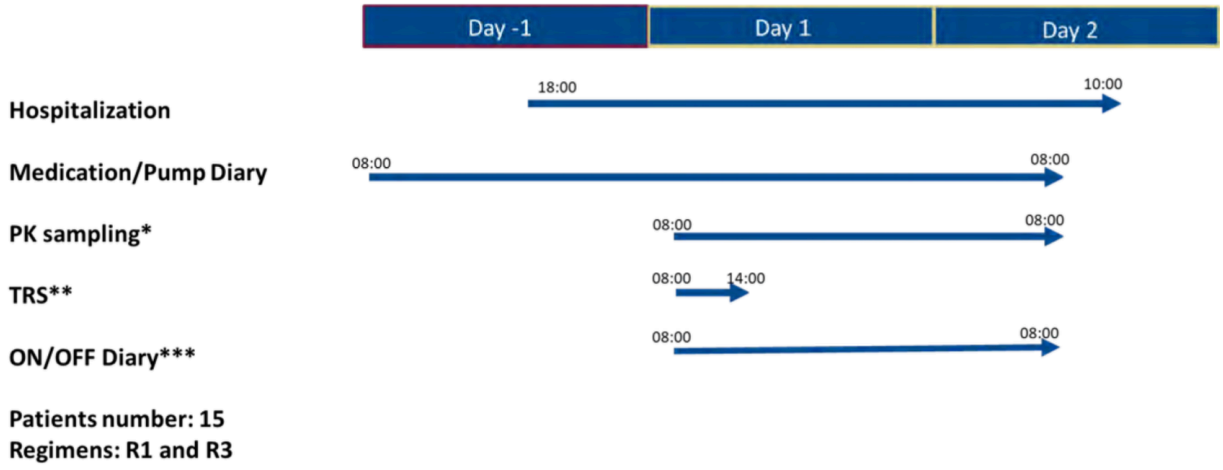


Figure 1: Diagram of the design of ND0612H-012-PK Sub-study.
* Time 0 (Prior to infusion initiation), 30 min, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 8 h, 10 h, 12 h, 14 h, 15 h, 16 h, 18 h ,20 h, 21 h, 23 h, 24 h
** Time 0 (immediately after the first PK sample collection), 30 min, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h
*** Every 30 min in parallel to PK , only during awaking hours

The study used the treatment response scale (TRS), a global clinical assessment of motor function in PD patients by video recording that combines bradykinesia and dyskinesia scores on the same scale. The TRS score ranges from -3 (severe OFF) to +3 (ON with severe dyskinesia), where 0 is ON without any dyskinesia. This pharmacodynamic TRS measurement was performed at 30-min intervals over the first 6 h, in parallel to PK sampling. The video sequences were centrally assessed by 3 independent blinded raters and the scores from all raters were used in the analysis.

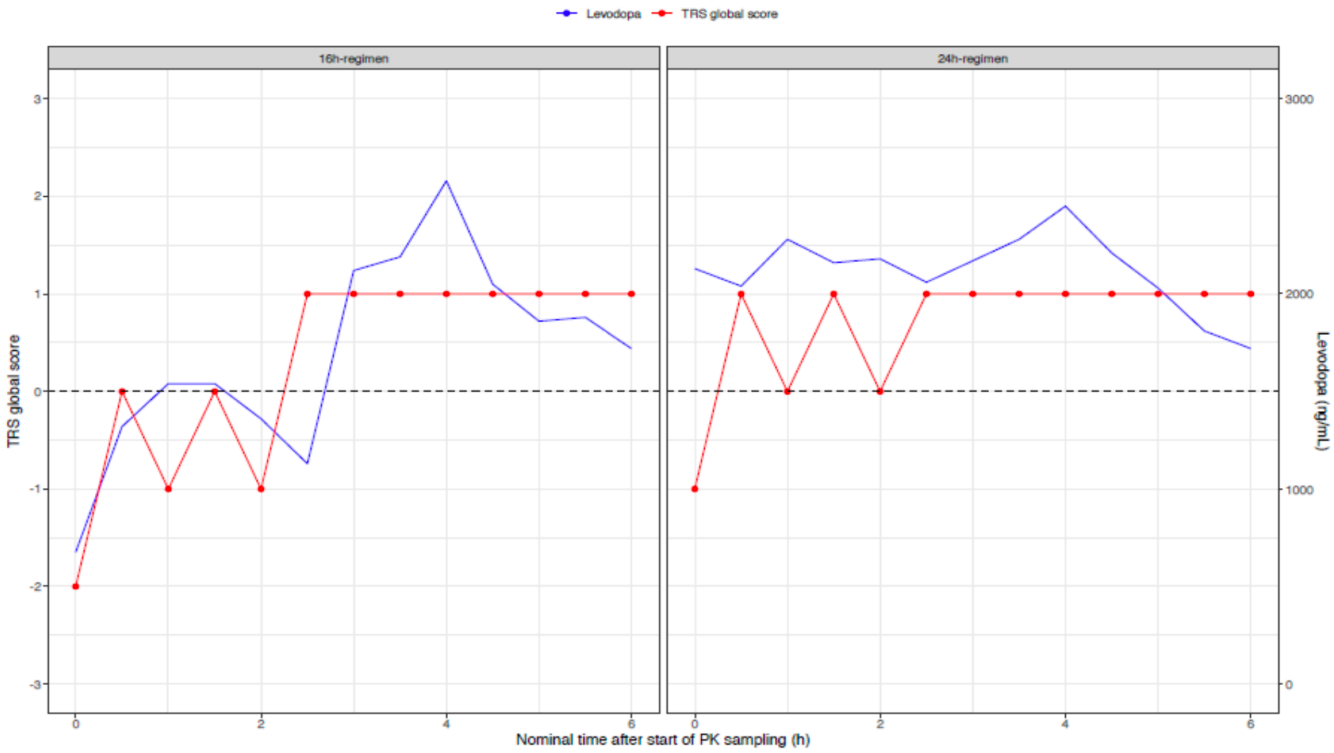
An additional/alternate tool to assess pharmacodynamics was the Hauser's PD home diary (Hauser's ON/OFF diary), a validated and widely accepted tool for the assessment of ON and OFF efficacy endpoints

in PD clinical trials, also considered in ND0612-317 pivotal efficacy study. This diary was completed by the subjects in parallel to the PK sampling at intervals of 30 minutes during waking hours.

Pharmacodynamics were also evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) items 23 (finger tapping), 25 (rapid alternating movements of hands), 27 (arising from chair), 29 (gait), 31 (body bradykinesia and hypokinesia), and dyskinesia (Goetz scale).

In the Figure below, the Median TRS global score versus time, by dosing regimen, is presented together with LD plasma concentrations.

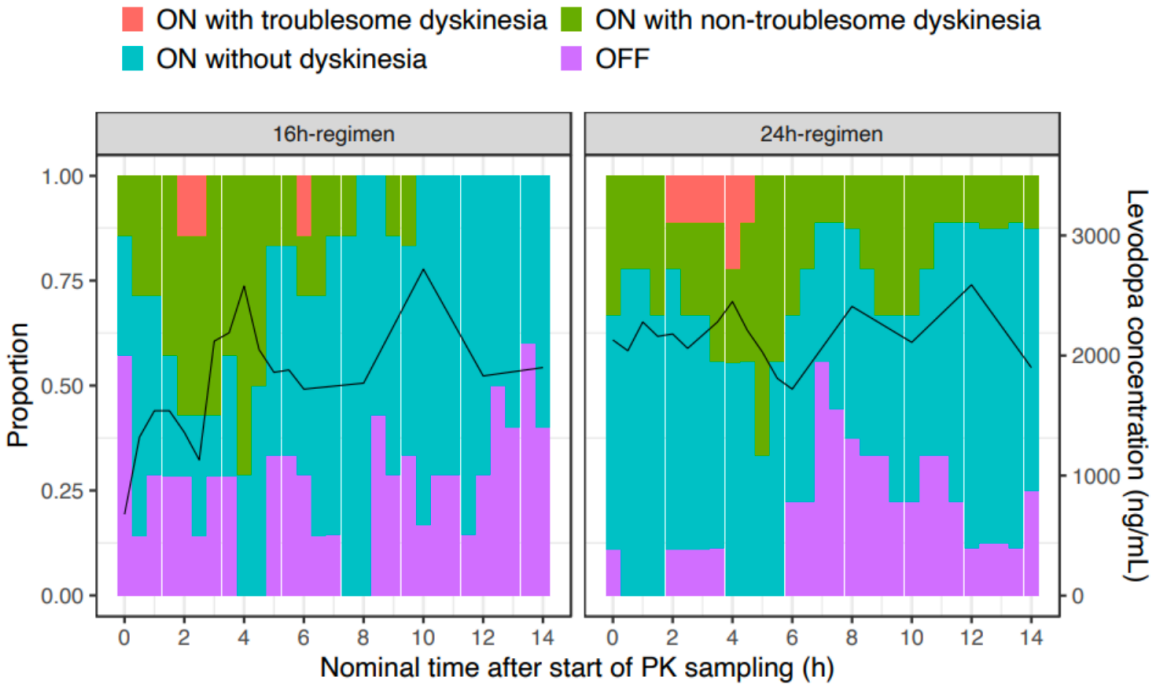
Figure 5. ND0612H-012 PK Sub-study: Median TRS Global Score and Median Observed LD Plasma Concentrations versus. Nominal Time after the Start of Pharmacokinetic Sampling, Stratified by Regimen



h: Hours; mL: Milliliter; ng: Nanogram; PK: Pharmacokinetic; TRS: Treatment response scale (-3 = severe "OFF", + 3 = "ON" with severe dyskinesia)
Source: ND0612H-012 PK Sub-study CSR, Figure 7
Profiles of median observed LD plasma concentrations are illustrated by the black lines. Time 0 represents the start of PK sampling, i.e. 8:00AM. Data for 6 h, i.e. until 14:00 are presented.

In Figure 6 the proportion of non-sleeping subjects with each ON/OFF score versus nominal time after start of pharmacokinetic (PK) sampling is showed. To illustrate the relationship with the levodopa exposure profile, median LD plasma concentrations were overlaid. A second y-axis is added to highlight the LD plasma concentrations.

Figure 6. ND0612H-012 PK Sub-study: Proportion of Non-Sleeping Subjects with each ON/OFF Score versus. Nominal Time after the Start of Pharmacokinetic Sampling, Stratified by Regimen in the Analysis Data Set



h: Hours; PK: Pharmacokinetic
Source: ND0612H-012 PK Sub-study CSR addendum, Figure 1
Note: Profiles of median observed LD plasma concentrations are illustrated by the black lines. Time 0 represents the start of PK sampling, i.e. 8:00 in the morning. Data for 14 h, i.e. to 22:00 are presented.

These figures are based on data from 16 (not 17) subjects in the ND0612H-012-PK Sub-study: one subject was excluded as timing of PK sampling in this subject was not according to the scheduled time.

The relationships between LD plasma exposure and the pharmacodynamic tools were explored.

Median TRS global scores versus time, by dosing regimen (16 h and 24 h regimen) starting in the morning hours, presented in Figure 5 above, together with LD plasma concentrations, pointed out that in the 16 h regimen the LD plasma concentrations were lower than in the 24-h regimen during the morning hours, and the TRS scores were also lower in the 16 h regimen during this time, which is similar to the OFF state observed for the Hauser's ON/OFF diary.

A plot of the proportion of non-sleeping subjects with each of the ON/OFF diary scores (OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, ON with troublesome dyskinesia) at each time point reported over 14 h (waking hours), stratified by dosing regimen, is presented in Figure 6 above together with LD plasma concentrations. Profiles of median observed LD plasma concentrations are illustrated by the black lines. Time 0 represents start of PK sampling, i.e. 8:00 in the morning. Data for 14 h, i.e. to 22:00 are presented.

Overall, the most frequent score was ON without dyskinesia (blue area). The 24-h regimen greatly reduced the proportion of OFF time in the morning hours and also demonstrated a reduction, but to a lesser extent, in the afternoon as compared to the 16 h regimen. The high day-time infusion rate in the 24 h regimen, started before the subject woke up (the default is 4:00 AM). Thus, upon waking, a higher plasma levels of LD (black line) were observed than the levels observed in the 16 h regimen in which

the infusion started only after waking up. Indeed, less morning akinesia was observed in the 24 h regimen than in the 16 h regimen. This finding supported the decision of using the 24 h regimen in the ND0612-317 pivotal efficacy study.

In general, higher concentrations of LD were associated with more ON (reported in the diaries) and higher TRS scores, although the relationships may have been distorted by adaptive concomitant oral administration of LD and other anti-Parkinson's medications. Since the subjects were allowed to take oral LD supplements, subjects requiring higher LD concentrations to achieve a satisfying effect could increase the add-on oral LD treatment, leading to higher plasma LD concentrations. This could be a reason why the subjects with a poor effect had higher concentrations than those who responded well to lower concentrations. Due to these confounding factors, it may have been difficult to capture the true concentration-response relationship.

No clear relationship between LD concentrations and other pharmacodynamic tools (UPDRS items 23, 25, 27, 29, 31 and dyskinesia (Goetz scale) was seen.

Moreover, the applicant acknowledged the need to provide additional data addressing the 3-O-methyldopa (3-OMD) exposure following ND0612 administration and its correlation with the clinical outcome as reflected in Hauser's ON/OFF diaries. Consequently, a PK/PD exploratory analysis was performed based on the data collected in the ND0612-012 PK sub-study, which was the only study where 3-OMD levels and efficacy measurements (ON/OFF diaries) were collected at the same timepoints over 24h (N=14). The results, presented in the Table below, showed no association between higher 3-OMD exposure and increased OFF time. In contrast, OFF periods were associated with lower LD concentrations. Overall, there was no indication that elevated 3-OMD concentrations adversely impact clinical efficacy. Within the limitations of the small sample size and the ad-hoc nature of the analysis, these findings do not support a clinically relevant detrimental effect of 3-OMD at the exposure levels achieved with ND0612.

Table 7. ND0612H-012 PK sub-study. LD and 3-OMD plasma levels in OFF state vs. ON state

ND0612-012 PK sub-study		**OFF state vs. ON state based on Hauser's ON/OFF diaries**				
PK parameter	n	OFF state	ON state	Mean difference	95% CI	p-value
LD concentration, ng/mL	14	2139	2518	-378.7	(-713.3, -44.1)	0.0295*
3-OMD concentration, ng/mL	14	10132	10462	-330.0	(-822.3, 162.3)	0.1713*

5.2.3.2.2. Study ND0612-317

For a detailed description of this study the reader should refer to section 5.3.2.1 of this document.

In the Table below the primary and secondary efficacy endpoints analyses are summarised.

As detailed by the applicant, the study met its primary endpoint (change from baseline in ON time without troublesome dyskinesia). There was a statistically significant and clinically meaningful treatment difference in "ON" time without troublesome dyskinesia of 1.72 hours ($p<0.0001$) at Week 12 of the DBDD period in favour of ND0612 DP over IR-LD/CD. In comparison to baseline, continued treatment with ND0612 DP during the DBDD period resulted in maintenance of the beneficial effect on ON time without troublesome dyskinesia seen during the ND0612 OL Conversion Period (least-squares [LS] mean

change of -0.48 hours), while randomisation to IR-LD/CD resulted in a clinically meaningful deterioration in ON time without troublesome dyskinesia (LS mean change of - 2.2 hours).

The study also met its key secondary endpoint (change from baseline in OFF time). Treatment with continuous infusion of ND0612 DP provided a significant and clinically meaningful benefit in OFF time compared to optimised treatment with IR-LD/CD during the DBDD Period of the study (LS mean difference of -1.4 hours, $p<0.0001$).

The next sequential endpoint in the hierarchical analysis was the change from baseline to Week 12 in MDS-UPDRS Part II (M-EDL) score. At the end of the DBDD period, a treatment difference of -3.05 ($p<0.0001$) favouring ND0612 DP was observed. This statistically significant and clinically meaningful difference on the MDS-UPDRS Part II showed that the improvement in motor function, as shown by diary's data, translated to improvement in a functional scale measuring activity of daily living.

ND0612 DP also demonstrated superior benefit over IR-LD/CD on the PGIC and CGI-I (next endpoints in the hierarchy). At the end of the DBDD period, a significantly higher proportion of subjects evaluated their status as "improved" (compared to the start of the ND0612 OL conversion period) in the ND0612 DP arm compared to the IR-LD/CD arm, with an odds ratio of 5.31 ($p<0.0001$). In addition, at the end of the DBDD period, a significantly higher proportion of subjects in the ND0612 DP arm were evaluated as improved by the investigator compared to the IR-LD/CD arm, with an odds ratio of 7.2 ($p<0.0001$).

The next endpoint according to the hierarchy, MDS-UPDRS Part III change from baseline to the end of the DBDD period, did not show statistically significant difference between ND0612 and IR-LD/CD, although there was a numerical benefit in favour of the ND0612 arm. Thus, based on the hierarchical pre-specification, subsequent endpoints were no longer considered to be statistically significant, and nominal p-values were provided for descriptive purposes only.

Table 8. Primary and Secondary Efficacy Endpoints Analyses in study ND0612-317

Endpoints	Oral IR-LD/CD (N=131) LS means (SE)	ND0612 (N=128) LS means (SE)	Treatment effect LS means (SE); 95% CI	P-value
Primary Efficacy Endpoint				
"ON" time without troublesome dyskinesia - CFB to DBW12 (h)	-2.20 (0.23)	-0.48 (0.23)	1.72 (0.33); 1.08, 2.36	<0.0001
Main supportive (MNAR)	-2.20	-0.53	1.66 (0.33); 1.02, 2.31	<0.0001
Likelihood-based - MMRM	-2.21	-0.51	1.70 (0.33); 1.06, 2.35	<0.0001
"Retrieved Data"- under MAR	-2.20	-0.47	1.73 (0.33); 1.09, 2.37	<0.0001
"Retrieved Data"- under MNAR	-2.19	-0.52	1.67 (0.33); 1.03, 2.32	<0.0001
Per-Protocol Analysis	-2.55	-0.40	2.15 (0.37); 1.43, 2.87	<0.0001
Key Secondary Endpoint				
"OFF" Time - CFB to DBW12 (h)	1.90 (0.22)	0.50 (0.22)	-1.40 (0.30); -1.99, -0.80	<0.0001
Other Secondary Endpoints (in hierarchical order)				
1st: MDS-UPDRS Part II (M-EDL) Sum Score- CFB to DBW12	2.75 (0.45)	-0.30 (0.45)	-3.05 (0.63); -4.28, -1.81	<0.0001
2nd: Improvement on PGIC from Start of the ND0612 OL Conversion Period to DBW12 (proportion)	0.31 (0.05)	0.70 (0.05)	Odds ratio: 5.31 (0.35); 2.67, 10.58	<0.0001
3rd: Improvement on CGI from Start of the ND0612 OL Conversion Period to DBW12 (proportion)	0.31 (0.05)	0.77 (0.05)	Odds ratio: 7.23 (0.36); 3.57, 14.64	<0.0001
4th: MDS-UPDRS Part III (Motor Examination) Sum Score- CFB to DBW12	3.39 (1.00)	0.98 (1.02)	-2.42 (1.42); -5.20, 0.37	0.0889[1]
5th: ON Time Without Dyskinesia CFB to DBW12 (h)	-2.53 (0.25)	-0.41 (0.26)	2.12 (0.36); 1.42, 2.82	<0.0001[2]
6th: ≥50% Reduction in "OFF" time from Start of the ND0612 OL Conversion Period to DBW12 (proportion)	0.10 (0.03)	0.29 (0.06)	Odds ratio: 3.63 (0.43); 1.56, 8.44	0.0027[2]
7th: PDQ-39 Summary Index - CFB to DBW12	4.29 (0.77)	1.60 (0.78)	-2.69 (1.09); -4.83, -0.55	0.0137[2]
8th: PDSS-2 Total Score - CFB to DBW12	1.47 (0.70)	0.05 (0.71)	-1.42 (0.99); -3.35, 0.52	0.1508[2]

DBW12: Week 12 of double-blind, double-dummy period; CGI: Clinical Global Impression; CFB: Change from Baseline; CI: Confidence interval; h: Hour(s); IR-LD/CD: Immediate release levodopa/carbidopa; LS mean: Least-squares mean; M-EDL: Motor aspects of experiences of daily living; MDS-UPDRS: Movement Disorder Society-sponsored Revision of the Unified Parkinson's Disease Rating Scale; MMRM: Mixed model repeated measures; MNAR: Missing not at random; N: Number of subjects; PDQ-39: 39-Item Parkinson's Disease Quality of Life Questionnaire; PDSS-2: Parkinson's Disease Sleep Scale-2; PGIC: Patient Global Impression of Change; SE: Standard error.

Specific comments on pharmacodynamic/efficacy endpoints assessed in the pivotal study ND0612-317 are presented below.

In this study, Onerji demonstrated statistically significant and clinically relevant improvements in the ON/OFF score (1.72h in ON time without dyskinesia and -1.40 in OFF time).

An assessment of the results showed that: UPDRS Part II was -3.05 which is borderline considered as the MCID and UPDRS Part III was -2.42, which is below what is considered as the MCID (≥3.25).

Applying the composite scoring to these results, for UPDRS Part II (-3.05) + Part III (-2.42) the composite overall result is 5.47 >4.9.

Although the results from the UPDRS Part II can be considered as complying to what is regarded as MCID (marginally), the results from Part III were surprisingly low, not considered as clinically relevant and in the area of the test that should be more applicable and relevant to this medicinal product.

The objective of MDS-UPDRS Part III is to perform motor examination, being an objective assessment performed by a clinician. It measures motor signs like tremor, rigidity, bradykinesia, postural stability, gait, etc, and is commonly used in clinical trials to evaluate the direct effect of a treatment on motor symptoms, being sensitive to short-term and dose-dependent changes, especially for dopaminergic treatments.

The fact that these results were not considered clinically relevant as well as the fact that the objective test was not significant (UPDRS Part III) compared to the positive results for the subjective assessment by patient reported diaries (ON/OFF time and UPDRS Part II) was addressed by the applicant the course of the procedure.

The absence of clinically relevant results was justified with the weak inter- and intra-rater reliability of MDS-UPDRS Part III and the difficulties of its consistent application due to day-to-day variability of motor symptoms, particularly in multicentre trials, and for long-term studies, where different raters may assess the same patient at different timepoints. Albeit not reaching statistical significance, results showed a benefit in MDS-UPDRS Part III favouring ND0612, consistent with the primary and other secondary endpoints. The applicant additionally highlighted that various studies in PD patients with motor fluctuations failed to show significant improvements in UPDRS/ MDS-UPDRS Part III, despite clinically meaningful improvements in motor fluctuations observed in the Hauser's diaries, as well as positive results in ON/OFF time and UPDRS Part II.

Given the relevance of the treatment response scale (TRS) in measuring acute effects of treatment (used in the ND0612H-012 PK sub-study to compare the 16h vs 24h regimens), the applicant was also questioned on why this was not assessed in selected days/weeks of the pivotal trial ND0612-317, thereby allowing a proper PK/PD comparison in the daily effects of the proposed product with a strictly oral LD/CD administration.

The absence of TRS as a PD endpoint in the pivotal study ND0612-317 was justified with logistic issues and the fact that TRS could only be considered as a surrogate marker to assess the efficacy of PD drugs and, as such, it would not be recommended as an efficacy endpoint in the EMA Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease (EMA/CHMP/330418/2012 rev. 2).

Indeed, it is acknowledged that TRS posed significant logistical challenges in large, long-term multicenter trials, requiring repeated, time-synchronised assessments that increase complexity, patient and site burden, and may compromise data quality and patients' retention.

The ND0612-317 pivotal trial was designed to evaluate the efficacy, safety, and tolerability of ND0612 DP in PD patients with motor fluctuations. It focused on patient-centred, clinically validated outcomes such as changes in ON time without troublesome dyskinesia and OFF time, assessed via Hauser home diaries, and other standard motor evaluations, in accordance with regulatory guidance and established clinical practice for advanced PD therapies, consistent with other studies in this population.

Given these considerations and limitations, TRS was not incorporated into ND0612-317 pivotal trial. Instead, a dedicated PK sub-study (**ND0612H-012 PK sub-study**) was conducted under standardised, controlled setting, where TRS assessments were feasible in a subset of study subjects (N=17), and provided PK/Pharmacodynamics insights. These data, although limited, complemented ND0612-317 pivotal trial findings and contributed to characterising the daily clinical effects of ND0612 relative to oral LD/CD therapy.

In ND0612-317 pivotal trial, sparse PK sampling performed in a larger number of study subjects (more than 200) demonstrated a higher gMean of LD plasma concentrations in subjects treated with ND0612 (ranging from 1888 to 1995 ng/mL at various timepoints) as compared to those administered with oral immediate release (IR)-LD/CD (ranging from 1050 to 1346 ng/mL) (reference: ND0612-317 CSR, Table 14.2.4.1). This exposure difference was associated with additional least squares (LS) mean of 1.72 hours of Good ON time (reference: ND0612-317 CSR, Table 14.2.1.2.3).

These findings were noted as generally consistent with the PK/PD conclusions from ND0612H-012 PK sub-study, therefore reinforcing the underlying rationale for continuous subcutaneous ND0612 SC infusion vs oral IR-LD/CD treatment.

In summary, although the absence of the treatment response scale as PD endpoint in the pivotal study was justified, its values could have increased the presented PK/PD correlation. Nevertheless, the CHMP accepted the Applicant's justifications and agree not to further pursue this issue.

5.2.3.3. Long-term exploratory efficacy data from study ND0612H-012

Of note, long-term exploratory efficacy data are also available from the core period (up to the end of the first year of treatment) of ND0612H-012 study.

ON Time without Troublesome Dyskinesia

At baseline, the mean daily ON time without troublesome dyskinesia was approximately 10 hours across dosing regimens. LS Means of daily ON time without troublesome dyskinesia increased from baseline at all timepoints, with a change at Month 1 of 1.81 hours in the 24-hour dosing regimen. This improvement was maintained at 12 months: 2.01 hours in the 24-hour dosing regimen. No statistically significant differences between the dosing regimens were observed at any timepoint.

OFF Time

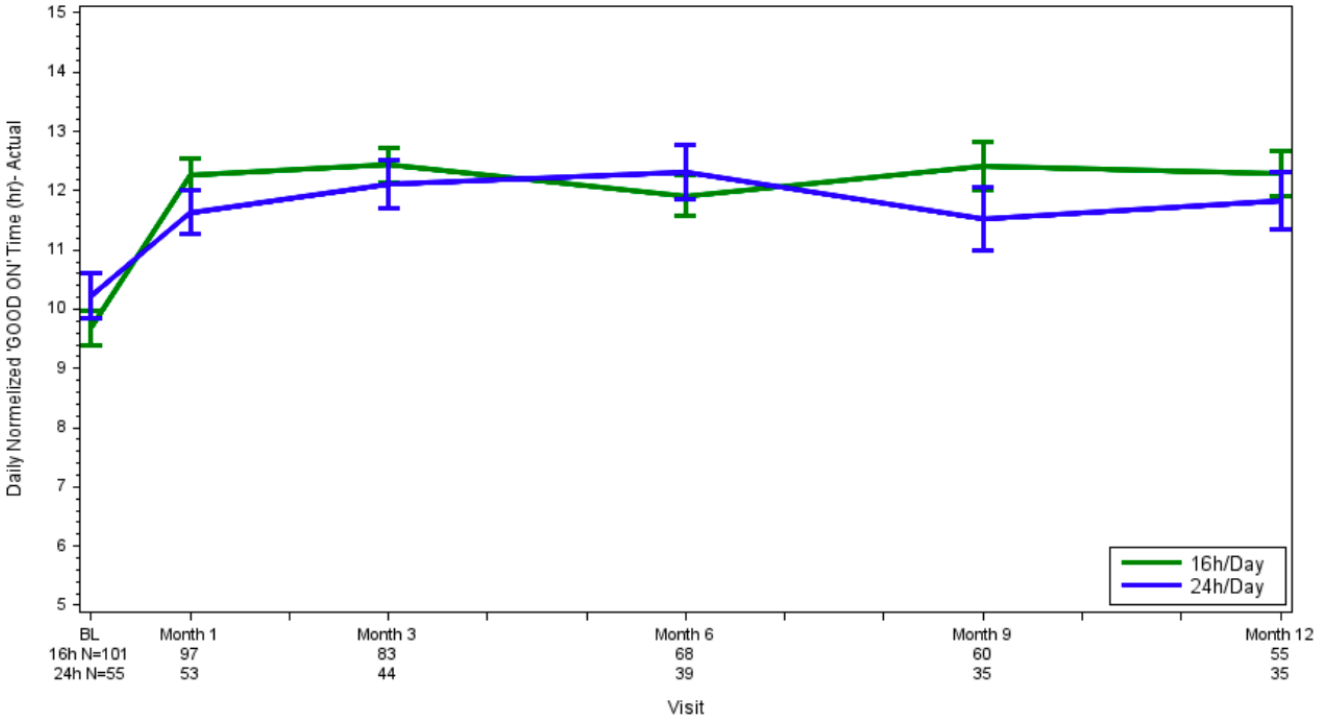
At baseline, the mean daily OFF time was approximately 5 hours across dosing regimens. For the 24-hour dosing regimen, the decrease was of 1.9 hours in the first month, a reduction that was maintained up to 12 months. No relevant differences were observed between the dosing regimens.

The proportion of responders (subjects with ≥50% reduction in mean daily OFF time) exceeded 40% beginning at Month 1 and throughout the 12-month treatment period across dosing regimens.

Other efficacy endpoints

Comparable long-term maintenance of efficacy was shown for the other efficacy endpoints (ON time without dyskinesia, UPDRS Part II and Part III, Subject Global Impression of Improvement (SGI-I) and CGI, QoL scales [EQ-5D-5L and PDQ-39] and PDSS-2).

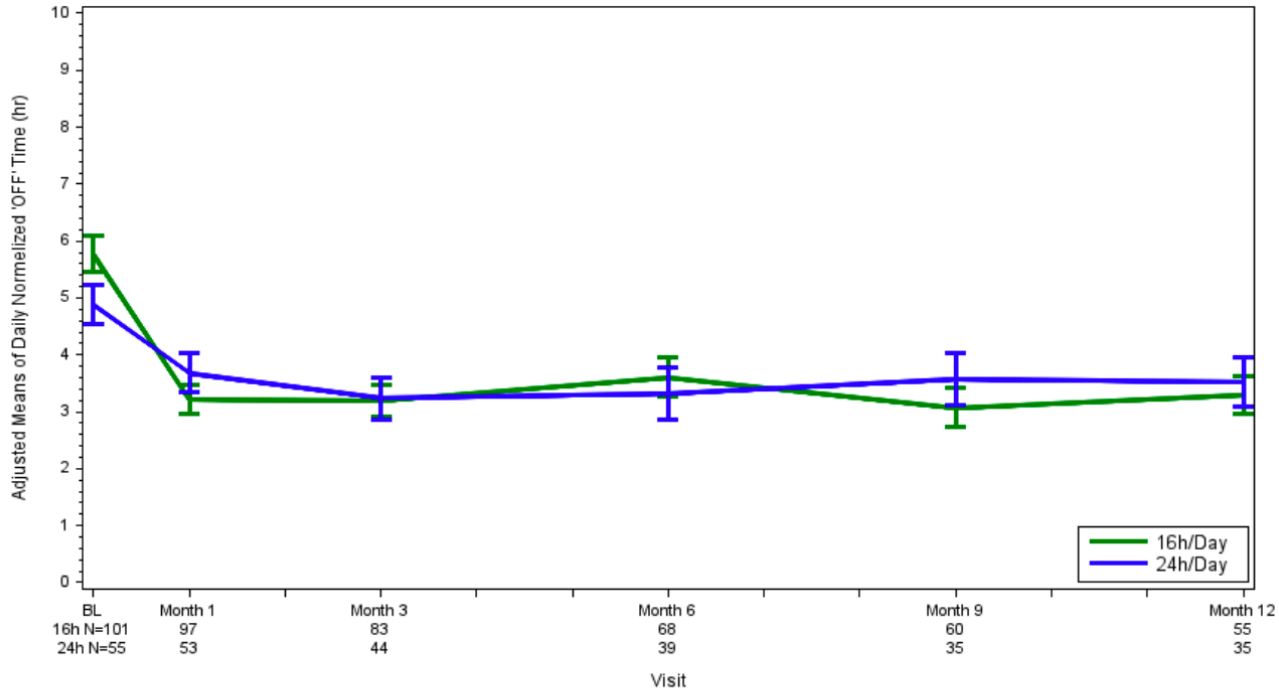
Figure 7. ND0612H-012: Least-squares Means of "ON" Time without Troublesome Dyskinesia ("GOOD ON") Actual Values by Visit (ITT)



BL: Baseline; h or hr: Hour(s); N: Number of subjects.

Source: ND0612H-012 CSR, Table 14.2.1.2

Figure 8. ND0612H-012: Least-squares Means of "OFF" Time - Actual Values by Visit (mITT Set)



BL: Baseline; h or hr: Hour(s); N: Number of subjects.

Source: ND0612H-012 CSR, Table 14.2.3.2

5.2.3.4. Secondary pharmacodynamics

The secondary pharmacodynamics profile of levodopa/carbidopa is well-known and reflected throughout the relevant sections of Onerji SmPC.

5.2.3.5. QTc prolongation effects

5.2.3.5.1. Study ND0612-317

No abnormal clinically significant ECG findings were reported during study ND0612-317.

There were no consistent trends of change in mean values of any ECG parameters over time in the study and no clinically relevant differences between the two treatment arms.

Analysis of QTcF intervals revealed mostly non-clinically significant findings.

In the enrolled set, QTcF values increasing >30 msec from V2 (Enrolment) to V7 (NDD1) were reported for four (1.3%) subjects and from V2 to V13 (DBD1/Randomization) for five (2.0%) subjects. No subject had an QTcF value >500 msec.

In the safety set, the Analysis of QTcF intervals revealed mostly non-clinically significant findings. From the first exposure to ND0612 (V7/ND0612 Conversion Period Day 1) to V13/Randomisation (start of DBDD period), a small and similar percentage of subjects in the two treatment arms (five (3.9%) subjects in each treatment arm) reported an increase of QTcF values >30msec. From the first exposure to ND0612 to the end of the DBDD period, the corresponding percentages were 0.9% and 2.6% in IR-LD/CD arm and ND0612 arm, respectively. No subject had a QTcF value >500 msec at any time during the study.

5.2.3.5.2. Study ND0612H-012

There were no consistent trends of change in mean values of any ECG parameters over time in the study.

Analysis of QTcF intervals revealed mostly non-clinically significant findings. The highest incidence was of Values increasing >30 msec from baseline at Month 1, reported for 6 subjects (2.8%) and at Month 12, reported for five subjects (2.3%; Table 14.3.6.3.2). Three subjects in the 24h regimen and five in the 16h regimen had QTcF intervals ≥440ms, however, all but one (383-002) had borderline (close to 450msec) QTcF at Screening, thus, these observations were deemed not related to the study product. There was also no discernible connection to any other type of medication taken by these subjects during the study.

Analysis of QTcB intervals revealed mostly non-clinically significant findings. The highest incidence was of Values increasing >30 msec from baseline at Month 2, reported for 6 subjects (2.8%) and at clinic visit 1b and Month 4, reported for five subjects (2.3%).

No abnormal clinically significant ECG findings were reported during studies ND0612-317 and ND0612H-012.

Upon FDA request, a TQT study to assess potential effects of a supratherapeutic CD dose on cardiac repolarisation, was conducted. The results of this study, made available in the course of this MAA, showed that a supratherapeutic single oral dose of CD 400 mg, which resulted in a gMean C_{max} of 1352 ng/mL, covering the high clinical exposure of ND0612 and adjunct oral LD/CD (1250 ng/mL as estimated by PK simulation), was safe and well tolerated and had no effect on cardiac repolarisation or other ECG parameters.

5.2.3.6. Pharmacodynamic interactions with other medicinal products or substances

No studies were performed with Onerji. The pharmacodynamic interactions described in SmPC section 4.5 are aligned with known information for levodopa/carbidopa combination. This approach is acceptable.

5.2.3.7. Genetic differences in PD response

No information was provided regarding genetic difference in PD response. This is acceptable.

5.2.3.8. Immunological events

Not applicable.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

The pharmacokinetic/pharmacodynamic relations were assessed in study **ND0612/003** and in the **ND0612H-012 PK sub- study** e.g. above described in sub-section 5.2.3.2 (Primary and secondary pharmacology). Data from the later study was analysed also using popPK/pharmacodynamic modelling.

5.2.4.1. Study ND0612/003

In this placebo-controlled Phase IIa study, repeated administration of ND0612 DP (60/14 mg/mL LD/CD) with alternating infusion rates at night (0.08 mL/h, for 8 hours) and during the day (0.24 mL/h, for 16 hours) in subjects with PD, were assessed for 14-21 days. The results demonstrated that ND0612 DP, given with standard of care oral LD/CD treatment, provides stable LD plasma levels in PD subjects experiencing motor fluctuations. Although the study used a low dose of ND0612 DP (daily LD/CD dose: 270/63 mg), continuous SC administration of ND0612 DP ameliorated both the troughs and the variability in LD plasma levels (as reflected in the FI values) versus. placebo. The exploratory efficacy measures included in this study suggested that this improved PK profile translates into a clinically meaningful mean reduction of OFF time. The mean time above LD plasma concentrations of 1000 ng/mL increased by 4.4 hours compared to baseline with no similar increase in time in the placebo treatment group.

5.2.4.2. ND0612H-012 PK sub-study

While ND0612H-012 PK sub-study supported the correlation between levodopa exposure and decreased variability of TRS score in measuring acute effects of treatment to compare the 16h vs 24h regimens, data pertained only to 17 PD subjects who completed at least 1-year treatment with ND0612 DP. Therefore, no difference in MDS-UPDRS was expected, especially with such a short duration of study. Additionally, subjects were allowed to supplement ND0612 therapy with adjunct anti-PD oral medications including LD/DDI-containing drugs to better manage PD symptoms. That impairs proper correlation of PK/PD results. No comparison was performed with patients taking oral LD/CD. The data submitted has important limitations in the analysis of the PK/PD profile advantages of the proposed product since it provides only a comparison of the PK/PD correlation of the 16h and 24h regimens. An analysis of TRS with levodopa levels would have been of high relevance if assessed during the pivotal study by comparing the acute PK/PD correlation between patients only taking oral LD/CD and the proposed product, as already detailed above in subsection 5.2.3.2.2 (Study ND0612-317).

5.2.5. Dose selection and therapeutic window

The Phase II study **ND0612H-006** compared two regimens: 24-hour regimen (LD/CD dose up to 720/90 mg/day) and 14-hour regimen (LD/CD dose up to 537.6/67.2 mg/day derived from ND0612 DP + a

morning oral dose of 150/15 mg LD/CD) in order to assess the effect of continuous subcutaneous infusion of these 2 dosing regimens of ND0612H on daily OFF time.

As detailed in the Table below, the 24-hr continuous infusion of ND0612 (Regimen 1) in this study demonstrated statistically significantly reduction in daily OFF time by 2.7 hrs, as assessed by a blinded study rater after 28 days of treatment. A mean reduction in daily OFF time by 1.3 hrs was also seen at Day 28 for Regimen 2 employing 14-hr daytime ND0612 infusion, but this improvement did not reach statistical significance. A post-hoc responder analysis showed that 42% of the subjects in Regimen 1 had a complete reduction in OFF time compared with 11% of the subjects in Regimen 2.

Table 9. Adjusted mean change from baseline to Day 28 in total day OFF time: mITT set (observed cases)

Characteristic	**Regimen 1 (24 hr infusion) N = 19**	**Regimen 2 (14 hr infusion) N = 19**	**Total N = 38**
Subjects with data at baseline	19	19	38
Subjects with data at Day 28	16	17	33
"OFF" time (hours)[a]			
Mean "OFF" time at baseline (SD)	5.55 (2.065)	5.01 (2.356)	5.28 (2.202)
Mean "OFF" time at Day 28 (SD)	2.96 (4.102)	4.04 (3.908)	3.51 (3.978)
Change from BL in "OFF" time (hours)			
Mean change (SD)	-2.69 (3.793)	-1.20 (3.619)	-1.93 (3.724)
LS mean change[b]	-2.75	-1.27	-2.01
95% CI	(-4.59, -0.91)	(-3.06, 0.52)	(-3.31, -0.71)
p-value	0.004	0.158	0.003
LS mean of R1 vs R2 for change from BL	-1.48		
95% CI	(-4.02, 1.06)		
p-value	0.244		
"OFF" time (% of awake time)[c]			
Mean "OFF" time at baseline (SD)	34.68 (12.905)	31.34 (14.723)	33.01 (13.760)
Mean "OFF" time at Day 28 (SD)	18.49 (25.639)	25.23 (24.427)	21.96 (24.863)
Change from BL in "OFF" time (hours)			
Mean change (SD)	-16.83 (23.706)	-7.51 (22.621)	-12.03 (23.274)
LS mean change[b]	-17.20	-7.95	-12.57
95% CI	(-28.70, -5.70)	(-19.13, 3.23)	(-20.69, -4.46)
LS mean of R1 vs R2 for change from BL	-9.25		
95% CI	(-25.10, 6.60)		

BL: Baseline; CI: confidence interval; LS: Least square; N: number of subjects in treatment group; R1, R2: Regimen 1, Regimen 2; SD: standard deviation.

[a] normalized to 16 hours of awake time

[b]The Mixed Model for Repeated Measures included the observed change from baseline to Day 3 and Day 28 in total daily "OFF" time with no imputation for missing data as dependent variable. The model included "OFF" time at baseline as covariate (p = 0.600); treatment regimen (p = 0.598), study day (p = 0.036), the interaction between treatment regimen and study day (p = 0.067) and the variable used to stratify the randomization (region, p = 0.684) were included as fixed factors. An unstructured covariance structure was assumed and the denominator degrees of freedom were computed using the Kenward-Roger method.

[c] Proportion out of awake time during the 8 hours of data collection. Only one p-value is provided as the p-values for time (hrs) and proportion (%) are identical

Source: Table 14.2.1.1.1, Table 14.2.1.1.2

Furthermore, as above described, study ND0612H-012 PK sub-study assessed the plasma exposure to LD, CD and 3-OMD, following SC infusion of ND0612 when used chronically in subjects with PD experiencing motor fluctuations. These subjects were optionally receiving adjunct anti-PD oral medications (to better manage PD symptoms), including LD/DDI-containing drugs according to clinical routine use and per investigator judgment.

The PK-pharmacodynamic relationships were explored for the two treatment regimens employed in this study, both delivering a total of 720 mg of LD and 90 mg CD by SC infusion, the first regimen over a 24 h period and the second one over a 16 h period.

The findings of this study (see sub-section 5.2.3.2.1) supported the ultimate decision of using the 24 h regimen in the ND0612-317 pivotal efficacy study.

5.2.6. Relationship between plasma concentration and effect and safety

An attempt to investigate the relationship between LD plasma concentration and pharmacodynamic endpoints (Hauser's ON/OFF diary and TRS), using popPK/pharmacodynamic modelling based on data from the ND0612H-012 PK Sub-study, was made.

Treatment Response Scale model

A consistent correlation between LD concentrations and TRS scores was observed. A popPK/Pharmacodynamic model was developed. This model related TRS scores to delayed LD concentrations in an effect compartment (representing hypothetical concentrations at the site of action) through a sigmoidal maximum effect (E_{max}) model. The PK/Pharmacodynamic parameter estimates were in line with previous findings.

Hauser's ON/OFF diary model

Although there was a subtle trend consisting of a higher proportion of OFF scores in the early morning when LD concentrations were low and a higher proportion of ON and ON-with-troublesome-dyskinesia scores in the daytime when LD concentrations were higher, the model-based analysis did not identify a statistically significant exposure-response relationship with respect to Hauser's ON/OFF home diary scores.

Study ND0612H-012 PK Sub-study

ND0612H-012 PK Sub-study included 17 PD subjects that completed at least 1-year treatment with ND0612 DP. ND0612 DP was co-administered with anti-PD oral medications, including LD/DDC inhibitor-containing drugs, as per investigator's judgment. As such, this PK/Pharmacodynamic assessment was limited by the fact that subjects were already on a PD treatment to achieve an optimised effect, thus narrowing the explored clinical effect range.

Figure 6 and Figure 7 above (see sub section 5.2.3.2 Primary and secondary pharmacology) are summary plots of the LD concentrations and the PD measurements at the corresponding times, based on 16 subjects: one subject was excluded as his timing of PK sampling was not according to the scheduled time.

The relationships between LD plasma exposure and the pharmacodynamic tools were explored.

Treatment Response Scale

Median TRS global scores versus time, by dosing regimen (16 h and 24 h regimen) starting in the morning hours, are presented in Figure 5 (see section 5.2.3.2 above), together with LD plasma concentrations. In the 16 h regimen the LD plasma concentrations are lower than in the 24-h regimen during the morning

hours, and the TRS scores are also lower in the 16 h regimen during this time, similar to the OFF state observed for the Hauser's ON/OFF diary (Figure 6, section 5.2.3.2 above).

Hauser's ON/OFF Diary

A plot of the proportion of the ON/OFF diary scores (OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, ON with troublesome dyskinesia) at each time point reported over 14 h (waking hours), by dosing regimen, is also presented in Figure 6 above (see sub-section 5.2.3.2) together with LD plasma concentrations.

5.2.6.1. Evaluation and Qualification of PK/PD Models

Treatment Response Scale

The parameter estimates of the final model for TRS are presented in the Table below.

Table 10. ND0612H-012 PK Sub-study - Parameter estimates of the final TRS model

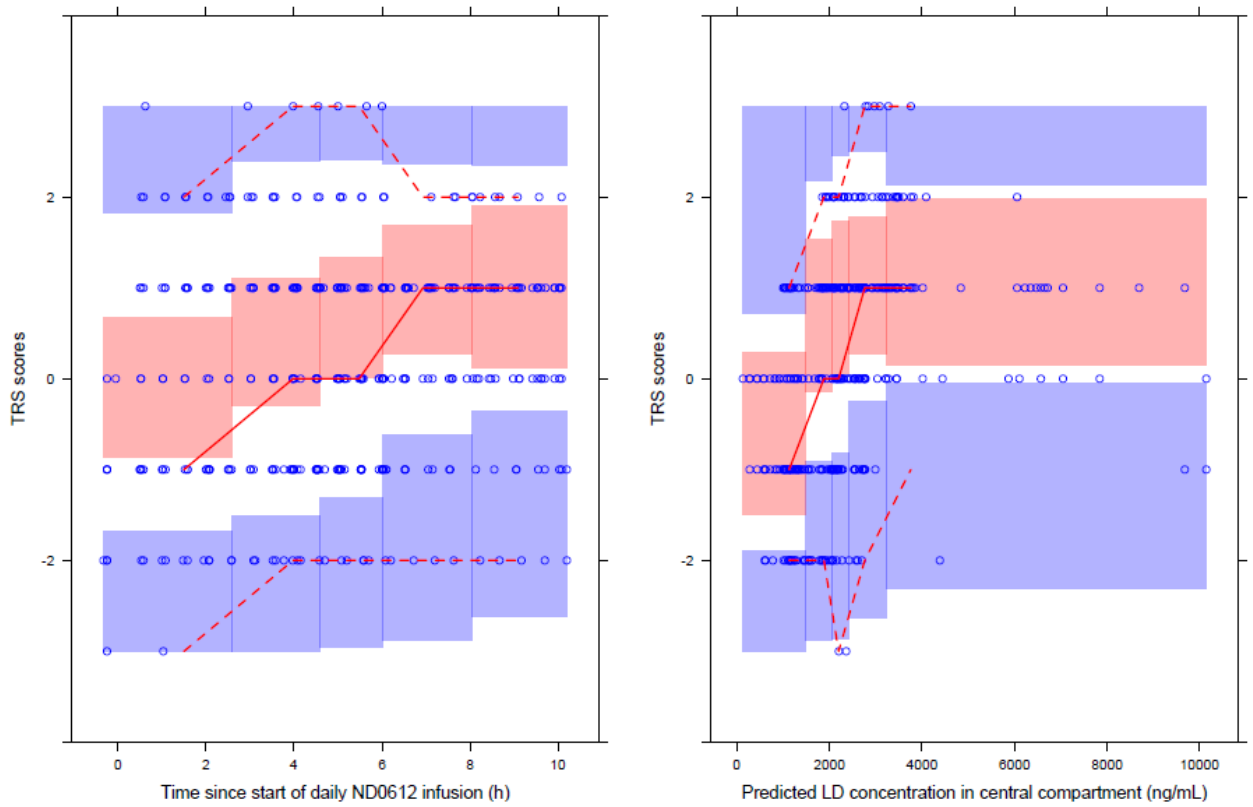
	Final model (run 4002, OFV=384)			
	Unit	**Typical value**	**RSE[a] (%)**	**SHR (%)**
TRS_0	TRS scale	-1.17	12.3	
TKE0	min	49.2	13.8	
EC_{50}	ng/mL	1440	1.73	
Hill coefficient		24.3	13.2	
E_{MAX}	TRS scale	1.92	11.1	
IIV TRS_0	CV	0.400	21.2	27.3
IIV TKE0	CV	1.38	17.5	44.1
IIV EC_{50}	CV	0.323	23.0	40.6
IIV E_{MAX}	CV	0.868	15.9	8.63
Additive residual error		0.736	3.00	2.56

a Obtained via sampling importance resampling methods.
RSE for IIV and RUV parameters reported on the approximate SD scale. EC_{50L}: LD concentration at half maximum effect; E_{max}: maximum effect; CV: coefficient of variation; IIV: interindividual variability; OFV: Objective function value, RSE: relative standard error; RUV: residual unexplained variability; SD: standard deviation; SHR shrinkage; TKE0: effect time constant TSR: Treatment Response Scale; TRS_0: baseline TRS response.

The parameter estimates of the final TRS model were similar to those reported by Westin *et al*. Assuming steady-state conditions (average plasma concentration = average effect compartment concentration), the medians of LD plasma concentrations observed in the ND0612H-012 – PK Sub-study were maintained above the estimated concentration at half maximum effect (EC50) of 1440 ng/mL during most of the infusion intervals.

The Figure 9 shows the Visual predictive checks (VPCs)of the Treatment Response Scale (TRS) scores for the final TRS model versus time since first ND0612 infusion and versus predicted LD concentration. The VPC confirmed that the model was able to capture the general tendency of the median data as well as the variability. The basic goodness of fit (GOF) plots as well as the VPC below indicate some minor over and underpredictions, but overall, the model describes the observed Treatment Response Scale (TRS) data generally well.

Figure 9. ND0612H-012 PK Sub-study: VPC of TRS scores for the final TRS model versus time since start of daily ND0612 infusion (left) and predicted LD concentration (right)



Note: The solid and dashed red lines represent the median, 2.5th and 97.5th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median, 2.5th and 97.5th percentiles predicted by the model. Open circles are TRS observations. LD: Levodopa. SC: subcutaneous

Hauser's ON/OFF diary model development

The starting point of the model development for Hauser's ON/OFF diary was a minimal continuous time Markov model with no drug effect (run 40). Several attempts were made to identify an exposure-response relationship, but all the drug effect models that were tested did not show a statistically significant improvement over the base model (ΔOFV>-2.9, in the Table below). Hence, a PK/PD model could not be established for the Hauser's ON/OFF diary data.

Table 11. ND0612H-012 PK Sub-study - Summary of key NONMEM runs for the Hauser's ON/OFF diary model

Run #[a]	Ref #[b]	OFV	ΔOFV	Description
40		**70913.76**		**Markov, no drug effect. (Base Model)**
400	40	70913.75	-0.01	With final PKPD data set
43	40	70913.69	-0.08	Drug effect EMAX (LD central)
44	40	70914.98	1.21	Drug effect EMAX (LD effect comp)
48	40	70913.13	-0.64	With Hill coeff
49	40	70912.06	-1.70	Drug effect linear (LD central)
65	40	70912.30	-1.46	Add LED effect
80		70876.91		No drug effect, remove SUBJID 265-002
81	80	70875.92	-0.99	Drug effect EMAX (LD central)
82	80	70876.87	-0.04	Drug effect EMAX (LD effect comp)
66		60774.58		Ignore SUBJID 231-001, 231-002 and 231-004 - Base
67	66	60773.25	-1.33	Ignore SUBJID 231-001, 231-002 and 231-004 - EMAX
205		30404.37		OFF vs. NON OFF - Base model
203	205	30401.47	-2.90	OFF vs. NON OFF - EMAX with effect comp LD

[a]Run number
[b]Reference run number

5.2.7. Overall discussion and conclusions on clinical pharmacology

5.2.7.1. Discussion

Pharmacokinetics

ND0612 DP is a sterile solution that contains levodopa (LD) at a concentration of 60 mg/mL and carbidopa (CD) at 7.5 mg/mL. It is intended for continuous SC administration using one of two delivery systems: the Crono Twin ND pump or the Twiko Delivery System (TDS). The recommended total daily dose is up to 720 mg of LD and 90 mg of CD. The solution is intended to be infused over 24 hours through two infusion sites, at a fixed rate of 0.08 mL/h during the night for 6 hours, and at a variable rate of 0.32 to 0.64 mL/h during the day for 18 hours.

As part of the clinical development of ND0612 DP, 10 studies were completed to evaluate the PK, safety, tolerability and efficacy (where applicable) of ND0612 DP, using formulations with different ratios of LD/CD, and a variety of dosing regimens. Six studies were conducted in healthy subjects (ND0612/001, ND0612/001b, ND0612-005, ND0612-114, ND0612-115, and ND0612-J01) and four studies in subjects with PD (ND0612/002, ND0612/003, ND0612-004, and ND0612H-006).

Additionally, two main clinical studies completed their core phases. The first is ND0612H-012, a long-term safety study that enrolled 214 PD patients, out of whom 120 completed the one-year treatment period. A PK sub-study was conducted as part of ND0612H-012, involving 17 patients who had completed at least one year of treatment with ND0612. The long-term extension of this study (lasting up to 102 months) is still in progress at the time of authoring this assessment report. The second is ND0612-317, a pivotal efficacy trial, in which 381 PD patients were enrolled. Out of these, 259 patients were randomised, and 243 completed the core phase of the study. During this study, sparse PK samples were taken. Obtained data were pooled with data from earlier studies to create the popPK database.

A TQT study, evaluating of the influence of a supratherapeutic dose of CD on the QTc interval, was also conducted, upon FDA request. The results were made available during the evaluation of this initial MAA.

Absorption and Bioavailability

During the development program of ND0612 DP it was concluded that a LD/CD ratio of 8:1 in the formulation assured the proper dopa decarboxylase (DDC) inhibition by CD, maximising LD exposure.

Regarding **absorption** of LD/CD, following administration of ND0612 DP as a continuous SC infusion over 24 hours, less variation in plasma levodopa levels, as compared to oral levodopa treatments alone (fluctuation index and peak to trough ratio reduction), was noted, as described in SmPC section 5.2. The location of the infusion site does not affect the absorption of LD and CD.

The estimated **bioavailability** of LD and CD relative to oral immediate-release LD/CD tablets is 1.3 and 5.7-fold higher, respectively. ND0612 DP versus relative BA of LD derived from Duodopa® was found to be 1.4-fold higher.

The absorption of ND0612 DP from different infusion sites (abdomen, back, or outer thighs) was also studied. It was demonstrated that the infusion site or cannula length did not influence the absorption. When comparing dose-normalised AUCs, ND0612 DP given as a subcutaneous infusion showed approximately 1.3 times higher exposure for LD and 7 to 8 times higher exposure for CD than oral IR LD/CD.

The mean LD C_{max} levels in healthy volunteers, following continuous SC infusion of ND0612 DP at LD dose of 720 mg, administered over 24 h, was 1450 ng/mL; the corresponding average plasma concentration at steady state was 1240 ng/mL. Relative BA of LD derived from ND section 4.2 recommends administration of Onerji in the abdomen, flanks, outer thigh and posterolateral upper arm, if needed, as the anatomically defined sites supported by clinical use. Of note, the support of an appropriately trained caregiver may be required for some hard-to-reach infusion sites such as the flanks.

As noted in SmPC Table 1, the recommended conversion factor for the currently administered LD includes adjustments based on both the formulation of LD being used and the type of COMT inhibitor co-administered. While the clinical studies evaluated the impact of immediate-release LD and entacapone on LD levels, the effects of controlled-release, extended-release formulations, as well as other COMT inhibitors, were not assessed. The Applicant provided an explanation regarding the multiplication factors required to calculate the daily total oral levodopa equivalent dose (LED) and initiate Onerji showed in SmPC Table 1.

These multiplication factors are based on published literature that is used widely in clinical practice as reference to calculate LED (Jost et al., 2023). A similar table was used in ND0612-317 study protocol to support investigators in the switching of medication.

If a COMT inhibitor is to be co-administered with Onerji, the bioavailability of total administered LD, including the LD Onerji component, is expected to increase.

In Study ND0612-004, co-administration of entacapone with ND0612 increased LD levels between 24% and 27%, and in the Pop-PK analysis the estimated effect was 22% (reference: section 2.7.2.3.6.5.1). This is consistent with the established 1.33 multiplication factor (33% increase) used to calculate the effect of entacapone on oral LD, suggesting no different effect of COMT inhibition whether LD is administered orally or subcutaneously. As such, the established factors for opicapone and tolcapone on oral LD (x1.5), are also expected to apply to ND0612 DP.

In addition, SmPC section 4.2 details that patients may continue to take oral levodopa and other Parkinson's disease medicines (e.g. dopamine agonists or MAO-B inhibitors) when treatment with Onerji is started, and that these treatments can be adjusted as needed.

Daytime and night-time infusion rates are also described accordingly in SmPC section 4.2, Table 2.

Distribution

Regarding distribution of LD and CD, description of protein binding is based on literature data: levodopa is approximately 10-30% bound to plasma proteins (Rizzo et al., 1996) and carbidopa is approximately 36% bound to plasma proteins (Vickers et al, 1974). The PK parameter Vc/F was estimated through popPK model. The SmPC details in section 5.2 that "levodopa is transported into the brain by the carrier mechanism for large neutral amino acids" and that "carbidopa does not cross the blood-brain barrier." This information was supported accordingly by literature data of Khor & Hsu, 2007, Vickers et al., 1974, Brod et al., 2012.

Metabolism and Excretion

No metabolism and excretion studies were conducted with ND0612 DP. As described in published literature, levodopa undergoes metabolism via four pathways. The two major ones are the decarboxylation by DDC to dopamine, which may be further metabolised to form 3,4-dihydroxyphenyl acetic acid and homovanillic acid, and, to a lesser extent, the 3-O-methylation by COMT to form 3-O-methyldopa (3-OMD). The other metabolic pathways are the transamination by tyrosine aminotransferase, and oxidation by tyrosinase or other oxidants (Khor et al., 2007).

The 3-OMD metabolite was measured in ND0612 DP clinical studies. The results showed that 3-OMD exposure following ND0612 DP SC administration, both alone and in combination with oral LD/CD, was within the range observed with other formulations, such as Duodopa. In studies comparing ND0612 DP SC to oral LD/CD, 3-OMD levels were similar or slightly higher after ND0612, probably as a result of its higher bioavailability. These findings support the efficiency and stability of ND0612 DP in delivering levodopa. Moreover, the applicant performed an exploratory PK/PD analysis linking 3-OMD plasma concentrations with clinical outcomes based on ON/OFF diary data collected in the ND0612-012 PK sub-study, where both 3-OMD and efficacy measures were sampled during the same 24-h period. The results showed no association between higher 3-OMD exposure and increased OFF time. In contrast, OFF periods were associated with lower LD concentrations. Overall, there was no indication that elevated 3-OMD concentrations adversely impact clinical efficacy. Within the limitations of the small sample size and the ad-hoc nature of the analysis, these findings do not support a clinically relevant detrimental effect of 3-OMD at the exposure levels achieved with ND0612.

Three main metabolites of carbidopa were detected in the urine of healthy volunteers and PD patients, after administration of C-labelled CD: 2-methyl 3-methoxy-4-hydroxy-phenylpropionic acid, 2-methyl-3,4- dihydroxy-phenylpropionic acid, and 3-hydroxy-α-methylphenylpropionic acid, each accounted for approximately 10% of the radioactivity excreted in the urine. These metabolites are excreted as glucuronides and unconjugated compounds. Unchanged CD accounts for about 30% of the total urinary excretion (Vickers et al., 1975).

Regarding elimination of LD and CD, the derived elimination half-life estimates are concordant between phase I studies. The SmPC (section 5.2) describes an overall mean value of 2.3 hours for LD and 2.7 hours for CD.

Additionally, the impact of possible genetic polymorphism in the pharmacokinetics of LD and CD was adequately addressed In summary, although genetic polymorphisms may contribute to the interpatient variability in LD PK, the magnitude of PK changes was generally shown to be modest and does not

warrant any genotyping or specific dosing recommendations, as the therapeutic regimen is adjusted according to individual response.

Special Populations

Renal Impairment

No dedicated studies to assess the impact of renal impairment and hepatic impairment on LD and CD PKs following SC administration of ND0612 DP were conducted, as no difference in the known elimination patterns of either LD or CD following different routes of administration, including SC, was anticipated. In addition, as LD and CD are eliminated via non-renal and non-hepatic routes such studies are not considered necessary.

In the presence of DDC inhibitors, majority of a LD dose is cleared by non-renal elimination mechanisms, and renal excretion of intact LD accounts for 10% or less of LD clearance (Yeh et al., 1989). Therefore, while impaired renal function in patients treated with ND0612 may contribute to some increased LD exposure, a clinically significant effect is considered unlikely. Also, about 30% of a CD dose, is excreted unchanged in the urine (Vickers et al., 1974). As such, a renal impairment study to evaluate the PK of CD would have had little value with respect to dosing of LD/CD.

However, during ND0612 PD OF SC administration at the proposed daily dose of 720 mg LD and 90 mg CD, a significantly higher systemic exposure to carbidopa was observed compared to conventional oral LD/CD formulations. Although no carbidopa-related safety signals have been observed in clinical studies to date, the overall exposure (AUC) to CD may exceed those reported for oral formulations. Therefore, the applicant discussed the potential safety consequences of this elevated carbidopa exposure, particularly in the context of long-term administration. It also evaluated how carbidopa PKs may be affected by renal impairment, as reduced renal clearance could further increase systemic CD levels.

The overall safety profile was consistent with known effects of standard oral LD/CD. In particular, subgroup analyses did not show differences in safety between patients on lower vs higher oral LD/CD, which could suggest higher total CD exposure. In addition, a TQT study performed with a supratherapeutic oral CD dose did not show any effect on QT prolongation or ECG parameters. This carbidopa increase was also confirmed as not clinically meaningful in patients with chronic kidney disease. However, as a small effect was noted in this sub-population it was ultimately agreed to detail in SmPC section 5.2 that *dose adjustment should be conducted with caution in patients with severe renal (or hepatic) impairment.*

Hepatic impairment

Literature data indicate that levodopa is largely metabolised by enzymes that are widely distributed in the body. Levodopa is mainly eliminated via metabolism by DDC (69%) and COMT enzymes (10%) (Nutt et al., 1984). Therefore, hepatic functional impairment is not likely to alter the exposure levels of LD, especially in the presence of CD which has a more profound effect on LD apparent clearance than the liver. LD and CD have minimal hepatic metabolism and lack of hepatotoxicity.

ND0612 DP administration to renal and hepatic impairment patients has no restrictions. As clarified in the SmPC the "dosing is individualised by titration to optimal effect (which corresponds to individually optimised levodopa and carbidopa plasma exposures). Therefore, as detailed in SmPC section 4.2 "*potential effects of hepatic or renal impairment on levodopa and carbidopa exposure are indirectly accounted for in dose titration (see sections 4.4 and 5.2).*

Paediatrics

A product-specific waiver for studies in paediatric populations was granted on 18 March 2020 (EMEA-002687-PIP01-19).

Elderly

Most of the patients exposed to ND0612 DP were under 65 years of age (e.g. in the pivotal study ND0612-317, over half of the randomised patients were under 65, with fewer participants in the older age groups). Nevertheless, efficacy and safety profiles were confirmed as consistent across all age subgroups. No meaningful differences were observed between patients under 65 and those aged 65 to 85 years. Furthermore, popPK analysis showed no age-related trends in levodopa or carbidopa exposure. However, given the very limited data in patients *aged 85 years and older*, the wording in SmPC section 4.2 advises that, for this subgroup, *dose adjustment should be conducted with caution.*

Drug Interactions

No drug-drug interaction studies were performed during the development of ND0612 DP, as literature provided adequate information. Regardless its route of administration, LD/CD derived from ND0612 DP is subject to the same, known drug-drug interactions that are common to other (already marketed) LD/CD products, as described accordingly in the SmPC.

The use of the COMT inhibitor entacapone during ND0612 therapy increases exposure to levodopa. In clinical studies (ND0612-003 and ND0612-004), this addition led to an increase in levodopa AUC by 22–35%, depending on the study. These results are consistent with the mechanism of action described in the literature for COMT inhibitors, which slow down the peripheral metabolism of levodopa and extend its half-life, leading to higher blood levels. Considering these data, the purpose of the dose conversion factor for entacapone administration (and their impact on levodopa levels) detailed in the SmPC is justified. Specific values for other COMT inhibitors (tolcapone and opicapone) are also included. Regarding ND0612 DP therapy, the applicant clarified that the absence of a fixed plasma concentration–effect relationship for levodopa and the high inter- and intra-individual variability that precludes the definition of absolute "no-effect boundaries" is based on exposure metrics. This reasoning aligns with the current regulatory understanding that the therapeutic response to levodopa is clinically, not concentration, driven. Given that dose titration in PD is individualised and guided by clinical response rather than LD plasma concentration targets, modest variations in systemic exposure do not generally necessitate LD dose adjustment nor raised safety concerns.

Pharmacodynamics

The mechanism of action of LD/CD combination is extensively well known.

Pharmacodynamic/efficacy endpoints were assessed in study ND0612-317 and specific analysis of the results are presented below.

In this study, Onerji was able, to obtain statistically significant and clinically relevant improvements in the ON/OFF score (1.72h in ON time without dyskinesia and -1.40 in OFF time).

The assessment of the results of showed that the Unified Parkinson's Disease Rating Scale (UPDRS) Part II was -3.05, which is borderline considered as the minimal clinically important difference (MCID) and UPDRS Part III was -2.42, which is below what is considered as MCID (≥3.25).

Applying the composite scoring to these results, for UPDRS Part II (-3.05) + Part III (-2.42) the composite overall result is 5.47 > 4.9.

Although the results from the UPDRS Part II can be considered as complying to what is regarded as MCID (marginally), the results from UPDRS Part III were surprisingly low, not considered clinically

relevant and in the area of the test that should be more applicable and relevant to the medicinal product.

The objective of MDS-UPDRS Part III is to perform motor examination, being an objective assessment performed by a clinician. It measures motor signs like tremor, rigidity, bradykinesia, postural stability, gait, etc., and is commonly used in clinical trials to evaluate the direct effect of a treatment on motor symptoms, being sensitive to short-term and dose-dependent changes, especially for dopaminergic treatments.

The applicant justified the absence of clinically relevant results with the weak inter- and intra-rater reliability of MDS-UPDRS Part III and the difficulties of its consistent application due to day-to-day variability of motor symptoms, particularly in multicentre trials, and for long-term studies where different raters may assess the same patient at different timepoints. In addition, albeit not reaching statistical significance, results showed a benefit in MDS-UPDRS Part III favouring ND0612, consistent with the primary and other secondary endpoints. It was additionally highlighted that various studies in PD patients with motor fluctuations failed to show significant improvements in UPDRS/ MDS-UPDRS Part III, despite clinically meaningful improvements in motor fluctuations observed in Hauser's diaries as well as positive results in ON/OFF time and UPDRS Part II.

Given the relevance of the Treatment Response Scale in measuring acute effects of treatment (used in ND0612H-012 PK sub-study to compare the 16h vs 24h regimens), the applicant was also questioned on why this was not assessed in selected days/weeks of the pivotal trial ND0612-317, thereby allowing a proper PK/PD comparison in the daily effects of the proposed product with a strictly oral LD/CD administration. The applicant justified the absence of TRS as a PD endpoint in the pivotal study with logistic issues and the fact that TRS could only be considered as a surrogate marker to assess the efficacy of PD drugs. Although that is acknowledged, its valued could have increased the PK/PD correlation that presented with some inconsistencies. Nevertheless, the CHMP agree not to further pursue this issue.

In study ND0612-317, there were no consistent trends of change in mean values of any ECG parameters over the core study period, and no clinically relevant differences between the ND0612 and IR-LD/CD arms. No subject had a QTcF interval $\geq$ 480ms. Similarly, in study ND0612H-012, there were no consistent trends of change in mean values of any ECG parameters over the core study period. As in the study ND0612-317 no subject had a QTcF interval $\geq$ 480ms.

A TQT study to assess the potential effects of a supratherapeutic CD dose on cardiac repolarisation was conducted, upon FDA request. The results showed that a supratherapeutic single oral dose of CD 400 mg, which resulted in a gMean C_{max} of 1352 ng/mL, covering the high clinical exposure of ND0612 and adjunct oral LD/CD (1250 ng/mL as estimated by PK simulation), was safe and well tolerated and had no effect on cardiac repolarisation or other ECG parameters. The ND0612H-012 PK sub-study supported the correlation between levodopa exposure and decreased variability of the treatment response scale (TRS) score based on data from 16 PD subjects who completed at least 1-year treatment with ND0612 DP. Therefore, no difference in MDS-UPDRS was expected, especially with such a short duration of study. Additionally, subjects were allowed to supplement ND0612 therapy with adjunct anti-PD oral medications including LD/DDI-containing drugs to better manage PD symptoms. That impaired proper correlation of PK/PD results. No comparison was performed with patients taking oral LD/CD.

5.2.7.1. Conclusions

The clinical pharmacology package presented data from Phase I and Phase II/III studies. It focused on PK parameters and optimalisation of the solution for infusion. Information presented is considered

adequate. Majority of (other) data derived from literature, which is acceptable.

5.3. Clinical efficacy

Please refer to the Table of studies in section 5.1.2 (Table 3).

5.3.1. Dose response study(ies)

ND0612/001, the first study conducted in humans, was a dose-escalation study that investigated ascending doses of SC administration of ND0612 DP for 24 h ('single dose' regimen) in various infusion rates, ranging from 0.08 mL/h to 0.24 mL/h, resulting in LD/CD dose range from 115.2/26.9 to 345.6/80.6 mg. The infusion rates remained constant throughout the dosing interval within each dose group.

The above was followed by study **ND0612/001b** that assessed the effects of a reduced rate of administration throughout the night, while maintaining the highest infusion rate (investigated in the previous study) during the day hours for a total daily LD/CD dose of 269/63 mg (Group B). This study also assessed the effects of a formulation with lower concentrations of LD/CD (Group A) and concomitant use of the catechol-O-methyl transferase (COMT) inhibitor, entacapone (Group C). Thereafter this study, the dosing regimen (used for treatment Group B) of 0.08 mL/h for 8 h and 0.24 mL/h for 16 h, for a total LD/CD daily dose of ND0612 DP LD/CD 269/63 mg or placebo was administered to PD subjects for 24 h ('single dose' regimen), together with oral LD/CD/entacapone treatment, in study **ND0612/002**, and later for 14-21 days ('multiple dose' regimen) with standard of care (SoC) oral LD/CD treatment in study **ND0612/003**. These two latter studies used what was considered, in the early stages of development, a "low" dose of ND0612 DP i.e., a total daily LD/CD dose of 269/63 mg, administered via one infusion site (ND0612 "low dose" (ND0612L). This dosing regimen was found safe and well tolerated in both PD subjects and healthy volunteers.

A higher ND0612 DP daily dose required an increase of the infusion rate and a higher infusion volume, which was evenly divided between two infusion sites to minimise the incidence and/or severity of infusion site reactions. This higher rate (total of 0.64 mL/h divided between two infusion sites) was first assessed in PD subjects over 8 h for a total maximal LD/CD dose of 307/72 mg in study **ND0612-004**, and then in healthy subjects, for 24 h for a total maximal daily LD/CD dose of 720/90 mg, in study **ND0612-005**. This maximal dose, considered then as "high" dose of ND0612 DP (**ND0612H**), was administered over 24 h at an infusion rate of 0.08 mL/h for 6 h (later defined as 'night-time rate') and 0.64 mL/h for 18 h (later defined as 'daytime rate') and was found to be safe and tolerable. This ND0612H dosing regimen resulted in stable and clinically relevant LD levels during the daytime. The mean (±SD) LD C_{max} levels were 1450 (±157) ng/mL, which is similar to the mean (± SD) LD C_{max} of the oral immediate-release levodopa/carbidopa (IR-LD/CD) regimen of 100/25 mg, administered four times a day (1635 [±655] ng/mL), observed in study **ND0612-115**. In addition, the mean (±SD) average LD plasma concentration during the daytime following ND0612 DP administration was 1240 (±141) ng/mL.

Study ND0612-005 also demonstrated that LD levels of around 800 ng/mL are achieved about three hours after the switch from night-time rate to daytime rate.

The same 24 h dosing regimen as used in study ND0612-005 was also tested in PD subjects in the phase 2 study **ND0612H-006**, in the long-term safety study **ND0612H-012** (Regimen 1), and was the recommended starting dosing regimen in the pivotal efficacy and safety phase 3 study, **ND0612-317**. In this study, the daytime infusion rate could be adjusted according to the patient's individual needs to achieve a maximal daily LD/CD dose of 720/90 mg.

ND0612 DP provides a basal LD plasma level which eliminates trough concentrations and maintains continuous and stable LD exposure in PD patients. The therapeutic LD levels for each PD subject are individually adjusted based on clinical response, by adding oral LD, as needed. The adjunct oral LD may range from a single morning dose to several dosing occasions throughout the day.

In Summary, ND0612 DP was designed to provide 720/90 mg of LD/CD over 24 h: 18 h of daytime rate and 6 h of night-time rate. This night-time flow rate is aimed at maintaining continuity of delivery and allowing the switch from night to day flow rate about 3 h before patient's wake up time, in order to reach clinically relevant LD levels faster in the morning and, as such, prevent or reduce morning akinesia. The provided night LD dose was set to be minimal, minimising the risk for dopaminergic adverse events, including nocturnal confusion or hallucinations (Olanow et al., 2006), and allowing for a great portion of LD to be remained for administration during the day.

Selection of LD/CD 8:1 Ratio Formulation

In the early stages of the development, an LD/CD ratio of 4:1 had been chosen based upon the ratio of commonly available LD/CD oral products. Four early-stage clinical trials (two in healthy subjects [ND0612/001 and ND0612/001b] and two in subjects with PD [ND0612/002 and ND0612/003]) were conducted using this 4:1 ratio.

In order to establish the CD concentration in the formulation, that would provide optimal levodopa BA derived from ND0612 DP administered continuously via SC infusion, two open-label studies were conducted: **ND0612-004** (in subjects with PD) and **ND0612-005a** (in healthy subjects), in which different carbidopa concentrations (4, 6, 7.5, and 14 mg/mL) were used in the ND0612 DP formulation, while the levodopa concentration was fixed (60 mg/mL). Both studies assessed the impact of CD dose on the BA of LD derived from **ND0612L** (low dose, total of 270 mg LD/day) and **ND0612H** (high dose, total of 720 mg LD/day).

Study ND0612H characterised the impact of two concentrations of CD, 7.5 and 14 mg/mL, on LD BA: LD/CD ratios of 8:1 and 4:1, respectively. No relevant difference in LD BA was observed between these two CD concentrations; therefore, it was decided not to go higher than 7.5 mg/mL with the CD concentration in the formulation.

In study ND0612-005a, it was further characterised the impact of three descending CD concentrations (7.5, 6, and 4 mg/mL) on LD BA (LD/CD ratios of 8:1, 10:1, and 15:1, respectively). Healthy subjects were allocated to three consecutive infusions of either ND0612H or ND0612L.

The results suggested that the difference in LD $AUC_{0\text{-}inf}$ between Dose 3 to Dose 1 in ND0612L (270 mg LD/day) and ND0612H (720 mg LD/day) were statistically significant (p=0.028 and 0.020, respectively). Further to that, a post-hoc exploratory trend analysis showed a positive trend between carbidopa dose levels used in the ND0612L and levodopa exposure, indicating that CD concentrations lower than 7.5 mg/mL (i.e., Dose 3 and Dose 2) could potentially compromise LD BA when low LD doses or low ND0612 rates are being administered.

Following the results of studies ND0612/004 and ND0612-005, the final LD:CD ratio was selected to be 8:1 with LD/CD concentrations of 60/7.5 mg/mL in the ND0612 DP formulation. This formulation was tested in subsequent Phase I studies in healthy subjects (**ND0612-114**, **ND0612-115** and **ND0612-J01**) and in Phase II-III studies in subjects with PD (**ND0612H-006, ND0612H-012** and **ND0612-317**) and constitutes the to-be-marketed formulation of ND0612 DP.

The selection of LD/CD ratio of 8:1 was adequately supported by the assessments done later in subjects with PD as part of the two main studies. The mean CD C_{avg}, observed in the ND0612H-012 PK sub-study was 512 ng/mL. The levels determined from sparse PK sampling in study ND0612-317 showed consistency and were in the range of 487-544 ng/mL. These CD concentrations associated with the

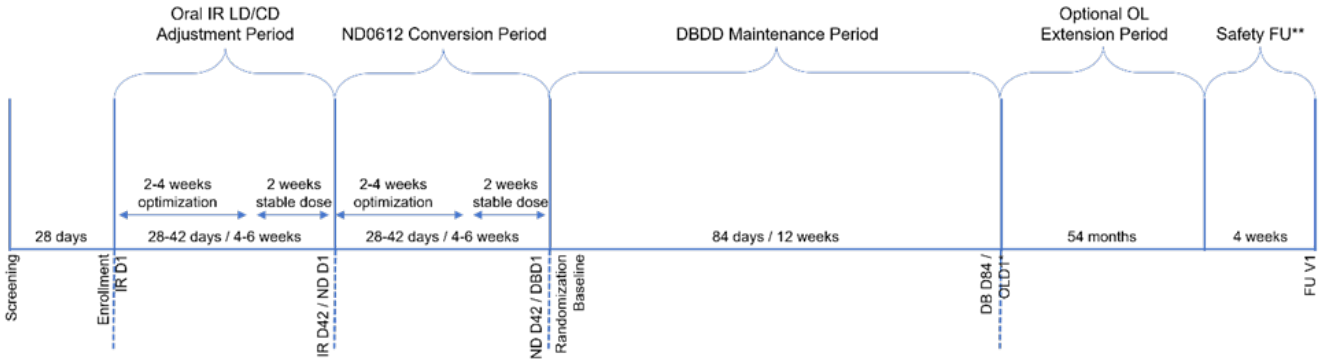
daytime SC infusion of ND0612 DP with oral LD/CD were shown to reduce the apparent dopa decarboxylase-mediated clearance (CL_{DDC}/F) of LD by 85-90% based on the population pharmacokinetics (popPK) analysis as described in the popPK report 2023 (REP-4-NEUD-612-PMX-5).

5.3.2. Main study(ies)

5.3.2.1. ND0612-317 (BouNDless)

A multicenter, randomised, active-controlled, double-blind, double-dummy, parallel group clinical trial, investigating the efficacy, safety, and tolerability of continuous SC ND0612 infusion in comparison to oral IR LD/CD in subjects with PD experiencing motor fluctuations (BouNDless). The study scheme is outlined in the Figure below.

Figure 10. Study scheme: ND0612-317 Study Design Flow Chart



D: day; DB: DBDD; DBDD: Double-blind double-dummy; FU: Follow-up; IR: IR-LD/CD Adjustment period; IR-LD/CD: Immediate release levodopa/carbidopa; N: Number of subjects; ND: ND0612 OL Conversion Period; OL: Open-label; V: Visit.
** For subjects who chose not to participate in the optional OL treatment extension period, the safety follow-up period was to occur directly after the DBDD period.

ND0612-317 was designed as a pivotal study to investigate the efficacy, safety and tolerability of ND0612 in a population of PD subjects with LD-related motor fluctuations. This study was a prospective, DBDD, active-controlled trial comparing a 24-h dosing regimen of ND0612 (complemented with oral IR-LD/CD) to standard oral IR-LD/CD. Oral LD remains the gold-standard treatment regimen in PD against which other medical and surgical therapies need to be compared. Therefore, IR-LD/CD was chosen as the active control (reference: Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease, 21 June 2012 EMA/CHMP/330418/2012 rev. 2).

Treatment

ND0612-317 study design used two sequential OL adjustment and stabilisation run-in periods of active control (adjustment period with IR-LD/CD) and experimental treatment (conversion period with ND0612 + at least one morning dose of oral IR-LD/CD and additional doses during the day according to patients' needs). Each of the OL run-in periods was 4-6 weeks long, sufficient time to allow proper titration (2-4 weeks) and then two weeks of optimised stable dose. Of note, this study design was intended to ensure a fair comparison between the two treatment groups by optimizing each patient on both study treatments before randomisation.

After these two run-in periods, eligible subjects were randomised into the 12-week DBDD Period, where they either continue their optimised treatment with ND0612 SC infusion + oral IR-LD/CD, or revert to

the previously optimised oral IR-LD/CD treatment. The randomised treatment duration of 12 weeks was recognised as sufficient to evaluate and interpret the effect of ND0612 DP on the primary endpoint (reference: EMA/CHMP/330418/2012 rev. 2). Other clinical studies in the same PD population also had a treatment duration of 12 weeks.

The overall study design is considered generally appropriate. It is acknowledged that there is no model design to mimic real-life situations. Transitioning levodopa formulations (immediate and sustained release) to immediate-release and keeping the patient in the study even if deteriorating were difficult tasks. The use of IR-LD/CD as active control is also supported. The applicant clarified that the duration of the run-in period of 4-6 weeks was aligned with other studies in PD patients with motor fluctuations. Adequate literature references were provided.

Randomisation and Blinding

Blinding of the study was primarily ensured by a DBDD design.

ND0612 and placebo solutions were supplied in identical vials and packaging and were similar in colour and appearance. The active IR-LD/CD capsules were identical in packaging and of similar colour and appearance to their placebo counterparts.

Effort was made to ensure that study site personnel remained blinded. Unblinded study personnel were to be assigned by each site to perform study drug accountability and manage potential situations of unintentional unblinding.

Study sites were to have at least three distinct personnel with non-overlapping roles:

- Blinded efficacy rater: to perform or record the efficacy assessments, specifically the evaluation of ON/OFF diaries, MDS-UPDRS, CGI-I, PGIC, and Non-motor Symptoms Scale (NMSS);
- Blinded safety investigator/sub-investigator: to perform the safety-related assessments.
- Drug accountability procedures were to be performed by a designated unblinded member of the study site staff.

All vials and ancillary supplies (e.g., infusion sets and syringes) used during the DBDD period were to be returned to the sites in opaque, sealed containers, as discoloration due to oxidation of the ND0612 solution could have led to unintentional unblinding. All accountability and returns of study drug and ancillary kits was performed only by the designated unblinded team members.

Monitoring of drug accountability by the contract research organisation (CRO) was performed by a dedicated unblinded clinical research associate not involved in other study activities. Clear separation between the blinded and unblinded CRO teams was maintained.

The subjects and partners were advised at the beginning of each study visit not to discuss any local reactions or other adverse reactions to the study drugs with the blinded efficacy rater. Whenever possible, study visits were to be scheduled so that different study subjects did not meet at the study site. Study subjects were instructed not to discuss study treatment effects among themselves.

In addition, subjects were to complete a blinding questionnaire at the end of the 12-week DBDD period aimed to evaluate potential unintentional unblinding.

Patient population

Study location

A total of 117 sites in the following countries were included: Austria, Belgium, Czech Republic, France,

Hungary, Israel, Italy, Netherlands, Poland, Portugal, Russia, Slovakia, Spain, Ukraine, UK and US.

Inclusion Criteria

- Male and female subjects with PD of any race, at least 30 years of age
- PD diagnosis consistent with the United Kingdom (UK) Brain Bank Criteria
- Modified Hoehn and Yahr Scale in ON state ≤3
- Subjects had to experience motor fluctuations and experience an average of at least 2.5 h daily (with a minimum of 2 h every day) in the OFF state during the waking hours as confirmed by an adequately completed ON/OFF diary over the 3 days preceding Screening
- Subject treatment had to be on at least four doses/day of LD/dopa decarboxylase inhibitor (DDI) (or at least three doses/day of extended-release LD/DDI) and at least 400 mg/day of LD, or equivalent, and, according to the Investigator's judgment, the subject's motor fluctuations could not be further improved by adjusting anti-PD medications
- Mini-Mental State Examination (MMSE) score ≥24
    - Approval for entry into the study by an independent enrolment authorisation committee (EAC);

Exclusion Criteria

- Atypical or secondary parkinsonism
- Subjects with clinically significant or unstable medical, surgical, or psychiatric condition or laboratory abnormalities
- Acute psychosis or troublesome hallucinations in the past 6 months prior to enrolment
- Impulse control disorder within the past 2 years before enrolment, if it was considered clinically significant by the Investigator
- Subjects with narrow-angle glaucoma
- Subjects who had previously undergone treatment for PD with surgical intervention (e.g., pallidotomy, thalamotomy, transplantation, deep brain stimulation procedures, gene therapy), Duodopa®/Duopa®, or continuous dopaminergic or apomorphine infusion
- Concomitant therapy or within 28 days before Enrolment of SC apomorphine injections, sublingual apomorphine, or inhaled LD; metoclopramide; neuroleptics (exception in case of quetiapine and pimavanserin); and non-selective MAO inhibitors
- Subjects who had previously participated in studies ND0612H-006 and/or ND0612H-012
- Subjects who did not have sufficient SC tissue for SC infusion treatment.

Clozapine is an effective antipsychotic for the treatment of refractory psychosis in PD. However, its use has been limited due to the risk of agranulocytosis, and stringent complete blood count monitoring.

To avoid any potential impact on study conduct/analysis, clozapine was not permitted in the pivotal ND0612-317 study. Pimavanserin is currently the first and only prescription medication approved by the FDA for the treatment of PD psychosis. Quetiapine, while not specifically approved for this indication, is widely available and commonly used in EU countries for the treatment of PD psychosis (Pirker, 2025; Weintraub et al., 2011; Friedmann, 2022).

Of note, exclusion of subjects treated with any neuroleptic is relatively common in pivotal motor fluctuation studies; examples include BIPARK-1, BIPARK-2 (opicapone), RISE-PD (IPX203), ADVANCE-PD (IPX066).

In study ND0612-317, 4.2% of all randomised patients (3.1% [four subjects] and 5.3% [seven subjects] in ND0612 and IR-LD/CD arms respectively) had a medical history of psychosis (Psychosis FDA Medical Queries [FMQ] Broad) and 3.5% were treated with anti-psychotics (3.9 % and 3.1% in ND0612 and IR-LD/CD arms, respectively), most commonly quetiapine (reference: Appendix 1, Table 14 and Table 14.1.4a).

Importantly in the long-term safety study ND00612H-012, where there was no restriction on clozapine, anti-psychotics (acute or chronic use) were reported in 15.0% of subjects, including 4.2% subjects receiving clozapine (reference: Appendix 1, Table 14).

In the applicant's view, he exclusion of clozapine-treated patients at enrolment in ND0612-317 study was not deemed to limit the applicability of the study findings to the intended EU population.

In summary, it may be assumed that Onerji can be used in controlled previously psychotic patients. It is nonetheless interesting that in the long-term safety study ND00612H-012 more patients required use of antipsychotics than initially (4.2 % versus 15%) which highlights the fact that the use of device assisted agents should be restricted to the more advanced severe fluctuations of PD.

Objectives and estimands

Primary objective

The primary objective of the study was to determine the effect of ND0612 on daily GOOD ON time (defined as the sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia) using subject completed ON/OFF diary assessments of motor function.

Estimand(s) for the primary objective

Table 12. Estimand(s) for primary objective

Population	Patients with Fluctuating PD who would not encounter the Intercurrent Event of ICE 1-3 under any treatment assignment. Patients with Fluctuating PD who would encounter the Intercurrent Event of ICE 1-3 under any treatment assignment.
Treatment condition	Assignment to ND0612 in the hypothetical scenario of no discontinuation compared to assignment to IR LDOPA/CD in the hypothetical scenario of no discontinuation.
Endpoint (variable)	Change from Baseline to the end of the DBDD Period in mean daily ON"time without troublesome dyskinesia (i.e., GOOD ON time) time adjusted to the subject's waking hours and normalized to 16 waking hours, based on self-completed subject's ON/OFF diary assessments on the three consecutive days before the visit.
Population-level summary	Difference in means
Intercurrent events and strategy to handle them	
Additional/New PD treatment during the DBDD Period	Hypothetical

Attributable early treatment discontinuation: Early treatment discontinuations during DBDD for reasons related to randomized treatment (e.g., lack of efficacy, treatment-emergent AE related to treatment, etc.).	Hypothetical
Non-attributable early treatment discontinuation: Early treatment discontinuation during DBDD for reasons NOT related to randomized treatment (e.g., lost to follow-up).	Hypothetical

1 During DBDD for reasons NOT related to randomized treatment (e.g., lost to follow-up).

The primary estimand was based on efficacy assumption (de-jure) using a hypothetical strategy. ICE1, ICE2, and ICE3 were to be addressed using the hypothetical strategy under missing at random (MAR) assumption. The treatment effect was to be attributable to the subject's initially randomised treatment using the population level summary. The treatment effect is assumed as if additional/new PD treatment had not been available (ICE1) and as if subjects who discontinued randomised treatment for all reasons (attributable or non-attributable to randomized treatment) had full adherence to treatment (study completion until end of the DBDD Maintenance Period [DB W12]).

The secondary estimand was to be based on effectiveness (de-facto) assumption in which ICE1 and ICE2 were addressed using Control-group based approach while ICE3 was addressed using the hypothetical strategy under MAR assumption. The treatment effect was to be attributed to the subject's initially randomised treatment using the population level summary assuming subjects treated with ND0612 ceased to have additional benefit over control following the use of additional/new PD treatment (ICE1) or following attributable early treatment discontinuation (ICE2). Treatment effect for subjects with non-attributable early discontinuations (ICE3) was assumed as if those subjects did not discontinue and had full adherence to treatment.

Data for primary and secondary endpoints following the occurrence of ICEs were censored. MI techniques were applied for continuous endpoints on the ITT analysis sets using the pattern mixture model (PMM) method. This method is based on a missingness pattern having a monotone structure, i.e., if among the observations over time, one data value is missing, all other values after this missing value will also be missing.

Efficacy analyses for the primary and continuous key and other secondary endpoints were performed for the ITT set (all randomly assigned participants) using the above MI techniques. A modified intention-to-treat (mITT) set was used in the analysis of PGI-C and CGI-I scoring, which included all randomized participants who had valid ON/OFF diary assessments prior to the start of OL ND0612 treatment, at randomization, and ≥1 post-randomization timepoint. Safety analyses were performed for the safety set (all randomised and treated participants). following the implementation of mi techniques with the PMM method, under the MAR assumption, the complete data for primary, key, and other secondary continuous endpoints were analysed using analysis of covariance adjusting for the response variable at run-in (prior to ND0612 intake) and baseline as well as region.

Several pre-planned supportive and sensitivity analyses to support the primary analysis were also performed. The main supportive analysis to address the secondary estimand used control group-based MI techniques with the PMM method under the assumption of MNAR.

The analysis of proportions of participants (e.g., improvement on PGIC and CGI-I scores or responder analysis) were analysed employing the generalised linear mixed models (GLIMMIX) procedure for binomial data with logit link function. The model included the treatment arm, region, visit and the interaction between the treatment arm and visit as fixed factors and the treatment odds ratio at week

12 was estimated using a contrast.

To maintain the overall familywise Type I error rate of 5%, a gatekeeping approach was used, and a hierarchical order of the endpoints was pre-defined. Each endpoint was assessed for statistical significance only if the preceding endpoint was found statistically significant.

In study ND0612-317, primary and key secondary endpoints were also re-analysed adding non-valid diaries or diaries with missing recording entries.

Statistical methods for estimation and sensitivity analysis on primary estimand(s)

The statistical analysis was performed using SAS® Version 9.4.

The data was summarised using either descriptive statistics (number of non-missing observations, mean, median, SD, standard error of the mean, minimum and maximum) for continuous data or frequency counts and percentages for categorical data. For visit-specific data, the number of subjects with non-missing observations at the visit in question was used as the denominator for percent calculations. Unknown, Not Done, Not Applicable, and other classifications of missing data were not considered.

Unless otherwise specified, all statistical tests were done as 2-sided at the 5% significance level. Point estimates of treatment differences will be accompanied with 2-sided 95% confidence intervals where applicable.

Primary Estimand

The primary endpoint is the change from baseline to end of the DBDD maintenance period (DB W12) in the mean duration (hours) of ON time without troublesome dyskinesia adjusted to the subject's waking hours and normalised to 16 waking hours on the three consecutive days before the visit.

The primary estimand postulates that the treatment effect will be attributed to the initially treatment as directed implying that observations under additional/new anti-PD treatment if applicable, will not be used and will be set as unascertainable for the purpose of this estimand. These data, as well as data collected following early treatment discontinuation for any reason (retrieved data), will not be used and will be imputed under MAR instead. That is, the imputation will be under the assumption that additional/new PD treatment had not been available and as if subjects who discontinued randomised treatment from all reasons (attributable or non-attributable to randomised treatment) had full adherence to treatment.

Secondary and tertiary objectives

Key secondary endpoint

The change from Baseline to the end of the DBDD period in mean daily OFF time.

Other secondary endpoints

Other secondary endpoints included patient-reported outcomes and physician assessments commonly used in studies in PD subjects with motor fluctuations. They were tested in the following hierarchical order for type I error control:

1. Change from Baseline to the end of the DBDD Period in Movement Disorder Society-sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II (Motor aspects of experiences of daily living [M-EDL]) sum score
2. Proportion of subjects with improvement (very much improved, much improved, minimally improved) on Patient Global Impression of Change (PGIC) scores from the start of the ND0612 OL Conversion Period to the end of the DBDD Period

3. Proportion of subjects with improvement (very much improved, much improved, minimally improved) on Clinical Global Impression of Improvement (CGI-I) score from the start of the ND0612 OL Conversion Period to the end of the DBDD Period
4. Change from baseline to the end of the DBDD Period in MDS-UPDRS Part III (Motor Examination) sum score measured in the "OFF" state or approximately 15 minutes before the next intake of oral study medication
5. Change from baseline to the end of the DBDD Period in mean duration (hours) of "ON" time without dyskinesia
6. Responders: proportion of subjects with a reduction of ≥ 50% in "OFF" time from the start of the ND0612 OL Conversion Period to end of the DBDD Period
7. Change from baseline to the end of the DBDD Period in 39-Item Parkinson's Disease Quality of Life Questionnaire (PDQ-39) summary index
8. Change from baseline to the end of the DBDD Period in Parkinson's Disease Sleep Scale (PDSS)-2 score.

Exploratory Endpoints

The exploratory efficacy endpoints were to be evaluated without any pre-defined hierarchical order and p-values will be nominally displayed.

- The primary, key secondary, and other secondary endpoints (excluding CGI-I, PGIC, and responders' analysis) analysed from 2 additional time points:

  (1) Enrolment visit – IR-LD/CD Adjustment Period start (V2/IR D1)

  (2) ND0612 Conversion Period start (V7/ND D1)

The following exploratory endpoints were to be analysed from baseline (Randomisation visit – DBDD Maintenance Period start [V13]):

- Changes from baseline to each of the DBDD maintenance period visits in NMSS score.
- Changes from baseline to each of the DBDD maintenance period visits in EQ-5D-5L questionnaire health-state index score.
- Changes from baseline to each of the DBDD maintenance period visits in EQ visual analog scale (EQ-VAS) score.
- Changes from baseline to each of the DBDD maintenance period visits in mean percentage of OFF time during the first 3 hours since the subject is awake after 06:00 (6 a.m.), based on subject's "ON/OFF" diary assessments on the three consecutive days before the visit.
- Changes from Baseline to each of the DBDD maintenance period visits in mean number of sleep hours using subject completed ON/OFF diary assessment on the 3 consecutive days before the visit.
- Changes from baseline to each of the DBDD maintenance period visits in number (frequency) and amount (in mg) of daily oral LD doses during the DBDD.

Maintenance Period

The following exploratory endpoints were analysed from the start of the ND0612 conversion period (V7/ND D1):

- Changes to each of the DBDD maintenance period visits in mean duration of ON time with troublesome dyskinesia adjusted to the subject's waking hours and normalized to 16 waking hours in a subset of subjects who had more than 1 hour of troublesome dyskinesia at the start of the ND0612 conversion period (V7/ND D1).
- Changes to each of the DBDD maintenance period visits in total daily oral LD dose or LD equivalent.
- Proportion of subjects with a reduction of ≥ 80% in mean OFF time from the start of the ND0612 Conversion Period (V7/ND D1) to end of the DBDD Maintenance Period (V19/DB W12).

Estimands for the secondary and tertiary objectives

Key secondary estimands: similar approach to primary endpoint.

The secondary estimand construction elements to be tested as supportive analysis for this study were:

- The treatment of interest will be the initially randomized treatments as actually taken – optimised ND0612 + oral IR-LD/CD to be compared with optimised oral IR-LD/CD alone during the DBDD Period.
- Population: as specified for the primary estimand.
- Variable: as specified for the primary estimand.
- ICEs: as specified for the primary estimand.
- Population-level summary: as specified for the primary estimand.

Statistical methods for estimation and sensitivity analysis on the secondary estimand

Main Supportive Analysis

The secondary estimand postulated that the treatment effect will be attributed to the initially randomised treatment as actually taken implying that observations under additional/new anti-PD treatment, if applicable, will not be used and be set as unascertainable for the purpose of this estimand. These data as well as data for subjects following attributable (treatment related) early treatment discontinuation (retrieved data) will not be used and will be imputed under MAR assumption for the control group and Missing Not at Random (MNAR) assumption for ND0612 group. That is, the imputation will be under the assumption that subjects treated with ND0612 ceased to have additional benefit over the control following these events. Also, in this strategy, in order to attribute the treatment effect to the randomised treatment, data for subjects following non-attributable (not related to treatment) early treatment discontinuation will have missing data post this event and these data will be imputed under MAR assumption. The main supportive analysis is associated with the secondary estimand and will address ICE1 and ICE2 using control-group based imputation under MNAR assumption. Data to be used for the main supportive analysis will use the same rules specified for the primary estimator.

Step 1 and Step 2 from the primary estimator will be repeated.

In addition, the following step were to be executed:

Step 3: the imputed datasets generated with the approach described in Step 2 do contain only non-missing values following imputation under the MAR assumption to handle nonattributable discontinuations not related to treatment (ICE3). In order to handle ICE1 or ICE2 under the MNAR assumption with Control based imputation, it will be necessary to recreate the missing data again after ICE1 and ICE2 occurrences only for those cases in the ND0612 group that were classified as having either ICE1 or ICE2 or both.

Step 4: MI with MNAR assumption. MI will be performed with the assumption that the data are not MAR. Control group-based imputation will be used, i.e., the trajectories of the subjects in the ND0612 group are assumed to follow those of similar subjects who completed DBW12 in the IR-LD/CD group after ICE1 or ICE2 occurrence. The missing data will be imputed sequentially for each visit (first DB Week 1, followed by DB Weeks 4, 8, and 12). Only the data from the control group will be used for the imputation. The MNAR statement of the following type will be used to generate the imputation: MNAR model ('DBW1' 'DBW4' 'DBW8' 'DBW12' / MODELOBS = (TRTP= 'IRLDCD')).

The imputed datasets generated with the approach described in Step 4 do contain only non-missing values following imputation under MAR assumption for ICE3 and MNAR assumption for ICE2 and ICE1. The ITT analysis set will be used for this analysis. The same analysis model employing SAS GLM and MIANALYZE procedures, as described for the primary analysis, will be used for this main supportive analysis.

Additional Supportive Analysis

The following additional supportive analyses to be performed for the primary efficacy analysis:

- Repeat the primary analysis with mixed model repeated measures (MMRM) methodology using the mITT analysis set. Data for analysis will use the rules specified for the primary analysis. The MMRM estimator will include change from baseline in GOOD ON as response data (observed cases only) from weeks DBW1, DBW4, DBW8, and DBW12. The model will include the following fixed factors (Further details will be provided in the SAP):
    - GOOD ON prior ND0612 conversion ('IRW6'/V7)
    - GOOD ON at Baseline (DBD1/V13)
    - Treatment group as class variable with 2 levels (ND0612, IR-LD/CD)
    - Scheduled visit as class variable
    - The interaction between treatment group and visit
    - The interactions of GOOD ON at Baseline and prior ND0612 conversion by visit
    - The variable used to stratify the randomization (region) as class variable
- Repeat the primary and main supportive analyses while using retrieved 3 data following all ICE occurrences
- Analysis using the subset of subjects with complete data (PP Set).

Sensitivity for the Primary Analysis

- Repeat the main supportive analysis with Tipping Point under MNAR assumption using the ITT analysis sets.
- Repeat the primary analysis if the proportion of non-valid ON/OFF diary is >2% of all completed half-hour periods in the total data during the DBDD period. In this analysis, the worst case will be taken out of the multiple entries that had been checked. Further details will be provided in the SAP.
- Repeat the primary analysis if the proportion of valid "ON/OFF" diary data completed under one-time rescue medication is >2% of all completed half-hour periods in the total study data during the DBDD period. In this analysis, "ON/OFF" diaries completed under one-time rescue medication will be excluded from the analysis.
- Effect of study center: The effect of the study center will be investigated in exploratory graphical manner. The mean "GOOD ON" time per treatment group as well as the differences between the

treatment groups will be plotted for all centers (using point estimate and 95% confidence interval). The centers that have less than 2 subjects in any of the treatment groups in the ITT population will be pooled with other centers. Details will be provided in the SAP.

Secondary Analyses

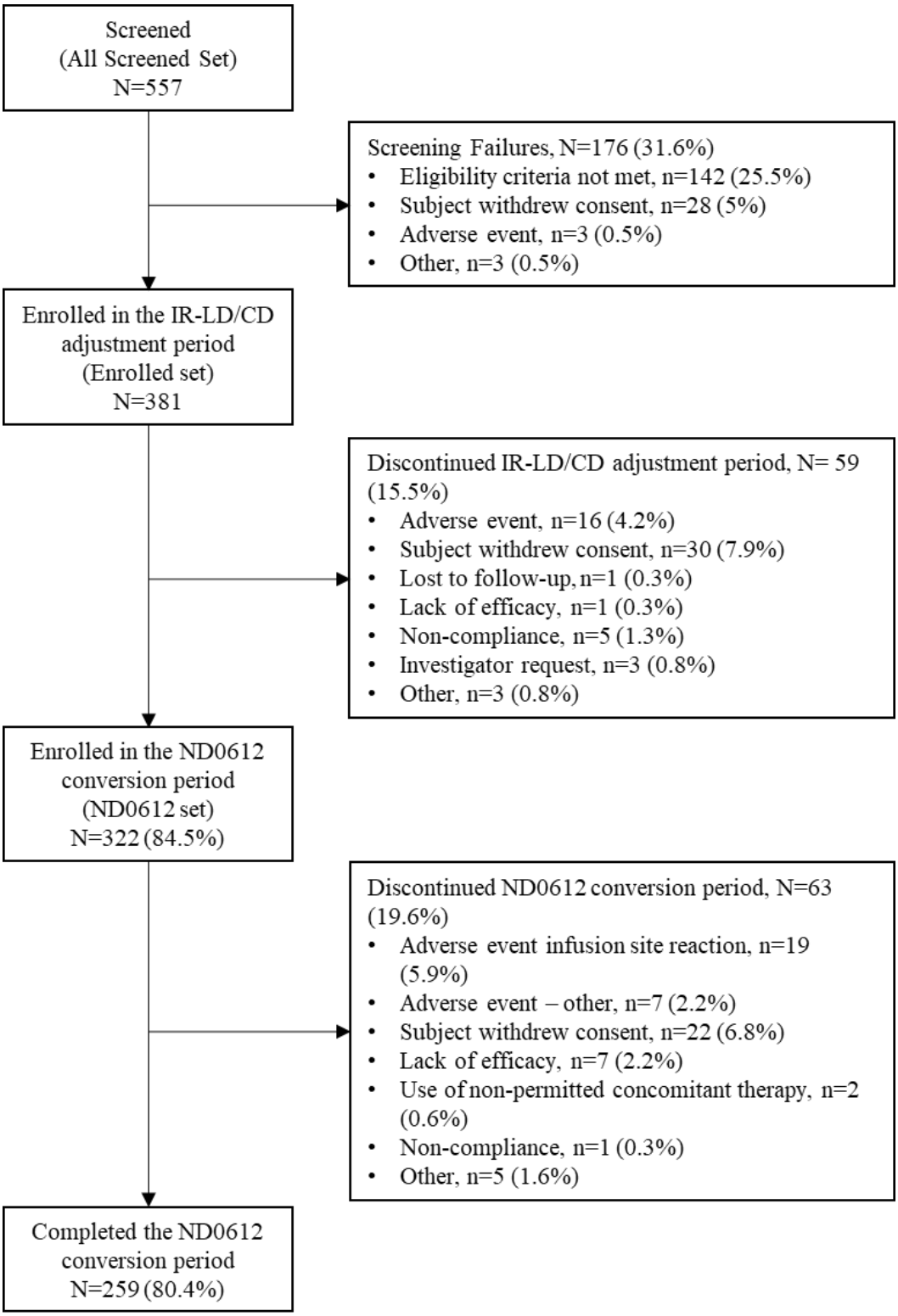
All analyses of the key and other secondary endpoints will be performed using the ITT and mITT analysis sets for continuous and categorical endpoints, respectively. The analyses will be performed sequentially according to the order specified in Section 11.6.2 while each secondary endpoint will be inferentially interpreted only in case the preceding endpoint will have a p-value less or equal to 0.05.

Results

Participant flow and numbers analysed

Patients were enrolled between 2019 and 2022: the first subject was enrolled on 30 September 2019. The last subject completed the core period on 01 November 2022.

Figure 11. Participant flow: Subject Disposition During the Screening, Open-label IR-LD/CD Adjustment, and Open-label ND0612 Conversion Periods



IR-LD/CD: Immediate release levodopa/carbidopa; N or n: Number of subjects; OL: Open-label.
Source: ND0612-317 CSR, Table 14.1.1

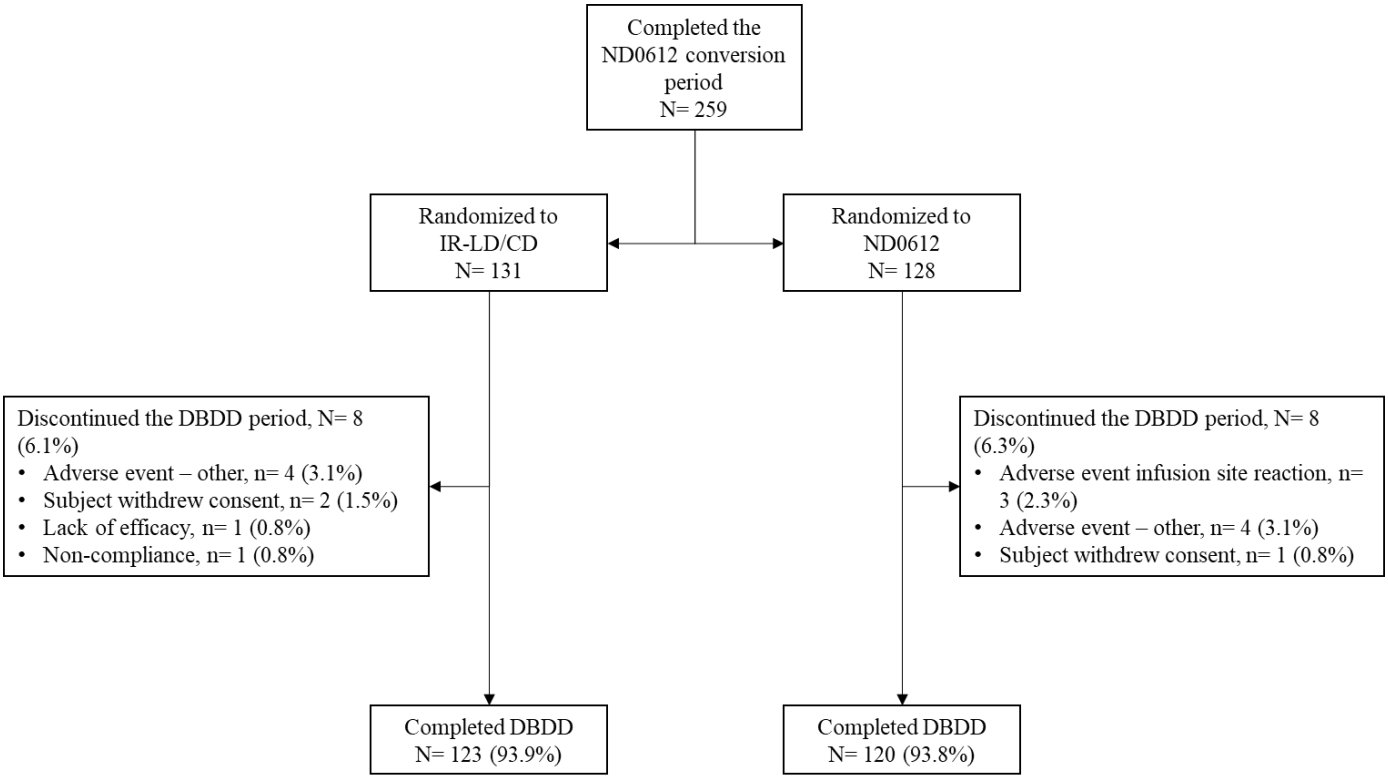
The two reasons for screening failure "Eligibility criteria not met" (141 subjects) and "Not approved by EAC" (1 subject) were combined under "Eligibility criteria not met" (142 subjects).

A total of 322 subjects entered the ND0612 OL conversion period. During this period, 63 (19.6%) subjects discontinued, the most common reasons for discontinuation being adverse events (19 [5.9%] due to infusion site reactions [ISR] and 7 [2.2%] due to other adverse events) and withdrawal of consent (22 [6.8%] subjects). A total of 259 subjects entered the DBDD period of the study. Of them, 128 were randomised to the ND0612 arm and 131 were randomised to the IR-LD/CD arm (intention-to treat [ITT] set).

The population enrolled to the DBDD period was filtered through the conversion to the immediate release (IR) levodopa and later to the SC infusion, reducing the 381 patients to 259, about 68% of those entering the study.

Discontinuation rate during the 12-week period was 6.3% and 6.1% in the ND0612 and IR-LD/CD arms, respectively (eight subjects each) as detailed in the Figure below. The main reason for treatment discontinuation was adverse events: seven (5.5%) subjects in the ND0612 arm (of which 3 [2.3%] due to ISRs) and four (3.1%) subjects in the IR-LD/CD arm.

Figure 12. Subject Disposition During the DBDD Period



DBDD: Double-blind, double-dummy; IR-LD/CD: Immediate release levodopa/carbidopa; N or n: Number of subjects.

The applicant discussed accordingly to what extent the results from these 2/3 refined patients (N = 259) could be extrapolated to the entire population.

ND0612-317 study design allowed for both treatment regimens (continuous SC ND0612 DP infusion in comparison to oral IR LD/CD in subjects with PD experiencing motor fluctuations) to be optimised for each participant before randomisation. The duration of each run-in period was 4–6 weeks, to allow for proper optimisation (2–4 weeks) and stabilisation (2 weeks).

Randomised withdrawal strategies have been widely used, including in PD trials, to reduce variability and placebo response (Hauser et al., 2023; Hauser et al., 2013; Kopsky et al., 2022; FDA CDER & CBER,

2019). As expected, and as seen in other studies, most discontinuations occurred in the initial run-in periods (15.5% discontinued during the switch to IR-LD/CD; of the 322 subjects starting ND0612, 19.6% discontinued during the Conversion Period, and only 2.5% during double-blind double-dummy (DBDD) ND0612 treatment [ND0612-317 CSR, Table 14.1.1]), when subjects got familiarised to study requirements and adjustment to the new treatment (Hauser et al., 2023; Hauser et al., 2013; Soileau et al., 2022). Of note, the run-ins required procedures that would not occur in clinical practice. In real-life, conversion to ND0612 will be simpler and shorter (no IR-LD/CD adjustment step needed), more precise (in the study, the oral LD dose adjustment could only be done with 100/25 mg IR-LD/CD encapsulated tablets), and with no need to discontinue COMT inhibitors, which can result in more patients being able to continue treatment.

Importantly, there were no clinically relevant differences in the demographic and PD characteristics between the total enrolled (n=381), ND0612 converted (n=322) and randomised populations (n=259), as outlined in the Table below, including the demographic and PD baseline characteristics of both the totally enrolled and the finally randomised population. On this premise, it is accepted that the pivotal study results can be extrapolated to the enrolled population.

Table 13. Demographics and Parkinson's Disease Characteristics Measured at Enrollment (Start of IR-LD/CD Open-label Adjustment Period) for the Enrolled, Converted to ND0612 and ITT Sets

Variable Statistics	**Enrolled set (Enrolled the IR-LD/CD OL Adjustment Period) (N=381)**	**Converted to ND0612 (ND0612 set) (N=322)**	**Randomized (ITT set) (N=259)**
Age (years)			
n	381	322	259
Mean	64.3	64.1	63.5
SD	8.84	8.85	8.99
Min, Max	35, 88	35, 84	35, 84
Age category, n (%)			
<65 years	192 (50.4)	165 (51.2)	143 (55.2)
≥65 - <75 years	155 (40.7)	131 (40.7)	97 (37.5)
≥75 - <85 years	33 (8.7)	26 (8.1)	19 (7.3)
≥85 years	1 (0.3)	0	0
Gender, n (%)			
Female	146 (38.3)	123 (38.2)	94 (36.3)
Male	235 (61.7)	199 (61.8)	165 (63.7)
Race, n (%)			
White	354 (92.9)	300 (93.2)	243 (93.8)
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5 (1.3)	5 (1.6)	5 (1.9)
Asian	14 (3.7)	12 (3.7)	9 (3.5)
American Indian or Alaska Native	0	0	0
Not Reported	8 (2.1)	5 (1.6)	2 (0.8)
Unknown	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	39 (10.2)	30 (9.3)	21 (8.1)
Not Hispanic or Latino	328 (86.1)	279 (86.6)	229 (88.4)
Not Reported	14 (3.7)	13 (4.0)	9 (3.5)
Region, n (%)			
United States (US)	124 (32.5)	99 (30.7)	82 (31.7)
Eastern Europe (EE)	84 (22.0)	80 (24.8)	66 (25.5)
Western Europe + Israel (WEI)	173 (45.4)	143 (44.4)	111 (42.9)
BMI at Screening (kg/m^2)			
n	380	322	259

Variable Statistics	Enrolled set (Enrolled the IR-LD/CD OL Adjustment Period) (N=381)	Converted to ND0612 (ND0612 set) (N=322)	Randomized (ITT set) (N=259)
Mean	26	26.2	26.4
SD	4.31	4.42	4.45
SE	0.22	0.25	0.28
Median	25.3	25.4	25.7
Min, Max	16, 40	17, 40	17, 40
BMI category, n (%)			
<20	18 (4.7)	15 (4.7)	9 (3.5)
≥20 - <30	291 (76.4)	240 (74.5)	193 (74.5)
≥30	71 (18.6)	67 (20.8)	57 (22.0)
Time since diagnosis of PD (years)			
n	381	322	259
Mean	9.73	9.71	9.61
SD	4.712	4.784	4.318
Min, Max	0.7, 34.7	0.7, 34.7	2.7, 25.8
Time since onset of motor fluctuation (years)			
n	381	322	259
Mean	4.62	4.69	4.49
SD	3.698	3.869	3.307
Min, Max	0.1, 28.7	0.1, 28.7	0.1, 20.8
Time since onset of dyskinesia (years)			
n	306	257	209
Mean	3.88	3.87	3.52
SD	3.737	3.822	3.116
Min, Max	0.0, 26.4	0.0, 26.4	0.0, 20.8
V2/IRD1 normalized "GOOD ON" time (h)			
n	379	321	259
Mean	9.35	9.4	9.41
SD	1.957	1.924	1.819
Min, Max	2.1, 13.5	2.1, 13.5	2.1, 13.5
V2/IRD1 normalized "OFF" time (h)			
n	379	321	259
Mean	6.02	5.98	6.07
SD	1.798	1.771	1.742
Min, Max	2.3, 11.3	2.3, 11.3	2.3, 11.3

Variable Statistics	Enrolled set (Enrolled the IR-LD/CD OL Adjustment Period) (N=381)	Converted to ND0612 (ND0612 set) (N=322)	Randomized (ITT set) (N=259)
V2/IRD1 normalized "ON" time without dyskinesia (h)			
n	379	321	259
Mean	6.94	7.01	7.06
SD	3.171	3.191	3.099
Min, Max	0.0, 13.5	0.0, 13.5	0.0, 13.5
Cognitive status: Mini–Mental State Examination (MMSE) total score, n (%)			
24	5 (1.3)	4 (1.2)	2 (0.8)
25	16 (4.2)	12 (3.7)	9 (3.5)
26	19 (5.0)	17 (5.3)	11 (4.2)
27	40 (10.5)	33 (10.2)	31 (12.0)
28	66 (17.3)	56 (17.4)	47 (18.1)
29	100 (26.2)	83 (25.8)	66 (25.5)
30	135 (35.4)	117 (36.3)	93 (35.9)
Modified Hoehn & Yahr scale stage, n (%)			
0	0	0	0
1	6 (1.6)	5 (1.6)	4 (1.5)
1.5	8 (2.1)	6 (1.9)	5 (1.9)
2	192 (50.4)	157 (48.8)	131 (50.6)
2.5	78 (20.5)	69 (21.4)	55 (21.2)
3	97 (25.5)	85 (26.4)	64 (24.7)
MDS-UPDRS PART II scores at Screening			
N	248	211	170
Mean	15.79	15.69	15.69
SD	6.549	6.478	6.526
Min, Max	1.0, 43.0	1.0, 43.0	1.0, 43.0

BMI: Body mass index; IRD1: Immediate release LD/CD OL Adjustment Period Day 1; max: Maximum; MDS-UPDRS: Movement disorder Society-Unified Parkinson's Disease Rating Scale; min: Minimum; N: Number of subjects; n: number of subjects available for each parameter; PD: Parkinson's disease; SD: Standard deviation.
Source: Table 14.1.3.4

Deviations from study plan

Changes to the initial global study protocol (version 1.0 dated 02May2019) included: a temporary addendum due to the COVID-19 pandemic (April 2020); two global amendments: version 2.0/2.1 (June 2020) and version 3.0 (February 2021); and a US-specific amendment (October 2021).

None of the amendments affected the characteristics of the study population, the primary, key secondary, and other secondary endpoints, or the design of the study.

Baseline data

Datasets Analysed

The ITT set consisted of 259 subjects, of which 128 (49.4%) were randomised to the ND0612 arm and 131 (50.6%) to the IR-LD/CD arm. The ITT was the main set for efficacy analyses. The modified intention-to-treat (mITT) set consisted of 253 subjects, as six subjects did not present valid diaries for analysis (n=1 in the ND0612 arm and n=5 in the IR-LD/CD arm). The per-protocol (PP) set excluded 66 subjects (25.5% of ITT) with a similar distribution of major protocol deviations between the ND0612 (34 subjects, 26.6% of ITT) and the IR-LD/CD (32 subjects, 24.4% of ITT) arms.

Enrolment Characteristics for the Randomised Population

Of the overall ITT population, 63.7% of the subjects were male and 93.8% were white. Mean age was 63.5 years, and 55.2% of subjects were below 65 years of age at study entry. The median body mass index (BMI) was 25.7 kg/m2 and most subjects (74.5%) had a BMI between ≥20 and <30 kg/m2. No relevant differences between the treatment arms were observed for demographic characteristics (as detailed in the Table below).

Table 14. ND0612-317: Demographic characteristics by treatment arm and overall (ITT Set)

Variable Statistics	**Oral IR-LD/CD (N=131)**	**ND0612 (N=128)**	**Overall (N=259)**
Age at Screening (years)			
N	131	128	259
Mean	63.53	63.53	63.53
SD	8.534	9.472	8.992
Min, Max	38.2, 83.0	34.8, 83.7	34.8, 83.7
Age category, n (%)			
< 65 years	75 (57.3)	68 (53.1)	143 (55.2)
≥ 65 - < 75 years	48 (36.6)	49 (38.3)	97 (37.5)
≥ 75 - < 85 years	8 (6.1)	11 (8.6)	19 (7.3)
≥ 85 years	0	0	0
Gender, n (%)			
Female	51 (38.9)	43 (33.6)	94 (36.3)
Male	80 (61.1)	85 (66.4)	165 (63.7)

Variable Statistics	Oral IR-LD/CD (N=131)	ND0612 (N=128)	Overall (N=259)
Race, n (%)			
White	122 (93.1)	121 (94.5)	243 (93.8)
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4 (3.1)	1 (0.8)	5 (1.9)
Asian	4 (3.1)	5 (3.9)	9 (3.5)
American Indian or Alaska Native	0	0	0
Not Reported	1 (0.8)	1 (0.8)	2 (0.8)
Unknown	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	8 (6.1)	13 (10.2)	21 (8.1)
Not Hispanic or Latino	117 (89.3)	112 (87.5)	229 (88.4)
Not Reported	6 (4.6)	3 (2.3)	9 (3.5)
Region, n (%)			
United States of America (USA)	42 (32.1)	40 (31.3)	82 (31.7)
Eastern Europe (EE)	33 (25.2)	33 (25.8)	66 (25.5)
Western Europe + Israel (WEI)	56 (42.7)	55 (43.0)	111 (42.9)
BMI at Screening (kg/m^2)			
N	131	128	259
Mean	26.27	26.60	26.43
SD	4.561	4.344	4.449
Median	25.66	25.80	25.73
Min, Max	17.8, 39.9	17.2, 37.0	17.2, 39.9
BMI category, n (%)			
< 20	6 (4.6)	3 (2.3)	9 (3.5)
≥ 20 - < 30	99 (75.6)	94 (73.4)	193 (74.5)
≥ 30	26 (19.8)	31 (24.2)	57 (22.0)

BMI: Body mass index; IR-LD/CD: Immediate release levodopa/carbidopa; max: Maximum; min: Minimum; N or n: Number of subjects; SD: Standard deviation.

Source: ND0612-317 CSR, Table 14.1.2.1

Percentages are based on ITT set subjects with available data.

At Screening, subjects in the ITT set had a mean (SD) time since PD diagnosis of 9.6 (4.3) years, a mean (SD) time from the onset of motor fluctuations of 4.5 (3.3) years and mean (SD) time from the onset of dyskinesia of 3.5 (3.1) years. Mean (SD) duration of GOOD ON time and OFF time at enrolment (start of IR-LD/CD OL Adjustment Period) were 9.4 (1.8) h and 6.1 (1.7) h, respectively.

Overall, no major differences across treatment arms were observed.

Table 15. ND0612-317 - Parkinson's Disease history: time since diagnosis, time since onset of motor fluctuations, time since onset of dyskinesia and diary variables by treatment arm and overall (ITT Set)

Variable	Oral IR-LD/CD (N=131)	ND0612 (N=128)	Overall (N=259)
Time since diagnosis of PD (at Screening) (years)			
N	131	128	259
Mean	9.91	9.31	9.61
SD	4.748	3.823	4.318
Min, Max	2.9, 25.8	2.7, 23.0	2.7, 25.8
Time since onset of motor fluctuations (at Screening) (years)			
N	131	128	259
Mean	4.85	4.11	4.49
SD	3.666	2.862	3.307
Min, Max	0.4, 20.8	0.1, 16.0	0.1, 20.8
Time since onset of dyskinesia (at Screening) (years)			
N	108	101	209
Mean	3.62	3.42	3.52
SD	3.502	2.655	3.116
Min, Max	0.0, 20.8	0.0, 16.0	0.0, 20.8
Normalised GOOD ON time (h) at Enrolment (V2/IRD1)			
N	131	128	259
Mean	9.39	9.42	9.41
SD	1.939	1.699	1.821
Min, Max	2.1, 13.5	4.4, 13.2	2.1, 13.5
Normalised OFF time (h) at Enrolment (V2/IRD1)			
N	131	128	259
Mean	6.06	6.09	6.07
SD	1.876	1.600	1.742

Variable	Oral IR-LD/CD (N=131)	ND0612 (N=128)	Overall (N=259)
Min, Max	2.3, 11.3	2.8, 9.8	2.3, 11.3
Normalised ON time without dyskinesia (h) at Enrolment (V2/IRD1)			
N	131	128	259
Mean	7.14	6.97	7.05
SD	3.193	3.008	3.098
Min, Max	0.0, 13.5	0.0, 12.8	0.0, 13.5
Normalised ON time with non-troublesome dyskinesia (h) at Enrolment (V2/IRD1)			
N	131	128	259
Mean	2.26	2.45	2.35
SD	2.492	2.593	2.539
Min, Max	0.0, 10.4	0.0, 11.2	0.0, 11.2
Normalised ON time with troublesome dyskinesia (h) at Enrolment (V2/IRD1)			
N	131	128	259
Mean	0.55	0.5	0.52
SD	1.024	1.095	1.058
Min, Max	0.0, 4.5	0.0, 5.7	0.0, 5.7

h: Hours; IR-LD/CD: Immediate release levodopa/carbidopa; max: Maximum; min: Minimum; N or n: Number of subjects; PD: Parkinson's disease; SD: Standard deviation; V: Visit.

Table 16. ND0612-317 - Other disease characteristics: cognitive status, stage, rating, non-motor symptoms, quality of life and sleep by treatment arm and overall (ITT Set)

	Oral IR-LD/CD (N=131)	ND0612 (N=128)	Overall (N=259)
Cognitive status: MMSE total score at Screening, n (%)			
24	2 (1.5)	0	2 (0.8)
25	4 (3.1)	5 (3.9)	9 (3.5)
26	5 (3.8)	6 (4.7)	11 (4.2)
27	15 (11.5)	16 (12.5)	31 (12.0)
28	20 (15.3)	27 (21.1)	47 (18.1)
29	34 (26.0)	32 (25.0)	66 (25.5)

	Oral IR-LD/CD (N=131)	ND0612 (N=128)	Overall (N=259)
30	51 (38.9)	42 (32.8)	93 (35.9)
Modified Hoehn & Yahr scale stage at Screening, n (%)			
0	0	0	0
1	3 (2.3)	1 (0.8)	4 (1.5)
1.5	4 (3.1)	1 (0.8)	5 (1.9)
2	71 (54.2)	60 (46.9)	131 (50.6)
2.5	24 (18.3)	31 (24.2)	55 (21.2)
3	29 (22.1)	35 (27.3)	64 (24.7)
MDS-UPDRS Part II scores at Screening[1]			
N	82	88	170
Mean	15.28	16.08	15.69
SD	6.096	6.915	6.526
Min, Max	2.0, 30.0	1.0, 43.0	1.0, 43.0
MDS-UPDRS Part III scores at Screening[1]			
N	82	88	170
Mean	44.22	46.45	45.38
SD	13.035	14.648	13.897
Min, Max	11.0, 80.0	20.0, 99.0	11.0, 99.0
PDQ-39 summary index at Enrolment (V2/IRD1)			
N	131	128	259
Mean	29.13	29.09	29.11
SD	13.394	13.507	13.424
Min, Max	3.1, 61.0	0.8, 65.1	0.8, 65.1
NMSS total score at Enrolment (V2/IRD1) – mITT Set			
N	126	127	253
Mean	52.36	51.51	51.93
SD	34.774	31.591	33.151
Min, Max	3.0, 192.0	3.0, 124.0	3.0, 192.0
PDSS-2 total score at Enrolment (V2/IRD1)			
N	130	127	257

	Oral IR-LD/CD (N=131)	ND0612 (N=128)	Overall (N=259)
Mean	19.78	18.69	19.24
SD	9.983	9.088	9.548
Min, Max	2.0, 46.0	1.0, 43.0	1.0, 46.0
EQ-5D-5L index score at Enrolment (V2/IRD1) – mITT Set			
N	53	66	119
Mean	0.68	0.70	0.69
SD	0.209	0.146	0.176
Min, Max	-0.1, 1.0	0.3, 1.0	-0.1, 1.0
EQ-VAS score at Enrolment (V2/IRD1) – mITT Set			
N	126	127	253
Mean	62.25	61.76	62.00
SD	17.940	17.552	17.713
Min, Max	10.0, 95.0	0.0, 95.0	0.0, 95.0

D: Day(s); EQ-5D-5L: EuroQol 5-Dimension 5-level Questionnaire; EQ-VAS: EuroQol-Visual Analogue Scale; IR-LD/CD: Immediate release levodopa/carbidopa; IR: IR-LD/CD Adjustment period; max: Maximum; MDS-UPDRS: Movement Disorder Society-sponsored Revision of the Unified Parkinson's Disease Rating Scale; min: Minimum; MMSE: Mini-Mental State Examination; N or n: Number of subjects; NMSS: Non-motor Symptoms Scale; PDQ-39: 39-Item Parkinson's Disease Quality of Life Questionnaire; PDSS: Parkinson's Disease Sleep Scale; V: Visit.

[1]MDS-UPDRS scores at Screening: data are available for only 170 subjects from the ITT set as this assessment was only added at Screening in the first global protocol amendment.

Baseline is defined as the last available, valid, non-missing assessment before or at visit V13. This definition does not exceed 2 weeks prior to V13/DBDD1 (Randomisation) visit. Percentages are based on ITT set subjects with available data.

No major differences were observed in demographic and disease characteristics at time of enrolment between the enrolled, ND0612 and ITT sets. No relevant differences between arms were observed through the adjustment and conversion periods. Importantly, at baseline (i.e., end of ND0612 OL conversion period, prior to randomization) the two arms were generally balanced for ON and OFF diary variables, MDS-UPDRS Part II, MDS-UPDRS Part III, PDQ-39, NMSS, PDSS-2, Epworth Sleepiness Scale (ESS), EQ-5D-5L and EQ-VAS.

ND0612 and Oral Levodopa Doses

Daily oral LD and ND0612 doses at enrolment (start of IR-LD/CD OL adjustment period), end of the IR-LD/CD OL adjustment period and end of the ND0612 OL conversion period are presented in the Table below.

All subjects were receiving LD at enrolment, with LD equivalent daily dose coming from LD and COMT inhibitors (LEDDLD + COMTi) ranging from 380 mg to 3325 mg per day. Overall, 248 (95.8%), 121 (46.7%), and 12 (4.6%) subjects were receiving IR, controlled release (CR) or extended release (ER) formulations, respectively, with no meaningful differences between treatment arms.

Anti-PD medications other than LD were taken by 223 (86.1%) subjects overall, with also no meaningful differences between treatment arms. The most common of these medications at Enrolment were dopamine agonists (164 [63.3%] subjects), MAO-B inhibitors (123 [47.5%] subjects), COMT inhibitors (91 [35.1%] subjects) and amantadine (90 [34.7%] subjects). Treatment arms were balanced with no differences of more than 10% for any of the concomitant PD medications, except for amantadine which was used by 28.9% of the ND0612 arm subjects compared to 40.5% of the IR-LD/CD treated subjects.

At the end of the ND0612 OL Conversion Period, overall (all subjects), the mean total daily LD dose was 1201 mg (700 mg from ND0612 + 501 mg from oral IR-LD/CD). The mean daily LD dose was approximately 120 mg higher than at the end of the IR-LD/CD OL Adjustment Period.

Upon randomization, the mean total daily LD doses were 1237 mg (compared to 1230 mg at the end of the ND0612 OL Conversion Period) for the ND0612 arm and 1065 mg (compared to 1067 mg at the end of the IR-LD/CD OL Adjustment Period) for the IR-LD/CD arm, as intended per study design to ensure randomization to optimized regimens.

Most subjects in both arms received a total daily LD dose ranging from 700 mg to 1500 mg during the DBDD Period (92 [71.9%] and 95 [72.5%] subjects in the ND0612 and IR-LD/CD arms, respectively). No subject in the study had a total daily LD dose at Baseline of <400 mg. The highest dose of oral IR-LD/CD in the ND0612 arm was 2100 mg/day.

Of the subjects randomised to the ND0612 arm, 19 (14.8%) received daily LD doses <720 mg and none received a daily LD dose <370 mg. The mean (SD) dose of oral LD was 534 (427) mg. The total daily LD dose (ND0612 plus IR-LD/CD) ranged from 496 mg to 2820 mg.

Table 17. ND0612-317: Oral Levodopa and ND0612 Doses at Enrolment, at the End of IR-LD/CD OL Adjustment and at the End of ND0162 OL Conversion Period by Treatment Arm and Overall (Safety Set)

	Doses at Enrollment (prior to start of the IR-LD/CD OL Adjustment Period)			Dose at the End of the IR-LD/CD OL Adjustment Period			Doses at the End of the ND0612 OL Conversion Period								
Treatment arms	**IR-LD/CD arm**	**ND0612 arm**	**Overall**	**IR-LD/CD arm**	**ND0612 arm**	**Overall**	**IR-LD/CD arm**			**ND0612 arm**			**Overall**		
Dose, mg	$LEDD_{LD+COMTi}$			IR-LD/CD			IR-LD/CD	ND0612	IR-LD/CD + ND0612	IR-LD/CD	ND0612	IR-LD/CD + ND0612	IR-LD/CD	ND0612	IR-LD/CD + ND0612
N	131	128	259	131	128	259	131	131	131	128	128	128	259	259	259
Mean	981	1079	1029	1067	1094	1080	476	697	1172	527	703	1230	501	700	1201
SD	450	487	470	408	406	406	366	68	393	423	50	442	395	60	418
Min, Max	380, 3325	400, 3188	380, 3325	400, 2900	400, 2300	400, 2900	0, 2000	342, 720	496, 2720	0, 2100	396, 720	496, 2820	0, 2100	342, 720	496, 2820
Dose, mg	LEDD (from all anti-PDs)			LEDD (from all anti-PDs)			LEDD (from all anti-PDs)			LEDD (from all anti-PDs)			LEDD (from all anti-PDs)		
N	131	128	259	131	128	259			131			128			259
Mean	1233	1330	1281	1324	1339	1331			1436			1475			1455
SD	492	565	531	482	480	480			465			523			494
Min, Max	380, 3561	400, 3488	380, 3561	500, 3136	400, 2660	400, 3136			582, 2956			496, 3160			496, 3160

Anti-PDs: Anti-PD treatments; COMTi: Catechol-O-methyltransferase inhibitor; IR-LD/CD: Immediate release levodopa/carbidopa; LD: Levodopa; LEDD: Levodopa equivalent daily dose; $LEDD_{LD+COMTi}$: LEDD coming from LD and COMTi; max: Maximum; min: Minimum; OL: Open-label; PD: Parkinson's disease; SD: Standard deviation.

Outcomes and estimation

Table 18. Summary of efficacy for trial ND0612-317

Title: A multicenter, randomized, active-controlled, double-blind, double-dummy, parallel-group clinical trial, investigating the efficacy, safety, and tolerability of continuous subcutaneous ND0612 infusion in comparison to oral IR-LD/CD in subjects with Parkinson's disease experiencing motor fluctuations (BouNDless)			
Study identifier	ND0612-317, EudraCT Number: 2018-004156-37 IND Number: 114367		
Design	Multicenter, randomized, active-controlled, double-blind, double-dummy, parallel-group study		
	Duration of Run-in 1 (adjustment of IR-LD/CD): Duration of Run-in 2 (conversion to ND0612 regimen): Duration of DBDD period: Duration of Extension phase:		4-6 weeks (open label) 4-6 weeks (open label) 12 weeks (double-blind double-dummy [DBDD]) Up to 54 months (open label)
Hypothesis	Superiority: ND0612 superior benefit over IR-LD/CD		
Treatments groups	1) Oral IR-LD/CD (Active control)		Oral IR-LD/CD, 12 weeks, N=131
	2) ND0612 (Test)		ND0612 with adjunct oral IR-LD/CD, 12 weeks, N=128
Endpoints and definitions	**Primary Endpoint** The change from Baseline (start of the DBDD Period) to the end of the DBDD Period (DB W12) in the mean daily "GOOD ON" time.	Change from Baseline to V19/DBW12 in "GOOD ON" time	The primary endpoint is the change from Baseline to the end of the DBDD Maintenance Period (DB W12) in the mean daily "ON" time without troublesome dyskinesia ("GOOD ON") adjusted to subject's waking hours and normalized to 16 waking hours, based on subject's "ON/OFF" diary assessments on 3 consecutive days before the visit. "GOOD ON" is defined as the sum of "ON" time without dyskinesia and "ON" time with non-troublesome dyskinesia.
	Key Secondary Endpoint The change from Baseline to the end of the DBDD Period (DB W12) in the mean daily "OFF" time.	Change from Baseline to V19/DBW12 in "OFF" time	The key secondary efficacy endpoint is the change from Baseline to the end of the DBDD Maintenance Period (DB W12) in the mean daily "OFF" time adjusted to subject's waking hours and normalized to 16 waking hours, based on subject's "ON/OFF" diary assessments
	Other secondary Endpoints		
	1. Change from Baseline to end of the DBDD Maintenance Period (DBW12) in MDS-UPDRS Part II (M-EDL) sum score.	Change from Baseline to V19/DBW12 in MDS-UPDRS Part II (M-EDL)	The MDS-UPDRS part II (M-EDL) sum score was calculated as the sum of the individual items 2.1-2.13. Missing individual items were not imputed. If there was at least 1 missing item, the corresponding sum score was set as missing.
	2. Proportion of subjects with improvement on Patient Global Impression of Change (PGIC) scores from start of the ND0612 Conversion Period (V7/NDD1) to the end of the DBDD Maintenance period (DBW12).	Improvement from V7/NDD1 to V19/DBW12 in PGIC scores	The PGIC scores were categorized as 'improvement' (very much improved, much, improved, minimally improved,) or 'No improvement/worsening' (no change, minimally worse, much worse, very much worse).
	3. Proportion of subjects with improvement on Clinical Global Impression – Improvement (CGI-I) scores from start of the ND0612 Conversion Period (V7/NDD1) to the end of the DBDD Maintenance period (DBW12).	Improvement from V7/NDD1 to V19/DBW12 in CGI-I scores	The CGI-I scores were categorized as Improvement' (very much improved, much improved, minimally improved) or 'No Improvement/worsening' (no change, minimally worse, much worse, very much worse).
	4. Change from Baseline to end of the DBDD Maintenance Period (DB W12) in MDS-UPDRS Part III (Motor Examination) sum score measured in the "OFF" state or approximately 15 minutes before the next encapsulated oral dose (LD/CD or placebo).	Change from Baseline to V19/DBW12 in MDS-UPDRS Part III (Motor Examination)	The MDS-UPDRS part III (Motor Examination) sum score were calculated as the sum of the individual items 3.1-3.18. Missing individual items were not imputed. If there was at least 1 missing item, the corresponding sum score was set as missing.
	5. Change from Baseline to the end of the DBDD Maintenance Period (DBW12) in the mean daily "ON" time without dyskinesia.	Change from Baseline to V19/DBW12 in	Change from Baseline to the end of the DBDD Maintenance Period (DBW12) in the mean duration (hours) of "ON" time

		"ON" time without dyskinesia	without dyskinesia (troublesome or non-troublesome) adjusted to the subject's waking hours and normalized to 16 waking hours based on subject "ON/OFF" diary assessment on the 3 consecutive days before the visit.
	6. Proportion of subjects with ≥50% reduction in "OFF" time from the start of the ND0612 Conversion Period (V7/NDD1) to the end of the DBDD Maintenance period (DBW12).	Responders of "OFF" from V7/NDD1 to V19/DBW12	The daily "OFF" time was calculated as defined for the key secondary efficacy endpoint. The percentage change was calculated as (OFF_{Week12} – OFF_{NDD1})/OFF_{NDD1} x 100%. The subjects were classified as 'Responder' if [(OFF_{Week12} –OFF_{NDD1})/OFF_{NDD1}] x 100 ≤-50% versus 'Non-Responder' if [(OFF_{Week12} – OFF_{NDD1})/OFF_{NDD1}] x 100 >-50%. Subjects with missing "OFF" time will be categorized as 'Non-Responder'
	7. Change from Baseline to the end of the DBDD Maintenance Period (DBW12) in PDQ-39 summary index.	Change from Baseline to V19/DBW12 in PDQ-39 summary index	Quality of Life in Parkinson's Disease-39 (PDQ-39) is a 39-item, self-administered questionnaire with 8 discrete dimensions. The PDQ-39 Summary Index is the sum of the dimension scores divided by the number of dimensions. The total score values range from 0 to 100%. Higher scores indicate a worse quality of life. If any item score was missing, the relevant dimension score and the summary index were set as missing.
	8. Change from Baseline to the end of the DBDD Maintenance Period (DB W12) in PDSS-2 total score.	Change from Baseline to V19/DBW12 in PDSS-2 score	Each of the 15 items is scored on a 5-point scale (from 0 indicating no symptoms to 4 indicating maximum symptoms). The total score was calculated as a sum score of the 15 items. In case a single item was missing, the total score was set as missing.

Database lock	Dec 5th, 2022			
Results and Analysis				
Analysis description	Primary Analysis (supporting primary estimand)			
Analysis population and time point description	Intent to treat (ITT) The ITT Set included all randomized subjects. The subjects were grouped according to the planned randomization group. This analysis set was used for the primary analysis as well as for the key and other secondary analyses.			
Descriptive statistics and estimate variability	Treatment group	Oral IR-LD/CD		ND0612
	Number of subjects (ITT set)	131		128
	Change from Baseline to V19/DBW12 in "GOOD ON" time	LS mean SE	-2.20 0.232	-0.48 0.234
	Change from Baseline to V19/DBW12 in "OFF" time	LS mean SE	1.90 0.215	0.50 0.217
	Change from Baseline to V19/DBW12 in MDS-UPDRS Part II (M-EDL)	LS mean SE	2.75 0.445	-0.30 0.451
	Improvement from V7/NDD1 to V19/DBW12 in PGIC scores	Adjusted proportion SE	0.31 0.052	0.70 0.053
	Improvement from V7/NDD1 to V19/DBW12 in CGI-I scores	Adjusted proportion SE	0.31 0.053	0.77 0.047
	Change from Baseline to V19/DBW12 in MDS-	LS mean SE	3.39 1.003	0.98 1.021

	UPDRS Part III (Motor Examination)			
	Change from Baseline to V19/DBW12 in "ON" time without dyskinesia	LS mean SE	-2.53 0.253	-0.41 0.256
	Responders in "OFF" from V7/NDD1 to V19/DBW12	Adjusted proportion SE	0.10 0.029	0.29 0.058
	Change from Baseline to V19/DBW12 in PDQ-39 summary index	LS mean SE	4.29 0.766	1.60 0.780
	Change from Baseline to V19/DBW12 in PDSS-2 score	LS mean SE	1.47 0.699	0.05 0.709

Effect estimate per comparison	Change from Baseline to V19/DBW12 in "GOOD ON" time	Comparison groups	ND0612 vs Oral IR-LD/CD
		LS-Means -difference between groups	1.72
		SE	0.327
		P-value used ANCOVA following Multiple imputation	<0.0001
	Change from Baseline to V19/DBW12 in "OFF" time	Comparison groups	ND0612 vs Oral IR-LD/CD
		LS-Means -difference between groups	-1.40
		SE	0.303
		P-value used ANCOVA following Multiple imputation	<0.0001
	Change from Baseline to V19/DBW12 in MDS-UPDRS Part II (M-EDL)	Comparison groups	ND0612 vs Oral IR-LD/CD
		LS-Means -difference between groups	-3.05
		SE	0.631
		P-value used ANCOVA following Multiple imputation	<0.0001
	Improvement from V7/NDD1 to V19/DBW12 in PGIC scores	Comparison groups	ND0612 vs Oral IR-LD/CD
		Odds Ratio between groups	5.31
		95% Confidence Interval	(2.67, 10.58)
		P-value using GLIMMIX Repeated measures model	<0.0001
	Improvement from V7/NDD1 to V19/DBW12 in CGI-I scores	Comparison groups	ND0612 vs Oral IR-LD/CD
		Odds Ratio between groups	7.23
		95% Confidence Interval	(3.57, 14.64)
		P-value using GLIMMIX Repeated measures model	<0.0001
	Change from Baseline to V19/DBW12 in MDS-UPDRS Part III (Motor Examination)	Comparison groups	ND0612 vs Oral IR-LD/CD
		LS-Means -difference between groups	-2.42
		SE	1.420
		P-value used ANCOVA following Multiple imputation	0.0889
	Change from Baseline to V19/DBW12 in "ON" time without dyskinesia	Comparison groups	ND0612 vs Oral IR-LD/CD
		LS-Means -difference between groups	2.12
		SE	0.357
		P-value used ANCOVA following Multiple imputation	<0.0001
	Responders in "OFF" from V7/NDD1 to V19/DBW12	Comparison groups	ND0612 vs Oral IR-LD/CD
		Odds Ratio between groups	3.63
		95% Confidence Interval	1.56, 8.44
		P-value using GLIMMIX Repeated measures model	0.0027
		Comparison groups	ND0612 vs Oral IR-LD/CD

	Change from Baseline to V19/DBW12 in PDQ-39 summary index	LS-Means -difference between groups	-2.69
		SE	1.092
		P-value used ANCOVA following Multiple imputation	0.0137
	Change from Baseline to V19/DBW12 in PDSS-2 score	Comparison groups	ND0612 vs Oral IR-LD/CD
		LS-Means -difference between groups	-1.42
		SE	0.987
		P-value used ANCOVA following Multiple imputation	0.1508
Notes	Discontinuation rate during the 12-week DBDD period was 6.3% and 6.1% in the ND0612 and IR-LD/CD arms, respectively (8 subjects each). The main reason for discontinuation was adverse events: 7 (5.5%) subjects in the ND0612 arm and 4 (3.1%) subjects in the IR-LD/CD arm.		
Analysis description	Main Supportive analysis (supporting secondary estimand)		
	Change from Baseline to V19/DBW12 in "GOOD ON" time	Comparison groups	ND0612 vs Oral IR-LD/CD
		LS-Means -difference between groups	1.66
		SE	0.329
		P-value used ANCOVA following control group Multiple imputation	<0.0001

Pre-defined and post-hoc subgroup analyses

The primary endpoint, change from baseline to the end of the DBDD Period (Week 12) in mean normalised GOOD ON time was analysed using MI under MAR in the ITT set in the following subgroups, to evaluate a potential effect of demographic and other relevant intrinsic or extrinsic factors on efficacy:

1 Non-elderly (<65 years) vs. elderly (≥65 years)

2 Male vs. female subjects

3 Race

4 Ethnicity (Hispanic or Latino vs. Not Hispanic or Latino)

5 Subjects with Baseline GOOD ON time less than or equal to the median vs. subjects with Baseline GOOD ON time above the median

6 Subjects enrolled in United States of America (USA) vs. European Union (EU) + Israel

7 Subjects enrolled in North America (NA) vs. Eastern Europe (EE) vs. Western Europe + Israel (WEI)

8 Subjects with Baseline BMI less or equal to the median vs. subjects with Baseline BMI above the median

9 Subjects with Baseline BMI <20 kg/m^2 vs. subjects with Baseline 20 ≤ BMI <30 kg/m^2 vs. subjects with Baseline BMI ≥30 kg/m^2

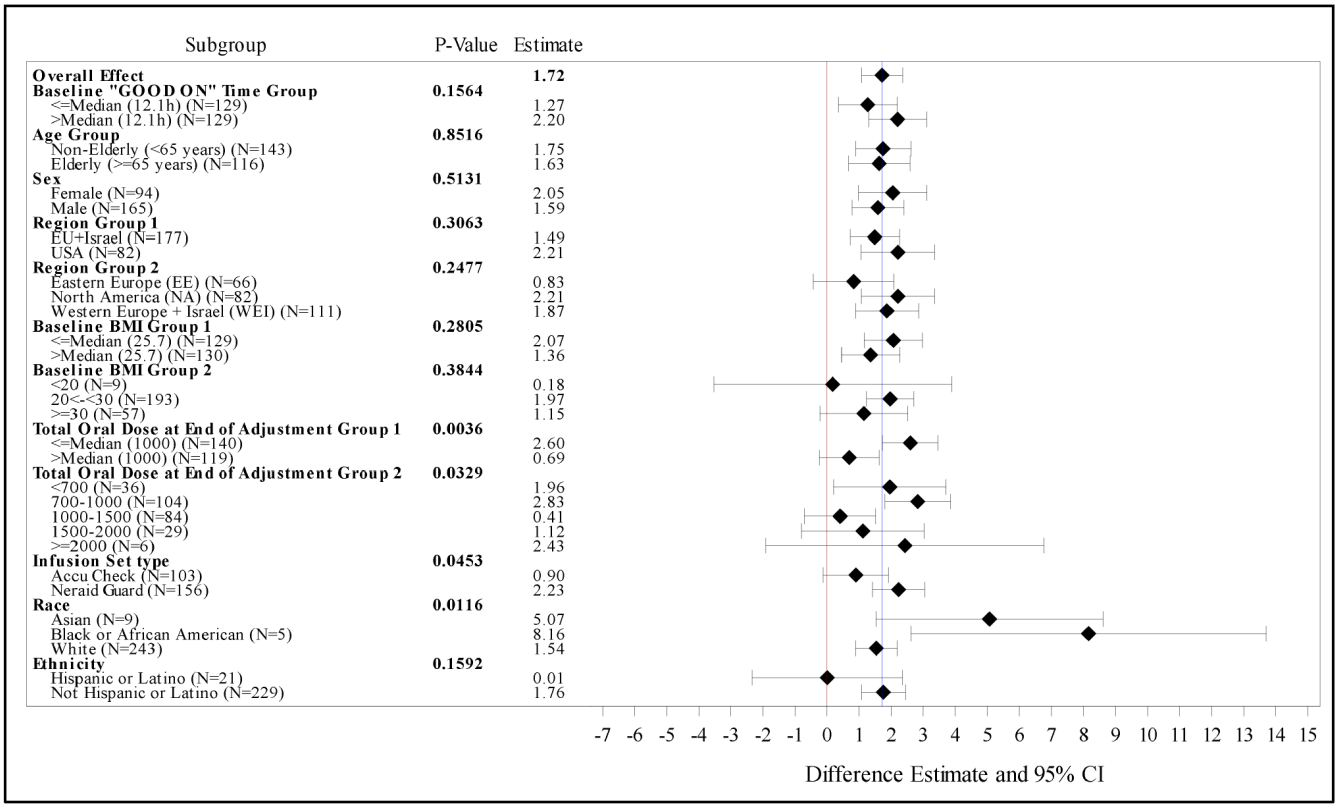
10 Subjects with optimised total oral LD less or equal to the median vs. subjects with optimized total oral LD above the median measured at the end of IR-LD/CD OL Adjustment Period

11 Subjects with optimised total oral LD at the end of IR-LD/CD OL Adjustment Period <700, 700-1000, 1000-1500, 1500-2000, >2000 mg

12 Subjects with ND0612 infusion set type Accu-Chek® vs. subjects with ND0612 infusion set type Neria Guard™

The forest plot of treatment effect for the primary endpoint including all the prespecified subgroup analyses is presented below.

Figure 13. ND0612: Subgroup analyses of the primary efficacy (GOOD ON)



BMI: Body mass index; CI: Confidence interval; EU: European Union; h: Hour(s); N: Number of subjects; USA: United States of America

The treatment effect of ND0612 DP was overall homogeneous across the different analysed subgroups and consistent with the overall effect of 1.72 h. A reversed effect (i.e., IR-LD/CD to be better) was not observed in any of the subgroups.

No statistically significant interaction between subgroups and treatment (p>0.1) were observed for most of the subgroups, except for the analyses testing oral LD dose at end of adjustment (p=0.0036 and p=0.0329), infusion set type (p=0.0453) and race (p=0.0116).

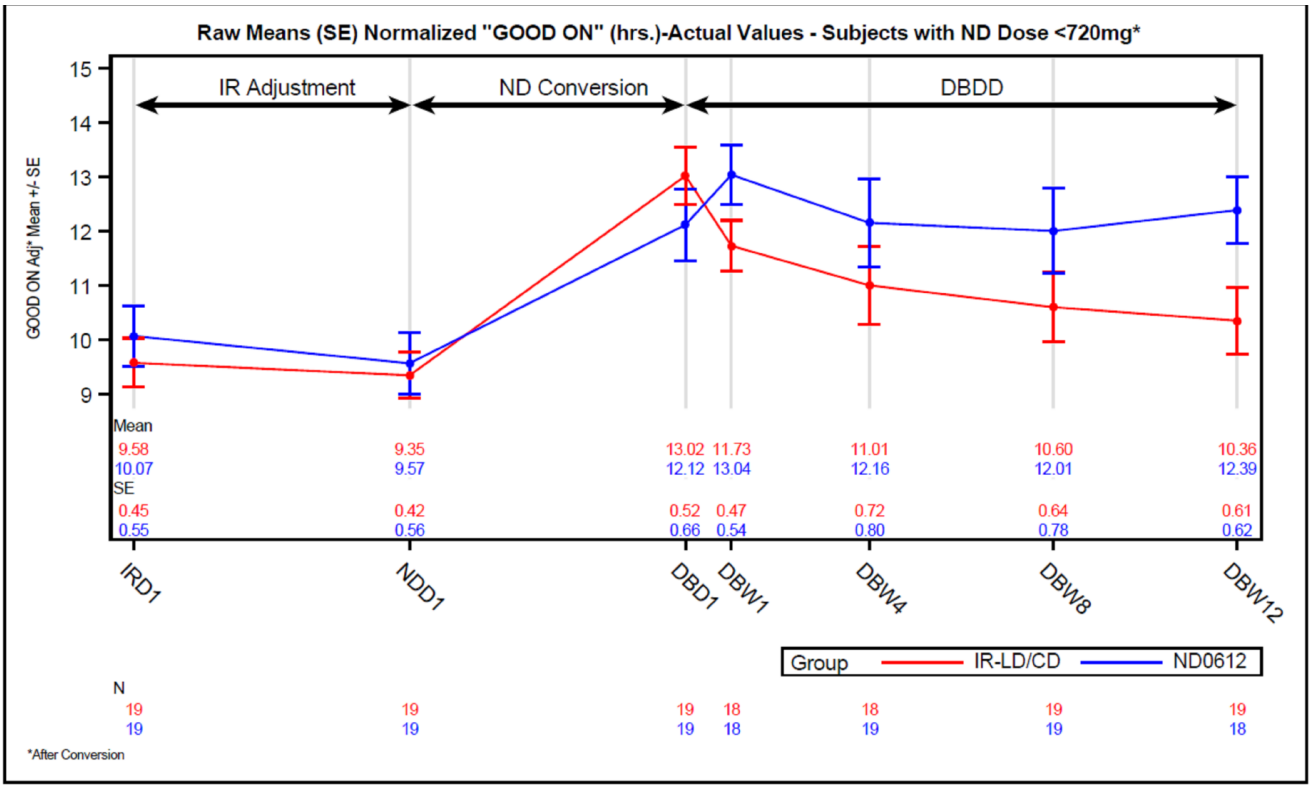
Caution is needed with subgroups interpretation, as they are considered exploratory in nature and randomisation was not stratified for each subgroup, thus not controlling for confounding factors.

Other subgroup analyses

In order to investigate if the efficacy of ND0612 DP was consistent throughout the dose range used in the study, a post-hoc analysis was performed to assess the GOOD ON time in subjects receiving less than the maximal dose of ND0612 720 mg/day at the end of the ND0612 OL conversion period. Descriptive statistics were used for this analysis.

Means for observed values of GOOD ON" time at enrolment, end of adjustment period and DBDD period for this subgroup of subjects are presented below.

Figure 14. ND0612-317: Raw means (Standard Error of GOOD ON time (hours) – Subjects with ND0612 dose < 720 mg - Actual values (ITT Set)



Adj: Adjusted (LS Mean); D: Day; DB or DBDD: Double-blind, double-dummy period; IR: IR-LD/CD Adjustment period; hr: Hour(s); IR-LD/CD: Immediate release levodopa/carbidopa; ND: ND0612 Conversion Period; SE: Standard error; W: Week.

The results observed for the subgroup were consistent with the overall population. GOOD ON time increased by more than 2 h upon conversion to ND0612 DP, this effect being overall maintained for subjects continuing ND0612 treatment in the DBDD period (Mean [SE] of 12.4 [0.6] h at Week 12), while for subjects switching back to IR-LD/CD, the LS means dropped as early as Week 1, continuing to drop until Week 12 (Mean [SE] of 10.4 [0.6] h).Pre-defined and post-hoc sensitivity analyses

Status of valid and non-valid diaries across study ND0612-317 visits and overall.

In study ND0612-317, daily diaries were completed three days before each visit. If a patient had one diary that was not valid, the other two were still used. The Table below outlines the status of valid and non-valid diaries across visits and overall.

Table 19. Distribution of valid and non-valid diaries by visit and overall

	Diaries			Subjects		
Visit Name	**Valid #(%)**	**Non-Valid #(%)**	**All #(%)**	**Valid* #(%)**	**Non-Valid** #(%)**	**All #(%)**
V2-IR Day 1	809 (100.0)	0	809 (100.0)	259 (100.0)	0	259 (100.0)
V7	807 (99.9)	1 (0.1)	808 (100.0)	258 (99.6)	1 (0.4)	259 (100.0)
V13-RANDOMISATION	811 (99.9)	1 (0.1)	812 (100.0)	258 (99.6)	1 (0.4)	259 (100.0)
V15-DB Day 7	683 (87.7)	96 (12.3)	779 (100.0)	221 (87.4)	32 (12.6)	253 (100.0)
V17-DB Day 28	753 (98.6)	11 (1.4)	764 (100.0)	243 (98.0)	5 (2.0)	248 (100.0)
V18-DB Day 56	757 (99.9)	1 (0.1)	758 (100.0)	244 (99.6)	1 (0.4)	245 (100.0)
V19 – End of DB	758 (98.8)	9 (1.2)	767 (100.0)	241 (98.8)	3 (1.2)	244 (100.0)
ET	22 (64.7)	12 (35.3)	34 (100.0)	7 (63.6)	4 (36.4)	11 (100.0)
Total	5400 (97.6)	131 (2.4)	5531 (100.0)	217 (83.8)	42 (16.2)	259 (100.0)

ET = early termination (maintenance)
* All 3 diaries at the visit are valid
** At least 1 diary at the visit is non-valid

Out of 5531 diaries being captured in the pivotal study ND0612-317 (from V2 to end of the DBDD period), only 131 (2.4%) were considered as non-valid (44 or more missing entries). Of these, only nine (1.2%) and one (0.1%) diary(ies) were/was non-valid for visits V19 (end of DBDD) and baseline, respectively, which were the most relevant study visits for efficacy assessment. Similarly, at the subject level, only three (1.2%) and one (0.4%) subject(s) had at least one non valid diary at visits V19 (end of DBDD) and baseline, respectively.

A proactive process was implemented to maximise the number of valid diaries, with a training process of study subjects on diary completion from the screening visit. In addition to the protocol's instructions, site staff called subjects approximately three days before each on-site visit to remind them to complete their study diaries. The applicant maintained a central review process, focusing on sites with diary quality issues. Diaries were required to be entered into the Electronic Data Capture (EDC) system within two business days or alternatively scanned and sent to the designated ND0612-317 mailbox. The team monitored diary entries, sent notifications for non-compliance, and arranged retraining when necessary. Persistent issues were escalated to study leaders for resolution.

Overall, completeness and quality of the diaries data was confirmed as adequate, with very few missing/non valid diaries as a result of a well-established and close monitoring process, with no impact of non-valid diaries on the study results.

It is acknowledged and supported that only valid diaries were analysed in the primary analysis. Moreover, the proposed definition of a valid diary is considered acceptable (if at least 44 of the 48 half-hour periods during the day have been completed per instructions). A post-hoc sensitivity analysis for the primary endpoint was performed adding non-valid diaries or diaries with missing recording entries. Invalid diaries with 44 missing entries or more were not imputed. A total of 262 missing entries were imputed, which were obtained from 95 subjects with 187 diaries. Nevertheless, since a vast majority (150 out of 187) of diaries had only a single 0.5-h item imputed, it can be agreed that the overall primary analysis results can be considered valid. In total 131 non-valid diaries from in total 42 subjects were not imputed due to more than 44 entries missing. The Applicant confirmed that out of 5532 diaries, 131 were considered

non-valid. However, at the subject level, three (1.2%) and one (0.4%) subject had at least one non valid diary at visits V19 (end of DBDD) and baseline, respectively. It is agreed that these numbers should not be expected to affect the study results. The applicant clarified that site staff called subjects approximately three days before each on-site visit to remind them to complete their study diaries.

Nevertheless, it is agreed that due to the minimal number of missing entries per diary that were imputed, these results of a post hoc sensitivity analysis for the primary endpoint adding missing recording entries were in line with the primary analysis results showing a treatment difference of 1.72h ($p<0.0001$).

Ancillary analyses

Not applicable

5.3.3. Clinical studies in special populations

Controlled trials enrolled 598 PD patients who received at least 1 dose of ND0612 DP. This population included 268 subjects aged 65-74 (82.5 patient-years) and 54 subjects aged 75-84 (18.8 patient-years); no subjects aged 85 and older were enrolled in the controlled studies of ND0612.

Non-controlled trials data covered the open-label extension periods of both ND0612H-012 and ND0612-317 studies, with 346 PD patients in total. Of those, 162 subjects were aged 65-74 (296 patient-years), 63 subjects 75-84 (130 patient-years), and two subjects 85 years and older (2.4 patient-years).

ND0612 DP was not studied in patients with renal (i.e. chronic kidney disease Stage 3b, 4 or 5) or hepatic impairment (i.e. Child-Pugh score B or C), as well as in the paediatric population.

Table 20. ND0612 Clinical studies in special populations

	Controlled Trials	**Non-controlled trials**
Renal impairment* patients (Subjects number /total number)	NA	NA
Hepatic impairment** patients (Subjects number /total number)	NA	NA
Paediatric patients <18 years (Subjects number /total number)	NA	NA
Older patients; Age 65-74 (Subjects number /total number)	268 / 598	162 / 346
Age 75-84 (Subjects number /total number)	54 / 598	63 / 346
Age 85+ (Subjects number /total number)	0 / 598	2 / 346
Other (Subjects number /total number)	NA	NA

5.3.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

5.3.5. Supportive study(ies)

ND0612H-012: a multicenter, international, open-label, non-controlled study evaluating the long-term safety, tolerability, and exploratory efficacy of two different dosing regimens (24 h infusion and 16 h

infusion) of ND0612 (LD/CD up to 720/90 mg/day) in PD subjects experiencing motor fluctuations.

Study Design, Population, and Objectives

A total of 214 subjects were enrolled. The main inclusion criteria included age ≥30 years, Hoehn-Yahr score ≤3 during ON, OFF time ≥2 h per day and a well-defined and predictable early morning OFF periods. Furthermore, subjects had to be on stable doses of standard oral LD (≥4 oral doses per day or ≥3 doses/day of ER LD/CD) and taking, or have attempted to take, at least one additional PD treatment.

The primary objective of the study was to assess the long-term safety and tolerability of ND0612 throughout the 12-month treatment period. Efficacy, as an exploratory objective, was evaluated based on ON/OFF home diaries (at Months 1, 3, 6, 9, and 12) and other efficacy measurements.

Dosing Regimens

ND0612 (LD/CD 60/7.5 mg/mL) was to be administered SC over 24 h or 16 h via two infusion sites (up to 6 mL per site) using the Crono Twin ND infusion pump system. A total volume of up to 12 mL/day (corresponding to 720/90 mg/day LD/CD) could be administered in both regimens.

- The 24 h regimen included a daytime rate (of up to 0.64 mL/h) and a fixed night-time rate (0.08 mL/h) for 18 h and 6 h, respectively, providing a maximum of 720/90 mg LD/CD for the 24 h period.
- In the 16 h regimen the dosing started upon waking with an infusion a rate up to 0.75 mL/h for 16 h. The total infusion volume during the infusion period was up to 12 mL, providing a maximum of 720/90 mg LD/CD for the 16 h period.

Oral LD/DDI medications were to be adjusted as needed. Use of other oral concomitant PD medication was allowed throughout the study.

Patient Flow, Exposure and Baseline Characteristics

Of the 276 subjects screened, 214 subjects were enrolled (24 h dosing regimen: N=90; 16 h dosing regimen: N=124) at 46 sites in 8 countries. A total of 120 (56.1%) subjects completed 12 months in the study and 94 (43.9%) subjects terminated early, with a similar proportion of discontinuations between the two regimens.

The overall exposure to ND0612 in the core study period (first 12 months) was 135.8 person-years. The median exposure in the safety population (N=214) was 337 days (range: 2-387 days), without major differences between the 24 h and 16 h dosing regimens.

Table 21. ND0612H-012: Summary of extend of exposure – All Cohorts (Safety Set)

	Statistics	24 h/day (N=90)	16 h/day (N=124)	Overall (N=214)
Duration of exposure (days)[1]	Mean	235.0	229.5	231.8
	SD	139.21	148.57	144.40
	Median	330.0	343.5	337.0
	Min, Max	2, 373	3, 387	2, 387
Total exposure in person years[2]		57.9	77.9	135.8

h: hours; Max: maximum; Min: minimum; N: number of subjects exposed to study drug; SD: Standard deviation

[1] Calculated as date of last dose received – date of first dose received + 1

[2] Calculated as the sum of duration of exposure to study treatment over all subjects in days divided by 365.25.

The mean age of the study population was 64.0 years (range: 39.8-80.3 years) and approximately 60% of subjects were male. The mean subjects' BMI was 27.1 kg/m^2 (range: 15.6-52.4 kg/m^2). Dosing regimens were balanced with respect to demographic parameters.

The ND0612H-012 study population was comparable to that of Study ND0612-317. The overall mean time from PD diagnosis in the ITT set was nine years and the mean time from onset of fluctuations was 5.3 years. The vast majority of the population had a modified Hoehn and Yahr between 2 and 3. In the analysis set of subjects for whom home diary information was available at Baseline, mean GOOD ON and OFF time were 9.9 h and 5.5 h, respectively, and similar across treatment regimens. The mean UPDRS Part III (Motor) score at Baseline was approximately 26 and similar across dosing regimens.

At baseline, approximately 70% of subjects received oral daily LD dose >720 mg.

Table 22. ND0612H-012: Demographics and baseline characteristics – All Cohorts (ITT / Safety Set)

Variable	Category	Statistics	24 h/day (N=90)	16 h/day (N=124)	Total (N=214)
Age (years)		Mean (SD)	64.2 (8.9)	63.9 (8.9)	64.0 (8.9)
	<65 years	n (%)	43 (47.8)	63 (50.8)	106 (49.5)
	≥65 years	n (%)	47 (52.2)	61 (49.2)	108 (50.5)
Gender	Female	n (%)	32 (35.6)	40 (32.3)	72 (33.6)
	Male	n (%)	58 (64.4)	84 (67.7)	142 (66.4)
Ethnicity	Caucasian	n (%)	86 (95.6)	116 (93.5)	202 (94.4)
	Other	n (%)	4 (4.4)	8 (6.4)	12 (5.7)
BMI (kg/m^2)		Mean (SD)	27.0 (5.5)	27.2 (5.9)	27.1 (5.7)
	<20	n (%)	11 (12.2)	11 (8.9)	22 (10.3)
	≥20	n (%)	79 (87.8)	113 (91.1)	192 (89.7)
Modified Hoehn & Yahr	<2	n (%)	4 (4.4)	5 (4.0)	9 (4.2)
	2	n (%)	37 (41.1)	52 (41.9)	89 (41.6)
	2.5	n (%)	17 (18.9)	32 (25.8)	49 (22.9)
	3	n (%)	32 (35.6)	35 (28.2)	67 (31.3)
MMSE Total Score		Mean (SD)	28.8 (1.2)	28.8 (1.2)	28.8 (1.2)
Time since PD Diagnosis (years)		Mean (SD)	10.6 (5.3)	7.9 (3.8)	9.0 (4.7)
Time since Onset of Fluctuations (years)		Mean (SD)	5.3 (4.3)	5.2 (4.2)	5.3 (4.2)
"GOOD ON" time		n	551	1011	1561
		Mean (SD)	10.2 (2.8)	9.7 (2.9)	9.9 (2.9)
		Min, Max	(2.2, 15.8)	(0.0, 14.8)	(0.0, 15.8)
"OFF" time		n	551	1011	1561
		Mean (SD)	4.9 (2.6)	5.8 (3.1)	5.5 (3.0)
		Min, Max	(0.3, 13.8)	(0.3, 16.0)	(0.3, 16.0)
Total Daily LD	Dose (mg)	Mean (SD)	1090.0 (623.3)	1004.4 (540.2)	1040.4 (576.7)
	LD >720 mg	n (%)	63 (70.0)	86 (69.4)	149 (69.6)
	LD ≥1000 mg	n (%)	40 (44.4)	52 (41.9)	92 (43.0)
Concomitant medications	Dopamine agonists	n (%)	52 (57.8)	58 (46.8)	110 (51.4)
	MAO-B inhibitors	n (%)	37 (41.1)	44 (35.5)	81 (37.9)
	COMTi	n (%)	28 (22.6)	24 (26.7)	52 (24.3)
	Amantadine	n (%)	25 (27.8)	30 (24.2)	55 (25.7)

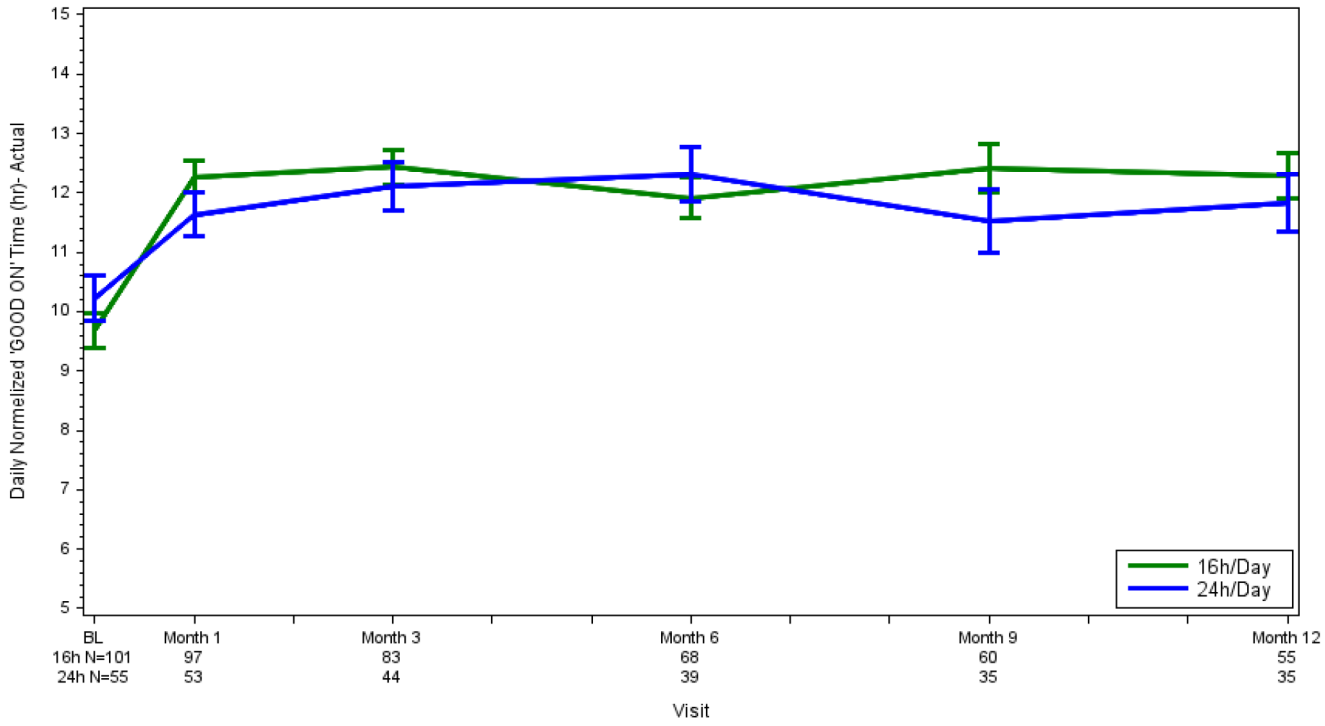
BMI: Body mass index; COMTi: Catechol-O-methyl transferase inhibitor(s); LD: Levodopa; MAO-B: Monoamine oxidase B; MMSE: Mini-Mental State Examination; N: Number of subjects; PD: Parkinson's disease; SE: Standard error.

Relevant Exploratory Efficacy Results

GOOD ON Time

At baseline, the mean daily GOOD ON time was approximately 10 h across dosing regimens. LS means of daily GOOD ON time increased from baseline at all timepoints, with a change at Month 1 of 1.81 h in the 24 h dosing regimen and 2.5 h in the 16 h dosing regimens, an improvement that was maintained for the 12 months: 2.0 h in the 24 h dosing regimen and 2.5 h in the 16 h dosing regimen. No statistically significant differences between the dosing regimens were observed at any timepoint.

Figure 15. ND0612H-012: Least-squares Means of ON time without troublesome dyskinesia (GOOD ON) - Actual values by visit (m ITT Set)

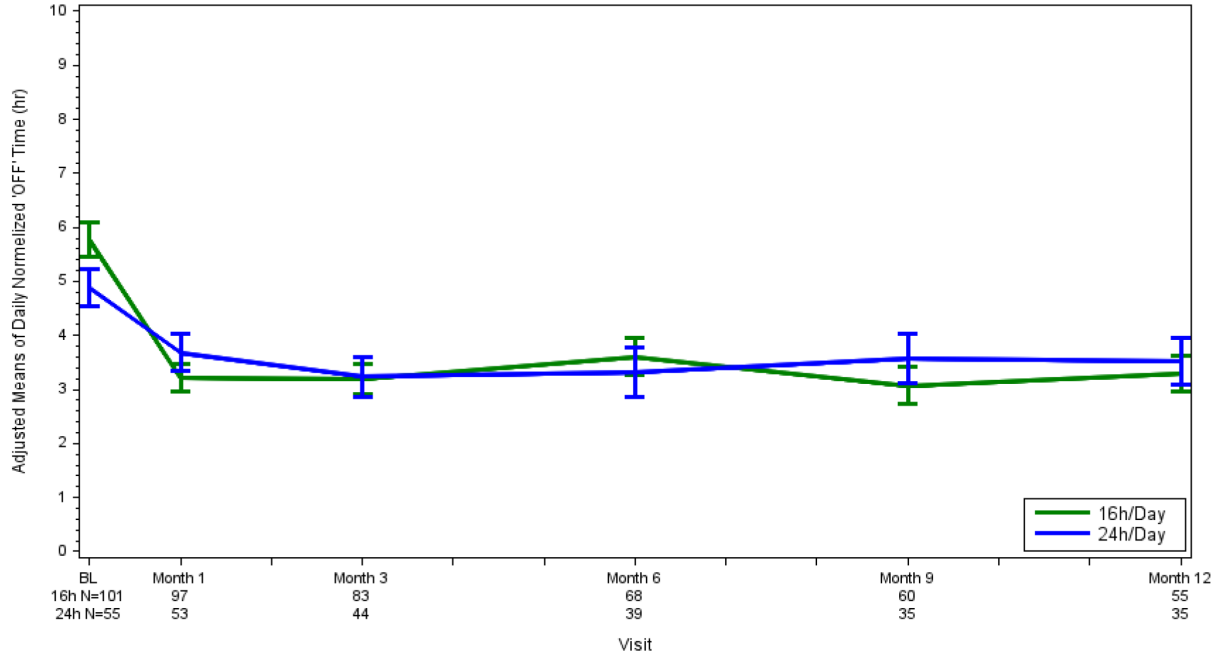


BL: Baseline; h or hr: Hour(s); N: Number of subjects.

OFF Time

At baseline, the mean daily OFF time was approximately 5 h across dosing regimens, and by Month 1 was 3.4 h, which was sustained until the end of the 12-month period, with no relevant differences between the dosing regimens. For the 24 h dosing regimen the decrease was of 1.9 h in the first month, a reduction that was maintained up to 12 months.

Figure 16. ND0612H-012: Least-squares Means of OFF time - Actual values by visit (m ITT Set)



BL: Baseline; h or hr: Hour(s); N: Number of subjects.

The proportion of responders (subjects with ≥50% reduction in mean daily OFF time) exceeded 40% beginning at Month 1 and throughout the 12-month treatment period across dosing regimens. In the 24 h dosing regimen, the proportion of responders ranged between 41.5% (Month 1) and 61.5% (Month 6).

ON Time without Dyskinesia

At baseline, mean daily ON time without any dyskinesia was approximately 7.8 h across dosing regimens, and by Month 1, adjusted mean was approximately 10.3 h, sustained until the end of the 12-month period without significant differences between the groups. Analysis of change from baseline revealed that the effect could be seen within one month of treatment, with LS means of approximately two additional hours of daily "ON" without any dyskinesia in the 24 h dosing regimen. This effect ranged between 1.6-3.0 throughout the 12 months.

UPDRS Part II (Activities of daily living [ADL]) and Part III (Motor)

UPDRS Part III (Motor) scores improved within the first month in both groups and this was maintained through Month 12. An LS mean change from baseline of -6.62 at Month 1 and -6.09 at Month 12 was observed in the 24 h regimen. UPDRS Part II (ADL) scores also improved with a change from baseline of -3.06 at Month 1 and -2.47 at Month 12 in the 24 h regimen. Results were comparable for the 16 h regimen.

Subject Global Impression of Improvement (SGI-I) and CGI

The majority of subjects rated themselves as having improved (very much improved, much improved, minimally improved) beginning at Month 1 and throughout the duration of the study (94.7% in Month 1 and 80.0% in Month 12 for the 24 h regimen). No meaningful differences between the dosing regimens were observed.

A high proportion of patients was also reported to have improvements on the CGI-I over the first year, ranging from 90.8% in Month 1 to 76.0% in Month 12 for the 24 h regimen. There was no consistent

trend of change in CGI-Severity scores over time in the study. Between 70% and 80% of the subjects were evaluated by Investigators to be in the range of Borderline ill/ Mildly ill/ Moderately ill, at all visits, with no differences between groups.

PDQ-39, EQ-5D-5L and PDSS-2

The LS Means for the PDQ-39 summary index showed improvements compared to baseline as early as Month 1 (-7.3) up to Month 12 (-4.2) for the 24 h regimen. No relevant differences were observed for the 16 h group. Improvements were observed in all PDQ-39 domains, but overall improvement was mainly driven by improvements in the domains of mobility, stigma, and activities of daily living. The generic EQ-5D-5L scale supported the overall improvement in quality of life.

Analysis of change from baseline in the PDSS-2 showed improvement in the overall score from Month 1 and throughout 1 year with LS means in the range of three points. No relevant differences across treatment groups were noticeable.

In summary, the exploratory evaluation of the efficacy parameters in Study ND0612H-012 using patient-reported outcomes (home ON and OFF diaries, UPDRS Part II, SGI-I, PDQ-39 and EQ-5D) and physician assessments (UPDRS Part III, CGI, PDSS) consistently showed a clinically relevant improvement beginning at Month 1 and sustained throughout the 12 months of treatment. These results are consistent with the effects observed in ND0612 treated subjects in the core period of study ND0612-317.

1) Analysis of Clinical Information Relevant to Dosing Recommendations

ND0612 Dose Range

The proposed ND0612 DP dose range and daytime/night-time flow rate schemes are based on data from the pivotal study ND0612-317 and study ND0612H-012. In these studies, the pump (Crono Twin ND) was pre-programmed to deliver flexible daytime rates over 18 h (the daytime flow rate starting about three hours before the anticipated patient's wake-up time) and a fixed night-time rate over 6 h. The day rate could be adjusted by the investigator to a maximal rate of 0.64 mL/h, providing approximately 690 mg LD over 18 h. The night rate was fixed at 0.08 mL/h providing approximately 30 mg LD for the 6 h period. Therefore, the daily LD/CD dose from ND0612 DP could be selected up to a maximal dose of 720 mg of LD and 90 mg of CD.

Accordingly, ND0612 DP is proposed to be used in a similar daytime/night-time dosing scheme. The total levodopa daily dose is to be prescribed by the physician according to the patient's needs, choosing from eight regimens ranging from 370 mg to 720 mg (SmPC Table 2, also noted below). The difference between each dose is approximately 50 mg LD, which corresponds to the minimal amount of levodopa in one LD/DDI tablet.

Table 23. Levodopa daily dose levels (mg)

Daytime – 18 hours		Nighttime – 6 hours		Total daily
Flow rate (mL/h)	**Levodopa dose (mg)**	**Flow rate (mL/h)**	**Levodopa dose (mg)**	**Levodopa dose (mg)**
0.64	690	0.08	30	720
0.59	640	0.08	30	670
0.55	590	0.08	30	620
0.50	540	0.08	30	570
0.45	490	0.08	30	520
0.41	440	0.08	30	470
0.36	390	0.08	30	420
0.32	340	0.08	30	370

LD: levodopa; mg: Milligrams; Ml: Milliliter; h: hours

The most common used dose of ND0612 in the pivotal trial ND0612-317 was 720 mg/day LD. Of the subjects randomised to the ND0612 arm, 19 (14.8%) received daily ND0612 doses < 720 mg and none received doses < 370 mg. The Table below displays the number (%) of subjects in the ND0612-317 trial receiving per selected ND0612 dosing categories.

Table 24. Doses upon randomisation (baseline) in the ND0612 (Safety Set)

Variable, Statistics	ND0612 (N=128)
ND0612	
Mean dose (mg/day)	703
SD	51
Min, Max	396, 720
	Frequency n (%)
720 mg/day	109 (85.2)
670 <720 mg/day	0
620 <670 mg/day	8 (6.3)
570 <620 mg/day	6 (4.7)
520 <570 mg/day	2 (1.6)
470 <520 mg/day	1 (0.8)
420 <470 mg/day	1 (0.8)
370 <420 mg/day	1 (0.8)
<370 mg/day	0

Mg: Milligram; N/n: Number of subjects studied; SD: Standard deviation.

In Study ND0612-317, a post-hoc analysis performed to assess the GOOD ON time in subjects receiving less than the maximal LD dose of 720 mg/day from ND0612 demonstrated that the efficacy was consistent throughout the ND0612 dose range used in the study.

For commercial use, the applicant intends to market ND0612 DP with the Crono Twin ND pump, or the Twiko Delivery System (TDS). The Crono Twin ND (a CE marked ambulatory pump intended for subcutaneous infusion of drugs for Parkinson's disease therapy) was the infusion pump used in most of the clinical studies, including Study ND0612-317 and ND0612H-012. The TDS is a new infusion pump system developed specifically for use with ND0612 DP. Both pumps are to be used with the CE marked

neria™ guard (CE 0459, FDA k122686) infusion sets, which were in use in both ND0612-317 and ND0612H-012 studies.

Both Crono Twin ND and the TDS support the ND0612 DP dosing schemes. Importantly, although the TDS was not used in the clinical studies of ND0612 DP, the established ND0612 DP efficacy and safety profile is expected not to be affected with the use of the TDS, which has a similar drug product delivery performance to the Crono Twin ND. Further details about the comparability of the Yurway/Twiko Delivery System and the Crono Twin ND pump are presented in Section 3.3.1 of this AR (Medical device issues).

Before initiating home use, the physician must assess whether the patient can safely use the Yurway Delivery System or Crono Twin ND independently. Following training, patients who are not able to perform all critical tasks safely must use the system with the support of a trained caregiver. Only patients and/or caregivers who have received training and have been assessed as competent may operate the Yurway Delivery System or Crono Twin ND at home. Refresher training should be provided if difficulties in use are identified (SmPC section 4.2 and 6.6).

Oral LD Doses

The mean dose of oral LD (including the morning dose) in subjects randomised to ND0612 was 534 mg/day, and doses ranged between 100 to 2100 mg/day (excluding two subjects who were treated only with ND0612).

ND0612 was shown to be effective at total daily LD doses between 500 mg and 2800 mg (ND0612 plus IR-LD/CD), covering the therapeutic range usually seen in the population of PD patients with motor fluctuations.

In Study ND0612-317, ND0612 treated subjects were to receive at least a morning oral dose of IR-LD/CD to attain faster clinically relevant LD levels and avoid morning akinesia. According to the protocol, additional oral IR-LD/CD doses could be administered during the day, as necessary based on subjects' individual clinical response.

Based on these data, ND0612 DP is to be administered with at least a morning dose of oral LD.

Conversion to ND0612 and Dose Adjustment

Due to the active-controlled design of the study, all subjects had to convert their previous formulations of LD to equivalent doses of IR-LD/CD. In addition, COMT inhibitor discontinuation was needed in order to avoid the confounding effect of COMT inhibition on LD exposure. In clinical practice, the applicant considered these steps as unnecessary for a number of reasons. First and foremost, at the end of the IR-LD/CD OL adjustment period (upon switching to IR-LD/CD and adjustment to optimal dose), the mean daily IR-LD/CD dose was 1080.3 mg, similar to the LEDDLD + COMTi at enrolment (1029.2 mg) (reference: ND0612-317 CSR, Section 11.3.2). In addition, it has been shown that COMT inhibitors taken concomitantly with ND0612 generated an increase of LD bioavailability similar to the one observed when COMT inhibitors are administered with oral formulations of LD. Lastly, the conversion to IR-LD/CD and the COMT inhibitor discontinuation may not be tolerated by some subjects, due to worsening of PD symptoms. As observed in Study ND0612-317, five (1.3%) subjects discontinued the OL IR-LD/CD adjustment period due to worsening of PD symptoms (Preferred Terms of ON and OFF phenomenon and Parkinson's disease).

In Study ND0612H-012 there was no requirement to convert previous formulations of LD to equivalent doses of IR-LD/CD before starting ND0612, and COMT inhibitor could be continued during the study.

In clinical practice, using different formulations of LD as well as allowing continuous use of COMT inhibitor when converting to ND0612 is expected to provide better optimisation of the ND0612 regimen.

Conversion to IR-LD/CD and/or discontinuation of COMT inhibitor would impose an unnecessary burden to patients and physicians in clinical routine use.

In study ND0612-317, the recommended starting dose of ND0612 was 720 mg/day in all patients, with subsequent dose reduction of ND0612 if needed. This was based on PK data. ND0612 treatment with an LD dose of 720 mg/day provides an LD C_{SS} mean (SD) of 1240 (141) ng/mL and a C_{max} of 1450 (157) ng/mL (reference: Study ND0612-005). These values do not exceed the C_{max} of 1635 ± 655 ng/mL achieved with oral IR-LD/CD 100/25 mg administered four times a day (reference: Study ND0612-115). Therefore, the ND0612 dose of 720 mg/day LD was considered a safe starting dose for all subjects. This is supported by data from Study ND0612-317 showing that only one (0.3%) subject discontinued study treatment during the conversion period due to a dopaminergic AE.

In Study ND0612-317, results observed for all subgroups (based on age, gender etc.) were consistent with the overall population, supporting that no dose adjustment is needed for any subgroups of patients.

Persistence of Efficacy and/or Tolerance Effects

Preliminary exploratory efficacy data of the ongoing 1-year extension of ND0612H-012 and 2-year ND0612-317 studies are also available. The results, presented in scientific congresses (Espay et al. 2024a; Stocchi et al., 2024), are supportive of maintenance of efficacy benefit and lack of development of tolerance effect.

5.3.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

5.3.7. Observational data/Data from registries

Not applicable.

5.3.8. Patient experience data (PED)

Not applicable.

5.3.9. Healthcare professional engagement

No information was gathered.

5.3.10. Overall discussion and conclusions on clinical efficacy

5.3.10.1. Discussion

The Applicant performed a single main pivotal randomised, active-controlled, double-blind, double-dummy (DBDD), parallel-group Phase 3 study (**ND0612-317**) to investigate the efficacy, safety, and tolerability of continuous ND0612 DP infusion (levodopa/carbidopa [LD/CD] dose up to 720/90 mg/day, 24-h infusion) in comparison to oral immediate release-levodopa/carbidopa (IR-LD/CD).

The primary objective was to identify the effect of ND0612 DP on daily GOOD ON time (defined as the sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia) using subject completed ON/OFF diary assessments of motor function. The key secondary objective was to observe the effect of ND0612 on daily OFF time using subject completed ON/OFF diary assessments of motor function. This was performed using the modified Hauser diary, where the patient registers the motor

status on each 30 minutes of the waking day.

The primary endpoint was the change from baseline to the end of the DBDD period (DB W12) on the mean daily GOOD ON time of ND0612 as compared to immediate release L-dopa/CD intake adjusted to the subject's waking hours and normalised to 16 waking hours, based on self-completed subjects' ON/OFF" diary assessments on the three consecutive days before the visit. Key secondary endpoint was similarly the change from baseline on daily off time normalised to 16 waking hours of ND0612 as compared to IR L-dopa/CD.

The key secondary endpoint was the change from baseline to the end of the DBDD period in the mean daily OFF time adjusted to subject's waking hours and normalized to 16 waking hours, based on subjects' ON/OFF diary assessments on the three consecutive days before the visit.

There were five periods in the study, followed by an optional OLE for 54 weeks. The main study periods were:

1) Screening period, of 1 to 4 weeks, when the patient and study partners are trained in the Hauser diary and identifying motor fluctuations.

2) IR-LD/CD Open-label Adjustment Period, of 4 to 6 weeks, where all formulations of LDOPA/CD and COMTi are converted into IR-LD/CD designed to switch and adjust to optimal IR-LD/CD regimen, comprising of two to four weeks of titration and two weeks on stable doses.

3) ND0612 Open-label Conversion Period, of four to six weeks, where patients are converted and adjusted to an optimal ND0612 regimen (i.e., ND0612 plus oral IR-LD/CD), comprising of two to four weeks of adjustment and two weeks on stable doses.

4) Randomised, double-blind double-dummy Period, of 12 weeks, where subjects were to be randomised in a 1:1 ratio at the randomization visit (V13/DBD1) to ND0612 regimen or IR-LD/CD, under DBDD conditions, according to the previously reached optimal doses at the end of each open-label period (2 or 3).

5) An optional OL treatment extension period of up to 54 months and a safety follow-up period (follow-up visit four weeks after treatment completion or early treatment discontinuation).

6) A safety follow-up period (follow-up visit four weeks after treatment completion or early treatment discontinuation). Patients who were not stabilised after two to four weeks of switch + two stable weeks in each period were excluded from the study.

Of the 381 enrolled into the study, only 259 entered the DBDD period.

The overall study design is considered generally appropriate. It is acknowledged that there is no model design to mimic real-life situations. Transitioning levodopa formulations (immediate and sustained release) to immediate-release and keeping the patient in the study even if deteriorating were difficult tasks. The use of IR-LD/CD as active control is supported. The applicant clarified that the duration of the run-in period of 4-6 weeks was aligned with other studies in PD patients with motor fluctuations. Adequate literature references were provided.

To be eligible to the study, the patients needed to be diagnosed with PD, experience motor fluctuations and experience an average of at least 2.5 hours daily (with a minimum of two hours every day) in the OFF state during waking hours as confirmed by an adequately completed ON/OFF diary over three days, have Modified Hoehn and Yahr Scale in ON state $\leqslant$3 and to be treated with at least four doses/day of LD/DDI (or at least three doses/day of extended release LD/DDI) and at least 400 mg/day of LD, or equivalent, and, according to the investigator's judgment, the subject experienced motor fluctuations that could not be further improved by adjusting anti-PD medications. The inclusion criteria are considered adequate.

Regarding the study population: 1) The mean age of 64.1 years is a rather a low age. In EU, patients below the age of 70 are offered deep-brain stimulation (DBS). Most patients with infusion treatments are above the age of 70. The time since PD diagnosis and the time since motor fluctuations is within the expected values for the range in cognition from fit to mild demented (MMSE 24 through 30) PD population. The BMI was shifted towards the higher values, which is less common in choreic patients with high energy expenditures in on time, and lack of appetite in OFF time. There were no patients above the age of 85 enrolled into the confirmatory study, and only two patients with 85 or more have been studied in the long-term safety study. Many patients with advanced PD nowadays are in the late 80s. For this sub-population, a cautionary wording on dosing adjustment is agreed for inclusion in the SmPC.

2) Subjects with atypical or secondary parkinsonism, acute psychosis or troublesome hallucinations in the six months prior to enrolment were not eligible for enrollment in the pivotal trial, which is considered acceptable. The applicant clarified that in study ND0612-317, 4.2% (n=11) of all randomised patients had a medical history of psychosis, including three patients who experienced a psychosis event in the previous six months before enrolment.

3) To avoid any potential impact on study conduct/analysis, clozapine was not permitted in the pivotal ND0612-317 study. Clozapine is an effective antipsychotic for the treatment of refractory psychosis in PD. However, its use has been limited due to the risk of agranulocytosis, and stringent complete blood count monitoring. As it is well known, infusion strategies are often used in patients who are no longer candidates to DBS, namely due to age and cognitive criteria. As CHMP expressed concern about the exclusion of clozapine-controlled patients, the applicant showed that 3.5% of the patients enrolled into this confirmatory study was previously psychotic but controlled patients. Furthermore, in the follow-up study, 15% of the patients were under antipsychotics, and 4.2% were on clozapine. In summary, it may thus be assumed that Onerji can be used in controlled previously psychotic patients. It is nonetheless interesting that in the long-term safety study ND00612H-012, where there was no restriction on clozapine, more patients required use of antipsychotics than initially (4.2 versus 15%), which highlights that the use of device assisted agents should be restricted to the more advanced severe fluctuations of PD. A total of 381 subjects were enrolled into the IR-LD/CD OL adjustment period. During this period, 59 (15.5%) subjects discontinued the treatment. The most common reasons for discontinuation were withdrawal of consent and AEs (7.9% and 4.2% subjects, respectively).

A total of 322 subjects entered the ND0612 OL conversion period. During this period, 19.6% subjects discontinued the treatment, and the most common reasons for discontinuation were AEs (5.9% due to ISRs and 2.2% due to other AEs) and withdrawal of consent (6.8% of subjects).

The population enrolled into the DBDD period was filtered through the challenging conversion to the immediate release levodopa and SC infusion, reducing the 381 patients to 259, about 68% of those entering the study. Of them, 128 were randomised to the ND0612 arm and 131 to the IR-LD/CD arm. The applicant claimed that randomised withdrawal strategies are common to reduce placebo variability. This, however, did not justify the righteousness to extrapolate the indication until provision of a table with the demographic and PD baseline characteristics of both the totally enrolled and the finally randomised populations, which did not significantly differ. On this premise, it was accepted that the results could be extrapolated to the enrolled population.

Discontinuation rate during the 12-week period was 6.3% and 6.1% in the ND0612 and IR-LD/CD arms, respectively (eight subjects each). The main reason for treatment discontinuation was adverse events in seven (5.5%) subjects in the ND0612 arm (of which 3 [2.3%] due to ISRs) and four (3.1%) subjects in the IR-LD/CD arm. Of the subjects who completed the DBDD Period, 113 (88.3%) in the ND0612 arm and 119 (90.8%) in the IR-LD/CD arm continued to the OLE period.

Both the primary endpoint and the key secondary endpoints were met: GOOD ON time mean difference from baseline showed a statistically significant treatment difference of 1.72 h (p<0.0001) at Week 12 in favour of ND0612 (worsening 0.48h in the DBDD as compared to the OL conversion) over IR-LD/CD (-2.02h). The mean OFF time reduction at week 12 was also in favour of ND0612, with 1.4h less off time with ND0612 than with IR LD/CD. Secondary endpoints also trended in favour of SC ND0612. The key secondary endpoint of the Study was met. The analysis of change from baseline to the end of the DBDD period in Mean Daily OFF" Time showed a statistically significant treatment difference of -1.4 h (95% CI: -2.0, -0.8; p<0.0001) in favour of ND0612 over IR-LD/CD in the change from baseline at Week 12. The results of the supportive analysis utilizing MI under MNAR mechanism was in line with the primary analysis and showed a treatment difference of -1.4 h (95% CI: -2.0, -0.8). It is relevant that the quality of ON time, as measured by the activities of daily living in part 2 of MDS-UPDRS (2nd secondary endpoint) and motor performance in part 3 of MDS-UPDRS (3rd secondary endpoint) also supported the benefit observed with the primary and key secondary endpoints.

The analysis results for MDS-UPDRS Part II at Week 12 showed a statistically significant treatment difference of -3.05 (95% CI: -4.28, -1.81, p<0.0001) for ND0612 over IR-LD/CD, with LS means (SE) of -0.30 (0.45) and 2.75 (0.45) for ND0612 and IR-LD/CD, respectively. In a supportive analysis, the MI under MNAR a treatment difference of -2.88 (95% CI: -4.12, -1.65) points was show.

Moreover, at Week 12, a significantly higher proportion of subjects evaluated their status as "improved" in the ND0612 arm compared to IR-LD/CD (adjusted proportions 0.70 vs 0.31, respectively, p<0.0001) in the patient global impression of change scores.

For the ND0612 arm, 12.7%, 26.3% and 28.8% of subjects considered themselves as "very much improved", "much improved" and "minimally improved", respectively. A total of 8.5% reported no change, and 2.5%, 8.5% and 12.7% considered themselves as "very much worse", "much worse" and "minimally worse", respectively. For the IR-LD/CD arm the proportions were 4.1%, 9.9% and 19.0% for "very much", "much" and "minimally improved", respectively, 19.8% for no change, and 5.0%, 26.4% and 15.7% for "very much", "much" and "minimally worse", respectively.

Furthermore, a significantly higher proportion of subjects in the ND0612 arm were evaluated as "improved" by the investigators compared to the IR-LD/CD arm (0.77 vs. 0.31, respectively; p<0.0001) at the end of the DBDD period. The odds of a subject receiving ND0612 to be evaluate with improvement by the clinician was 7.2 times higher than the odds for IR-LD/CD (95% CI: 3.6, 14.6).

For the ND0612 arm, 10.9%, 31.9% and 31.9% of subjects considered themselves as "very much improved", "much improved" and "minimally improved", respectively, 8.4% reported no change, and 0.0%, 9.2% and 7.6% considered themselves as "very much worse", "much worse" and "minimally worse", respectively. For the IR-LD/CD arm the proportions were 2.6%, 12.8% and 17.9% for "very much improved", "much improved" and "minimally improved", respectively, 29.9% for "no change", and 1.7%, 17.1% and 17.9% for "very much worse", "much worse" and "minimally worse", respectively.

The 4th secondary endpoint - change from Baseline to the End of the DBDD Period in Movement Disorder Society-Sponsored Revision of the Unified PD Rating Scale Part III (Motor Examination) Sum Score Measured at OFF State at Week 12 showed a LS mean treatment difference of -2.4 for ND0612 over IR-LD/CD, but not reaching statistical significance (LS mean [SE] 1.0 [1.0] for ND0612 vs 3.4 [1.0] for IR-LD/CD; p=0.0889. Since hierarchical testing for significance was terminated at this endpoint, p-values for other secondary endpoints are nominal

The 5th secondary endpoint - treatment difference of 2.1 h (95% CI: 1.4, 2.8, p<0.0001) in ON time without dyskinesia was observed, favouring ND0612 compared to IR-LD/CD at Week 12 (LS mean [SE] -0.4 [0.3] for ND0612 vs -2.5 [0.3] for IR-LD/CD.

The 6th secondary endpoint - the proportion of subjects reaching at least 50% decrease in mean daily OFF time from End of Adjustment to End of DBDD Period was 29% (95% CI: 0.19, 0.41) in the ND0612 arm compared to 10% (95% CI: 0.05, 0.17) in the IR-LD/CD arm (p=0.0027 for treatment odds ratio, favouring ND0612 compared to IR-LD/CD.

The 7th secondary endpoint - a treatment difference of -2.7 (95% CI: -4.8, -0.6, p=0.0137) was observed in favour of ND0612 over IR-LD/CD in change from Baseline in PDQ-39 summary index score at Week 12 (LS mean [SE] 1.6 [0.8] for ND0612 vs 4.3 [0.8] for IR-LD/CD.

The primary endpoint, change from baseline to the end of the DBDD Period (Week 12) in mean normalised GOOD ON time was analysed using MI under MAR in the ITT set by the subgroups. No statistically significant interaction between subgroups and treatment (p>0.1) were observed for most of the subgroups except for the analyses testing oral LD dose at end of adjustment (p=0.0036 and p=0.0329), infusion set type (p=0.0453) and race (p=0.0116).

Following open-label optimisation of ND0612 during the ND0612 OL conversion period, continued treatment with ND0612 during the DBDD Period resulted in an LS mean "GOOD ON" time change of -0.48 h (95% CI: -0.94, -0.02), while IR-LD/CD led to LS mean deterioration of -2.2 h (95% CI: -2.65, -1.74).

At enrolment (start of IR-LD/CD OL adjustment period), the mean (SE) GOOD ON time was 9.4 (0.2) h in both ND0612 and IR-LD-CD arms, which increased slightly upon IR-LD/CD adjustment to 9.8 (0.2) and 10 (0.2) h, respectively. Following conversion to ND0612, the GOOD ON time increased by approximately 2h to 11.8 (0.2) h and 12.1 (0.2) h in ND0612 and IRLD/ CD arms, respectively. The effect was maintained overall for subjects continuing ND0612 treatment during the DBDD period (LS means [SE] ranging from 11.2 [0.2] h at Week 4 to 11.5 [0.2] h at Week 12), while for subjects switching back to IR-LD/CD, the LS means dropped as early as Week 1 to 10.5 (0.2) h, continuing to drop until Week 12 to values similar to those observed at the end of the IR-LD/CD OL Adjustment Period, 9.8 (0.2) h.

Relevant differences between groups (LS mean change from baseline) were observed at all post-baseline timepoints, from 1.0 h (95% CI: 0.4, 1.6) at Week 1, increasing to 1.7 h (95% CI: 1.1, 2.4) at Week 12. In the conducted supportive analysis, a treatment difference of 1.66h (95% CI: 1.0, 2.3) was shown.

It is acknowledged and supported that only valid diaries were analysed in the primary analysis. Moreover, the proposed definition of a valid diary is considered acceptable (if at least 44 of the 48 half-hour periods during the day have been completed per instructions). A post hoc sensitivity analysis for the primary endpoint was performed adding non-valid diaries or diaries with missing recording entries. Invalid diaries with 44 missing entries or more were not imputed. Overall, 262 missing entries were imputed, which were obtained from 95 subjects with 187 diaries. Nevertheless, since a vast majority (150 out of 187) of diaries had only a single 0.5-h item imputed, it can be agreed that the overall primary analysis results can be considered valid. In total 131 non-valid diaries from in total 42 subjects were not imputed due to more than 44 entries missing. The Applicant confirmed that out of 5532 diaries, 131 were considered non-valid. However, at the subject level, three (1.2%) and one (0.4%) subject had at least one non valid diary at visits V19 (end of DBDD) and baseline, respectively. It is agreed that these numbers should not be expected to affect the study results. The applicant clarified that site staff called subjects approximately three days before each on-site visit to remind them to complete their study diaries.

Nevertheless, it is agreed that, due to the minimal number of missing entries per diary that were imputed, these results of a post hoc sensitivity analysis for the primary endpoint adding missing recording entries were in line with the primary analysis results showing a treatment difference of 1.72h (p<0.0001).

Two Phase 2a studies and one Phase 2b study were submitted to support this MAA.

Study ND0612/003 was a Phase 2a randomised, double-blind, placebo-controlled, 2-period study evaluating the safety, tolerability and pharmacokinetics of ND0612 (LD/CD 270/63 mg/day) 24-hour infusion. Efficacy was evaluated as exploratory in 30 subjects, who were randomised 2:1 to ND0612 or placebo over two weeks and was assessed by subject's home diaries. In the pooled analysis of change from baseline to the end of Week 1 and Week 2, ND0612 led to a reduction in OFF time of -2.1 h, compared to -1.4 h in the placebo control arm. The reduction in OFF time from baseline to end of Week 2, as assessed by in-clinic site raters, was -2.4 h for ND0612 compared to -0.8 h for placebo.

Another supportive trial was ND0612H-006:a Phase 2a randomised parallel-group study, assessing the efficacy and tolerability of two dosing regimens of ND0612: 24 h infusion (LD/CD dose up to 720/90 mg/day) and a daytime 14 h infusion (LD/CD dose up to 538/67 mg/day) over 4 weeks in 38 subjects, randomised in a 1:1 ratio. However, since the study was not designed for a formal statistical comparison between the 24-h and 14-h regimens, the efficacy results should be treated with caution. Nevertheless, the 24-h ND0612 dosing regimen reduced least-squares (LS) Means daily OFF time from baseline by 2.8 h, while increasing GOOD ON time by 3.7h (Day 28). Improvements were also observed in the 24-h dosing regimen across other assessed efficacy endpoints (Unified Parkinson's Disease Rating Scale [UPDRS] Part II, UPDRS Part III, global clinical impression, impression of disease severity and PD related quality of life).

Thereafter, study ND0612H-012, a phase 2b, multicentre, international, open-label, 12-month study followed, to assess the long-term safety, tolerability, and exploratory efficacy of two dosing regimens of ND0612 (LD/CD dose up to 720/90 mg/day): 24 h infusion and daytime 16 h infusion in 214 subjects. A total of 90 subjects were treated with the 24 h dosing regimen and 124 with the 16 h dosing regimen. The optional OLE (up to 102 months) of this study is ongoing at the time of authoring this assessment report. Two dosing regimens were initially evaluated: Regimen 1 of 720 mg LD and 90 mg CD over 24 hours, and Regimen 2 of 537.6mg LD and 67.2mg CD over 14 hours. However, regimen 2 (14h) was discontinued following the recommendation of the Oversight Committee, based on interim data from ND0612-006, suggesting that Regimen 2 (14hr at a rate of 0.64 mL/hr) was suboptimal with respect to the therapeutic response as reflected by the daily OFF time. Regimen 3 of 720 mg LD and 90 mg CD over 16 hours was introduced instead.

The primary objective of this study was to assess the long-term safety and tolerability of continuous SC infusion of ND0612 thought the 12-month treatment period. Efficacy was assessed as exploratory, based on daily ON time without troublesome dyskinesia and OFF time during waking hours as determined from ON/OFF home diary entries. Efficacy was further explored using PDQ-39 (QoL), EQ-5D-5L (QoL), rating of PD (UPDRS), CGI for severity and improvement, Subject Global Impression (SGI-I: improvement score assessed by subject), Parkinson's Disease Sleep Scale (PDSS), and sleepiness assessment (ESS).

It is noted that subjects recorded prolonged temporary discontinuations (over 3 hours) of IP infusion in a pump diary. In case of any problem in the pump system that could not be fixed within 3 hours, the subject contacted the investigator and resumed a regimen of oral LD/CD until the IP administration could be continued.

Improvement was observed throughout the one-year treatment in both 24-h and 16-h regimens. LS Means of daily GOOD ON time increased from baseline at all timepoints for the 24-h dosing regimen, with an increase from baseline of 1.8h at Month 1 and 2.0h at Month 12. Corresponding reductions in daily OFF time were observed with an LS Means change from baseline of -2.04 hours at Month 12.

Overall, it can be agreed that results of the study support the proposed dosing regimen. However, since the study was open label, the efficacy results should still be treated with caution.

5.3.10.2. Conclusions on the clinical efficacy

The results of the pivotal phase 3 study ND0612-317, supported by two Phase 2a and one Phase 2b study are considered adequate to support the indication of Onerji: treatment of motor fluctuations in patients with advanced Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medicinal products.

The primary endpoint (PEP) of the pivotal study was met and also supported by the key and other hierarchically tested secondary endpoints. Overall, this study demonstrated that continuous, SC treatment with ND0612 provides significant and clinically meaningful benefits for PD subjects with respect to ON time without troublesome dyskinesia and OFF time. This benefit was reflected by multiple assessments of global and motor functional scales, including MDS-UPDRS Part II (M-EDL), CGI-I and PGIC.

ND0612 SC infusion thus represents a new minimally invasive therapeutic option for PD subjects who suffer from poorly controlled motor fluctuations.

5.4. Clinical safety

Please refer to the Table of studies in section 5.1.2 (Table 3).

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.

5.4.1. Safety data collection

The safety data available for the ND0612 drug product clinical development program included six Phase I studies in healthy volunteers and six studies in patients with Parkinson's disease.

In addition, a thorough QT study (TQT) in healthy subjects to assess the potential effects of a supratherapeutic dose of CD on the QTc interval was conducted upon FDA request.

Safety data from the core periods of studies ND0612-317 and ND0612H-012 are presented individually, as these are the two main studies contributing to summary of clinical safety (SCS) for Onerji.

Integrated safety analyses included in the SCS were performed for 3 different safety pools:

Safety Pool 1, including data from all PD patients (N=598) enrolled in ND0612 DP clinical studies ND0612/002, ND0612/003, ND0612/004, ND0612H-006, ND0612H-012 (including ongoing Extension)

and ND0612-317 (including ongoing Extension) who received at least one dose of ND0612 DP. Of note these studies were conducted with:

- Different formulations of ND0612 DP (LD/CD concentrations of 60/14 mg/mL or 60/7.5 mg/mL and different excipients or different concentrations of the excipients);
- Various dosing regimens (24 h, 16 h and others);
- Different LD doses: from 115 mg (the lowest daily dose in Study ND0612/004) to 720 mg (the highest daily dose).

Safety Pool 2, which is a subset of Safety Pool 1 and included data from PD patients (N=419) who received at least one dose of the to-be-marketed ND0612 DP formulation under the 24-hour dosing regimen, as detailed below:

- Final ND0612 DP formulation (LD/CD concentrations of 60/7.5 mg/mL)
- 24-h dosing regimen
- Administration via two infusion sites, with a total infusion volume of up to 12 mL (up to 6 mL at each infusion site), corresponding to a daily dose of up to 720 mg LD and 90 mg CD
- It includes subjects from studies ND0612H-006, ND0612H-012 (including ongoing Extension), and ND0612-317 (including ongoing Extension)

Safety Pool 3, including data from all healthy volunteers (N=146) who participated in studies ND0612/001, ND0612/001b, ND0612/005, ND0612-114, ND0612-115 and ND0612-J01, and who received at least one dose of ND0612 DP. These studies were conducted with different formulations of ND0612, different dosing regimens, and different LD doses.

The safety assessments performed in Studies ND0612H-012 and ND0612-317, and respective Extensions (and discussed in the SCS) are summarised in the Tables below.

Table 25. Safety parameters

Safety parameters
TEAEs: seriousness, severity, discontinuation of study treatment. AESI: ISRs, hypersensitivity and polyneuropathy.
Clinical laboratory evaluations: Hematology – white cell count and differential count, red cell count, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelet count. Clinical Chemistry – sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, calcium, phosphate, bilirubin, alkaline phosphatase, gamma glutamyl transpeptidase, AST, ALT, total protein, albumin, and cholesterol. Urinalysis – pH, protein, glucose, ketones, urine microscopic (if required): white blood cell count, red blood cell count, and casts. Vitamin B6, vitamin B12 and folate (in ND0612-317 only). Dipstick urine pregnancy test for women of childbearing potential was performed during the extension period.
Vital signs: Heart rate, standing and supine blood pressure, weight and height
12-lead ECG
Physical examination
Neurological examination by a neurologist
Assessment of suicidal ideation and behavior: - Columbia-Suicide Severity Rating Scale
Assessment of Excessive Daytime Sleepiness: - Epworth Sleepiness Scale
Assessment of Impulsive-Compulsive Disorders in PD-Rating Scale: - Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale
Monitoring of infusion pump system issues/problems and temporary interruptions in study drug infusion
VAS for infusion site pain

AESI: Adverse events of special interest; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ECG: Electrocardiogram; ISR: Infusion site reaction; TEAE: Treatment-emergent adverse events; VAS: Visual Analog Scale.

Safety parameters in Study ND0612-317	Safety parameters in Study ND0612H-012
TEAEs: seriousness, severity, discontinuation of study treatment. AESI: ISRs, hypersensitivity and polyneuropathy.	TEAEs: seriousness, severity, discontinuation of study treatment. AESI: ISRs, hypersensitivity and polyneuropathy.
Clinical laboratory evaluations: -Hematology, clinical chemistry and urinalysis: once a year (and analysed by central lab). Lab data were recorded. In case of an abnormal and clinically significant lab result, an AE was reported.	Clinical laboratory evaluations: -Hematology, clinical chemistry and urinalysis: at early termination visit at investigator's discretion (and analysed by local lab). Lab data were not recorded in EDC. In case of an abnormal and clinically significant lab result, an AE was reported.
-Vitamin B6, vitamin B12 and folate were measured every six months.	-Vitamin B6, vitamin B12 and folate were measured every six months (added upon protocol amendment).
Vital signs: -Heart rate, standing and supine blood pressure: at all on-site visits, except those conducted only for investigational product (IP) dispensing	Vital signs: Heart rate, standing and supine blood pressure: at all on-site visits.
	Physical examination (including body weight): at early termination visit
	12-lead ECG: at early termination visit, at investigator's discretion (and done locally). ECG data were not recorded in EDC. In case of an abnormal and clinically significant ECG result, an AE was reported.
	Assessment of suicidal ideation and behavior: - Columbia-Suicide Severity Rating Scale: at early termination visit
	Assessment of Excessive Daytime Sleepiness: - Epworth Sleepiness Scale: at early termination visit
	Assessment of Impulsive-Compulsive Disorders in PD-Rating Scale: - Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale: at early termination visit
Monitoring of infusion pump system issues/problems and temporary interruptions in study drug infusion	Monitoring of infusion pump system issues/problems and temporary interruptions in study drug infusion
VAS for infusion site pain	VAS for infusion site pain

AE: Adverse event; AESI: Adverse events of special interest; ECG: Electrocardiogram; EDC: Electronic data capture; TEAE: Treatment-emergent adverse event; VAS: Visual Analog Scale.

5.4.2. Patient exposure

At the data cut-off date (3 May 2024) for the SCS analyses, 598 subjects with PD had received at least one dose of ND0612 DP, with a cumulative exposure of 974.2 person years. Of those 598 subjects, 223 had been treated for at least one year with the final ND0612 DP formulation and the to-be-marketed 24-hour dosing regimen, including 206 subjects treated with the maximum recommended daily dose of ND0612 (LD/CD 720/90 mg/day).

As of 3 May 2024, of the 598 subjects in Safety Pool 1, 134 (22.4%) were still under treatment in the open-label extensions of studies ND0612H-012 and ND0612-317, 74 (12.4%) had completed the treatment and 390 (65.2%) had discontinued the treatment.

Of the 419 subjects in the Safety Pool 2, 111 (26.5%) were still under treatment in the open-label extensions of study ND0612H-012 or ND0612-317, 15 (3.6%) had completed the treatment and 293 (69.9%) had discontinued the treatment.

In Safety Pool 1, the total duration of exposure was 974.2 person-years, with a mean (SD) exposure of 595.0 (681.31) days and median (range) exposure of 328.0 (2, 2769) days. Exposure by age category, <65 years; ≥65 - <75 years; ≥75 - <85 years; and ≥85 years, was 444.8, 378.3, 148.6 and 2.4 person-years, respectively.

In Safety Pool 2, the total duration of exposure was 663.0 person-years, with a mean (SD) exposure of 578.0 (580.61) days and a median (range) of 478.0 (2, 2769) days. Exposure by age category, <65 years; ≥65 - <75 years; ≥75 - <85 years; and ≥85 years, was 308.2, 260.6, 92.4 and 1.9 person-years, respectively.

The largest exposure (517.3 person-years) was accumulated in the long-term safety study ND0612H-012. At the cut-off date for the integrated safety analyses, 112 (52.3%) subjects in this study had been exposed to ND0612 for at least one year and 49 (22.9%) for at least five years.

In study ND0612-317, subjects were exposed for a total of 452.4 person-years. At the cut-off date for the integrated safety analyses, of the 322 subjects that had received at least one dose of ND0612, 175 (54.3%) had been exposed for at least one year.

Of the 419 subjects in Safety Pool 2, 371 (88.5%) received the highest daily dose of ND0612 (LD/CD 720/90 mg/day), including 206 (49.2%) who received this treatment (modal dose) for at least one year. Exposure adjusted for treatment interruptions showed comparable results.

Please refer to the Table below for a complete overview of treatment exposure by study and Safety Pools 1 and 2.

Table 26. ND0612 Treatment Exposure by Study and Safety Pools 1 and 2

Variable	Statistic	ND0612/002 (N = 8)	ND0612/003 (N = 24)	ND0612/004 (N = 16)	ND0612H-006 (N = 38)	ND0612H-012 (N = 214) Core Period + OLE	ND0612-317 (N = 322) Core Period + OLE	Safety Pool 1 (N = 598)	Safety Pool 2 (N = 419)
Subjects Exposed to ND0612 Treatment	n (%)	8 (100)	24 (100)	16 (100)	38 (100)	214 (100)	322 (100)	598 (100)	419 (100)
Duration of Exposure to ND0612 Treatment (days)	Mean	2	16.6	2.9	27.3	882.9	513.2	595.0	578.0
	SD	0	5.75	0.25	5.66	911.04	425.20	681.31	580.61
	SE	0	1.17	0.06	0.92	62.28	23.70	27.86	28.36
	Median	2	15.0	3.0	29.0	556.0	509.0	328.0	478.0
	Min, Max	2, 2	7, 24	2, 3	4, 38	2, 2739	4, 1453	2, 2769	2, 2769
Total Exposure to ND0612 Treatment in Person Years[1]		0	1.1	0.1	2.8	517.3	452.4	974.2	663.0
Categorical Yearly Distribution									
< 1 Year	n (%)	8 (100)[2]	24 (100)[2]	16 (100)[2]	38 (100)[2]	102 (47.7)	147 (45.7)	311 (52.0)	196 (46.8)
≤29 Days	n (%)	8 (100)	24 (100)	16 (100)	31 (81.6)	33 (15.4)	43 (13.4)	136 (22.7)	64 (15.3)
30 - 89 Days	n (%)	0	0	0	7 (18.4)	26 (12.1)	43 (13.4)	71 (11.9)	52 (12.4)
90 - 179 Days	n (%)	0	0	0	0	25 (11.7)	33 (10.2)	58 (9.7)	42 (10.0)
180 - 364 Days	n (%)	0	0	0	0	18 (8.4)	28 (8.7)	46 (7.7)	38 (9.1)
≥ 1 Year - < 2 Years	n (%)	0	0	0	0	18 (8.4)	57 (17.7)	75 (12.5)	67 (16.0)
≥ 2 Years - < 3 Years	n (%)	0	0	0	0	18 (8.4)	88 (27.3)	106 (17.7)	97 (23.2)
≥ 3 Years - < 4 Years	n (%)	0	0	0	0	12 (5.6)	30 (9.3)	42 (7.0)	36 (8.6)
≥ 4 Years - < 5 Years	n (%)	0	0	0	0	15 (7.0)	0	15 (2.5)	8 (1.9)
≥ 5 Years - < 6 Years	n (%)	0	0	0	0	19 (8.9)	0	19 (3.2)	3 (0.7)
≥ 6 Years - < 7 Years	n (%)	0	0	0	0	22 (10.3)	0	22 (3.7)	4 (1.0)
≥ 7 Years - < 8 Years	n (%)	0	0	0	0	8 (3.7)	0	8 (1.3)	8 (1.9)

LD/CD: Levodopa carbidopa; Max: Maximum; mg: Milligram; Min: Minimum; mL: Milliliter; OLE: Open-label extension; SD: Standard deviation; SE: Standard error.
Source: SCS TFLs, Tables 3.1, 3.2, 3.3; Listing 3.1

[1] Total exposure to ND0612 in person years: sum of exposure to ND0612 across all subjects in a study.

[2] Study duration of 24 hours (single dose, cross-over design with one week washout) in Study ND0612/002, 21 days in Study ND0612/003, three days in Study ND0612/004 and up to four weeks in Study ND0612H-006.

A total of 419 subjects with PD were included in Safety Pool 2. At enrolment, the subject mean (SD) age was 64.1 (8.91) years (range: 35-84 years). About 62.3% of subjects were males. The median BMI of the subjects was 26.42 kg/m2, with 6.7% of them having a BMI <20 kg/m2; 34.8% of subjects were from the US, 43.9% from Western Europe and Israel, and 21.2% from Eastern Europe; the majority of subjects were white (93.8%).

Subjects had a mean time since PD diagnosis of 9.93 years, a mean "OFF" time of 5.37 h, with 96.6% of subjects having a modified Hoehn and Yahr score of 2-3.

At screening/baseline, the mean (SD) oral daily LD dose was 986 (464.69) mg. Of the 419 subjects in Safety Pool 2, 24.8% had been receiving an oral LD dose of <700 mg, 42.2% ≥700≤1000 mg, 29.4% >1000-≤2000 mg and 3.6% of subjects had been receiving an LD dose of >2000 mg.

Table 27. Demographics and other subjects characteristics – Safety Pool 1 and 1

Variable	Statistic	Safety Pool 1 (N=598)	Safety Pool 2 (N=419)
Age (years)	n	598	419
	Mean	64.1	64.1
	SD	8.73	8.91
	SE	0.36	0.44
	Median	64.8	64.9
	Min, Max	35, 84	35, 84
Age Category			
<65 years	n (%)	304 (50.8)	212 (50.6)
≥65 - <75 years	n (%)	251 (42.0)	173 (41.3)
≥75 - <85 years	n (%)	43 (7.2)	34 (8.1)
≥85 years	n (%)	0	0
Gender			
Female	n (%)	216 (36.1)	158 (37.7)

Variable	Statistic	Safety Pool 1 (N=598)	Safety Pool 2 (N=419)
Male	n (%)	382 (63.9)	261 (62.3)
Race			
White	n (%)	564 (94.3)	393 (93.8)
Native Hawaiian or Other Pacific Islander	n (%)	1 (0.2)	0
Black or African American	n (%)	10 (1.7)	8 (1.9)
Asian	n (%)	16 (2.7)	13 (3.1)
American Indian or Alaska Native	n (%)	1 (0.2)	0
Not Reported	n (%)	5 (0.8)	5 (1.2)
Other	n (%)	1 (0.2)	0
Ethnicity			
Hispanic or Latino	n (%)	44 (7.4)	36 (8.6)
Not Hispanic or Latino	n (%)	493 (82.4)	370 (88.3)
Not Reported	n (%)	61 (10.2)	13 (3.1)
Region Category 1			
US	n (%)	238 (39.8)	146 (34.8)
Non-US	n (%)	360 (60.2)	273 (65.2)
Region Category 2			
US Sites	n (%)	238 (39.8)	146 (34.8)
Western Europe & Israel	n (%)	260 (43.5)	184 (43.9)
Eastern Europe	n (%)	100 (16.7)	89 (21.2)
Baseline BMI (kg/m^2)	n	595	416
	Mean	26.77	26.42
	SD	5.035	4.736
	SE	0.206	0.232
	Median	26.08	25.79
	Min, Max	15.6, 52.4	16.2, 44.1
BMI Category (kg/m^2)			
<20	n (%)	39 (6.6)	28 (6.7)
20≤BMI<30	n (%)	411 (69.1)	294 (70.7)
≥30	n (%)	145 (24.4)	94 (22.6)
Time since Diagnosis of PD (years)	n	598	419
	Mean	9.40	9.93
	SD	4.686	4.917
	SE	0.192	0.24
	Median	8.74	9.29
	Min, Max	0.4, 34.7	0.7, 34.7

Variable	Statistic	Safety Pool 1 (N=598)	Safety Pool 2 (N=419)
Time since Onset of Motor Fluctuations (years)	n	598	419
	Mean	4.93	4.83
	SD	4.031	4.015
	SE	0.165	0.196
	Median	3.69	3.66
	Min, Max	0.1, 28.7	0.1, 28.7
Time since Onset of Dyskinesia (years)	n	465	337
	Mean	3.82	3.81
	SD	3.552	3.582
	SE	0.165	0.195
	Median	2.92	2.92
	Min, Max	0.0, 26.4	0.0, 26.4
Cognitive Status: Mini–Mental State Examination (MMSE) Total Score	n	577	406
	Mean	28.7	28.7
	SD	1.36	1.42
	SE	0.06	0.07
	Median	29.0	29
	Min, Max	24, 30	24, 30
Cognitive Status: Mini–Mental State Examination (MMSE) Total Score			
24	n (%)	4 (0.7)	4 (1.0)
25	n (%)	13 (2.3)	12 (3.0)
26	n (%)	23 (4.0)	17 (4.2)
27	n (%)	65 (11.3)	48 (11.8)
28	n (%)	113 (19.6)	74 (18.2)
29	n (%)	137 (23.7)	99 (24.4)
30	n (%)	222 (38.5)	152 (37.4)
Modified Hoehn & Yahr scale stage			
Any	n (%)	583 (100)	404 (100)
0	n (%)	1 (0.2)	1 (0.2)
1	n (%)	6 (1.0)	5 (1.2)
1.5	n (%)	18 (3.1)	8 (2.0)
2	n (%)	258 (44.3)	187 (46.3)
2.5	n (%)	129 (22.1)	86 (21.3)
3	n (%)	169 (29.0)	117 (29.0)

Variable	Statistic	Safety Pool 1 (N=598)	Safety Pool 2 (N=419)
4	n (%)	2 (0.3)	0
5	n (%)	0	0
Baseline UPDRS Part III Motor Scores	n	585	416
	Mean	34.49	37.81
	SD	15.863	15.663
	SE	0.656	0.768
	Median	34.00	37
	Min, Max	4.0, 104.0	4.0, 104.0
Baseline “OFF” Time (h)	n	540	416
	Mean	5.45	5.37
	SD	2.289	2.018
	SE	0.098	0.099
	Median	5.24	5.20
	Min, Max	0.0, 16.0	0.0, 13.8
Screening/Baseline LD Daily Dose (mg)	n	598	419
	Mean	944.67	986
	SD	495.365	464.691
	SE	20.257	22.702
	Median	850.00	900
	Min, Max	50.0, 4020.0	275.0, 4020.0
Screening/Baseline LD Daily Dose (mg)	n (%)	598 (100)	419 (100)
BL LD<700	n (%)	178 (29.8)	104 (24.8)
700<=BL LD<=1000	n (%)	237 (39.6)	177 (42.2)
1000<BL LD<=2000	n (%)	163 (27.3)	123 (29.4)
BL LD>2000	n (%)	20 (3.3)	15 (3.6)

BL: Baseline; BMI: Body mass index; cm: Centimeters; h: Hours; kg: Kilogram; LD: Levodopa; m: Meter; max: Maximum; mg: Milligram; min: Minimum; N: Number of subjects; n: Number of subjects for each category; PD: Parkinson’s Disease; SD: Standard deviation; SE: Standard error; UPDRS: Unified Parkinson’s Disease Rating Scale; US: United States.

Sources: SCS TFLs, Tables 2.1 and 2.2

Age was derived as a difference between date of birth and date of informed consent.

Baseline was defined as the last available, valid, non-missing assessment before the first ND0612 treatment in the specific study.

Baseline “OFF” time for studies ND0612/002, ND0612/003 and ND0612/004 was not included as it was measured with in-clinic diaries.

Cognitive Status: MMSE Total Score was not included for Study ND0612/002 as it was not captured.

Table 28. Patient exposure (cut-off date: 3 May 2024)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
Blinded studies (placebo-controlled)	38	32	0	0
- ND0612/002	8	8	0	0
- ND0612/003	30	24	0	0
Blinded studies (active-controlled)	381	322	322	175
- ND0612-317	381	322	322	175
Open studies	268	268	114	112
- ND0612-004	16	16	0	0
- ND0612H-006	38	38	24	0
- ND0612H-012* **	214	214	90	112
Healthy volunteers studies	146			

* Received at least 1 dose of active treatment

** 12+ months exposure data

*** Includes participants from ND0612/002, ND0612/003, ND0612-004 and ND0612H-006

5.4.3. Adverse events

Data was presented for ND0612-317 core period, ND0612H-012 1-year study, and the integrated Safety Pools.

The table provides a summary for the Safety Pools 1 and 2, including incidence (number and percentage), exposure-adjusted incidence rate (EAIR), number of TEAE events and event rates. The EAIR was calculated as the total number of subjects who experienced an event (at least once) divided by the total time at risk for the event (person-years) of the group. The event rate was calculated as the total number of events divided by the total exposure time.

Considering the continuous SC administration of ND0612 DP, infusion site reactions (ISRs) were expected. AEs were classified upon medical review as "AE-ISR" or "AE-other" to ensure consistency of ISR classification across all studies. In addition, closely related ISR Medical dictionary for regulatory activities (MedDRA) preferred terms (PTs) were analysed as grouped PTs to avoid dilution of safety signals. ISRs grouped PTs were defined for infusion site infection, infusion site haematoma, infusion site nodule, infusion site eschar, infusion site erythema, infusion site pain and infusion site swelling.

In the safety Pools, to avoid dilution of a potential safety signal, a pooling strategy was implemented for the analysis of systemic AEs of interest. The following FDA MedDRA Queries (FMQs), Standardized MedDRA Queries (SMQs) and Sponsor Customized MedDRA Queries (CMQs) were used:

- FDA MedDRA Queries (FMQs) for hypotension, depression, psychosis, falls, somnolence, insomnia, peripheral edema and anemia.
- Standardized MedDRA Query (SMQ) for drug abuse, dependence and withdrawal.

- Sponsor Customized MedDRA Queries (CMQs) for impulse-control disorder, folate deficiency, vitamin B12 deficiency, vitamin B6 deficiency and abuse liability.

In addition, all AEs coded to the SMQ hypersensitivity and peripheral neuropathy underwent a 2-step review, that included the sponsor's medical review followed by adjudication by an external expert.

The overall summary of TEAEs for Safety Pool 1 and 2 is presented in Table 29. Data were overall similar in both Safety Pools.

Table 29. Overall summary of Treatment-Emerging Adverse Events – Safety Pools 1 and 2

	Safety Pool 1				Safety Pool 2			
	(N=598; PY=974.2)				(N=419; PY=663.0)			
	Subjects n (%)	EAIR	Events m	Event Rate	Subjects n (%)	EAIR	Events m	Event Rate
Any TEAEs	541 (90.5)	9.935	6540	6.713	398 (95.0)	11.916	5109	7.705
Drug-related TEAEs	496 (82.9)	4.106	3824	3.925	385 (91.9)	6.490	3294	4.968
Severe TEAEs	127 (21.2)	0.155	280	0.287	96 (22.9)	0.173	208	0.314
Serious TEAEs	142 (23.7)	0.181	357	0.366	103 (24.6)	0.187	271	0.409
Drug-related Serious TEAEs	41 (6.9)	0.045	58	0.060	31 (7.4)	0.049	42	0.063
TEAEs Leading to Study Drug Discontinuation	155 (25.9)	0.163	292	0.300	112 (26.7)	0.172	235	0.354
TEAEs Leading to Dose Adjustment/Temporary Withdrawal	107 (17.9)	0.130	187	0.192	77 (18.4)	0.134	132	0.199
TEAEs Leading to Death	24 (4.0)	0.025	27	0.028	18 (4.3)	0.027	21	0.032

EAIR: Exposure-adjusted incidence rate; m: Number of TEAEs occurred; N: Number of subjects; n: Number of subjects for each parameter; PY: Person-years; TEAE: Treatment-emergent adverse event.

Source: SCS TFLs, Tables 4.1.1 and 4.1.2

Common Adverse Events – Study ND0612-317

During the ND0612 Open Label (OL) Conversion Period, 287 (89.1%) subjects reported at least one TEAE (reference: ND0612-317 CSR, Table 14.3.1.1.1b). The most common TEAEs were ISRs: infusion site nodule (206 [64.0%] subjects), infusion site haematoma (205 [63.7%] subjects), infusion site pain (55 [17.1%] subjects), infusion site erythema (25 [7.8%] subjects), infusion site infection (18 [5.6%] subjects), and infusion site swelling (15 [4.7%] subjects) (Table 2.7.4-11). Other TEAEs reported in at least 5% of subjects included dyskinesia (9.3% of subjects), ON and OFF phenomenon and fall (each reported in 5.3% of subjects).

Table 30. Most common (reported in at least 5% of subjects [rounded] treatment-emerging adverse events by Grouped Preferred Term / Preferred Term (ND0612 set)

Most common TEAEs by grouped PT/PT	ND0612 Open-label Conversion Period N=322, PY=35.5
Infusion site nodule[1]	206 (64.0%)
Infusion site haematoma[1]	205 (63.7%)
Infusion site pain[1]	55 (17.1%)
Dyskinesia	30 (9.3%)
Infusion site erythema[1]	25 (7.8%)
Infusion site infection[1]	18 (5.6%)
On and off phenomenon	17 (5.3%)
Fall	17 (5.3%)
Infusion site swelling[1]	15 (4.7%)

N: Number of subjects; PT: Preferred term; PY: Person-years; TEAE: Treatment-emergent adverse event.

Source: ND0612-317 CSR, Table 14.3.1.2.1b.

Adverse events were coded using MedDRA version 25.0

[1] Grouped PTs.

During the double-blind double-dummy (DBDD) period, 103 (80.5%) subjects in the ND0612 arm and 97 (74.0%) subjects in the IR-LD/CD arm reported at least one TEAE (reference: ND0612-317 CSR, Table 14.3.1.1.1).

The following ISRs were reported with a higher incidence (at least 1.5 times more frequent) in the ND0612 arm compared to the IR-LD/CD arm: infusion site hematoma (30.5% vs. 13.0% of subjects, respectively), infusion site infection (10.2% vs. 2.3% of subjects, respectively), and infusion site erythema (9.4% vs. 2.3% of subjects, respectively).

Infusion site nodule and infusion site pain were reported at a comparable incidence in both ND0612 arm and IR-LD/CD arm (infusion site nodule: 25.8% vs. 27.5% of subjects, respectively; and infusion site pain: 8.6% vs. 6.9% of subjects, respectively). Infusion site haemorrhage was reported at a lower incidence (at least 1.5 times less frequent) in the ND0612 arm compared to the IR-LD/CD arm (0.8% vs. 5.3% of subjects, respectively).

Of the TEAEs reported in at least 5% of subjects in any treatment arm during the DBDD Period, no TEAE was reported at a higher incidence (at least 1.5 times more frequent) in the ND0612 arm compared to the IR-LD/CD.

Table 31. Study ND0612-317 – Most common (reported in at least 5% of subject within a treatment arm) treatment-emerging adverse events by SOC, Grouped Preferred Term / Preferred Term during the open-label conversion and the DBDD periods (Safety set)

	Oral IR-LD/CD (N=131)						ND0612 (N=128)					
	Conversion[1] PY=15.6			DBDD PY=29.0			Conversion PY=15.3			DBDD PY=28.9		
System Organ Class Grouped PT/PT	Subjects n (%)	No. of Events	Event Rate	Subjects n (%)	No. of Events	Event Rate	Subjects n (%)	No. of Events	Event Rate	Subjects n (%)	No. of Events	Event Rate
Infections and infestations	8 (6.1)	8	0.51	3 (2.3)	3	0.1	4 (3.1)	5	0.33	13 (10.2)	16	0.55
Infusion site infection[2]	8 (6.1)	8	0.51	3 (2.3)	3	0.1	4 (3.1)	5	0.33	13 (10.2)	16	0.55
Metabolism and nutrition disorders	2 (1.5)	2	0.13	1 (0.8)	1	0.03	8 (6.3)	8	0.52	4 (3.1)	4	0.14
Vitamin B6 deficiency	2 (1.5)	2	0.13	1 (0.8)	1	0.03	8 (6.3)	8	0.52	4 (3.1)	4	0.14
Psychiatric disorders	0	0	0	9 (6.9)	11	0.38	1 (0.8)	1	0.07	6 (4.7)	7	0.24
Anxiety	0	0	0	9 (6.9)	11	0.38	1 (0.8)	1	0.07	6 (4.7)	7	0.24
Nervous system disorders	20 (15.3)	21	1.35	24 (18.3)	29	1.00	16 (12.5)	18	1.17	10 (7.8)	10	0.35
On and off phenomenon	9 (6.9)	9	0.58	13 (9.9)	14	0.48	3 (2.3)	3	0.20	5 (3.9)	5	0.17
Dyskinesia	11 (8.4)	11	0.71	5 (3.8)	5	0.17	10 (7.8)	12	0.78	3 (2.3)	3	0.10
Headache	1 (0.8)	1	0.06	8 (6.1)	10	0.34	3 (2.3)	3	0.20	2 (1.6)	2	0.07
General disorders and administration site conditions	114 (87.0)	471	30.22	51 (38.9)	148	5.1	102 (79.7)	335	21.84	64 (50.0)	256	8.86
Infusion site haematoma[2]	89 (67.9)	203	13.02	17 (13.0)	46	1.59	78 (60.9)	146	9.52	39 (30.5)	82	2.84
Infusion site nodule[2]	92 (70.2)	215	13.79	36 (27.5)	80	2.76	80 (62.5)	151	9.84	33 (25.8)	140	4.85
Infusion site erythema[2]	8 (6.1)	9	0.58	3 (2.3)	3	0.10	8 (6.3)	13	0.85	12 (9.4)	17	0.59
Infusion site pain[2]	18 (13.7)	31	1.99	9 (6.9)	10	0.34	13 (10.2)	15	0.98	11 (8.6)	14	0.48

			Oral IR-LD/CD (N=131)						ND0612 (N=128)					
			Conversion[1] PY=15.6			DBDD PY=29.0			Conversion PY=15.3			DBDD PY=28.9		
)														
;	Event Rate	System Organ Class Grouped PT/PT	Subjects n (%)	No. of Events	Event Rate	Subjects n (%)	No. of Events	Event Rate	Subjects n (%)	No. of Events	Event Rate	Subjects n (%)	No. of Events	Event Rate
8)	0.07	Infusion site haemorrhage[2]	7 (5.3)	7	0.51	7 (5.3)	7 (5.3)	0.21	3 (2.3)	3 (1.6)	0.12	1 (0.8)	1 (0.	
8)	1	0.03	Infusion site swelling[2]	5 (3.8)	5	0.32	0	0	0	7 (5.5)	8	0.52	1 (0.	
0)	12	0.42	Injury, poisoning and procedural complications	8 (6.1)	11	0.71	16 (12.2)	20	0.69	6 (4.7)	8	0.52	9 (7.	
.52	9 (7.0)	12	0.42	Fall	8 (6.1)	11	0.71	16 (12.2)	20	0.69	6 (4.7)	8	0.	

one TEAE; PT: Preferred term; PY: Person- DBDD: Double-blind double-dummy; IR-LD/CD: Immediate release levodopa/carbidopa; N: Number of subjects; n: Number of subjects with at least years; TEAE: Treatment-emergent adverse event.

Source: ND0612-317 CSR, Table 14.3.1.2.2

idomization in the DBDD Period of the study.

[1] All subjects were exposed to ND0612 in the ND0612 OL Conversion Period and then received either ND0612 or IR-LD/CD after rar

[2] Grouped PT.

Adverse events were coded using MedDRA version 25.0.

ing to the relevant treatment.

Event rates are calculated as number of events divided by exposure to study treatment expressed as patient years accord

jects reporting TEAEs in the ND0612 group during the DBDD Period.

The table is sorted using the internationally agreed order for MedDRA SOC sorting and by descending frequency of sub

Common Adverse Events - ND0612H-012

In study ND0612H-012 infusion site reactions (ISRs) with an incidence of ≥5% in the overall population included infusion site nodule (66 [30.8%] subjects), infusion site hematoma (54 [25.2%] subjects), infusion site pain (28 [13.1%] subjects), infusion site infection (25 [11.7%] subjects), infusion site eschar (17 [7.9%] subjects) and infusion site erythema (16 [7.5%] subjects), as detailed in the Table below.

Systemic AEs with an incidence of ≥5% in the overall population were fall and urinary tract infection (each reported in 20 [9.3%] subjects), nausea (18 [8.4%] subjects), and dyskinesia (16 [7.5%] subjects).

Table 32. Study ND0612H-012 – Summary of most common (reported in at least 5% of subject [rounded]) treatment-emerging adverse events by Grouped Preferred Term / Preferred Term during the open-label conversion and the DBDD periods (Safety set)

	Total (N=214 PY=135.8)	
Grouped Preferred Term / Preferred Term	**Subjects n (%)**	**Incidence Rate**
Infusion site nodule	66 (30.8)	0.49
Infusion Site Hematoma[1]	54 (25.2)	0.4
Infusion site pain	28 (13.1)	0.21
Infusion Site Infection[1]	25 (11.7)	0.18
Fall	20 (9.3)	0.15
Urinary tract infection	20 (9.3)	0.15
Nausea	18 (8.4)	0.13
Infusion Site Eschar[1]	17 (7.9)	0.13
Infusion site erythema	16 (7.5)	0.12
Dyskinesia	16 (7.5)	0.12
Infusion site edema	10 (4.7)	0.07
Anxiety	10 (4.7)	0.07

N: Number of subjects; n: Number of subjects with at least one TEAE; TEAE: Treatment-emergent adverse event, PY: Person-years.

Source: ND0612H-012 CSR, Table 14.3.1.2.2d

[1] Grouped PTs

AE were coded into system organ class (SOC) and preferred term (PT) using MedDRA version 22.0.

The incidence rate is calculated as number of subjects with events divided by exposure to study treatment expressed as cases for one person-year.

AEs were sorted by decreasing incidence.

Common Adverse Events - Safety Pool 1 and 2

The most common TEAEs (PTs or grouped PTs reported in at least 10% of subjects) in the Safety Pool 2 were:

- ISRs: infusion site nodule (70.4%), infusion site hematoma (64.9%), infusion site pain (23.2%), infusion site infection (19.3%), infusion site erythema (18.4%), infusion site eschar (12.9%);
- Other AEs: fall (20.5%), dyskinesia (13.6%), ON and OFF phenomenon (12.4%), COVID-19 (11.2%) and vitamin B6 deficiency (10.0%).

Table 33. Safety Pool 2, treatment-emerging adverse events reported in at least 5% of subjects by SOC and Grouped Preferred Term / Preferred Term

	Safety Pool 2 (N=419; PY=663.0)			
Systems Organ Class Grouped PT/PT	**Subjects n (%)**	**EAIR**	**Events m**	**Event Rate**
Any TEAEs	**398 (95.0)**	**11.916**	**5109**	**7.705**
Infections and infestations	**169 (40.3)**	**0.433**	**394**	**0.594**
Infusion Site Infection[1]	81 (19.3)	0.152	152	0.229
Urinary tract infection	33 (7.9)	0.053	56	0.084
COVID-19	47 (11.2)	0.078	52	0.078
Metabolism and nutrition disorders	**79 (18.9)**	**0.143**	**133**	**0.201**
Vitamin B6 deficiency	42 (10.0)	0.070	53	0.080
Psychiatric disorders	**117 (27.9)**	**0.235**	**230**	**0.347**
Anxiety	31 (7.4)	0.050	36	0.054
Insomnia	27 (6.4)	0.043	27	0.041
Nervous system disorders	**198 (47.3)**	**0.488**	**428**	**0.646**
Dyskinesia	57 (13.6)	0.095	81	0.122
On and off phenomenon	52 (12.4)	0.087	70	0.106
Parkinson's disease	30 (7.2)	0.048	32	0.048
Headache	22 (5.3)	0.035	27	0.041
Dizziness	21 (5.0)	0.032	24	0.036

Table 33 (continued). Safety Pool 2, treatment-emerging adverse events reported in at least 5% of subjects by SOC and Grouped Preferred Term / Preferred Term

	Safety Pool 2 (N=419; PY=663.0)			
Musculoskeletal and connective tissue disorders	**92 (22.0)**	**0.183**	**192**	**0.290**
Arthralgia	25 (6.0)	0.041	35	0.053
Back pain	25 (6.0)	0.040	30	0.045
Pain in extremity	22 (5.3)	0.035	27	0.041
General disorders and administration site conditions	**371 (88.5)**	**5.363**	**2813**	**4.243**
Infusion Site Nodule[1]	295 (70.4)	1.638	1240	1.870
Infusion Site Haematoma[1]	272 (64.9)	1.232	917	1.383
Infusion Site Pain[1]	97 (23.2)	0.172	164	0.247
Infusion Site Erythema[1]	77 (18.4)	0.142	129	0.195
Infusion Site Eschar[1]	54 (12.9)	0.093	84	0.127
Infusion Site Swelling[1]	37 (8.8)	0.062	47	0.071
Infusion Site Haemorrhage	22 (5.3)	0.034	28	0.042
Injury, poisoning and procedural complications	**111 (26.5)**	**0.213**	**319**	**0.481**
Fall	86 (20.5)	0.152	175	0.264
Contusion	23 (5.5)	0.036	31	0.047

EAIR: Exposure-adjusted incidence rate; m: Number of TEAEs occurred; N: Number of subjects; n: Number of subjects for each parameter; PT: Preferred term; PY: Person-years; TEAE: Treatment-emergent adverse event.

Source: SCS TFLs, Table 4.12.4a

[1] Grouped PT.

Adverse events were coded using MedDRA version 26.1.

Table 34. Summary of treatment-emerging adverse events by SOC, Grouped Preferred Terms / Preferred Terms and Time of Onset (Cohort 2)

System Organ Class Preferred Term	Time of Onset	Cohort 2 (N=419; PY=663.0) Subjects n (%)	EAIR	Events m	Event Rate
Any TEAEs	Total (N=419; PY=663.0)	397 (94.7)	11.984	5085	7.669
	<7 Days (N=419; PY=663.0)	236 (56.3)	0.791	608	0.917
	7-30 Days (N=411; PY=662.9)	270 (65.7)	1.013	854	1.288
	>30 Days - 1 Year (N=354; PY=659.9)	294 (83.1)	1.963	2120	3.212
	>1 Year - 2 Years (N=223; PY=609.6)	150 (67.3)	0.386	890	1.460
	>2 Years - 3 Years (N=156; PY=502.8)	92 (59.0)	0.232	338	0.672
	>3 Years - 4 Years (N=59; PY=259.4)	35 (59.3)	0.170	127	0.490
	>4 Years - 5 Years (N=23; PY=138.7)	18 (78.3)	0.164	67	0.483
	>5 Years - 6 Years (N=15; PY=103.1)	11 (73.3)	0.128	47	0.456
	>6 Years - 7 Years (N=12; PY=86.4)	9 (75.0)	0.114	29	0.336
	>7 Years - 8 Years (N=8; PY=59.1)	3 (37.5)	0.052	5	0.085

System Organ Class Preferred Term	Time of Onset	Cohort 2 (N=419; PY=663.0) Subjects n (%)	EAIR	Events m	Event Rate
General disorders and administration site conditions(Cont'd)					
Infusion Site Nodule*	Total (N=419; PY=663.0)	295 (70.4)	1.638	1233	1.860
	<7 Days (N=419; PY=663.0)	84 (20.0)	0.166	130	0.196
	7-30 Days (N=411; PY=662.9)	164 (39.9)	0.379	301	0.454
	>30 Days - 1 Year (N=354; PY=659.9)	131 (37.0)	0.293	539	0.817
	>1 Year - 2 Years (N=223; PY=609.6)	27 (12.1)	0.047	214	0.351
	>2 Years - 3 Years (N=156; PY=502.8)	17 (10.9)	0.036	43	0.086
	>3 Years - 4 Years (N=59; PY=259.4)	2 (3.4)	0.008	3	0.012
	>4 Years - 5 Years (N=23; PY=138.7)	2 (8.7)	0.015	2	0.014
	>5 Years - 6 Years (N=15; PY=103.1)	0	0	0	0
	>6 Years - 7 Years (N=12; PY=86.4)	1 (8.3)	0.012	1	0.012
	>7 Years - 8 Years (N=8; PY=59.1)	0	0	0	0

System Organ Class Preferred Term	Time of Onset	Cohort 2 (N=419; PY=663.0) Subjects n (%)	EAIR	Events m	Event Rate
General disorders and administration site conditions(Cont'd)					
Infusion Site Haematoma*	Total (N=419; PY=663.0)	272 (64.9)	1.232	915	1.380
	<7 Days (N=419; PY=663.0)	137 (32.7)	0.325	205	0.309
	7-30 Days (N=411; PY=662.9)	131 (31.9)	0.274	223	0.336
	>30 Days - 1 Year (N=354; PY=659.9)	104 (29.4)	0.210	338	0.512
	>1 Year - 2 Years (N=223; PY=609.6)	22 (9.9)	0.038	119	0.195
	>2 Years - 3 Years (N=156; PY=502.8)	9 (5.8)	0.018	29	0.058
	>3 Years - 4 Years (N=59; PY=259.4)	0	0	0	0
	>4 Years - 5 Years (N=23; PY=138.7)	1 (4.3)	0.007	1	0.007
	>5 Years - 6 Years (N=15; PY=103.1)	0	0	0	0
	>6 Years - 7 Years (N=12; PY=86.4)	0	0	0	0
	>7 Years - 8 Years (N=8; PY=59.1)	0	0	0	0

System Organ Class Preferred Term	Time of Onset	Cohort 2 (N=419; PY=663.0) Subjects n (%)	EAIR	Events m	Event Rate
General disorders and administration site conditions(Cont'd)					
Infusion Site Eschar*	Total (N=419; PY=663.0)	54 (12.9)	0.093	84	0.127
	<7 Days (N=419; PY=663.0)	1 (0.2)	0.002	1	0.002
	7-30 Days (N=411; PY=662.9)	12 (2.9)	0.019	13	0.020
	>30 Days - 1 Year (N=354; PY=659.9)	26 (7.3)	0.041	34	0.052
	>1 Year - 2 Years (N=223; PY=609.6)	13 (5.8)	0.022	18	0.030
	>2 Years - 3 Years (N=156; PY=502.8)	5 (3.2)	0.010	5	0.010
	>3 Years - 4 Years (N=59; PY=259.4)	6 (10.2)	0.024	6	0.023
	>4 Years - 5 Years (N=23; PY=138.7)	1 (4.3)	0.007	1	0.007
	>5 Years - 6 Years (N=15; PY=103.1)	4 (26.7)	0.041	4	0.039
	>6 Years - 7 Years (N=12; PY=86.4)	2 (16.7)	0.024	2	0.023
	>7 Years - 8 Years (N=8; PY=59.1)	0	0	0	0

System Organ Class Preferred Term	Time of Onset	Cohort 2 (N=419; PY=663.0) Subjects n (%)	EAIR	Events m	Event Rate
Infections and infestations(Cont'd)					
Infusion Site Infection*	Total (N=419; PY=663.0)	80 (19.1)	0.150	151	0.228
	<7 Days (N=419; PY=663.0)	1 (0.2)	0.002	1	0.002
	7-30 Days (N=411; PY=662.9)	13 (3.2)	0.020	14	0.021
	>30 Days - 1 Year (N=354; PY=659.9)	53 (15.0)	0.093	87	0.132
	>1 Year - 2 Years (N=223; PY=609.6)	15 (6.7)	0.026	19	0.031
	>2 Years - 3 Years (N=156; PY=502.8)	10 (6.4)	0.021	13	0.026
	>3 Years - 4 Years (N=59; PY=259.4)	4 (6.8)	0.016	7	0.027
	>4 Years - 5 Years (N=23; PY=138.7)	6 (26.1)	0.046	8	0.058
	>5 Years - 6 Years (N=15; PY=103.1)	2 (13.3)	0.020	2	0.019
	>6 Years - 7 Years (N=12; PY=86.4)	0	0	0	0
	>7 Years - 8 Years (N=8; PY=59.1)	0	0	0	0

Infusion site nodule and infusion site haematoma were mainly reported within the first year of treatment. Of note: as per the reporting rules in Studies ND0612H-012 and ND0612-317, the sites could report just the first occurrence of these events and keep the AE open in case events were multiple and recurrent (provided severity and skin location did not change).

Infusion site infection was reported more frequently in the first year of treatment, with incidence decreasing in the following years, and being overall stable in the long-term. In the first year, infusion site infection was reported by 0.2% of subjects in the first week (<7 days), 3.2% in the first month (7-30 days) and by 15.0% of subjects thereafter (>30 days – 1 year). In the 2nd, 3rd and 4th year of treatment the incidence of infusion site infection was 6.7%, 6.4% and 6.8%, respectively. In the following years the incidence ranges between 0% and 26.1%, but caution is needed in the interpretation of these results, due to the limited number of subjects with exposure above 5 years (n=23) (reference: SCS TFLs, Table 4.11.2a).

The analysis of time to onset for systemic events that may be reported with LD treatment (such as psychotic events, dyskinesia, hypotension, impulse-control disorders, vitamin B6 deficiency) did not reveal any relationship with long-term exposure to ND0612.

Common ADVERSE EVENTS - Safety Pool 3

The most commonly reported TEAEs in healthy volunteers' studies (PTs reported in ≥10% of subjects) were infusion site pain (83 [56.8%] subjects), infusion site nodule (55 [37.7%]), infusion site haematoma (16 [11.0%]), and headache (15 [10.3%]) (reference: SCS TFLs, Table 4.3.3).

Adverse Events by severity - ND0612-317

During the Conversion Period (ND0612 set), most AEs were of mild intensity. Twelve (3.7%) subjects reported at least one severe TEAE (total of 22 severe TEAEs). The only severe AEs reported in more than one subject were ISRs: infusion site pain (reported by three subjects), infusion site infection (reported by two subjects) and infusion site nodules (reported by two subjects) (reference: ND0612-317 CSR, Table 14.3.1.1.5b).

Table 35. Overall summary of treatment-emerging adverse events by SOC, Grouped Preferred Terms / Preferred Terms, Severity and Treatment Groups during the Conversion Period (ND0612 Set)

		Overall (N=322)		
		Conversion PY=35.5		
System Organ Class Grouped PT/PT	Severity	Subjects n (%)	No. of Events	Event Rate
Any TEAEs	Total	287 (89.1)	1417	39.91
	Mild	167 (51.9)	1117	31.46
	Moderate	108 (33.5)	278	7.83
	Severe	12 (3.7)	22	0.62
Any ISR	Total	266 (82.6)	1052	29.63
	Mild	203 (63.0)	874	24.62
	Moderate	58 (18.0)	166	4.68
	Severe	5 (1.6)	12	0.34
Infections and infestations	Total	36 (11.2)	39	1.10
	Mild	17 (5.3)	19	0.54
	Moderate	17 (5.3)	18	0.51
	Severe	2 (0.6)	2	0.06

During the DBDD Period, in both treatment arms, most TEAEs were of mild intensity. In the ND0612 arm, out of 484 TEAEs, 404 (83.5%) were mild, 69 (14.3%) moderate and 11 (2.3%) severe. In the IR-LD/CD arm, out of 373 TEAEs, 278 (74.5%) were mild, 83 (22.3%) moderate and 12 (3.2%) severe (reference: ND0612-317 CSR, Table 14.3.1.1.5).

The incidence of subjects reporting severe AEs was low: five (3.9%) subjects in ND0612 arm and eight (6.1%) subjects in IR-LD/CD arm. The only severe AEs reported in more than one subject in any treatment arm during the DBDD Period were anxiety (reported by two subjects in the IRLD/CD arm) and fall (reported by two subjects in the ND0612 arm). All other severe AEs were reported in single subjects (reference: ND0612-317 CSR, Table 14.3.1.1.5).

Table 36. Summary of treatment-emerging adverse events by SOC, Grouped PT / PT, Severity and Treatment Groups side-by-side during the Conversion Period and DBDD periods (ND0612 Set)

		Oral IR-LD/CD (N=131)						ND0612 (N=128)					
		Conversion PY=15.6			DBDD PY=29.0			Conversion PY=15.3			DBDD PY=28.9		
System Organ Class Grouped PT/PT	Severity	Subjects n (%)	No. of Events	Event Rate	Subjects n (%)	No. of Events	Event Rate	Subjects n (%)	No. of Events	Event Rate	Subjects n (%)	No. of Events	Event Rate
Any TEAEs	Total	119 (90.8)	634	40.67	97 (74.0)	373	12.86	113 (88.3)	502	32.73	103 (80.5)	484	16.75
	Mild	72 (55.0)	510	32.72	53 (40.5)	278	9.58	76 (59.4)	439	28.62	62 (48.4)	404	13.98
	Moderate	43 (32.8)	118	7.57	36 (27.5)	83	2.86	37 (28.9)	63	4.11	36 (28.1)	69	2.39
	Severe	4 (3.1)	6	0.38	8 (6.1)	12	0.41	0	0	0	5 (3.9)	11	0.38
Any ISR	Total	115 (87.8)	500	32.08	56 (42.7)	158	5.45	102 (79.7)	355	23.14	73 (57.0)	288	9.97
	Mild	93 (71.0)	421	27.01	48 (36.6)	148	5.10	86 (67.2)	327	21.32	56 (43.8)	265	9.17
	Moderate	21 (16.0)	78	5.00	7 (5.3)	9	0.31	16 (12.5)	28	1.83	16 (12.5)	21	0.73
	Severe	1 (0.8)	1	0.06	1 (0.8)	1	0.03	0	0	0	1 (0.8)	2	0.07
Infections and infestations	Total	12 (9.2)	12	0.77	13 (9.9)	13	0.45	13 (10.2)	15	0.98	22 (17.2)	27	0.93
	Mild	6 (4.6)	6	0.38	8 (6.1)	8	0.28	7 (5.5)	8	0.52	10 (7.8)	12	0.42
	Moderate	6 (4.6)	6	0.38	4 (3.1)	4	0.14	6 (4.7)	7	0.46	11 (8.6)	14	0.48

Adverse Events by Severity - ND0612H-012

Severe AEs were reported for 36 (16.8%) subjects. Out of 908 AEs reported during the first 12 months of treatment, 48 (5.3%) were of severe intensity (reference: ND0612H-012 CSR, Table 14.3.1.5.2). The AEs reported for 25 (11.7%) subjects were considered by the investigators to be severe and drug-related (reference: ND0612H-012 CSR, Table 14.3.1.6.2a). The only severe AEs reported in more than one

subject were infusion site infection (grouped term; reported by seven subjects), infusion site nodule (reported by five subjects), infusion site pain and ON and OFF phenomenon (each reported for two subjects. Reference: ND0612H-012 CSR, Table 14.3.1.6.2a).

Adverse Events by Severity - Safety Pool 1 and 2

In the Safety Pool 2, 96 (22.9%) subjects had at least one TEAE assessed as severe by the investigator (reference: SCS TFLs, Table 4.5.2). Of the 208 severe TEAEs, 56 events in 38 (9.1%) subjects were considered to be drug-related (reference: SCS TFLs, Table 4.6.3). Severe drug-related TEAEs reported in at least two subjects included:

- ISRs (grouped terms): infusion site infection reported in 11 (2.6%) subjects; infusion site nodule (six [1.4%]); infusion site pain (five [1.2%]); and infusion site swelling (two [0.5%]. Reference: SCS TFLs, Table 4.6.3).
- PD-related events: dyskinesia, ON and Off phenomenon, Parkinson's disease and therapeutic response shortened (each reported in two [0.5%] subjects).

All other severe drug-related TEAEs were reported for single subjects of Safety Pool 2 (reference: SCS TFLs, Table 4.6.3).

Adverse Events by Severity - Safety Pool 3

No severe TEAEs were reported in studies conducted in healthy volunteers (reference: SCS TFLs, Table 4.5.3).

5.4.3.1. Adverse drug reactions

ND0612-317

In the Conversion Period of the pivotal trial ND0612-317, 275 (85.4%) subjects reported at least one drug-related TEAE. Drug-related TEAEs reported in at least 5% of subjects included mainly ISRs: infusion site nodule (64.0%), infusion site haematoma (63.7%), infusion site pain (17.1%), infusion site erythema (7.8%), and infusion site infection (5.6%). Systemic drug-related TEAEs reported in at least 5% of subjects included only dyskinesia (8.4%) (reference: ND0612-317 CSR, Table 14.3.1.1.4b).

The most common (at least 5% of subjects, rounded) treatment-related adverse events in subjects exposed to ND0612 during the Conversion or DBDD periods are listed in the Table below for the Safety Set.

Table 37. ND0612-317 Treatment-related Treatment-emerging adverse events reported in at least 5% of the subjects during the ND0612 Open-label Conversion Period of DBDD Maintenance Period, by Grouped PT / PT (Safety Set)

	ND0612 Arm (N=128)		IR-LD/CD Arm (N=131)	
	Conversion Period (%)	DBDD Period (%)	Conversion Period (%)	DBDD Period (%)
Infusion site hematoma[1]	**61**	**31**	**68**	**13**
Infusion site nodule[1]	63	26	70	28
Infusion site infection[1]	**3**	**10**	**6**	**2**
Infusion site erythema[1]	**6**	**9**	**6**	**2**
Infusion site pain[1]	10	9	14	7
Infusion site eschar[1]	**5**	**4**	**4**	**1**
Dyskinesia	8	2	7	2
Infusion site swelling[1]	**5**	**1**	**4**	**0**

DBDD: Double-blind double-dummy; IR-LD/CD: Immediate release levodopa carbidopa; N: Number of subjects.

Source: ND0612-317 CSR, Table 14.3.1.1.3c.

[1] Grouped PTs.

Adverse events were coded using MedDRA version 25.0

Drug-related AEs more frequent (i.e., at least 1.5 times more frequent) with ND0612 than IR-LD/CD during the DBDD Period are bolded in the table. Sorted by decreasing frequency in the ND0612 arm during the DBDD Period.

The adverse reactions more common (at least 1.5 times more frequent) with ND0612 than with IRLD/CD during the DBDD Period were infusion site hematoma, infusion site infection, infusion site erythema, infusion site eschar, and infusion site swelling. Infusion site nodule, infusion site pain and dyskinesia were reported at comparable incidence in the two arms.

ND0612H-012

In study ND0612H-012 the AEs considered by the investigators to be related to the study drug were reported by 143 (66.8%) subjects (reference: ND0612H-012 CSR, Table 14.3.1.4.2).

The most common (at least 5% of subjects) related AEs were: - ISRs: infusion site nodule (66 [30.8%] subjects), infusion site haematoma (grouped PT; 52 [24.3%] subjects), infusion site pain (27 [12.6%] subjects), infusion site infection (grouped PT; 24 [11.2%] subjects), and infusion site erythema (15 [7.0%] subjects; reference: ND0612H-012 CSR, Table 14.3.1.4.2a) - Dyskinesia (12 [5.6%] subjects) (Reference: ND0612H-012 CSR, Table 14.3.1.4.2a).

Safety Pool 1 and 2

The results of the analysis of related-TEAEs were overall similar in Safety Pools 1 and 2 (Reference: SCS TFLs, Tables 4.4.1, 4.6.1 for Safety Pool 1 and SCS TFLs, Tables 4.4.2, 4.6.2 for Safety Pool 2). The description of

Safety Pool 2 data is provided below.

A summary of drug-related TEAEs displayed by SOC and Grouped PT/PT for Safety Pool 2 is presented in the Table below.

Table 38. Summary of drug-related TEAEs reported by at least 2% of subjects by SOC and Grouped PT / PT (Safety Pool 2)

	Safety Pool 2 (N=419; PY=663.0)			
System Organ Class Grouped PT/PT	**Subjects n (%)**	**EAIR**	**Events m**	**Event Rate**
Any Drug-Related TEAEs	**385 (91.9)**	**6.490**	**3294**	**4.968**
Infections and infestations	**82 (19.6)**	**0.154**	**153**	**0.231**
Infusion site infection[1]	81 (19.3)	0.152	152	0.229
Metabolism and nutrition disorders	**26 (6.2)**	**0.041**	**36**	**0.054**
Vitamin B6 deficiency	19 (4.5)	0.029	21	0.032
Nervous system disorders	**111 (26.5)**	**0.201**	**195**	**0.294**
Dyskinesia	48 (11.5)	0.077	59	0.089
On and off phenomenon	30 (7.2)	0.048	39	0.059
Skin and subcutaneous tissue disorders	**19 (4.5)**	**0.030**	**26**	**0.039**
Dermatitis contact	10 (2.4)	0.015	12	0.018
General disorders and administration site conditions	**369 (88.1)**	**5.082**	**2714**	**4.094**
Infusion site nodule[1]	295 (70.4)	1.638	1238	1.867
Infusion site haematoma[1]	270 (64.4)	1.194	913	1.377
Infusion site pain[1]	97 (23.2)	0.172	164	0.247
Infusion site erythema[1]	77 (18.4)	0.142	126	0.190
Infusion site eschar[1]	54 (12.9)	0.093	84	0.127
Infusion site swelling[1]	36 (8.6)	0.060	46	0.069
Infusion site haemorrhage	22 (5.3)	0.034	28	0.042
Infusion site pruritus	11 (2.6)	0.017	13	0.020

EAIR: Exposure-adjusted incidence rate; m: Number of TEAEs occurred; N: Number of subjects; n: Number of subjects with at least one TEAE; PT: Preferred term; PY: Person-years; SOC: System organ class; TEAE: Treatment-emergent adverse event.

Source: SCS TFLs, Table 4.6.3

[1] Grouped PT.

Adverse events were coded using MedDRA version 26.1.

The reader should refer below for the presentation of drug-related TEAEs by Incidence Categories and PTs/ additional ad-hoc PT grouping for closely related adverse reactions. This table should be included in Onerji SmPC Section 4.8.

Table 39. Summary of drug-related TEAEs by SOC and PT / Additionally Grouped PT and Incidence Categories (Safety Pool 2)

Safety Pool 2 (N=419; PY=663.0)		
System Organ Class	**Incidence categories**	**Adverse reactions**
Infections and infestations	Very common	Infusion site infection[1]
Immune system disorders	Uncommon	Hypersensitivity[1]
Metabolism and nutrition disorders	Common	Hyperhomocysteinaemia, Vitamin B6 deficiency[1], Folate deficiency[1], Vitamin B12 deficiency[1]
	Uncommon	Decreased appetite
Psychiatric disorders	Common	Anxiety, Hallucinations[1], Insomnia
	Uncommon	Abnormal dreams, Confusional state, Delusion, Depression[1], Impulse-control disorder[1], Rapid eye movement sleep behaviour disorder, sleep disorder
Nervous system disorders	Very Common	Dyskinesia
	Common	Dizziness, Headache, On and off phenomenon, Parkinson's disease, Peripheral neuropathy[1], Tremor
	Uncommon	Akinesia, Dysaesthesia, Dyskinesia hyperpyrexia syndrome, Dystonia, Hypokinesia, Paraesthesia, Presyncope, Somnolence, Taste disorder
Vascular disorders	Common	Hypotension
	Uncommon	Orthostatic hypotension
Gastrointestinal disorders	Common	Nausea
	Uncommon	Dry mouth, Vomiting
Skin and subcutaneous tissue disorders	Common	Dermatitis contact
	Uncommon	Panniculitis, Rash
Musculoskeletal and connective tissue disorders	Uncommon	Pain in extremity
General disorders and administration site conditions	Very Common	Infusion Site Erythema[1], Infusion Site Eschar[1], Infusion Site Haematoma[1], Infusion Site Nodule[1], Infusion Site Pain[1]
	Common	Infusion Site Discolouration, Infusion Site Haemorrhage, Infusion Site Induration, Infusion Site Pruritus, Infusion Site Reaction (unspecified), Infusion Site Swelling[1], Infusion Site Vesicles, Therapeutic response shortened
	Uncommon	Asthenia, Discomfort, Other Infusion Site Reactions[1], Peripheral Edema[1], Pyrexia
Injury, poisoning and procedural complications	Common	Fall
	Uncommon	Skin Abrasion,
Product issues	Uncommon	Product leakage

Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Adverse reactions occurring in just one subject were excluded, except adverse reactions considered clinically relevant upon medical review.

[1] Grouped Terms that include closely related Preferred Terms (PTs) upon medical review: Depression (includes PTs such as depression; persistent depressive disorder); Folate deficiency (includes PTs such as blood folate decreased; folate deficiency); Hallucinations (includes PTs such as hallucination; hallucination, auditory; hallucination, olfactory; hallucination, visual); Hypersensitivity (only events confirmed per the adjudication process); Impulse control disorder (includes PTs such as impulse-control disorder; impulsive behaviour; obsessive-compulsive disorder); Infusion site erythema (includes PTs such as infusion site irritation; infusion site inflammation; infusion site erythema); Infusion site eschar (includes PTs such as infusion site injury; eschar; infusion site eschar; infusion site necrosis; infusion site ulcer; infusion site scar); Infusion site hematoma (includes PTs such as infusion site haematoma; infusion site bruising; haematoma); Infusion site infection (includes PTs such as infusion site infection; infusion site cellulitis; infusion site abscess; abdominal abscess; abdominal wall abscess); Infusion site swelling (includes PTs such as oedema, infusion site oedema; infusion site swelling); Infusion site pain (includes PTs such as injection site pain; infusion site pain); Other Infusion Site Reactions (uncommon infusion site reactions such as infusion site dermatitis, infusion site discharge, infusion site erosion, infusion site exfoliation, infusion site hypoaesthesia); Peripheral edema (includes PTs such as oedema peripheral; peripheral swelling); Peripheral Neuropathy (only events confirmed per the adjudication process); Vitamin B6 deficiency (includes PTs such as vitamin B6 decreased; vitamin B6 deficiency); Vitamin B12 deficiency (includes PTs such as vitamin B12 decreased; vitamin B12 deficiency)

Adverse events were coded using MedDRA version 26.1.

Source: SCS TFLs, Table 4.6.5a

Safety Pool 3

In the healthy volunteers' studies, 121 subjects (82.9%) had at least one TEAE assessed as drug-related by the investigator. Drug-related ISRs reported in at least 5% of subjects included infusion site pain (83 [56.8%] subjects), infusion site nodule (55 [37.7%] subjects), infusion site haematoma (16 [11.0%] subjects), and infusion site induration (13 [8.9%] subjects). Other drug-related AEs, reported for at least 5% of the Safety Pool 3 included headache (11 [7.5%] subjects) and nausea (10 [6.8%] subjects) (reference: SCS TFLs, Table 4.6.4).

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Deaths

In the entire population of subjects with Parkinson's disease exposed to ND0612 (Safety Pool 1, n=598) up to the cut-off date of 3 May 2024, 24 (4.0%) subjects had a TEAE that led to subject's death .

The TEAEs leading to death were:

- Respiratory infection / Urinary tract infection and related sepsis: 8 subjects
- Sudden death/cardiac arrest: 6 subjects
- Worsening PD / General physical health deterioration: 5 subjects
- Fall/Traumatic Brain Injury; Road traffic accident: 2 subjects
- Hiatal hernia / Acute kidney injury: 1 subject
- Pulmonary embolism: 1 subject
- Food choking: 1 subject

None of the fatal events was assessed as related to the study drug, either by the investigator or the Sponsor. No death was reported in studies conducted in healthy volunteers (reference: SCS TFLs, Table 4.1.6).

There were 6 cases of fatal cardiac arrest TEAEs in ND0612 DP clinical studies. One additional fatal cardiac arrest event occurred two months after study drug discontinuation and was defined as non-treatment emergent. Except for one patient, who had a prolonged QTc interval at screening, which gradually shortened thereafter, none of the other subjects displayed any QTcF interval abnormalities. All

subjects had preexisting cardiac disease or other risk factors. In addition, for all the cases, there was no relationship between the events and start or changes in ND0612 treatment, no association with duration of exposure, and no pertinent ECG or lab findings.

Other Serious Adverse Events - ND0612-317

In this study, during the ND0612 Conversion Period, six (1.9%) subjects reported a total of ten SAEs. During the DBDD Period, the incidence of SAEs was similar across treatment arms (seven [5.5%] subjects in the ND0612 arm and five [3.8%] in the IR-LD/CD arm; reference: ND0612-317 CSR, Table 14.3.1.1.7). The only SAE reported in the ND0612 arm in more than one subject was infusion site infection (three [2.3%] subjects). All other SAEs in the ND0612 arm and the IR-LD/CD arm were reported in single subjects. In most cases, the seriousness criterion was hospitalization (for SAE cases of infusion site infection: hospitalization for drainage of an abscess and/or intravenous antibiotic treatment). (reference: Appendix 3, Listing 16.2.7.1).

Other Serious Adverse Events - ND0612H-012

In this study a total of 48 SAEs were reported by 31 (14.5%) subjects. The SAEs reported by more than 1 subject were infusion site infection (grouped PT, five [2.3%] subjects), ON and OFF phenomenon (three [1.4%] subjects), and rib fracture (two (0.9%) subjects) (reference: ND0612H-012 CSR, Table 14.3.1.7.2a). All other SAEs were reported as isolated events for a single subject, each.

Other Serious Adverse Events - Safety Pool 1 and 2

There were no clinically meaningful differences in the SAEs between Safety Pool 1 (reference: SCS TFLs, Tables 4.7.1 and 4.8.1) and Safety Pool 2 (reference: SCS TFLs, Tables 4.7.2 and 4.8.2). In Safety Pool 2, 103 (24.6%) subjects had at least one SAE (reference: SCS TFLs, Table 4.7.2), most being unrelated to study medication. Drug-related SAEs were reported in 31 (7.4%) subjects (a total of 42 related SAEs) (reference: Table 2.7.4-21).

Polyneuropathy and hypersensitivity SAEs (adjudicated cases across ND0612 studies) were reported in 4 and 1 subjects, respectively.

Table 40. Summary of drug-related serious TEAEs reported by SOC and PT (Safety Pool 2)

	Safety Pool 2 (N=419; PY=663.0)			
System Organ Class PT	**Subjects n (%)**	**EAIR**	**Events m**	**Event Rate**
Any Drug-Related Serious TEAEs	**31 (7.4)**	**0.049**	**42**	**0.063**
Infections and infestations	**19 (4.5)**	**0.029**	**23**	**0.035**
Infusion site abscess	10 (2.4)	0.015	10	0.015
Infusion site cellulitis	7 (1.7)	0.011	8	0.012
Abdominal wall abscess	2 (0.5)	0.003	2	0.003
Cellulitis	2 (0.5)	0.003	2	0.003
Abscess limb	1 (0.2)	0.002	1	0.002
Immune system disorders	**1 (0.2)**	**0.002**	**1**	**0.002**
Hypersensitivity	1 (0.2)	0.002	1	0.002
Psychiatric disorders	**2 (0.5)**	**0.003**	**2**	**0.003**
Hallucination, visual	1 (0.2)	0.002	1	0.002
Jealous delusion	1 (0.2)	0.002	1	0.002
Nervous system disorders	**6 (1.4)**	**0.009**	**10**	**0.015**
Acute polyneuropathy	1 (0.2)	0.002	1	0.002
Ataxia	1 (0.2)	0.002	1	0.002
Dyskinesia	1 (0.2)	0.002	1	0.002
Dyskinesia hyperpyrexia syndrome	1 (0.2)	0.002	1	0.002
Hyperkinesia	1 (0.2)	0.002	1	0.002
Neuropathy peripheral	1 (0.2)	0.002	1	0.002
On and off phenomenon	1 (0.2)	0.002	1	0.002
Paraesthesia	1 (0.2)	0.002	1	0.002
Peripheral sensorimotor neuropathy	1 (0.2)	0.002	1	0.002
Polyneuropathy chronic	1 (0.2)	0.002	1	0.002
Gastrointestinal disorders	**1 (0.2)**	**0.002**	**1**	**0.002**
Nausea	1 (0.2)	0.002	1	0.002
Skin and subcutaneous tissue disorders	**2 (0.5)**	**0.003**	**2**	**0.003**
Panniculitis	2 (0.5)	0.003	2	0.003

	Safety Pool 2 (N=419; PY=663.0)			
System Organ Class PT	**Subjects n (%)**	**EAIR**	**Events m**	**Event Rate**
General disorders and administration site conditions	**2 (0.5)**	**0.003**	**2**	**0.003**
Infusion site haematoma	1 (0.2)	0.002	1	0.002
Infusion site ulcer	1 (0.2)	0.002	1	0.002
Product issues	**1 (0.2)**	**0.002**	**1**	**0.002**
Device dislocation	1 (0.2)	0.002	1	0.002

EAIR: Exposure-adjusted incidence rate; m: Number of TEAEs occurred; N: Number of subjects; n: Number of subjects with at least one TEAE; PT: Preferred term; PY: Person-years; SOC: System organ class; TEAE: Treatment-emergent adverse event.

Source: SCS TFLs, Table 4.8.2

Adverse events were coded using MedDRA version 26.1.

Other Serious Adverse Events - Safety Pool 3

No serious TEAEs were reported in healthy volunteers' studies (reference: SCS TFLs, Table 4.7.3).

Adverse Events of Special Interest

Infusion site reactions (ISRs), hypersensitivity reactions and peripheral neuropathy were predefined as AEs of special interest (AESI). Closely related ISR MedDRA PTs were analysed as grouped PTs to avoid dilution of safety signals. ISRs grouped PTs were defined for infusion site infection, infusion site haematoma, infusion site nodule, infusion site eschar, infusion site erythema, infusion site pain and infusion site swelling. Hypersensitivity and peripheral neuropathy AEs were triaged by respective MedDRA SMQs and subsequently medically reviewed and adjudicated by an external expert.

Adverse Events of Special Interest - Infusion Site Reactions

ISRs were the most commonly reported TEAEs for ND0612 (372 [88.8%] Safety Pool 2 subjects), (reference: SCS TFLs, Table 5.2.2). The most common (≥5% of subjects) ISRs (grouped terms) in the Safety Pool 2 included infusion site nodule (70.4% of subjects), infusion site haematoma (64.9%), infusion site pain (23.2%), infusion site infection (19.3%), infusion site erythema (18.4%), infusion site eschar (12.9%), infusion site swelling (8.8%) and infusion site haemorrhage (5.3%), as summarised in the Table below.

Table 41. Summary of infusion site reactions by Grouped PT/PT – Cohort 2

Grouped PT/PT	Cohort 2 (N=419; PY=663.0) Subjects n (%)	EAIR	Events m	Event Rate
Infusion Site Reactions TEAEs	372 (88.8)	5.259	2860	4.313
INFUSION SITE NODULE*	295 (70.4)	1.638	1240	1.870
INFUSION SITE HAEMATOMA*	272 (64.9)	1.232	917	1.383
INFUSION SITE PAIN*	97 (23.2)	0.172	164	0.247
INFUSION SITE INFECTION*	81 (19.3)	0.152	152	0.229
INFUSION SITE ERYTHEMA*	77 (18.4)	0.142	129	0.195
INFUSION SITE ESCHAR*	54 (12.9)	0.093	84	0.127
INFUSION SITE SWELLING*	37 (8.8)	0.062	47	0.071
INFUSION SITE HAEMORRHAGE	22 (5.3)	0.034	28	0.042
INFUSION SITE DISCHARGE	4 (1.0)	0.006	18	0.027
INFUSION SITE REACTION	7 (1.7)	0.011	17	0.026
INFUSION SITE PRURITUS	11 (2.6)	0.017	14	0.021
INFUSION SITE DISCOLOURATION	8 (1.9)	0.012	8	0.012
INFUSION SITE INDURATION	5 (1.2)	0.008	7	0.011
INFUSION SITE VESICLES	6 (1.4)	0.009	6	0.009
INFUSION SITE DERMATITIS	3 (0.7)	0.005	5	0.008
INFUSION SITE EROSION	3 (0.7)	0.005	3	0.005
INFUSION SITE INJURY	3 (0.7)	0.005	3	0.005
INFUSION SITE EXFOLIATION	2 (0.5)	0.003	2	0.003
INFUSION SITE EXTRAVASATION	2 (0.5)	0.003	2	0.003
INFUSION SITE HYPOAESTHESIA	2 (0.5)	0.003	2	0.003
INFUSION SITE THROMBOSIS	1 (0.2)	0.002	2	0.003
INFUSION SITE URTICARIA	2 (0.5)	0.003	2	0.003
PANNICULITIS	2 (0.5)	0.003	2	0.003
SKIN ABRASION	2 (0.5)	0.003	2	0.003
INDURATION	1 (0.2)	0.002	1	0.002
INFUSION RELATED REACTION	1 (0.2)	0.002	1	0.002
INFUSION SITE CYST	1 (0.2)	0.002	1	0.002
INFUSION SITE RASH	1 (0.2)	0.002	1	0.002

* are grouped terms; PT = Preferred Term; PY = Person Years; n = the number of subjects with at least one Infusion Site Reaction;
m = the number of Infusion Site Reactions occurred. Subject is counted only once within a PT.
The Exposure Adjusted Incidence Rate (EAIR) was calculated as the total number of subjects who experienced the event at least once divided by the total time at risk for the event in years of the cohort x 100. For subjects with at least one event, the subject-year at risk is the treatment duration until the first event. For subjects without the event, the subject-year is the entire follow-up.
Exposure Adjusted Event Rate was calculated as the total number of events divided by the total exposure time (person years).
Adverse events were coded using the MedDRA Dictionary Version 26.1.
Table is presented by descending order of Preferred Term.

The majority of ISRs were mild in severity. Of 2860 ISR TEAEs reported in the Safety Pool 2 subjects, 2430 (85.0%) were mild, 395 (13.8%) moderate and 33 (1.2%) severe. Severe ISRs reported in more than one subject included infusion site infection (11 subjects [2.6%]), infusion site nodule (six subjects [1.4%]), infusion site pain (five subjects [1.2%]) and infusion site swelling (two subjects [0.5%]) as summarised in the Table below.

Table 42. Summary of the Infusion Site Reactions reported by at least 5% of subjects by Grouped PT (Safety Pool 2)

	N (%) subjects [N events]	Mild	Moderate	Severe	Serious related	Leading to ET
All ISRs	372 (88.8) [2860]	212 (50.6) [2430]	138 (32.9) [395]	21 (5.0) [33]	21 (5.0) [27]	58 (13.8) [143]
Infusion site Nodule[1]	295 (70.4) [1240]	230 (54.9) [1129]	59 (14.1) [105]	6 (1.4) [6]	0	35 (8.4) [63]
Infusion site Haematoma[1]	272 (64.9) [917]	226 (53.9) [846]	45 (10.7) [70]	1 (0.2) [1]	1 (0.2) [1]	15 (3.6) [26]
Infusion site Pain[1]	97 (23.2) [164]	59 (14.1) [112]	33 (7.9) [46]	5 (1.2) [6]	0	20 (4.8) [25]
Infusion site Infection[1]	81 (19.3) [152]	19 (4.5) [32]	51 (12.2) [106]	11 (2.6) [14]	19 (4.5) [23]	16 (3.8) [17]
Infusion site Erythema[1]	77 (18.4) [129]	53 (12.6) [103]	23 (5.5) [25]	1 (0.2) [1]	0	5 (1.2) [5]
Infusion site Eschar[1]	54 (12.9) [84]	38 (9.1) [66]	15 (3.6) [17]	1 (0.2) [1]	1 (0.2) [1]	2 (0.5) [2]
Infusion site Swelling[1]	37 (8.8) [47]	25 (6.0) [34]	10 (2.4) [11]	2 (0.5) [2]	0	3 (0.7) [3]
Infusion site Haemorrhage	22 (5.3) [28]	18 (4.3) [24]	4 (1.0) [4]	0	0	0

ET: Early termination; ISRs: Infusion site reactions; N: Number of subjects/events.

Source: SCS TFLs, Tables 5.2.3.3 and 4.1.5

[1] Grouped PT.

Serious ISRs were reported in 26 (4.3%) subjects (for a total of 33 SAEs) (reference: SCS TFLs, Table 4.1.4). Most of these SAEs were cases of infusion site infections or associated events, reported in 24 subjects. The two other subjects reported SAEs of infusion site hematoma/panniculitis, and panniculitis. None of these SAEs were fatal or life-threatening. The most common seriousness criterion was hospitalisation, usually required for intravenous antibiotic treatment and/or abscess drainage. Seven of the subjects discontinued the treatment due to the SAEs (six due to infection and one due to panniculitis).

The most significant cases were one case of infusion site abscess leading to Staphylococcal bacteraemia and hip prothesis infection (this case resolved and the subject continued the treatment in the study) and one case of infusion site abscess which required wound debridement, removal of subcutaneous skin and muscle and skin graft (this event led to treatment discontinuation).

One additional medically significant SAE was reported post cut-off date. This was a case of recurrent infection of abdominal infusion site wounds that, despite ND0612 discontinuation, required successive hospitalisations for wound care over six months, and ultimately surgical debridement. Of note, this case was not captured in the summary of clinical safety (SCS) TFLs (tables, figures and listings) as reported after the cut-off date for the SCS analyses of 3 (May 2024).

Adverse Events of Special Interest - Hypersensitivity

Overall, three of 744 (0.4%) subjects reported an AE adjudicated as hypersensitivity, at least possibly related to ND0612 within the whole clinical development program: one subject in the core period of study ND0612-317, one in the core period of study ND0612H-012 and one in the OLE period of study ND0612H-012. Cases adjudicated as hypersensitivity were all non-life-threatening, not needing life support treatment and resolved with discontinuation of ND0612. Of these, one case (reported in the core period of study ND0612H-012) was an SAE (seriousness criterion: hospitalisation).

Adverse Events of Special Interest - Polyneuropathy

Overall, 18of 598 (3.0%) subjects with PD had at least one event adjudicated as polyneuropathy, at least possibly related to ND0612.

Most cases were reported in association with low vitamin B levels; vitamin B supplementation was commonly given to these subjects. The potential association between peripheral neuropathy and vitamin B (B6, B12, and folate) deficiency/decreased levels in the plasma has been described in the literature (Loens et al.,2017; reviewed in Taher et al., 2021).

All adjudicated cases of polyneuropathy occurred in subjects receiving relatively high LD daily dose (ranging from approximately 1000 to 3000 mg/day) and who were exposed to LD for a relatively long period of time (diagnosed with PD for up to 19 years). This finding of polyneuropathy associated with high LD daily doses and more advanced Parkinson's disease has also been described in the literature (Ceravolo et al., 2013; reviewed in Romagnolo et al., 2019).

Adverse Events of Special Interest - Other

Table 43. Summary of treatment-emerging adverse events by FMQ/SMQ/CMQ and PT – Safety Pools 1 and 2

	Safety Pool 1 (N=598; PY=974.2)				**Safety Pool 2 (N=419; PY=663.0)**			
FMQ/SMQ/CMQ Preferred Term	Subjects n (%)	EAIR	Events m	Event Rate	Subjects n (%)	EAIR	Events m	Event Rate
Abuse liability (CMQ)	63 (10.5)	0.072	88	0.090	45 (10.7)	0.074	59	0.089
Dizziness	32 (5.4)	0.034	38	0.039	21 (5.0)	0.032	24	0.036
Hallucination	26 (4.3)	0.028	37	0.038	18 (4.3)	0.028	25	0.038
Somnolence	9 (1.5)	0.010	11	0.011	6 (1.4)	0.009	8	0.012
Euphoric mood	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Thinking abnormal	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002

	Safety Pool 1 (N=598; PY=974.2)				Safety Pool 2 (N=419; PY=663.0)			
Drug abuse, dependence and withdrawal (SMQ)	3 (0.5)	0.003	4	0.004	3 (0.7)	0.005	4	0.006
Toxicity to various agents	1 (0.2)	0.001	2	0.002	1 (0.2)	0.002	2	0.003
Accidental overdose	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Intentional overdose	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Vitamin B6 deficiency (CMQ)	61 (10.2)	0.069	77	0.079	53 (12.6)	0.090	68	0.103
Vitamin B6 deficiency	48 (8.0)	0.053	60	0.062	42 (10.0)	0.070	53	0.080
Vitamin B6 decreased	13 (2.2)	0.014	15	0.015	12 (2.9)	0.018	14	0.021
Hypovitaminosis	2 (0.3)	0.002	2	0.002	1 (0.2)	0.002	1	0.002
Vitamin B12 deficiency (CMQ)	28 (4.7)	0.030	29	0.030	23 (5.5)	0.037	24	0.036
Vitamin B12 deficiency	23 (3.8)	0.025	23	0.024	19 (4.5)	0.030	19	0.029
Vitamin B12 decreased	6 (1.0)	0.006	6	0.006	5 (1.2)	0.008	5	0.008
Folate deficiency (CMQ)	24 (4.0)	0.025	27	0.028	22 (5.3)	0.034	25	0.038
Folate deficiency	17 (2.8)	0.018	19	0.020	15 (3.6)	0.023	17	0.026
Blood folate decreased	7 (1.2)	0.007	8	0.008	7 (1.7)	0.011	8	0.012
Impulse-control disorder (CMQ)	7 (1.2)	0.007	13	0.013	5 (1.2)	0.008	10	0.015
Impulse-control disorder	2 (0.3)	0.002	3	0.003	2 (0.5)	0.003	3	0.005
Impulsive behaviour	2 (0.3)	0.002	3	0.003	1 (0.2)	0.002	1	0.002
Libido increased	2 (0.3)	0.002	2	0.002	1 (0.2)	0.002	1	0.002
Compulsive shopping	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Obsessive-compulsive disorder	1 (0.2)	0.001	4	0.004	1 (0.2)	0.002	4	0.006
Fall (FMQ Narrow)	109 (18.2)	0.130	240	0.246	86 (20.5)	0.152	175	0.264
Fall	109 (18.2)	0.130	240	0.246	86 (20.5)	0.152	175	0.264
Hypotension (FMQ Broad)	55 (9.2)	0.061	67	0.069	37 (8.8)	0.059	44	0.066
Orthostatic hypotension	30 (5.0)	0.032	33	0.034	17 (4.1)	0.026	19	0.029
Hypotension	21 (3.5)	0.022	25	0.026	18 (4.3)	0.028	21	0.032
Dehydration	5 (0.8)	0.005	5	0.005	3 (0.7)	0.005	3	0.005
Blood pressure decreased	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Blood pressure diastolic decreased	1 (0.2)	0.001	1	0.001	0	0	0	0
Blood pressure systolic abnormal	1 (0.2)	0.001	2	0.002	0	0	0	0
Insomnia (FMQ Broad)	49 (8.2)	0.055	53	0.054	33 (7.9)	0.054	35	0.053
Insomnia	42 (7.0)	0.047	44	0.045	27 (6.4)	0.043	27	0.041

	Safety Pool 1 (N=598; PY=974.2)				Safety Pool 2 (N=419; PY=663.0)			
Sleep disorder	7 (1.2)	0.007	7	0.007	6 (1.4)	0.009	6	0.009
Poor quality sleep	2 (0.3)	0.002	2	0.002	2 (0.5)	0.003	2	0.003
Depression (FMQ Broad)	43 (7.2)	0.047	50	0.051	29 (6.9)	0.046	34	0.051
Depression	32 (5.4)	0.035	37	0.038	20 (4.8)	0.031	23	0.035
Suicidal ideation	3 (0.5)	0.003	3	0.003	3 (0.7)	0.005	3	0.005
Anhedonia	2 (0.3)	0.002	2	0.002	2 (0.5)	0.003	2	0.003
Depressed mood	2 (0.3)	0.002	2	0.002	2 (0.5)	0.003	2	0.003
Apathy	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Emotional disorder	1 (0.2)	0.001	1	0.001	0	0	0	0
Intentional overdose	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Mood altered	1 (0.2)	0.001	1	0.001	0	0	0	0
Persistent depressive disorder	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Suicide attempt	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Psychosis (FMQ Broad)	57 (9.5)	0.064	101	0.104	45 (10.7)	0.075	78	0.118
Hallucinations (grouped)#	45 (7.5)	0.049	62	0.064	35 (8.4)	0.058	48	0.072
Hallucinations	26 (4.3)	0.028	37	0.038	18 (4.3)	0.028	25	0.038
Hallucination, visual	15 (2.5)	0.016	20	0.021	14 (3.3)	0.022	19	0.029
Delirium	6 (1.0)	0.006	7	0.007	4 (1.0)	0.006	5	0.008
Delusion	6 (1.0)	0.006	7	0.007	3 (0.7)	0.005	3	0.005
Hallucination, auditory	4 (0.7)	0.004	4	0.004	3 (0.7)	0.005	3	0.005
Paranoia	4 (0.7)	0.004	4	0.004	3 (0.7)	0.005	3	0.005
Psychotic disorder	4 (0.7)	0.004	5	0.005	3 (0.7)	0.005	4	0.006
Jealous delusion	3 (0.5)	0.003	6	0.006	3 (0.7)	0.005	6	0.009
Parkinson's disease psychosis	2 (0.3)	0.002	5	0.005	2 (0.5)	0.003	5	0.008
Persecutory delusion	2 (0.3)	0.002	2	0.002	1 (0.2)	0.002	1	0.002
Hallucination, olfactory	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Illusion	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Psychotic symptom	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Thinking abnormal	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Peripheral Edema (FMQ Narrow)	30 (5.0)	0.032	39	0.040	20 (4.8)	0.032	26	0.039
Oedema peripheral	19 (3.2)	0.020	25	0.026	13 (3.1)	0.020	18	0.027
Peripheral swelling	11 (1.8)	0.012	14	0.014	7 (1.7)	0.011	8	0.012

	Safety Pool 1 (N=598; PY=974.2)				Safety Pool 2 (N=419; PY=663.0)			
Somnolence (FMQ Broad)	31 (5.2)	0.034	38	0.039	14 (3.3)	0.022	17	0.026
Fatigue	20 (3.3)	0.021	22	0.023	8 (1.9)	0.012	8	0.012
Somnolence	9 (1.5)	0.010	11	0.011	6 (1.4)	0.009	8	0.012
Lethargy	3 (0.5)	0.003	3	0.003	1 (0.2)	0.002	1	0.002
Hypersomnia	2 (0.3)	0.002	2	0.002	0	0	0	0
Anaemia (FMQ Narrow)	21 (3.5)	0.022	25	0.026	11 (2.6)	0.017	13	0.020
Anaemia	13 (2.2)	0.013	14	0.014	8 (1.9)	0.012	9	0.014
Iron deficiency anaemia	4 (0.7)	0.004	4	0.004	2 (0.5)	0.003	2	0.003
Haemoglobin decreased	2 (0.3)	0.002	2	0.002	0	0	0	0
Anaemia macrocytic	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Hypochromic anaemia	1 (0.2)	0.001	1	0.001	0	0	0	0
Microcytic anaemia	1 (0.2)	0.001	1	0.001	1 (0.2)	0.002	1	0.002
Normochromic normocytic anaemia	1 (0.2)	0.001	1	0.001	0	0	0	0
Normocytic anaemia	1 (0.2)	0.001	1	0.001	0	0	0	0

EAIR: Exposure adjusted incidence rate; m: Number of events; N: Number of subjects; n: Number of subjects with at least one TEAE PT: Preferred term; PY: Person-years; TEAE: Treatment-emergent adverse event.

Source: SCS TFLs, Tables 4.13.1, 4.13.2, 4.14.1, 4.14.2, 4.15.1 and 4.15.2.

Includes the Preferred Terms: Hallucination, Hallucination, visual; Hallucination, auditory; Hallucination, olfactory.

Overall, vitamin B6, B12 and folate deficiency AEs were reported in 53 (12.6%), 23 (5.5%) and 22 (5.3%) subjects from Safety Pool 2, respectively. One (0.2%) subject discontinued the study due to vitamin B deficiency (1 subject with both vitamin B12 and folate deficiency). No vitamin B6 deficiency AE led to study treatment discontinuation (reference: SCS TFLs, Table 4.15.2).

Consistently, in ND0612 clinical studies, most cases of vitamin B6 deficiency were asymptomatic. Peripheral neuropathy was the main clinical manifestation reported in association to such (vitamin B6) deficiency. Of the total cases of peripheral neuropathy (3.0% of ND0612 treated patients), most occurred in association with low vitamin B levels.

Of note, one case of new-onset seizures potentially caused by vitamin B6 deficiency was reported post cut-off date and assessed as potentially related to ND0612. Seizures worsened, including an episode with asystole and ventricular tachycardia upon cardioversion. The patient ultimately died due to aspiration pneumonia. This case was not captured in the SCS TFLs as reported after cut-off date.

Overall, anaemia AEs were reported in eleven (2.6%) subjects from the Safety Pool 2. No anaemia AE led to study treatment discontinuation (reference: SCS TFLs, Table 4.15.2). During the DBDD Period of ND0612-317 Study, one (0.8%) subject from the ND0612 arm compared to two (1.5%) subjects in the IR-LD/CD arm reported an AE of anaemia (reference: ND0612-317 CSR, Section 12.3.4).

5.4.5. Discontinuation due to adverse events

ND0612-317

During the Conversion Period of this pivotal trial, 63 (19.6%) subjects discontinued the study drug. The most common reasons for discontinuation were:

- AEs: 26 (8.1%) subjects (19 [5.9%] subjects due to AE-ISR and seven [2.2%] due to AE-other [systemic]). TEAEs leading to discontinuation in at least two subjects include infusion site nodule (14 [4.3%] subjects), infusion site pain (11 [3.4%] subjects), infusion site hematoma (nine [2.8%] subjects), infusion site erythema (three [0.9%] subjects), and infusion site infection (two [0.6%] subjects (reference: ND0612-317 CSR, Table 14.3.1.1.9a).
- Consent withdrawn: 22 (6.8%) subjects. The two main reasons for consent withdrawn were that subjects had difficulties using the pump or due to the burden of daily infusions (six subjects), and subjects considered the benefit from the study treatment to be insufficient (five subjects) (reference: ND0612-317 CSR, Listing 16.2.1.3).

During the DBDD period, eight (6.3%) subjects in the ND0612 arm and eight (6.1%) in the oral IR-LD/CD arm discontinued the study drug.

In the ND0612 arm, seven (5.5%) discontinued due to an AE (three [2.3%] subjects due to an AE-ISR and four [3.1%] due to AE-other [systemic]). In the IR-LD/CD arm, no subject discontinued due to an AE-ISR, and four [3.1%] discontinued due to another AE.

Adverse events leading to early discontinuation in at least two subjects, were infusion site infection (three [2.3%] subjects in the ND0612 arm), ON and OFF phenomenon (two [1.6%] subjects in ND0612 arm and two [1.5%] subjects in the IR-LD/CD arm) and fall (two [1.6%] subjects in the ND0612 arm) (reference: ND0612-317 CSR, Table 14.3.1.1.9).

ND0612H-012

Out of the 214 subjects enrolled in this study 94 (43.9%) discontinued prematurely. The leading causes were consenting withdrawal (42 [19.6%] subjects) and AEs (37 [17.3%] subjects).

AEs leading to early termination, reported for more than one subject, were infusion site nodule (12 subjects, 5.6%), infusion site pain (five subjects, 2.3%), infusion site hematoma and dyskinesia (each reported for three subjects, 1.4%) (reference: ND0612H-012 CSR, Table 14.3.1.8.2). All other AEs leading to early termination were reported as single events for a single subject.

Twenty-two (10.3%) subjects discontinued the study treatment due to ISRs (reference: ND0612H-012 CSR, Listing 16.2.7.1). Apart from these 22 subjects, ISRs were noted as the underlying reason for consent withdrawal by eight subjects. For the most part, subjects claimed that nodules made it difficult for them to find viable sites for further SC infusion, although the investigators did not evaluate these nodules as being clinically significant and did not report them as AEs.

Safety Pool 1 and 2

Of the 419 Safety Pool 2 subjects, 223 (53.2%) were treated with ND0612 for at least one year (reference: SCS TFLs, Table 3.2). At the cut-off date for the SCS, 111 subjects were still under treatment with ND0612 (reference: SCS TFLs, Table 1.4): 19, 56, 27, 2 and 7 subjects in the 2nd, 3rd, 4th, 7th and 8th year of treatment, respectively.

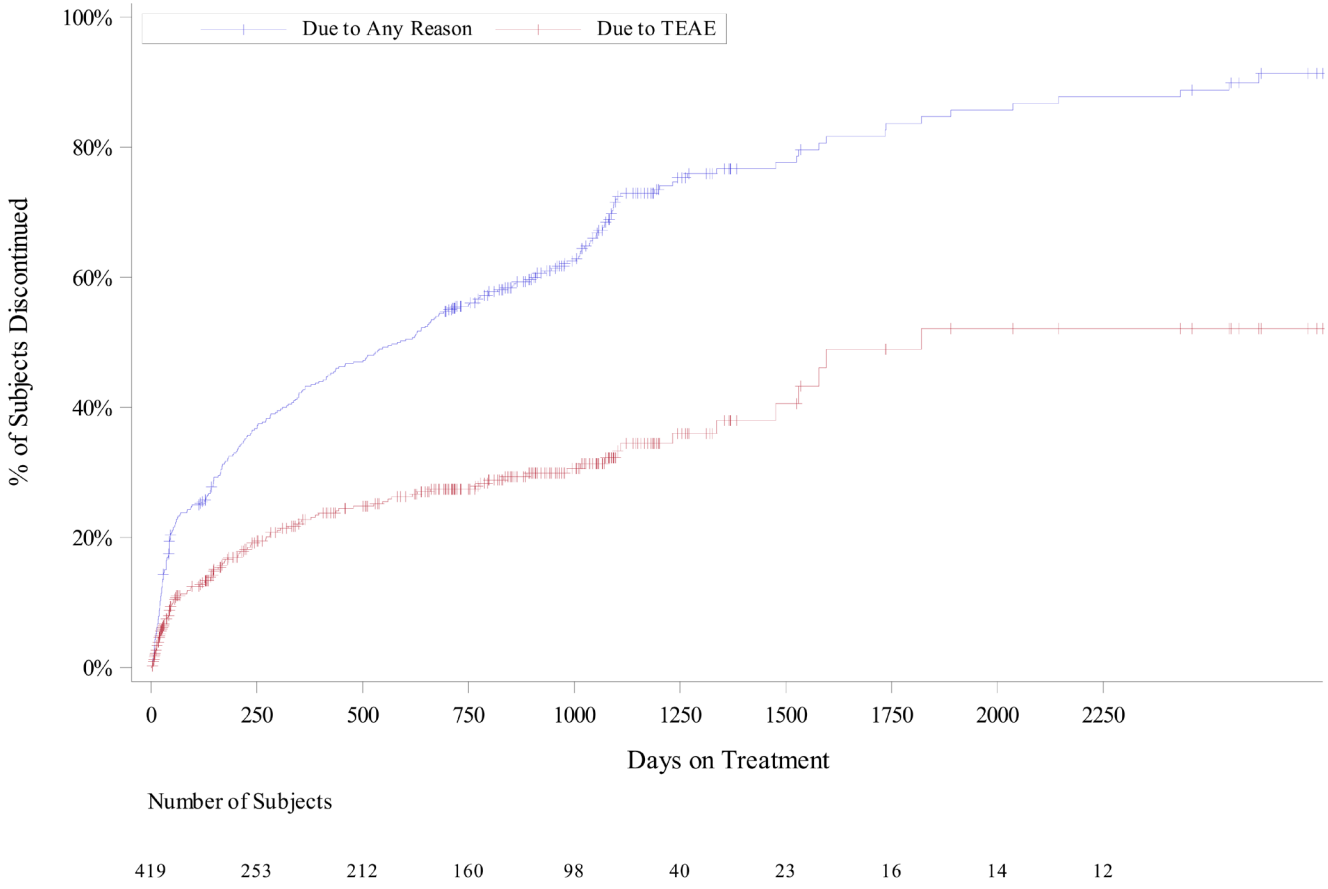
Cumulatively, 293 (69.9%) subjects from the Safety Pool 2 discontinued due to any reason. The three main reasons for discontinuation were TEAEs (overall 111 [26.5%] subjects: 57 [13.6%] due to AE-ISR and 54 [12.9%] due to AE-other), followed by withdrawal of consent (96 [22.9%] subjects) and lack of efficacy (18 [4.3%] subjects) (reference: SCS TFLs, Table 1.4).

The most common ISRs leading to study drug discontinuation were infusion site nodule (8.4% of subjects), infusion site pain (4.8% of subjects), infusion site infection (3.8% of subjects), infusion site haematoma (3.6% of subjects) and infusion site erythema (1.2% of subjects) (reference: SCS TFLs, Table 4.1.5).

The most common systemic AEs leading to treatment discontinuation was Parkinson's disease (2.4% of subjects). All other AEs leading to early termination were reported in ≤ 1% of the Safety Pool 2 subjects (reference: SCS TFLs, Table 4.9.2).

In the Safety Pool 2, the Kaplan-Meier (KM) estimate of the median time to discontinuation for any reason was 590 days (95% CI: 425 – 702) and the KM estimate of the median time to discontinuation due to AE was 1821 days (95% CI: 1530 – not evaluable), as outlined in the Table below (reference: SCS TFLs, Table 6.1.2 and Figure 6.2.2).

Figure 17. Kaplan-Meier curve of time (days) from ND0612 treatment start to early discontinuation (Cohort 2)



AEs led to dose adjustment or temporary withdrawal in 77 (18.4%) subjects from the Safety Pool 2. The most common event leading to dose adjustment or temporary withdrawal (more than 5% of subjects) was dyskinesia (5.7 % of subjects) (reference: SCS TFLs, Table 4.10.2). Results were comparable for the Safety Pool 1 (reference: SCS TFLs, Table 4.10.1).

5.4.6. Safety in special populations

No dedicated studies were performed in special populations (including in subjects with hepatic or renal impairment). As detailed in the SmPC (e.g., sections 4.2 4.4 and 5.2) Onerji dosing is individualised by titration to the optimal effect (which corresponds to individually optimised levodopa and carbidopa plasma exposures). Therefore, potential effects of hepatic or renal impairment on LD and CD exposure are indirectly accounted for in dose titration.

ND0612-317

Predefined safety analyses were done for subgroups based on age, gender, region, BMI, and infusion set. No consistent and relevant differences were observed within subgroup categories for the overall incidence of AEs, drug-related AEs, severe AEs, SAEs, AEs leading to treatment discontinuation, AEs leading to dose adjustment/ temporary withdrawal, AEs leading to death, or any specific drug-related AE.

Safety Pools 1 and 2

Overall, there were no clinically meaningful differences between subgroups analyses by intrinsic factors. A summary of results is provided below for the Safety Pool 2.

No relationship to BMI was found for the overall frequency of AEs, related AEs, severe AEs, AEs leading to treatment discontinuation or those leading to dose adjustment/temporary withdrawal, or drug-related AE. SAEs were reported more frequently in the BMI ≥ 30 subgroup (31.9%) than in the lower BMI subgroups (14.3% and 23.5% in <20 and 20≤BMI<30, respectively). However, interpretation of the results is limited in the lowest BMI category due to the small number of subjects in this BMI category (N=28) (reference: SCS TFLs, Tables 4.1.2.5 and 4.4.2.5).

The overall frequencies of AEs, severe AEs, SAEs, AEs leading to treatment discontinuation or those leading to dose adjustment/temporary withdrawal and treatment-related AEs were comparable across the subgroups by age categories (<65 years, ≥65-<75 years, ≥75-<85 years).

Table 44. AEs by age range (Cohort 2)

	Active			
MedDRA Terms	**Age <65 (N=212) n (%)**	**Age 65-74 (N=173) n (%)**	**Age 75-84 (N=34) n (%)**	**Age 85+ (N=0) n (%)**
Total AEs	204 (96.2)	162 (93.6)	32 (94.1)	
Drug-related TEAEs	198 (93.4)	158 (91.3)	29 (85.3)	
Serious TEAEs	45 (21.2)	47 (27.2)	11 (32.4)	
Drug-related serious TEAEs	14 (6.6)	14 (8.1)	3 (8.8)	
Severe TEAEs	44 (20.8)	41 (23.7)	11 (32.4)	
TEAE leading to drop-out	50 (23.6)	51 (29.5)	11 (32.4)	
TEAEs leading to death	5 (2.4)	10 (5.8)	3 (8.8)	

5.4.7. Immunological events

Not applicable.

5.4.8. Safety related to drug-drug interactions and other interactions

This section (and Onerji SmPC, accordingly), include interactions that are known for the combination of levodopa/carbidopa:

- Administration of levodopa with non-selective MAO inhibitors accentuates the actions of levodopa and may precipitate life-threatening hypertensive crisis and hyperpyrexia. For that reason, the use of non-selective MAO inhibitors with levodopa is contraindicated. Non-selective MAO inhibitors should be discontinued at least two weeks before LD is administered (Yates et al., 2011).
- The use of selective MAO-B inhibitors (e.g., rasagiline and selegiline) with levodopa may be associated with orthostatic hypotension (He et al., 2022). Patients who are taking these drugs should be monitored.
- The concurrent use of LD with antihypertensive medications can cause symptomatic postural hypotension (Liu et al., 2023; Bitner et al., 2015). Dose reduction of the antihypertensive medication may be considered.
- Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, and risperidone), and isoniazid, can reduce the therapeutic effect of levodopa (Wisidagama, et al., 2021; Gershanik et al., 1988).

5.4.9. Vital signs and laboratory findings

Laboratory Findings - ND0612-317 Conversion Period and DBDD Period

During the DBDD Period of study ND0612-317, shifts from normal vitamin B12 and folate (vitamin B9) at the first exposure to ND0612 to below Lower Limit of Normal (LLN) were reported with an overall low and comparable incidence across treatment arms (three [2.9%] subjects in the ND0612 arm and four [3.9%] subjects in the IR-LD/CD arm for vitamin B12, and five [7.2%] subjects, and two [3.4%] subjects for folate, respectively). Shifts in vitamin B6 from normal value at first exposure to ND0612 to below the LLN were observed with a higher frequency in the ND0612 arm (20 [20.6%] subjects and eight [8.5%] subjects) (reference: ND0612-317 CSR, Table 14.3.4.2.2).

Laboratory AEs related to vitamin B6, B12 and folate deficiency (CMQs) were reported in 3.9%, 0% and 0.8% in ND0612 arm, compared to 0.8%, 1.5% and 1.5% in IR-LD/CD arm, respectively (reference: ND0612-317 CSR, Table 14.3.1.5).

Laboratory Findings - ND0612-317 OLE

For group B vitamins, shifts from normal results to below the LLN during the open-label extension (OLE) of the study are reported below:

- Vitamin B12: shifts from normal results to below the LLN during OLE were reported in nine (4.9%) subjects overall (2.2% and 7.4% of subjects who received prior treatment with ND0612 or IR-LD/CD in the DBDD, respectively (reference: SCS TFLs, Table 14.3.4.2.2);
- Folate: shifts from normal results to below the LLN during OLE were reported in 15 (12.7%) subjects overall (19.0% and 5.5% of subjects who received prior treatment with ND0612 or IR-LD/CD in the DBDD, respectively (reference: SCS TFLs, Table 14.3.4.2.2);
- Vitamin B6: shifts from normal results to below the LLN during OLE were reported in 50 (28.6%) subjects overall (29.4% and 27.8% of subjects who received prior treatment with ND0612 or IR-LD/CD in the DBDD, respectively). For subjects treated with IR-LD/CD during the DBDD who continued the OLE period with ND0612 treatment, the incidence of shifts from normal to below the

LLN increased during the OLE (from 8.5% to 27.8%), consistent with the difference observed between the two arms in the DBDD (reference: SCS TFLs, Table 14.3.4.2.2).

Laboratory Findings - ND0612H-012

During the open-label extension of study ND0612H-012, laboratory safety tests (except vitamin B measurements) were to be performed at local laboratories per investigators' discretion, and only findings deemed clinically relevant were to be recorded (as AEs). The proportion of subjects with values below the LLN for vitamin B6, B9 and B12 was approximately 40%, 10% and 15%, respectively across the different visits from Month 18 to 90.

Electrocardiogram - ND0612-317

In this pivotal trial, the analysis of QTcF intervals revealed mostly non-clinically significant findings. From the first exposure to ND0612 (ND0612 Conversion Period Day 1) to the end of the DBDD Period, a small percentage of subjects (0.9% and 2.6% in the IR-LD/CD arm and ND0612 arm, respectively) reported an increase of QTcF values >30 ms (reference: ND0612-317 CSR, Table 14.3.6.3).

By-subject analysis of QTcF and QTcB ≥450 ms, ≥ 480 ms and ≥ 500 ms post-treatment initiation revealed mostly non-clinically significant findings (reference: ND0612-317 CSR, Listings 16.2.8.3.1 and 16.2.8.3.2). Overall, seven (2.2%) subjects had a QTcF interval ≥450 ms under ND0612 treatment (Conversion and DBDD periods) and one (0.8%) subject under IR-LD/CD (DBDD period).

Electrocardiogram - ND0612H-012

Analysis of QTcF intervals revealed mostly non-clinically significant findings. Three subjects in the 24h regimen and 5 subjects in the 16h regimen had QTcF intervals ≥ 450ms post-baseline. No subject had a QTcF interval ≥ 480ms.

TQT study - ND-CD-101

A TQT study in healthy subjects was conducted upon FDA request to assess the effect of a supratherapeutic CD dose on cardiac repolarisation. The results of this study, made available during the evaluation of this initial MAA, showed that a supratherapeutic oral dose of carbidopa was safe and well tolerated and had no effect on cardiac repolarisation or other ECG parameters.

5.4.10. Post marketing experience

Not applicable. ND0612 is not yet marketed in any country worldwide.

5.4.11. In vitro biomarker test for patient selection for safety

Not applicable.

5.4.12. Overall discussion and conclusions on clinical safety

5.4.12.1. Discussion

5.4.12.1.1. Overall assessment of available safety data

The safety data presented to support Onerji MAA included results from six phase I studies in healthy volunteers and six studies in PD patients.

The applicant performed integrated safety analyses in three cohorts. Safety Pool 1 included data from all PD patients enrolled in ND0612 DP clinical studies (N=598), while Safety Pool 2, which is the most

relevant for the current assessment, focused on those receiving the final ND0612 DP formulation under the 24-hour dosing regimen (N=419). Safety Pool 3 included data from all healthy volunteers.

The two main studies contributing to the safety dataset are the comparative Phase III pivotal efficacy study ND0612-317 and the long-term safety Phase IIb study ND0612H-012.

The collection of safety data appears to have been conducted adequately.

A thorough QT study in healthy subjects was also conducted, upon FDA request, showing that a supratherapeutic dose of carbidopa had no effect on cardiac repolarization or other ECG parameters.

The safety database included a substantial number of PD patients (N=598), with a cumulative exposure of 974.2 person-years (Safety Pool 1), with some subjects being in their eighth year of treatment as of the cut-off date (3 May 2024) for the safety pooled analyses.

Safety Pool 2, representing subjects exposed to the final ND0612 formulation, included 419 patients, with cumulative exposure of 663.0 person-years, with a mean (SD) exposure of 578.0 (580.61) days and a median (range) of 478.0 (2, 2769) days. Most subjects involved (371 out of 419 in Safety Pool 2) received the highest recommended daily dose (720 mg/day) of levodopa.

A total of 223 subjects were exposed to the final formulation for at least one year. Considering that the active substances are well-known, the overall safety database is considered sufficiently large and adequately representative. Available exposure data, including long-term exposure, meets expectations for the intended use of the product, particularly, considering the previous experience with the active substances.

In Study ND0612H-012, which included long-term safety data, the median exposure in the safety population (N=214) was 337 days (range 2-387 days). The total exposure was higher in the 16 h dosing regimen than in the 24 h dosing regimen (77.9 and 57.9 person years, respectively). A total of 48 patients were exposed to the 24h dosing treatment for at least 12 months.

While ND0612 DP did not include a new chemical entity, two aspects make it distinct from more typical oral formulations of LD/CD: the subcutaneous route of administration and the significantly higher exposure to carbidopa.

Expectedly, given the SC route, the most significant ADRs reported were mainly associated with infusion site reactions (ISRs) such as nodules, hematomas, pain, erythema, and infections. The most common TEAEs in the Safety Pool 2 were ISRs: infusion site nodule (70.4%), infusion site haematoma (64.9%), infusion site pain (23.2%), infusion site infection (19.3%), infusion site erythema (18.4%), infusion site eschar (12.9%). Other commonly observed AEs included fall (20.5%), dyskinesia (13.6%), ON and OFF phenomenon (12.4%), COVID-19 (11.2%) and vitamin B6 deficiency (10.0%).

In the pivotal Phase 3 study ND0612-317, during the DBDD study period, 103 (80.5%) subjects in the ND0612 arm and 97 (74.0%) subjects in the IR-LD/CD arm reported at least one AE. Generally, the incidence of AE was slightly higher in the ND0612 group compared to the IR-LD/CD arm. TEAEs assessed as related to the study treatment by the investigator were reported with a higher frequency in the ND0612 arm compared to the IR-LD/CD arm (67.2% vs. 52.7% of subjects, respectively).

During the DBDD period, the following ISRs were reported with a higher incidence (at least 1.5 times more frequent) in the ND0612 arm compared to the IR-LD/CD arm: infusion site haematoma (30.5% vs. 13.0% of subjects, respectively), infusion site infection (10.2% vs. 2.3% of subjects, respectively), infusion site erythema (9.4% vs. 2.3% of subjects, respectively).

Infusion site nodule and infusion site pain were reported at a comparable incidence in the ND0612 arm and the IR-LD/CD arm (infusion site nodule: 25.8% vs. 27.5% of subjects, respectively; and infusion site pain: 8.6% vs. 6.9% of subjects, respectively). Infusion site haemorrhage was reported at a lower

incidence (at least 1.5 times less frequent) in the ND0612 arm compared to the IR-LD/CD arm (0.8% vs. 5.3% of subjects, respectively).

During the double-blind, double-dummy (DBDD) period, the following TEAEs were reported at a lower incidence (at least 1.5 times less frequent) in the ND0612 arm compared to the IR-LD/CD arm: fall (7.0% vs. 12.2% of subjects, respectively), ON and OFF phenomenon (3.9% vs. 9.9% of subjects, respectively), and headache (1.6% vs. 6.1% of subjects, respectively).

During the DBDD period in both treatment arms, the majority of TEAEs were of mild intensity. In the ND0612 arm, out of 484 TEAEs, 83.5% were mild, 14.3% moderate and 2.3% severe. In the IR-LD/CD arm, out of 373 TEAEs, 74.5% were mild, 22.2% moderate and 3.2% severe. A total of 3.9% of subjects in the ND0612 arm and 6.1% of subjects in the IR-LD/CD arm reported severe AEs. The only severe AEs reported in more than one subject in any treatment arm during the DBDD period were anxiety (two subjects in the IR-LD/CD arm) and fall (two subjects in the ND0612 arm). All other severe AEs were reported in single subjects. There were seven severe AEs (infusion site abscess and infusion site ulcer, infusion site extravasation, fall and ON and OFF phenomenon, paraesthesia and peripheral sensorimotor neuropathy reported in four subjects, which were assessed by the investigator as drug related.

The most common (at least 5% of subjects) treatment-emergent adverse events (TEAEs) for the ND0612 group were infusion site hematoma (30.5%), infusion site nodule (25.8%), infusion site infection (10.2%), infusion site erythema (9.4%), infusion site pain (8.6%) and fall (7.0%).

During the ND0612 open-label (OL) conversion period, where study subjects started treatment with ND0612, infusion site nodule and infusion site hematoma were reported respectively in 64.0% and 63.7% of subjects, (i.e., at a higher incidence than in the DBDD period).

For the Safety Pool 1, it is noted that discontinuation of ND0612 DP due to ISRs was reported in 77 (12.9%) subjects. Most common ISRs leading to discontinuation were cases of infusion site nodules (7.0%), infusion site pain (4.2%) and infusion site haematoma (3.3%).

The following most common ISRs (at least 5% of subjects during the DBDD period) were reported with a higher incidence (at least 1.5 times more frequent) in the ND0612 arm compared to the IR-LD/ CD arm: infusion site hematoma (30.5% vs. 13.0% of subjects, respectively), infusion site infection (10.2% vs. 2.3% of subjects, respectively), and infusion site erythema (9.4% vs. 2.3% of subjects, respectively).

While it is acknowledged that during the DBDD Period infusion site nodule and infusion site pain were reported at a comparable incidence in the ND0612 and IR-LD/CD arms (infusion site nodule: 25.8% vs. 27.5% of subjects, respectively; and infusion site pain: 8.6% vs. 6.9% of subjects, respectively), that these two ISRs were most likely caused by a mechanical effect of the cannula placement and the administered volume of the solution, a concern regarding the very high prevalence of these ISR remains.

However, it is noted that incidence of systemic AEs reported in the ND0612 arm was generally lower compared to the IR-LD/CD arm: fall (7.0% vs. 12.2% of subjects, respectively), ON and OFF phenomenon (3.9% versus. 9.9% of subjects, respectively), and headache (1.6% versus 6.1% of subjects, respectively). I

In the overall Safety 2 Pool, the most common ISRs (at least 5% of subjects) were: infusion site nodule (70.4%), infusion site hematoma (64.9%), infusion site pain (23.2%), infusion site infection (19.3%), infusion site erythema (18.4%), infusion site eschar (12.9%), infusion site swelling (8.8%) and infusion site haemorrhage (5.3%). Other AEs reported in at least 5% of subjects were: fall (20.5%); dyskinesia (13.6%); ON and OFF phenomenon (12.4%); COVID-19 (11.2%); vitamin B6 deficiency (10.0%); urinary tract infection (7.9%); anxiety (7.4%); Parkinson’s disease (7.2%); insomnia (6.4%),

arthralgia (6.0%); back pain (6.0%); contusion (5.5%), headache (5.3%); pain in extremity (5.3%); and dizziness (5.0%). Most of these AEs are expected in the population of PD patients with motor fluctuations and/or are common in elderly subjects.

Three cases (0.4%) of hypersensitivity were reported. These cases did not require life support treatment and resolved with discontinuation of ND0612 DP. However, one case required hospitalisation and was classified as a SAE.

There were 15 cases (3%) of polyneuropathy, at least possibly related to ND0612. These cases included neuropathy peripheral, hypoesthesia, acute polyneuropathy, polyneuropathy, paraesthesia, dysesthesia, peripheral sensorimotor neuropathy, muscular weakness and axonal and demyelinating polyneuropathy. Most of them were classified as subacute or chronic. Neuropathy was most often characterised as sensory or sensorimotor. There were four cases that required discontinuation of treatment.

Psychosis was reported in 45 (10.7%) subjects from the Safety Pool 2. Six (1.4%) of them had psychosis AEs leading to study treatment discontinuation. Hallucinations were reported in 8.4% of subjects. Serious hallucinations were reported in two (0.5%) subjects. During the DBDD Period of Study ND0612-317, two subjects (1.6%) from the ND0612 arm reported a psychotic event: one AE of delusion (moderate, not related, study drug dose not changed due to the event) and one AE of hallucination, auditory (mild, related to study drug, study drug dose not changed due to the event). No subject in the IR-LD/CD arm reported a psychotic AE. The incidence of psychosis was overall relatively low. During the DBDD Period of Study ND0612-317, one (0.8%) subject from the ND0612 arm experienced ICD (compulsive shopping and increased libido), compared to no subject within the IR-LD/CD arm. The events were assessed as mild and not related to the study drug.

Somnolence AEs were reported in 14 (3.3%) subjects from the Safety Pool 2. No somnolence AE was severe, serious, or led to study treatment discontinuation. During the DBDD Period of study ND0612-317, somnolence AEs were reported by five (3.8%) subjects from the IR-LD/CD arm, versus no subject in ND0612 arm.

Overall, depression AEs were reported in 29 (6.9%) subjects from the Safety Pool 2. No depression AE led to study treatment discontinuation. During the DBDD Period of study ND0612-317, seven (5.5%) subjects in the ND0612 arm compared to five (3.8%) subjects in the IR-LD/CD arm had a depression AE. No positive trends indicative of suicidal ideation or behaviour were observed in the Columbia-Suicide Severity Rating Scale (C-SSRS) across studies ND0612H-012 and ND0612-317.

With respect to the SAEs, during the DBDD period, the incidence of SAEs was similar across treatment arms (5.5% in the ND0612 arm and 3.8% subjects in the IR-LD/CD arm). The only SAE reported in the ND0612 arm in more than one subject was infusion site infection (reported in three subjects). Six treatment-related SAEs were reported in four subjects (all in the ND0612 arm): infusion site abscess and infusion site ulcer (2 SAEs); infusion site cellulitis (two SAEs); paraesthesia and peripheral sensorimotor neuropathy (two SAEs).

Vitamin B6 deficiency, a well-known ADR associated with LD/CD therapy, was observed in 12.6% of the Safety Pool 2 participants. According to the ND0612-317 CSR, vitamin B6 deficiency TEAE (CMQ) was reported by five (3.9%) subjects in the ND0612 arm, versus one (0.8%) subject in the IR-LD/CD arm. A higher incidence of shift in vitamin B6 values from normal at baseline to < LLN during the DBDD Period was reported in the ND0612 arm versus the IR-LD/CD arm (20.6% vs. 8.5%). The higher rates of vitamin B6 deficiency observed may be caused by the significantly higher carbidopa exposure (3- to 4-fold higher) derived from ND0612 therapy compared to the known exposure from oral LD/CD therapies. Overall, the assessment of the available evidence supported a causal association between ND0612 treatment and vitamin B6 deficiency.

Vitamin B6 deficiency is therefore listed as very common (⩾10%) in the adverse reaction table of SmPC section 4.8. Monitoring of vitamin B levels is recommended in patients who develop signs or symptoms of neuropathy. Furthermore, as detailed in SmPC section 4.4, vitamin B6 supplement is advisable in case of deficiencies, particularly if markedly low levels are observed.

In the Safety Pool 2, 24.6% of subjects had at least one SAE. Serious ADRs were reported for 7.4% (31 participants), with serious infusion site infections constituting most of those, 4.5% (19 participants), mostly abscesses and cellulitis that required hospitalisation for treatment. Overall, serious infusion site infections are a significant concern, emphasising the need for careful monitoring, which is addressed in section 4.4 of the SmPC.

There were in total 24 (4.0%) cases of death in PD subjects. These included respiratory / urinary tract infection and related sepsis (eight subjects), sudden death/cardiac arrest (six subjects), worsening PD / general physical health deterioration (five subjects), fall/traumatic brain injury, road traffic accident (2 subjects), hiatal hernia/acute kidney injury (one subject), pulmonary embolism (one subject) and food choking (one subject). None of the death cases were assessed as treatment-related by the investigators or the sponsor.

The available data indicates a high rate of treatment discontinuations. For example, 43.9% prematurely discontinued ND0612H-012 (< 1 year follow-up). In the ND0612-317 pivotal study, 19.6% subjects discontinued the study drug during the conversion period, while during the DBDD Period 5.5% subjects in the ND0612 arm discontinued due to an AE (2.3% subjects due to an AE-ISR and 3.1% subjects due to systemic AE). In the IR-LD/ CD arm, no subject discontinued due to an AE-ISR, and 3.1% subjects discontinued due to a systemic AE. AEs leading to early discontinuation in at least two subjects, were infusion site infection (3 subjects in the ND0612 arm), ON and OFF phenomenon (2 subjects in each treatment arm), and fall (2 subjects in the ND0612 arm). The high rate of treatment discontinuation reflects the tolerability challenges associated with continuous subcutaneous administration, largely driven by infusion site reactions. Considering the risks associated with sudden withdrawal or rapid dose reduction from dopaminergic therapies, the SmPC includes recommendations on the management of therapy interruptions or discontinuations and the need to maintain dopaminergic coverage to avoid withdrawal-related complications.

In the Safety Pool 2, a total of 212 participants were aged between 65 and 75 years, while only 34 subjects were aged 75 years or older. Furthermore, no participants aged 85 or older were enrolled in the clinical trials. Overall, no relevant differences were observed between age subgroups, despite the low representation in older subgroups. As detailed in the SmPC, Onerji dose adjustment should be conducted with caution in patients of 85 years and older.

No drug interactions studies were conducted with ND0612 DP. The SmPC includes interactions that are known from the typical combination of LD/CD.

The table in SmPC section 4.8 is based on the drug-related TEAEs for Safety Pool 2, which included subjects treated with the final formulation under the intended 24-hour dosing regimen and provides the most representative and conservative estimate of the product’s safety profile.

The PIL includes clear instruction for use accompanied by clarifying pictures, particularly to mitigate the risk of premature infusion site reuse by the patient.

5.4.12.1.2. Adverse drug reactions in the SmPC

The ADRs proposed by the applicant for inclusion in the SmPC are described above, in section 5.4.3.1. of this assessment report.

5.4.12.2. Conclusions on clinical safety

While ND0612 drug product is not a new chemical entity, it is distinct from the more standard oral LD/CD therapies due to its subcutaneous administration route and the significantly higher exposure to carbidopa.

As expected, SC administration resulted in infusion site reactions, which are the focus of risk minimisation activities. Although infrequent, some serious infusion site infections were also observed. In addition, the significantly higher exposure to carbidopa appears to be linked to a higher incidence of vitamin B6 deficiency.

Overall, apart from ISRs, reported with a higher incidence in the ND0612 arm compared to IR-LD/CD arm, no new AEs, in comparison to the already known safety profile of LD/CD were identified

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 45. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Infusion site reactions
Important potential risks	None
Missing information	None

6.1.2. Discussion on the proposed safety specification

In the applicant's proposed RMP, the key risks of Onerji treatment were appropriately identified, including infusion site reactions (ISR) and polyneuropathy.

About polyneuropathy, suggested to be added in the RMP as an important identified risk, the applicant did not propose additional pharmacovigilance (PhV) activities or risk minimisation measures (RMMs). Instead, only a clinical recommendation to monitor patients for onset of neuropathy while receiving Onerji treatment was suggested for inclusion in SmPC section 4.4. Of note, no detailed instructions (e.g., clear time points for patient check-up) or specific steps to minimise this risk were outlined. Ultimately, PRAC and CHMP considered sufficient monitoring this risk throughout PSUR procedures. Therefore, polyneuropathy was confirmed for inclusion (as an important identified risk) only in the PSUR list of safety concerns. Furthermore, the warning text on neuropathy in SmPC section 4.4 was revised accordingly. In addition, the applicant proposed to include "Effect of carbidopa (from Onerji® administered with oral adjunct LD/CD) on cardiac repolarisation" as missing information in the list of RMP safety concerns. This was triggered by the FDA requested study to evaluate the electrocardiographic effects of a supratherapeutic dose of carbidopa in healthy subjects. However, the final results of this study were made available and assessed during this initial MAA. These results showed that a supratherapeutic oral dose of carbidopa was safe, well tolerated and had no effect on

cardiac repolarisation or other ECG parameters. Thus, the "Effect of carbidopa on cardiac repolarisation" was ultimately removed as mission information from the list of safety concerns.

Ultimately, only ISR was confirmed for inclusion in Onerji RMP as an important identified risk.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan

With reference to the important identified risk of ISR, as routine PhV activity beyond ADR reporting and signal detection the applicant proposed the "adverse reaction targeted questionnaire for serious infusion site reactions" to further characterise the important identified risk of ISR, with focus on the serious ones. In addition, as additional PhV activities, the applicant proposed an observational post-marketing cohort study and a thorough QT/QTc (TQT) study, both detailed in sub-section 6.222.

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

According to the guideline on specific adverse drug reaction (ADR) follow-up questionnaires (AR FUQs), targeted AR FUQ should, in principle, not be used to collect information on important identified risks, but only in some special situations, where the reversibility, severity or other aspects of the (important identified) risk need to be further characterised. The proposed FUQ did not contain any specific question enabling the collection of additional information not already asked/expected to be provided in the standard form for ADRs reporting. Instead, further characterisation of serious infusion site reactions could be carried out throughout PSURs.

In conclusion, the proposed specific AR FUQ for the important identified risk of infusion site reactions was not considered warranted and, consequently, removed from the proposed PhV plan.

6.2.2.2. Additional pharmacovigilance activities

The Applicant proposed an observational post-marketing cohort study to collect real-world data on Onerji administration via the YURWAY® Delivery System, ultimately to address the important identified risk of infusion site reactions. However, the objectives of the study were mainly related to assessing the safety, actual use and performance of the Yurway® Delivery System. The trigger for such proposal was the fact that the studies presented in this initial MAA (i.e. with ND0612 as the investigational product) had been conducted with other delivery systems rather than Yurway®. Of note it was confirmed that technological differences between devices (specifically the Yurway Delivery System or the Crono Twin ND pump) would not introduce any new risks related to Onerji safety and effectiveness.

The PRAC and CHMP concluded that the important identified risk of infusion site reactions did not requirefurther characterisation through additional PhV activities, while the effectiveness of the additional risk minimisation measures (RMMs) proposed by the applicant for this safety concern (i.e., the patient guide) could be adequately evaluated via routine pharmacovigilance (e.g., within PSUR submissions). Thus, the proposed study was removed from the PhV plan.

In addition, the applicant suggested to include in the PhV plan a (Phase 1) thorough QT/QTc (TQT) study, initially requested by FDA, to address the proposed missing information "Effect of carbidopa (from Onerji® administered with oral adjunct LD/CD) on cardiac repolarization". As previously mentioned, the final CSR, assessed during this initial MAA, showed that a supratherapeutic oral dose of carbidopa was safe, well tolerated and had no effect on cardiac repolarisation or other ECG parameters. Consequently,

also the TQT study was removed from the proposed PhV plan.

In conclusion, no additional pharmacovigilance activities are considered necessary for Onerji.

6.3. Plans for post-authorisation efficacy studies

Not applicable.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

The following RMMs were proposed by the applicant.

Table 46. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infusion site reactions	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8. PL sections 2, 3, 4 and 7. Legal status: subject to medical prescription. Additional risk minimisation measures: Patient Guide.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none. Additional pharmacovigilance activities: none.

Patient Guide

Objectives: To minimise the risk of infusion site reactions.

Rationale for the additional RMM: to enhance patients' awareness about the risks of infusion site reactions and to educate patients on measures to help mitigate these risks.

Target audience and planned distribution path: all Parkinson's disease adult patients treated with Onerji. The educational material (EM)should be disseminated to healthcare professionals (HCP) prescribing Onerji, who will provide this EM should be disseminated to healthcare professionals (HCP) prescribing Onerji, who will provide this EM to patients (and, if applicable, to their caregivers) at the time of prescription.

Plans to evaluate the effectiveness of the interventions and criteria for success:

effectiveness measured by means of routine pharmacovigilance activities. Assessment by routine PhV activities should include signal detection, follow-up requests and review of received case reports relevant to this safety concern. Therefore, the success of the proposed RMMs will be based on close monitoring of the ADR and trends where distribution of the EM has taken place.

Also of note, a User Manual is provided with the drug delivery system, the Yurway Delivery System or the Crono Twin ND pump, detailing instructions for use and appropriate management of the infusion pump device required to administer Onerji.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The PRAC and CHMP considered the proposed routine RMMs as adequate. As recommended by PRAC, clear instruction for use (IFU) were included (with accompanying pictures) in section 7 of the PL on how to prepare Onerji infusion, together with information on infusion site selection, use and appropriate management of the infusion pump device (Yurway Delivery System or Crono Twin ND pump), also ensuring that the sub-cutaneous infusion site location is changed daily and systematically rotated to avoid reusing an infusion site for at least 2 weeks.

6.4.2.2. Additional risk minimisation measures

The PRAC and CHMP considered the proposed additional RMMs above described as adequate. They also agreed that the effectiveness of the patient guide can be adequately evaluated via routine PhV activities and summarised in future PSURs.

6.5. RMP Summary and RMP Annexes overall conclusion

The RMP Part VI is considered acceptable.

6.6. Overall conclusion on the Risk Management Plan

☒ The CHMP and PRAC consider that the risk management plan version 1.0 is acceptable.

6.7. 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.

6.8. Periodic Safety Update Reports submission requirements

As Onerji will be administered subcutaneously, via a route of administration that leads to higher systemic exposure to carbidopa compared to the existing oral formulations, the PRAC and CHMP concluded that this medicinal product cannot follow the already existing entry in the list of Union reference dates (EURD list) for oral carbidopa/levodopa. Therefore, a separate entry in the EURD list is deemed necessary for Onerji. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant indicated the wish to align the PSUR cycle with the international birth date (IBD).

7. Product information

7.1. Summary of Product Characteristics (SmPC)

7.1.1. SmPC section 4.1 justification

The wording of the indication has been agreed to be as follows:

- Onerji is indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medicinal products.

In the course of this MAA, the applicant recognised the CHMP request for modifying the indication

initially proposed (which was treatment of motor fluctuations in patients with Parkinson's disease) to align with other device-aided therapies for Parkinson's disease (PD) patients with motor fluctuations. It therefore accepted the inclusion in the indication of "*advanced Parkinson's disease*", as well as the additional wording "*not sufficiently controlled by oral anti-Parkinson medicinal products*", generally aligned with the eligibility criteria of the pivotal trial ND0612-317 and study ND0612H-012.

It is acknowledged that patient's progression to advanced PD has conventionally not been well-defined (Aslam et al. 2024; Titova et al., 2017). However, independently of the lack of an established definition, it is generally accepted that patients reaching an advanced stage of the disease, as PD symptoms become increasingly refractory to oral treatments, are candidates for device-aided therapy (Deuschl et al., 2022).

7.2. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show 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.

8. Benefit-risk assessment

8.1. Therapeutic context

8.1.1. Disease or condition, proposed therapeutic indication

Parkinson's Disease (PD) is a progressive neurodegenerative movement disorder clinically characterised by the presence of cardinal motor features (including bradykinesia along with, at least, tremor or rigidity) and pathologically characterised by degeneration of dopaminergic neurons in the substantia nigra pars compacta, resulting in striatal dopamine deficiency.

PD is the second most common neurodegenerative disorder after Alzheimer and a major increasing burden on patients, families, carers and healthcare systems. The prevalence of PD is approximately 1 million people in the US and 6 million people worldwide. It is estimated to affect 1% of people over the age of 60 and 3% over the age of 80 years.

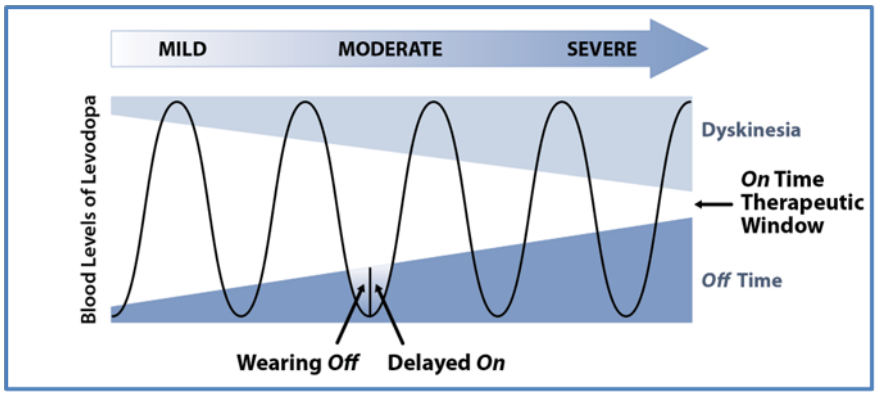
Between 1990 and 2015, the global prevalence of Parkinson's Disease doubled, a trend primarily attributed to an aging population. Data from a global burden of disease study projected that the number of individuals living with PD will increase to approximately 13 million by 2040.

8.1.2 Available therapies and unmet medical need

For a detailed description, please see section 2.1 of this document.

The administration of levodopa (LD) in combination with the peripheral dopa-decarboxylase (DDC) inhibitor carbidopa (CD) remains the gold standard of care for Parkinson's Disease. To date, this combination continues to be the most potent pharmacological intervention to manage the cardinal motor symptoms of the disease. Most PD patients experience satisfactory control with intermittent doses of oral LD/DDC inhibitor therapy, particularly during the early stages of the disease. At these early stages, patients typically obtain a long-lasting response following each dose of LD despite its relatively short half-life of only 45-90 minutes. However, chronic LD treatment and disease progression are associated with the development of motor complications in the form of motor fluctuations (wearing OFF, ON-OFF phenomenon) and dyskinesia (as illustrated in the Figure below), which can be severe and disabling.

Figure 18. Motor Fluctuations and Dyskinesias over time in Parkinson's Disease



There are several options to treat motor fluctuations in PD, but no drug has yet been able to manage them satisfactorily in the long-term. Oral therapies fail to provide sufficient control of motor fluctuations in many patients with advancing PD. One option is adjusting the levodopa dose or frequency; however, increasing the dose can lead to worsening of dyskinesia, while lowering the dose can increase OFF time. Extended-release formulations have not proven to be more effective. Different adjunct therapies have been developed to try to reduce OFF time. These include dopamine agonists, MAO-B inhibitors, COMT inhibitors, and/or the adenosine antagonist istradefylline. None of these options provides benefits superior to levodopa. In addition, each option has its own set of potentially serious side effects such as sleep disturbances, psychosis, impulse-control disorders, etc. Surgical therapies such as Deep-Brain Stimulation (DBS) can also be considered for the treatment of motor complications not adequately controlled by oral therapies. Indeed, they may provide benefit for both OFF time and dyskinesia. Nevertheless, they require a brain operation that can be associated with potentially serious complications, such as haemorrhage, infection, or seizure. In addition, complications related to the stimulation system or the stimulation itself, such as dysarthria, may also develop. Furthermore, frequent adjustments are necessary and occasional repeat of surgical procedures may be required (e.g. related to the stimulation system or for battery replacement). Importantly, no procedure has been shown to provide superior anti-parkinsonian benefits in comparison to levodopa (perhaps except for tremor).

The mechanism by which levodopa causes motor fluctuations and dyskinesia has been the source of intense investigation over the past two decades. Evidence indicates that motor complications are related to the non-physiologic (i.e., pulsatile) restoration of brain dopamine following intermittent doses of standard LD/CD. Under physiological conditions, brain dopamine is maintained at relatively constant levels, with continuous activation of brain dopamine receptors, even following the administration of a LD dose. In PD, where dopaminergic nigrostriatal projection neurons' dopamine terminals have degenerated, striatal dopamine levels are dependent on the peripheral availability of LD. Levodopa has a short half-life, and its absorption varies with the speed of gastric emptying and the presence of dietary protein competing for uptake in the small intestine. Thus, intermittent dosing with standard oral LD (even when co-administered with DDC inhibitor) is associated with prominent fluctuations of LD plasma levels, which translates into oscillations of striatal dopamine levels and pulsatile stimulation of striatal dopamine receptors. This, in turn, has been shown to result in post-receptor molecular changes in striatal neurons, neurophysiologic changes in pallidal output neurons, and the development of motor complications. These observations led to the hypothesis that continuous delivery of levodopa would reduce the variability of LD plasma concentration, and restore brain dopamine in a more physiologic manner, leading to a reduced risk of motor complications. Studies in both animal models and PD patients have demonstrated that continuous delivery of a dopaminergic agent is associated with a reduction of motor complications in comparison to intermittent doses of the same agent. These findings were confirmed in a prospective, DBDD clinical study of continuous intrajejunal levodopa infusion (Olanow et

al., 2014) showing a benefit on primary and secondary outcome measures (OFF time and ON time without troublesome dyskinesia) of a greater magnitude than, to date, has not been seen with any of the approved LD oral therapies. Based on these findings, Duopa® (CD/LD enteral suspension) was approved by FDA, and Duodopa in the European Economic Area. However, LD/CD intestinal gel treatment is associated with potentially serious side effects, linked to the surgical procedure (e.g., subjected to peritonitis, pancreatitis, pain, infection, as detailed in Duodopa® SmPC) and the need of a permanent intrajejunal tube (e.g., potentially subjected to blockage, dislocation, infection) which may require periodic invasive procedures. Additionally, it does not solve the issue of competitive absorption of LD in the jejunum.

Consequently, an unmet medical need remains for an alternate treatment method that could provide continuous LD delivery without the risks associated with surgical or an indwelling jejunal catheter.

Foslevodopa/foscarbidopa, a pro-drug of LD/CD administered continuously SC over 24 h through a single infusion site, was approved in some European countries (as Produodopa®), in Canada, Japan and more recently in the US (as Vyalev®), for the "treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results". It had been developed as a full replacement therapy, providing a maximum recommended daily dosage of levodopa equivalent to 2500 mg (Vyalev® USPI) or 4260 mg (Produodopa® SmPC).

Unlike Produodopa®, ND0612 DP 24 h SC infusion was developed as a partial replacement therapy, providing up to 720 mg levodopa daily. This treatment was designed to be complemented with an oral levodopa formulation to meet patients' individual needs. The approach was intended to provide the foundational levodopa concentrations enabling the benefits of continuous levodopa delivery, while minimising the risk of excessive dopaminergic load, as discussed further below. Moreover, it would avoid the need to infuse large solution volumes necessary to fully substitute oral levodopa intake, while compromising skin tolerability. Additionally, ND0612 treatment was designed to allow drug delivery through two infusion sites, rather than just one, to further dilute the volume burden at each infusion site.

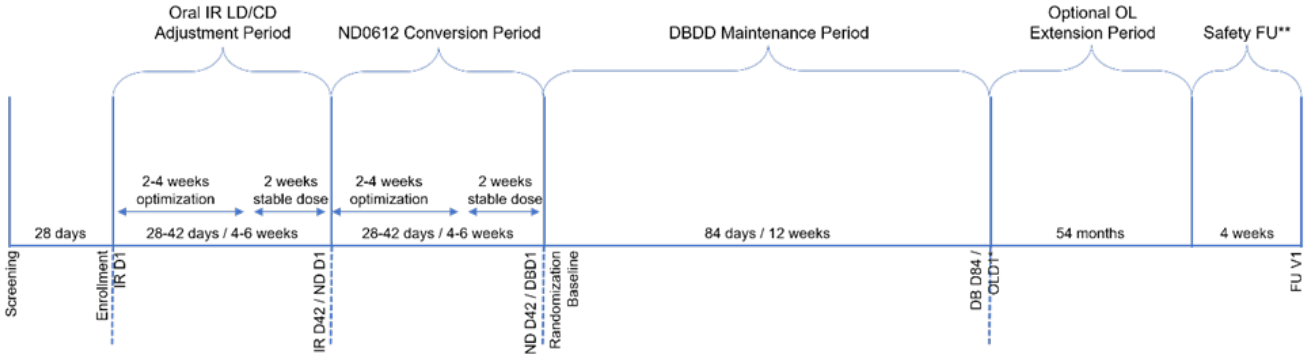
8.2. Main clinical studies

For a detailed description of the main clinical studies supporting this initial MA application, please refer to section 5.1.2 of this document.

The pivotal trial ND0612-317 was a multicentre, international, randomised, active-controlled, DBDD, parallel-group Phase III study investigating the efficacy, safety, and tolerability of continuous ND0612 DP infusion (LD/CD dose up to 720/90 mg/day, 24-hour regimen) in comparison to oral IR-LD/CD. The core period of this study (from enrolment up to the end of the DBDD period, plus additional safety follow-up, when applicable) has been completed while its optional open-label extension (OLE) (up to 54 months) is still ongoing.

A total of 259 subjects (ITT set) who completed the IR-LD/CD OL adjustment period and the ND0612 OL conversion period entered the DBDD maintenance period: 128 (49.4%) were randomised to ND0612 arm and 131 (50.6%) to the IR-LD/CD control arm.

Figure 19. Study design flow chart



Primary and key secondary endpoints:

The change from baseline to the end of the DBDD Period in mean daily ON time without troublesome dyskinesia (i.e., GOOD ON time) and in mean daily OFF time were defined as the primary and key secondary efficacy endpoints, respectively, as done in other clinical studies conducted in similar PD population (Hauser et al., 2013; Olanow et al., 2014; Soileau et al., 2022). OFF time is disabling for many patients, but it is important to ensure that a decrease in OFF time is not converted into an increase in ON time with troublesome dyskinesia. Home diary measures of motor function, as captured in the patient Hauser's diaries, have been reliably used as a clinical outcome measure in the assessment of new therapies for patients with PD experiencing motor fluctuations (Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease, 21 June 2012 EMA/CHMP/330418/2012 rev. 2; Hauser et al., 2013; Katzenschlager et al., 2018; Olanow et al., 2014) and led to approval of multiple therapies in this patient population.

Other secondary endpoints

Other secondary endpoints included patient-reported outcomes and physician assessments commonly used in studies in PD subjects with motor fluctuations. They were tested in the following hierarchical order for type I error control.

Table 47. Primary and Secondary Efficacy Endpoints Analyses

Endpoints	Oral IR-LD/CD (N=131) LS means (SE)	ND0612 (N=128) LS means (SE)	Treatment effect LS means (SE); 95% CI	P-value
Primary Efficacy Endpoint				
"ON" time without troublesome dyskinesia - CFB to DBW12 (h)	-2.20 (0.23)	-0.48 (0.23)	1.72 (0.33); 1.08, 2.36	<0.0001
Main supportive (MNAR)	-2.20	-0.53	1.66 (0.33); 1.02, 2.31	<0.0001
Likelihood-based - MMRM	-2.21	-0.51	1.70 (0.33); 1.06, 2.35	<0.0001
"Retrieved Data"- under MAR	-2.20	-0.47	1.73 (0.33); 1.09, 2.37	<0.0001
"Retrieved Data"- under MNAR	-2.19	-0.52	1.67 (0.33); 1.03, 2.32	<0.0001
Per-Protocol Analysis	-2.55	-0.40	2.15 (0.37); 1.43, 2.87	<0.0001
Key Secondary Endpoint				
"OFF" Time - CFB to DBW12 (h)	1.90 (0.22)	0.50 (0.22)	-1.40 (0.30); -1.99, -0.80	<0.0001
Other Secondary Endpoints (in hierarchical order)				
1st: MDS-UPDRS Part II (M-EDL) Sum Score- CFB to DBW12	2.75 (0.45)	-0.30 (0.45)	-3.05 (0.63); -4.28, -1.81	<0.0001
2nd: Improvement on PGIC from Start of the ND0612 OL Conversion Period to DBW12 (proportion)	0.31 (0.05)	0.70 (0.05)	Odds ratio: 5.31 (0.35); 2.67, 10.58	<0.0001
3rd: Improvement on CGI from Start of the ND0612 OL Conversion Period to DBW12 (proportion)	0.31 (0.05)	0.77 (0.05)	Odds ratio: 7.23 (0.36); 3.57, 14.64	<0.0001
4th: MDS-UPDRS Part III (Motor Examination) Sum Score- CFB to DBW12	3.39 (1.00)	0.98 (1.02)	-2.42 (1.42); -5.20, 0.37	0.0889[1]
5th: ON Time Without Dyskinesia CFB to DBW12 (h)	-2.53 (0.25)	-0.41 (0.26)	2.12 (0.36); 1.42, 2.82	<0.0001[2]
6th: ≥50% Reduction in "OFF" time from Start of the ND0612 OL Conversion Period to DBW12 (proportion)	0.10 (0.03)	0.29 (0.06)	Odds ratio: 3.63 (0.43); 1.56, 8.44	0.0027[2]
7th: PDQ-39 Summary Index - CFB to DBW12	4.29 (0.77)	1.60 (0.78)	-2.69 (1.09); -4.83, -0.55	0.0137[2]
8th: PDSS-2 Total Score - CFB to DBW12	1.47 (0.70)	0.05 (0.71)	-1.42 (0.99); -3.35, 0.52	0.1508[2]

DBW12: Week 12 of double-blind, double-dummy period; CGI: Clinical Global Impression; CFB: Change from Baseline; CI: Confidence interval; h: Hour(s); IR-LD/CD: Immediate release levodopa/carbidopa; LS mean: Least-squares mean; M-EDL: Motor aspects of experiences of daily living; MDS-UPDRS: Movement Disorder Society-sponsored Revision of the Unified Parkinson's Disease Rating Scale; MMRM: Mixed model repeated measures; MNAR: Missing not at random; N: Number of subjects; PDQ-39: 39-Item Parkinson's Disease Quality of Life Questionnaire; PDSS-2: Parkinson's Disease Sleep Scale-2; PGIC: Patient Global Impression of Change; SE: Standard error.

8.3. Favourable effects

Both primary endpoint and key secondary endpoints were met: good on time mean difference from baseline showed a statistically significant treatment difference of 1.72 h ($p<0.0001$) at Week 12 in favour of ND0612 (worsening 0.48h in the DBDD as compared to the OL conversion) over IR-LD/CD (-2.02h); mean OFF time reduction at week 12 was also in favour of ND0612, with 1.4h less off time with ND0612 than with IR-LD/CD. Secondary endpoints also trended in favour of SC ND0612. It is relevant that the quality of ON time, as measured by the activities of daily living in Part 2 of MDS-UPDRS (2nd secondary endpoint) and motor performance in part 3 of MDS-UPDRS (3rd secondary endpoint) also supported the benefit observed with the primary and key secondary endpoints.

8.3.1. Uncertainties and limitations about favourable effects

The Applicant presented a single main trial. Study ND0612-317 was a DBDD parallel group with continuous ND0612 SC infusion *versus* immediate release oral LD formulations. It is acknowledged there is no model design to mimic real-life situations. Transitioning levodopa formulations (immediate and sustained release) to immediate-release, and keeping the patient in the study, even if deteriorating, were difficult tasks.

Regarding the study population:

1) The mean age of 64.1 years is a rather low. In EU, patients below the age of 70 are offered DBS. Most patients with infusion treatments are above the age of 70. The time since PD diagnosis and the time since motor fluctuations is within the expected values for the range in cognition from fit to mild demented (MMSE 24 through 30) PD population. The BMI is shifted towards the higher values, which is less common in choreic patients with high energy expenditures in on time, and lack of appetite in off time. No patients above 85 years were enrolled into the confirmatory study, and only two patients aged 85 or more have been studied in the long-term safety study. Many patients with advanced PD nowadays are in the late 80s. For this sub-population, a cautionary wording on dosing adjustment has been included in SmPC section 4.2.

2) Subjects with atypical or secondary parkinsonism, acute psychosis or troublesome hallucinations in the past six months prior to enrolment were not eligible to the study, which is considered acceptable. The applicant clarified that in study ND0612-317, 4.2% (n=11) of all randomised patients had a medical history of psychosis, including three patients who experienced a psychosis event in the previous 6 months before enrolment.

3) To avoid any potential impact on study conduct/analysis, clozapine was not permitted in the pivotal trial ND0612-317. Clozapine is an effective antipsychotic for the treatment of refractory psychosis in PD. However, its use has been limited due to the risk of agranulocytosis, and stringent complete blood count monitoring. As it is well known, infusion strategies are often used in patients who are no longer candidates to DBS, namely due to age and cognitive criteria. Concern was expressed about the exclusion of clozapine-controlled patients. Therefore, the applicant clarified that 3.5% of the patients enrolled into this confirmatory study was previously psychotic but controlled patients. Furthermore, in the follow-up study, 15% of the patients were under antipsychotics, and 4.2% were on clozapine. It may thus be assumed that Onerji can be used in controlled previously psychotic

patients. It is nonetheless interesting that in the long-term safety study ND00612H-012, where there was no restriction on clozapine, more patients required use of antipsychotics than initially (4.2 vs 15%), which highlights that the use of device assisted agents should be restricted to the more advanced severe fluctuations of PD

In the pivotal study ND0612-317 the Crono Twin ND pump was used. In the SmPC, the applicant detailed that another type of delivery system may also be used: the Yurway Delivery System, previously referred to as the Twiko Delivery System (TDS). Importantly, although this delivery system was not used in the clinical studies, the established efficacy and safety profile of Onerji is expected not to be affected with the use of the Yurway Delivery System, which a has similar drug product delivery performance to the Crono Twin ND pump.

8.4. Unfavourable effects

The safety data included results from six phase I studies in healthy volunteers and six studies in PD patients.

The applicant performed integrated safety analyses in three cohorts. Safety Pool 1, Safety Pool 2, which is the most relevant for the current assessment, and Safety Pool 3, which included data from all healthy volunteers.

Safety Pool 1 included data from all PD patients enrolled in ND0612 DP clinical studies (N=598), while Safety Pool 2 focused on those receiving the final ND0612 DP formulation under the 24-hour dosing regimen (N=419). The two main studies contributing to the safety data are the comparative Phase III pivotal efficacy study ND0612-317 and the long-term safety Phase IIb study ND0612H-012.

Given the SC route, the most significant ADRs reported were mainly associated with infusion site reactions (ISRs) such as nodules, hematomas, pain, erythema, and infections. The most common TEAEs in the Safety Pool 2 were ISRs: infusion site nodule (70.4%), infusion site haematoma (64.9%), infusion site pain (23.2%), infusion site infection (19.3%), infusion site erythema (18.4%), infusion site eschar (12.9%). Serious ADRs were reported for 7.4% (31 participants), with serious infusion site infections constituting majority of those, and reported in 4.5% (19 participants), mostly abscesses and cellulitis, that required hospitalisation for treatment. Overall, serious infusion site infections are a significant concern, emphasising the need for careful monitoring.

A higher incidence of shift in vitamin B6 values from normal at baseline to < LLN during DBDD Period was also reported in ND0612 arm vs. IR-LD/CD arm (20.6% vs. 8.5%). The higher rates of vitamin B6 deficiency observed may be caused by the significantly higher CD exposure (3- to 4-fold higher) derived from ND0612 therapy compared to the known exposure from oral LD/CD therapies.

Available data also indicated a concerning rate of treatment discontinuations: e.g., 19.6% subjects discontinued the study drug during ND0612-317 conversion period, 43.9% prematurely discontinued ND0612H-012 (< 1 year follow-up). Most of these discontinuations were due to adverse events, with infusion site reactions being the most significant factor. The high rate of treatment discontinuation raises questions about the overall tolerability of the treatment, given the frequency of infusion site complications. Therefore, to complement routine risk minimisation measures, a patient guide has been agreed to minimise occurrence of this safety concern.

8.4.1. Uncertainties and limitations about unfavourable effects

ND0612 therapy results in a significantly higher CD exposure (3- to 4-fold higher) compared to the known exposure from oral LD/CD therapies.

This significantly higher CD exposure is also likely responsible for the higher incidence of participants experienced a shift in vitamin B6 levels from normal to below the LLN in participants treated with ND0612. Uncertainties remain regarding the impact of this effect outside the clinical trial setting.

The high incidence of infusion site reactions is of concern. The high rate of treatment discontinuation raises questions about the overall tolerability of the treatment. It remains uncertain if, in the real-world setting, discontinuation of treatment will be also reported so frequently. The risks associated with sudden withdrawal or rapid dose reduction from dopaminergic therapies may be increased outside the controlled trial setting.

In the Safety Pool 2, a total of 212 participants were aged between 65 and 75 years, while only 34 subjects were aged 75 years or older. Furthermore, no participants aged 85 or older were enrolled. The low representation in older subgroups limits the ability to draw robust conclusions regarding the safety profile in this particularly vulnerable demographic.

8.5. Effects Table

Table 48. Effects Table for Onerji (data cut-off: 3 May 2024)

Effect (short description)	Treatment	Control	Uncertainties/ Strength of evidence	Ref
Favourable Effects				
Change from Baseline to V19/DBW12 in "GOOD ON" time during DBDD period LS mean (SE)	-0.48h (0.234)	-2.20 h (0.232)	**SoE:** LS-Means -difference between groups of 1.72h, clinically relevant for patients **Unc:** The rather artificial conditioning before DBDD, which reduced the number of enrolled patients by 1/3; change in infusion pump proposed to be used.	ND0612-317 DBDD
Change from Baseline to V19/DBW12 in "OFF" time LS mean (SE)	0.50 h (0.217)	1.90 h (0.215)	**SoE:** LS-Means -difference between groups of 1.40h, clinically relevant for patients **Unc:** The rather artificial conditioning before DBDD, which reduced the number of enrolled patients by 1/3; change in infusion pump proposed to be used.	ND0612-317 DBDD
Change from Baseline to V19/DBW12 in MDS-UPDRS Part II (M-EDL) LS mean (SE)	-0.30 (0.451)	2.75 (0.445)	**SoE:** Activities of daily living improving 3.05 pts, clinically relevant: not only ON is extended, but the quality of ON time did not decrease **Unc:** The rather artificial conditioning before DBDD, which reduced the number of enrolled patients by 1/3; change in infusion pump proposed to be used.	ND0612-317 DBDD
Unfavourable Effects				

Effect (short description)	Treatment	Control	Uncertainties/ Strength of evidence	Ref
Infusion site reactions (ISRs): participants affected by at least one ISR during treatment (grouped terms)	372/419 (88.8%)	Not applicable	Most events were mild in severity (mild: 85.0%; moderate: 13.8%; severe 1.2%) During the DBDD period, the following ISRs were reported with a higher incidence in ND0612 arm compared to IR-LD/CD arm: infusion site haematoma (30.5% vs. 13.0% of subjects, respectively), infusion site infection (10.2% vs. 2.3% of subjects, respectively), infusion site erythema (9.4% vs. 2.3% of subjects, respectively).	Safety Pool 2
Serious infusion site infections: participants affected by at least one serious infusion site infection during treatment (grouped terms)	19/419 (4.5%)	Not applicable	Annual event rate: 0.035	Safety Pool 2
Vitamin B6 decreased: participants who experienced a shift from normal to below the LLN	20/97 (20.6%)	8/96 (8.5%)	Consistent with shift observed for participants treated with IR-LD/CD who continued to OLE period with ND0612 (from 8.5% to 27.8%)	ND0612-317 DBDD

Abbreviations: DBDD: double-blind double-dummy period; LLN: lower limit of normal; OLE: open-label extension; OR: odds ratio; Ref: reference; SE: standard error; SoE: strength of evidence; Unc: uncertainties.

8.6. Benefit-risk assessment and discussion

8.6.1. Importance of favourable and unfavourable effects

Levodopa is the most effective treatment for the motor symptoms of Parkinson's disease. LD, in a fixed dose combination with a DDI has been the gold standard for the treatment of PD for over 50 years, and its effect is well known. Long-term oral administration of LD causes development of fluctuations in motor response and dyskinesia, depending on several factors (daily dose, concomitant medication, age of the patient, etc). This can cause substantial impairments in quality of life (Hechtner et al., 2014). To mitigate these complications, several strategies have been developed, including the use of sustained release formulations, addition of MAOi or COMTi. When oral formulation approach no longer suffices, advanced therapies for PD are indicated. These include deep brain stimulation and the use of levodopa / carbidopa gel via gastrostomy and jejunal probe. Both are invasive procedures requiring surgery, and therefore new forms of administering levodopa are needed. Besides availability of these pharmacological effective treatments, some patients with Parkinson's disease eventually progress to device-aided therapies, such as continuous subcutaneous (SC) apomorphine infusion, intrajejunal levodopa infusion, or deep brain stimulation (Nijhuis et al., 2021).

ND0612 is a sterile solution containing levodopa and carbidopa in 8:1 ratio combination for continuous SC administration. ND0612 is proposed to be used in advanced PD for the treatment of motor fluctuations, injected subcutaneously over 24h through two infusion sites, at a fixed rate of 0.08 mL/h during the night for 6 hours, and at a variable rate of 0.32 to 0.64 mL/h during the day for 18 hours. Given the high quantity of levodopa and the limited concentration required, two injection sites are

required for simultaneous LD delivery, rather than just one, to further dilute the volume burden at each site.

In the study ND0612-317 subjects were treated with ND0612 DP plus oral IR-LD/CD and compared to the treatment with oral IR-LD/CD only. Response to levodopa has been shown in ND0612-317 and is in line with oral levodopa response plus the stabilisation obtained by the delivery method. Treatment with ND0612 demonstrated superiority over oral IR-LD/CD, with a statistically significant difference ($p<0.0001$) of 1.72 h in GOOD ON time (primary endpoint). Similarly, the analysis of OFF time (Key secondary endpoint) showed a statistically significant treatment difference of -1.4 h (95% CI [-2.0, -0.8]; $p<0.0001$) in favour of ND0612 over IR-LD/CD. The results indicated the improvement in the motor response to LD in patients with PD with motor fluctuations. However, local reactions have been identified, and the long-term levodopa subcutaneous exposure risks are yet to be thoroughly known, both in frequency and severity.

8.6.2. Balance of benefits and risks

Levodopa, in a fixed dose combination with a DDI, has been the gold standard for the treatment of PD for over 50 years.

ND0612 is a sterile solution containing levodopa and carbidopa in 8:1 ratio combination for continuous SC administration in patients with advanced PD, administered with LD oral (morning) dose (and additionally, as needed) to ensure continuous LD delivery, associated with a reduction of motor complications in comparison to (intermittent) oral doses of the same agent.

Infusion site reactions have been identified.

8.7. Additional considerations on the benefit-risk balance

Not applicable.

8.8. Benefit-risk conclusions

Based on the review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Onerji is positive in the treatment of motor fluctuations in patients with advanced Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medicinal products.