25 July 2019
EMA/CHMP/450567/2019
Committee for Medicinal Products for Human Use (CHMP)

CHMP Assessment report

Inbrija

International non-proprietary name: levodopa

Procedure No. EMEA/H/C/004786/0000

Note

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

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Administrative information

Name of the medicinal product:	Inbrija
Applicant:	Acorda Therapeutics Ireland Limited 10 Earlsfort Terrace Dublin 2 D02 T380 IRELAND
Active substance:	LEVODOPA
International Non-proprietary Name:	Levodopa
Pharmaco-therapeutic group (ATC Code):	Anti-Parkinson drugs, dopaminergic agents (N04BA01)
Therapeutic indication:	Inbrija is indicated for the intermittent treatment of episodic motor fluctuations (OFF episodes) in adult patients with Parkinson's disease (PD) treated with a levodopa/dopa-decarboxylase inhibitor.
Pharmaceutical form:	Inhalation powder, hard capsule
Strength:	33 mg
Route of administration:	Inhalation use
Packaging:	blister (alu/PVC/alu)
Package sizes:	60 x 1 capsules (unit dose) + 1 inhaler and 92 x 1 capsules (unit dose) + 1 inhaler

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List of abbreviations

Abbreviation	Definition
6-OHDA	6-hydroxydopamine
3-OMD	3-O-methyldopa
AAAD	L-aromatic amino acid decarboxylase
AAP	All available population
Acorda	Acorda Therapeutics
ADL	Activities of daily living
ADME	absorption, distribution, metabolism and excretion
AE	Adverse event
ALT	alanine aminotransferase
APSD	Aerodynamic particle size distribution
AUC	Area under the plasma concentration curve
AUC_{0-4h}	Area under plasma concentration-time curve from time 0 to 4 hours postdose
AUC_{0-24h}	Area under the plasma concentration time curve from time 0 to 24 hours postdose
AUC_{0-t}	Area under the plasma concentration time curve
BBB	blood brain barrier
CEP	Certificates of Suitability of the European Pharmacopoeia
CI	Confidence interval
CD	Carbidopa
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum plasma concentration
CNS	Central nervous system
COMT	Catechol-O-methyltransferase
COPD	chronic obstructive pulmonary disease
CPPs	Critical process parameters
CSR	Clinical study report
CQAs	Critical Quality Attributes
CRS	Compendial Reference Standard
CV	Coefficient of variance
CV%	Percentage coefficient of variance
CVT-301	Development code for levodopa inhalation powder formulation
$C_{10\ min}$	Plasma concentration at 10 minutes post dose
DA	Dopamine
DBP	Diastolic blood pressure

Abbreviation	Definition
DDI	Dopa-decarboxylase inhibitor
DL	Dose level
DLco	Carbon monoxide diffusing capacity
DOPAC	Dihydroxyphenylacetic acid
DPPC	Dipalmitoyl phosphatidylcholine colfosceril palmitate 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FMEA	Failure mode effect analysis
FPD	Fine particle dose
FVC	Forced vital capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GI	Gastrointestinal
HFE	Human Factors Engineering
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
HPRA	Health Products Regulatory Authority
HVA	Homovanillic acid
IR	Infrared
ISCTM	International Society for CNS Clinical Trials and Methodology
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
LD	Levodopa, L-DOPA
LD50	Lethal Dose for 50% of subjects
LLOQ	Lower Limit of Quantification
LS	Least square
LC-MS/MS	Liquid chromatography-mass spectroscopy
MAO-B	Monoamine oxidase-B
MEB	Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MMRM	Mixed model for repeated measurements
NaCl	Sodium chloride

Abbreviation	Definition
NDA	New Drug Application
NHANES III	Third National Health and Nutrition Examination Survey
NOAEL	no-observed-adverse-effect level
OFF	Periods when the medication wears off
ON	Time at which improvement in motor function was deemed sufficient or of adequate degree to enable a subject to manage most activities of daily living
PARs	Proven Acceptable Ranges
PD	Parkinson's disease
PGI-C	Patient Global Impression of Change
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PT	Preferred term
PVC	Polyvinyl chloride
QRD	Quality Review of Documents Group
QTc	QT time for the heart rate
QTPP	Quality Target Product Profile
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
S&E	Schwab and England
SE	Standard error
SmPC	Summary of product characteristics
SOC	system organ class
tmax	Time to maximum plasma concentration
TK	toxicokinetic
TV	Treatment visit
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
USP	United States Pharmacopoeia
XRPD	X-ray powder diffraction
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Acorda Therapeutics Ireland Limited submitted on 23 March 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Inbrija, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 April 2017. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication:

"Treatment of symptoms of OFF periods in Parkinson's disease as an adjunct to a dopa-decarboxylase inhibitor/levodopa regimen."

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/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0117/2016 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request(s) for consideration

New active Substance status

The applicant indicated the active substance levodopa contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The applicant received scientific advice from the CHMP on 23 June 2016 (EMA/CHMP/SAWP/433871/2016). The Scientific advice pertained to non-clinical and clinical aspects of the dossier.

The nonclinical aspects pertained to the acceptability of the nonclinical programme to support a new route of administration and new presentation of an established drug substance, and the confirmation that the safety margins and the approach to the testing of the excipients within the formulation were acceptable.

The clinical questions in the advice related to the adequacy of the single pivotal Phase 3 study to support the MAA (patient population, study duration, endpoints statistical approach, treatment duration, characterisation and selection of doses); the adequacy of the long-term safety and special population studies; the justification not to conduct a thorough QT study; the proposed safety database (number of patients and duration of treatment).

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Jayne Crowe

The application was received by the EMA on	23 March 2018
The procedure started on	24 May 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 August 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	13 August 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	28 August 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 September 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 March2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	6 May 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	29 May 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 June 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	23 May 2019
The CHMP, in the light of the overall data submitted and the scientific	25 July 2019

discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Inbrija on	

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Parkinson's disease (PD) is a progressive, degenerative neurologic disorder characterized by a loss of dopamine-containing neurons in the basal ganglia. PD causes motor symptoms including resting tremor, rigidity, bradykinesia and postural instability, as well as non-motor symptoms including cognitive impairment, mood disorders, sleep dysfunction, fatigue, pain, gastrointestinal (GI) dysmotility and urinary dysfunction. Both motor and non-motor symptoms can have a substantial negative impact on a patient's quality of life and activities of daily living (ADL).

Motor fluctuations (OFF episodes) occur with disease progression, when patients are no longer able to store dopamine in dopaminergic neurons, due to their progressive degeneration.

OFF episodes may present in several forms. "End-of-dose" or "wearing-off" episodes are commonly the first to be experienced by PD patients during the course of their chronic illness. These are frequently predictable and occur towards the end of the levodopa (LD) inter-dosing interval. A second major category of motor fluctuations entails random fluctuations that are not predictable based on the LD dosing schedule. Such ON/OFF episodes may occur without warning. Other types of motor fluctuations have also been described (e.g., "early-morning-OFF"). The onset of motor fluctuations may be accompanied by a variety of motor, sensory and/or autonomic symptoms, the development of which impacts greatly on a patient's quality of life.

2.1.2. Epidemiology

PD affects more than 1.2 million people in Europe and the prevalence is expected to double by 2030. The average age of onset of disease is 60 years while more than 1 in 10 people are diagnosed before the age of 50 years.

2.1.3. Biologic features, Aetiology and pathogenesis

PD is characterized by a loss of dopaminergic neurons in the basal ganglia. Levodopa (LD), the metabolic precursor to dopamine, is readily able to cross the blood-brain barrier, where it is converted to dopamine in the central nervous system.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Many people with Parkinson's fluctuate between ON states during which their symptoms are controlled and OFF episodes (also known as OFF periods) when their symptoms return. OFF periods may occur even when patients are taking their usual LD/carbidopa (CD) Parkinson's regimen and are typically seen in more advanced PD, i.e. Parkinson with motor fluctuations. OFF episodes may present in several forms. "End-of-dose" or "wearing-off" episodes are commonly the first to be experienced by PD patients during the course of their chronic illness. These are frequently predictable and occur towards the end of the LD inter-dosing interval. A second major category of motor fluctuations entails random fluctuations that are

not predictable based on the LD dosing schedule. Such ON/OFF episodes may occur without warning. Other types of motor fluctuations have also been described (e.g., "early-morning-OFF"). The onset of motor fluctuations may be accompanied by a variety of motor, sensory and/or autonomic symptoms, the development of which impacts greatly on a patient's quality of life.

2.1.5. Management

Treatment of an OFF episode is managed most frequently by oral administration of a scheduled or unscheduled dose of LD, which is associated with considerable variability in response and can require one hour or more to improve motor function.

Currently there is another product, subcutaneous apomorphine (APO-go), on the marked allowing fine-tuning of the daily L-dopa however, the pharmacodynamics of this product were not assessed.

APO-go is currently used for the acute, intermittent treatment of motor fluctuations ('ON-OFF' phenomena) in patients with PD which are not sufficiently controlled by oral anti-Parkinson medication. These patients are generally in more advanced PD stages.

About the product

Inbrija (CVT-301, levodopa inhalation powder) is a dry powder formulation of LD for inhalation. Capsules contain powder for oral inhalation and breath-actuated inhaler. The combination of particle size and formulation composition has been designed to provide therapeutic levels of LD following inhalation and absorption into the pulmonary circulation. The formulation contains the inactive ingredients sodium chloride (NaCl) and dipalmitoyl phosphatidylcholine (DPPC). The Inbrija formulation consists of levodopa, DPPC and NaCl. Inbrija is given on top of background LD/CD therapy, so the current formulation does not contain CD.

Inbrija is delivered to the lung using a proprietary, capsule-based, breath-actuated inhaler that has been used previously in patients in clinical trials to deliver other medications. The inhaler is capable of delivering therapeutics over a range of inspiratory flow rates. The Inbrija inhaler is approximately 13 cm long and is composed of plastic parts and stainless steel parts.

For dose administration, the capsule is placed in the inhaler and punctured during a simple actuation process. The patient inhales the powder contents of the capsule through the mouthpiece. The inhaler can be loaded, operated, and unloaded multiple times. Data from in vitro testing shows the inhaler is capable of delivering the desired dose of 33.4 mg of LD of the 42mg capsule over a wide range of flow rates from 20 to 90 L/min. In Study CVT-301-002, peak inspiratory flow rates were evaluated in PD patients and ranges of 39 to 98 L/min were seen in the ON state and 29 to 98 L/min in the OFF state. Therefore, PD patients generate sufficient flow rates to receive the desired dose.

The Inbrija inhaler used in the Phase 1 Study CVT-301-001 and Phase 2a Study CVT-301-002 was updated before the Phase 2b CVT-301-003 to improve the reliability of the staple retention mechanism and to change the colour of the housing from green to blue; all other characteristics, including the geometry of the gas flow path, were unchanged. No further changes were made to the inhaler between the Phase 2b Study CVT-301-003 and the Phase 1 high-dose pharmacokinetic Study CVT-301-006.

Some inhaler external design features were optimized prior to Phase 3, such as adding a removable dust cap. The final commercial version of the inhaler was used in the Phase 3 clinical studies; the geometry of

the gas flow path and capsule puncture mechanism will not be changed, nor will the materials of construction be altered.

Type of Application and aspects on development

The legal basis for this application refers to:

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

Inbrija clinical development program followed recommendations received from medical experts and the US FDA and has been aligned to the clinical Phase 2 and 3 efficacy studies supporting registration of subcutaneous apomorphine in PD (e.g., Menon and Stacy 2007, Stacy and Silver 2008). The Committee for Medicinal Products for Human Use (CHMP) Guideline on clinical investigation of medicinal products in the treatment of PD (EMA/CHMP/330418/2012 rev. 2) has also been considered.

Scientific Advice on the clinical aspects of the late-stage Inbrija development program pertained to the adequacy of the single pivotal Phase 3 study to support the MAA (patient population, study duration, endpoints statistical approach, treatment duration, characterisation and selection of doses); the adequacy of the long-term safety and special population studies; the justification not to conduct a thorough QT study; the proposed safety database (number of patients and duration of treatment).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as an inhalation powder, hard capsule, containing 42 mg of levodopa. Each delivered dose per capsule contains 33 mg levodopa.

Other ingredients are: colfosceril palmitate (DPPC) and sodium chloride. The capsule shell is made of: hypromellose, titanium dioxide (E 171), carrageenan, potassium chloride, carnauba wax, maize starch. The ink used to print the capsule shell contains: shellac, black iron oxide (E 172), propylene glycol, and potassium hydroxide.

The product is available in a carton containing 60 or 92 hard capsules in aluminium / PVC / aluminium peel-off blisters and is supplied with 1 inhaler. Each perforated unit-dose blister strip contains 4 hard capsules. The Inbrija inhaler is made of polybutylene terephthalate, polycarbonate and polypropylene. Puncturing tines and springs are made from stainless steel.

2.2.2. Active substance

General information

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

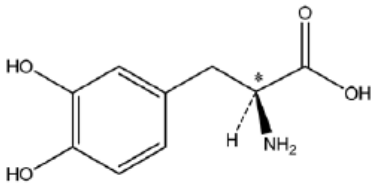


Figure 1**:** active substance structure

Levodopa is a white or almost white, non-hygroscopic crystalline powder.

Levodopa has an enantiomer referred as impurity D in Ph. Eur. No polymorphic forms are reported in literature. Since the active substance is completely dissolved during the manufacture of the finished product (at the beginning of the spray drying process) the applicant has not provided characterisation data of the solid properties of the active substance. This is accepted.

As there is a monograph of levodopa in the European Pharmacopoeia, the manufacturer of the active substance has been granted Certificates of Suitability of the European Pharmacopoeia (CEP) which have been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

Levodopa is supplied by one manufacturer. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The active substance is packaged in two plastic bags inside a fibre drum. The first bag (primary packaging) is made from linear low-density polyethylene, which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity (IR), appearance of solution, pH (potentiometric, Ph. Eur.), assay (potentiometric titration, Ph.Eur.), impurities (HPLC, Ph.Eur.), enantiomeric purity (HPLC, Ph.Eur.) loss on drying (Ph.Eur.) and sulphated ash (Ph. Eur.).

The control tests are carried out to comply with the specifications and test methods of the Ph. Eur. monograph. An additional related substance (L-Veratrylglycine) is specified in line with the USP monograph.

The applicant's specification does not include a limit for microbial purity; its absence has been justified in line with ICH Q6A: the active substance is not capable of supporting microbial growth or viability.

Physical properties of the active substance which could impact product performance of a dry powder inhaler such as particle size, polymorphic form and powder morphology are not of relevance for control of the levodopa, because the active substance is completely dissolved during the manufacture of the finished product; this justification is provided at section 3.2.P.2 - Pharmaceutical development. The specifications are appropriate to control the quality of the active substance.

Batch analysis data (10 batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three commercial batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines

were provided. Results on photostability testing, following the ICH guideline Q1B, and on stress conditions thermal (heat), acidic, and alkaline were also provided.

The following parameters were tested*:* appearance of solution, related substances, enantiomeric purity, loss on drying, assay, and pH. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications.

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 48 months, no special storage conditions, in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as an inhalation powder, hard capsule, containing 42 mg of levodopa (each delivered dose contains 33 mg levodopa per capsule). The inhalation powder is a new dosage form of levodopa (drug and device combination product) designed to provide orally-inhaled delivery of levodopa using a proprietary capsule-based, breath-actuated inhaler.

The capsules contain levodopa inhalation powder, composed of a mixture of levodopa , 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC) and sodium chloride (NaCl), filled into white, size 00 hydroxypropyl methylcellulose (HPMC) capsules in product strength 42 mg (33 mg delivered dose) levodopa per capsule. The composition of the printing ink is provided.

NaCl and DPPC are the two only excipients administered to the patients. NaCl is a well-known pharmaceutical ingredient. DPPC is a non-compendial excipient; the applicant has provided adequate justification, in response to a major objection raised during the procedure, that DPPC is not a novel excipient. Toxicological studies have been provided demonstrating that, in its selected content, it is considered safe. The excipients used to manufacture the capsule and are well known, standard pharmaceutical excipients. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

Compatibility between the active substance and the two excipients, sodium chloride and DPPC, was established by conducting forced degradation studies and stability studies on the formulation, monitoring both chemical and physical properties of the finished product at long-term (25ºC/60%RH) and accelerated conditions (40ºC/75%RH).

The intent of pharmaceutical development was to overcome the obstacles inherent to oral delivery of levodopa by developing a powder for oral inhalation.

A Quality Target Product Profile (QTPP) was developed which included considerations of the patient population, the need to rapid uptake to systemic circulation, the stability of the drug substance, and the relevant physicochemical parameters that will affect the performance of the drug product. From the QTTP, the following Critical Quality Attributes (CQAs) were identified: identification, assay, related substances, water content, residual solvents, aerodynamic particle size distribution (APSD), content uniformity of the pre-metered dose and emitted dose.

Formulation development focused on producing a manufacturable powder with the desired fine particle and emitted dose, while minimising the amount excipients to reduce the amount of inhaled powder, and reduce the number of inhalations needed per dose. In this manner, the levodopa:DPPC:NaCl formulation

was selected and has not changed since the initiation of toxicological and clinical studies. The formulation used during clinical studies is the same as that intended for marketing.

The powder is comprised of large porous particles, with a high degree of dispersibility, which are capable of efficient delivery to and deposition in the lung.

The powder is produced by spray-drying followed by capsule filling and packaging.

The formulation and manufacturing development have been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the experience from formulation development, process design and scale-up studies. The critical process parameters (CPPs) have been adequately identified. The supporting justification of the spray-drying incudes full APSD data and is acceptable. While the overall principles of the process are unchanged from Phase 1 studies to the proposed commercial process, the individual process parameters and scales have been modified. A discussion is provided on the development of these parameters at each clinical phase and it is adequate.

The applicant has adequately described all aspects applicable to inhalation powders that are mentioned in the Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products. The applicant has sufficiently demonstrated that the batches used in the clinical study and the batches manufactured in accordance with the proposed commercial process will behave similar and have comparable deposition patterns (APSD and fine particle dose).

The primary packaging material, Aluminium / PVC / Aluminium peel-off blisters, was selected based on the requirements for protection of the finished product capsules from moisture, compatibility/safety of the materials of construction, and performance of the materials over shelf life. The material complies with Ph.Eur. and EC requirements. A summary of the interaction studies carried out on the packaging components is provided and considered adequate. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The finished product powder is delivered using a proprietary breath-actuated inhaler, which is designed to puncture and disperse the levodopa inhalation powder from a capsule. The inhaler is made of polybutylene terephthalate, polycarbonate and polypropylene. Puncturing tines and springs are made from stainless steel. The inhalation device is CE marked and well-known. The Essential Requirements List of Annex 1 of the Medical device Directive has been provided. The inhaler has not been significantly modified since Phase 1 studies began and the inhaler used in Phase 3 studies is functionally identical to that proposed for commercial use. Similarly, there have been no relevant changes to the manufacturing process of the inhaler since Phase 3. Pharmaceutical development studies have been carried out on the finished product as per the Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (EMEA/CHMP/QWP/49313/2005 Corr) and all the required aspects have been discussed, supported by sufficient data that is in line with the guideline, including the inhaler development studies.

Manufacture of the product and process controls

The manufacturing process consists of three main steps: spray drying, encapsulation, and packaging. The process is considered to be a non-standard manufacturing process.

The powder is produced by spray-drying a defined-ratio mixture of aqueous stock solution (containing levodopa and NaCl) and an organic stock solution (containing DPPC) to produce levodopa inhalation powder. The powder for inhalation is automatically filled into white HPMC capsules size 00 (pre-printed with a commercial print) to the target fill weight under controlled temperature and humidity conditions.

The filled capsules are individually packaged into a heat-sealed foil-foil blister under controlled temperature and humidity conditions.

A detailed description of the manufacturing process is provided in line with the pharmaceutical development section. Proven Acceptable Ranges (PARs) are proposed for each step of the manufacture of the medicinal product based on design-of-experiment activities. In the manufacturing process, the ratio of feeds for spray-drying, feed filters, and measures used to dissipate the build-up of electrostatic charge are defined. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. The holding times and quality of the hold container closure systems are laid down in the process description and are acceptable.

The applicant had initially provided process validation data only on the spray-drying step. Although this is the most complex step of the manufacture of an inhalation powder that is pre-metered, since it determines the APSD of the powder, a major objection was raised to request full process validation data for all manufacturing steps. Process validation was performed on the spray-drying operation and on the subsequent filling step and packaging step for four consecutive production batches manufactured at the same batch size and manufacturing process as the intended commercial-scale batches. Capsule target fill weight is included as IPC in the dossier. No validation results regarding this parameter are included, however, the active substance content was tested during filling and the results are well within the product release limits. For the packaging step, adequate results are provided for the seal integrity of the blister, among others.

Two GMP major objections were raised during the procedure. The first major objection was in reference to proof of demonstration of GMP compliance for the USA based finished product manufacturer. This was resolved when FDA conducted a pre-approval inspection, also on behalf of EMA, which was finalised with a positive outcome. The second GMP major objection was in reference to the GMP control testing arrangements which has been addressed by removing non EU-based control testing and adding EU-sites with valid MIA.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form (appearance, identity, assay, impurities, water content, residual solvent content, content uniformity of pre-metered dose, mean delivered dose, delivered dose uniformity, emitted dose, APSD by Andersen Cascade Impactor method, microscopic evaluation of the emitted powder, powder morphology (XRPD), foreign particulates, microbial enumeration and specified organisms).

The presented specification covers the parameters required by EMEA/CHMP/QWP/49313/2005 Corr, as well as including additional testing that is considered appropriate for an inhaled product delivered to the systemic circulation via the lung (such as multiple controls of particle size, as well as the physical form). The justification of specification takes into consideration the results of clinical batches and is considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities, 'inhalation' category. Batch analysis data on the stability 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. The information on the control of elemental impurities is satisfactory.

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 assay and impurities testing has been presented.

Batch analysis results are provided for 27 representative 42 mg product batches (pivotal clinical and stability batches manufactured at least 20% of the proposed commercial scale) 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 one commercial scale batch and three pilot (semi-production) scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (30 ºC / 65% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, impurities, water content, emitted dose, APSD, microscopic evaluation of the emitted powder, powder morphology (XRPD), and microbial limits (microbial enumeration and specified microorganisms). The analytical procedures used are stability indicating. No significant changes have been observed during the long term stability studies.

Small changes on powder morphology and water content were observed during the intermediate and accelerated conditions stability studies, the changes are not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Forced degradation studies have been carried out under acid, base, oxidative, thermolytic and photolytic conditions and demonstrate the stability-indicating nature of the assay and impurity methods. Some degree of degradation is noted under each condition, with it being more pronounced under base and thermal conditions.

The Ph.Eur. monograph for Levodopa states that it should be stored protected from light. Hence, ICH Q1B photo-stability stability studies have not been performed by the applicant; however, since the active substance is not stable to light, the finished products should be stored protected from light, as indicated in the SmPC.

Based on available stability data, the proposed shelf-life of 36 months and storage conditions (Store below 25°C. Store in the original package in order to protect from light and moisture and remove immediately before use.) as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

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

and characterised, including its aerodynamic performance through its shelf-life, in line with the current requirements for inhalation products also taking into consideration its systemic effect.

2.2.5. 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.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

As the efficacy and nonclinical safety of orally administered levodopa has been well-established, an abbreviated nonclinical program was conducted, focusing on the new oral inhalation route of administration and contains original studies as well as published literature.

A nonclinical pharmacology study was conducted to compare the effects of levodopa following oral administration and intratracheal insufflation in the rodent model of Parkinson's disease and 6 safety/toxicology studies utilising CVT-301 Inbrija (levodopa inhalation powder) with the same composition as the to be marketed commercial formulation. Further studies to assess the safety of the primary excipient DPPC have also been submitted. For sections for which no data has been generated with Inbrija additional relevant information on levodopa was provided from a review of the literature.

Scientific Advice was received CHMP on the acceptability of the non-clinical programme to support a new route of administration and new presentation of an established drug substance, and the confirmation that the safety margins and the approach to the testing of the excipients within the formulation were acceptable.

Table 1: A summary of submitted studies GLP compliance is presented below:

Type of Study	**Study Number**	**Species/strain**	**Route of administration**	**GLP (Y/N)**
Primary pharmacodynamic				
Pulmonary levodopa in parkinson's disease model	Bartus et al. 2004 Alkermes-101600-Pharm	6-OHDA-lesioned rat	IV, oral, Pulmonary	N
Safety pharmacology				
CV and Respiratory	11-6770	Dog/Beagle	Inhalation (facemask)	Y
Repeat dose toxicity				

7-day	11-6380	Rat/Sprague Dawley	Inhalation (nose-only)	N
28 day + 21 day recovery	11-6382	Rat/Sprague Dawley	Inhalation (nose-only)	Y
6-month + 28 day recovery	13-6422	Rat/Sprague Dawley	Inhalation (nose-only)	Y
7-day	11-6831	Dog/Beagle	Inhalation (oro-nasal)	N
28-day + 21 day recovery	11-6383	Dog/Beagle	Inhalation (oro-nasal)	Y
Excipient qualification				
28-day repeat dose toxicity	AIRT-00-09-DPPC	Rat/Sprague Dawley	Inhalation (nose-only)	Y
28-day repeat dose toxicity	AIRT-00-10-DPPC	Dog/Beagle	Inhalation (oro-nasal)	Y

2.3.2. Pharmacology

Primary pharmacodynamic studies

Levodopa is converted in the brain into dopamine, which reduces the symptoms of OFF periods in Parkinson's disease as an adjunct to a LD/dopa-decarboxylase inhibitor (DDI) regimen.

The applicant has submitted a single non-GLP compliant *in vivo* proof of concept study utilising a unilateral 6-hydroxydopamine (6-OHDA) lesion rodent model of Parkinson's disease. The data presented demonstrate that levodopa delivered via pulmonary insufflation (not in the proposed clinical formulation) results in a more rapid and robust rise in blood L-dopa levels in rats and is associated with more rapid attenuation of 6-OHDA induced deficits in performance in a number of behavioural tasks designed to assess contralateral limb function relative to orally administered levodopa. This study provides sufficient rationale to suggest a more rapid onset of action of levodopa following pulmonary administration.

Secondary pharmacodynamic studies

The applicant has not conducted any specific secondary pharmacodynamic studies on levodopa, but has instead provided a summary of recent literature on the topic. The majority of secondary pharmacologic effects of levodopa identified in the literature search are attributable to the effects of dopamine rather than levodopa itself. Levodopa shows a potential neuroprotective effect, may enhance recovery of lost brain function, and may also act as an immunomodulator with inhibitory effects on cytotoxic T-cell accumulation and inflammatory cytokine production in the ischemic hemisphere of the post-stroke brain.

Safety pharmacology programme

According to literature, levodopa may cause both hypotensive and vasoconstrictive effects in animal models. In rats with 6-OHDA lesions, levodopa administration resulted in vascular endothelial growth

factor-dependent microvascular plasticity and local blood brain barrier increased permeability. No nonclinical studies citing a direct effect of levodopa on pulmonary function were identified.

A GLP-compliant cardiovascular and pulmonary safety pharmacology study in conscious, telemetered male dogs administered 9.9 mg/kg levodopa via oronasal (facemask) inhalation for 60 minutes revealed no test article-related effects on any cardiovascular (hemodynamic or electrocardiographic) or respiratory endpoints. The exposure achieved after a dose of 10 mg/kg in dogs will be approximately the same as clinical exposure.

A literature search did not identify any relevant references directly relating to untoward Central Nervous System (CNS) effects of inhalation-administered levodopa. The applicant did not conduct any nonclinical CNS safety pharmacology studies, however inhalation repeat-dose toxicity studies (28-days in docs and 6-months in rats) did not reveal behavioural abnormalities including general condition, appearance, activity and behaviour.

Pharmacodynamic drug interactions

The applicant did not conduct any dedicated non-clinical PD interaction studies. Levodopa is subject to a number of well-characterized pharmacodynamics drug interactions that are exploited to either help modulate central dopamine (DA) availability (e.g. inhibitors of L-aromatic amino acid decarboxylase (AAAD), Catechol-O-methyltransferase (COMT) or Monoamine oxidase-B (MAO-B)) or directly mitigate PD symptoms (e.g. DA agonists). Since the inhalation route of administration is not expected to substantially alter the known pharmacologic profile of levodopa once in the systemic circulation the same pharmacodynamics drug interactions of levodopa in the approved products should apply to the use of Inbrija.

2.3.3. Pharmacokinetics

The pharmacokinetic profile in terms of absorption, distribution, metabolism and excretion (ADME) of orally administered levodopa has been extensively studied and well-established. No dedicated nonclinical ADME studies were conducted with Inbrija.

Administration of Inbrija via the pulmonary route provides rapid absorption of levodopa into the systemic circulation. Once in the bloodstream, the overall distribution, metabolism, and excretion of levodopa following pulmonary administration is not expected to be different from the distribution, metabolism, and excretion following oral administration of levodopa.

However, extensive toxicokinetic (TK) analysis was conducted as part of the Inbrija inhalation toxicity studies in rats and dogs.

Methods of analysis

A suitable and validated method was provided for the quantitative determination of plasma concentration of levodopa: liquid chromatography-mass spectrometry (LC-MS/MS), validated in rat and dog plasma. Samples were analysed using a protein precipitation extraction procedure followed by LC-MS/MS. Plasma samples were modified with carbidopa (5 µg/ml) and with metabisulfite treatment to protect levodopa from degradation in rat plasma, and to mimic the plasma samples to be provided from the toxicology studies. Recovery in both rat (67-75%) and dog (64-67%) plasma was low, however, since reproducibility was within the guidance criteria, this is not considered to impact the assay. The Lower Limit of Quantification (LLOQ) was 25 ng/ml.

Absorption

Specific nonclinical absorption studies with Inbrija have not been conducted. However, plasma TK of CVT-301 was investigated in the repeated dose toxicity studies with once daily inhalation administration in rats (28 days or 6 months) and dogs (28 days). All animals were co-administered with carbidopa. CVT-301 was rapidly absorbed following inhalation, with Tmax within 15 (rats) to 30 (dogs) minutes after the end of the inhalation period, compared to 30 minutes in humans after inhalation and 30-120 minutes following an oral dose of levodopa. Bioavailability of Inbrija following inhalation was not investigated. Oral levodopa is poorly absorbed, especially when not co-administered with carbidopa (30% without carbidopa).

Apparent plasma clearance (Cl/F) at steady state in rats in the inhalation studies was 3240-10500 ml/h/kg. The systemic elimination was fast, with a terminal half-life (t½) of 0.57-2.1h in rats and slightly increased with increasing doses. T1/2 in humans was 2.3 hours. Repeated inhalation showed an approximately dose-proportional increase in the mean AUC and Cmax at steady state. There was no accumulation (in rats, Cmax and AUC decreased after repeated administration; accumulation ratios varied between 0.21 and 0.91). No clear and consistent pattern for gender-related differences was observed in the studies with Inbrija.

In addition, plasma pharmacokinetics of exploratory alternative levodopa powder formulations was investigated in rats and dogs following pulmonary administration and compared to oral and IV administration of levodopa. It was shown that plasma levels of levodopa were rapidly elevated following pulmonary administration. Absorption was more rapid and less variable when compared to oral administration. Pulmonary delivery of levodopa resulted in higher Cmax and AUC compared to oral gavage. This was also shown for Inbrija in humans.

No data are available to assess the relative contribution of pulmonary and GI absorption to the observed systemic exposure following inhalation administration. Although GI absorption following mucociliary clearance of non-absorbed LD from the lungs will take place, the contribution of this to observed systemic exposures is likely minimal. The more rapid absorption and PD effects evident following insufflation administration suggest that the drug is primarily absorbed through the lungs. Although characterising the relative contribution of each route of absorption following inhalation administration in non-clinical species may have been reassuring with regard to local tissue concentrations achieved given the lack of such data acquired in repeat dose toxicity studies, it is accepted that the translational relevance of such characterisation is questionable.

Distribution

The inhalation route is a novel administration route for levodopa. When administered intravenously in rats, 14C-L-DOPA is distributed especially to high perfused tissues (kidney > pancreas ~ intestine > liver > adrenal > skin ~ skeletal muscle > lung > cardiac muscle > brain > blood). Similar patterns are observed following oral administration (intestine >> kidney > liver > pancreas > blood > skin > lung > adrenal >cardiac muscle ~ skeletal muscle > brain). Levodopa is not highly bound to plasma proteins (free fraction 76±8% at a concentration of 500 ng/ml). Specific nonclinical distribution studies with Inbrija have not been conducted. It is agreed that the inhalation route of administration is not expected to substantially alter the known distribution profile of levodopa once in the systemic circulation, although concentrations in lung tissue are expected to be higher compared to other administration routes. However, in a study with an early levodopa inhalation formulation in rats, it was shown with HPLC that more than 95% of the levodopa was cleared (or metabolised) from the lungs at 30 minutes post-dose (single intrapulmonary administration). It is unknown to what degree observed systemic exposures are related to lung or gastrointestinal routes of absorption.

It is expected that, similar to other administration routes, only a small amount of levodopa will reach the central nervous system after inhalation. Co-administration with a decarboxylase inhibitor will increase the amount of levodopa that will pass the blood-brain barrier, although the amount will still be limited.

Metabolism

Specific nonclinical metabolism studies with Inbrija have not been conducted. After oral absorption, levodopa is rapidly transformed to dopamine, which on its turn is quickly metabolized by COMT and MAO into 3-O-methyl dopa (3-OMD), 3,4 dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA). Co-administration with a decarboxylase inhibitor slows the transformation of levodopa to dopamine. The applicant indicates that the inhalation route of administration is not expected to substantially alter the known metabolic profile of levodopa once in the systemic circulation. Indeed, in humans, the metabolic profile with regard to the three main metabolites was consistent (both qualitatively as well as quantitatively) with that described following oral administration of LD (see clinical assessment).

Excretion

Levodopa is predominantly metabolized via decarboxylation, followed by excretion of metabolites in the urine. Approximately 80% of a radioactively labelled dose was recovered within 24 hours with the principal metabolites (DOPAC and HVA) constituting up to 50% of the administered dose and negligible amounts found in faeces.

Following IV administration of 14C-L-DOPA, 80% of the radioactivity was excreted in the urine and 2-3% of the radioactivity was recovered in faeces while 85% of the radioactive dose was excreted in the urine and 5% of the radioactivity was recovered in the faeces following oral administration of 14C-L-DOPA. After oral and intravenous administration of 14C-L-DOPA to rats, there was minimal excretion of unchanged L-DOPA in the urine (<1% of urine radioactivity), indicating extensive metabolism of L-DOPA..

Pharmacokinetic drug interactions

No dedicated pharmacokinetic (PK) interaction studies have been performed with Inbrija, as inhalation administration is not expected to alter the known drug interaction profile of LD once in systemic circulation. The submitted literature review is considered adequate. The results on the pharmacokinetic drug interaction potential are presented in the clinical assessment report.

2.3.4. Toxicology

The applicant has submitted an abridged safety package for Inbrija citing the long history of clinical use with a well-established systemic toxicity profile in humans. The submitted safety package for Inbrija consists of a literature review of the known systemic toxicity of LD, repeat dose toxicity studies of 6 months and 28 days duration in rats and dogs respectively to assess the local and general toxicity of the proposed Inbrija formulation and a safety assessment of primary excipient DPPC. Literature sources are provided for genotoxicity, carcinogenicity, and reproductive and developmental toxicity.

Single dose toxicity

No single dose toxicity studies have been conducted with the proposed Inbrija formulation. The applicant has presented literature derived LD50 values for non-clinical species. GLP-compliant single dose toxicity studies utilising an early stage levodopa inhalation formulation (containing 50% levodopa) administered to the lungs have been conducted in Sprague-Dawley rat, Beagle dog and Cynomolgus monkey. No significant toxicities were reported in these studies with lung findings including epithelial changes and mild inflammation in all three species attributed to the method of administration.

Repeat dose toxicity

In rats, a 7-day repeat-dose administration of levodopa by nose-only inhalation at doses up to 121 mg/kg/day following oral administration of carbidopa was well tolerated. Test article-related microscopic

findings consisted of minimal focal to multifocal degeneration of the olfactory epithelium in the nasal turbinates and minimal intra-alveolar haemorrhage in a few animals. Based on their minimal severity and very limited distribution, changes in the nasal turbinates and lungs would not be expected to affect organ function and are not considered adverse by the applicant. The highest dose was associated with a statistically significant but minimal decrease (-6.9% when compared to controls) in absolute testicular weight, but no histopathological evaluation had been done.

A 28 days repeated dose study in rats with up to 103 mg/kg/day showed statistically significant reductions in alanine aminotransferase (ALT) at doses ≥14.1 mg/kg/day (-34% to -42% vs air control), and marginal but statistically significant decreases in triglycerides in males at doses ≥14.1 mg/kg/day (-31% to -47% vs air control). None of these findings were considered adverse as they were not observed at the end of the recovery period and clinical chemistry effects were not associated with liver weight changes or microscopic liver findings. No decrease in testicular weight was found. Oronasal inhalation of up to 157 mg/kg/day levodopa for 26 weeks was well tolerated in rats with findings limited to piloerection, minimal epithelial thinning and cilia loss at the tracheal bifurcation in all animals, including controls, and nasal inflammation associated with powder accumulation. A no-observed-adverse-effect level (NOAEL) of 157 mg/kg/day levodopa was established, which is about 3 times the human exposure based on AUC.

In dogs, a 7-day repeat-dose administration of levodopa by nose-only inhalation at doses up to 29.8 mg/kg/day following oral administration of carbidopa was well tolerated. Achieved doses of ≥13.3 mg/kg were associated with high incidence of emesis, but the incidence of emesis declined as study progressed. There were no macroscopic or microscopic pathology findings. Emesis is a well-characterized observation in dogs following levodopa administration. A 28 days repeat-dose toxicity study in dogs with doses up to 42 mg/kg/day showed only reversible emesis and a reversible slight decrease in ALT, with probably no significant meaning. However, the exposures at this NOAEL based on AUC are about the same as in humans, so there is no exposure margin.

Genotoxicity and Carcinogenicity

No new genotoxic and carcinogenicity studies have been conducted for the product. Levodopa is considered non-genotoxic and non-carcinogenic.

A 6-month inhalation study with the product in rats did not show neoplastic or pre-neoplastic lesions. No non-clinical carcinogenicity data following long term inhalation administration are available.

Reproduction Toxicity

No reproductive and developmental toxicity studies on Inbrija were conducted by the applicant. Previous studies in rabbits have shown that levodopa alone and in combination with carbidopa cause visceral and skeletal malformations in offspring. In another study levodopa produced foetal toxicity in the rabbit demonstrated by decreased litter weights, and an increased incidence of stunted and resorbed foetuses. Levodopa has been reported to cross the human placenta.

Local Tolerance

Dedicated local tolerance studies have not been conducted by the applicant. Local tolerance was assessed as part of the repeat-dose toxicity studies with relatively minor findings observed. In rats after inhalation of the product, microscopic findings were observed in respiratory tract tissues (larynx and the lungs), but were not considered related to levodopa, but rather to the route of administration.

Safety margin calculations based on delivered dose per alveolar surface area at the NOAEL exposures are 14 and 1 relative to a single administration of the proposed human dose and 3 and 0.2 relative to the

maximum recommended human dose for rat and dog respectively. The maximum human dose is split over 5 doses and therefore the margins following a single exposure may be more useful for the assessment of potential local toxicity effects. There were no adverse effects on pulmonary tissue identified following inhalation administration to either species and it is accepted that the non-clinical safety data submitted do not indicate that inhalation administration of Inbrija is associated with adverse local toxicity effects.

Toxicokinetic data

The toxicokinetics of Inbrija were studied in rats and dogs. Absorption of Inbrija following inhalation administration was fast in rats and dogs (Tmax 15-30 minutes after the end of inhalation period), which is similar to humans (30 minutes). The apparent plasma clearance (Cl/F) in rats is 3240-10500 ml/h/kg. Following single or multiple dosing (once or twice daily for up to 6 months in rats or 28 days in dogs) an approximately dose proportional increase in exposure was observed at doses of 11-22 mg/kg in dogs and 40-180 mg/kg in rats, as well as in humans (60- 84-mg dose, equivalent to 35 mg and 50 mg Fine Particle Dose (FPD)). There was no plasma Cmax or AUC accumulation following repeated inhalation of Inbrija in rats or dogs (accumulation ratios varied between 0.21 and 0.91 for rats and 0.9-1.7 in dogs). Elimination of Inbrija was fast, with elimination half-life ranging from 0.57-2.1 hours in rats and 2.3 hours in humans. No clear or consistent gender differences were observed in the pharmacokinetics of Inbrija.

Dependence

The applicant has provided an adequate review of the non-clinical literature related to the abuse potential of LD. The literature provided is limited but does not indicate a significant risk of dependence associated with LD administration. LD is a well-established active substance via the oral route with extensive clinical experience and hence available clinical data are more relevant for the assessment of this risk, it is noted that dopamine dysregulation syndrome and impulse control disorders are recognised undesirable effects on levodopa/carbidopa containing products.

Other toxicity studies

Studies on impurities

Three potential organic process-related impurities have been identified: D1, D2, and D3. The actual levels of these impurities are each not more than 0.02% in the final drug substance at release or on stability. This level is below the ICH Q3A(R2) reporting threshold of 0.05% (< 2g/day). Besides, two complementary in silico methodologies to assess the potential mutagenicity of D1, D2, and D3, namely DEREK Nexus (rule-based system) and Leadscope FDA Model Applier (LSMA; statistical-based system), predicted negative for mutagenicity.

Dipalmitoylphosphatidylcholine (DPPC) excipient toxicology

DPPC is an excipient used in the Inbrija formulation, and it is currently not approved for use via oral inhalation. Although DPPC is endogenous to the human body as a common constituent of cell membranes and is found at high levels in the lungs as the majority component of lung surfactant, toxicological studies have been performed. 28-Day inhalation toxicity studies in rats and dogs up to 20 mg/kg DPPC did not reveal major findings of concern. Also, as part of the 6 months repeat-dose toxicity study in rats, a placebo arm containing 14.4 mg/kg DPPC did not show any toxicity. In silico analysis of DPPC by DEREK did not reveal any new important structural alerts not covered by the repeat-dose toxicity studies. Exposure multiples based on mg/kg body weight were 4 to 7 times and based on mg/g lung weight 10 to 13 times. The exposure multiples based on lung weight may be more appropriate since they relate directly to possible local lung effects for inhaled DPPC.

Alternative Levodopa inhalation powder formulations

At an early stage of development single-dose toxicity studies evaluating the pulmonary effects of an alternative levodopa inhalation powder formulation (AIR-L-dopa: levodopa, DPPC, sodium citrate and calcium chloride) were conducted in rats (up to 10 mg/kg levodopa), dogs (up to 50 mg/kg), and monkeys (10 mg/kg). A 14-day repeat-dose inhalation toxicity study using a neat, micronized levodopa dry powder was conducted in dogs (up to 20 mg/kg). No significant toxicological effects were found, besides, these studies using alternative levodopa powder formulations are not considered so relevant to the clinical safety assessment of Inbrija given the differences in powder formulations and the differences in animal administration techniques.

2.3.5. Ecotoxicity/environmental risk assessment

Levodopa is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore levodopa is not expected to pose a risk for the environment.

2.3.6. Discussion on non-clinical aspects

The marketing authorisation application for Inbrija (levodopa inhalation powder, hard capsule) is submitted as a full mixed application and consists of both novel data and summaries of bibliographic references prepared according to EMA guidelines.

Pharmacology

A nonclinical pharmacology study was conducted to compare the effects of levodopa following oral administration and intratracheal insufflation in the rodent model of Parkinson's disease. The applicant sufficiently showed that when administered pulmonary, the effect of levodopa is more rapid and robust than given orally and at the same time that the amount of levodopa required to produce equivalent efficacy is significantly less.

A safety pharmacology study in dogs does not indicate any effects on the cardiovascular or respiratory systems. No adverse effects on the central nervous system are reported, and issues regarding drug interactions are assumed to be the same as for levodopa given orally.

Pharmacokinetics

The applicant showed that absorption after inhalation was more rapid and less variable when compared to oral administration. Pulmonary delivery of levodopa resulted in higher Cmax and AUC compared to oral gavage. Distribution, metabolism and excretion of levodopa are not expected to be different compared to oral administration.

Toxicology

In repeat-dose inhalation studies with Inbrija in rats and dogs, no relevant toxic effects were seen at the highest doses, which were about three times, respectively equivalent to the proposed human exposure based on AUC. Although the safety margins are small, because of the long experience with oral levodopa in humans it is not expected that inhalation will pose a serious risk. However, the microscopic findings of minimal focal to multifocal degeneration of the olfactory epithelium in the nasal turbinates and minimal intra-alveolar haemorrhage in rats, which were not considered adverse by the applicant, might be related to human adverse effects like cough, upper respiratory tract infection and throat irritation which were reported frequently. The exposure in humans is much shorter and thus more concentrated than in rats. As

opposed to rats and humans, no effects on the respiratory tract were seen in dogs. But possibly this is because the amount of levodopa per gram lung weight in the dog is much lesser than that in the rat.

The new administration route did not show neoplastic or pre-neoplastic lesions in the 6 month rat study, and together with the information from literature, Inbrija can be considered non-genotoxic and non-carcinogenic. Literature studies in animals have shown reproductive toxicity.

There are no impurities of concern and the new excipient DPPC has been thoroughly investigated and found non-toxic.

2.3.7. Conclusion on the non-clinical aspects

CHMP considers that the abridged non-clinical program on Inbrija, focusing on assessment of pharmacology and safety, specifically related to the inhalation route of administration of levodopa, and the published literature, support the marketing authorisation application.

2.4. Clinical aspects

2.4.1. Introduction

Inbrija (levodopa inhalation powder, CVT-301) is intended to be used as an intermittent (as needed) adjunctive therapy to improve motor function in PD patients who continue to experience OFF periods not controlled by their standard DDI/LD plus other concomitant PD medication regimens.

The recommended dose of Inbrija is 2 hard capsules up to 5 times per day each delivering 33 mg levodopa. The maximum daily dose of Inbrija should not exceed 10 capsules (330 mg). It is not recommended to take more than 2 capsules per OFF period.

The applicant applied for the following indication:

"Treatment of symptoms of OFF periods in Parkinson's disease as an adjunct to a dopa-decarboxylase inhibitor/levodopa regimen."

The approved indication is:

"Intermittent treatment of episodic motor fluctuations (OFF episodes) in adult patients with Parkinson's disease (PD) treated with a levodopa/dopa-decarboxylase inhibitor."

To characterize the pharmacological profile, the safety and therapeutic effects of Inbrija the applicant has conducted an extensive clinical program comprising clinical Phase 1 studies in healthy subjects and special populations (smokers, asthmatics) as well as Phase 2 and Phase 3 studies in PD patients on standard LD regimens using Inbrija as an adjunctive add-on treatment to reduce OFF period symptoms.

The applicant sought Scientific Advice on the clinical aspects of the late-stage Inbrija development program regarding the design of the pivotal Phase 3 Study CVT-301-004, the acceptability of the design of the long-term safety Studies CVT-301-004E and CVT-301-005, the acceptability of the clinical pharmacology program and the acceptability of the safety database.

- ***GCP***

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- **Tabular overview of clinical studies**

Table 2: Overview of CVT-301 Clinical program

Study Number Region	Objective / Developmental Need	Study Population; Study Type	CVT-301 Dose
Clinical Phase 1			
CVT-301-001 European Union	Safety and dose-ranging PK study in healthy volunteers: To evaluate the safety and PK of single ascending doses of CVT-301; To compare the PK of CVT-301 (fasted) to oral LD administered in the fasted and fed state; To compare the PK and tolerability of CVT-301 with or without pre-treatment with CD.	Healthy volunteers (n=18); Crossover, non-randomized	10 mg, 20 mg, 30 mg, 40 mg, 50 mg LD FPD
CVT-301-006 United States	Safety and metabolite-profiling PK study in healthy volunteers: To investigate the safety, tolerability and PK of higher doses of CVT-301; To characterize the PK of LD metabolites following a single inhaled dose of CVT-301 and a single oral LD/CD administration; To explore the dose proportionality of LD following single inhaled dose administration and a single oral LD/CD administration.	Healthy volunteers (n=13); Uncontrolled, non-randomized	50 mg, 70 mg, 105 mg, 50 mg (higher capsule fill weight) LD FPD
CVT-301-010 United States	Safety and PK relative bioavailability study in healthy volunteers: To compare two dose strengths of CVT-301 with an oral dose of LD/CD tablets.	Healthy volunteers (n=24); Crossover, non-randomized	35 mg, 50 mg, LD FPD
CVT-301-007 United States	Special population safety and PK study in smokers and non-smoker, otherwise healthy volunteers: To characterize the PK, safety, tolerability and pulmonary safety following a single dose of CVT-301 in smoking and non-smoking adults.	Healthy volunteers (smoker [n=28], non-smoker [n=35]) Parallel group, non-randomized	50 mg LD FPD
CVT-301-008 United States	Special population safety study in asthmatic subjects: To investigate the PK, safety, tolerability and pulmonary safety (spirometry) of CVT-301 in adults with asthma.	Asthmatic subjects (n=26) Placebo-controlled, randomized, crossover	50 mg LD FPD
CVT-301-009 United States	Single-dose safety early morning OFF study in PD patients: To evaluate the safety and tolerability of CVT-301 84 mg (50 mg FPD), when administered for early morning OFF symptoms along with the first daily dose of oral LD/CD.	PD patients (n=36) Placebo-controlled, randomized	50 mg LD FPD
Clinical Phase 2			
CVT-301-002 (Phase 2a) European Union Serbia Israel	Single-dose safety and efficacy study in PD patients: To evaluate the pharmacodynamics, PK, safety and tolerability of single, inhaled doses of LD (25 mg, 50 mg LD FPD) or a standard oral dose of LD.	PD patients (n=24) Placebo-controlled, randomized	25 mg, 50 mg LD FPD
CVT-301-003 (Phase 2b) European Union	Multiple-dose safety and efficacy study in PD patients. To investigate the efficacy and safety of 35 mg and 50 mg LD FPD in PD patients with motor response	PD patients (n=89) Placebo-controlled, randomized	35 mg, 50 mg LD FPD

Study Number Region	Objective / Developmental Need	Study Population; Study Type	CVT-301 Dose
Serbia United States	fluctuations (OFF phenomena).		
Clinical Phase 3			
CVT-301-004 European Union United States Canada	Pivotal 12-week safety and efficacy study in PD patients: To investigate the efficacy and safety of 35 mg and 50 mg LD FPD in PD patients with motor response fluctuations (OFF phenomena).	PD patients (n=351) Placebo-controlled, randomized	35 mg, 50 mg LD FPD
CVT-301-004E European Union United States Canada	12-month long-term safety extension study in PD patients who participated in study CVT-301-004: To investigate the safety and therapeutic effect of 35 mg and 50 mg LD FPD over a 12-month period; To characterize the pulmonary safety.	PD patients(n=325) (from study CVT-301-004, other CVT-301 studies and de novo) Uncontrolled, dose level-blinded	35 mg, 50 mg LD FPD
CVT-301-005 European Union United States Serbia Israel	12-month long-term safety study in PD patients: To evaluate the safety and effects of 50 mg LD FPD for the treatment of up to 5 OFF episodes per day compared to an observational cohort control over a 12-month period; To characterize the pulmonary safety.	PD patients (n=408) Observational cohort-controlled, randomized	50 mg LD FPD
RPT-2202	To demonstrate the safe, effective and usability of the system and to identify any residual use related risks	27 PD patients (7 untrained, 20 trained), 15 health care professionals, 15 care givers (7 trained, 8 untrained)	50 mg LD FPD

Abbreviations: CD = carbidopa; FPD = fine-particle dose; LD = levodopa; PD = Parkinson's disease; PK = pharmacokinetics.

2.4.2. Pharmacokinetics

Pharmacokinetic information on levodopa following inhalation of levodopa dry powder (CVT-301 formulation) was obtained from studies conducted in healthy adult volunteers (studies 001, 006 and 010) and in patients with Parkinson (study 002). In addition, pharmacokinetics was evaluated in subjects with asthma (study 008) and in smokers (study 007) (see Table 2). The clinical program focused on the characterisation of levodopa pharmacokinetics following inhalation of levodopa.

The aim of levodopa inhalation powder was to develop a levodopa formulation that could result in fast, high (>400 ng/ml) levodopa plasma concentrations to shorten the OFF periods. No mass balance, drug/drug interaction studies or characterisation of special population were conducted and this is considered acceptable as the pharmacokinetics of levodopa are well known.

CVT-301 capsules containing 19.6 mg to 42 mg levodopa were used in clinical studies to deliver target fine particle dose (FPD) of 10 mg to 25 mg levodopa to the lung. The clinical study reports for earlier Phase 1 and Phase 2 studies (001, 002, and 006) reported the levodopa FPD dose, while the clinical study reports for later Phase 1 studies (007, 008, 009, and 010) reported the levodopa capsule dose as is used in the label. In this document, all FPDs are identified as 'mg FPD' while capsule doses are identified as 'mg'. In the pharmacokinetic session usually, the fine particle dose is being used as there were changes in levodopa capsule content and emitted dose throughout the clinical program while the targeted fine particle dose remained constant.

Table 3: Summary of CVT-301 Levodopa Content, Emitted Dose and FPD per Capsule and Dosing Regimen

Study/ Phase	LD Content (Per Capsule)	Emitted Dose[a] (Per Capsule)	FPD (Per Capsule)	Capsules Per Dose[b]	LD Content (Per Dose)	Emitted Dose[a] (Per Dose)	FPD (Per Dose)
CVT-301-002/ Phase 2a	23.8 mg	19.5 mg	12.5 mg	2 capsules/ 4 capsules	47.6 mg/ 95.2 mg	39 mg/ 78 mg	25 mg/ 50 mg
CVT-301-003/ Phase 2b	27.6 mg	20.4 mg	17.5 mg	2 capsules/ 3 capsules	55.2 mg/ 82.8 mg	40.8 mg/ 61.2 mg	35 mg/ 50 mg
CVT-301-004/ Phase 3	30 mg/ 42 mg	24 mg/ 33 mg	17.5 mg/ 25 mg	2 capsules	60 mg/ 84 mg	48 mg/ 66 mg	35 mg/ 50 mg
CVT-301-004E/ Phase 3	30 mg/ 42 mg	24 mg/ 33 mg	17.5 mg/ 25 mg	2 capsules	60 mg/ 84 mg	48 mg/ 66 mg	35 mg/ 50 mg
CVT-301-005/ Phase 3	30 mg/ 42 mg	24 mg/ 33 mg	17.5 mg/ 25 mg	2 capsules	60 mg/ 84 mg	48 mg/ 66 mg	35 mg/ 50 mg
CVT-301-009/ Phase 1	42 mg	33 mg	25 mg	2 capsules	84 mg	66 mg	50 mg

Abbreviations: CD = carbidopa; FPD = fine particle dose (FPD is the estimated pulmonary delivered dose); LD = levodopa.

[a] The dose leaving the mouthpiece of the inhaler corresponding to the product dose in the Product Information. In the Product Information, the emitted dose will be rounded to 33 mg.

[b] Number of capsules required to obtain the total LD dose (total capsule dose and target FPD). All doses in the table are nominal.

[c] Pharmacokinetic study analyzing 2 separate fill weights: "low" is indicated by normal font; "high" is indicated by italic font.

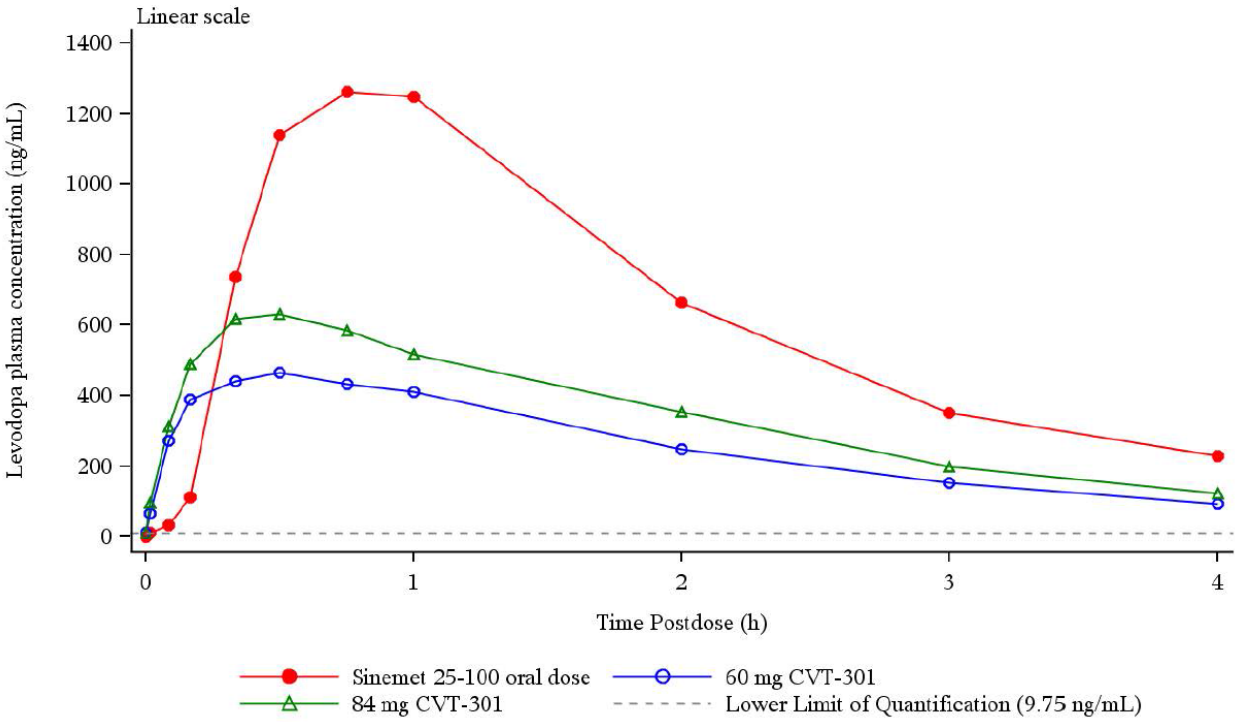
Note: Three low-fill capsules deliver a 50 mg FPD. Two high-fill capsules deliver a 50 mg FPD. See individual study summaries for CD pretreatment schedule and dosing in the fed and fasted states.

Two bioanalytical methods 415/25191HV and 415/25716HV were used to determine levodopa plasma concentrations. The methods are sufficiently validated and cross-validated.

Levodopa is extensively metabolized by decarboxylase in the periphery. Therefore, for oral treatment of levodopa, levodopa is always co-administered with a dopa-decarboxylase inhibitor such as carbidopa. Following inhalation, levodopa plasma exposure was 4-fold higher with carbidopa pre-treatment than without. Therefore, in all studies in healthy subjects, subjects were pre-treated with carbidopa 50 mg every 8 hours the day before levodopa inhalation to inhibit decarboxylase. As the intended use for inhaled levodopa is as an adjunct therapy in patients already on a levodopa/carbidopa regimen, no further addition of carbidopa is needed for inhaled levodopa in Parkinson patients.

The mean concentration-time curves of levodopa following 2 inhalations of the commercial CVT-301 product 30 and 42 mg (equivalent to 35 and 50 mg fine particle dose (FPD), respectively (relevant for deposition in the lung)) and after oral administration of a reference carbidopa 25 mg / levodopa 100 mg formulation (Sinemet) is shown in Figure 2. Following inhalation, levodopa plasma concentrations increased fast reaching peak plasma concentrations about 30 minutes after administration while Cmax was reached 45-60 min post-dosing for the oral formulation under fasting conditions. When oral carbidopa/levodopa is taken with a meal, the absorption of levodopa is much slower with a tmax of about 120 min. The rapid increase in levodopa plasma concentration during the first 10 min after inhalation can be attributed to absorption in the lung because of the 10 min lag time following oral administration of levodopa.

Figure 2: Plasma concentration profile of levodopa (0 to 4 hours) following inhalation of 35 mg FPD and 50 mg FPD, and oral administration of Sinemet 25 mg/100 mg under fasted conditions in healthy volunteers (Study 010)



Relative bioavailability of the inhaled levodopa was comparable to the oral levodopa administration under fasting conditions, but Cmax was approximately 20% lower for inhaled levodopa.

Exposure of levodopa was dose proportional over the inhaled levodopa dose range tested (10-105 mg FPD). Pharmacokinetic bridging between formulations used in early clinical studies and the to-be-market formulation was not conducted. In early studies the absorption of levodopa following inhalation seemed somewhat faster than for the to-be-market formulation. The early development formulation appeared to have a higher fraction of low particles 0.5-2 µm and this might have affected the absorption rate in the lungs. Product specifications have been correctly based on the material used in the pivotal studies (see quality part).

The to-be-market formulation of Inbrija has been used in the phase 3 studies in Parkinson patients.

Pharmacokinetic parameters of levodopa following levodopa inhalation powder 60 mg and 84 mg (corresponding to 35 mg FPD and 50 mg FPD, respectively; to-be-market product) or oral levodopa (Sinemet, 25 mg/100 mg) under fasted in healthy subjects (study 010) are summarised in Table 4. Following inhalation, levodopa is faster absorbed than following oral administration but there is a high inter-subject variability in tmax, ranging from 10 to 120 min, indicating that some subjects may not have an optimal inhalation technique and swallow most of the orally inhaled levodopa.

Table 4: Study 010 - Summary of pharmacokinetic parameters for levodopa following inhalation and oral administration in healthy subjects

Parameter	Treatment		
	Sinemet 25/100 (N = 24)	**60 mg CVT-301 (N = 24)**	**84 mg CVT-301 (N = 24)**
$AUC_{0\text{-}4h}$ (h•ng/mL)	2430 (28.8)	1000 (24.9)	1320 (32.9)
DN-$AUC_{0\text{-}4h}$ (h•ng/mL/mg)	24.3 (28.8)	16.7 (24.9)	15.8 (32.9)
$AUC_{0\text{-}24h}$ (h•ng/mL)	3080 (29.0)	1300 (27.2)[b]	1790 (31.8)[b]
DN-$AUC_{0\text{-}24h}$ (h•ng/mL/mg)	30.8 (29.0)	21.7 (27.2)[b]	21.4 (31.8)[b]
C_{max} (ng/mL)	1640 (35.7)	532 (29.2)	708 (33.9)
DN-C_{max} (ng/mL/mg)	16.4 (35.7)	8.86 (29.2)	8.43 (33.9)
C_{10min} (ng/mL)	89.9 (158.1)	352 (43.2)	434 (54.4)
C_{min} (ng/mL)	23.7 (50.8)[b]	20.4 (48.2)	24.8 (40.4)
T_{max}[a] (minute)	45 (19-122)	30 (10-120)	30 (10-120)
$t_{1/2}$ (h)	2.16 (52.0)[b]	2.16 (53.1)[b]	2.38 (72.0)[b]
V_z/F (L)	124 (87.2)[b]	172 (64.6)[b]	172 (66.0)[b]

Abbreviations: AUC = area under plasma concentration curve; C10min = plasma concentration at 10 minutes postdose; Cmax = maximum plasma concentration; Cmin = minimum plasma concentration; CV% = percent coefficient of variation; DN = dose-normalized; N = number of subjects; t1/2 = apparent terminal elimination half-life; Tmax = time to maximum plasma concentration; Vz/F = apparent terminal volume of distribution.
Note: Geometric mean (CV%) data are presented unless otherwise noted.
[a] Median (range).
[b] N <24.
See Section 2.6.2 for pretreatment and concurrent carbidopa dosing information.

Distribution and elimination half-life of levodopa were similar following administration via inhalation and oral route (Table 4). The metabolic profile of levodopa was similar when administered as inhaled CVT-301 and oral Sinemet (study 006). As carbidopa was present, 3-OMD was the predominant metabolite of levodopa regardless of the route of administration.

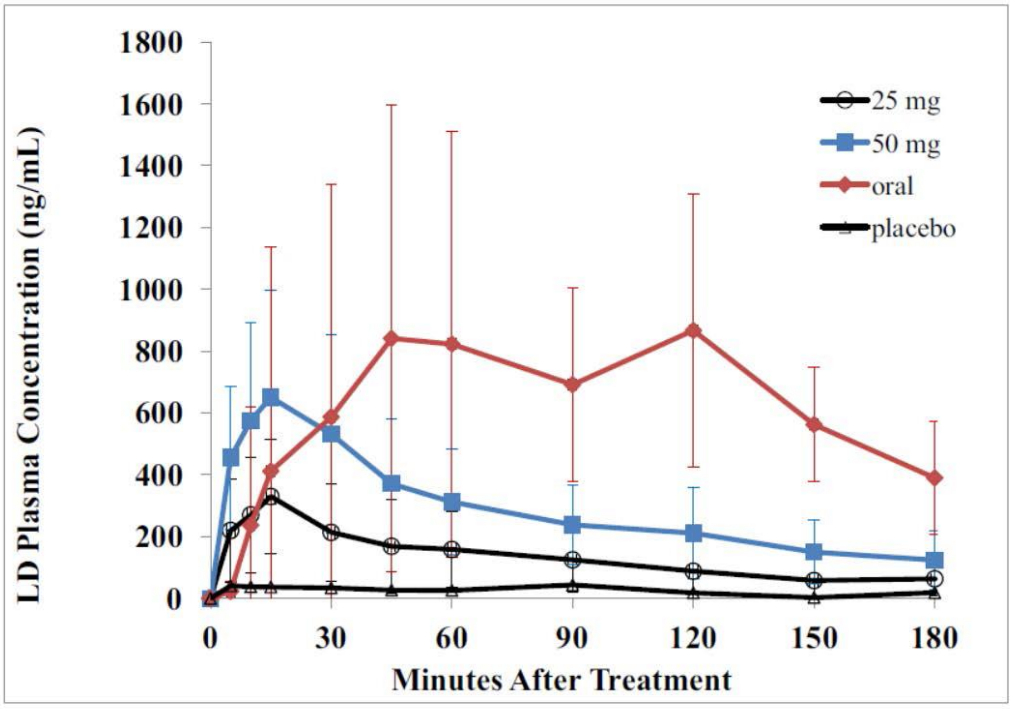
Pharmacokinetics in the target population (Study 002)

Study 002 was a randomized, placebo- and active-controlled, double-blind (with respect to placebo) study in Parkinson's disease patients experiencing motor fluctuations (OFF periods). This study evaluated pharmacokinetics of inhaled CVT-301 compared with placebo and a standard dose of oral carbidopa/levodopa in Parkinson's disease patients in a clinic setting established to simulate an end-of-dose wearing-off episode.

On the morning of each in-clinic visit day, the subject took his/her usual morning (AM) levodopa dosage and other usual Parkinson medications prior to the visit. Upon arrival at each (in-clinic) dosing visit in a presumed ON state, subjects underwent baseline blood sampling for pharmacokinetic assessment. Approximately 4 to 5 hours following the AM dose, after subjects were in a full OFF state, subjects were to receive a dose of study medication. All subjects received open-label oral carbidopa/levodopa at the first dosing visit. On subsequent dosing visits, subjects received in a double-blinded manner CVT-301 25 mg and 50 mg FPD and placebo in the order of an assigned randomized configuration. Treatment visits were separated by at least 48 hours.

Pre-dose levodopa values at start of the OFF period were highly variable and ranged from 46 ng/ml to 2980 ng/ml. Within a subject the variability between the 4 treatment periods was much smaller. To correct for baseline levodopa plasma concentrations from their prior morning dose of carbidopa/levodopa treatment, each subject's post-dose levels were individually corrected using a variable decay method using the baseline pharmacokinetic sample at arrival in the clinic (ON state) and the pre-dose pharmacokinetic sample at start of the OFF state. Figure 3 shows that applying the variable baseline adjustment the curves for the placebo treatment stayed very near zero throughout the sampling period supporting the variable baseline adjustment method was an appropriate approach for accounting for levodopa plasma concentrations present prior to dosing.

Figure 3: Study CVT-301-002: Variable Baseline-Adjusted Plasma Levodopa Concentration versus Time after Treatment in with Parkinson's Disease – Mean (±SD)



Abbreviations: LD = levodopa; SD = standard deviation. Note: Doses noted in legend for CVT-301 are estimated fine particle doses.

Figure 3 shows that plasma levodopa concentrations increased rapidly; Peak plasma levodopa exposures following treatment with CVT-301 50 mg FPD were generally similar to those observed in carbidopa-pre-treated healthy subjects. The baseline-adjusted Cmax and AUC of inhaled levodopa increased in a dose-proportional manner. Incremental plasma levodopa concentrations exceeding 400 ng/mL within 10 minutes were observed in 19% (3/16), 77% (17/22), and 27% (4/15) of subjects following administration of CVT-301 25 mg FPD, CVT-301 50 mg FPD, and oral CD/levodopa, respectively.

The inter-subject variability in levodopa exposure was lower for orally inhaled than for oral administered levodopa (Table 5).

Table 5: Study CVT-301-002: Pharmacokinetics summary immediately following CVT-301 administration to subjects with Parkinson's disease, baseline-adjusted values

Treatment[a]	**$C_{max0\text{-}10min}$[b] (ng/mL)**	**$C_{max0\text{-}30min}$[b] (ng/mL)**	**$AUC_{0\text{-}10min}$[b] (ng•min/mL)**	**$AUC_{0\text{-}30min}$[b] (ng•min/mL)**	**$T_{50\%Cmax}$[b] (min)**	**ΔC_c > 400 ng/mL by 10 min [N (%)]**
CVT-301						
25 mg LD FPD	273 ± 183	322 ± 201	1957 ± 1522	7188 ± 4739	4.50 ± 2.34	3 (19)
50 mg LD FPD	578 ± 315	690 ± 351	3833 ± 2202	15711 ± 8296	4.96 ± 2.43	17 (77)
Oral CD/LD	242 ± 379	620 ± 810	758 ± 1166	9813 ± 14701	51.6 ± 33.2	4 (27)

Abbreviations: AUC = area under the plasma concentration curve; CD = carbidopa; Cmax0-10min = maximal concentration achieved within the first 10 minutes postdose; Cmax0-30min = maximal concentration achieved within the first 30 minutes postdose; FPD = fine particle dose; LD = levodopa; SD = standard deviation; T50%Cmax = time to reach 50% of Cmax.
a CVT-301 dose indicates LD FPD.
b Mean (SD).
c ΔC = incremental change in plasma LD concentration.
N = 24 per treatment.

Cough was a treatment related AE for inhaled levodopa. Plasma levodopa concentrations were 42.6% and 32.8% (25 mg and 50 mg respectively) lower in subjects who reported mild-to-moderate cough than in subjects without cough. However, the Cmax concentrations achieved for those who coughed after 50 mg FPD were within the potentially therapeutic range.

Special populations

Pharmacokinetics of levodopa following inhalation was comparable in healthy subjects and in Parkinson patients. Smoking appeared not to affect the exposure of levodopa (Study 007). In addition, the levodopa exposure was comparable subjects with asthma (Study 008) although the absorption seemed somewhat slower (median tmax was 47 min). Because of the risk of bronchospasm, use of inhaled levodopa is not recommended in patients with asthma, chronic obstructive pulmonary disease (COPD), or other chronic underlying lung disease. This is reflected in the Summary of Product Characteristics (SmPC) section 4.4.

As systemic levodopa exposure is representative for its activity, effects of renal and hepatic impairment, gender, race, body-weight and age on clearance and volume of distribution are expected to be similar for the oral and inhalation route. Indeed, levodopa exposure was 40 to 50% higher in females compared to males following levodopa inhalation and oral administration. After correction for bodyweight, AUC values were about 15% higher in females than in males. Hence, most of the gender differences are accounted for by difference in body weight.

A two-compartment popPK model including two absorption compartments and first-order elimination was submitted to characterize both lung and gastrointestinal absorption and to evaluate if absorption of levodopa in the lungs was dependent on various intrinsic factors. Observations after oral levodopa/carbidopa were excluded from the popPK analysis with the exception of predose concentrations in Study CVT-301-002 that were included in the analysis. This was done to account for the high predose concentrations observed prior to CVT-301 administration. Both clearance and apparent volume of central

compartment were linearly correlated with bodyweight. Absorption rate constants for lung and gastrointestinal absorption were 8.0 h^{-1} and 0.56 h^{-1}, respectively. The model was adjusted to account for a higher ka in Study CVT-301-001. The early formulation had a higher fraction of smaller particles 0.5 – 2.0 µm than the phase 3 and commercial formulation, this could have resulted in a faster rise in levodopa plasma concentrations in this study. Gender, race, body weight or age, were not significant factors influencing the absorption of levodopa in the lungs.

Elderly

Clinical studies specifically designed to analyse the effects of age on the pharmacokinetics of levodopa were not conducted with Inbrija. The mean age of participants in the pivotal efficacy and long-term safety studies was 63.3 years (range: 37 – 82 years) and 49% of the subjects were ≥65 years old (CVT-301-004, CVT-301-004E, and CVT-301-005).

Pharmacokinetics interaction studies

No *in vitro* and *in vivo* interaction studies were conducted with Inbrija. Levodopa is not a new chemical entity and therefore the absence of *in vitro* and *in vivo* interactions studies is acceptable. Drug drug interactions with monoamine oxidase (MAO) inhibitors (contraindication) and dopamine D2 receptor antagonists and isoniazid (potential reduction of effectiveness of levodopa) are known interactions for levodopa and have been adequately described in section 4.5 of the SmPC.

As Inbrija is administered as orally inhaled powder, Inbrija potentially could influence the lung deposition of other inhaled medicines. However, as use of Inbrija is not recommended in patients with asthma, COPD, or other chronic underlying lung disease co-medication of Inbrija with other orally inhaled products is unlikely and it has not been investigated. This is reflected in the SmPC.

In conclusion, the pharmacokinetic data following levodopa oral inhalation support the concept that administration of inhaled levodopa 50 mg FPD results in a rapid increase of systemic levodopa plasma concentrations >400 ng/ml within 10 min of administration in Parkinson's disease patients, taking an oral dopa-decarboxylase inhibitor/levodopa based regimen.

2.4.3. Pharmacodynamics

Mechanism of action

Parkinson's disease is characterized by a loss of dopamine-containing neurons in the basal ganglia. Levodopa, the metabolic precursor to dopamine, is readily able to cross the blood-brain barrier, where it is converted to dopamine in the central nervous system. Pharmacologic treatment of Parkinson's disease has been directed primarily at enhancing striatal dopamine replacement through oral administration of levodopa, which continues to be the foundation and gold standard for the symptomatic treatment of the disease.

As the disease progresses, more patients experience motor complications ranging from increasing frequency and duration of OFF periods which may be disabling. The development of OFF episodes relates to both pharmacokinetic and pharmacodynamic factors.

Primary and Secondary pharmacology

Safety, pharmacokinetics, and pharmacodynamics of Inbrija was evaluated in phase 2 Study 002 in Parkinson's patients in a clinic setting to simulate an end-of-dose wearing-off episode to select the dose of inhaled levodopa for the phase 3 studies.

Study CVT-301-002 was a Phase 2a, randomized, placebo- and active-controlled, double-blind (only with respect to inhaled treatments) study in 24 PD subjects who experienced motor fluctuations (OFF periods) for a minimum of 2 hours of average daily OFF time per waking day. Each subject received a single dose of open-label oral Sinemet 25 mg/100 mg (carbidopa/levodopa [CD/levodopa]) during the first treatment visit and then in a randomized, double-blind manner using a 3-way crossover design, single doses of 3 inhaled treatments: placebo, CVT-301 25 mg FPD and CVT-301 50 mg FPD at subsequent treatment visits. Treatment visits were to be separated by at least 2 days.

On the morning of each in-clinic visit day, the subject took his/her usual morning (AM) levodopa dosage and other usual PD medications prior to the visit. Upon arrival at each (in-clinic) dosing visit in a presumed ON state, subjects underwent baseline blood sampling for pharmacokinetic, pharmacodynamic and safety assessments. Approximately 4 to 5 hours following the AM dose, after subjects were in a full OFF state, subjects were to receive a dose of study medication. Subjects received the open-label oral dose of carbidopa/levodopa in a fasted state; during the double-blind treatment period, the inhaled study treatments were administered in the fasted state.

Pharmacodynamic assessments evaluated were the time to onset of meaningful ON, duration of ON state, Unified Parkinson's Disease Rating Scale, Part III motor section (UPDRS-III) score (arrival, pre-dose, 15, 30, 45, 60, 90, 120, 150 and 180 minutes post-dose), timed tapping test and requirement for rescue medication.

Results for the response analysis of meaningful ON, the UPDRS-III and tapping efficacy endpoints are summarized in Table 6. Treatment with CVT-301 50 mg FPD resulted in a greater proportion of patients achieving a meaningful ON response, UPDRS III response, and tapping response compared to placebo. After taking into account the extent of the placebo effect, the percentage of responders increased with increasing levodopa dose, regardless of route of delivery (i.e., levodopa doses CVT-301 25 mg FPD, CVT-301 50 mg FPD, and oral carbidopa/levodopa 25 mg/100 mg).

Table 6: Summary of response analysis for selected PD parameters (Study CVT-301-002 ITT Population)

Summary of Responses to Study Treatment (ITT Population)				
StudyTreatment	Achieved a Meaningful ON Response[a]	UPDRS III Responder[b]	Tapping Responder[c]	Required Rescue Medication[d]
Double-Blind				
Placebo	12/23 (52.2%)	10/23 (43.5%)	8/23 (34.8%)	12/23 (52.2%)
CVT-301 25 mg FPD	13/23 (56.5 %)	13/23 (56.5 %)	11/23 (47.8%)	10/23 (43.5%)
CVT-301 50 mg FPD	21/24 (87.5%)	17/24 (70.8%)	14/24 (58.3%)	6/24 (25.0%)
Open Label				
Oral CD/LD[e] (25 mg/100 mg)	*23/24 (95.8%)*	*24/24 (100.0%)*	*18/24 (75.0%)*	*4/24 (16.7%)*

[a] The subjective endpoint, "meaningful ON" state, was defined as when improvement in motor function was deemed sufficient or of adequate degree to enable a patient to manage most activities of daily living.
[b] A UPDRS III responder was defined as a patient who had a ≥30% reduction in total UPDRS III score from

pre-dose to post-dose.
[c] A tapping test responder was defined as a patient who had a ≥20% increase in tapping test total score from pre-dose to post-dose.
[d] Number of patients administered rescue medication
[e] Oral CD/LD was administered as an open-label dose.

Responses at the earlier nominal time points were observed more frequently following treatment with CVT-301 50 mg FDP. The median time to onset of meaningful ON was more rapid following administration of CVT-301 25 mg FDP and CVT-301 50 mg FDP (median [range]: 29 [4 to 97] minutes and 36 [12 to 105] minutes, respectively) compared to oral carbidopa/levodopa (45 [15 to 105] minutes). The onset of ON for placebo was 32.4 [16 to 110] minutes. The median duration of ON was longer after the administration of CVT-301 25 mg FDP (median [range]: 83 [38 to 280] minutes) and CVT-301 50 mg FDP (110 [4 to 268] minutes) compared with placebo (69 [25 to 167] minutes). The duration of ON following treatment with open-label oral carbidopa/levodopa was 132 (40 to 265) minutes.

The exposure-response analyses in form of UPDR-III response at 15 minutes indicated a numerically better response in subjects with an increase in levodopa plasma concentrations > 400 ng/ml than in subjects with plasma concentrations < 400 ng/ml. Similarly patients with higher than median levodopa plasma concentrations at time of onset of the OFF period, had a numerically better response than patients with lower than median levodopa plasma concentrations at time of onset of the OFF period.

The proportion of patients who experienced dyskinesia was greatest after the administration of oral carbidopa/levodopa treatment (37.5%), and lower for CVT-301 25 mg FDP and CVT-301 50 mg FDP with 17.4% and 25%, respectively.

The magnitude of the pharmacodynamic effects, including dyskinesia, following CVT-301 50 mg FPD inhalation was less than the effects of oral levodopa (Sinemet 25 mg /100 mg) but responses were in general observed somewhat earlier with CVT-301 50 mg FPD inhalation compared to oral levodopa.

2.4.4. Discussion on clinical pharmacology

Oral administration of levodopa is the gold standard for the symptomatic treatment of Parkinson's disease. As the disease progresses, more patients experience motor complications including increased frequency and duration of OFF periods, which may be disabling. The development of OFF episodes relates to both pharmacokinetic and pharmacodynamic factors of the applied therapy.

The levodopa dry powder inhalation formulation was aimed at delivering levodopa at doses on top of treatment with regular dopa-decarboxylase inhibitor/levodopa medication, in order to compensate for OFF symptoms due to low levodopa plasma levels, more rapidly and less variably as compared to intermittent oral dosing. The proposed inhalation levodopa dose to be delivered-66 mg (corresponding to 50 mg fine particle dose) is lower than the usual oral doses and therefore has a lower risk of inducing dyskinesia (at levodopa plasma levels above 800 ng/ml).

The pharmacokinetic data following levodopa inhalation support the concept that administration of inhaled levodopa 50 mg FPD results in the majority of subjects (77%) in a rapid increase (within 10 min) of systemic levodopa plasma concentrations >400 ng/ml. Inter-subject variability following inhalation was less than the variability following oral levodopa administration. Gender, race, body weight or age did not influence the absorption of levodopa in the lungs.

Pharmacodynamics of inhaled levodopa, compared with placebo, and a standard dose of oral carbidopa/levodopa in Parkinson's disease patients in a clinic setting, established an end-of-dose wearing-off episode in study 002. The results show that levodopa inhalation powder dose 50 mg FPD that potentially could lead to a clinical meaningful improvement of OFF periods, were reached faster than

compared to oral LD administration, although a wide inter-individual variety was observed. Although numeric responses were evident, CVT-301 25 mg FDP was not statistically different from placebo. In general, the magnitude of the pharmacodynamics effects was smaller compared to oral levodopa which could be due to the lower administered dose following inhalation. The data from study 002 support the selection of the doses 60 mg and 84 mg (corresponding to 35 mg and 50 mg FPD, respectively) for the phase 3 studies.

It was hypothesised that achieving levodopa plasma concentrations > 400 ng/ml 5 to 10 min following levodopa inhalation should be high enough to counteract the emergent OFF period. The exposure-response in form of UPDRS-III response at 15 minutes indicated a better response with an increase in levodopa concentrations > 400 ng/ml upon Inbrija treatment compared to patients with a levodopa increase < 400 ng/ml. As more patients achieved this increase with the 50 mg FDP dose compared to the 25 mg FDP dose, this is supportive of the selection of the 50 mg FDP dose of CVT-301. The shortened tmax following levodopa inhalation did not increase the risk of dyskinesia and is not of concern.

2.4.5. Conclusions on clinical pharmacology

The applicant has shown that Inbrija's levodopa plasma levels, which could lead to a clinical meaningful improvement of OFF periods, were reached faster following oral inhalation than compared to oral levodopa administration. The proposed inhalation levodopa dose to be delivered-66 mg (corresponding to 50 mg fine particle dose) is lower than the usual oral doses and therefore has a lower risk of inducing dyskinesia (at levodopa plasma levels above 800 ng/ml).

The pharmacokinetics and pharmacodynamics of levodopa following inhalation have been sufficiently characterised at the intended dose of 50 mg FPD.

2.5. Clinical efficacy

The efficacy of levodopa inhalation powder for the treatment of OFF symptoms in PD patients experiencing motor fluctuations was assessed in 4 clinical trials (see Table 7). Studies CVT-301-003 (referred to as study 003) and CVT-301-004 (referred to as study 004) were considered pivotal. Both were randomized, multicentre, double blind, placebo controlled studies in PD patients experiencing >2hrs/daily OFF periods. In both studies efficacy of CVT-301 60 mg and CVT-301 84 mg were compared to placebo. In study 004 this was at 12 weeks and for study 003 this was after 2 weeks of treatment at each dose levels. Study 004E and Study 005 were both long term safety studies with exploratory efficacy endpoints.

Table 7: Overview clinical efficacy studies of Inbrija

Study / Region	**Design**	**Treatment arms**	**Key Efficacy Endpoints**
Studies with Efficacy as Primary Objective			
CVT-301-004 (Phase 3) *North America & Europe*	RD MC DB PC PA study Subjects: PD patients with average OFF ≥ 2 hours Age: 30-85 years old	CVT-301 60 mg n=113 CVT-301 84 mg n=114 Placebo n=112	Primary: Change in UPDRS-III motor score 30 minutes post dose at Week 12 Main secondary: Responder ON, PCG-I, total daily OFF time at week 12

CVT-301-003 (Phase 2b) *North America & Europe*	RD MC DB PC PA study 4 weeks Subjects: PD patients with average OFF ≥ 2 hours Age: 30-85 years old	CVT-301 60 mg for 2 weeks followed by 84 mg for the next 2 weeks n=44 Placebo n=45	Primary: Change in UPDRS-III motor score at 10 to 60 minutes postdose at ET Main secondary: Examiner rated time to ON, responder ON, PGI-C, daily OFF and ON time (with /without (troublesome) dyskinesia
Studies with Efficacy as Secondary Objective or Exploratory Endpoint			
CVT-301-002 (Phase 2a) *Europe & Israel*	RD MC DB/open PC CO study	CVT-301 25 mg CVT-301 50 mg Sinemet 25 mg/100 mg Placebo	Primary: safety/tolerability Exploratory endpoint: UPDRS-III score, Examiner rated time to ON and duration of ON state, time to onset / duration of dyskinesia, Timed tapping test
CVT-301-004E (Phase 3) *North America & Europe*	Long term extension of study 004 DB was maintained for the dose levels Study duration up to 12 months	CVT-301 60 mg n=144 CVT-301 84 mg n=153	Primary: on safety Secondary: responder ON, total daily OFF time, total daily ON time without dyskinesia, total daily ON time with non-troublesome dyskinesia and total daily ON time with troublesome dyskinesia, PGI-C, UPDRS-II score
CVT-301-005 (Phase 3) Long term safety *North America, Europe & Israel*	RD MC Open study Subjects were randomized 2:1 for CVT-301 and SOC. (SOC is referred to as observational cohort); 12 months	CVT-301 84 mg and opportunity to down titrate to 60 mg; usual standard of care in the observational cohort	Primary: on safety Exploratory endpoints: Change in UPDRS-III motor score, proportion of patients with ≥3, ≥6 and ≥11 point reduction in the UPDRS-III motor score, responder ON, PGI-C, change in UPDRS-II score, total daily OFF and ON (with or without (troublesome) dyskinesia) time, PDQ-39, S&E ADL score

Abbreviations: DB= double blind, ET=end of treatment, FPD= fine particle dose, MC= multicentre, PA= PC= placebo controlled, RD= randomized. SOC=standard of care
CVT-301 60mg corresponds to 48mg emitted, 35mg FPD and CVT-301 84mg corresponds to 66mg emitted dose and 35mg FPD.
[1] Source: Module 2.5, overview of clinical pharmacology applicants original table adapted by assessor
[2] The described dose is indicated as dose of the capsules, not the emitted, nor the fine particle dose

In addition to the above mentioned trials, the applicant performed an additional trial (RPT-2202) to demonstrate the safe, effective and usability of the system and to identify any residual use related risks. The trial included 27 PD patients, 15 PD care givers and 15 health care professionals. Seven PD patients and 8 caregivers were untrained. The study showed that training is needed to become familiar and successful with the device and the application procedure; hence reference to training in section 4.2 of the SmPC has been included.

2.5.1. Dose response study(ies)

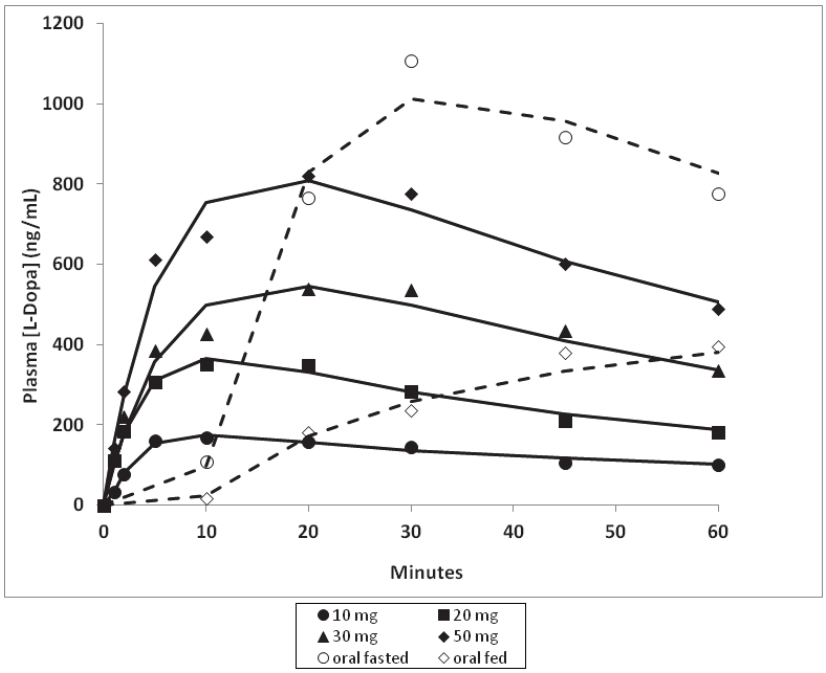
There were no dose response studies performed, however multiple doses were assessed in study 001.

Study CVT-301-001 was a safety and pharmacokinetic study of single ascending doses of CVT-301 in 26 healthy subjects was conducted in 2 parts. Using a crossover design, volunteers received CVT-301 at

escalating doses ranging from 10 to 50 mg LD FPD. Part A, the dose escalation phase, was an open-label, 3-period crossover, single-ascending dose study of 4 CVT-301 dose levels, in which 1 to 5 CVT-301 capsules were administered sequentially to reach the target dose. Each capsule delivered an approximate 10 mg LD FPD. FPDs of approximately 10, 20, 30, and 50 mg LD were administered, corresponding to 1, 2, 3, and 5 sequential inhalations of CVT-301 10 mg FPD capsules, respectively. Part B concerned the exposure to oral LD/CD 100mg/25mg.

Dose-normalized data demonstrated proportionality across the four dose strengths. When compared to oral LD/CD 100 mg/25 mg, inhaled CVT-301 produced a more rapid increase in plasma concentrations than with oral administration of LD/CD 100 mg/25 mg (See Figure 4). Potentially therapeutically-relevant plasma LD concentrations, i.e. 400 ng/µL, were achieved within 5 to 10 minutes after CVT-301 doses of 20 to 50 mg FPD in healthy adults. Based on these results, the highest tested dose of 50 mg LD FPD and a 25 mg LD FPD dose were selected.

Figure 4: Pharmacokinetic modeling of Mean Plasma Concentrations (Study CVT-301-001)



Note: N=9 per treatment group.

2.5.2. Main studies

2.5.2.1. Study CVT-301-004

Study CVT-301-004 was a Phase 3, randomized, double-blind, placebo-controlled, 12-week, multicenter (North America and Europe) study of inhaled CVT-301 or placebo for the treatment of up to 5 OFF periods per day in PD subjects experiencing motor fluctuations (OFF periods). Each OFF period was to be treated with inhalation of 2 capsules of study drug (i.e., 2 capsules used in the inhaler per treated episode, to deliver the intended dose). Subjects were not to use study drug for the treatment of early morning OFF periods. The double-blind treatment period was 12 weeks.

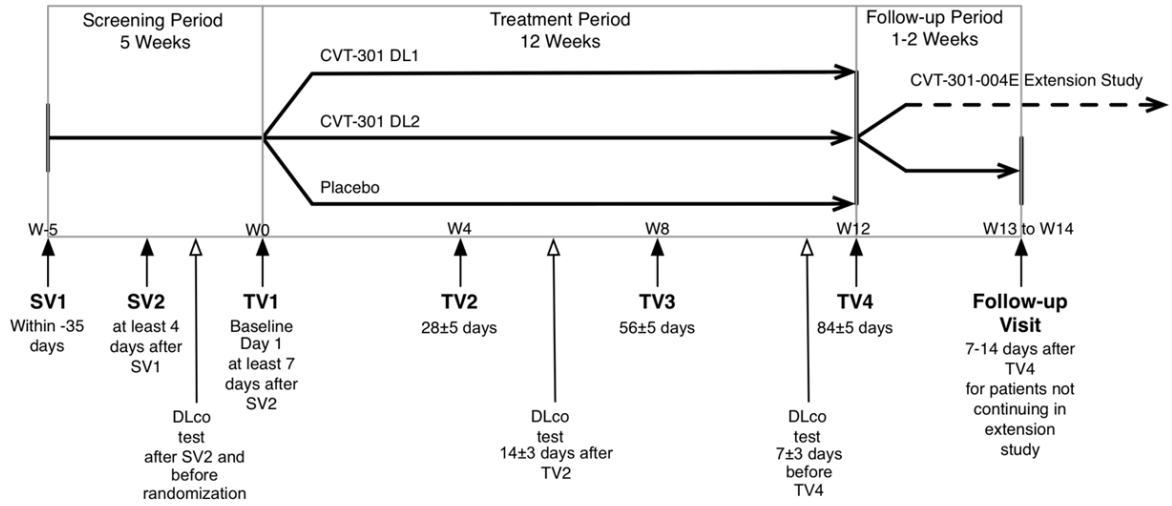
Methods

- ***Study participants***

Main inclusion criteria were a PD Diagnosis, stable LD/CD medication (daily dose ≤1600 mg divided over 3 gits), experiencing OFF ≥ 2hours daily, 30-85 years of age, modified Hoehn & Yahr stage 1-3, motor fluctuations, ability to discriminate OFF, ability to handle device.
Furthermore patients should have a ≥ 25% difference between UPDRS-III scores recorded in their ON and OFF states at screening and must have been able to perform a spirometry manoeuvre in the ON and OFF states and must have had a screening FEV1 ≥ 50% of predicted, and an FEV1/FVC ratio > 60% in the ON state at screening.

Exclusion criteria were: severe dyskinesia, previous surgery for PD (or planned during study period), psychotic symptoms, COPD, asthma or other chronic respiratory diseases within the last 5 years, and any contraindication to perform routine spirometry or who were unable to perform a spirometry manoeuvre.

Figure 5: CVT-301-004 Study Design Schematic



Abbreviations: DL1 = dose level 1 (60 mg); DL2 = dose level 2 (84 mg); DLco = carbon monoxide diffusing capacity; SV = Screening visit; TV = treatment visit; W = week.
Note 1: Spirometry was performed on the same day as the DLco test.
Note 2: The baseline DLco test was scheduled after SV2 but in order to widen the window for drug shipment, protocol amendment v4.0 removed the requirement to have randomization occur after this DLco test.

- ***Treatment***

The study drugs, CVT-301 (active) and placebo (control), were administered by the inhalation route using the CVT-301 inhaler. Two CVT-301 dose levels were investigated as described in Table 8, below.
The first dose of blinded inhaled study drug was administered in the clinic on Day 1 (Treatment Visit [TV] 1) and the last scheduled dose was at Week 12 (Day 84 ± 5 days; TV4). In between clinic visits, subjects were to administer double-blind study drug at home as needed to treat up to 5 OFF periods per day, as close as possible to the time when they began to experience OFF symptoms. The study design is depicted schematically in Figure 5.

All patients were trained on use of the inhaler utilizing the Instructions for Use (IFU) in both the ON and OFF states during the screening visit. All patients needed to demonstrate an ability to use the inhaler while in the OFF state prior to randomization. All in-clinic dosing (in OFF state) was observed by site staff.

Table 8: Description of study drugs

Study Drug	Dose Level	Dosage Form	Total Levodopa Capsule Dose	Total Levodopa Fine Particle Dose
CVT-301	DL1	Capsules (2)	60 mg	35 mg FPD
CVT-301	DL2	Capsules (2)	84 mg	50 mg FPD
Placebo	-	Capsules (2)	-	-

Abbreviations: DL = Dose Level. FPD = fine particle dose (ie, the estimated amount delivered to the lung).

Because Inbrija contains levodopa only (i.e., with no DDI), study drug will be administered only to patients taking a DDI-containing levodopa formulation (e.g., CD or benserazide).

The 2 selected CVT-301 dose levels 60 mg and 84 mg are based on safety and PK data from Studies CVT-301-001 and CVT-301-006 in healthy adult volunteers, the safety, PK and pharmacodynamic data from Study CVT-301-002 in PD patients with motor fluctuations, and the safety and efficacy data from study CVT-301-003 in PD patients with motor fluctuations.

- **Outcomes /endpoints**

The primary endpoint of the study was the change in the UPDRS-III score from (same day) pre-dose to 30 minutes post-dose following treatment (CVT-301 84 mg) of subjects experiencing an OFF period at the study clinic at the Week 12 visit.

Key secondary endpoints (and also associated with the Week 12 visit) were:

1. proportion of subjects achieving resolution of an OFF to an ON state (Responder ON) within 60 minutes after study drug is administered in the clinic and maintaining the ON state at 60 minutes after study drug administration (per the examiner's subjective assessment);
2. change in the UPDRS-III score from (same day) predose to 20 minutes postdose following treatment of subjects experiencing an OFF period at the study clinic;
3. proportion of subjects who improved based on the PGI-C rating scale (subjects were defined as "improved on the PGI-C Rating Scale" if their PGI-C rating was "much improved," "improved," or "a little improved");
4. change in the UPDRS-IIII score from (same day) predose to 10 minutes postdose following treatment of subjects experiencing an OFF period at the study clinic;
5. change from baseline in total daily OFF time assessed by the subject and recorded in the PD Diary.

Subjects had to take their regular oral PD medications in the morning prior to their planed clinic visit. Visits were between 2-5 hours post oral PD medications. The dosing time of Inbrija was to be defined when the subjects OFF state was recognized by both the patient and investigator, preferably between 205 hours after their prior oral PD medication. Patients prepared and self-administered their dose of Inbrija.

- **Sample size**

The sample size determination (calculation performed using nQuery Advisor, Version 7.0) was based on the primary endpoint. The study was powered to detect a difference of 5 points in the mean change in the average UPDRS-III score, assuming a standard deviation (SD) of 10.0 points. To achieve a power of 90%, a total of 86 patients per group was required using a 2-sided significance level of 0.05. To account for a dropout rate of approximately 25%, 115 patients per group were randomly assigned to treatment. If the

withdrawal rate exceeded 25%, additional patients could be enrolled to ensure that at least 258 patients completed the study.

- **Randomization**

Patients were randomly assigned in a 1:1:1 ratio to receive CVT-301 60 mg, CVT-301 84 mg, or placebo using an Interactive Web Response System (IWRS). Randomization was stratified by Hoehn & Yahr state (<2.5 vs ≥2.5) and by spirometry variables i.e. FEV1 <60% of predicted or FEV1/FVC ratio <70% versus FEV1≥60% of predicted or FEV1/FVC ratio≥70%).

- **Blinding**

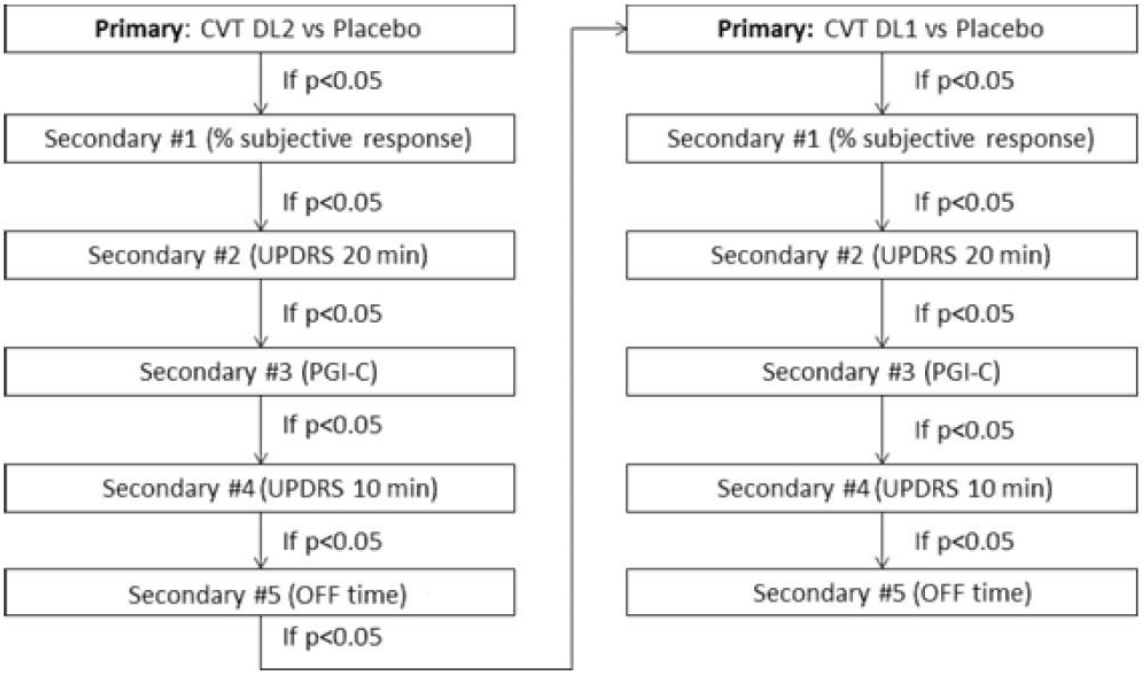
In order to maintain blinding of administered study drug, capsules for each of the 3 possible study treatments were identical in appearance, and packaging was labelled in a manner that did not reveal which treatment the capsules contained.

- **Statistical methods**

Analysis sets

- All available population (AAP): Patients who consented to the study, including screen failures. The AAP was used in patient listings and the summary of patient disposition.
- Safety population: Patients who received at least 1 dose of inhaled CVT-301 or placebo. The safety population was used in all safety analyses.
- Intent-to-treat (ITT) population: Patients who were randomly assigned to inhaled CVT-301 or placebo and received at least one dose of study drug. The ITT population was used in all efficacy analyses and summaries of patient demographic and baseline characteristics.
- Completer population: A subset of the ITT population that included patients with a UPDRS-III score at week 12. The completer population was used in the sensitivity analysis of the primary endpoint.

Figure 6: schematic representation of the hierarchical testing approach



Abbreviations: CVT-301 DL1 = 60 mg LD; CVT-301 DL2 = 84 mg LD; PGI-C = Patient Global Impression of Change; UPDRS = Unified Parkinson's Disease Rating Scale.

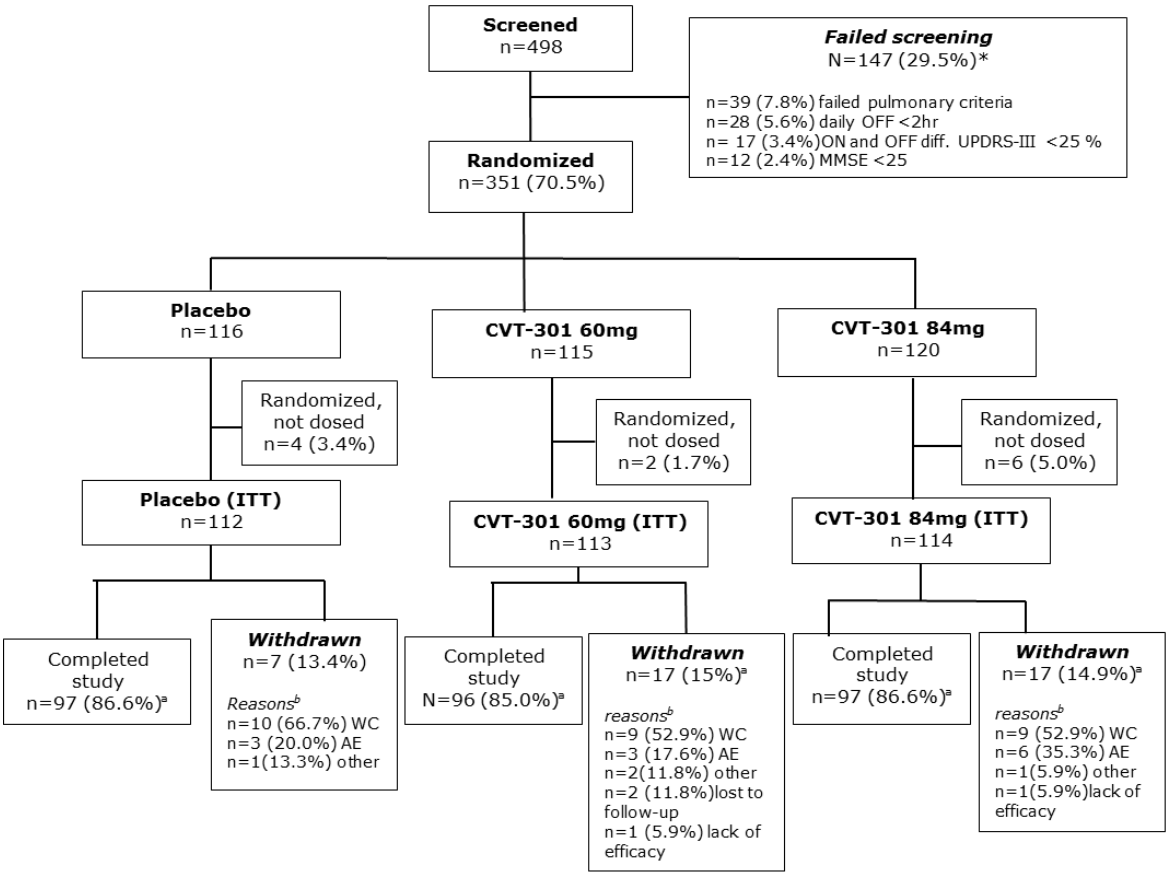
In order to maintain an overall alpha-level of 0.05 and claim statistical significance on selected efficacy variables for both doses of CVT-301 versus placebo, a fixed-sequence hierarchy was pre-specified. First, CVT-301 84 mg and placebo were compared on the primary endpoint and the 5 key secondary endpoints presented in the order above (Figure 6: schematic representation of the hierarchical testing approachFigure 6). Next, CVT-301 60 mg and placebo were compared in the same order with the same hierarchical rules as applied for CVT-301 84 mg and placebo comparisons. According to the hierarchical rules, formal testing for statistical significance could proceed until a nonsignificant result was obtained (i.e., a nominal p-value greater than 0.05).

The changes in the UPDRS-III from predose to the each postdose time point (10, 20, 30 and 60 minutes) and the changes from baseline in Hauser Diary OFF Time were analysed using a mixed model for repeated measurements (MMRM). Missing data were implicitly handled by the MMRM analysis with the underlying assumption that the missing data were missing at random. Categorical endpoints (responder ON and PGI-C) were analysed at a particular double-blind visit via the Cochran Mantel Haenszel test. In the case of missing categorical data for a nonmissed visit, the outcome was imputed to be a nonresponder.

Results

There were 339 randomized patients who took at least 1 dose of study medication: 112 patients were randomized to placebo, 113 patients to CVT-301 60 mg, and 114 patients to CVT-301 84 mg. All efficacy (ITT Population) and safety analyses (Safety Population) are based on these patients. Among the 339 patients included in the efficacy and safety analyses, 290 patients (85.5%) completed the study.

Figure 7: Participant flow



Abbreviations: AE= adverse event, ITT = intent-to-treat, WC= withdrew consent
*Two patients failed 2 pulmonary screening criteria; [a] percentages are based on the number of patients in the safety population; [b] percentages are based on the number of withdrawn from study [1] Source: CVT-301-004CRS

- **Conduct of study**

Overall, there were 297 (84.6%) patients with at least 1 protocol deviation. Of the patients who had deviations, 43 (12.3%) had major protocol deviations, with most occurring in the CVT-301 84mg group, 22 (18.3%). No patients were excluded from the ITT analyses due to a protocol deviation.

- **Baseline data**

Baseline characteristics were generally similar among treatment groups (see Table 9).
The median age was 65 years. Most study participants were White. The majority of participants were treated in the USA (73.2%) followed by Poland (19.5%). Males made up over 70% of study participants. The majority of patients (212 patients, 62.5%) reported no smoking history, 119 (35.1%) patients were former smokers, and 8 (2.4%) patients were current smokers.

Average daily LD dose was 750 mg, mean daily OFF time was 5.3hrs and number of OFF periods per day was 3.5. Baseline UPDRS-III score in OFF was 38.9

Table 9: Demographic and baseline characteristics (ITT population)

Characteristics	Statistic	Placebo	CVT-301 60mg	CVT-301 84mg	Overall
	n	112	113	114	339
Age					
	Mean (SD)	62.6 (8.83)	63.9 (9.24)	63.5 (7.97)	63.3 (8.69)
	Median	65.0	66.0	64.0	65.0
	Min, Max	38, 80	40, 82	45, 82	38, 82
Modified Hoehn & Yahr stage					
Stage 1: Symptoms are very mild; unilateral involvement only	n (%)	6 (5.4)	6 (5.3)	6 (5.3)	18 (5.3)
Stage 1.5: Unilateral and axial involvement	n (%)	4 (3.6)	4 (3.5)	5 (4.4)	13 (3.8)
Stage 2: Bilateral involvement without impairment of balance	n (%)	64 (57.1)	64 (56.6)	60 (52.6)	188 (55.5)
Stage 2.5: Mild bilateral disease with recovery on pull test	n (%)	20 (17.9)	21 (18.6)	28 (24.6)	69 (20.4)
Stage 3: Mild to moderate bilateral disease; some postural instability; physically independent	n (%)	18 (16.1)	18 (15.9)	15 (13.2)	51 (15.0)
Time since diagnosis of PD (months)	Mean (SD)	97.4 (54.05)	104.3 (56.41)	95.7 (46.3)	99.1 (52.39)
	Median	85	96	98	93
	Min, Max	3, 305	11, 308	11, 243	3, 308
Duration of levodopa treatment (months)	Mean (SD)	81.6 (53.58)	84.8 (54.61)	75.0 (44.63)	80.4 (51.12)
	Median	65.5	73.0	66.0	67.0
	Min, Max	3, 281	5, 284	7, 220	3, 284
duration since onset of fluctuation (wearing off) periods (months)	Mean (SD)	46.7 (40.67)	51.7 (41.95)	44.2 (34.80)	47.5 (39.25)
	Median	32.0	40.0	35.5	37.0
	Min, Max	1, 191	1, 221	0, 183	0, 221
average daily Levodopa dose (mg)	Mean (SD)	841.4 (396.46)	822.7 (364.05)	818.6 (401.04)	827.5 (386.53)
	Median	800.0	750.0	700.0	750.0
	Min, Max	200, 1800	300, 1600	285, 2340	200, 2340
average of daily OFF periods	Mean (SD)	3.28 (1.099)	3.54 (1.240)	3.58 (1.094)	3.47 (1.151)
	Median	3.33	3.67	3.67	3.50
	Min, Max	0.0, 6.7	1.3, 9.7	1.0, 6.3	0.0, 9.7
mean daily OFF time (hours)	Mean (SD)	5.59 (2.251)	5.60 (1.927)	5.35 (2.261)	5.51 (2.149)
	Median	5.43	5.40	5.28	5.33
	Min, Max	1.0, 11.4	1.6, 10.2	0.5, 16.0	0.5, 16.0
mean daily OFF time during screening					
< 4.5 hours	n (%)	37 (33.0)	39 (34.5)	41 (36.0)	117 (34.5)
≥ 4.5 hours	n (%)	75 (67.0)	74 (65.5)	73 (64.0)	222 (65.5)
screening UPDRS-III total score (ON state)	Mean (SD)	16.1 (8.33)	15.8 (8.02)	14.9 (7.40)	15.6 (7.92)
	Median	16.0	15.0	14.0	15.0
	Min, Max	2, 48	3, 45	3, 36	2, 48
screening UPDRS-III total score (OFF state)	Mean (SD)	35.4 (12.44)	35.0 (10.25)	33.0 (10.99)	34.5 (11.27)
	Median	35.0	34.0	31.0	33.0
	Min, Max	8, 73	9, 61	10, 75	8, 75
Dyskinesia					

Characteristics	Statistic	Placebo	CVT-301 60mg	CVT-301 84mg	Overall
Dyskinetic before TV1	n (%)	46 (41.1)	43 (38.1)	53 (46.5)	142 (41.9)
Nondyskinetic before TV1	n (%)	66 (58.9)	70 (61.9)	61 (53.5)	197 (58.1)
MMSE total score	Mean (SD)	28.8 (1.46)	28.6 (1.46)	29.0 (1.30)	28.8 (1.41)
	Median	29.0	29.0	29.5	29.0
	Min, Max	25, 30	25, 30	25, 30	25, 30
Smoking History					
Never	n (%)	72 (64.3)	75 (66.4)	65 (57.0)	212 (62.5)
Former	n (%)	37 (33.0)	38 (33.6)	44 (38.6)	119 (35.1)
Current	n (%)	3 (2.7)	0	5 (4.4)	8 (2.4)
Screening spirometry					
FEV1<60% or FEV1/FVC ratio <70%	n (%)	6 (5.4)	6 (5.3)	7 (6.1)	19 (5.6)
FEV1≥60% or FEV1/FVC ratio ≥70%	n (%)	106 (94.6)	107 (94.7)	107 (93.9)	320 (94.4)

- **Outcome and estimation**

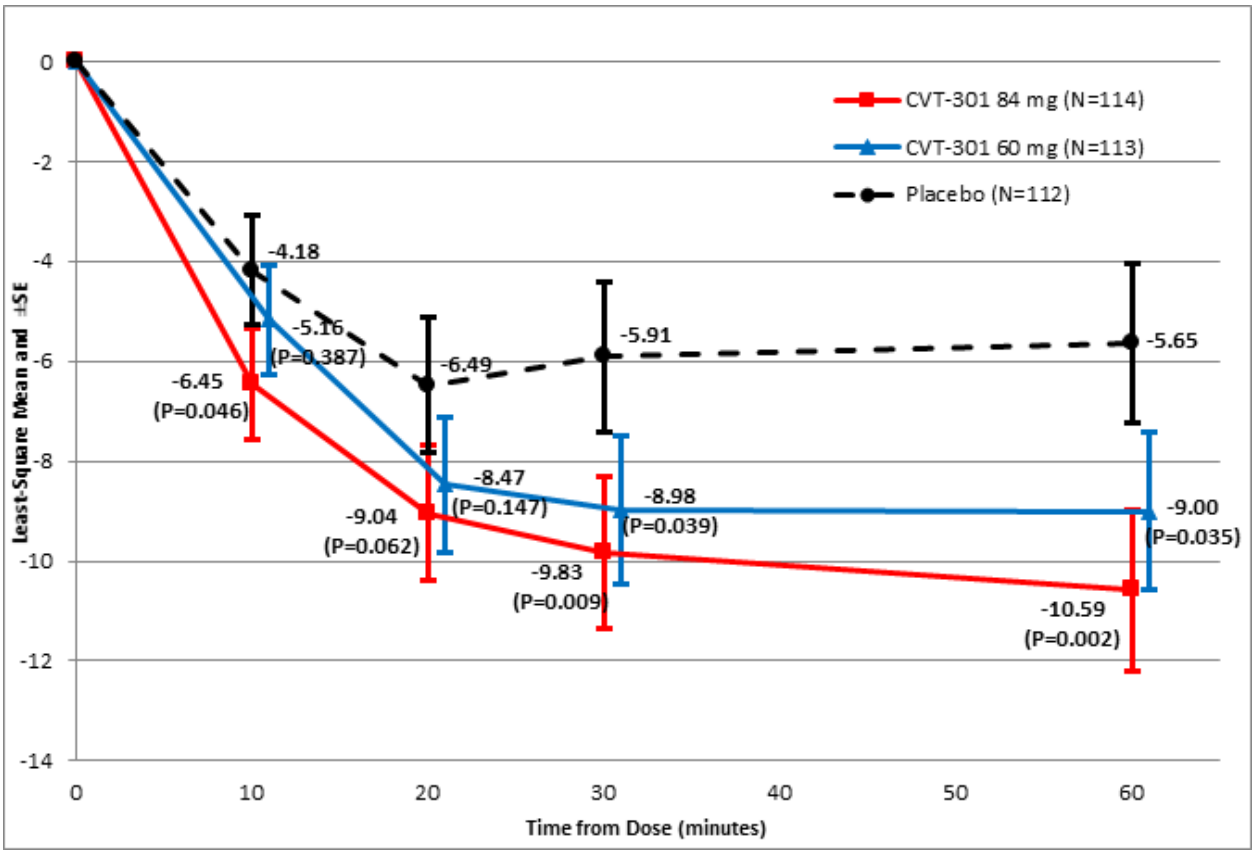
The primary efficacy endpoint was the change in the UPDRS-III score from (same day) predose to 30 minutes postdose at Week 12 based on the CVT-301 84 mg versus placebo comparison (Step 1 of the hierarchical testing order). Reductions in UPDRS-III scores are indicative of improvement.

The LS mean (SE) change from predose in UPDRS-III score at 30 minutes postdose at 12 weeks was -5.91 (1.500) for the placebo group and -9.83 (1.506) for the CVT-301 84mg group. The LS mean difference between CVT-301 84mg and placebo was -3.92, which was statistically significant (p = 0.009).

As the change in UPDRS-III from predose to 30 minutes was statistically significantly different for CVT-301 84mg compared to placebo (p = 0.009), formal statistical testing of the treatment comparisons proceeded to the next endpoint. The percentage of ON responders within (and maintained at) 60 minutes at Week 12 was also statistically significant (p = 0.003) for CVT-301 84 compared to placebo.
The hierarchical sequence failed to reach statistical significance for change from predose in UPDRS-III at 20 minutes (p = 0.062) in the CVT-301 84 mg treatment arm (see Figure 8). While subsequent steps in the hierarchy are technically ineligible for being declared statistically significant, nominal p-values < 0.05 were observed for PGI-C (p < 0.001) (see Figure 9) and change from predose in UPDRS-III at 10 minutes (p = 0.046) (Figure 8).

Key secondary endpoints:
The change in UPDRS-III score from predose was assessed at 10-60minutes postdose and is graphically presented in the Figure 8 below. The trend in change of UPDRS-III score 30 post dose is similar for all groups, i.e. CVT-301 60 gm, CVT-301 84 mg and placebo. There is an initial improvement observed after 10 minutes, this continuous to improve for an additional 10-20minutes and an improvement from baseline is maintained for up to 60 minutes post dose. The improvement in UPDRS-III from baseline is statistically significant different from placebo CVT-301 84 mg dose at t=10min, t=30min and t-60min. For CVT-301 60 mg the differences from placebo were significant fore t=30min and t=60min.

Figure 8: Change in the UPDRS-III Score from Predose to 10, 20, 30, and 60 Minutes Postdose at Week 12: CVT-301 84 mg and CVT-301 60mg Versus Placebo (Study CVT-301-004, ITT Population)



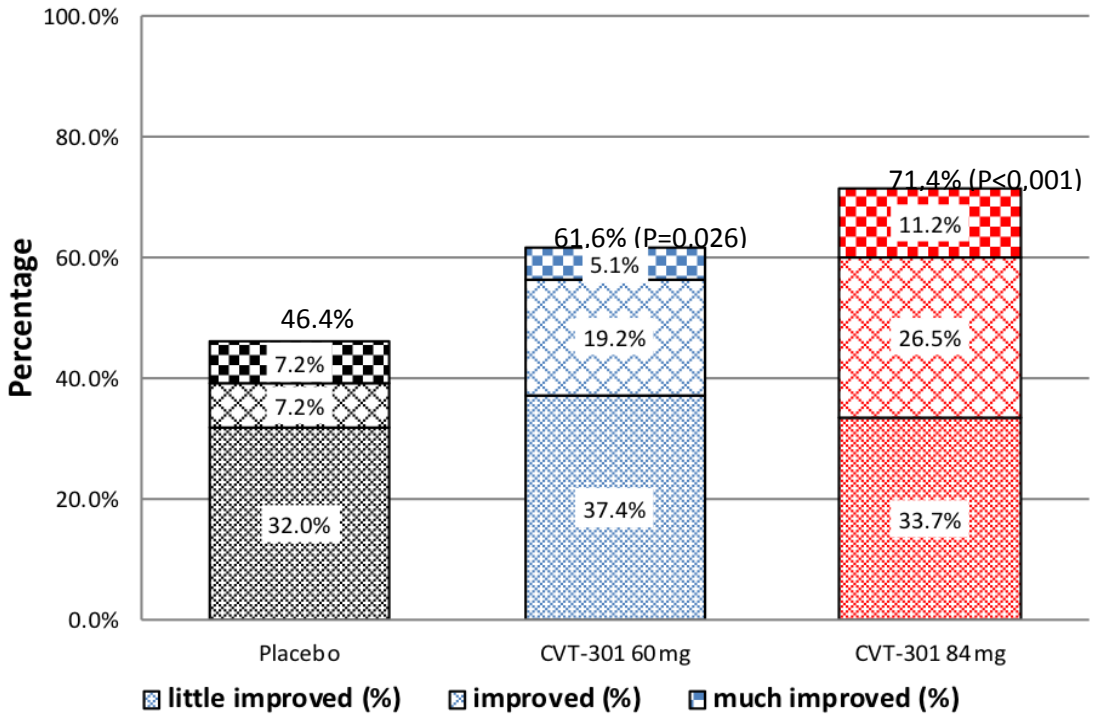
Abbreviations: ITT = intent-to-treat; UPDRS = Unified Parkinson's Disease Rating Scale.

The daily OFF time at week 12 was 4.92, 4.92 and 5.59 hours for CVT-301 60mg, CVT-301 84mg and placebo, respectively. The difference from placebo in daily OFF was -0.10 hr (95% CI -0.66; 0.46, p=0.722) for the CVT-301 60mg and -0.01hr (95% CI -0.55; 0.56, p=0.978) for the 84mg treatment group.

The responders ON, was 55.6% for the 60mg and 57.7% for the 84mg dose group and 36.1% for placebo. This difference from placebo was statistically significant for the 84mg dose (p=0.006), but not for the 60mg dose, due to the hierarchical analysis (p=0.003).

The PGI-C score for the proportion of subjects that perceived any improvement, i.e. including little improved, improved and much improved, is presented in Figure 9, below. The proportion of any improvement was 71.4 % for CVT-301 84 mg, 61.6% for CVT-301 60 mg and 46.4% for the placebo arm. Both CVT-301 treatment arms were significantly different from placebo (p= 0.026 for 60mg dose and p<0.001 for the 84mg dose).

Figure 9: Proportion of Subjects Improved on the PGI-C Rating Scale at Week 12: CVT-301 84 mg, CVT-301 60mg and Placebo (ITT Population) [1]



Abbreviations: ITT = intent-to-treat; PGI-C = Patient Global Impression of Change.

[1] by CHMP assessor

During the course of the trial subjects administered an average approximately 2 doses per day. The proportion of days with >5 doses, 5 doses, 4 doses, 3 doses, 2 doses, 1 dose and 0 doses per day were 0.17%, 1.87%, 7.57%, 16.86%, 24.44%, 29.12%, 19.98%, respectively. This was not different for placebo and the two treatment arms, i.e. CVT-301 60 mg and CVT-301 84 mg.

- ***Ancillary analysis***

Sensitivity Analysis for UPDRS-III

The results from each of the model based sensitivity analyses of the primary efficacy endpoint were very similar to that from the primary analysis (i.e., statistically significant results for MMRM ANCOVA model based on overall ITT population), with the exception of the analysis with the addition of region by treatment interaction in the model, which resulted in p-values that were not statistically significant (p=0.094 for CVT-301 84 mg).

Table 10: Pre-specified Sensitivity Analysis of the Primary Endpoint

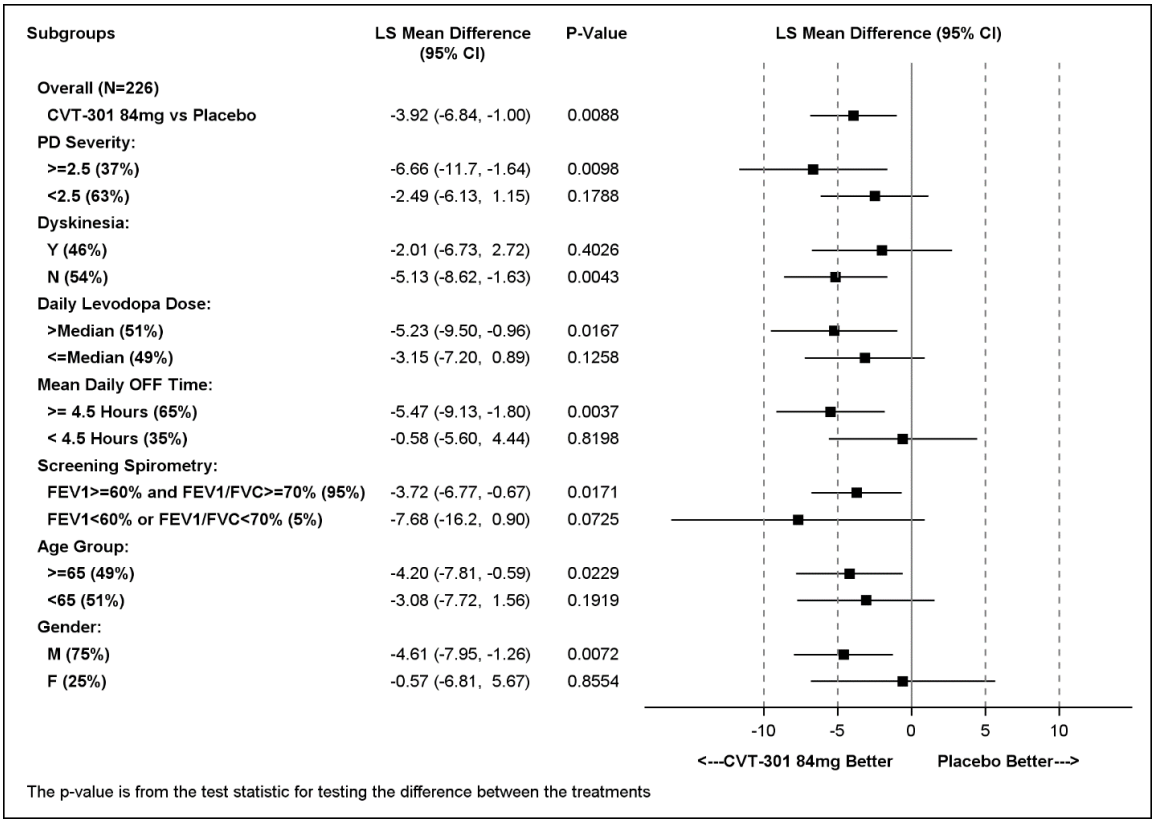
	LS Mean Difference (p-value)	
Sensitivity Analysis	CVT-301 DL1 vs Placebo	CVT-301 DL2 vs Placebo
Completer Population	-3.14 (p = 0.039)	-4.04 (p = 0.009)
Multiple Imputation (Missing at-Random Assumption)	-3.23 (p = 0.029)	-3.99 (p = 0.007)
Multiple Imputation (Missing Not-at-Random Assumption)	-3.14 (p = 0.033)	-3.84 (p = 0.009)
Effect of Region	-3.35 (p = 0.014)	-3.08 (p = 0.025)
Effect of Region with Interaction between Region and Treatment Group	-3.41 (p = 0.042)	-2.61 (p = 0.094)
Mean at TV2, TV3, and TV4	-3.70 (p = 0.004)	-4.51 (p < 0.001)

Abbreviations: CVT-301 DL1 = 60 mg levodopa; CVT-301 DL2 = 84 mg levodopa; levodopa=levodopa; LS = least square; TV = Treatment Visit; vs = versus.

Subgroup Analysis for UPDRS-III

The improvement of UPDRS-III score 30 min post dose at week 12 were comparable across, age, gender, PD severity, (Hoehn & Yahr stage), dyskinesia, Daily Levodopa dose, mean daily OFF time and screening spirometry. A notable trend of a slight better improvement was generally observed in more severe PD population characteristics.
In terms of PD severity, PD patients apparently benefitted from CVT-301 84 mg as an adjunctive treatment irrespective of baseline PD severity (defined by Hoehn & Yahr Scale), with the treatment benefit as per UPDRS-III score being more pronounced in patients with more severe baseline PD (Figure 10).

Figure 10: Forest Plot of Change from Predose in UPDRS-III Score at 30 Minutes Postdose at Week 12 by Subgroups CVT-301 84 mg versus placebo (Study CVT-301-004 ITT Population)



The p-value is from the test statistic for testing the difference between the treatments

The applicant performed a comparative analysis of the efficacy observed in the North America study centres compared to the EU study centres. The baseline values where different between the two groups, however, the effect sizes were comparable for all outcomes between both regions.

2.5.2.2. Study CVT-301-003

This study was a Phase 2b randomized, double-blind, placebo-controlled, multicenter (North America and Europe) study of inhaled CVT-301 or placebo for the treatment of up to 3 OFF episodes per day in PD subjects experiencing motor fluctuations. Patients were randomized in a 1:1 ratio to receive either placebo or CVT-301.

The study had a screening period (7-35 days) a double bind treatment period (2 weeks at 60mg) and followed by a 2 weeks 84mg treatment.

Methods

- ***Study Participants***

Inclusion and exclusion criteria were similar to the population in study CVT-301-004.

The main inclusion criteria were PD diagnoses , modified Hoehn & Yahr stage 1-3, OFF ≥ 2hours daily, recognise "wearing off" symptoms, not smoking during the entire clinic visit days, have a ≥ 25% difference between UPDRS-III scores recorded in their ON and OFF states at screening and must have been able to perform a spirometry manoeuvre in the ON and OFF states and must have had a screening FEV1 ≥ 50% of predicted, and an FEV1/FVC ratio > 60% in the ON state at screening.

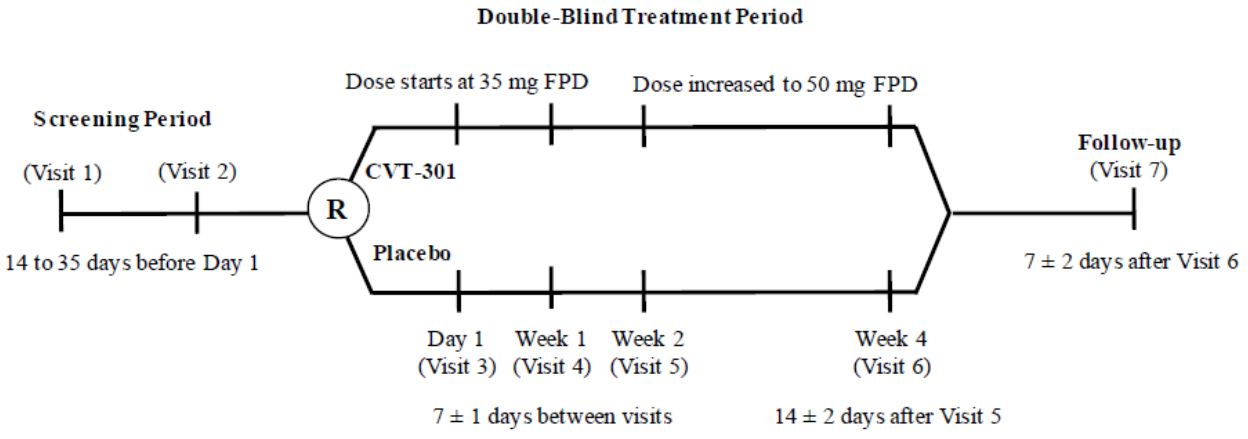
Exclusion criteria were: severe dyskinesia, previous surgery for PD (or planned during study period), psychotic symptoms, COPD, asthma or other chronic respiratory disease, contraindication to the use of levodopa, were diagnosed with caffeine/nicotine related disorder (DSM-IV), had been treated with investigational drugs within the last 4 weeks.

- ***Treatment***

The treatment period included 4 separate in-clinic visits over a 4-week period. The first dose of blinded study drug at 60mg was given in the clinic at week 1 (i.e., 2 capsule inhalations of either CVT-301 or placebo). The first dose of blinded study drug at 84 mg was given in the clinic at 3 weeks (i.e., 3 capsule inhalations of either CVT-301 or placebo). For the duration of the study, each subject's background PD medication regimen was to remain unchanged.

The study design is depicted schematically in Figure 11.

Figure 11: Study CVT-301-003 Design Schematic



Abbreviations: FPD = fine particle dose; R = randomization.

- ***Outcomes/endpoints***

The primary endpoint was the change in UPDRS-III motor score at 10-60 minutes post-dose at week 4 assessed in a similar clinical setting as study CVT-301-004.

Key secondary endpoints were examiner rated time to ON, responder ON, PGI-C, daily OFF and ON time assessed after 2 weeks use of CVT-301 84 mg and 2 weeks use of CVT-301 60 mg.

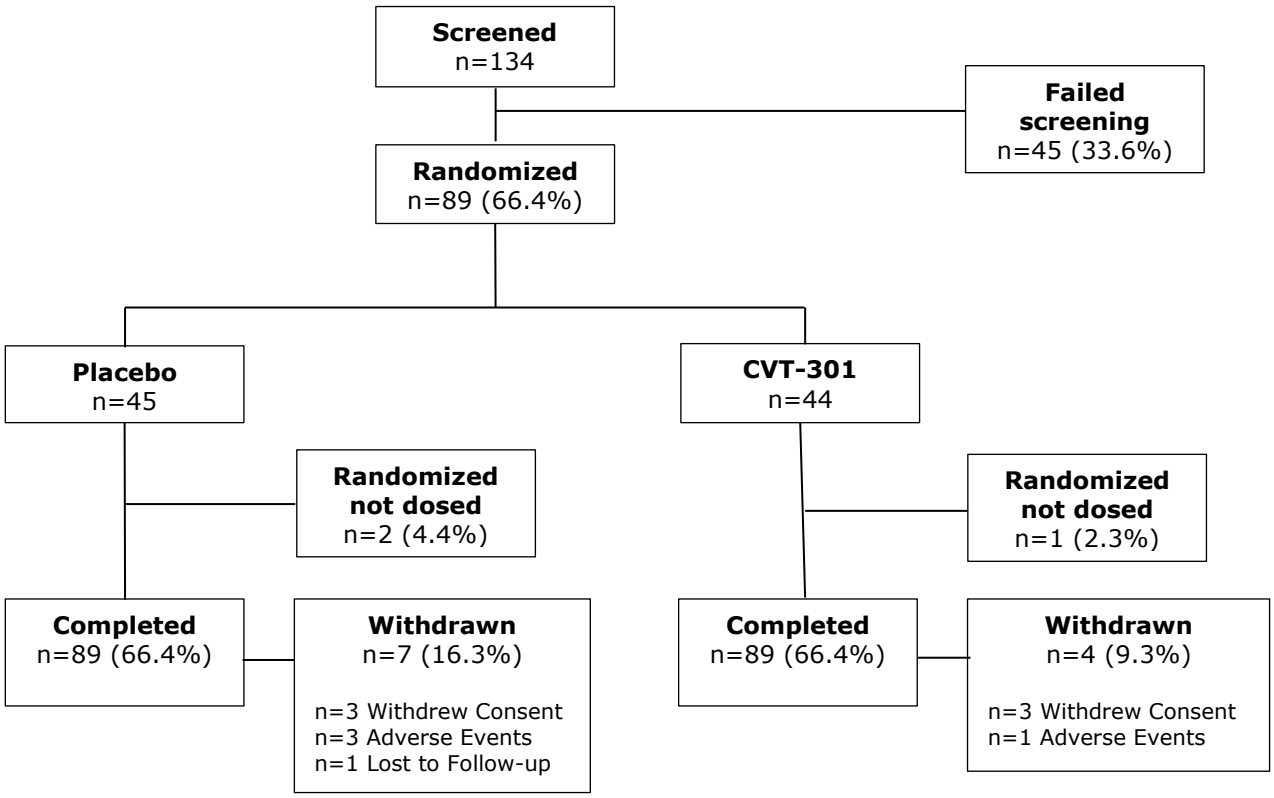
- ***Statistical methods***

The primary endpoint was the mean change from predose in average UPDRS-III score averaged over 10, 20, 30 and 60 minutes following treatment of an OFF episode at Visit 6 (i.e., Week 4 of the treatment period). The primary endpoint was analysed using a MMRM. Missing data were implicitly handled by the MMRM analysis with the underlying assumption that the missing data were missing at random.

Results

The disposition of subjects is shown in Figure 12. Of the 45 screen failures, 15 (11% of those screened) were due to subjects either not being able to perform spirometry or not meeting spirometry eligibility criteria. Four screen failure subjects were unable to perform the spirometry manoeuvre; 11 subjects were excluded due to failure to achieve a FEV1 or FEV1/FVC ratio value that met eligibility criteria at screening. There were 115 protocol deviations overall. Of those, 36 were major protocol deviations and the majority were deemed to have no impact on efficacy assessments.

Figure 12: Participants flow



[1] By CHMP assessor

Table 11 presents a summary of demographic and baseline characteristics for the ITT population. Baseline demographics and outcomes measured were comparable between treatment arms and in line with the findings reported in Study CVT-301-004. The mean age for the overall ITT population was 62.4 years, and they were mostly white (96.5%) and non-Hispanic (94.2%). Approximately 66% of the overall study population was male, and slight gender imbalances existed in the CVT-301 group (25 [58.1%] male) and in the placebo group (32 [74.4%] male). Most (74.4%) of the study population was from the United States; 25.6% were from Europe. Most subjects (67.4%) reported that they had never smoked. Smoking history and mean MMSE scores at screening were generally similar between treatment groups.

Table 11: Baseline characteristics (ITT population)

Characteristics	**Statistic**	**Placebo**	**CVT-301**	**Overall**
	n	43	43	86
Age	Mean (SD)	62.7 (9.08)	62.0 (8.26)	62.4 (8.68)
	Median	63.0	62.0	62.5
	Min, Max	43, 79	37, 77	37, 79
Modified Hoehn & Yahr stage				
Stage 1.5:	n (%)	2 (4.7)	1 (2.3)	3 (3.5)
Stage 2	n (%)	24 (55.8)	26 (60.5)	50 (58.1)
Stage 2.5	n (%)	11 (25.6)	9 (20.9)	20 (23.3)
Stage 3	n (%)	6 (14.0)	7 (16.3)	13 (15.1)
Time since diagnosis of PD (months)	Mean (SD)	117.2 (48)	108 (46)	112.7 (47)
	Median	111	99	105
	Min, Max	41, 255	38, 254	38, 255
Duration of levodopa treatment (months)	Mean (SD)	95.1 (47.7)	91.5 (45.6)	93.3 (46.4)
	Median	87	85	86
	Min, Max	15, 243	24, 254	15, 254
duration since onset of fluctuation (wearing off) periods (months)	Mean (SD)	46.3 (39.7)	56.0 (46.6)	51.1 (43.3)
	Median	30.0	48.0	40.0
	Min, Max	0, 150	1, 254	0, 254
average daily Levodopa dose (mg)	Mean (SD)	852.91 (315.2)	686.63 (276.3)	769.77 (306.3)
	Median	850.0	687.5	750.0
	Min, Max	400, 1700	250, 1800	250, 1800
Standard Levodopa dose or schedule changed During Screening				
No for All Days	n (%)	20 (46.5	17 (39.5)	37 (43.0)
Yes for All Days	n (%)	23 (53.5)	26 (60.5)	49 (57.0)
Moved up Time for Any Day	n (%)	17 (39.5)	21 (48.8)	38 (44.2)
Took Extra Dose for Any Day	n (%)	10 (23.3)	11 (25.6)	21 (24.4)
Screening PD diary average daily OFF time (hours)	Mean (SD)	5.79 (1.75)	5.71 (2.22)	5.75 (1.99)
	Median	5.76	5.52	5.60
	Min, Max	1.9, 9.4	2.2, 11.4	1.9, 11.4
PD Diary Mean Daily OFF time during screening				

Characteristics	Statistic	Placebo	CVT-301	Overall
<4.5 hours	n (%)	11 (25.6)	16 (37.2)	27 (31.40
≥ 4.5 hours	n (%)	32 (74.4)	27 (62.8)	59 (68.6)
screening UPDRS-III total score (ON state)	Mean (SD)	18.9 (9.76)	16.2 (8.08)	17.5 (9.01)
	Median	18.0	14.0	16.0
	Min, Max	5, 53	5, 44	5, 53
screening UPDRS-III total score (OFF state)	Mean (SD)	36.2 (12.07)	19.2 (8.61)	18.3 (8.10)
	Median	36	33	34,5
	Min, Max	12, 71	13, 62	12, 71
Dyskinesia				
Dyskinetic before visit 3	n (%)	24 (55.8)	26 (60.5)	50 (58.1)
Nondyskinetic before visit 3	n (%)	19 (44.2)	17 (39.5)	36 (41.9)
MMSE total score	Mean (SD)	29.2 (1.1)	28.9 (1.4)	29.1 (1.3)
	Median	30.0	30.0	30.0
	Min, Max	27, 30	25, 30	25, 30
Smoking History				
Never	n (%)	31 (72.1)	27 (62.8)	58 (67.4)
Former	n (%)	11 (25.6)	14 (32.6)	25 (29.1)
Current	n (%)	1 (2.3)	2 (4.7)	3 (3.5)

Abbreviations: ITT = intent-to-treat; Max = maximum; min = minimum; PD = Parkinson's disease; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.
Note: Baseline average daily levodopa dose calculated from 'Baseline PD Treatment'.
Note: Subjects 1004-007 and 4003-005, although not appearing in the database due to site error, were reviewed and found to be eligible for the study based on UPDRS score at screening, and were included in the analysis.
a Percentage was calculated as OFF-ON/OFF * 100%.
b Minimum UPDRS ON to OFF difference was 25% for all enrolled subjects, as per protocol. Subjects had the opportunity to repeat UPDRS assessments if this difference was not achieved in the first screening visit; however, some of the incorrect UPDRS screening values were included in the database accidentally. The error was not noticed until after database lock and was therefore unable to be changed. Documentation of all correct UPDRS screening values that show 25% or greater difference are available for all subjects.

- ***Outcome and estimation***

Efficacy data were analysed by treatment group and study visit. As depicted schematically in Figure 11, the double-blind treatment period was 4 weeks in duration, included 4 separate in-clinic visits (Visits 3, 4, 5 and 6) and evaluated 2 dose levels of CVT-301 (60 mg and 84 mg). For clarity, study visits are used as follows to indicate the time point of interest:

Visit 4: Week 1 of the double-blind treatment period; following 1 week of CVT-301 60 mg exposure;

Visit 5: Week 2 of the double-blind treatment period; following the first administration of CVT-301 84 mg;

Visit 6: Week 4 of the double-blind treatment period; following 2 weeks of CVT-301 84 mg exposure.

Figure 13 presents the primary efficacy analysis of UPDRS-III score mean change from predose at 10 to 60 minutes postdose at Visit 6 (CVT-301 50 mg levodopa FPD vs placebo) for the ITT population. The difference in LS mean (SE) between the CVT-301 response (-10.02 [1.5]) and the placebo response (-3.07 [1.54]) was statistically significant ($p < 0.001$).

Figure 13 Primary Efficacy Analysis of UPDRS-III score mean change from predose at 10-60 minutes post dose at visit 6 (ITT population)

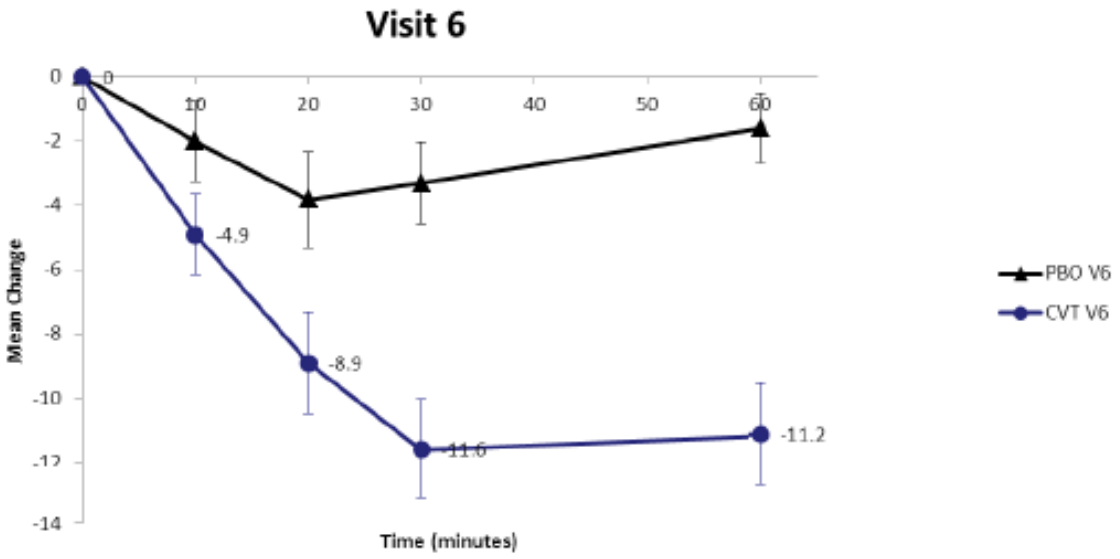


Figure 11–5. Mean (SE) Change of UPDRS Part 3 Score From Predose to Postdose at Visit 6
Abbreviations: CVT = CVT-301; PBO = placebo; V6 = Visit 6.
Source: Table 14.2.2.4.

The difference in UPDRS-III score from placebo was -6.95 (95% CI -10.31, -3.60) and was statistically significant ($p < 0.001$). A similar change from pre-dose values was observed also for CVT-301 60mg-treated subjects at week 2; i.e. the absolute change from pre-dose was -9.90 for 60 mg and -5.30 for placebo. The difference from placebo was -4.6 (95% CI -7.9,-1.3) and significant (p=0.007).

A dose-ordered reduction from pre-treatment values in daily OFF time was observed (mean [SE]) for CVT-301 60mg at Week 2 (-1.1 [0.4] hr) and CVT-301 84mg at Week 4 (-1.6 [0.4] hr). The difference from placebo was statistically significant only for CVT-301 84mg at Week 4 (-0.9hr (95% CI -1.73, -0.02; p=0.045)).

Subjects recorded using CVT-301 at home an average of 2 times per day. The mean proportion of days with 0 dose, 1 dose, 2 dose and 3 dose per day was 13%, 25%, 31% and 28% in the CVT-301 treatment group, respectively. The dose frequency was slightly higher in the placebo group where the mean proportion of days with 0, 1, 2 and 3 doses administered was 10%, 26%, 26% and 36%, respectively.

In study CVT-301-003 where subjects switched from the 60 mg dose to a 84 mg dose, the results were consistent with the findings observed in the fixed dose 12 week study CVT-301-004. The observed improvement in UPDRS-III score from baseline increased when switching from the 60 mg to the 84 mg.

2.5.2.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main clinical studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12: Summary of efficacy for trial CVT-301-004

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Investigating the Efficacy and Safety of CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients with Motor Response Fluctuations (OFF Phenomena)			
Study identifier	**CVT-301-004**		
Design	Phase 3 randomized, double-blind, placebo-controlled, 12-week, multicenter (North America and Europe)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks not applicable Up to 12 months (long term extension study CVT-301-004E)
Hypothesis	Superiority to placebo in treatment of motor response fluctuations (OFF phenomena) in PD patients		
Treatments groups	Placebo		112 randomized (ITT), 97 (86,6%) completed study
	CVT-301 60mg[a]		113 randomized (ITT), 96 (85%) completed study
	CVT-301 84mg[a]		114 randomized (ITT), 97 (85.1%) completed study
Endpoints and definitions	Primary endpoint	**UPDRS-III[1]**	change in the UPDRS-III score from (same day) predose to 30 minutes postdose following treatment of patients experiencing an OFF period at the study clinic at the Week 12
	Key-Secondary endpoints	**ON Responders**	proportion of subjects where the OFF episode was relieved within 60 minutes post dose and stayed ON up to 60 minutes post dose
		UPDRS-III[2]	change in the UPDRS-III score from (same day) predose to 20 minutes postdose following treatment of subjects experiencing an OFF period at the study clinic
		PGI-C	proportion of subjects who improved based on the PGI-C rating scale (defined as "much improved," "improved," or "a little improved")
		UPDRS-III[3]	change in the UPDRS-III score from (same day) predose to 10 minutes postdose following treatment of subjects experiencing an OFF period at the study clinic
		Total daily OFF-time	change from baseline in total daily OFF Time assessed by the patient and recorded in the PD Diary
Database lock	06 December 2016		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT population Week 12			
Descriptive statistics and estimate variability	Treatment group	**Placebo**	**CVT-301 60mg[a]**	**CVT-301 84mg[q]**
	Number of subject	95	97	94
	UPDRS-III [1] (LS mean (SE))	-5.91	-8.98	-9.83
	ON Responders % (n)	36.1% (35)	55.6% (55)	57.7 (56)

	UPDRS-III [2] (LS mean (SE))	-6.49 (1.35)	-8.47 (1.35)	-9.04 (1.36)
	PGI-C Any improvement % (n) Much improved Improved Little improved	46.4% (45) 7.2% (7) 7.2% (7) 32.0% (31)	61.6% (61) 5.1% (5) 19.2% (19) 37.4% (37)	71.4% (70) 11.2% (11) 26.5% (26) 33.7% (33)
	UPDRS-III [3] (LS mean (SE))	-4.18 (1.04)	-5.16 (1.096)	-6.45 (1.107)
	Change in daily **OFF time**[4] (LS mean (SE))	-0.48 (0.28)	-0.58 (0.28)	-0.47 (0.28)

Effect estimate per comparison	Primary endpoint (**UPDRS-III**) [1]	**CV-301 84mg[a] vs Placebo**	**CV-301 60mg[a] vs Placebo**
	δ from placebo	-3.92	-3.07
	95% CI	-6.84; -1.00	-5.99; 0.16
	p-value	0.009	0.039*
	Secondary endpoint **ON Responders**	**CV-301 84mg[a] vs Placebo**	**CV-301 60mg[a] vs Placebo**
	δ from placebo	21.6%	19.5%
	P-value	0.003	0.006*
	Secondary endpoint (**UPDRS-III** [2])	**CV-301 84mg[a] vs Placebo**	**CV-301 60mg[a] vs Placebo**
	δ from placebo	-2.55	-1.98
	95% CI	-5.22, 0.13	-4.65
	p-value	0.062	0.70
	Secondary endpoint (PGI-C)	**CV-301 84mg[a] vs Placebo**	**CV-301 60mg[a] vs Placebo**
	δ from placebo	25%	15.2%
	P-value	<0.001*	0.026*
	Secondary endpoint (**UPDRS-III** [3])	**CV-301 84mg[a] vs Placebo**	**CV-301 60mg[a] vs Placebo**
	δ from placebo	-2.26	-0.97
	95% CI	-4.48,-0.04	-3.19; 1.24
	p-value	0.046*	0.387
	Secondary endpoint (Change in daily **OFF time**[4])	**CV-301 84mg[a] vs Placebo**	**CV-301 60mg[a] vs Placebo**
	δ from placebo	-0.01	-0.10

	95% CI	-0.55; 0.56	-0.66; 0.46
	p-value	0.975	0.722
Notes	[a] Dose corresponds to 2 capsules. Not emitted dose or fine drug particle dose [1] UPDRS-III assessed at 30 minutes post dose [2]UPDRS-III score assessed at 20minutes post dose [3]UPDRS-III score assessed at 10 minutes post dose [4]Change in total daily OFF time from baseline *Values are not considered statistically significant due to the chosen hierarchal analysis. The hierarchical testing was performed in the order of the presented endpoint above, where first the endpoints in the 84mg dose were assessed The average daily dose administered was 2x a day. This was similar for CVT-301 60mg, CVT-301 84mg and placebo. Patients were allowed to administered up to 5 times a day.		
Analysis description	The UPDRS-III score and responders were assessed in an artificial setting, i.e. in the clinical after forced OFF, which does not reflect real life setting use. Duration of ON was not assessed, this assessment was truncated at 60 minutes		

Table 13: Summary of efficacy for trial CVT-301-003

Title: A Phase 2b, Randomized, Double-blind, Placebo-controlled Study Investigating the Efficacy and Safety of Inhaled CVT-301 (Levodopa Inhalation Powder) in Parkinson's Disease Patients with Motor Response Fluctuations (OFF Phenomena)			
Study identifier	**CVT-301-003**		
Design	Randomized, double-blind, placebo-controlled, multicentre		
	Duration of main phase: Duration of screening phase: Duration of follow-up phase:		4 weeks treatment period, with clinic visits 1 week apart 14-35 days before start of treatment period 7±2 days after treatment or early withdrawal
Hypothesis	Superiority of CVT-301-DL 2 to placebo		
Treatments groups	Placebo		N=34 (ITT)
	CVT-301		N=43 (ITT)
Endpoints and definitions	Primary endpoint	Changes in UPDRS-III score	The mean change and percent change from pre-dose in the average UPDRS-III scores obtained over 10-60 minutes post-dose at week 4
	Key-Secondary endpoints		The mean change and percent change from pre-dose in the average UPDRS-III scores obtained over 10-60 minutes post-dose at week 2 (60mg) and week 4 (84mg)
			Proportion of subject achieving ON, examiner rated in office at visit 6
			Time to resolution of OFF state to ON state at week 4
			PD Diary mean daily OFF time
Database lock	21 January 2014		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	ITT Week 4, Initial 2 weeks of study was 60mg and last 2 weeks of the treatment period 84mg were used in the treatment arm		
Descriptive statistics and estimate variability	Treatment group	Placebo	**CVT-301**
	Number of subject	40	42
	UPDRS-III score mean change from predose at 10-60min at week 4[a] (LS mean (SE))	-3.07 (1.54)	-10.02 (1.50)
	UPDRS-III score mean change from predose at 10-60min at week 2[b] (LS mean (SE))	-5.30 (1.53)	-9.90 (1.49)
	UPDRS-III score mean change from predose at 10-60min at week 3[a] (LS mean (SE))	-3.53 (1.50)	-10.15 (1.46)
	Proportion achieving ON % (n)	36.1 % (13)	78.7 (29)
	Time to resolution of OFF state (min)[c] 25% Quantile 50% Quantile 75% Quantile	 13.5 - -	 10.0 21.0 51.0
	OFF time (h) [c] (LS mean (SE))	-0.8 (0.4)	-1.6(0.4)
Effect estimate per comparison	Primary endpoint: UPDRS-III score mean change from predose at 10-60min at week 4[a]	Comparison groups	**Placebo vs CVT-301**
		δ from placebo	-6.95
		95% CI (LS mean diff.)	-10.31; -3.60
		p-value (LS mean diff.)	<0.001
	Key secondary endpoint: UPDRS-III score mean change from predose at 10-60min at week 2[b]	δ from placebo	-4.60
		95% CI (LS mean diff.)	-7.90; -1.30
		p-value (LS mean diff.)	0.007
	Key secondary endpoint: UPDRS-III score mean change from predose at 10-60min at week 3[a]	δ from placebo	-6.63
		95% CI (LS mean diff.)	-9.84; -3.41
		p-value (LS mean diff.)	<0.001
	Key secondary endpoint: Time to resolution of OFF state[a]	95% CI (25% quantile)	8.0; 18.0
		95% CI (50% quantile)	15.0; 30.0
		95% CI (75% quantile)	25.0 ; 61.0
		Log rank p-value	0.002
	Key secondary endpoint: OFF time (h) [a]	δ from placebo	-0.9
		95% CI (LS mean diff.)	-1.73;-0.02
		p-value (LS mean diff.)	0.045

Notes	[a] dose level was 84mg at week 4. Patients were 2 weeks on 60mg dose followed by 2 weeks on 84mg [b] dose level was 60mg [c] measured at week 4 at dose level 84mg Subjects administered approximately 2 dosses a day during the full treatment period of 4 weeks out of a maximum administration of 3 doses Doses are total of 2 capsules The mean proportion of 3 doses administered a day was higher for the placebo group compared to the treatment group
Analysis description	The outcomes were assessed in an artificial setting and could therefore be higher than the true value.

2.5.2.4. Clinical studies in special populations

Elderly

In line with PD epidemiology, the mean age of PD patients in the Phase 3 studies was 63.3 years (range; 37 to 82 years) and 49% of the subjects were ≥ 65 years old (Studies CVT-301-004, CVT-301-004E, CVT-301-005). These studies indicate that no dose adjustments of Inbrija is required for elderly patients, and therefore no specifically designed studies of age on pharmacokinetics of LD were conducted with Inbrija, and this is acceptable. As there is only limited data available in very elderly patients (≥75 years) Inbrija's use in this population will be monitored in the PSURs.

Smokers and Asthma

Due to the nature of the administration of LD, i.e. inhalation, the applicant performed separate studies to assess the pharmacokinetics in smokers (CVT-301-007) and asthmatic subjects (CVT-301-008).

A clinical study (Study CVT-301-007) was performed with Inbrija 66 mg (2 x 33 mg capsules) administered to 56 healthy subjects (31 non-smokers and 25 smokers). After administration of Inbrija the C_{max} and $AUC_{0\text{-}24\ h}$ for smokers was 11% to 12% higher for smokers than for non-smokers. No dose adjustment is required based on smoking status.

Study CVT-301-008 was a placebo-controlled, randomized, double-blind, crossover study to evaluate the safety and pharmacokinetics of multiple administrations of CVT-301 84 mg LD doses in 24 adult subjects with asthma. Subjects received a total of 3 doses of CVT-301 or placebo per dosing period at intervals of approximately 4 hours. There was no active drug comparator arm in this study; however, the mean C_{max} and $AUC_{0\text{-}4\ h}$ were similar to the results of the bridging pharmacokinetic study performed in healthy subjects. Overall, the pharmacokinetics of LD after CVT-301 was similar between asthmatic subjects and subjects in other CVT-301 pharmacokinetic studies.

2.5.2.5. Analysis performed across trials (pooled analyses AND meta-analysis)

A pooled analysis was conducted for study CVT-301-003 and study CVT-301-004 which shared several similarities that facilitated pooling of the data. The improvement in UPDRS-III score, responders ON and PGI-C was analysed at week 4. Statistically significant difference between CVT-301 84 mg and placebo were observed 10 minutes post-dose ($p = 0.014$), and through 60 minutes post-dose ($p < 0.001$). A statistically significant greater proportion of subjects in the CVT-301 84mg group (64.2%) were considered responders compared with the placebo group (35.3%) at Week 4 ($p < 0.001$). This was also reflected by the PGI-C score which showed an improvement perceived in a significant greater proportion

of subjects in CVT-301 84mg group (64.8%) compared to the placebo group (47.6%) at week 4 (p=0.008). The change from baseline in daily OFF time after 4 weeks was -0.79 hours for CVT-301 and -0.34hrs for placebo (p=0.051).

Post-hoc subgroup analysis in more severe PD patients defined as patients who used CVT-301 ≥ 3 times in study CVT-301-004, show numerically greater reduction in OFF time for CVT-301 compared to placebo. At 4 weeks, patients taking ≥ 3 doses, the change from baseline in total daily OFF time was -0.71hrs in CVT-301 and -0.20hrs for placebo. At 12 weeks the reduction in daily OFF time was -0.50hrs in the placebo group and -0.66hrs in the CVT-301 group.

Similar results were obtained for subgroup analysis of study CVT-301-004 where the severity of PD patients was defined as ≥ 3 OFF episodes at baseline. At 4 weeks, a reduction of daily OFF time of -0.36hrs was observed for the CVT-301 group and an increase of 0.099hrs for the placebo group. At 12 weeks a reduction of total daily OFF-time was observed for both groups, however, the decrease was numerically greater for the CVT-301 treatment group (-0.25hrs) compared to the placebo (-0.14hrs).

2.5.2.6. Supportive studies

The supportive studies concerned the long-term extension study, CVT-301-004E, and the open-label randomized trial, CVT-301-005.

Study CVT-301-004E was primarily a rollover, long-term extension study to Study CVT-301-004. The study duration was up to 52 weeks. The placebo group was randomized to either CVT-301 60mg or CVT-301 84mg. In total 312 patients were dosed. Patients in both CVT-301 dose groups showed an improvement in proportion ON responders (between 63% and 66% for CVT-301 84 mg), PGI-C (approximately 60-92% for both doses) and a reduction in daily OFF time (approximately -0.3hr up to -0.84hr for both doses).

Study CVT-301-005 was a 12-month, open-label, randomized, multicenter (North America, Europe and Israel) study investigating the safety and effects of CVT-301 84 mg for the treatment of up to 5 OFF periods per day in PD patients. Patients were randomized in a 2:1 ratio to the CVT-301 84 mg or the observational cohort, where they received the standard of care treatment. The duration was 12 months. At study completion, 271 patients were randomized to the CVT-301 treatment group and dosed, and 127 patients were randomized to the observational cohort. Patients receiving CVT-301 84 mg demonstrated improvement on the UPDRS-III change from predose at 30 minutes postdose, proportions of patients achieving an ON state within 60 minutes and maintaining the ON at 60 minutes, and the PGI-C, which were maintained throughout the 52-week treatment period.

Exploratory efficacy endpoints were assessed in long term safety studies **CVT-301-004E and CVT-301-005**. These showed consistent results over a 52-week treatment duration. A proportion of responder ON (worst case input) of 65% and 85% was reported for study CVT-301-004E and CVT-301-005, respectively. This was reflected by the PGI-C proportion improvers of 61% in CVT-301-004E and 77% CVT-301-005. The reduction of OFF time was -0.84hr [95%CI -1.38, -0.30] for study 004 and -1.36hr [95%CI -1.80, -0.92] for study 005.

2.5.3. Discussion on clinical efficacy

In support of the claimed indication, the applicant submitted two phase 3 studies, CVT-301-004 and CVT-301-003 which are both considered pivotal. Studies CVT-301-002, CVT-301-004E and study CVT-301-005 are considered supportive.
The pivotal and supportive studies were designed in agreement with the Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease (EMA/CHMP.330418/2012 rev.2).

Study CVT-301-004 was a 12 weeks, randomized, multicentre, double-blind, placebo-controlled study, evaluating the efficacy of Inbrija in PD patients with OFF periods. Subjects were 1:1:1 randomized to placebo, CVT-301 60mg and CVT-301 84 mg. The selected population is acceptable. Patients included in the trial had to be able to use the device and had the ability to recognise ON and OFF. This is reflected in section 4.2 of the SmPC.
The primary endpoint was a change in UPDRS-III at 30 minutes post-dose compared to pre-dose OFF motor. The UPDRS part III is designed to assess the severity of the cardinal motor findings (e.g. tremor, rigidity, bradykinesia, postural instability) in patients with Parkinson's disease. Main secondary endpoints were the responder ON, PGI-C and total daily OFF time at week 12. The sample size calculation, randomization and blinding are considered acceptable.
This study confirmed the clinical efficacy of Inbrija 84 mg in the treatment of symptoms of OFF periods experienced by patients with PD. Inbrija 84 mg demonstrated statistically superior reduction of the UPDRS-III score at 30 minutes postdose in a clinical setting. The clinical relevance of this effect is supported by the statistically superior results in Responder ON within 60 minutes at Week 12, as well as the self-reported improvements on the PGI-C rating scale at Week 12 compared with placebo. CVT-301 60 mg treatment showed nominal p-values less than 0.05 for UPDRS-III at 30 minutes postdose, percent responder ON, and improvement in PGI-C. Both investigator-assessed efficacy endpoints (UPDRS-III and ON response within 60 minutes) and a patient-reported assessment (PGI-C) showed numerically better results for CVT-301 84 mg compared with CVT-301 60 mg. The consistent numerical trend suggests potentially better efficacy of CVT-301 84 mg compared to CVT-301 60 mg. With regard to change of PD Diary OFF time, in contrast to the clinical Phase 2b Study CVT-301-003, no significant difference versus placebo could be noted. This contrasts also to the outcomes of the completed long-term safety Study CVT-301-005 and to the interim outcomes of the safety extension Study CVT-301-004E, showing patient-assessed improvements in terms of OFF periods.

Study CVT-301-003 was a 4 week, randomized, multicentre, placebo-controlled study, assessing the efficacy of Inbrija in PD patients. Subjects were similar to the population in study CVT-301-004. The primary endpoint was the change in UPDRS-III motor score at 10-60 minutes post-dose at week 4 assessed in a similar clinical setting as study CVT-301-004. Key secondary endpoints were examiner rated time to ON, responder ON, PGI-C, daily OFF and ON time assessed after 2 weeks use of CVT-301 84 mg and 2 weeks use of CVT-301 60mg.
The statistical methods used in the studies were acceptable. Sensitivity analyses assuming missing not at random were requested for the primary endpoint in study CVT-301-003 and for the secondary endpoint daily OFF time. These analyses were presented and the results were not influenced by the choice of missing data handling.
In study CVT-301-003, where subjects switched from the 60 mg dose to a 84 mg dose, the results were consistent with the findings observed in the fixed dose 12 week study CVT-301-004. The observed improvement in UPDRS-III score from baseline increased when switching from the 60mg to the 84 mg dose.

A pooled analysis was conducted for study CVT-301-003 and study CVT-301-004. The improvement in UPDRS-III score, responders ON and PGI-C was analysed at week 4. Statistically significant difference between CVT-301 84 mg and placebo were observed 10 minutes post-dose ($p = 0.014$), and through

60 minutes post-dose ($p < 0.001$). A statistically significant greater proportion of subjects in the CVT-301 84 mg group (64.2%) were considered responders compared with the placebo group (35.3%) at Week 4 ($p < 0.001$). This was also reflected by the PGI-C score which showed an improvement perceived in a significant greater proportion of subjects in the Inbrija 84 mg group (64.8%) compared to the placebo group (47.6%) at week 4 ($p=0.008$).

Long-term safety studies with exploratory efficacy endpoints (Studies CVT-301-004E, CVT-301-005) showed consistent results over a 52-week treatment duration (UPDRS-III, responder ON within 60 minutes, PGI-C, reduction of OFF time [without troublesome dyskinesia]), demonstrating persistence of effects and supporting efficacy conclusions from Study CVT-301-004.

2.5.4. Conclusions on the clinical efficacy

Efficacy data were collected in PD subjects who experienced motor fluctuations (OFF periods) in the Phase 2a Study CVT-301-002, the Phase 2b Study CVT-301-003 and the three Phase 3 studies, Study CVT-301-004, Study CVT-301-004E and Study CVT-301-005. Study CVT-301-009, a Phase 1 safety study in PD subjects with early morning OFF symptoms, also contained some efficacy measures.

The available data showed an improvement of motor symptoms within 30 minutes when Inbrija is given on top of background oral LD/DC during an OFF period. This motor improvement is considered clinically relevant and beneficial, as it is also reflected by the PGI-C score in subjects in the treatment arms. The external validity of the results is accepted based on the demonstrated effects on: 1) Responders ON which is independently but subjectively assessed from UPDRS-III, 2) patient-reported clinical improvement, registered on PGI-C, and 3) the greater OFF time reduction >3 points on the UPDRS-III in more severe patients.

Overall, the clinical experience in this development program supports the clinical efficacy of Inbrija in the treatment of symptoms of OFF periods in PD patients with motor fluctuations.

2.6. Clinical safety

The safety profile of Inbrija was evaluated by describing the overall exposure to Inbrija, placebo, and observation on standard regimen: adverse events (AEs) including incidence, severity, and seriousness; acute and chronic pulmonary safety parameters; and laboratory parameters, vital signs and electrocardiograms (ECGs). Since Inbrija is delivered by the pulmonary route, pulmonary safety was specifically assessed by spirometry, a standard test of pulmonary function, and carbon monoxide diffusing capacity (DLco), a measure of gas exchange in the lung. Spirometry assessments followed the guideline specified by the Third National Health and Nutrition Examination Survey (NHANES III), while DLco was acquired in accordance with the American Thoracic Society criteria. Acute pulmonary safety was assessed by spirometry during the 60 minutes following the first dose of CVT-301, while chronic pulmonary safety was assessed by both spirometry and DLco at regular intervals for up to 15 months of exposure (subjects completing both Studies CVT-301-004 and CVT-301-004E).

Patient exposure

The overall exposure as of the most recent database snapshot date comprised a total of 1103 subjects enrolled in the Inbrija clinical development program of 11 clinical studies, including 951 PD patients. A total of 897 subjects received at least 1 dose of Inbrija across all studies, including 754 PD patients.

Table 14: Exposure to Study Treatment (Safety Population)

	POOL 1		POOL 2	POOL 3
	CVT-301 N=270	**Placebo N=155**	**CVT-301 N=583**	**CVT-301 N=705**
Exposure to study treatment, categorical,[a] DL1 (60 mg), n (%)				
N	156	0	153	237
< 3 months	58 (37.2)		24 (15.7)	66 (27.8)
≥ 3 months	98 (62.8)		129 (84.3)	171 (72.2)
≥ 6 months			119 (77.8)	122 (51.5)
≥ 9 months			107 (69.9)	111 (46.8)
≥ 12 months			81 (52.9)	85 (35.9)
Exposure to study treatment, categorical,[a] DL2 (84 mg), n (%)				
N	154		430	508
< 3 months	55 (35.3)		38 (8.8)	90 (17.6)
≥ 3 months	99 (63.5)		392 (91.2)	418 (82.0)
≥ 6 months			359 (83.5)	365 (71.6)
≥ 9 months			339 (78.8)	339 (66.5)
≥ 12 months			302 (70.2)	302 (70.2)

a.Cumulative number of subjects is presented. Categories are defined as follows: 3 months = 12 weeks ± 2 weeks, 6 months = 24 weeks ± 2 weeks, 9 months = 36 weeks ± 2 weeks and 12 months = 52 weeks ± 2 weeks.
b.n = number of days, % = percentage of all study days.
Note: POOL 1 includes studies CVT-301-003 and CVT-301-004. POOL 2 includes CVT-301 groups from studies CVT-301-004E and CVT-301-005. POOL 3 includes CVT-301 groups from all studies (CVT-301-003, CVT-301-004, CVT-301-004E and CVT-301-005). Pool 3 combines exposure from Pool 1 and Pool 2 for unique subjects and tallies the cumulative exposure. Therefore, the number of subjects exposed to CVT-301 for durations of ≥ 6 months is greater in Pool 3 than in Pool 2 due to the longer exposure for subjects who enrolled in multiple studies.
For Observational Cohort exposure is counted as time from start of study to end of study instead of not applicable treatment duration.
Abbreviation: SD = standard deviation.

Adverse events

Adverse events were analysed for the placebo controlled short term studies (Pool1), the long term studies (Pool 2) and the overall exposed population (Pool 3). An observational cohort was also included from a randomized trial, where subjects were randomized to either Inbrija treatment or SOC. Data was collected from the observational cohort for the full duration of the study, i.e. 12 months.

Adverse events reported at database snap shot date are presented by system organ class in Table 15**Error! Reference source not found.**.

Table 15: Treatment-emergent Adverse Events by System Organ Class (Safety Population)

System organ class	POOL 1		POOL 2	POOL 3	Observational cohort N=127 n (%)
	CVT-301 N=270 n (%)	Placebo N=155 n (%)	CVT-301 N=583 n (%)	CVT-301 N=705 n (%)	
Respiratory, thoracic and mediastinal disorders	60 (22.2)	10 (6.5)	129 (22.1)	179 (25.4)	3 (2.4)
Infections and infestations	36 (13.3)	10 (6.5)	131(22.5)	161 (22.8)	27 (21.3)
Nervous system disorders	29 (10.7)	20 (12.9)	110 (18.9)	131 (18.6)	20 (15.7)
Injury, poisoning and procedural complications	21 (7.8)	6 (3.9)	93 (16.0)	108 (15.3)	11 (8.7)
Musculoskeletal and connective tissue disorders	17 (6.3)	7 (4.5)	85 (14.6)	99 (14.0)	24 (18.9)
Gastrointestinal disorders	24 (8.9)	11 (7.1)	68 (11.7)	92 (13.0)	9 (7.1)
Psychiatric disorders	19 (7.0)	5 (3.2)	65 (11.1)	81 (11.5)	20 (15.7)
Investigations	19 (7.0)	3 (1.9)	43 (7.4)	59 (8.4)	8 (6.3)
General disorders and administration site conditions	13 (4.8)	6 (3.9)	38 (6.5)	51 (7.2)	7 (5.5)
Vascular disorders	6 (2.2)	3 (1.9)	33 (5.7)	38 (5.4)	8 (6.3)
Skin and subcutaneous tissue disorders	3 (1.1)	2 (1.3)	21 (3.6)	24 (3.4)	2 (1.6)
Cardiac disorders	4 (1.5)	1 (0.6)	19 (3.3)	23 (3.3)	4 (3.1)
Metabolism and nutrition disorders	4 (1.5)	3 (1.9)	19 (3.3)	23 (3.3)	2 (1.6)
Renal and urinary disorders	4 (1.5)	1 (0.6)	19 (3.3)	21 (3.0)	3 (2.4)
Eye disorders	3 (1.1)	3 (1.9)	15 (2.6)	18 (2.6)	3 (2.4)
Ear and labyrinth disorders	2 (0.7)	2 (1.3)	11 (1.9)	13 (1.8)	
Blood and lymphatic system disorders		1 (0.6)	12 (2.1)	12 (1.7)	3 (2.4)
Reproductive system and breast disorders	1 (0.4)	2 (1.3)	9 (1.5)	10 (1.4)	
Hepatobiliary disorders	1 (0.4)		7 (1.2)	8 (1.1)	1 (0.8)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			11 (1.9)	11 (1.6)	1 (0.8)
Endocrine disorders			6 (1.0)	6 (0.9)	
Congenital, familial and genetic disorders	1 (0.4)			1 (0.1)	
Immune system disorders			1 (0.2)	1 (0.1)	
Social circumstances					1 (0.8)
Product issues			1 (0.2)	1 (0.1)	

Note: POOL 1 includes Studies CVT-301-003 and CVT-301-004. POOL 2 includes CVT-301 groups from Studies CVT-301-004E and CVT-301-005. POOL 3 includes CVT-301 groups from all studies (CVT-301-003, CVT-301-004, CVT-301-004E and CVT-301-005).

AEs occurring during the first clinic visit day were assessed to look for *acute tolerability* and for AEs potentially suggesting abuse liability; Among all Inbrija-treated subjects (Pool 3), 116/705 (16.2%) had AEs on the clinic visit day (first dose day). Cough and throat irritation were reported for 62 (8.8%) and 17 (2.4%), respectively, of Inbrija-treated subjects. No placebo subjects or observational subjects experienced cough or throat irritation on the first dose day. Reports of orthostatic hypotension on the first dose day were rare, reported for 2 Inbrija-treated subjects and 1 observational subject.

In the placebo-controlled studies (Pool 1), the most commonly reported treatment-related AEs (i.e. those occurring at a frequency of 2% or greater) for subjects treated with Inbrija and placebo, respectively, were cough (37 [13.7%] versus 3 [1.9%]), dyskinesia (10 [3.7%] versus 1 [0.6%]), upper respiratory tract infection (9 [3.3%] versus 3 [1.9%]), throat irritation (9 [3.3%] versus 1 [0.6%]), and nausea (9 [3.3%] versus 3 [1.9%]). Dizziness was reported for fewer Inbrija-treated subjects compared with placebo subjects (2.2% versus 4.5 % respectively).

In the long-term studies, the most commonly reported AE for subjects treated with CVT-301 (Pool 2) was cough (80 [13.7%]), followed by fall (56 [9.6%]), upper respiratory tract infection (32 [5.5%]), dyskinesia (32 [5.5%]), nasopharyngitis (29 [5.0%]), back pain (22 [3.8%]), and throat irritation (20 [3.4%]) (Table 16). Common AEs reported more frequently for the CVT-301 group (Pool 2) than for observational cohort, respectively, included cough (80 [13.7%] versus 1 [0.8%]), fall (56 [9.6%] versus 7 [5.5%]), dyskinesia (32 [5.5%] versus 5 [3.9%]), upper respiratory tract infection (32 [5.5%] versus 3 [2.4%]), and throat irritation (20 [3.4%] versus 0%).

Among all Inbrija-treated subjects (Pool 3) who had TEAEs of cough, for most subjects the cough started within the first 30 days of treatment (83 [75.5%] of 110 subjects reporting cough). Most subjects with coughs reported coughs of mild severity (77 of 110 subjects [70%]) or moderate severity (25 of 110 subjects [22.7%])). Eight (7.3%) of the 110 subjects with cough reported a severe cough. Overall, 13 (1.8%) subjects withdrew from a study due to an AE of cough in Pool 3.

Serious adverse event and deaths

Serious adverse events

Among all Inbrija-treated subjects (Pool 3), 129 SAEs were reported for 83 (11.8%) subjects.

In the placebo-controlled studies (Pool 1), SAEs were reported for 8/270 (3.0%) Inbrija-treated patients and 4/155 (2.6%) placebo-treated patients. In the long-term studies (Pool 2), the frequency of SAEs was also similar between Inbrija-treated patients and the observational cohort (76/583 [13.0%] and 13/127 [10.2%], respectively.

Serious Treatment-emergent Adverse Events by System Organ Class are presented in Table 16.

Among all subjects treated with CVT-301 (Pool 3), SAEs reported for more than 1 subject included osteoarthritis (6 subjects), urinary tract infection (5 subjects), atrial fibrillation (5 subjects) and intervertebral disc protrusion (4 subjects), chest pain, inguinal hernia, femoral neck fracture, Parkinson's disease, hip fracture, dehydration (3 subjects each), and back pain, dyspnoea, intestinal obstruction, ischaemic stroke, syncope, radius fracture, angina pectoris and suicidal ideation (2 subjects each).

Table 16:

Serious Treatment-emergent Adverse Events by System Organ Class (Safety Population)

	POOL 1				**POOL 2**		**POOL 3**		**Observational cohort N=127**	
	CVT-301 N=270		**Placebo N=155**		**CVT-301 N=583**		**CVT-301 N=705**			
System Organ Class	**F**	**n (%)**	**F**	**n (%)**	**F**	**n (%)**	**F**	**n (%)**	**F**	**n (%)**
All SAEs	16	8 (3.0)	4	4 (2.6)	113	76 (13.0)	126	83 (11.8)	18	13 (10.2)
Musculoskeletal and connective tissue disorders	2	1 (0.4)	1	1 (0.6)	16	15 (2.6)	18	16 (2.3)	3	3 (2.4)
Injury, poisoning and procedural complications					19	16 (2.7)	19	16 (2.3)	2	2 (1.6)
Nervous system disorders	3	3 (1.1)	1	1 (0.6)	11	11 (1.7)	14	12 (1.8)	3	3 (2.4)
Infections and infestations					12	11 (1.9)	12	11 (1.6)	3	3 (2.4)
Cardiac disorders	4	3 (1.1)	1	1 (0.6)	7	7 (1.2)	11	10 (1.4)	1	1 (0.8)
Gastrointestinal disorders	1	1 (0.4)	1	1 (0.6)	13	8 (1.4)	14	9 (1.3)	2	2 (1.6)
Respiratory, thoracic and mediastinal disorders					8	7 (1.2)	8	7 (1.0)		
Psychiatric disorders	1	1 (0.4)			6	5 (0.9)	7	6 (0.9)		
General disorders and administration site conditions	2	2 (0.7)			2	2 (0.3)	4	4 (0.6)	3	2 (1.6)
Metabolism and nutrition disorders	1	1 (0.4)			4	3 (0.5)	5	4 (0.6)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					6	4 (0.7)	6	4 (0.6)		
Hepatobiliary disorders					3	3 (0.5)	3	3 (0.4)		
Renal and urinary disorders	1	1 (0.4)			1	1 (0.2)	2	2 (0.3)		

	POOL 1				POOL 2		POOL 3		Observational cohort N=127	
System Organ Class	CVT-301 N=270 F	n (%)	Placebo N=155 F	n (%)	CVT-301 N=583 F	n (%)	CVT-301 N=705 F	n (%)	F	n (%)
Investigations					1	1 (0.2)	1	1 (0.1)		
Vascular disorders	1	1 (0.4)					1	1 (0.1)		
Endocrine disorders					1	1 (0.2)	1	1 (0.1)		
Skin and subcutaneous tissue disorders					1	1 (0.2)	1	1 (0.1)		
Product issues					1	1 (0.2)	1	1 (0.1)		
Blood and lymphatic system disorders					1	1 (0.2)	1	1 (0.1)	1	1 (0.8)

Note: POOL 1 includes studies CVT-301-003 and CVT-301-004. POOL 2 includes CVT-301 groups from studies CVT-301-004E and CVT-301-005. POOL 3 includes CVT-301 groups from all studies (CVT-301-003, CVT-301-004, CVT-301-004E and CVT-301-005). F = event count, n = subject count and % = percentage of all subjects within the group. Source: ISS Table 3.8.1.1.

SAEs were reported more commonly in patients who received ≥ 5 doses of Inbrija per day at least once than for patients who received < 5 doses per day (15.6% versus 8.6%, respectively).

Deaths

Two fatal AEs were reported in clinical studies of Inbrija. One subject in Study CVT-301-004 died of completed suicide, and 1 subject in Study CVT-301-005 died of hypoxic-ischaemic encephalopathy subsequent to drowning. Both deaths were considered by the investigators to be definitely not related to study treatment.

Adverse events of special interest

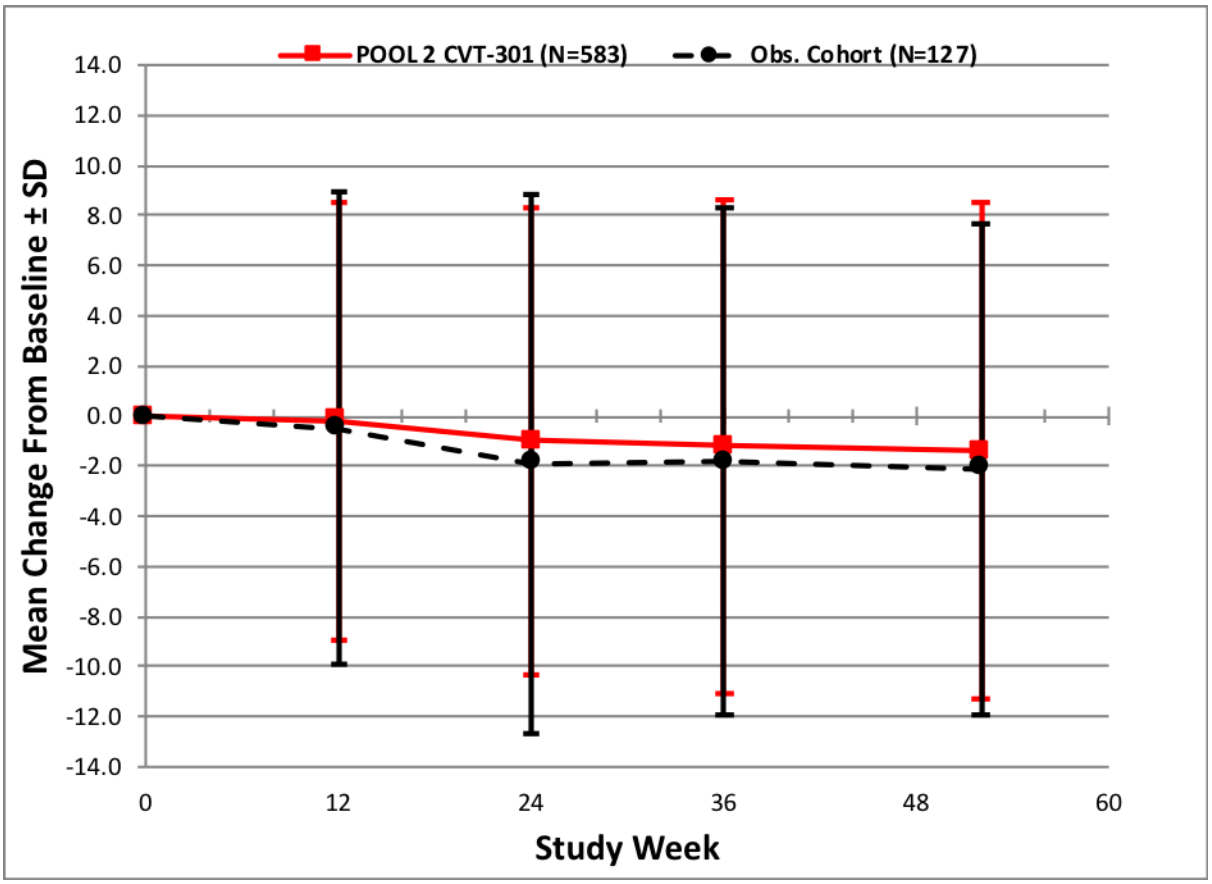
Adverse events related to fractures, hypotension, dyskinesia, abuse and pulmonary safety are considered of special interests and are discussed below.

Pulmonary Safety

Acute pulmonary safety was assessed by measuring the change from predose to postdose in spirometry parameters at 15, 30 and 60 minutes postdose at the first clinic visit (Neurology office). There were no notable mean changes from predose in FEV_1 (L), FEV_1 percent predicted, FVC (L), or FEV_1/FVC ratio at any postdose time point for any of the analysis groups at the first dose.

Chronic pulmonary safety was assessed by the change from baseline in FEV_1 (L), FEV_1 percent predicted, FVC (L), FEV_1/FVC ratio and DLco (Hg-adjusted) reported from the pulmonary function laboratory. The overall mean percent change from baseline for FEV_1, FVC, and FEV_1/FVC were similar across analysis groups. The mean changes from baseline in FEV_1 (L), FEV_1 percent predicted, FVC (L), and DLco (Hg-adjusted) decreased by small percentages over the course of treatment up to 15 months in all treatment groups including placebo and the observational cohort, and the magnitude of these changes were similar between CVT-treatment and placebo/observational control (see Figure 14).

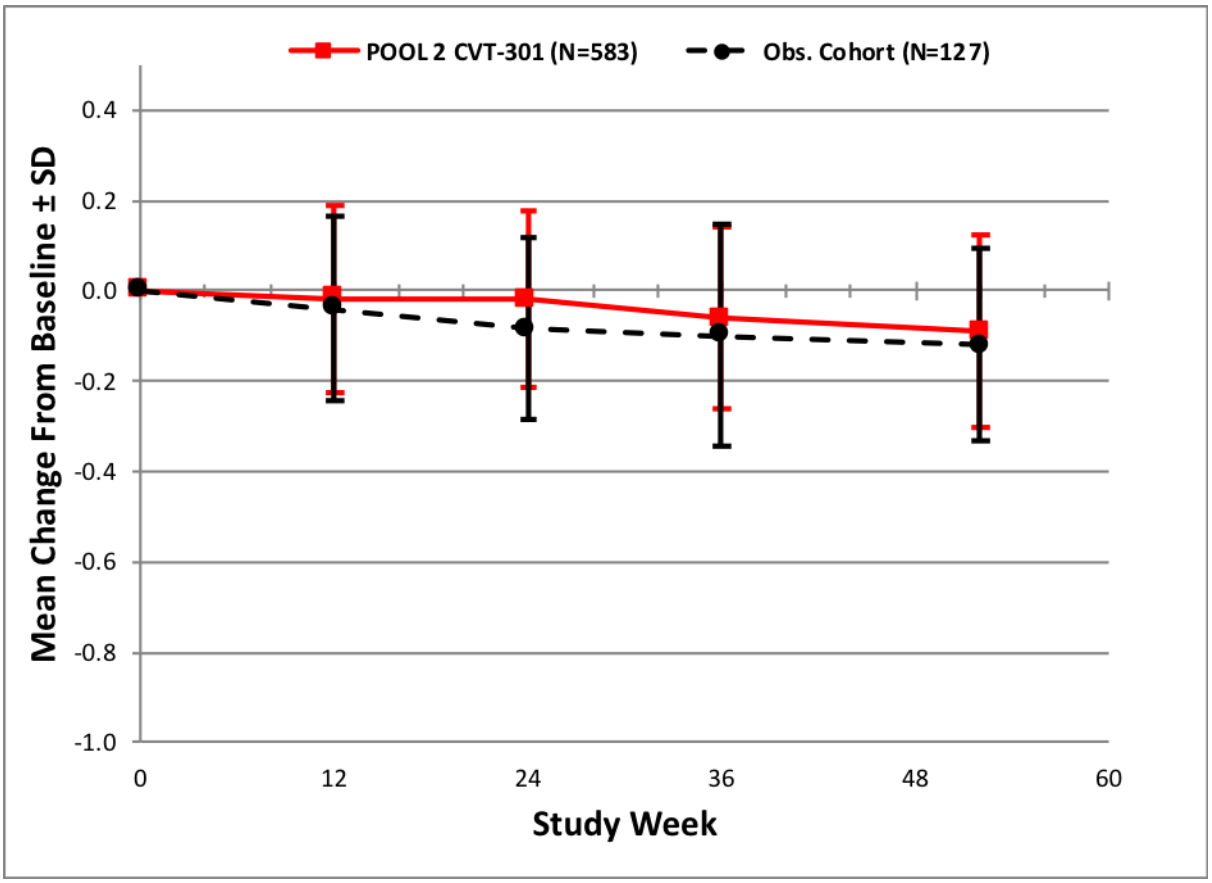
Figure 14: Mean Change from Baseline in DLco (Hemoglobin-adjusted; Percent Predicted) (Results from Pulmonary Function Laboratory; Safety Population)



Abbreviations: DLco = carbon monoxide diffusing capacity; Obs = observational; SD = standard deviation.
Source: ISS Table 7.7.1.1.

The mean changes from baseline in FEV_1/FEV_1 increased for CVT-301 for exposures ≥ 6 months while the observational cohort declined during the same time (see Figure 15).

Figure 15: Mean Change from Baseline in FEV_1 (L) (Results from Pulmonary Function Laboratory; Safety Population)



Abbreviations: FEV_1 = forced expiratory volume in 1 second; Obs = observational; SD = standard deviation.
Source: ISS Table 7.16.1.1.

Assessments of acute and chronic pulmonary safety concluded no notable difference between Inbrija treatment compared to either placebo treatment or observational cohort in spirometry parameters and DLco. Additionally, post hoc subgroup analyses in Pool 2 showed no differential effects on FEV_1 percent predicted between subjects with lower pulmonary function compared to subjects with normal pulmonary function, and between subjects taking a lower average daily dose of Inbrija compared to subjects taking a higher average daily dose. These results suggest that Inbrija treatment does not contribute to pulmonary function impairment regardless of baseline pulmonary status or the number of daily Inbrija inhalations.

Hypotension

Data is presented in Table 17 for both Orthostatic hypotension and dizziness as this the letter can be a symptom of hypotension. The data is presented as incidence rate per 100 subject-years.

Table 17: Number of hypotension-related adverse events

Preferred term	**Number of hypotension-related adverse events (incidence rate per 100 subject-years)**				
	POOL 1		**POOL 2**	**POOL 3**	**Observational Cohort**
	CVT-301	**Placebo**	**CVT-301**	**CVT-301**	
Subject-years	52.4	27.6	400.6	452.9	126.7
Dyskinesia					
All events	10 (19.1)	1 (3.6)	33 (8.2)	43 (9.5)	5 (3.9)
Possible	4 (7.6)	1 (3.6)	13 (3.2)	17 (3.8)	
Probable	4 (7.6)		5 (1.2)	9 (2.0)	
Related	2 (3.8)		11 (2.7)	13 (2.9)	
Orthostatic hypotension					
All events	3 (5.7)	1 (3.6)	14 (3.5)	17 (3.8)	4 (3.2)
Possible	1 (1.9)	1 (3.6)	3 (0.7)	4 (0.9)	
Probable	2 (3.8)		10 (2.5)	12 (2.6)	
Related			1 (0.2)	1 (0.2)	

Note: POOL 1 includes studies placebo controlled short term studies. POOL 2 includes long term safety studies. POOL 3 includes CVT-301 groups from all studies. Incidence rate = (number of events/ treatment exposure in subject-years)*100.
Source: ISS Table 3.6.1.1.

Dyskinesia

The incidence rate (per 100 subject-years) of dyskinesia is shown in Table 18.

Table 18: Overview of Dyskinesia reported[1]

Dyskinesia	**POOL 1**		**POOL 2**	**POOL 3**	**Observational Cohort**
	CVT-301	**Placebo**	**CVT-301**	**CVT-301**	
Reported overall %[a]	10 (3.7)	1 (0.6)	32 (5.5)	40 (5.7)	5 (3.9)
Reported acute %[b]	2 (0.7)	1 (0.6)	4 (0.7)	5 (0.7)	
Per 100 subject years %[c,d]	10 (19.1)	1 (3.6)	33 (8.2)	43 (9.5)	5 (3.9)

Note: POOL 1 includes studies placebo controlled short term studies. POOL 2 includes long term safety studies. POOL 3 includes CVT-301 groups from all studies.
[1]by assessor
a the total numer of dyskinesia reported at snap shot database date 30 June 2017
b Dyskinesa observed after first treatment
cTotal reported Dyskinesia indicated per 100 subject years.
aIncidence rate = (number of events/ treatment exposure in subject-years)*100.

Drug Abuse

The applicant assessed data from integrated analysis for known adverse events in incidence associated with oral levodopa to abuse potential occurring in more than 1 subject. There results were similar

between Inbrija treatment and either placebo or observational control groups for the most frequently reported adverse event (see Table 19). However, the overall frequency of adverse events potentially related drug abuse was higher in the Pool 1 and Pool 2 where the inhalator was used.

Table 19: Treatment-emergent Adverse Events Potentially Related to Drug Abuse (Safety Population)

	POOL 1		POOL 2	Observational cohort N=127 n (%)
Preferred Term	**CVT-301 N=270 n (%)**	**Placebo N=155 n (%)**	**CVT-301 N=583 n (%)**	
Any event	14 (5.2)	9 (5.8)	29 (5.0)	4 (3.1)
Dizziness	6 (2.2)	7 (4.5)	13 (2.2)	1 (0.8)
Hallucination	4 (1.5)	2 (1.3)	10 (1.7)	1 (0.8)
Hallucination, visual			3 (0.5)	1 (0.8)
Somnolence	2 (0.7)	2 (1.3)		1 (0.8)
Euphoric mood			2 (0.3)	
Feeling abnormal			1 (0.2)	
Intentional product misuse			1 (0.2)	
Cognitive disorder			1 (0.2)	
Disturbance in attention			1 (0.2)	
Dizziness postural			1 (0.2)	
Memory impairment				1 (0.8)
Agitation	1 (0.4)			
Dopamine dysregulation syndrome			1 (0.2)	
Irritability	1 (0.4)			
Paranoia	1 (0.4)			
Psychotic disorder			1 (0.2)	
Confusional state		1 (0.6)		
Orthostatic hypotension[a]			1 (0.2)	

[1] table truncated by assessor: the overall exposure group, i.e. POOL3 was removed as this is a repetation of the events reported for both POOL1 and POOL2.
[a]Verbatim term was "dizziness (orthostatic hypotension)."
Note: POOL 1: includes AEs reported in placebo controlled short term studies. POOL 2: includes AEs reported in Long term study.

Adverse Events of Fractures

The incidence of fracture AEs were similar between Pool 1 CVT-301 (0.7%) and placebo (1.3%) and between Pool 2 (4.3%) and the observational cohort (3.9%). The same query was conducted for medical history of fracture to identify any baseline propensity for fracture. A medical history of fracture was more prevalent in placebo (12.3%) versus Pool 1 CVT-301 (6.3%), while a medical history of fracture was similar between Pool 2 (8.7%) and the observational cohort (6.3%). The incidence rate of fracture AEs per 100 subject-years was lower in Pool 1 CVT-301 (3.8 events) compared to placebo (7.3 events), but higher in Pool 2 (7.7 events) compared to the observational cohort (3.9 events). Overall, the absolute incidence of fractures was low, and the incidence rate per 100 subject-years in Pool 2 was consistent with the risk of fractures in PD reported in literature (5.9 fracture incidence per 100 participant-years).

Laboratory findings

There were no clear trends in shifts from baseline for out-of-range values in hematological parameters at Months 1 to 3, 6, 9, 12 or 15, and no notable differences between the Inbrija-treated group and the placebo group or observational cohort.

There were no notable differences in mean systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate or respiration rate observed prior to dose across all 3 analysis pools and the observational cohort.

Across all Inbrija studies, there were few potentially clinically significant changes in ECG, and no notable difference between Inbrija-treated subjects and placebo-treated subjects or subjects in the observational cohort. No safety signals have been identified for any ECG parameters.

Safety in special populations

Due to the pulmonary route of administration subjects with chronic lung diseases, such as asthma or COPD can be regarded as special population. The applicant performed a study in asthmatic subjects (Study 008) who were otherwise healthy that showed that bronchospasm can occur. The effects on bronchospasm in patients with other pulmonary diseases, e.g. COPD patients, were not investigated. Therefore, an appropriate statement was added to the SmPC, stating that the use of levodopa inhalation powder in patients with asthma, chronic obstructive pulmonary disease (COPD), or other chronic underlying lung disease is not recommended.

While the overall incidence of AEs was similar among the three age groups, there appears to be a numerically higher incidence in specific AEs in the age group of 75 to 84 years. The most common AE in Pool 3 in all three age groups was cough with an incidence of 15.4%, 14.7%, and 21.0% with age groups < 65 years, 65 to < 75 years, and 75 to 84 years, respectively. The second most common AE in Pool 3 was fall with incidence of 7.3%, 9.5%, and 12.9% with age groups < 65 years, 65 to < 75 years, and 75 to 84 years,) respectively. The AEs that occurred in > 5% of patients in Pool 3 in all three age groups were dyskinesia (5.6%, 5.3%, and 8.1% with age groups < 65 years, 65 to < 75 years, and 75 to 84 years, respectively) and upper respiratory tract infection (5.3%, 6.3%, and 6.5% with age groups < 65 years, 65 to < 75 years, and 75 to 84 years, respectively).

It is considered that the use in very elderly patients (>75) needs to be monitored within PSUR. The SmPC reflects that there are limited data available for very elderly patients.

Table 20: Age-subgroup analysis of Total AEs, SAEs, presented by System Organ Class

MedDRA Terms	**Age <65 (N=358) n (%)**	**Age 65-74 (N=285) n (%)**	**Age 75-84 (N=62) n (%)**	**Age 85+ (N=0) n (%)**
Total AEs	242 (67.6%)	203 (71.2%)	44 (71.0%)	0
Serious AEs – Total	34 (9.5%)	39 (13.7%)	10 (16.1%)	0
- Disability/incapacity	2 (0.6%)	0	1 (1.6%)	0
- Fatal	0	2 (0.7%)	0	0
- Hospitalization/prolong existing hospitalization	32 (8.9%)	38 (13.3%)	10 (16.1%)	0
- Life-threatening	0	4 (1.4%)	1 (1.6%)	0
- Other (medically significant)	5 (1.4%)	8 (2.8%)	1 (1.6%)	0
AE leading to drop-out	22 (6.1%)	28 (9.8%)	7 (11.3%)	0
Organ system class of adverse event				
- Cardiac disorders	8 (2.2%)	13 (4.6%)	2 (3.2%)	0
- Infections and infestations	89 (24.9%)	62 (21.8%)	10 (16.1%)	0
- Injury, poisoning and procedural complications	52 (14.5%)	46 (16.1%)	10 (16.1%)	0
- Nervous system disorders	69 (19.3%)	52 (18.2%)	10 (16.1%)	0
- Psychiatric disorders	36 (10.1%)	39 (13.7%)	6 (9.7%)	0
- Vascular disorders	11 (3.1%)	22 (7.7%)	5 (8.1%)	0
Multiple Events*	42 (11.7%)	41 (14.4%)	10 (16.1%)	0
Anticholinergic syndrome	0	0	0	0
Cerebrovascular disorder	0	0	0	0
Quality of life decrease	0	0	0	0

* Sum of Postural hypotension, Falls, Loss of consciousness, Syncope, Dizziness, Ataxia and all Fractures. Subjects with multiple events are counted once.

Table 21: Age-subgroup analysis of AEs

		Age >=65 (N=347)				
AE by Preferred Term	**Age <65 (N=358) n (%)**	**Age 65-74 (N=285) n (%)**	**Age 75-84 (N=62) n (%)**	**Age 85+ (N=0) n (%)**	**Age >=65 (N=347) n (%)**	**Percentage Difference (Older - Younger)**
Fall	26 (7.3%)	27 (9.5%)	8 (12.9%)	0	35 (10.1%)	2.8%
Hallucination	3 (0.8%)	10 (3.5%)	1 (1.6%)	0	11 (3.2%)	2.3%

		Age >=65 (N=347)				
AE by Preferred Term	**Age <65 (N=358) n (%)**	**Age 65-74 (N=285) n (%)**	**Age 75-84 (N=62) n (%)**	**Age 85+ (N=0) n (%)**	**Age >=65 (N=347) n (%)**	**Percentage Difference (Older - Younger)**
Hypertension	3 (0.8%)	9 (3.2%)	2 (3.2%)	0	11 (3.2%)	2.3%
Diarrhoea	0	7 (2.5%)	0	0	7 (2.0%)	2.0%
Contusion	3 (0.8%)	7 (2.5%)	2 (3.2%)	0	9 (2.6%)	1.8%
Insomnia	3 (0.8%)	7 (2.5%)	2 (3.2%)	0	9 (2.6%)	1.8%
Dry mouth	2 (0.6%)	7 (2.5%)	1 (1.6%)	0	8 (2.3%)	1.7%
Urinary tract infection	7 (2.0%)	10 (3.5%)	2 (3.2%)	0	12 (3.5%)	1.5%
Pain in extremity	5 (1.4%)	6 (2.1%)	4 (6.5%)	0	10 (2.9%)	1.5%
Weight decreased	1 (0.3%)	5 (1.8%)	1 (1.6%)	0	6 (1.7%)	1.4%
Blood urea increased	0	3 (1.1%)	2 (3.2%)	0	5 (1.4%)	1.4%
Toothache	0	3 (1.1%)	2 (3.2%)	0	5 (1.4%)	1.4%
Oedema peripheral	3 (0.8%)	5 (1.8%)	2 (3.2%)	0	7 (2.0%)	1.2%
Vertigo	3 (0.8%)	6 (2.1%)	1 (1.6%)	0	7 (2.0%)	1.2%
Atrial fibrillation	2 (0.6%)	6 (2.1%)	0	0	6 (1.7%)	1.2%
Hypotension	1 (0.3%)	5 (1.8%)	0	0	5 (1.4%)	1.2%
Haemoglobin decreased	0	3 (1.1%)	1 (1.6%)	0	4 (1.2%)	1.2%
Hypoaesthesia	0	3 (1.1%)	1 (1.6%)	0	4 (1.2%)	1.2%
Productive cough	0	4 (1.4%)	0	0	4 (1.2%)	1.2%
Upper respiratory tract infection	19 (5.3%)	18 (6.3%)	4 (6.5%)	0	22 (6.3%)	1.0%

Immunological events

Not applicable

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies were conducted with Inbrija. All subjects on Inbrija were also on a background regimen of levodopa/DDI (either carbidopa or benserazide). With some exceptions (e.g. apomorphine, which was prohibited), subjects were allowed to take concomitant PD medications.

The applicant presented literature data, known for LD or LD/CD interaction. No studies have been conducted to examine drug-demographic interactions or drug-disease interactions of Inbrija.

Discontinuation due to adverse events

In the placebo-controlled studies (Pool 1), AEs led to withdrawal from the study in 10 (3.7%) Inbrija -treated subjects and 6 (3.9%) placebo-treated subjects.

In the long-term studies, AEs led to withdrawal from the study in 47 (8.1%) subjects treated with Inbrija (Pool 2). Among all Inbrija -treated subjects (Pool 3), 57 (8.1%) subjects withdrew from the study due to AEs. Among all Inbrija -treated subjects, cough was the most commonly reported AE leading to study withdrawal (13 [1.8%]). No placebo subjects withdrew from the study due to cough. Hallucination and throat irritation led to study discontinuation in 3 (0.4%) subjects each, and bronchitis, dyskinesia,

dyspnea, euphoric mood, upper respiratory tract irritation and blurred vision led to study discontinuation in 2 (0.3%) subjects each. All other AEs leading to withdrawal were reported for 1 subject each. One subject in the Pool 1 Inbrija treatment group (Study CVT-301-004) reported a spirometry-associated AE (spirometry abnormal) resulting in withdrawal from the study.

Adverse events leading to withdrawal from the study were analyzed by daily dose frequency (mean daily dose < median; mean daily dose ≥ median). The incidence of AEs leading to withdrawal from the study in Pool 3 was higher in subjects with mean daily dose < median (8.2%) compared to subjects with mean daily dose ≥ median (5.7%), but the difference remained small. There was no clinically meaningful difference between the two subgroups in AEs leading to withdrawal from the study.

2.6.1. Discussion on clinical safety

Safety if Inbrija treatment has been determined in four multiple-dose studies in PD subjects (Studies CVT-301-003, CVT-301-004, CVT-301-004E and CVT-301-005).

An adequate number of PD patients were exposed to multiple Inbrija doses in placebo-controlled studies (270 patients) and in long-term uncontrolled or observational cohort-controlled studies (583 patients) to allow a comprehensive safety assessment. Data on the long-term (6 months or more) adverse effects of Inbrija are available from Study CVT-301-004E (up to 12 to 15 months) and Study CVT-301-005 (up to 12 months). Long-term pulmonary safety was evaluated using spirometry and DLco (carbon monoxide diffusing capacity).

Post-hoc analyses on the integrated safety datasets for Inbrija 84 mg group only using the data from Studies CVT-301-004, CVT-301-004E, and CVT-301-005 were performed regarding the number of patients exposed to CVT-301 84 mg, 5 times daily, for > 3 months, > 6 months, and > 12 months. Among the 469 exposed patients, 166 patients took ≥ 5 doses per day at least once.

The safety profile of Inbrija is consistent with the known safety profile of levodopa, along with the addition of cough associated with the inhalation of a dry powder. The most frequent adverse reactions reported in the Inbrija clinical studies were cough (15.6%), fall (8.7%), upper respiratory tract infection (5.8%), dyskinesia (5.7%) and sputum discoloured (2.8%). No events of fall were considered at least possibly causally drug-related by the investigators. The acute and chronic pulmonary safety evaluations showed no notable differences between treatment with Inbrija compared to a placebo or observational control in spirometry parameters and DLco. Evaluations of vital signs, clinical laboratory, and ECG showed no apparent safety signals.

In general, the Pool analysis showed that the reported adverse events did not differ between short term and long term exposure and thus do not change over time. The submitted data concerning upper respiratory tract infection, indicate that that this AE was not only reported more frequently in the 84 mg dose compared to placebo, but also lasted longer compared to placebo and the observational cohort. As the route of administration leads to relative more respiratory tract related adverse events reported, use in (chronic) pulmonary disorder (asthma, COPD) is mentioned in the SmPC in the section warning and precaution. It is difficult to conclude based on these data whether the efficacy is compromised or not in case of a concomitant upper respiratory tract infection. Therefore it is advised in the SmPC section 4.4 to leave the decision whether to discontinue the use of the product temporarily or permanently, to the patient and medical professional, as Inbrija treatment is an on-demand, add-on treatment.

The CHMP concluded that there was no increased abuse potential with the use of an on-demand system as Inbrija because the frequency of events related to potential abuse was similar between the placebo

controlled studies and the long term studies. Dizziness and hallucination were also reported with a high frequency in the placebo arm.

Overall, the clinical experience in supports the conclusion that Inbrija was well tolerated as an adjunctive treatment for PD subjects experiencing motor fluctuations. The totality of safety data from Studies CVT-301-003, CVT-301-004E, CVT-301-004 and CVT-301-005 and the high frequency of use complies with the ICH E1 requirements for safety.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The most frequent adverse events reported in are cough, upper respiratory tract infection, throat irritation, sputum discoloured, dyskinesia, dizziness, hallucinations, fall, and nasopharyngitis. They were either adverse events already known for levodopa or related to the route of administration. The route of administration leads to irritation of the pulmonary tract, however the lung functions are not affected.

Based on individual assessments of the severity of the intercurrent respiratory infection Inbrija may be continued or discontinued until the respiratory symptoms resolve. This particular safety issues will be monitored closely within PSURs.

Because of the risk of bronchospasm, use of levodopa inhalation powder in patients with asthma, chronic obstructive pulmonary disease (COPD), or other chronic underlying lung disease is not recommended. The applicant will monitor closely respiratory compromised patients, the ADR cough and use in current smokers in post-marketing setting.

2.7. Risk Management Plan

Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	none
Important potential risks	Bronchospasm in patients with lung disease
Missing information	Use in patients with asthma, COPD, or other chronic underlying lung diseases

Pharmacovigilance plan

Not applicable. Only routine pharmacovigilance activities have been proposed.

Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Bronchospasm in patients with lung disease	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Legal status (prescription only medicine) Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for cases reported with bronchospasm, wheezing, asthma, asthmatic crisis, or dyspnoea. Cumulative review of line lists for all reported cases with PTs including bronchospasm, wheezing, asthma, asthmatic crisis, and dyspnoea. Additional pharmacovigilance activities: None
Use in patients with asthma, COPD, or other chronic underlying lung diseases	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Legal status (prescription only medicine) Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for cases reported with bronchospasm, wheezing, asthma, asthmatic crisis, or dyspnoea. Cumulative review of line lists for all reported cases with PTs including bronchospasm, wheezing, asthma, asthmatic crisis, and dyspnoea or a medical history of asthma, COPD, or other chronic underlying lung diseases. Additional pharmacovigilance activities: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 (dated 10 June 2019) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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 did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21.12.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. 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.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Motor fluctuations (OFF episodes) occur with PD progression, when patients are no longer able to store dopamine in dopaminergic neurons, due to progressive degeneration of dopamine neurons. OFF episodes can be unpredictable and may impact patient's quality of life greatly.

Inbrija is a dry powder formulation of LD for inhalation. Capsules contain powder for oral inhalation and breath-actuated inhaler. The combination of particle size and formulation composition has been designed to provide therapeutic levels of LD following inhalation and absorption into the pulmonary circulation.

The applicant initially sought approval for the indication:

"Treatment of symptoms of OFF periods in Parkinson's disease as an adjunct to a dopa-decarboxylase inhibitor/levodopa regimen."

The approved indication is:

"Intermittent treatment of episodic motor fluctuations (OFF episodes) in adult patients with Parkinson's disease (PD) treated with a levodopa/dopa-decarboxylase inhibitor."

3.1.2. Available therapies and unmet medical need

Treatment of an OFF episode is managed most frequently by oral administration of either a scheduled or unscheduled dose of LD, which is associated with a considerable variability in response and can require >1 hour to improve motor function. Dispersible tablets for dose dispenser with a dose of 5mg/1.25mg LD/CD per tablet was registered in 2016, allowing individualized therapy and administration of optimum daily dose. The Cmax of this product occurs approximately 30 minutes after dose. Treatment of OFF episodes

in more advanced stages of PD can be achieved with subcutaneous apomorphine injection in patients on stable oral anti-Parkinson medication.

3.1.3. Main clinical studies

The clinical program consisted of 10 studies examining the efficacy, PK and safety in healthy voluntaries, PD patients and special populations, i.e. asthmatic subjects and smokers.

Study 004 was a randomized, double-blind, placebo-controlled, multicentre study, evaluating the efficacy of Inbrija in 343 PD patients with OFF periods. The study duration was 12 weeks.

The primary endpoint was a change in UPDRS-III at 30 minutes post-dose compared to pre-dose OFF motor at 12 weeks.

After the treatment phase of 12 weeks, subjects could enter an extension phase (study 004E). The subjects on active treatment continued with their treatment dose and subjects on placebo were re-randomized to 60mg or 84mg. Follow up was up to 52 weeks and blinding was maintained.

Study 003 was a randomized, multicentre, placebo-controlled study, assessing the efficacy of Inbrija in 89 PD patients. Subjects were similar to the population in study CVT-301-004. The primary endpoint was change in UPDRS-III motor score at 10-60 minutes post-dose at week 4 assessed in a similar clinical setting as study CVT-301-004.

3.2. Favourable effects

The results from the pharmacokinetics investigation of Inbrija, confirm that it can deliver successfully levodopa plasma levels (>400 ng/ml) needed for a meaningful improvement of OFF periods faster and independently from food intake compared to oral levodopa administration (20 min compared to 45 and 120 min after oral fasted and oral fed). The proposed inhalation levodopa dose is lower than the usual oral doses and therefore has a lower risk of inducing dyskinesia (at levodopa plasma levels above 800 ng/mL).

The efficacy of Inbrija was supported by Study CVT-301-003 and confirmed in Study CVT-301-004. The available efficacy data show that Inbrija provides an effective and timely improvement of motor symptoms within 30 minutes when given on top of background oral LD/DDI during an OFF period. This motor improvement is considered clinically relevant and beneficial, which is also reflected by the reduction of mean daily OFF time an improvement on the PGI-C score (a patient reported outcome of the overall improvement and satisfaction) in subjects in the treatment arms. The effects were consistent across trials and dose, with generally a larger effect observed in the Inbrija 84 mg compared to the 60 mg dose group.

Overall, the clinical safety experience supports the conclusion that Inbrija's safety profile is consistent with the known safety of levodopa and that it was well tolerated as an adjunctive treatment for PD subjects experiencing motor fluctuations.

3.3. Uncertainties and limitations about favourable effects

Exposure-response analyses indicated a numerically better response with a higher increase in levodopa concentrations upon Inbrija treatment and in patients with high levodopa plasma levels at onset of the OFF period 15 min after Inbrija administration. However, the data are considered exploratory because of the low numbers included in the analysis, i.e. 24 patients. A rapid treatment effect has not conclusively been shown in the clinical trials. Moreover, a statistically significant difference in the UPDRS-III between placebo and Inbrija 84 mg is observed after 30 minutes.

The primary endpoint and key secondary endpoints are assessed in a 'clinical setting', i.e. waiting for an OFF period to occur. The clinical relevance of the UPDRS-III result is supported by the statistically superior result in responder ON within 60 minutes at Week 12 and the subject-reported improvement on the PGI-C rating scale at Week 12 favouring Inbrija treatment over placebo.

A difference in mean total daily OFF time between Inbrija and placebo is more evident in a more severe PD patient population. When the patient population is less severe, the sensitivity of the PD diary may not be sufficient to detect a difference for an intermittent treatment that is used on an as needed basis.

There is only a limited amount of subjects within the worst-case scenario (when the highest daily doses of Inbrija were taken in addition to the maximum doses of baseline therapy) available for assessment, therefore this subgroup requires monitoring post-marketing.

3.4. Unfavourable effects

The adverse events were pooled for the placebo controlled short term, study (Pool 1), long term study (Pool 2) and for the observational cohort. The most frequent reported adverse events and related to the drug or route of administration are dyskinesia (0.6%; 3.7%; 5.5%; 3.9%), cough (1.9%; 13.7%; 13.7%; 0.8%), upper respiratory tract infection (1.9%; 3.3%; 5.5%; 0.8%), throat irritation (0.6%; 3.3%; 3.1%; -), sputum discoloured (- ; 3.0%; 1.4%; -), reported for placebo, CVT-301 Pool 1, CVT-301 Pool 2, and the observation cohort, respectively.

In Study 004, upper respiratory tract infection lasted 10 days in placebo, 10 days in CVT-301 60 mg taking and 17 days in CVT-301 84 mg cohort. This particular safety issues will be monitored closely within PSURs.

Study 008 performed showed that bronchospasm can occur in non-PD asthmatic subjects. The effects on bronchospasm in PD patients with other pulmonary diseases, e.g. COPD patients, were not investigated and therefore the use of Inbrija is not recommended. The applicant will monitor closely respiratory compromised patients, the ADR cough and use in current smokers in post-marketing setting.

There was only a small number of subjects aged 75-84 and no subjects aged >84 included in studies. Taking into account that the use in very likely it was recommended to monitor the use in >75 within PSUR. The SmPC has been updated highlighting that there are only limited data available for very elderly patients.

Adverse event related to abuse potential included: euphoric mood (0.3%, Pool 2 only), impulse control disorder (0.2%, Pool 2 only), dopamine dysregulation syndrome (0.2% pool 2 only), dizziness (4.5%, 2.2%, 2.2%, 0.8%), hallucination (1.3%, 1.5%, 1.7%, 0.8%) and (for Pool 1 placebo, Pool 1 CVT-301, CVT-301 Pool 2 and observational cohort, respectively).

3.5. Uncertainties and limitations about unfavourable effects

The percentage of adverse events reported in the short term pooled and long term pooled data are generally similar. However, as the adverse events are presented in a short term data pool and a long term data pool, and not per dose, it is unknown how this relates to the 60 mg and 84 mg dose. As the adverse event profile of levodopa is well known, the difference in low dose and high dose is small. Small amounts are given on top of background levodopa treatment on an on demand basis, and are not expected to significantly affect the safety profile.

The route of administration leads to relative more respiratory tract related adverse events, e.g. respiratory infections, cough. Respiratory tract infections appear to be related to the dose, as the duration of infection is prolonged in the higher dose. Therefore, respiratory tract infection will be monitored in the PSUR and the SmPC warns that, based on individual assessments of the severity of the intercurrent respiratory infection, Inbrija may be continued or discontinued until the respiratory symptoms resolve.

Bronchospasm has been seen in non-PD asthmatic subjects and there is limited data regarding chronic effect of Inbrija in respiratory compromised patients, therefore use of levodopa inhalation powder in patients with asthma, chronic obstructive pulmonary disease (COPD), or other chronic underlying lung disease is not recommended. The effect of cough in respiratory compromised population and smokers is unknown; this will be monitored in the PSUR.

Although the frequency of adverse events relating to potential abuse are observed in the Inbrija exposed group with higher frequency than seen in the observational cohort, these are known effects of LD and are therefore incorporated in the SmPC.

There is only limited data in very elderly patients (≥75 years) and therefore the use of Inbrija will be monitored within PSUR.

Inbrija has not been studied in patients with renal impairment and therefore it is recommended to administer this medicinal product cautiously to patients with severe renal disease.

Inbrija has not been studied in patients with hepatic impairment and therefore it is recommended to administer this medicinal product cautiously to patients with severe hepatic impairment.

3.6. Effects Table

Table 22: Effects Table for Inbrija for the 'Intermittent treatment of episodic motor fluctuations (OFF episodes) in adult patients with Parkinson's disease (PD) treated with a levodopa/dopa-decarboxylase inhibitor'.

Effect	Short Description	CVT-301 60 mg	CVT-301 84 mg	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
UPDRS-III[2]	UPDRS-III score mean change from predose at 10-60min at week 2 (LS mean (SE))	-9.90 (1.49)	-	-5.30 (1.53)	**Unc:** assessed in artificial setting (e.g. forced OFF) **SoE**: 60mg vs Pl -4.60 (-7.90;-1.30) p=0.007	CVT-301-003
UPDRS-III[2]	UPDRS-III score mean change from predose at 10-60min at week 4 (LS mean (SE))	-	-10.02 (1.50)	-3.07 (1.54)	**Unc:** assessed in artificial setting (e.g. forced OFF) **SoE:** 84mg vs Pl -6.95 (-10.31;-3.60) p<0.001	CVT-301-003
Daily OFF time[2]	change from baseline in total daily OFF Time recorded in PD diary (LS mean (SE))	-1.1 (0.4)	-	-0.8 (0.4)	**Unc:** reduction in total daily OFF depended on severity of the disease **SoE:** p=0.498	CVT-301-003
Daily OFF time[2]	change from baseline in total daily OFF Time recorded in PD diary (LS mean (SE))	-	-1.6 (0.4)	-0.8 (0.4)	**Unc:** reduction in total daily OFF depended on severity of the disease **SoE:** p=0.045	CVT-301-003
ON responders[2]	proportion of subjects ON within 60 minutes post dose and stayed ON up to 60 minutes post dose	67%	78%	36%	**Unc:** Subjective assessed by treating physician, not pre-defined **SoE:** 60 mg vs Pl P=0.032, 84 mg vs Pl P=0.002	CVT-301-003
UPDRS-III[1]	Change in UPDRS-III at 12 weeks from baseline assessed 30min post dose (LS mean)	-8,98	-9.83	-5.91	**Unc:** assessed in artificial setting (e.g. forced OFF) **SoE:** 60 mg vs Pl -3.07 95%CI (-5.99; -0.16) p=0.039, 84mg vs Pl -3.92 (-6.84; -1.00) p=0.009 >3 point on UPDRS-III is clinically relevant	CVT-301-004
PGI-C[1]	proportion of subjects who improved (incl little and much)	61.6%	71.4%	46.4%	**SoE:** 60 mg vs Pl P=0.026, 84 mg vs Pl P<0.001	CVT-301-004
ON responders[1]	proportion of subjects ON within 60 minutes post dose and stayed ON up to 60 minutes post dose	55.6%	57.7%	36.1%	**Unc:** ON state was subjective; assessed in artificial setting **SoE:** 60 mg vs Pl p=0.006, 84 mg vs Pl p=0.003	CVT-301-004

Daily OFF time[1]	change from baseline in total daily OFF Time recorded in PD diary (LS mean (SE))	-0.58 (0.28)	-0.47 (0.28)	-0.48 (0.28)	**Unc:** reduction in total daily OFF depended on severity of the disease **SoE:** 60mg vs Pl -0.1 (-0.66;0.46) p=0.722, 84mg vs Pl -0.01(-0.55; 0.56)	CVT-301-004

Effect	Short description	control	CVT-301 Pool1	CVT-301 Pool 2	Obser. cohort	Uncertainties/ Strength of evidence	References
Unfavourable Effects[3]							
TEAEs drug related	Dyskinesia	0.6%	3.7%	5.5%	3.9%	**Unc:** Unknown if is related to dose; effect in respiratory compromised population and smokers unknown; followed in PSUR	ISS table 3.31.1.1
TEAEs related to route of administration	Cough	1.9%	13.7%	13.7%	0.8%	**Unc:** Unknown if it is related to dose; effect in respiratory compromised population and smokers unknown; followed in PSUR	ISS tables 3.2.1.1;& 3.3.1.1
	Upper respiratory tract infection	1.9%	3.3%	5.5%	2.4%	**Unc:** possibly related to dose; effect in respiratory compromised population and smokers unknown; followed in PSUR; efficacy may be compromised; unknown how to handle when respiratory infections occur (SmPC, warning)	
	Throat irritation	0.6%	3.3%	3.4%	-	**Unc:** Unknown if it is related to dose	
	Sputum discoloured	-	3.0%	1.4%	-		
TEAEs related to drug abuse	Dizziness	4.5%	2.2%	2.4%	0.8%	**SoE:** known long term effect of LD. Warning included in the SmPC	ISS table 3.3.1.1 & 3.16.1.1
	Hallucination	1.3%	1.5%	1.7%	0.8%		
	Impulse control disorder	-	-	0.2%	-		
	Dopamine dysregulation syndrome	-	-	0.2%	-		
	Euphoric mood	-	-	0.3%	-		

Abbreviations: ISS = integrated summery of safety, Obser. cohort = Observational cohort on standard of care treatment, PGI-C= Patient Global Impression of Change, Pl=placebo, SoE= Strength of evidence, TEAE= treatment emergent adverse event, Unc = uncertainties

[1]assessed at 12 weeks ; [2]Treatment group received 2 weeks CVT-301 60mg dose followed by 2 weeks CVT-301 84mg dose; [3]pooled data: Pool 1 is short term placebo controlled studies (up to 3 months), Pool 2 is long term studies (up to 12 months), Placebo is short term and observational cohort includes patients randomized in study CVT-301-005 into the standard of care arm and observed for 12months.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pulmonary delivery of the active allows for a more rapid increase in levodopa plasma concentrations compared to regular oral LD/CD formulation. The Cmax is reached after approximately 20 minutes compared to 45-120 minutes of Sinemet IR. Subjects who started inhaled levodopa on top of background LD/CD medication, after the emerging of an OFF episode, had a quicker improvement in the UPDRS-III motor score as compared to placebo. The UPDRS III score improved with -9.83. - 8.98 and –5.91 points within 30 minutes for levodopa inhaler 48mg, levodopa inhaler 66mg and placebo respectively. Despite the fact that the available data did not show a statistically significant or clinically relevant differences between placebo and UPDRS-III within the first 10-20 minutes (which would have been considered a rapid effect), Inbrija has the benefit that the increase in levodopa plasma concentrations is independent of food intake, which is in contrast to the available oral formulations, which are influenced by fed and fasted state.

Preventing an upcoming OFF period from becoming a full-blown one suggests that there will be an improvement in motor function, which would also be translated in a reduction in total daily OFF time in the real-life setting. This was reflected by a greater numerical difference in more severe patients in reduction of OFF time, and the significant reduction in daily OFF time seen in study CVT-301-003 at 4 weeks.

The safety of Inbrija is in line with that of levodopa medicinal products. The applicant presented pooled data for short term, 4-12 weeks, and long term, up to 52 weeks, exposure. Adverse events of special interests were adverse events related to the route of administration, such as respiratory tract infection, cough, and throat irritation. The assessment of pulmonary parameters showed that these were unchanged compared to the placebo-treated groups. However, some patients suffered from respiratory tract infections during the study. It is unclear if the respiratory tract infection compromises the efficacy or safety of Inbrija. Based on individual assessments of the severity of the intercurrent respiratory infection Inbrija may be either continued or discontinued until the respiratory symptoms resolve.

Because of the risk of bronchospasm (seen in non-PD asthmatic subjects), use of Inbrija in patients with asthma, chronic obstructive pulmonary disease (COPD), or other chronic underlying lung disease is not recommended.

3.7.2. Balance of benefits and risks

Inbrija is a pulmonary delivery of levodopa only and should, therefore, be administered with background LD/CD oral formulation. The efficacy and safety data are in line with known efficacy and safety from clinical experience with LD/CD products.

A rapid relief of an OFF period was aimed at, hence justifying the pulmonary delivery route. This is considered a worthwhile treatment goal on its own as OFF periods are recognized to greatly affect the quality of life of PD patients.

The pharmacokinetics of Inbrija indicate that a rise in levodopa plasma concentration of > 400 ng/ml can be reached 10 min after inhalation compared to approximately 30 min (fasted) or > 1 hour (following a meal) for regular oral administration. The current formulation has the benefit that when properly administered, levodopa absorption is unaffected by food intake.

Clinical relevance, e.g. translation from the artificial setting to real life setting, is considered demonstrated by the improvement of UPDRS-III score, responders ON and patient-reported outcome PGI-C. Moreover, more considerable numerical differences in reduction of daily OFF-time between placebo and treatment arms were observed in more severe PD patients, e.g. patients with ≥3 doses or patients with longer daily OFF episodes.

Due to the known safety profile of levodopa, the additional safety concerns relate to the route of administration. The SmPC advices that based on individual assessments of the severity of the intercurrent respiratory infection Inbrija may be continued or discontinued until the respiratory symptoms resolve.

Because of the risk of bronchospasm, use of levodopa inhalation powder in patients with asthma, chronic obstructive pulmonary disease (COPD), or other chronic underlying lung disease is not recommended.

Overall, the data from the presented studies show that Inbrija provides a clinically relevant improvement of episodic motor fluctuations (OFF episodes) in adult patients with Parkinson's disease treated with a levodopa/dopa-decarboxylase inhibitor.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Inbrija is positive subject to the conditions listed in section 4. Recommendations.

4. Recommendations

Outcome

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

Inbrija is indicated for the intermittent treatment of episodic motor fluctuations (OFF episodes) in adult patients with Parkinson's disease (PD) treated with a levodopa/dopa-decarboxylase inhibitor.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Other conditions and requirements of the marketing authorisation

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.

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

Risk Management Plan (RMP)

The 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.