LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Produodopa
(foslevodopa, foscarbidopa)

SE/H/415/03/DC

This module reflects the scientific discussion for the approval of Produodopa. The procedure was finalised on 2022-07-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Produodopa, 240 mg/ml + 12 mg/ml, solution for infusion.

The active substances are foslevodopa and foscarbidopa. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application is an extension to the previously authorised product: Duodopa, 20 mg/ml + 5 mg/ml, intestinal gel (SE/H/415/01/DC). The differences compared to Duodopa is:

- change in active substance (prodrug)
- new strength
- new pharmaceutical form
- different route of administration (subcutaneous infusion versus intestinal gel)

The application for Produodopa, 240 mg/ml (foslevodopa) + 12 mg/ml (foscarbidopa), solution for infusion, is submitted according to Article 8(3) of Directive 2001/83/EC. The applicant, AbbVie AB applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, HR, HU, IE, IS, IT, LI, LT, LU, NL, NO, PL, PT, RO, SI, SK, UK(NI) as concerned member states (CMS).

Extension – Qualitative change in declared active substance

The available non-clinical and pharmacokinetics data indicate that the substances in Produodopa, foslevodopa and foscarbidopa, are rapidly converted to the pharmacologically active forms of levodopa and carbidopa, i. e. the same therapeutic moieties as in Duodopa and that the patients will mainly be exposed to levodopa and carbidopa. The steady state levels of foslevodopa and foscarbidopa in plasma during infusion are at least 10 times lower compared to carbidopa and levodopa. From non-clinical studies foslevodopa and foscarbidopa did not differ significantly in properties with regard to safety and/or efficacy versus levodopa and carbidopa. Foslevodopa and foscarbidopa are not regarded as “new active substances”, hence a line extension to Duodopa is acceptable.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substances has been adequately proven and their physico-chemical properties are sufficiently described.

The manufacture of the drug substances has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specifications include relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology
No primary pharmacodynamics studies were performed with foslevodopa and foscarbidopa which are prodrugs that are readily converted to the active substances levodopa (LD) and carbidopa (CD). Clinical efficacy of the drug combination levodopa/carbidopa has been well established from its decades of use in Parkinson's disease patients.

Foslevodopa up to 10 µM (2.8 µg/mL) and foscarbidopa 10 µM (3.1 µg/mL) were tested in a screening panel of radioligand assays for examining off-target binding affinity, including dopamine receptors and the dopamine transporter. Neither prodrug demonstrated pharmacologic activity at any receptor at the maximum tested concentration corresponding to t 7- and 160-fold, respectively, the clinical plasma C_{ss}.

Studies have been performed to evaluate effects of foslevodopa/foscarbidopa on the CNS, respiratory and cardiovascular systems in line with guideline recommendations. All *in vivo* studies were performed using continuous IV administration.

In the rat CNS study, various neurobehavioral observations were noted, including salivation and findings indicative of a general increase in activity/reactivity at the highest dose tested, foslevodopa/foscarbidopa at 500/125 mg/kg. In the rat respiratory study, effects were observed at the highest dose tested, foslevodopa/foscarbidopa at 500/125 mg/kg. The observed effects included a slight increase in respiratory rate and slight decreases in tidal volume and minute volume. The NOEL for both CNS and respiratory endpoints were set at foslevodopa/foscarbidopa at 250/62.5 mg/kg. At the NOELs, the plasma C_{ss} was 0.506, 0.109, 8.05 and 1.07 µg/mL for foslevodopa, foscarbidopa, LD and CD, respectively. The exposure margins at NOEL were 1.2-, 5.7-, 1.4- and 1.5-fold the clinical C_{ss} for foslevodopa, foscarbidopa, LD and CD, respectively. Overall, the functional side effects of foslevodopa/foscarbidopa appear to be related to the level of the active drug, LD.

In the *in vitro* hERG assay, both prodrugs and their active moieties were tested. Neither of the substances had appreciable effects on hERG current at the tested concentrations.

In anesthetized dogs, IV administration of foscarbidopa had no effects on cardiovascular function through the highest plasma concentration tested, 0.93 µg/mL of foscarbidopa and 3.37 µg/mL of CD corresponding to about 48- and 5-fold the plasma C_{ss} at the maximum clinical dose. When foslevodopa was administered IV to anesthetized dogs, there was an increase in cardiac contractility at a plasma concentration of 5.20 µg/mL of foslevodopa and 4.65 µg/mL LD, an increase in cardiac output at 19.5

μg/mL of foslevodopa and 16.33 μg/mL LD, and an increase in mean arterial blood pressure at 21.10 μg/mL of foslevodopa and 23.40 μg/mL LD. These CV effects are considered to be related to LD since the same pattern of CV effects was observed at similar LD plasma concentrations in a separate study in dogs administered LD.

In conscious, telemetered monkeys administered a continuous IV infusion of foslevodopa/foscarbidopa for 24 hours, no CV effects were observed through the highest dose tested, 300/75 mg/kg. At this dose, the plasma concentrations of foslevodopa, foscarbidopa, LD and CD are about 6.6-, 39-, 3.4- and 7.6-fold the clinical C_{ss}, respectively.

Overall, the no unique CV effects of foslevodopa/foscarbidopa have been identified. The CV effects of LD are well known in the clinic.

No pharmacodynamic drug interaction studies were performed with foslevodopa/foscarbidopa. Interactions of the active substances LD and CD with other medicinal products are well known and outlined in SmPC section 4.5.

Pharmacokinetics

The pharmacokinetics of foslevodopa/foscarbidopa (ratio 4:1) following a single IV and SC dose was studied in rats, dogs, and monkeys. Pharmacokinetics/toxicokinetics of foslevodopa/foscarbidopa (ratio 4:1) was evaluated in repeat-dose studies using a continuous IV administration of up to 4-weeks in rats and monkeys. The toxicokinetics of the clinical ratio of foslevodopa/foscarbidopa 20:1 was assessed in a 13-week repeat-dose study continuous SC administration in dogs.

The absorption, distribution, metabolism and excretion of levodopa and carbidopa have previously been characterized.

The methods of analyses were adequately validated.

Foslevodopa and foscarbidopa were rapidly cleared following IV dosing in rats, dogs and monkeys. The elimination half-life averaged 0.1 to 0.3 hours across species. Levodopa and carbidopa were rapidly formed following concomitant IV dosing of the prodrugs with the T_{max} of 0.1 hours. Following a single SC dose in rat and dog, foslevodopa and foscarbidopa were quickly absorbed (T_{max} 0.25 hours). An estimate of levodopa bioavailability was 67% in rats and ~100% in dogs; an estimate of carbidopa bioavailability was >90% in rats and dogs. Foslevodopa/foscarbidopa administered as a continuous IV infusion in both rats and monkeys provided constant concentrations of levodopa and carbidopa over the 4-week dosing interval. The prodrugs were rapidly converted to the respective parent compounds, with steady state values attained within the first day of dosing. There were no consistent sex differences in the measured foslevodopa, foscarbidopa, levodopa and carbidopa concentrations in either species. Levodopa and carbidopa concentrations were ~10-fold higher than the concentrations of the corresponding prodrugs, foslevodopa and foscarbidopa, respectively. Steady state levodopa and carbidopa concentrations (C_{ss}) and AUC values were roughly proportional to the administered doses.

Foslevodopa and foscarbidopa exhibit low cell permeability. The bioconversion of foslevodopa and foscarbidopa to levodopa and carbidopa is mediated by ubiquitous alkaline phosphatase.

The protein binding of foslevodopa and foscarbidopa were both low, with f_u >0.5 in rat, dog, monkey and human plasma.

The bioconversion of foslevodopa and foscarbidopa to levodopa and carbidopa is mediated by ubiquitous alkaline phosphatase. In preclinical species (rat, dog and monkey), both foslevodopa and foscarbidopa were efficiently converted to levodopa and carbidopa with a mean bioconversion ratio of 0.9 and 0.7, respectively.

Toxicology

The toxicology program of foslevodopa and foscarbidopa include studies on repeat-dose toxicity of up to 28 days in rats and monkeys, local tolerance studies up to 13 weeks in dogs, *in vitro* and *in vivo* genotoxicity studies and impurity qualifying studies. In the rat and monkey repeat dose studies, continuous IV administration was employed given technical issues in administering the test material

by continuous SC infusion in these species. However, continuous SC infusion was used in the local tolerance studies in dogs.

The non-clinical testing strategy was designed to evaluate systemic toxicity of foslevodopa/foscarbidopa and compare that to the toxicity profile of the parent drugs LD/CD. By demonstrating comparable general toxicity profiles between the prodrugs and the parent compounds, the approach is to leverage data previously generated with LD/CD (Duodopa MAA SE/H/415/001) to support special toxicity assessments (e.g., carcinogenicity and reproductive/developmental studies) of the prodrugs. Given that no apparent differences in the effects of foslevodopa and foscarbidopa versus LD and CD were observed in the secondary pharmacology screen, the safety pharmacology studies or in the limited toxicology studies and the rapid conversion of the prodrugs to their active moieties, also in humans, the above strategy was considered acceptable.

Repeat dose toxicity

Sprague-Dawley rats, beagle dogs and cynomolgus monkeys were used in the foslevodopa/foscarbidopa repeat-dose studies. In all species, foslevodopa and foscarbidopa were rapidly converted to levodopa and carbidopa, respectively. The continuous IV (rat, monkey) or SC (dog) dosing provided constant concentrations of levodopa and carbidopa over the dosing interval (4 weeks in rat and monkey; 13 weeks in dogs). Levodopa and carbidopa concentrations were approximately 10-fold higher than the concentrations of the corresponding prodrugs, foslevodopa and foscarbidopa, respectively, a profile comparable to that noted in the clinical studies.

The rat, monkey and dog are pharmacologically relevant for the safety assessment of foslevodopa/foscarbidopa.

Clinical observations

Noteworthy foslevodopa/foscarbidopa-related clinical signs indicative of CNS-behavioral effects occurred in the rat and cynomolgus monkey following IV administration, and in the dog following SC administration. These effects are consistent with that observed with LD/CD formulations in the cynomolgus monkey (this MAA) and previously in rats and dogs.

In the 2-week rat IV continuous infusion study, administration of foslevodopa/foscarbidopa resulted in clinical signs at ≥ 250/62.5 mg/kg that included vocalization and increased sensitivity to touch. In the 28-day rat GLP IV continuous infusion study, administration of ≥ 250/62.5 mg/kg foslevodopa/foscarbidopa resulted in CNS-related clinical signs that included, vocalization, stereotypy (rearing, hyper-reactivity), sensitivity to touch, aggression, and increased activity. These foslevodopa/foscarbidopa-related effects on clinical signs in rats did not reach a level of severity to be considered adverse.

In the 5-day monkey IV continuous infusion study, administration of foslevodopa/foscarbidopa resulted in CNS-related clinical signs at doses ≥ 100/25 mg/kg and included decreased activity and/or hunched posture and stereotypic behavior. Monkeys administered 200/50 mg/kg foslevodopa/foscarbidopa exhibited increased activity. In the 14-day monkey IV continuous infusion study, administration of foslevodopa/foscarbidopa resulted in increased activity and stereotypic behavior at ≥100/25 mg/kg. In the 28-day monkey GLP IV continuous infusion study, administration of foslevodopa/foscarbidopa resulted in CNS-related clinical signs at doses ≥ 200/50 mg/kg that included aggression, increased activity, and stereotypy (gnawing, head bobbing, hyper-reactivity). These clinical signs increased in incidence and severity at 300/75 mg/kg and additional clinical signs noted included hunched posture, and ataxia. The CNS-related signs in the 300/75 mg/kg group were associated with the expected pharmacological activity of foslevodopa/foscarbidopa and were consistent with IV continuous administration of the active LD/CD drug, the level of severity reached was considered adverse.

CNS effects observed in an early range-finding study in the dog included compulsive behavior, decreased activity, abnormal gait and lateral recumbency. Subsequent dog studies by the SC route were at lower exposures, which resulted in food consumption/body weight effects, but no prominent CNS effects.

Rats, monkeys, and dogs administered foslevodopa/foscarbidopa exhibited a dose-related decrease in food consumption resulting in a decrease in body weight/body weight gain. These effects are attributed to the expected pharmacological activity of LD/CD

Clinical Pathology

In the 4-week rat IV study, test article-related clinical pathology changes included minimal to mild decreases in hemoglobin concentration and hematocrit in both sexes at ≥ 250/62.5 mg/kg/day, mild decreases in mean corpuscular volume and mean corpuscular hemoglobin in males at 250/62.5 mg/kg/day and both sexes at 500/125 mg/kg/day, a mild decrease in reticulocyte count in females at 500/125 mg/kg/day, and minimal to mild decreases in lymphocyte counts, in both sexes at 500/125 mg/kg/day when compared to control values. The decreased lymphocyte counts correlated with the microscopic findings of minimal generalized lymphoid depletion in the thymus. Additional, findings included decreased urinary excretion of phosphorus in both sexes at ≥ 250/62.5 mg/kg/day, a mild increase in serum phosphorus concentration in males at 500/125 mg/kg/day, a mild increase in urine volume in females at ≥250/62 mg/kg/day, and minimal to mild increases in urea nitrogen and potassium concentrations and a minimal decrease in sodium concentration in males at 500/125 mg/kg/day when compared to the control group.

In the 4-week monkey IV study, evidence of an inflammatory response was observed in females at 100/25 mg/kg/day and both sexes at ≥200/50 mg/kg/day, which included increased fibrinogen and globulin concentration and decreased albumin concentration. This inflammatory response may be related to inflammation at the infusion site. Also noted were decreases in red blood cell mass in both sexes at 300/75 mg/kg/day; cholesterol concentration in males at ≥ 200/50 mg/kg/day and females at 300/75/ mg/kg/day; sodium in both sexes at 300/75 mg/kg/day; and serum phosphorus concentration in individual males and females at 300/75 mg/kg/day. These clinical pathology findings were all considered non-adverse.

In the 13-week dog SC study, there were no clinical pathology alterations considered test-article related.

Anatomic Pathology

In the 4-week rat IV study, test article-related findings were limited to the thymus and included decreased organ weights in males at ≥250/62.5 mg/kg/day and in females at 500/125 mg/kg/day. The organ weight changes correlated microscopically with non-adverse findings of minimal generalized lymphoid depletion.

In the 4-week monkey IV study, macroscopic findings were limited to severe small thymus were seen in one male and one female at 300/75 mg/kg/day which correlated with decreased mean thymus weights and microscopic findings of decreased lymphocytes in the thymus at this dose level. Thymic weights were also decreased in females at ≥100/25 mg/kg/day. Microscopically, generalized decreased lymphocytes (minimal to severe) were seen in the thymus of males and females at all dose levels in a dose-dependent manner.

In the 13-week SC dog study, macroscopic findings were limited to non-adverse brown/dark black discoloration at the local infusion site of high dose animals, which correlated with pigmented macrophages microscopically. Pigmented macrophages were also noted microscopically in all low dose animals and persisted at both dose levels at the infusion site and axillary lymph node during the 4-week recovery period. There were no systemic microscopic findings related to the test items.

The toxicity observed when studying the combination of foslevodopa/foscarbidopa was mainly displayed as clinical signs and largely attributed to exaggerated dopaminergic pharmacology. Normal animals are more sensitive to the dopaminergic stimulation of LD/CD when compared to patients with PD as dopamine deficiency is a key aspect of the disease state. This is particularly apparent for foslevodopa/foscarbidopa in the dog, where maximum tolerable doses result in exposures below those required for clinical efficacy. In rats and monkeys, margins of exposure greater than one are achievable.

Genotoxicity

Genotoxicity testing of foslevodopa/foscarbidopa consisted of *in vitro* testing of foslevodopa and foscarbidopa alone and *in vivo* testing of foslevodopa/foscarbidopa in combination. In the *in vitro* bacterial mutagenicity test, foslevodopa alone was negative with or without metabolic activation; foscarbidopa alone was positive without metabolic activation, which is consistent with existing CD data and does not represent a novel risk. Foslevodopa alone and foscarbidopa alone were not clastogenic in human lymphocyte cells *in vitro* with or without metabolic activation. Lastly foslevodopa/foscarbidopa was negative in an *in vivo* rat micronucleus test. Given the consistent findings of foslevodopa and foscarbidopa with those reported for LD and CD, and the lack of a tumorigenic response of LD/CD in an oral gavage 2-year rat carcinogenicity study, the overall genotoxic risk for foslevodopa/foscarbidopa is considered acceptable.

Carcinogenicity

No carcinogenicity studies with foslevodopa/foscarbidopa have been conducted.

In rat, oral administration of LD/CD for 2 years resulted in no evidence of tumorigenesis. The carcinogenic potential of LD/CD was assessed in rats given 25/10, 50/10 or 100/10 mg/kg/day daily by gavage for two years. Survival was similar in control and drug-treated groups. Transient ptyalism (excessive salivation) and decreased activity were observed at 100/10 mg/kg/day. Body weight gain in males was decreased at 50/10 and at 100/10 mg/kg/day; no effects on body weight were observed in females. There were no drug-related non-neoplastic pathologic changes, and the incidence of tumors was similar in control and drug-treated groups. Thus, LD/CD was not carcinogenic in rats.

Reproductive toxicity

No reproductive toxicity studies with foslevodopa/foscarbidopa have been conducted. This is considered acceptable, and available information on reproductive and developmental toxicity identifies a risk of embryofoetal toxicity, if used in pregnancy, for combinations of levodopa and carbidopa. This risk is largely attributed to effects of levodopa. Levodopa alone, and in combination with carbidopa, has caused visceral and skeletal malformations in rabbits. Consequently, Produodopa should not be used during pregnancy unless the benefits for the mother outweigh the possible risks to the foetus (see SmPC 4.6).

Local tolerance

The dog was used to assess local tolerability as it was the only species where continuous SC administration was technically feasible. In a 13-week dog study, clinically relevant formulations were tested (i.e., identical foslevodopa/foscarbidopa concentrations 20:1, vehicle and pH). The dose volumes tested in the dog were necessarily lower than those tested in humans based on body weight differences and pharmacologic sensitivity of normal animals to dopaminergic stimulation; however, the exposures in the dog are considered to represent an exaggerated tissue exposure as the same site was used continuously for the duration of the study This contrasts with the clinical setting where a particular injection site is used for three days and then rotated among 12 different sites.

The 13-week dog study did not demonstrate any foslevodopa/foscarbidopa-mediated exaggeration of the infusion site inflammation. A number of procedure-related changes associated with the presence of the SC catheter, the catheter loop or the catheter port were observed in all animals and considered to be due to the expected response in the SC tissue to an indwelling foreign material. Overall, the infusion site changes were comparable between the two foslevodopa/foscarbidopa-treated groups (continuous infusion versus alternating dosing for 91 days), and between these two groups and the concurrent controls, in terms of incidence and severity, suggesting that foslevodopa/foscarbidopa was generally locally well tolerated and similar to the vehicle formulation under the conditions of this study.

Hydrazine

Hydrazine is a well-known degradation product of carbidopa and potentially forms in foslevodopa/foscarbidopa during storage and handling. Hydrazine is reported to be genotoxic and

carcinogenic in animals and classified as possible carcinogenic in humans, however in humans, the main concern is via inhalation exposure). Four *in vitro* studies and one *in vivo* study were conducted with hydrazine to better characterise its mechanism for genotoxicity. However, the conclusion that hydrazine is mutagenic in mammalian cells remains, and thus the recommendations in ICH M7 (R1) are applicable.

The proposed specification limit for hydrazine in foscarbidopa is 0.175%. At the maximum clinical dose (300 mg/day foscarbidopa), this corresponds to a worst-case daily hydrazine dose of 525 µg. Most patients will be exposed to the hydrazine levels above the lifetime AI of 39 µg/day as outlined in ICH M7 (R1) and many patients may also be exposed to levels above a less-than-lifetime (10 years) adjusted AI of 273 µg/day indicating a potential risk to the patients. This risk should be communicated and weighed against the benefit of the product in the intended patient population, i. e. a limited number of severely disabled patients with advanced Parkinson´s disease where available combination of Parkinson medications has not given satisfactory effect. This is further discussed in the benefit risk assessment.

A warning for hydrazine content in Produodopa in SmPC section 4.4 is included and also information on hydrazine in section 5.3. Foslevodopa/foscarbidopa does not absorb light at 290 to 700 nm and therefore further phototoxicity assessments were not conducted, consistent with ICH S10. The risk for phototoxicity is considered low.

The distinguishing feature of foslevodopa/foscarbidopa that differentiates it from LD and CD is the monophosphate group attached to each active drug moiety. The anticipated daily phosphorus load from the highest proposed clinical dose of 6000/300 mg/day of foslevodopa/foscarbidopa is approximately 700 mg, which is considerably less than the 3,000 mg/day National Academy of Sciences dietary reference intake upper limit (2006). According to EFSA (2015), the AI for phosphorus is 550 mg/day for adults including pregnant and lactating women.

Environmental Risk Assessment (ERA)
Produodopa consists of foslevodopa and foscarbidopa which are readily biotransformed into the active substances levodopa and carbidopa. Therefore, two ERAs (one for levodopa and one for carbidopa) were conducted.

Levodopa

Levodopa has a molecular weight of 197.19 g/mol. It is hydrophilic with a water solubility of 3.32 mg/mL and a log K_{OW} of - 2.59. The Phase I surface water PEC (PEC_{SW}) for levodopa was calculated to 0.19 µg/L using a refined Fpen based on incidence (obtained from Orphanet)

The aerobic transformation study, using whole fresh water-sediment systems, showed that levodopa disappears rapidly in water (though a DT_{50} value could not be determined), with a slight tendency to accumulation sediment (13.5% AR after 14d> 10%). A range of minor transformation products were detected. The adsorption coefficient Koc of 7.7 L/Kg (estimated using TG121) is well below the action limit (10 000 L/Kg), suggesting a low risk of levodopa to the terrestrial environment due to agricultural use of sludge. OECD TG106 tests with levodopa to determine adsorption constants were unsuccessful due to rapid degradation of the substance.

For aquatic toxicity, the lowest NOEC and LOEC values reported were 0.20 mg/L and 0.59 mg/L, respectively, for freshwater algae cell density/yield. For sediment-dwelling chironomid larvae survival, the NOEC and LOEC were 458 mg/kg and > 853 mg/kg, respectively.

Ecological risk: Levodopa is not classified as a PBT candidate. The applicant reports PEC/PNEC ratios for levodopa based on an incidence-refined Fpen (derived from Orphanet). The reported risk ratios for the different environmental compartments (i. e. surface water, ground water, sludge and sediment) are well below the action limits suggesting that levodopa is unlikely to represent a risk to the environment.

Summary of main study results for levodopa:

Substance (INN/Invented Name): Levodopa					
CAS-number (if available): 59-92-7					
PBT screening		Result			Conclusion
Bioaccumulation potential - log K_{ow}	OECD TG107	log K_{ow} = - 2.59, well below trigger value 4.5			Potential PBT (N)
Phase I					
Calculation	Value	Unit			Conclusion
PEC $_{surface\ water}$, refined (e.g. prevalence, literature)	0.19	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD TG121	K_{oc} = 7.7 L/Kg (estimated using TG 121)			K_{doc} sludge < 10 000 L/kg Indirect HPLC method due to rapid transformation of levodopa
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	DT_{50} not determined. % shifting to sediment = 9.4-13.5 % AR at 14d, thereafter 9.4-11.1 % AR until d 102, excl NER.			%AR in sediment (14d) > 10, triggers an OECD TG218 test.
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species*	OECD TG 201	NOEC Average cell density and yield	200	µg/L	*Raphidocelis subcapitata*
Daphnia sp. Reproduction Test	OECD TG 211	NOEC	1900	µg/L	*D. magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD TG 210	NOEC	8900	µg/L	*P. promelas*
Activated Sludge, Respiration Inhibition Test	OECD TG 209	NOEC	1000	mg/L	Sludge from Easton WWTP, MD, US.
Phase IIb Studies					
Sediment dwelling organism	OECD TG218	$NOEC_{survival}$ NOECoc10	458000 3271000	µg/kg	*C. riparius*

Carbidopa

Carbidopa has a molecular weight of 226.23 g/mol. It is hydrophilic with a water solubility of 1.29 mg/mL and a log K_{OW} of - 2.18 (pH 7). The Phase I surface water PEC (PEC_{SW}) for carbidopa was determined to 0.027 µg/L µg/L using a refined Fpen based on incidence (obtained from Orphanet). The PEC_{SW} value exceeds the action limit of 0.01 µg/L and triggers ERA phase IIA assessment.

In whole fresh water-sediment systems, carbidopa is biodegradable in water with DT_{50} values of less than 2 d (12°C) with a low tendency to accumulate in sediment (~10% AR after 14d). A range of minor transformation products were detected. The adsorption coefficient Koc of 19.6 L/kg (estimated

using TG121) is well below the action limit (10 000 L/Kg), suggesting a low risk of levodopa to the terrestrial environment due to agricultural use of sludge. OECD TG106 tests with carbidopa to determine adsorption constants were unsuccessful due to rapid degradation of the substance.

For aquatic toxicity, algal growth rate was the most sensitive endpoint reported, with NOEC and LOEC values of 0.13 and 0.24 mg/L. An OECD TG209 study was conducted but the results were difficult to interpret and no NOEC value for sludge microorganisms could be determined. That being said, as carbidopa is not an anti-microbial substance, no new test is required. For sediment-dwelling chironomid larvae survival, the NOEC and LOEC were 730 mg/kg and > 730 mg/kg, respectively.

Ecological risk: Carbidopa is not classified as a PBT candidate. The applicant reports PEC/PNEC ratios for carbidopa based on a refined Fpen obtained from Orphanet. The reported risk ratios for different environmental compartments (i.e. surface water, ground water and sediment) are well below the action limits suggesting that carbidopa is unlikely to represent a risk to the environment.

Summary of main study results for carbidopa:

Substance (INN/Invented Name): Carbidopa					
CAS-number (if available): 38821-49-7					
PBT screening		Result			Conclusion
Bioaccumulation potential - log K_{ow}	OECD TG107	log K_{ow} = - 2.18, well below trigger value 4.5			Potential PBT (N)
Phase I					
Calculation	Value	Unit			Conclusion
$PEC_{surface\ water}$, refined (prevalence, literature)	0.027	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD TG121	K_{oc} = 19.6 L/kg at 25 °C (estimated using TG 121)			K_{doc} sludge < 10 000 L/kg Indirect HPLC method due to rapid trans-formation
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = ~0.67-1.7d % shifting to sediment = 10.8 % AR after 14d.			%AR(14d) > 10 Triggers an OECD TG218 test.
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species*	OECD TG 201	NOEC Growth rate	130	µg/L	*Raphidocelis subcapitata*
Daphnia sp. Reproduction Test	OECD TG 211	NOEC	1700	µg/L	*D. magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD TG 210	NOEC	1500	µg/L	*P. promelas*
Activated Sludge, Respiration Inhibition Test	OECD TG 209	NOEC	Not available	mg/L	Sludge from Easton WWTP, MD, US.
Phase IIb Studies					
Sediment dwelling organism	OECD TG218	NOEC NOECoc10	730 000 000 5 214 000	µg/kg	*C. riparius*

IV. CLINICAL ASPECTS

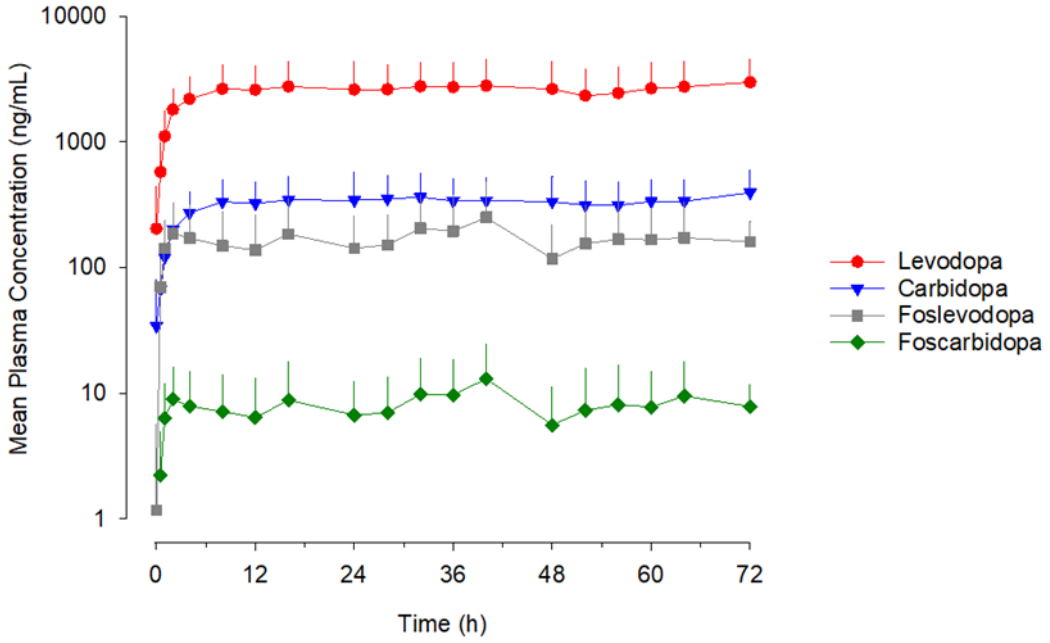
Pharmacokinetics

Produodopa is intended as a line extension to Duodopa. The application is based upon PK comparability of Produodopa to Duodopa (LCIG) from Study M17-220 supported by comparability study M20-141 and is further supported by a long-term open-label safety and tolerability study of Produodopa. Produodopa contains foslevodopa and foscarbidopa which are highly soluble prodrugs to levodopa and carbidopa which enables administration as a continuous subcutaneous infusion.

Plasma concentrations of foslevodopa (LDP4), foscarbidopa (CDP4), levodopa (LD), carbidopa (CD) and 3-O-methyldopa (3-OMD) in human K2EDTA plasma treated with disodium hydrogen arsenate and sodium metabisulfite were determined using validated LC/MS/MS methods.

From study M15-738 the following exposure of both prodrugs and LD and CD was achieved in patients with Parkinson's disease (figure 1). This figure is an average across all of the CDP/LDP dose levels from Part 2 of the study (n=14).

Figure 1. Exposure of foslevodopa, foscarbidopa, levodopa and carbidopa during 72 hour infusion of produodopa in patients with PD (study M15-738).



The two main bridging studies provide the following summary statistics.

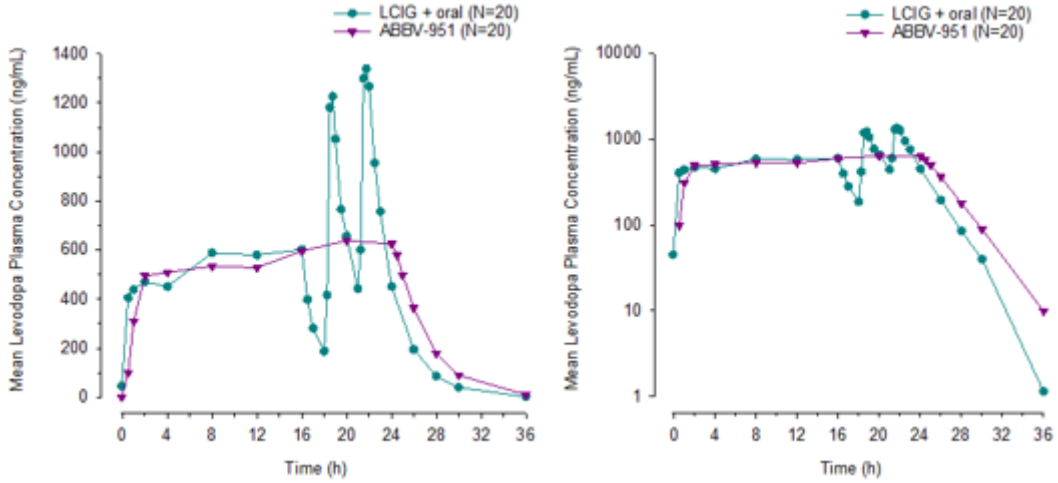
Table 1. Study M17-220: Relative Bioavailability and 90% Confidence Intervals of Levodopa for Subjects Who Completed Both Levodopa/carbidopa Intestinal Gel and ABBV-951 Regimens

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen B vs. Regimen A	$C_{max,0-16}$	606	656	0.923	0.873, 0.975
	AUC_{0-16}	7810	8220	0.951	0.893, 1.012
	AUC_{∞}	14900	14700	1.009	0.969, 1.049

Regimen A: Levodopa/carbidopa intestinal gel (12.5/50 mg carbidopa/levodopa loading dose followed by 87.5/350 mg carbidopa/levodopa over 16 hours followed by two 25/100 mg carbidopa/levodopa oral doses at 18 and 21 hours after the start of infusion). Levodopa/carbidopa intestinal gel was delivered via a portable infusion pump through a nasojejunal tube.

Regimen B: ABBV-951 (4/80 mg foscarbidopa/foslevodopa loading dose followed by 35/700 mg foscarbidopa/foslevodopa over 24 hours). ABBV-951 was delivered via a portable infusion pump subcutaneous into the abdomen.

Figure 2. Study M17-220: Mean Levodopa Exposure Following 24-hour CDP/LDP Infusion and 16-hour LCIG Infusion Followed by Nighttime Oral LD/CD Doses



Study M20-141 was performed to assess the pharmacokinetics of CD and LD from ABBV-951 relative to that from LCIG in healthy adults, with both ABBV-951 and LCIG infused for 24 hours. Due to an incorrectly listed priming volume for the nasojejunal tube used for LCIG approximately 5 mL (100 mg LD) were delivered during the LCIG priming phase prior to when dosing was intended to start which could explain the differences in observed Cmax.

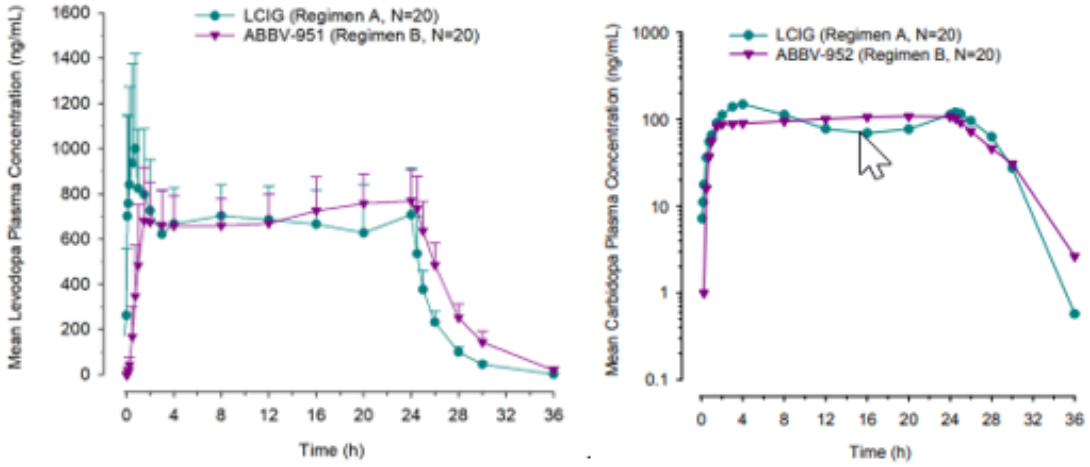
Table 2. Study M20-141: Relative Bioavailability and 90% Confidence Intervals of Levodopa for Subjects Who Completed Both Levodopa/carbidopa Intestinal Gel and ABBV-951 Regimens.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen B vs. Regimen A	C_{max}	831	1260	0.662	0.599, 0.731
	AUC_t	18800	17400	1.081	1.043, 1.122
	AUC_∞	18900	17500	1.082	1.043, 1.122

Regimen A: Levodopa/carbidopa intestinal gel (15/60 mg carbidopa/levodopa loading dose followed by 168/672 mg carbidopa/levodopa over 24 hours). Levodopa/carbidopa intestinal gel was delivered via a portable infusion pump through a nasojejunal tube.

Regimen B: ABBV-951 (4.8/96 mg foscarbidopa/foslevodopa loading dose followed by 43.2/864 mg foscarbidopa/foslevodopa over 24 hours). ABBV-951 was delivered via a portable infusion pump subcutaneous into the abdomen.

Figure 3. Study M20-141: Mean (+ SD) Levodopa (left) and Carbidopa (right) Exposure Following 24 hour CDP/LDP Infusion and 24-hour Duodopa Infusion



Foslevodopa and foscarbidopa prodrugs are rapidly converted by phosphatases into LD and CD. Study M17-220 shows that 4 hours following discontinuation of infusion there is no longer detectable foslevodopa in the systemic circulation while the majority of the foscarbidopa concentrations were below the limit of quantitation.

The interaction potential of both foslevodopa and foscarbidopa has been investigated in vitro for all mandatory enzymes and transporters. According to the Applicant no interactions are expected at the projected clinically maximal exposure, however limitations in the experimental setup renders this uncertain, see discussion below.

Discussion on pharmacokinetics

Produodopa contains foslevodopa (LDP) and foscarbidopa (CDP). Foslevodopa and foscarbidopa are as prodrugs new active substances, however the active entities levodopa and carbidopa have been used in the clinic for nearly 50 years as oral formulation and also previously characterised and approved as an intestinal gel under the tradename Duodopa® (MAA SE/H/415/001) for which Produodopa is intended as a line extension. The application is based upon PK comparability of Produodopa to Duodopa (LCIG) from Study M17-220 and is further supported by a long-term open-label safety and tolerability study of Produodopa. Thus, the pharmacokinetics of levodopa (LD) and carbidopa (CD) is based on the previous approvals.

Following subcutaneous infusion (commonly in abdomen) of CDP/LDP via a portable pump, the compounds are rapidly absorbed and by alkaline phosphatase converted to the active moieties, levodopa (LD) and carbidopa (CD). LD and CD could be detected in plasma at 30 minutes after start of infusion, which was the earliest PK collection time point in any of the completed clinical studies. The intended administration is a 24 h continuous infusion and therefore constant but low levels of CDP and LDP will circulate in plasma. Neither foslevodopa nor foscarbidopa has pharmacologic activity on target.

Produodopa is indicated for the treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of Parkinson's medicinal products have not given satisfactory results. CDP/LDP is intended to be used in place of CD/LD therapy and the recommended starting dose of CDP/LDP is based on each patient's previous individualised LD containing medications using conversion factors to levodopa equivalents. The CDP/LDP infusion rate is further on intended to be modified on an individual patient level to optimally control motor symptoms. This is appropriate as the patients' previous treatment was not adequate (per indication).

ADME: No absolute bioavailability and mass balance studies have been performed in humans with foslevodopa/foscarbidopa. In rat and dog following a single subcutaneous dose of foslevodopa and foscarbidopa, an estimate of levodopa bioavailability was 67% in rats and ~100% in dogs and an estimate of carbidopa bioavailability was >90% in rats and dogs (see further data in the nonclinical assessment). The lack of human mass balance and absolute bioavailability studies is acceptable for this application.

The relative bioavailability of carbidopa was higher after SC administration of foscarbidopa compared to oral administration of CD. Different CDP:LDP ratios were explored and a 1:20 ratio resulted in similar CD:LD AUC ratio compared to a 1:4 ratio after oral administration. The Applicant showed that the SC administration in abdomen, arm and thigh resulted in similar exposure of LD and CD. The supporting data related to absorption of CDP/LDP is adequate.

In study M17-220 comparable exposure of levodopa (LD) between the produodopa and duodopa (LCIG) regimens was shown using standard bioequivalence criteria for the primary PK variables AUC_{0-16}, AUC_{∞} and $Cmax_{0-16}$ of LD. For the produodopa (CDP/LDP 35/700 mg) infusion over 24 hours, levodopa $Cmax_{0-16}$ and AUC_{0-16} exposures were 8% and 5% lower, respectively, and AUC_{∞} exposure was 0.9% higher relative to duodopa (CD/LD 87.5/350 mg) infusion over 16 hours plus two 25/100 mg carbidopa/levodopa oral doses at 18 and 21 hours after the start of infusion. Importantly also the exposure of CD was similar (less than 10% difference) although not analysed using BE-criteria. This is acceptable as it is LD that drives pharmacological efficacy, and the role of CD is to inhibit the DOPA decarboxylase enzyme to boost the exposure of LD. PK comparability for AUC is also supported by results from study M20-141 where both CDP/LDP and LCIG infused for 24 hours. Dosing errors precludes concluding comparability for Cmax for this study.

The plasma protein binding is low for CDP, LDP, CD and LD which is adequately described in the SmPC.

Special populations: No specific studies or analysis has been performed in most of the special population subgroups. The lack of data is in general acceptable as the conversion to LD/CD is dependent on phosphatases with high capacity and therefore the risk is considered to be low for differences between subpopulations. In addition, the treatment is individualised and the starting dose of CDP/LDP is based on each patient's previous individualised LD treatment regimen and the CDP/LDP infusion rate is modified on an individual patient level to optimally control motor symptoms. The lack of data in the paediatric population is acceptable as there is no relevant use of CDP/LDP continuous subcutaneous infusion (CSCI) in this population for the intended indication.

The lack of dedicated studies is acceptable, and no dose adjustment is considered necessary in RI/HI

population or due to weight, gender, age, and race. It is still not convincingly shown that absorption is not slower in the overweight population, however it is believed that this will be handled in clinical praxis as the SmPC contains several recommendations enabling individualization of the dose with e.g. oral doses of LD.

Interactions: No clinical DDI studies have been performed with Produodopa, this is also the case for Duodopa, and the SmPCs of these products contain information in section 4.5 based on other oral LD and CD. The levels of circulating CDP and LDP are relatively low. LD Cmax was approx. 10 times higher than LDP and CD Cmax was 20 – 30 times higher than CDP.

Regulatory required in vitro interaction studies with CDP and LDP as perpetrator have been performed, i.e., CYP inhibition, CYP induction and drug transporter inhibition. However, there was no information on the stability of LDP and CDP during the incubations when investigating the CYP inhibition and drug transporter inhibition. The duration of these incubations is short, and based on the information regarding phosphatase activity and the degradation data of the compound from the induction experiments, loss of compound in these assays is not a concern. Still the transporter inhibition experiments does not include LDP-concentrations above the cut-off and an in vivo interaction risk can therefore not be excluded. The Applicant has agreed to provide new in vitro experiments post-approval and the results are expected Q1 2023 awaiting these results a warning has been included in the SmPC reflecting the interaction risk.

For the CYP induction it was shown that both CDP and LDP were unstable during the incubation time, e.g. for CDP, in general, ca. 50% and 10% was remaining after 4 h and 24 h, respectively and thus the actual exposure to CDP is uncertain. The Applicant has based on three concentration measurements calculated time-weighted average concentrations to account for compound loss during the incubation. These are based on 3 concentration measurements and thus rather crude and not unlikely to overestimate the actual concentration. Using the TWA concentration there is a positive signal for CYP1A2 induction by CDP and this risk is reflected in the SmPC.

Clinical efficacy

Introduction

The clinical development program for ABBV-951 includes 8 Phase 1 studies (6 in healthy subjects and 2 in subjects with PD) and 2 ongoing Phase 3, open-label, single-arm, safety and tolerability studies in subjects with aPD that are being conducted in Europe, North America, Japan, and Australia (Table 3). At the time of submission of the MAA, a Phase 3 controlled clinical study, Study M15-736 ("Randomized, Double-Blind, Double-Dummy, Active-Controlled Study Comparing the Efficacy, Safety and Tolerability of ABBV-951 to Oral Carbidopa/Levodopa in Advanced Parkinson's Disease Patients"), was ongoing in the United States and Australia. Data from this study and its extension Study M20-098 are intended to be submitted, along with any supporting labeling changes, as a post-approval variation, as agreed upon with the Swedish Medical Products Agency (MPA).

The MAA for ABBV-951 is a line extension to Duodopa as discussed and previously agreed with the Swedish MPA (Ref ID 5.4.1-2021-006605), the Reference Member State. The application is based upon PK comparability of ABBV-951 to Duodopa (LCIG) from Study M17-220 and is further supported by a long-term open-label safety and tolerability study of ABBV-951 (Study M15-741) in subjects with aPD.

Table 3. Descriptions of Clinical Efficacy and Safety Studies

Study ID/ No. of Centers/ Locations/ Duration	Study Start Date, Enrollment Status, Total Enrollment/ Enrollment Goal	Design Type	Study Drug Dose, Route & Regimen	Study Objectives	No. of Subjects Entered/ Completed	Sex M/F Median Age (Min, Max)	Diagnosis Inclusion Criteria	Primary Endpoints[a]
M15-741/ 56/ Australia, Belgium, Canada, Denmark, Germany, Italy, Japan, Netherlands, Spain, Sweden, UK, US/ up to 52 weeks	29 April 2019 Ongoing, 223/~240	Phase 3, open-label, single-arm multicenter	Individualized therapeutic dose of ABBV-951, CSCI, 24 hours daily	Primary Assess the local and systemic safety and tolerability of ABBV-951 delivered as a CSCI for 24 hours daily for up to 52 weeks Secondary Assess the efficacy of ABBV-951 as measured by patient-reported and rater-measured efficacy endpoints	223/77	134 males 89 females 65.0 years (34, 86)	Adult male or female subjects, ≥ 30 years of age at Screening with a diagnosis of idiopathic PD that is LD-responsive. Subjects must have been judged by the investigator to be inadequately controlled by current therapy, have recognizable/ identifiable "Off" and "On" states (motor fluctuations), and have a minimum of 2.5 hours of "Off" time per day	1. Percentage of subjects with AEs and SAEs during the study 2. Percentage of subjects with AESIs during the study 3. Percentage of subjects with numeric grade equal to or higher than 5 and percentage of subjects with letter grade equal to or higher than D on the Infusion Site Evaluation Scale at any time during the study 4. Change in clinical laboratory test data from BL to end of study 5. Change in vital sign measurements from BL to end of study 6. Change in ECGs from BL to end of study

Study ID/ No. of Centers/ Locations/ Duration	Study Start Date, Enrollment Status, Total Enrollment/ Enrollment Goal	Design Type	Study Drug Dose, Route & Regimen	Study Objectives	No. of Subjects Entered/ Completed	Sex M/F Median Age (Min, Max)	Diagnosis Inclusion Criteria	Primary Endpoints[a]
M15-737/ 37/ Australia, Belgium, Canada, Denmark, Japan, Netherlands, Spain, UK, US/ up to 96 weeks	08 June 2020 Ongoing, 72/~130	Phase 3, open-label, single-arm multicenter extension of Study M15-741	Individualized therapeutic dose of ABBV-951, CSCI, 24 hours daily	Primary Assess the local and systemic safety and tolerability of continued ABBV-951 treatment delivered as a CSCI for 24 hours daily	72/0	49 males 23 females 63.5 years (34, 86)	Subjects who completed Study M15-741 and remained on study drug	1. Percentage of subjects with AEs and SAEs during the study 2. Percentage of subjects with AESIs during the study 3. Percentage of subjects with numeric grade equal to or higher than 5 and percentage of subjects with letter grade equal to or higher than D on the Infusion Site Evaluation Scale at any time during the study 4. Change in clinical laboratory test data from BL to end of study 5. Change in vital sign measurements from BL to end of study 6. Change in ECGs from BL to end of study

Dose-response studies and main clinical studies

In a randomized, 2-period crossover, Phase 1 study in healthy volunteers (Study M17-220), LD PK was shown to be comparable between administration of ABBV-951 over 24 hours and administration of LCIG over 16 hours followed by 2 night-time LD/CD oral doses (at 18 and 21 hours after the start of LCIG infusion). The oral LD night-time doses were chosen to represent all sources of LD taken during a 24-hour period as an example of a typical treatment day in patients with aPD who use LCIG for their motor and nonmotor fluctuations but continue to experience symptoms (such as, nocturnal akinesia, morning akinesia, early morning dystonia, and difficulty turning in bed) once the infusion of LCIG is suspended for the night. Scientific evidence supports providing continuous dopaminergic stimulation as a strategy to control these nocturnal symptoms (Barone 2004). LD remains the recommended therapeutic approach for nighttime symptoms as it bears less risk of undesirable adverse events compared to long-acting dopamine agonists. In Study M17-220, two tablets of LD/CD were chosen as a representation of this commonly adopted therapeutic strategy. By demonstrating PK

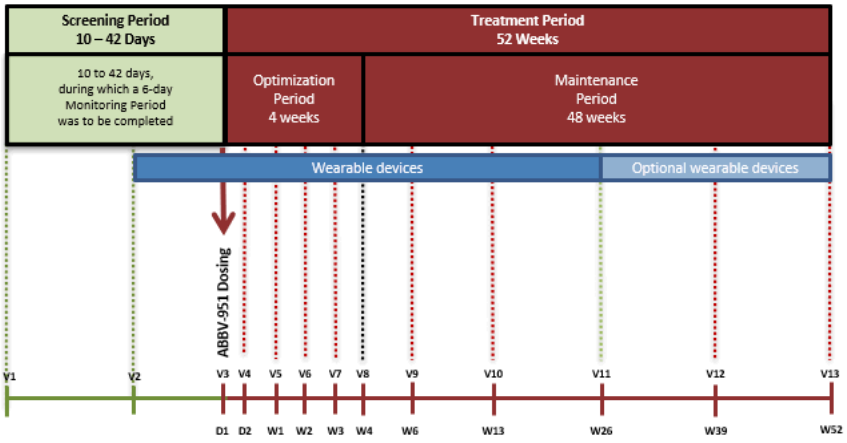
comparability of LD, efficacy for ABBV-951 is extrapolated from the efficacy of LCIG as described in the Duodopa Summary of Product Characteristics (SmPC).

The proposed dose was based on data obtained from a PK study in healthy volunteers (Study M17-220). In principle such approach is acceptable. The separate assessment of the Study M17-220 is presented in a separate PK report.

Main study(ies)

The efficacy of ABBV-951 was evaluated as secondary endpoints in a Phase 3, 52-week, open-label study (Study M15-741) and in a Phase 3, 96-week, open-label extension of Study M15-741 (Study M15-737). Study M15-741 is a Phase 3, open-label, single-arm, multicenter, global study in subjects 30 years of age or older, with a diagnosis of LD-responsive idiopathic PD and whose motor symptoms were inadequately controlled by oral medications. The study consists of a Screening Period of 10 to 42 days and a 52-week Treatment Period as shown in Figure 1. Subjects are receiving an individualized continuous subcutaneous infusion (CSCI) (24 hours daily) of ABBV-951 for up to 52 weeks.

Figure 3. Study M15-741 Schematic



This open label study is primarily a safety study. Efficacy endpoints are evaluated as secondary endpoints.

Methods

- **Study Participants**

Subjects are required to have identifiable "Off" and "On" states (motor fluctuations) and have a minimum of 2.5 hours of "Off" time per day prior to study entry. Eligible subjects who completed the 52-week Treatment Period can enter a separate extension study (Study M15-737) for 96 weeks of additional treatment with ABBV-951.

The patient population included into the study reflects the patient population described in the proposed indication.

- **Treatments**

Following an initial oral loading dose of LD, administered with a peripheral DDCI, such as CD or benserazide, ABBV-951 is initiated and delivered continuously (24 hours daily) via an infusion set connected to a portable pump. The oral loading dose should correspond as closely as possible to the subject's habitual first morning dose of LD + DDCI and is meant to expedite achievement of the

individualized LD plasma concentration, which exerts the optimal therapeutic effect. Each subject's initial base continuous infusion rate is calculated based on the subject's oral LD therapy taken over the 16-hour treatment period for a typical waking day prior to ABBV-951 initiation and using an algorithm developed following a combination of PK and clinical considerations from ABBV-951 Phase 1 studies to account for 24-hour dosing. The ABBV-951 base infusion rate can be adjusted at the investigator's discretion at any time throughout the study to achieve and maintain an optimal therapeutic response for the individual subject, which means maximizing the functional "On" time during the day by minimizing the number and duration of "Off" episodes (bradykinesia) and minimizing "On" time with troublesome dyskinesia. At the investigator's discretion, subjects can also select from 2 prescribed, alternative infusion rates: one higher and one lower than the base infusion rate. The high infusion rate is within a 20% limit above the prescribed base infusion rate; the low infusion rate is within a 20% limit below the prescribed base infusion rate. The low infusion rate is permitted to be reduced beyond the 20% limit from the prescribed base infusion rate if medically necessary and only with approval from the AbbVie therapeutic area medical director.

The initial loading dose as well as continuous infusion rate of treatment is calculated based on previous treatment with oral LD+DDCI. The dose adjustment is allowed in order to achieve the optimal treatment effect, which is acceptable.

- **Objectives**

The primary objective is to assess the local and systemic safety and tolerability of ABBV-951 delivered as a CSCI for 24 hours daily for up to 52 weeks. The secondary objective is to assess the efficacy of ABBV-951 as measured by patient-reported and rater-measured efficacy endpoints.

- **Outcomes/endpoints**

Primary endpoints (safety)

The primary endpoints include the following safety variables:

1. Percentage of subjects with adverse events (AEs) and serious adverse events (SAEs) during the study

2. Percentage of subjects with AEs of special interest (AESI) during the study

3. Percentage of subjects with numeric grade equal to or higher than 5 and percentage of subjects with letter grade equal to or higher than D on the Infusion Site Evaluation Scale at any time during the study

4. Change in clinical laboratory test data from Baseline to end of study

5. Change in vital sign measurements from Baseline to end of study

6. Change in electrocardiograms (ECGs) from Baseline to end of study

Secondary endpoints (efficacy)

The efficacy endpoints are change from baseline to end of study for the following:

1. Average normalized daily "Off" time and "On" times as assessed by the PD Diary

2. PD symptoms as assessed by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I-IV scores and Hoehn and Yahr Stage

3. Sleep symptoms as assessed by the PD Sleep Scale-2 (PDSS-2): total score and domain scores

4. Quality of life as assessed by the PD Questionnaire-39 items (PDQ-39): summary index and domain scores

5. Health-related quality of life as assessed by the EuroQol 5-dimensions questionnaire (EQ-5D-5L): summary index and visual analogue scale (VAS)

6. Early morning motor symptom derived from PD Diary

Cane pump-specific endpoints are as follows:

Safety

1. Percentage of subjects with AEs and SAEs associated with pump specific product quality complaints.

2. The percentage of pumps that were replaced due to pump malfunction

Effectiveness

1. The number of times a subject was required to take rescue medication due to pump malfunction

Neria™ Guard infusion set-specific endpoints are as follows:

Safety

1. Percentage of subjects with AEs and SAEs associated with Neria™ Guard infusion set-specific product quality complaints.

Effectiveness

1. The number of product complaints associated with the Neria™ Guard infusion set that resulted in the subject replacing the infusion set.

- **Sample size**

At the planning stage, it was expected to enrol approximately 130 subjects to obtain exposure data from 100 subjects treated with 24 hour daily CSCI of ABBV-951 for at least 12 months assuming a 23% study dropout rate. The sample size could be increased if the dropout rate was shown to be higher than expected.

With the initially planned 130 subjects receiving ABBV-951, the probability to observe an AE with an annual incidence rate of 0.01, 0.02 and 0.05 was 73%, 93%, and 99.9%, respectively.

During the study the sample size has been increased. With 240 subjects receiving ABBV-951, the probability to observe an AE with an annual incidence rate of 0.005, 0.01, and 0.02 is 70%, 91%, and 99%, respectively.

The aim is to obtain exposure data from 100 subjects treated with 24 hour daily CSCI of ABBV-951 for at least 12 months. Initially, the drop-out rate was assumed to be 23% implying that enrolment of 130 subjects would suffice. Due to a higher than anticipated number of premature discontinuations, the sample size has been increased twice. First to 160 (CSP version 3.0, SAP version 3.0) and, as clear from the SAP version 4.0, to 240.

As has been clarified in the study report, the main reasons for the premature discontinuations were determined to be attributed to difficulties with using the drug delivery system and infusion site skin AEs. This led to retraining for the study sites and subjects on the correct use and application of the infusion set cannula. In addition, the *primary intended* commercial infusion set for delivery of ABBV-951 (Neria™ guard), was added in protocol version 6 which implied that subjects who enrolled under version 6 were required to begin the study using the Neria guard infusion set rather than the Cleo 90 infusion set. Subjects enrolled under protocol versions 1 through 5 could switch from the Cleo 90 infusion set to the Neria guard infusion set after protocol Version 6 was approved at their sites.

Analyses were added to assess the result of discontinuation mitigations and have been presented comparing sample 1 and sample 2, defined using the date for protocol version 6 as cut-off (08-Jul-2020).

The data cut-off date for the current interim analysis was chosen as to have data from at least 100 subjects treated for at least 26 weeks. At the time-point for the cut-off, 223 subjects had been enrolled.

- **Randomisation**

Not applicable. This is a single-arm study.

- **Blinding (masking)**

Not applicable. This is an open-label study.

- **Statistical methods**

The current application refers to an interim analysis of study M15-741. The interim analysis data cut-off date was 30 March 2021. The submitted SAP version 4.0 was dated 10 March 2021.

Two interim analyses were planned during the course of this study. The first (and current) interim analysis was performed after at least 100 subjects had completed at least 26 Weeks of therapy. A second interim analysis is planned to be performed after at least 100 subjects have completed 52 Weeks of therapy (added with SAP version 4). Interim locks will occur to preserve the clinical database to be used for these interim analyses. All the analyses described in the SAP were to be performed, except for analysis of change from baseline to the final visit.

Subgroups

Unless otherwise noted, all analyses were to be conducted by subgroup defined by dose category (low dose or high dose) according to total daily levodopa dose from levodopa phosphate (LDP) by molecular weight calculated from dosing diary. Each subject will be categorized to a dose subgroup based on the modal total daily dose over the treatment period.

Analyses of dosing diary data were to be performed on valid dosing diary days. A valid dosing diary day was defined as one in which ABBV-951 has been infused ≥ 80% of the entire 24-hour period (i.e., ≥ 19.2 hours).

Subgroup analyses

Subgroup analyses were further pre-planned for gender, race, age, geographic region, and PD duration with additional subgroup analyses to be conducted as considered appropriate.

Analysis populations

The Safety Analysis Set consisted of all subjects who received any ABBV-951 infusion.

The Full Analysis Set (FAS) consisted of all subjects who received any ABBV-951 infusion and had a baseline and treatment observation for at least 1 efficacy outcome measure.

The Treatment Naive Analysis Set (TNAS) consisted of all subjects in the FAS who had the initial exposure to ABBV-951 in the current study, i.e., excluding subjects who had received ABBV-951 in another study prior to participating in Study M15-741. The TNAS, in addition to the FAS, was used for certain efficacy analyses.

Samples

For analyses to assess discontinuation mitigation, sample 1 was defined as subjects enrolled prior to 08-Jul-2020 and sample 2 subjects enrolled on or after 08-Jul-2020.

Safety

Safety endpoints are primary in this study. All analyses on safety variables, with the exception of Adverse Events and Infusion Site Evaluation Scale, were to be performed using data collected no more than 1 day after the end of the infusion of ABBV-951. Treatment-emergent AEs (TEAEs) were defined as all events that began or worsened on or after ABBV-951 CSCI initiation through 30 days

after the last infusion. All observations from the Infusion Site Evaluation Scale were included in the analysis, regardless the date of assessment relative to the last date of study drug infusion.

For continuous safety outcomes, the change from baseline were analysed in a descriptive manner by visit for each dose category subgroup and overall subjects. For categorical safety outcomes, the number and percentage of each category were summarized by visit for each dose category subgroup and overall subjects. Hypothesis testing was not performed.

In addition, the number and percentage of subjects experiencing one or more TEAEs in a number of pre-defined adverse event categories were summarized by sample 1 (subjects enrolled prior to 08-Jul-2020) and sample 2 (subjects enrolled on or after 08-Jul-2020).

The number and percentage of subjects experiencing one or more TEAEs that were associated with product quality complaints were to be summarized by product including but not limited to ABBV-951, Cleo 90 infusion set, and Neria Guard infusion set.

Statistical Analyses for Pump-Specific Endpoints

The number and percentage of subjects with AEs and SAEs associated with pump-specific product complaints were to be provided.

The number and percentage of subjects who took rescue medication due to pump malfunction were to be provided. For these subjects, the number of times that rescue medication was taken due to pump malfunction will be summarized in a descriptive manner with the number of subjects, mean, standard deviation, minimum, median, and maximum.

The number and percentage of pumps that were replaced due to pump malfunction were to be provided.

Statistical Analyses for Neria™ Guard Infusion Set-Specific Endpoints

The number and percentage of subjects with AEs and SAEs associated with Neria Guard infusion set-specific product complaints were to be presented.

The number of product complaints associated with the Neria Guard infusion sets that resulted in the subject replacing the infusion set were to be summarized.

Efficacy

All analyses on efficacy variables were performed with the FAS using data collected no more than 1 day after the end of the infusion of ABBV-951. Paired-sample t-tests were used for testing change from baseline. For all efficacy endpoints, the change from baseline to each planned visit were summarized in a descriptive manner for each dose category subgroup and overall subjects. No multiplicity adjustment was considered since efficacy was not the primary objective.

Exploratory

The change from baseline to each planned visit in normalized daily "Off" time and "On" times were also to be summarized by sample 1 (subjects enrolled prior to 08-Jul-2020) and sample 2 (subjects enrolled on or after 08-Jul-2020).

Missing Data Imputation

PD Diary

If more than 2 valid diary days are available prior to Day 1 or post-baseline visits, the 2 days closest to the clinical visit (or closest to Day 1 for Baseline) was to be used. If only 1 valid diary day was available, that valid diary day was to be used. If no valid diary day was available for a visit, the average daily normalized "Off" or "On" times was to be set to missing for that visit.

A sensitivity analysis was planned to be performed for average normalized daily "Off" time and "On" times by modifying the definition of the valid PD diary day as "a PD diary recording day with no more than 2 hours of missing data (4 or less missing entries) for the entire 24-hour diary."

MDS-UPDRS

The MDS-UPDRS total score and score of each part was to be calculated as long as no more than 15% of the answers were missing for that assessment. The missing item was then to be imputed as the average of the non-missing items from the same MDS-UPDRS assessment. Imputation for Part I, Part II, Part III or Part IV scores should use the non-missing items within the particular part, but the imputation for the total score of Parts I-III should use the non-missing items from all 59 items across the 3 parts.

PDSS-2

There was no imputation of missing responses. If any item score was missing, the total score and the corresponding domain scores was not calculated.

PDQ-39

The PDQ-39 summary index was to be calculated as long as no more than 15% (i.e., 5) of the answers were missing for that assessment. It was then to be imputed as the average of the non-missing items from the same PDQ-39 assessment. The domain score was only to be calculated if all the questions for that domain had been answered.

EQ-5D-5L

The EQ-5D-5L summary index was only to be calculated if answers were provided for all 5 individual questions. The EQ-5D-5L VAS is a single value collected and there was to be no imputation if the VAS value was missing.

This open-label, single-arm study was designed to evaluate safety and tolerability. The study design allows no firm efficacy conclusions. Concerning both safety and efficacy (secondary objective), analyses were descriptive, and no hypothesis testing was planned.

What regards conclusions on safety, a total of 7 of enrolled subjects had previously received ABBV-951 in phase 1 studies. The fact that they agreed to continue ABBV-951 treatment implies that they did not experience any safety or tolerability issues. Despite their limited number and thereby expectedly minor impact on analysis outcomes, analyses provided based on a safety subset comprising treatment naïve subjects only (TNAS) are appreciated.

Efficacy analyses were based on baseline comparisons in the subset of subjects who received any ABBV-951 infusion and had a baseline and treatment observation for at least one efficacy outcome measure (FAS). The way FAS was defined is not supported. Since none of the subjects enrolled were excluded from the FAS, this is not further pursued. Efficacy estimations appears to have been based on both observed data alone in that there was no imputation in case data was missing for some of the PROs while imputation rules had been defined for example in case of missing PD diary data. Only ignoring missing data is not agreed. The fact that a higher proportion of subjects than expected discontinued the study prematurely is a concern. Although the risk mitigation seemingly had effect, the majority of patients, approximately 70% (157/223), were enrolled before the implementation of CSP version 6. They constitute what the MAH has denoted sample 1 whereof almost 50% (76/157) discontinued early. Sample 2 comprise 66 subjects whereof 53 is still ongoing. At the current data cut-off, 19.7% (13/66) had discontinued early.

Currently, efficacy outcomes are presented in the SmPC (section 5.1). The presentation of efficacy outcomes is proposed to be shortened. For the efficacy outcomes that subsequently may be agreed to be kept, the MAH was requested to clarify the number of subjects included in each analysis and to present new estimations for which missing data had been replaced by a method that can be considered not to lead to that efficacy is overestimated.

In response to the raised question the Applicant agreed that only information on number of patients who finished 52 weeks treatment period were presented in the SmPC.

Results

- **Recruitment**

A total of 223 subjects in the M15-741/M15-737 Analysis Set received ABBV-951 infusion (Table 3). Adverse event and withdrew consent were the most frequently reported primary reasons overall for study drug discontinuation.

Table 3. Subject Disposition: M15-741/M15-737 Analysis Set

	Number (%) of Subjects		
	ABBV-951 Dose Category		
Disposition	Low Dose N = 119	High Dose N = 104	All Subjects N = 223
Completed ABBV-951 treatment in Study M15-741 and did not enter Study M15-737	2 (1.7)	3 (2.9)	5 (2.2)
ABBV-951 ongoing	71 (59.7)	58 (55.8)	129 (57.8)
ABBV-951 prematurely discontinued	46 (38.7)	43 (41.3)	89 (39.9)
Primary reason for premature ABBV-951 discontinuation			
Adverse event	23 (19.3)	23 (22.1)	46 (20.6)
Withdrew consent	15 (12.6)	10 (9.6)	25 (11.2)
Lost to follow-up	0	1 (1.0)	1 (0.4)
Lack of efficacy	3 (2.5)	4 (3.8)	7 (3.1)
COVID-19 infection	0	0	0
COVID-19 logistical restrictions	0	0	0
Difficulty with drug delivery system	1 (0.8)	2 (1.9)	3 (1.3)
Other	4 (3.4)	3 (2.9)	7 (3.1)

The majority of patients included into analysis set represents patients who entered the M15-741 study. It is understood that the study is still ongoing. It is reported that 5 patients who finished the study M15-741 did not continue into the long-term extension study M15-737. However, it is unclear how many patients in the presented analysis set have completed the M15-741 study and entered study M15-737. The Applicant explained that at the cut-off date 05 November 2021, 105 patients out of 115 who completed the Study M15-741 entered the M15-737. Rather high number of patients (39.9%) prematurely discontinued ABBV-951. It should be clarified whether these patients discontinued the M15-741 study or the long-term extension M15-737 study. The Applicant explained that 5 patients completed the Study M15-741 but have chosen not to continue treatment into the Study M15-737. It appears that majority of patients, especially in the high dose group discontinued due to adverse events (22.1%) or difficulty with drug delivery system (1.9%).

- **Baseline data**

A majority of subjects in the M15-741/M15-737 Analysis Set were white, and a majority of subjects were male. Eleven subjects (4.9%) reported that they use tobacco; 133 subjects (59.6%) reported that they drink alcohol. Selected demographic characteristics are presented in Table 4.

Table 4. Demographic Characteristics: M15-741/M15-737 Analysis Set

Parameter		ABBV-951 Dose Category		
		Low Dose N = 119	High Dose N = 104	All Subjects N = 223
Sex, n (%)	Male	60 (50.4)	74 (71.2)	134 (60.1)
	Female	59 (49.6)	30 (28.8)	89 (39.9)
Race, n (%)	White	90 (75.6)	96 (92.3)	186 (83.4)
	Black or African American	0	1 (1.0)	1 (0.4)
	Asian	27 (22.7)	7 (6.7)	34 (15.2)
	American Indian or Alaska Native	1 (0.8)	0	1 (0.4)
	Native Hawaiian or other Pacific Islander	0	0	0
	Multiple	1 (0.8)	0	1 (0.4)
Ethnicity, n (%)	Hispanic or Latino	8 (6.7)	12 (11.5)	20 (9.0)
	Not Hispanic or Latino	111 (93.3)	92 (88.5)	203 (91.0)
Age, years	Mean (SD)	63.4 (8.97)	64.2 (9.67)	63.8 (9.29)
	Median (min, max)	65.0 (34, 83)	64.0 (43, 86)	65.0 (34, 86)
Age category, n (%)	< 65 years	58 (48.7)	53 (51.0)	111 (49.8)
	≥ 65 years	61 (51.3)	51 (49.0)	112 (50.2)
Weight, kg	Mean (SD)	68.20 (17.283)	77.37 (16.480)	72.47 (17.488)
	Median (min, max)	67.30 (34.1, 120.7)	78.35 (41.4, 110.9)	72.85 (34.1, 120.7)
Geographic region, n (%)	North America	39 (32.8)	51 (49.0)	90 (40.4)
	Europe and Australia	58 (48.7)	48 (46.2)	106 (47.5)
	Japan	22 (18.5)	5 (4.8)	27 (12.1)
Duration of PD since diagnosis, n (%)	< 10 years	62 (52.1)	58 (55.8)	120 (53.8)
	≥ 10 years	57 (47.9)	46 (44.2)	103 (46.2)
Concomitant dopamine agonist use during the study, n (%)	User	73 (61.3)	66 (63.5)	139 (62.3)
	Non-user	46 (38.7)	38 (36.5)	84 (37.7)

Selected baseline characteristics are presented in Table 5.

Table 5. Baseline Characteristics: M15-741/M15-737 Analysis Set

	ABBV-951 Dose Category					
	Low Dose		High Dose		All Subjects	
Parameter	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
PD diary, normalized hours						
"Off" time	115	5.66 (2.24)	100	6.16 (2.30)	215	5.89 (2.28)
"On" time without troublesome dyskinesia[a]	115	9.19 (2.61)	100	9.24 (2.21)	215	9.21 (2.43)
"On" time without dyskinesia	115	6.48 (3.45)	100	6.61 (3.22)	215	6.54 (3.34)
"On" time with non-troublesome dyskinesia	115	2.71 (2.45)	100	2.63 (2.80)	215	2.67 (2.61)
"On" time with troublesome dyskinesia	115	1.15 (1.93)	100	0.60 (1.21)	215	0.89 (1.66)
MDS-UPDRS, score						
Total	119	49.6 (20.18)	104	52.5 (17.89)	223	51.0 (19.16)
Part I	119	11.1 (6.96)	104	11.6 (6.04)	223	11.3 (6.54)
Part II	119	14.8 (7.54)	104	16.9 (7.32)	223	15.8 (7.49)
Part III	119	23.7 (11.99)	104	24.1 (11.10)	223	23.9 (11.56)
Part IV	119	9.5 (3.26)	104	9.5 (3.15)	223	9.5 (3.21)
PDQ-39 summary index	119	33.3 (15.67)	103	35.4 (13.89)	222	34.3 (14.87)
EQ-5D-5L summary index	113	0.659 (0.1889)	96	0.625 (0.1696)	209	0.643 (0.1807)
MMSE total score	119	28.8 (1.62)	103	28.5 (1.90)	222	28.7 (1.76)

In general, the baseline characteristics of all patients could be considered to reflect the intended for treatment patient population of advanced PD as described in the proposed indication. It should be noted that only one Black or African American patient was included into the study. Thus, information about the use of ABBV-951 in this racial group is missing.

- **Numbers analysed**

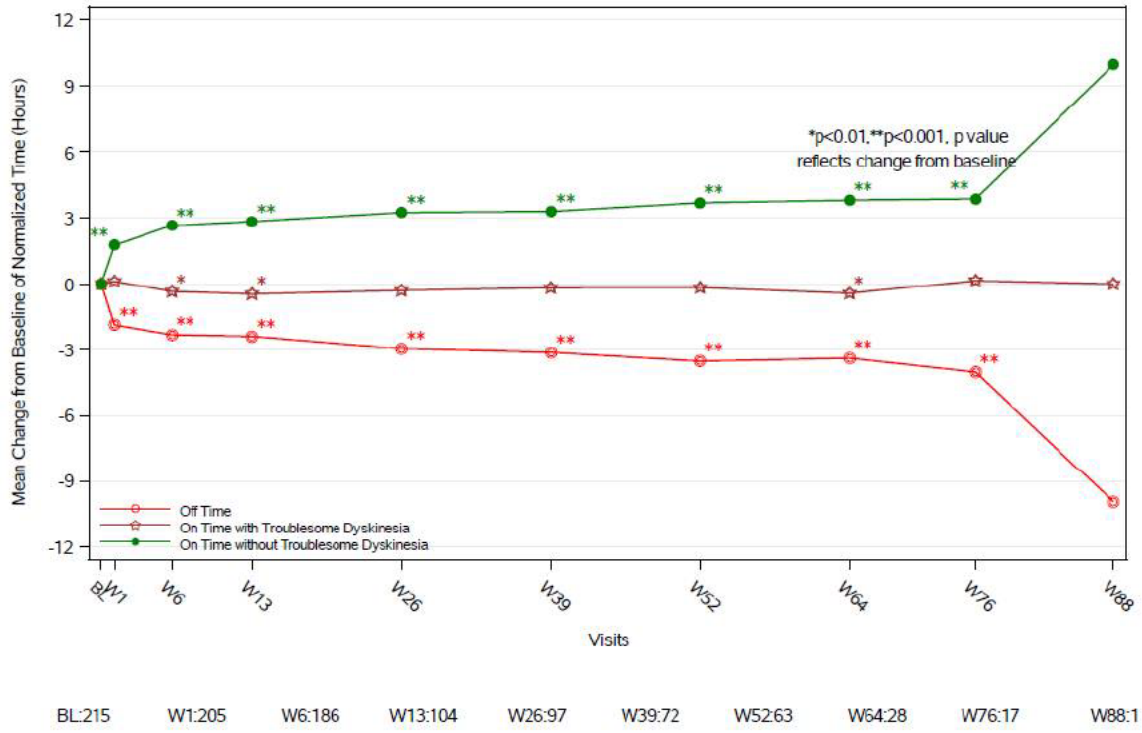
As of the data cutoff, 109 subjects have been exposed to ABBV-951 for at least 6 months (180 days) including infusion interruptions, and 102 subjects have been exposed to ABBV-951 for at least 6 months excluding infusion interruptions.

- **Outcomes and estimation**

Parkinson's Disease Diary

The PD Diary is a validated tool that is used to assess patient-defined clinical status of various motor symptoms ("Off" time, "On" times, and "Asleep" time) over a period of time. Treatment with ABBV-951 resulted in significant (nominal $P < 0.001$) and clinically meaningful improvements from Baseline in "On" time without troublesome dyskinesia (the sum of "On" time without dyskinesia and "On" time with non-troublesome dyskinesia) and in "Off" time (Figure 2). The mean decrease in "Off" time, increase in "On" time without troublesome dyskinesia, and increase in "On" time without dyskinesia at Week 64 were 3.37, 3.80, and 5.44 hours, respectively.

Figure 2. Mean Change from Baseline in Average Daily Normalized "On" Time Without Troublesome Dyskinesia, "On" Time with Troublesome Dyskinesia, and "Off" Time Based on the PD Diary: M15-741/M15-737 Analysis Set



The percentage of subjects who reported awakening in the morning in the "Off" state (as a proxy for morning akinesia) decreased substantially from Baseline after initiation of treatment with ABBV-951 (Figure 3). At Baseline, 77.8% of subjects reported awakening in the "Off" state. At Week 1, 31.1% of subjects reported awakening in the "Off" state, while 50.7% of subjects reported awakening in the "On" without dyskinesia state; these improvements increased over time through Week 26 (20.8% in "Off" and 68.8% in "On" without dyskinesia) and then stabilized; however, the number of subjects with assessments after Week 64 is too small to be interpretable.

As expected from the experience with Duodopa, the product used for bridging the clinical efficacy, the “Off” time was reduced compared to the baseline and “On” time without troublesome dyskinesia was increased compared to the baseline. while study M15-741 is still on-going, the only meaningful information provided in the SmPC could be related to the proportion of patients still on treatment after 52 weeks. Information regarding “Off” time and “On” time without troublesome dyskinesia currently is available only from 96 patients (39.3%), which is considered too small proportion and might be changing, and therefore, premature for reporting in the SmPC. In response to the raised question the Applicant agreed that only information on number of patients who finished 52 weeks treatment period were presented in the SmPC.
The relevance of information regarding “Off” time and “On” time without troublesome dyskinesia for the prescribers could be evaluated after the study is finished and final numbers are available.

MDS-UPDRS

Treatment with ABBV-951 resulted in significant (nominal P < 0.001) and clinically meaningful improvements from Baseline in the m-EDL score at all time points through Week 52 as measured by the MDS-UPDRS Part II score. Significant improvements (nominal P < 0.001) from Baseline in the motor complications score (MDS-UPDRS Part IV) were also observed at all time points measured through Week 52. These improvements began as early as Day 2. The number of subjects with assessments after Week 52 is too small to be interpretable.
However, interpretation of results is difficult in the absence of control group and taking into account absence of randomisation and the open label nature of the study.

PDSS-2

Treatment with ABBV-951 resulted in significant improvements (nominal $P \leq 0.01$) and clinically meaningful changes from Baseline in the PDSS-2 total score, PD symptoms at night score, motor symptoms at night score, and disturbed sleep score at all time points measured as stated by the Applicant. However, interpretation of results is difficult in the absence of control group and taking into account absence of randomisation and the open label nature of the study.

Quality of Life Analyses

Through Week 52, ABBV-951 significantly (nominal $P \leq 0.01$) improved PD- and health-related quality of life as measured by the PDQ-39 summary index, specifically domain scores of mobility, activities of daily living, stigma, and bodily discomfort, as well as by the EQ-5D-5L summary index and VAS as stated by the Applicant. The change in the PDQ-39 summary index exceeded the established minimally important difference (MID) (2 to 4 points) for a clinically meaningful change in subjects with PD (Fitzpatrick 2004, Peto 2001). However, interpretation of results is difficult in the absence of control group and taking into account absence of randomisation and the open label nature of the study.

The cutoff date of 30 March 2021 was chosen to obtain data from a minimum of 100 subjects with at least 26 weeks of treatment with ABBV-951. As of this cutoff date, 109 subjects have had at least 6 months of exposure to ABBV-951. A summary of the efficacy results from Study M15-741 at Week 26 are presented in Table 7.

Table 7. Change from Baseline to Week 26 in Efficacy Endpoints: Study M15-741

Measure	N	Baseline Mean (SD)	Week 26 Mean (SD)	Mean Change (SD)
"Off" time (hours)[a]	97	5.79 (2.35)	2.85 (3.02)	–2.94 (3.16)
"On" time without troublesome dyskinesia (hours)[a]	97	9.62 (2.42)	12.87 (3.08)	3.24 (3.16)
"On" time without dyskinesia (hours)[a]	97	7.01 (3.39)	11.02 (4.23)	4.00 (4.42)
Motor aspects of experiences of daily living[b]	104	15.9 (7.17)	12.7 (7.65)	–3.2 (6.82)
Sleep symptoms[c]	104	20.6 (9.93)	15.0 (9.64)	–5.7 (11.20)
Quality of life[d]	104	34.5 (14.93)	27.3 (15.05)	–7.2 (11.36)
Health-related quality of life[e]	86	0.662 (0.184)	0.744 (0.1375)	0.082 (0.1712)
Measure	**N**	**Baseline (%)**	**Endpoint (%)**	**Difference (%)**
Morning akinesia (%)[f]	77	77.8%	20.8%	–57.0%

SD = standard deviation

a. Parkinson's disease (PD) diary.

b. Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II score.

c. Parkinson's Disease Sleep Scale 2 (PDSS-2) total score.

d. Parkinson's Disease Questionnaire-39 item (PDQ-39) summary index.

e. EQ-5D-5L summary index.

f. Percentage of subjects with early morning "Off" status based on the first morning symptom upon awakening derived from the PD diary.

The results from 109 patients are expected to be presented in the Table above since the Applicant stated that at least 109 patients were exposed to ABBV-954 for 6 months treatment. Explanation why only 97 patients contribute with results for “Off” and “On” time calculations was requested. The Applicant explained that 19 patients had incomplete PD diaries defined as containing less than 44 missing entries. The Applicant included into the analysis additional 7 subjects who had not reached 6 months of study drug exposure but who had valid PD Diary assessments within the Week 26 analysis window.

Clinical studies in special populations

No studies in special population were performed.

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

Based on PK comparability, the efficacy for ABBV-951 is extrapolated from the efficacy of LCIG and is supported by the efficacy results from Study M15-741.

Table 6. Efficacy Assessments in the Duodopa SmPC and in ABBV-951 Study M15-741

Assessment	Duodopa SmPC	ABBV-951 Study M15-741[a]	Comments
PD Diary			
Reduction of "Off" time and increase in "On" time without troublesome dyskinesia	✓	✓	Consistent with the Duodopa SmPC, both the hours of "Off" time and hours of "On" time with dyskinesia (whether troublesome or non-troublesome) decreased in the ABBV-951 Study M15-741, with a corresponding increase in the most desirable status of "On" time without any dyskinesia.
Morning akinesia		✓	In ABBV-951 Study M15-741, the percentage of subjects who reported awakening in the morning in the "Off" state (as a proxy for morning akinesia) decreased substantially from Baseline through Week 26 and then stabilized.
UPDRS/MDS-UPDRS			
ADL/m-EDL (Part II)	✓	✓	The confirmed improvement in ADLs from the Duodopa SmPC, assessed as Part II of the UPDRS, is presented as improvement in m-EDL with ABBV-951 based on the revised version of the UPDRS (MDS-UPDRS) and following the guidance proposed by the MDS (Goetz 2007).
Motor complications (Part IV)		✓	The improvement in MDS-UPDRS Part IV from Baseline through Week 52 in ABBV-951 Study M15-741 is significant.
PD- and health-related quality of life			
PDQ-39	✓	✓	Consistent with the Duodopa SmPC, improvement in the PDQ-39 was observed in ABBV-951 Study M15-741. Duodopa did not show a statistically significant difference for the EQ-5D; however, ABBV-951 Study M15-741 showed a significant improvement in the EQ-5D-5L summary index and visual analogue scale.
EQ-5D[b]	✓	✓	

Assessment	Duodopa SmPC	ABBV-951 Study M15-741[a]	Comments
Other			
CGI-I	✓		Duodopa demonstrated statistically significant improvements compared to oral LD/CD for the Clinical Global Impression (CGI-I).
ZBI	✓		Duodopa did not meet statistical significance for ZBI based on the hierarchical testing procedure.
PDSS-2		✓	ABBV-951 Study M15-741 study showed a significant improvement from Baseline in the PDSS-2 total score, PD symptoms at night score, motor symptoms at night score, and disturbed sleep score at all time points measured.

The comparison between Duodopa studies described in the SmPC and results from M15-741 is difficult to interpret due to differences in study designs, inclusion/exclusion criteria of the studies resulting in different study populations and statistical analyses.

Supportive study(ies)

Study M15-737 is a Phase 3, open-label, multicenter extension study for eligible subjects who completed the long-term safety and tolerability Study M15-741.

The study consists of an Enrollment Visit on Day 1 and a Treatment Period of up to 96 weeks that includes 4 additional clinic visits (Weeks 24, 48, 72, and 96 [Final Visit]) and 4 remote assessments (Weeks 12, 36, 60, and 84). All subjects are to receive an individualized CSCI (24 hours daily) of ABBV-951 for up to 96 weeks.

The primary objective is to assess the local and systemic safety and tolerability of continued ABBV-951 treatment delivered as a CSCI for 24 hours daily. The primary endpoints (safety) are presented in Table 1 and the secondary endpoints (efficacy) are presented in Table 2.

The initial base continuous infusion rate in Study M15-737 is the same as the final day of the parent study (Study M15-741). See Section 2.7.3.1.4.2.1 for a description of the parent study

The Applicant explain that at the cut-off date 05 November 2021, 105 patients out of 115 who completed the Study M15-741 entered the M15-737.

Discussion and overall conclusions on clinical efficacy

The MAA for ABBV-951 is a line extension to Duodopa. The application is based upon PK comparability of ABBV-951 to Duodopa (LCIG) from Study M17-220 and is further supported by a long-term open-label safety and tolerability study of ABBV-951 (Study M15-741) in subjects with aPD.

The efficacy of ABBV-951 was evaluated as secondary endpoints in a Phase 3, 52-week, open-label study (Study M15-741) and in a Phase 3, 96-week, open-label extension of Study M15-741 (Study M15-737). Study M15-741 is a Phase 3, open-label, single-arm, multicenter, global study in subjects 30 years of age or older, with a diagnosis of LD-responsive idiopathic PD and whose motor symptoms were inadequately controlled by oral medications.

This open-label, single-arm study was designed to evaluate safety and tolerability. The study design allows no firm efficacy conclusions. Concerning both safety and efficacy (secondary objective), analyses were descriptive, and no hypothesis testing was planned.

Efficacy analyses were based on baseline comparisons in the subset of subjects who received any ABBV-951 infusion and had a baseline and treatment observation for at least one efficacy outcome measure (FAS). The way FAS was defined is not supported. Since none of the subjects enrolled were excluded (from FAS), this is not further pursued. Efficacy estimations appears to have been foremost based on observed data although some imputation rules had been defined for example in case of missing PD diary data. Only ignoring missing data is not agreed. The fact that a higher proportion of subjects than expected discontinued the study prematurely is a concern.

Analyses were added to assess the result of discontinuation mitigations and have been presented comparing sample 1 and sample 2, defined using the date for protocol version 6 as cut-off (08-Jul-2020). Although the risk mitigation seemingly had effect, the majority of patients, approximately 70% (157/223), were enrolled before the implementation of CSP version 6. They constitute what the MAH has denoted sample 1 whereof almost 50% (76/157) discontinued early. Sample 2 comprise 66 subjects whereof 53 is still ongoing. At the first interim analysis data cut-off, 19.7% (13/66) had discontinued early.

The proposed dose calculation was based on data obtained from PK study in healthy volunteers (Study M17-220). In principal, such approach is acceptable. The initial loading dose as well as continuous infusion rate of treatment is calculated based on previous treatment with oral LD+DDCI. The dose adjustment is allowed in order to achieve the optimal treatment effect, which is acceptable.

The efficacy endpoints used in study M15-741 are well-described in the field and are used in studies of different treatments of patients with Parkinson disease and also were used in Duodopa studies. However, some of the endpoints are used only in M15-741/M15-737 studies.

The majority of patients included into analysis set represents patients who entered the M15-741 study. It is understood that the study is still ongoing. It is reported that 5 patients who finished the study M15-741 did not continue into the long-term extension study M15-737. The Applicant explain that at the cut-off date 05 November 2021, 105 patients out of 115 who completed the Study M15-741 entered the M15-737.

Rather high number of patients (39.9%) prematurely discontinued ABBV-951. It appears that majority of patients, especially in the high dose group discontinued due to adverse events (22.1%) or difficulty with drug delivery system (1.9%).

In general, the baseline characteristics of all patients could be considered reflect the intended for treatment patient population of advanced PD as described in the proposed indication. It should be noted that only one Black or African American patient was included into the study. Thus, information about the use of ABBV-951 in this racial group is missing.

The results from 109 patients are expected to be presented in the Table above since the Applicant stated that at least 109 patients were exposed to ABBV-954 for 6 months treatment. Explanation why only 97 patients contribute with results for “off” and “on” time calculations was requested. The Applicant explained that 19 patients had incomplete PD diaries defined as containing less than 44 missing entries. The Applicant included into the analysis additional 7 subjects who had not reached 6 months of study drug exposure but who had valid PD Diary assessments within the Week 26 analysis window.

As expected from the experience with Duodopa, the product used to for bridging the clinical efficacy, treatment with produodopa resulted in the “off” time reduction compared to the baseline and “on” time without troublesome dyskinesia increase compared to the baseline.

The described changes of MDS-UPDRS, PDSS-2 scores, changes of scores on instruments evaluating quality of life from baseline until treatment end are acknowledged. However, interpretation of these results is difficult in the absence of control group and taking into account absence of randomisation and the open label nature of the study.

A number of efficacy outcomes were initially presented in the SmPC (section 5.1). They have, upon request, been shortened. In addition, new analyses were requested handling missing data by a method considered not to lead to that efficacy was overestimated. With the D106 answer new analyses have been performed based on a second data cut-off (05 November 2021). Two interim analyses were planned during the course of this study, the second interim analysis after at least 100 subjects had completed 52 weeks of therapy and, it is the results from this second interim analysis that currently is proposed to be included in the SmPC. In section 5.1, the MAH refer to that 244 patients were enrolled in the study failing to report the number of subjects still on treatment week 52 contributing with data. Results from the observed case analysis (OC), reported in the CSR, and an additional analysis using multiple imputation (MI) methods have been provided for both the first and the second interim analysis data cut-off set. In comparing the OC analysis and the MI analysis it was clarified that a substantial number of subjects lacked data. Hence, a substantial amount of data needed to be imputed and thus is the MI analysis considered less relevant. Study M15-741 is still to be completed. The number of subjects completing the study still on treatment should be reported in section 5.1 of the SmPC.

Provided that PK bridge between duodopa and produodopa is established, the efficacy could be extrapolated. The data from MK15-741 open label study could be considered as supportive. Also, since the study is currently on-going, the only meaningful information provided in the SmPC could be related to the proportion of patients still on treatment after 52 weeks. Information regarding "Off" time and "On" time without troublesome dyskinesia currently is available only from 96 patients (39.3%), which is considered too small proportion and might be changing, and therefore, premature for reporting in the SmPC.

Clinical safety

Introduction

The safety of ABBV-951was evaluated in a clinical development program that included data from 8 Phase 1 studies (6 in healthy subjects and 2 in subjects with PD) and 2 Phase 3 studies (in subjects with PD). Data from the Phase 3 study (Study M15-741) and its extension (Study M15-737) were integrated and are presented in this clinical summary of safety (CSS) as the M15-741/M15-737 Analysis Set. In addition, data from 7 of the Phase 1 studies along with the Phase 3 studies were integrated and are presented in this CSS as the All ABBV-951 Analysis Set. Phase 1 Study M20-141 in healthy subjects was not integrated because final data were not available at the time of the integrated summary of safety (ISS) data cutoff.

The primary integrated analysis set is the M15-741/M15-737 Analysis Set, which is described in Table 1. The studies in this analysis set allow the evaluation of AEs that develop during exposure to ABBV-951 for up to 148 weeks.

Table 1. Primary Integrated Analysis Set

Analysis Set	Studies Included	Subjects Included	Treatment Exposure
Primary Integrated Analysis Set			
M15-741/M15-737 Analysis Set	Study M15-741[a] Extension Study M15-737[a]	All subjects who received ABBV-951 infusion in Study M15-741	Up to 148 weeks of open-label ABBV-951 (up to 52 weeks in Study M15-741 and up to 96 weeks in Study M15-737)

a. Data cutoff date 30 March 2021.

The All ABBV-951 Analysis Set is used to summarize ABBV-951 exposure and AEs across all phases of the ABBV-951 development program. Subjects were grouped by study phase and population: Phase 1 healthy volunteers, Phase 1 PD, Phase 3 PD, and total. Due to the inclusion of healthy volunteers and the limited treatment exposure of subjects in the Phase 1 studies, this analysis set is used to provide a comprehensive overview of AEs among all subjects exposed to ABBV-951 in the interventional clinical trials and not to estimate the AE rates that may occur in the population of interest.

The All Treated Analysis Set is used to summarize exposure to ABBV-951 and study drug comparators across the ABBV-951 development program. The Phase 1 Study M20-141 in healthy volunteers is not included in the integrated analysis sets because final data were not available at the time of the data cutoff.

Table 2. Supportive Analysis Sets

Analysis Set	Studies Included	Subjects Included
All ABBV-951 Analysis Set	Phase 1 healthy volunteers: Study M15-733 Study M16-769 Study M17-220 Study M18-763 Study M18-764 Phase 1 in subjects with PD: Study M15-738 Study M15-739 Phase 3 in subjects with PD: Study M15-741[a] Extension Study M15-737[a]	All subjects who received ABBV-951 infusion in a completed Phase 1 ABBV-951 interventional clinical trial or in Phase 3 Study M15-741.
All Treated Analysis Set	Phase 1 healthy volunteers: Study M15-733 Study M16-769 Study M17-220 Study M18-763 Study M18-764 Phase 1 in subjects with PD: Study M15-738 Study M15-739 Phase 3 in subjects with PD: Study M15-741[a] Extension Study M15-737[a]	All subjects who received at least 1 dose of any study drug, including active comparator or placebo, in a completed Phase 1 ABBV-951 interventional clinical trial or in Phase 3 Study M15-741.

a. Data cutoff date 30 March 2021.

The Applicant identified two safety analysis set All ABBV-951 analysis set including all subjects who received ABBV-951 infusion and All treated analysis set which included all subjects who received any study drug. The Applicant first of all focused analysis on All ABBV-951 analysis set.

Patient exposure

All ABBV-951 Analysis Set

Overall, 439 unique subjects have been exposed to ABBV-951 in the clinical development program for a total of 147.9 person-years. The Phase 1 studies included 174 healthy subjects and 49 subjects with PD. The Phase 3 studies included 223 subjects with aPD, 7 of whom previously participated in a Phase 1 study (Study M15-738 or Study M15-739). Overall, the mean number of days that subjects were exposed to ABBV-951 was 123.1, with 109 subjects (24.8%) exposed for ≥ 6 months and 77 subjects (17.5%) exposed for ≥ 12 months.

ABBV-951 Exposure
(All ABBV-951 Analysis Set)

	ABBV-951			
	Phase 1 Healthy (N=174) n (%) PY	Phase 1 PD (N=49) n (%) PY	Phase 3 PD (N=223) n (%) PY	Total (N=439) n (%) PY
Duration of exposure				
At least 1 infusion	174 (100) 2.1	49 (100) 1.6	223 (100) 144.2	439 (100) 147.9
At least 180 days (6 months)	0	0	109 (48.9) 120.9	109 (24.8) 121.2
At least 360 days (12 months)	0	0	77 (34.5) 101.0	77 (17.5) 101.3
At least 540 days (18 months)	0	0	11 (4.9) 17.8	12 (2.7) 19.5
Duration of exposure (day)				
n	174	49	223	439
Mean (SD)	4.5 (3.93)	11.7 (11.56)	236.2 (193.84)	123.1 (180.45)
Median	2.0	4.0	170.0	15.0
Min, Max	1, 11	2, 30	3, 664	1, 664
Sex				
Female	68 (39.1) 0.7	17 (34.7) 0.5	89 (39.9) 54.9	172 (39.2) 56.2
Male	106 (60.9) 1.4	32 (65.3) 1.0	134 (60.1) 89.3	267 (60.8) 91.8
Age (year)				
< 18	0	0	0	0
18 to < 50	41 (23.6) 0.5	4 (8.2) 0.2	21 (9.4) 12.7	66 (15.0) 13.4
50 to < 65	113 (64.9) 1.4	19 (38.8) 0.7	90 (40.4) 62.5	218 (49.7) 64.5
65 to < 75	20 (11.5) 0.3	21 (42.9) 0.5	88 (39.5) 53.6	126 (28.7) 54.3
>= 75	0	5 (10.2) 0.2	24 (10.8) 15.5	29 (6.6) 15.7
Ethnicity				
Hispanic or Latino	17 (9.8) 0.3	3 (6.1) 0.1	20 (9.0) 11.3	40 (9.1) 11.6
Not Hispanic or Latino	157 (90.2) 1.8	46 (93.9) 1.5	203 (91.0) 133.0	399 (90.9) 136.3
Region				
Europe and Australia	0	0	106 (47.5) 65.9	106 (24.1) 65.9
Japan	0	0	27 (12.1) 13.1	27 (6.2) 13.1
North America	174 (100) 2.1	49 (100) 1.6	90 (40.4) 65.3	306 (69.7) 69.0

At least one ABBV-951 infusion received 439 subjects including healthy volunteers and PD patients. One year exposure is rather limited including only 77 subjects.

M15-741/M15-737 Analysis Set

Overall, 223 subjects have been exposed to ABBV-951, with 109 subjects exposed for at least 6 months (≥ 180 days) and 77 subjects exposed for at least 12 months ABBV-951 (≥ 360 days). The mean number of days that subjects were exposed to ABBV-951 was 236.2.

Table 3. Duration of Phase 3 ABBV-951 Exposure: M15-741/M15-737 Analysis Set

	ABBV-951 Dose Category		
	Low Dose N = 119	High Dose N = 104	All Subjects N = 223
Duration (day)			
Mean (SD)	228.0 (191.76)	245.6 (196.69)	236.2 (193.84)
Median (min, max)	162.0 (3, 653)	181.5 (4, 664)	170.0 (3, 664)
Duration interval – n (%)			
At least 6 months (≥ 180 days)	56 (47.1)	53 (51.0)	109 (48.9)
At least 12 months (≥ 360 days)	38 (31.9)	39 (37.5)	77 (34.5)
At least 18 months (≥ 540 days)	5 (4.2)	6 (5.8)	11 (4.9)
Patient-Years of Exposure	74.3	69.9	144.2

The mean duration of exposure of PD patients was 236.2 days. Only 77 PD patients were exposed more at least 12 months.

A summary of demographic and baseline characteristics for the M15-741/M15-737 Analysis Set is presented in the efficacy section. The mean age of subjects was 63.8 years (ranging from 34 to 86

years), with 112 subjects (50.3%) at least 65 years of age and 24 subjects (10.8%) at least 75 years of age. A majority of subjects were white (83.4%), and a majority of subjects were male (60.1%). A total of 103 subjects (46.2%) had PD for ≥ 10 years. The majority of subjects (83.9%) had been responsive to LD for > 5 years, and medical history conditions were as expected for this population. Concomitant PD medications for the M15-741/M15-737 Analysis Set are presented in Table 4. Most subjects took one or more dopaminergic agents during the ABBV-951 treatment period (87.9%, all subjects), with 62.3% taking dopamine agonists.

Table 4. Concomitant PD Medications: M15-741/M15-737 Analysis Set

	Number (%) of Subjects[a]		
	ABBV-951 Dose Category		
ATC Level 3 ATC Level 4	Low Dose N = 119	High Dose N = 104	All Subjects N = 223
Anticholinergic agents	4 (3.4)	0	4 (1.8)
Ethers of tropine or tropine derivatives	1 (0.8)	0	1 (0.4)
Tertiary amines	3 (2.5)	0	3 (1.3)
Dopaminergic agents	102 (85.7)	94 (90.4)	196 (87.9)
Adamantane derivatives	30 (25.2)	30 (28.8)	60 (26.9)
Dopa and dopa derivatives	60 (50.4)	59 (56.7)	119 (53.4)
Dopamine agonists	73 (61.3)	66 (63.5)	139 (62.3)
Monoamine oxidase B inhibitors	55 (46.2)	38 (36.5)	93 (41.7)
Other dopaminergic agents	4 (3.4)	13 (12.5)	17 (7.6)

It is noted that rather large proportion of patients (N=196, 87.9%) received other dopaminergic concomitant medications.

Adverse events

AEs were integrated for the M15-741/M15-737 Analysis Set and the All ABBV-951 Analysis Set. Unless otherwise stated, AEs refer to treatment-emergent events (defined as AEs that began or worsened after ABBV-951 initiation and within 30 days from the last infusion of ABBV-951). All AEs were summarized using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1.

Clinical laboratory parameters, vital signs, ECG variables, the C-SSRS, and QUIP-RS were not integrated because of the limited amount of data available in Study M15-737 at the time of the data cutoff.

An overview of AEs for the M15-741/M15-737 Analysis Set is presented in Table 5. A total of 206 subjects (92.4%) experienced at least 1 AE. In the majority of subjects with AEs, the events were nonserious and mild or moderate in severity.

Table 5. Overview of AEs and All Deaths: M15-741/M15-737 Analysis Set

	Number (%) of Subjects[a]		
	ABBV-951 Dose Category		
	Low Dose N = 119	High Dose N = 104	All Subjects N = 223
Subjects with any treatment-emergent:			
AE	107 (89.9)	99 (95.2)	206 (92.4)
Serious AE	27 (22.7)	28 (26.9)	55 (24.7)
AE leading to death	0	3 (2.9)	3 (1.3)
AE leading to study drug discontinuation	27 (22.7)	27 (26.0)	54 (24.2)
Severe AE	26 (21.8)	33 (31.7)	59 (26.5)
AE considered related to study drug[b]	103 (86.6)	98 (94.2)	201 (90.1)
AE associated with product complaints[b]	87 (73.1)	77 (74.0)	164 (73.5)
AESIs:			
Infusion site infections	31 (26.1)	41 (39.4)	72 (32.3)
Infusion site reactions	88 (73.9)	87 (83.7)	175 (78.5)
Hallucinations/psychosis	28 (23.5)	26 (25.0)	54 (24.2)
Polyneuropathy	10 (8.4)	10 (9.6)	20 (9.0)
Somnolence	9 (7.6)	2 (1.9)	11 (4.9)
Weight loss	12 (10.1)	11 (10.6)	23 (10.3)
Falls and associated injuries	17 (14.3)	22 (21.2)	39 (17.5)
All deaths:			
Occurring ≤ 30 days after last dose	0	3 (2.9)	3 (1.3)
Occurring > 30 days after last dose	0	2 (1.9)	2 (0.9)

M15-741/M15-737 Analysis Set

The most common AEs (≥ 10% of all subjects) were infusion site events, hallucination, fall, anxiety, and dizziness (Table 6). The most frequently reported system organ classes (SOCs) (≥ 10% of all subjects) for AEs considered reasonably possibly related to study drug were general disorders and administration site conditions (76.7%), psychiatric disorders (31.8%), nervous system disorders (31.4%), infections and infestations (30.0%), investigations (10.8%), and gastrointestinal disorders (10.3%).

Most patients experienced AEs (92.4%) and the majority of patients experienced infusion site reactions (78.5%). It is noted that SAEs were reported in 24.7% patients and 5 patients died. All deaths occurred in the high dose group and 3 out 5 deaths occurred ≤ 30 days after the last dose.

Table 6. AEs that Occurred in ≥ 10% of All Subjects: M15-741/M15-737 Analysis Set

	Number (%) of Subjects		
	ABBV-951 Dose Category		
Preferred Terms[a]	Low Dose N = 119	High Dose N = 104	All Subjects N = 223
Any AE	107 (89.9)	99 (95.2)	206 (92.4)
Infusion site erythema	56 (47.1)	57 (54.8)	113 (50.7)
Infusion site nodule	30 (25.2)	31 (29.8)	61 (27.4)
Infusion site cellulitis	26 (21.8)	27 (26.0)	53 (23.8)
Infusion site oedema	16 (13.4)	29 (27.9)	45 (20.2)
Hallucination	18 (15.1)	21 (20.2)	39 (17.5)
Fall	16 (13.4)	21 (20.2)	37 (16.6)
Infusion site pain	18 (15.1)	15 (14.4)	33 (14.8)
Infusion site reaction	12 (10.1)	19 (18.3)	31 (13.9)
Anxiety	10 (8.4)	15 (14.4)	25 (11.2)
Dizziness	15 (12.6)	9 (8.7)	24 (10.8)

Most common AEs were related to injection site reaction. The Applicant proposes to report these AEs under the collective terms “infusion site reaction “ and “infusion site infection” in the ADR Table and the details about most common observe events describe in the footnote under the Table. The Applicant updated SmPC upon the request.

Analysis Over Time

The first occurrence of the most common AEs is summarized by 90-day time intervals in Table 7. The first occurrence rate was highest in the first 90 days and decreased to rates typically < 5% in the later time intervals.

Table 7. First Occurrence of AEs that Occurred in ≥ 10% of Subjects by 90-Day Time Intervals: M15-741/M15-737 Analysis Set

	Number of subjects with first event during time interval/Number of subjects at risk for first event during time interval (%)					
Preferred Terms[a]	Days 1 to 90 N = 223	Days 91 to 180 N = 164	Days 181 to 270 N = 122	Days 271 to 360 N = 84	After Day 360 N = 81	At Any Time N = 223
Any AE	202/223 (90.6)	3/12 (25.0)	1/4 (25.0)	0	0	206/223 (92.4)
Infusion site erythema	104/223 (46.6)	4/81 (4.9)	3/55 (5.5)	1/30 (3.3)	1/27 (3.7)	113/223 (50.7)
Infusion site nodule	49/223 (22.0)	9/118 (7.6)	1/75 (1.3)	2/46 (4.3)	0	61/223 (27.4)
Infusion site cellulitis	40/223 (17.9)	5/132 (3.8)	5/99 (5.1)	3/61 (4.9)	0	53/223 (23.8)
Infusion site oedema	35/223 (15.7)	5/142 (3.5)	1/97 (1.0)	3/63 (4.8)	1/58 (1.7)	45/223 (20.2)
Hallucination	29/223 (13.0)	4/147 (2.7)	3/106 (2.8)	1/73 (1.4)	2/71 (2.8)	39/223 (17.5)
Fall	22/223 (9.9)	5/145 (3.4)	4/102 (3.9)	3/71 (4.2)	3/67 (4.5)	37/223 (16.6)
Infusion site pain	29/223 (13.0)	3/140 (2.1)	1/103 (1.0)	0	0	33/223 (14.8)
Infusion site reaction	23/223 (10.3)	4/149 (2.7)	2/107 (1.9)	2/71 (2.8)	0	31/223 (13.9)
Anxiety	20/223 (9.0)	2/148 (1.4)	1/110 (0.9)	1/72 (1.4)	1/68 (1.5)	25/223 (11.2)
Dizziness	22/223 (9.9)	2/145 (1.4)	0	0	0	24/223 (10.8)

It is noted that the vast majority of AEs occurred within first 90 days of treatment.

Analysis by Dose Category

Subjects were categorized by dose category for analysis based on their most frequent (modal) TDD of ABBV-951. Each subject's modal TDD in Study M15-741 was used to determine their dose category; either low dose (modal TDD < 1800 mg LD) or high dose category (modal TDD ≥ 1800 mg LD). Although subjects are categorized by dose category for the statistical analyses, there are limitations in the ability to interpret any differences observed between the dose categories. Any difference between dose categories is not expected to reflect a dose-response given that randomization was not used to control for bias nor to create groups that are comparable with respect to known and unknown confounding factors.
In general, AEs, SAEs, and study drug discontinuations were comparable between the low and high dose groups. AEs that occurred more frequently (≥ 5% difference) in the high dose group than in the low dose group are presented in (Table 8). Other than urinary tract infection (UTI), all of these events are considered adverse drug reactions (ADRs) for ABBV-951. UTI is not considered an ADR as all subjects with UTI had confounding factors that could have contributed to the event. In addition, the risk of UTI is increased in the elderly population (Rodriguez-Mañas 2020) and in patients with Parkinson's Disease (Pepper 1999).

Table 8. AEs that Occurred More Frequently in the High Dose Category than in the Low Dose Category (≥ 5% Difference): M15-741/M15-737 Analysis Set

	Number (%) of Subjects[a]	
	ABBV-951 Dose Category	
Preferred Term (at any time)	Low Dose N = 119	High Dose N = 104
Infusion site oedema	16 (13.4)	29 (27.9)
Infusion site reaction	12 (10.1)	19 (18.3)
Infusion site erythema	56 (47.1)	57 (54.8)
Fall	16 (13.4)	21 (20.2)
Infusion site extravasation	5 (4.2)	11 (10.6)
Urinary tract infection	5 (4.2)	11 (10.6)
Anxiety	10 (8.4)	15 (14.4)
Infusion site abscess	7 (5.9)	12 (11.5)
Infusion site papule	6 (5.0)	11 (10.6)
Hallucination	18 (15.1)	21 (20.2)

The comparison between dose groups is difficult to interpret, since there was no randomization to these dose groups. Since the dose adjustments were allowed in order to achieve the optimal clinical response it could be assumed that it could be many underlying factors why the specific patient might need the higher dose. On the other hand, the higher frequency of AEs in the higher dose group might indicate that further increase of dose in order to achieve better clinical response could be related to increased risk for ADRs.

Adverse Events Associated with a Product Complaint

AEs associated with product complaints were summarized for the M15-741/M15-737 Analysis Set. For each AE in the Phase 3 studies, the investigator recorded whether the event was associated with a product complaint. A product complaint was any complaint related to the drug component or to the medical device component of the product. The most common AEs associated with product complaints (≥ 10% of subjects) are presented in (Table 11). SAEs associated with product complaints in ≥ 2% of subjects were infusion site cellulitis (7 subjects [3.1%]) and infusion site abscess (6 subjects [2.7%]).

Twenty-three subjects (10.3%) discontinued study drug because of AEs associated with product complaints. The most common events (≥ 2% of subjects) resulting in discontinuation of study drug due to an AE associated with product complaints were infusion site cellulitis (6 subjects [2.7%]) and infusion site erythema (6 subjects [2.7%]).

Table 11. TEAEs Associated with Product Complaints that Occurred in ≥ 10% of All Subjects: M15-741/M15-737 Analysis Set

	Number (%) of Subjects[a]		
	ABBV-951 Dose Category		
Preferred Term	Low Dose N = 119	High Dose N = 104	All Subjects N = 223
Any AE associated with a product complaint	87 (73.1)	77 (74.0)	164 (73.5)
Infusion site erythema	48 (40.3)	41 (39.4)	89 (39.9)
Infusion site nodule	25 (21.0)	26 (25.0)	51 (22.9)
Infusion site cellulitis	20 (16.8)	18 (17.3)	38 (17.0)
Infusion site oedema	10 (8.4)	23 (22.1)	33 (14.8)
Infusion site pain	14 (11.8)	10 (9.6)	24 (10.8)
Infusion site reaction	10 (8.4)	14 (13.5)	24 (10.8)

Most of AEs related to the product complaints are related to injection site reactions and injection site infections. It is noted that 3 patients also discontinued the study because of difficulty with drug delivery system (Table 3 Clinical efficacy). How many such AEs were reported as AEs related to product complain is unclear.

Analysis of Adverse Events of Special Interest by Organ System or Syndrome

Adverse events of special interest (AESIs) for ABBV-951 are as follows:

- Infusion site infections
- Infusion site reactions
- Hallucinations/psychosis
- Polyneuropathy (peripheral neuropathy)
- Falls and associated injuries
- Weight loss
- Somnolence

Infusion site infection event

Seventy-two subjects (32.3%) experienced at least 1 infusion site infection event. The most commonly reported PTs (≥ 5% of all subjects) were infusion site cellulitis, infusion site abscess, and infusion site infection. In the majority of subjects with infusion site infections, the events were nonserious (57/72 subjects [79.2%]) and were mild or moderate in severity (60/72 subjects [83.3%]). The median time to onset was 38 days and the median duration of the events was 15 days. In the majority of subjects with infusion site infections, the events resolved spontaneously or with treatment with antibiotics and/or incision and drainage. Overall, 11 subjects discontinued study drug because of infusion site infection events, the majority of which were considered to be reasonably possibly related to study drug. Serious infusion site infections were reported for 15 subjects; however, cellulitis in 1 subject was on the leg following an injury, was not at the infusion site, and was not related to treatment with ABBV-951. The events in the remaining 14 subjects were infusion site cellulitis alone (7 subjects), infusion site abscess alone (3 subjects), infusion site cellulitis and infusion site abscess (3 subjects), and infusion site infection; 4 of these subjects discontinued treatment with ABBV-951 and 12 of these subjects were hospitalized. In 4 subjects, infusion site infection events led to systemic complications

of sepsis and/or metabolic encephalopathy that resulted in hospitalization. The events were treated with antibiotics and/or incision and drainage, and the subjects were subsequently discharged from the hospital. One of the 4 subjects discontinued study drug because of the event. None of the infusion site infections were life threatening or fatal.

Three subjects (6.1%) experienced events of infusion site infections in the Phase 1 studies (all in subjects with PD); 2 of these 3 subjects discontinued study drug. The events were considered by the investigator to be reasonably possibly related to study drug.

Infusion site infection including infusion site cellulitis and infusion site abscess were most common AEs. The information regarding infusion site infection is provided in the ADR Table section 4.8 and as warning in section 4.4. However, the type of infusion site infection is described only in the footnote to the ADR Table in section 4.8. It is recommended to lift the information regarding the infusion site cellulitis and infusion site abscess into the ADR Table in section 4.8. In addition, the information regarding infusion site cellulitis and infusion site abscess should be also mentioned in section 4.4 (see SmPC comments). This information was updated by the Applicant.

Infusion Site Reactions

A total of 175 subjects (78.5%) experienced at least 1 infusion site reaction. In the majority of subjects with infusion site reactions, the events were nonserious (172/175 subjects [98.3%]) and were mild or moderate in severity (167/175 subjects [95.4%]). The median time to onset was 8 days and most events resolved, with a median duration of 12 days. Serious infusion site reactions were reported for 3 subjects. The events were infusion site injury (2 subjects) and infusion site hematoma (1 subject). Each subject with a serious infusion site reaction event had a concurrent serious infusion site infection event. None of the events was fatal or life-threatening. Eighteen subjects discontinued study drug because of infusion site reactions, the majority of which were considered by the investigator to be reasonably possibly related to study drug.

PTs that included the term "nodule" were grouped for analyses. Nodule events were reported for 66 subjects (29.6%). No serious events were reported, and in the majority of subjects with nodule events, the events were mild or moderate in severity and all were considered by the investigator to be reasonably possibly related to study drug. Four subjects discontinued study drug because of infusion site nodule events. The median time to onset was 22 days and most events resolved, with a median duration of 35.5 days.
In the Phase 1 studies in healthy volunteers, 74 subjects (42.5%) experienced infusion site reactions, of which 57 subjects had events that were considered by the investigator to be reasonably possibly related to study drug.
In the Phase 1 studies in subjects with PD, 28 subjects (57.1%) experienced infusion site reactions, of which 23 subjects had events that were considered by the investigator as reasonably possibly related to study drug. All of the events in the Phase 1 studies were nonserious. One subject in the Phase 1 studies discontinued study drug because of an infusion site reaction.

Relatively high number of infusion site reactions were reported (78.5%). The information in the ADR Table is limited to the very common ADR “Infusion site reaction” with more precise description of specific reactions observed in the footnote under the Table. This is not agreed. The specific infusion site reactions observed, - erythema, oedema, nodule, pain, bruising, papule, extravasation, haematoma, haemorrhage, induration, pruritus, exfoliation, rash, swelling, and inflammation – should be included into the ADR Table.
The median time to onset for infusion site reactions was 8 days and each of 3 patients with serious infusion site experienced also infusion site infection. Therefore, it is considered that information that infusion site infection was developed in all three patients who also reported serious infusion site reaction should be also added to the warning in 4.4. section.

The SmPC was updated upon the request.

Hallucinations/Psychosis

An overview of hallucinations/psychosis events for the M15-741/M15-737 Analysis Set is presented in Table 16. Fifty-four subjects (24.2%) experienced at least 1 hallucination/psychosis event. The most commonly reported PTs (≥ 2 of all subjects) were hallucination, hallucination visual, delusion, hallucination auditory, psychotic disorder, and paranoia (Table 17). In the majority of subjects with hallucination/psychosis events, the events were nonserious and were mild or moderate in severity. The median time to onset was 32 days and most events resolved with a median duration of 15 days. Serious hallucinations/psychosis events were reported for 12 subjects. The events were hallucination (5 subjects), hallucination and delusion (1 subject), psychotic disorder (5 subjects), and delusional disorder, unspecified type (1 subject). No events were fatal or life-threatening. Eleven subjects discontinued study drug because of hallucinations/psychosis events, all of which were considered to be reasonably possibly related to study drug.

Dopamine agonist use has been associated with a higher risk of hallucination in PD patients (Kulisevsky 2013, Zhou 2014). Overall, dopamine agonist use at Baseline was reported for 143 subjects (64.1%) and concomitant dopamine agonist use was reported for 139 subjects (62.3%). A higher frequency of hallucination events was observed in concomitant dopamine agonists users (30.9%, 43/139) than in non-users (13.1%, 11/84). Additionally, in the 54 subjects who experienced a hallucinations/psychosis event, underlying aPD was considered to be a contributing factor and 9 subjects had a medical history of hallucination, psychotic disorder, or paranoid thoughts.

The hallucinations, delusion, psychotic disorders and paranoia discussed above are listed in the ADR Table in section 4.8.
The warning for other psychiatric disorders is included into the Duodopa SmPC. Since higher frequency of hallucinations was observed in concomitant dopamine agonists users (30.9%, 43/139) than in non-users (13.1%, 11/84) in study M15-741, similar warning could be included in the proposed SmPC.
The SmPC was updated as requested.

Polyneuropathy

Five subjects (2.2%) experienced at least 1 polyneuropathy event. The only PT in the SMQ narrow search
reported in more than 1 subject was polyneuropathy (Table 19). In the majority of subjects with polyneuropathy events, the events were mild or moderate in severity. The median time to onset of the events was 74 days. No polyneuropathy events in the peripheral neuropathy SMQ narrow search were serious or resulted in study drug discontinuation.

Vitamin deficiencies, particularly B12 and B6, have been associated with reports of peripheral neuropathy in subjects with PD taking LD medications (Miller 2003, Rajabally 2011, Toth 2010). To minimize the confounding effect of vitamin deficiencies, subjects with a low vitamin B12 level (< 200 pg/mL) or those with low-normal vitamin B12 level (< 300 pg/mL), and elevated methylmalonic acid (MMA > 0.41 μmol/L) at initial screening, were not eligible to enroll in Study M15-741, although subjects could undergo supplemental vitamin therapy and enroll if successfully retested. During Screening, 4 of the 5 subjects with polyneuropathy events had low vitamin B6 levels, with elevated homocysteine and the remaining subject had an elevated MMA level. The majority of the subjects (4 out of 5 subjects) that had a polyneuropathy event had relevant confounding medical histories that included vitamin B12 deficiency, numbness of fingers, Morton's metatarsalgia, irritable bowel syndrome, or Crohn's disease.

Polyneuropathy events were reported in 5 (2.2%) of patients. It appears that higher risk of polyneuropathy was observed in the high dose group (4 out 5 patients). Duodopa SmPC has polyneuropathy listed as a common ADR in the ADR Table in section 4.8.

Therefore, it is recommended to include the ADR of polyneuropathy in the ADR Table with frequency common.

The SmPC was updated as requested.

Falls and Associated Injuries

Thirty-nine subjects (17.5%) experienced at least 1 fall and associated injury event. PTs reported in ≥ 3 of all subjects in the falls and associated injuries CMQ are presented in (Table 21). In the majority of subjects with falls and associated injuries, the events were mild or moderate in severity and were considered to have no reasonable possibility of being related to study drug (Table 20). The median time to onset was 35 days.
Serious events of falls and associated injuries were reported for 5 subjects. The events were fall in 1 subject, fall and face injury in 1 subject, hip fracture in 2 subjects, and scapula fracture in 1 subject. One subject died from an intracranial mass and subdural hematoma after a fall that was reported as nonserious with no reasonable possibility of being related to study drug. The 67-year-old female subject, who had a history of hypertension, depression, arthritis, bilateral knee replacements, and daytime somnolence, fell while trying to get out of bed. No events of falls and associated injuries resulted in study drug discontinuation.

The falls are included in the ADR Table in section 4.8. This is agreed.

Orthostatic Hypotension

Orthostatic hypotension was analyzed because of its role as a risk factor for falls. Thirty-seven subjects (16.6%) experienced at least 1 orthostatic hypotension event, and the most common PT reported was dizziness, which was reported in 24 subjects (10.8%) (Table 23). In the majority of subjects with orthostatic hypotension events, the events were mild or moderate in severity and considered to have a reasonable possibility of being related to study drug. The median time to onset was 21 days and most events resolved, with a median duration of 8 days. One serious event of dizziness was reported after an accidental fall that resulted in hospitalization for a 71-year-old male subject with multiple comorbidities. The event resolved on the same day. Four subjects reported a preceding, ongoing, or concurrent event of dizziness or orthostatic hypotension at the time of the fall. All 4 falls were considered accidental and 3 out of 4 were considered by the investigator to have no reasonable possibility of being related to study drug. None of the concurrent events resulted in a change in the ABBV-951 dose.

Of the 39 subjects who experienced a fall event, 6 subjects had a medical history of falls or high risk for falls, and 20 subjects had other relevant medical history including arthritis, osteoarthritis, daytime somnolence, cervical/lumbar spondylosis, scoliosis, or hip/pelvic fractures. Of the 37 subjects who experienced orthostatic hypotension events, 8 subjects had a medical history of orthostatic hypotension, hypotension, postprandial hypotension, or dizziness.

In the Phase 1 studies, 6 subjects experienced at least 1 fall and associated injury event (4 healthy subjects and 2 subjects with PD) and 8 subjects experienced at least 1 orthostatic hypotension event (3 healthy subjects and 5 subjects with PD). The majority of the events were considered by the investigator as having no reasonable possibility of being related to study drug. None of the events was serious or led to discontinuation of study drug.

Dizziness, postural dizziness, orthostatic hypotension were reported as ADRs in the clinical studies and listed in the ADR Table. Syncope, particularly in the high dose group, was also observed in the M15-741 study, but not listed in the ADR Table even though it is listed in the Duodopa SmPC. It is recommended to add ADR Syncope in the ADR Table in section 4.8 with frequency common.
The SmPC was updated as requested.

Somnolence

Eleven subjects (4.9%) experienced at least 1 somnolence event. In the majority of subjects, these events were considered by the investigator as reasonably possibly related to study drug. The median time to onset was 82 days and most events resolved, with a median duration of 6 days. None of the events was serious or led to study drug discontinuation. Somnolence events were reported for 2 subjects in the Phase 1 studies. None of the events was serious or led to study drug discontinuation. No events of sleep attack were reported in the ABBV-951 clinical development program.

Weight Loss

Twenty-three subjects (10.3%) experienced at least 1 weight loss event. The PTs reported in more than 1 subject were weight decreased (20 subjects [9.0%]) and decreased appetite (4 subjects). In the majority of subjects with weight loss events, the events were mild or moderate in severity and considered by the investigator as reasonably possibly related to study drug. The median time to onset was 85 days and most events resolved, with a median duration of 67 days. None of the events was serious or led to discontinuation of study drug. In the Phase 1 studies, an AE of weight decreased was reported for 1 subject; it was considered by the investigator as reasonably possibly related to study drug. The event was nonserious and did not result in study drug discontinuation.

Serious adverse events and deaths

Deaths

Five deaths were reported in the Phase 3 studies. Three subjects died as a result of TEAEs (cardio-respiratory arrest and cerebrovascular accident in 1 subject each, and subdural hematoma and intracranial mass in 1 subject) and 2 subjects died as a result of non-TEAEs (multiple organ dysfunction syndrome and cachexia in 1 subject each). No deaths occurred in the Phase 1 studies (All ABBV-951 Analysis Set).

Other Serious Adverse Events

Fifty-five subjects (24.7%) experienced at least 1 serious adverse event (SAE) (Table 9). SAEs that were reported in ≥ 2% of all subjects are presented in Table 9. The events were considered by the investigator as reasonably possibly related to study drug except for Parkinson's disease in 3 subjects, infusion site abscess in 1 subject, and infusion site cellulitis in 1 subject. SAEs resulted in study drug discontinuation in 8 subjects (infusion site abscess in 3 subjects, infusion site cellulitis in 2 subjects, Parkinson's disease in 2 subjects, and hallucination in 1 subject).

Table 9. SAEs that Occurred in ≥ 2% of All Subjects: M15-741/M15-737 Analysis Set

	Number (%) of Subjects		
	ABBV-951 Dose Category		
Preferred Terms[a]	Low Dose N = 119	High Dose N = 104	All Subjects N = 223
Any SAE at any time during treatment period	27 (22.7)	28 (26.9)	55 (24.7)
Infusion site cellulitis	4 (3.4)	6 (5.8)	10 (4.5)
Infusion site abscess	4 (3.4)	2 (1.9)	6 (2.7)
Hallucination	5 (4.2)	1 (1.0)	6 (2.7)
Psychotic disorder	3 (2.5)	2 (1.9)	5 (2.2)
Parkinson's disease	4 (3.4)	1 (1.0)	5 (2.2)

Subgroup analyses of SAEs were performed by dose category, age, race, sex, BMI, PD duration, region, and concomitant dopamine agonist use for the M15-741/M15-737 Analysis Set. No notable differences between the subgroups were observed.

SAEs were experienced by 3 subjects in the Phase 1 studies: abdominal abscess and cellulitis in 1 subject in Study M15-739, seizure in 1 subject in Study M17-220, and arthralgia (coded to musculoskeletal pain in the study CSR) in 1 subject in Study M18-763. The subject who experienced seizure was a 62-year-old male with history of brain surgery for a benign tumor. The outcome of the event was reported as resolved. The event of seizure was considered as having no reasonable possibility of being related to the study drug. The SAEs of abdominal abscess and cellulitis were considered to have a reasonable possibility of being related to study drug.

Adverse Events Leading to Discontinuation of Study Drug

M15-741/M15-737 Analysis Set
AEs that led to study drug discontinuation reported in ≥ 3 subjects overall were PTs associated with infusion site events, hallucination, Parkinson's disease, or dyskinesia (Table 10).

Table 10. AEs that Led to Study Drug Discontinuation in ≥ 3 of All Subjects: M15-741/M15-737 Analysis Set

	Number (%) of Subjects		
	ABBV-951 Dose Category		
Preferred Terms[a]	Low Dose N = 119	High Dose N = 104	All Subjects N = 223
Any AE that led to study drug discontinuation	27 (22.7)	27 (26.0)	54 (24.2)
Hallucination	4 (3.4)	5 (4.8)	9 (4.0)
Infusion site cellulitis	4 (3.4)	5 (4.8)	9 (4.0)
Infusion site erythema	5 (4.2)	3 (2.9)	8 (3.6)
Infusion site nodule	1 (0.8)	3 (2.9)	4 (1.8)
Infusion site oedema	2 (1.7)	2 (1.9)	4 (1.8)
Infusion site reaction	2 (1.7)	1 (1.0)	3 (1.3)
Infusion site abscess	1 (0.8)	2 (1.9)	3 (1.3)
Parkinson's disease	2 (1.7)	1 (1.0)	3 (1.3)
Dyskinesia	3 (2.5)	0	3 (1.3)

AEs of suicidal ideation were reported for 2 subjects that were nonserious, and 1 subject had an SAE of suicide attempt. The SAE of suicide attempt was considered by the investigator to have no reasonable possibility of being related to study drug. None of the 3 events led to discontinuation of study drug. There was no evidence of increase in suicidality with ABBV-951 based on the review of the AEs and the current C-SSRS data.

Overdose

One subject, who had a history of anxiety, overmedicated themselves with oral LD/CD (100/25 mg [3 tablets per day]) while on ABBV-951 and felt panicky. Per the investigator, this was not considered to be an overdose with ABBV-951. Both the events of overdose and panic reaction were nonserious, mild in severity, and resolved with no action taken with ABBV-951 in response to these events.

The treatment of an acute overdose of foslevodopa/foscarbidopa, in general, is the same as that of an acute overdose of levodopa. In the event of overdosage, the infusion should be stopped, and the pump disconnected immediately. General supportive measures should be employed. Intravenous fluids should be administered judiciously, and an adequate airway maintained. Electrocardiographic monitoring should be instituted, and the patient carefully observed for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other medicinal products with foslevodopa/foscarbidopa should be considered.

Drug Abuse

ABBV-951 has not been systemically studied in animals or in humans for its potential for abuse, tolerance, or physical dependence. Levodopa-containing medications are not controlled substances. There are rare postmarketing reports of abuse and dependence. The (US Food and Drug Administration [FDA] 2017) and the (European Medicines Agency 2006) guidelines recommend that drug products that are under development be evaluated for abuse potential as a component of their safety package.

AEs included in the AbbVie abuse liability CMQ have been reported for 95 subjects (21.6%) in the ABBV-951 clinical development program; for the majority of subjects, the events were nonserious and were mild or moderate in severity. The majority of these events are known effects of PD disease or LD (e.g., dizziness, hallucinations, somnolence) and are not suggestive of abuse. The only events reported that are also in the MedDRA drug abuse and dependence SMQ were the previously described event of overdose and an event of dopamine dysregulation syndrome (DDS) in 1 subject. The event of DDS was considered by the investigator to have no reasonable possibility of being related to study drug and did not lead to discontinuation of study drug. Based upon the available data and the understanding of the mechanism of action of ABBV-951, there was no evidence of abuse liability or dependency potential with ABBV-951.

Impulsive-Compulsive Behaviors

Impulsive-compulsive behaviors such as DDS, pathological gambling, compulsive sexual behavior, pounding, compulsive shopping, and binge eating are recognized complications of dopaminergic treatment that affect at least 1 in 7 patients with PD (Averbeck 2014). While the prevalence of impulse control disorders (ICDs) in PD patients are not precisely known, studies have reported ICD prevalence ranging from 14% to 40% in patients with PD (Baig 2019, Antonini 2017, Saez-Francas 2016). The impulse control disorder CMQ was used to identify AEs related to impulsive compulsive behaviors and the QUIP-RS was administered in the Phase 3 studies. The QUIP-RS is a questionnaire specifically developed to monitor changes in ICDs and related symptoms in PD patients over time. Scores for each ICD and related disorder range from 0 to 16 with a higher score indicating greater severity (i.e., frequency) of symptoms.
AEs related to impulsive-compulsive behaviors were reported for 8 subjects (3.6%) in the Phase 3 studies; for the majority of subjects, these AEs were nonserious and were mild or moderate in severity. None of the events resulted in study drug discontinuation. The only SAE was an event of DDS, which is discussed in the abuse liability section above. At each time point, scores on the QUIP-RS were low for each ICD and related behavior parameter with mostly small mean decreases from Baseline.

Withdrawal and Rebound

Withdrawal or rebound effects with ABBV-951 have not been studied. AEs with the MedDRA PT of drug withdrawal syndrome was reported in 2 subjects (0.5%) in the ABBV-951 clinical development program. Both events were related to concomitant dopamine agonists and not ABBV-951. A symptom complex resembling neuroleptic malignant syndrome (NMS), including muscular rigidity, increased body temperature, mental changes (e.g., agitation, confusion, coma) and increased serum creatine phosphokinase, has been reported when anti-Parkinsonian medicinal products were withdrawn

abruptly. Rhabdomyolysis secondary to NMS or severe dyskinesias have been observed rarely in patients with PD.
Therefore, patients should be carefully observed when the dose of levodopa/carbidopa combinations are abruptly reduced or discontinued, especially if the patient is receiving antipsychotics.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies on the effects on the ability to drive and use machines have been performed with ABBV-951.
Levodopa and carbidopa may cause dizziness and orthostatic hypotension. Patients must be informed of this and advised to exercise caution while driving or using machines. In addition, patients being treated with foslevodopa/foscarbidopa and presenting with somnolence and/or episodes of sudden onset of sleep must be advised to refrain from driving or operating machines while being treated.

I.1 Laboratory findings

As of the data cutoff date for Study M15-737 interim CSR, 13 subjects had completed Week 24 assessments (the first time point at which laboratory measurements were collected). Based on review of the current data available, no trends or safety concerns were identified.

No clinically meaningful changes from Baseline in laboratory values were observed in the ABBV-951 clinical development program. No subject in the ABBV-951 clinical program has had an alanine transaminase (ALT) or aspartate transaminase (AST) value > 3 × upper limit of normal (ULN).

No clinically meaningful changes from Baseline in laboratory parameters, vital signs, ECG were observed.

I.2 Safety in special populations

Use in Pregnancy and Lactation

The ABBV-951 was not studied in pregnant or breastfeeding women.

I.3 Immunological events

Not applicable

I.4 Safety related to drug-drug interactions and other interactions

No drug interaction studies have been performed with ABBV-951.

Metabolites and Degradation Products: Potential Hydrazine Toxicity

Hydrazine is a degradation product of CD and is expected to be present in ABBV-951. Hydrazine is considered by the International Agency for Research on Cancer (IARC) as a probable human carcinogen based on preclinical data; however, human data with respect to hydrazine carcinogenicity is limited. The permissible daily exposure of hydrazine as defined by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M7 guidance of 39 μg/day for a 1 in 100,000 risk is calculated based on a lifetime exposure (70 years). At the proposed maximum recommended ABBV-951 daily dose of foslevodopa/foscarbidopa 6000/300 mg/day, the daily hydrazine exposure will not exceed 525 μg/day. When appropriate adjustments are made to account for duration of use of up to 20 years of exposure, the resultant risk is 0.1 to 3.8 in 100,000, depending on duration of exposure. The benefits of treatment with ABBV-951 in patients with aPD outweigh the potential risks associated with hydrazine exposure due to ABBV-951, given the severity of disease and the limitations of available therapeutic options for aPD.

Malignancies in the ABBV-951 Clinical Development Program

Malignancy events were reported for 3 subjects (basal cell carcinoma in 2 subjects and squamous cell carcinoma of skin in 1 subject) in Study M15-741. Two of the events were mild in severity. All 3 events were nonserious and were considered by the investigator to have no reasonable possibility of being related to study drug. None of the events resulted in the discontinuation of study drug.

Malignancies in the LCIG Postmarketing Safety Database

The expected hydrazine exposure from ABBV-951 represents a 12-fold reduction in hydrazine levels relative to the levodopa/carbidopa intestinal gel (LCIG) drug product. The clinical relevance of hydrazine content was added to the LCIG Risk Management Plan (RMP) as important missing information in 2010.
In LCIG RMP version 7.2, the malignancy rate in the LCIG postmarketing safety database was compared to published cancer incidence rates. There had been 77 reports of neoplasms since first launch. A spectrum of different cancer types and locations were reported without any apparent clustering. The 77 spontaneous cases of neoplasms were reported from an estimated 19,096 patient treatment years of postmarketing exposure to LCIG since first launch and represented an approximate cancer incidence rate of 403 cases per 100,000 PTYs of LCIG exposure. In the US, the incidence rate of cancer, all types excluding non-melanoma skin cancer, for the 70-to-74-year age group was 2,030.3 per 100,000 population in the period from 2008 to 2012 (from the National Institutes of Health [NIH] Surveillance, Epidemiology, and End Results program 2015). In England, the cancer incidence rate for the same age group ranged from 1477.3 per 100,000 in females to 2310.9 per 100,000 in males (from the Office for National Statistics 2012). Therefore, there was no indication that the number of cases in the LCIG postmarketing safety database exceeded the number of incident cases expected in a population of comparable age. During over 7 years of close monitoring, no safety signals related to malignancies were identified in the LCIG program and in LCIG RMP version 8.0 (DLP 01 October 2019) the clinical relevance of hydrazine toxicity was removed as important missing information. Based on the ABBV-951 clinical data and LCIG's postmarketing data, the ABBV-951 carcinogenicity risk due to hydrazine exposure appears to be low.

The Duodopa SmPC contains warning for the melanoma. It is considered that PD patients has higher risk to develop melanoma compared to general population. The effect of LD/CD on the development of melanoma in PD patients is unclear. However, it is recommended regularly check the skin of PD patients for melanoma in the Duodopa SmPC. Similar warning, as class warning, is recommended to be added to section 4.4 of the produodopa SmPC.
The SmPC was updated as requested.

Discontinuation due to AES

The Effect of Mitigation Measures to Address Treatment Discontinuation in Study M15-741

During the course of Study M15-741, an internal investigation determined the causes of treatment discontinuations to be infusion site AEs and difficulties with using the drug delivery system, subsequent to which mitigation measures were implemented. As part of the mitigation measures, study sites and subjects underwent retraining, with a specific focus on the correct use of the infusion set and cannula and on aseptic techniques. The mitigation measures were effective and, as of the 30 March 2021 data cutoff date, resulted in a substantially lower number of discontinuations and lower percentage of infusion site reactions, infusion site infections, and TEAEs associated with product complaints.

Subgroup analyses of AEs leading to study drug discontinuation were performed by dose category, age, race, sex, BMI, PD duration, region, and concomitant dopamine agonist use for the M15-741/M15-737 Analysis Set. No notable differences between the subgroups were observed.
Two healthy subjects discontinued study drug because of AEs in the Phase 1 studies: viral infection (nonserious) in 1 subject in Study M18-764, and seizure (serious) in 1 subject in Study M17-220. The events were considered to have no reasonable possibility of being related to study drug. In the Phase 1 studies in subjects with PD, 3 subjects discontinued study drug because of AEs: cellulitis (serious) and infusion site infection (nonserious) in 1 subject each in Study M15-739 and nonserious events of infusion site swelling and anxiety in 1 subject in Study M15-738. The events were considered to be reasonably possibly related to study drug.

It is understood that substantial number of observed discontinuations early during the study M15-741 were due to infusion site reactions/infections. The mitigation measures, described above, were applied by the Applicant. The result of these mitigation measures seems reduced discontinuation rate, infusion site reactions/infections and treatment emergent AEs associated with product complains. It is understood that these mitigation measures are intended to be used with the commercial product.

Post marketing experience/Risk management

ABBV-951 is not approved for use in any country.

Overall discussion and conclusions on clinical safety

The safety profile of ABBV-951 is based on relatively small number of patients treated for rather short period of time. As of the data cutoff date (30 March 2021), 439 unique subjects had received ABBV-951 as part of the clinical development program.
The key safety analysis set used to characterize safety profile is from study M15-741/M15-737 Analysis set. It contains 223 PD patients who started treatment with ABBV-951. The mean duration of exposure of PD patients was 236.2 days. Only 77 PD patients were exposed more at least 12 months. It is noted that rather large proportion of patients (N=196, 87.9%) received other dopaminergic concomitant medications.

Each subject's modal TDD in Study M15-741 was used to determine their dose category; either low dose (modal TDD < 1800 mg LD) or high dose category (modal TDD ≥ 1800 mg LD). Although subjects are categorized by dose category for the statistical analyses, there are limitations in the ability to interpret any differences observed between the dose categories. Any difference between dose categories is not expected to reflect a dose-response given that randomization was not used to control for bias nor to create groups that are comparable with respect to known and unknown confounding factors. The comparison of AEs between dose groups is difficult to interpret, since there was no randomization to these dose groups. Since the dose adjustments were allowed in order to achieve the optimal clinical response it could be assumed that it could be many underlying factors why the specific patient might need the higher dose. On the other hand, the higher frequency of AEs in the higher dose group might indicate that further increase of dose in order to achieve better clinical response could be related to increased risk for ADRs.

Most patients experienced AEs (92.4%) and the majority of patients experienced infusion site reactions (78.5%). It is noted that the vast majority of AEs occurred within first 90 days of treatment. Most of AEs related to the product complaints are related to injection site reactions and injection site infections. It is noted that 3 patients also discontinued the study because of difficulty with drug delivery system.

Infusion site infection including infusion site cellulitis and infusion site abscess were most common AEs. Also, the most common SAEs were infusion site cellulitis and infusion site abscess. The

information regarding infusion site infection is provided in the ADR Table section 4.8 and as warning in section 4.4.

The hallucinations, delusion, psychotic disorders and paranoia discussed above are listed in the ADR Table in section 4.8. The warning for other psychiatric disorders is included into the Duodopa SmPC. Also, higher frequency of hallucinations was also observed in concomitant dopamine agonists users (30.9%, 43/139) than in non-users (13.1%, 11/84) in study M15-741, a warning for concomitant use of dopamine agonists is also included in the proposed SmPC.

Polyneuropathy events were reported in 5 (2.2%) of patients. It appears that higher risk of polyneuropathy was observed in the high dose group (4 out 5 patients). Duodopa SmPC has polyneuropathy listed as a common ADR in the ADR Table in section 4.8. Syncope, particularly in the high dose group, was also observed in the M15-741 study. Both ADRs Polyneuropathy and Syncope in the updated ADR Table in section 4.8 with frequency common.

In addition, The Duodopa SmPC contains warning for the melanoma. It is considered that PD patients has higher risk to develop melanoma compared to general population. The effect of LD/CD on the development of melanoma in PD patients is unclear. However, it is recommended regularly check the skin of PD patients for melanoma in the Duodopa SmPC.

Substantial number of observed discontinuations early during the study M15-741 were due to infusion site reactions/infections. The Applicant introduced the mitigation measures, like e.g. - study sites and subjects underwent retraining, with a specific focus on the correct use of the infusion set and cannula and on aseptic techniques. In addition, the neria™ guard, the primary intended commercial infusion set for delivery of ABBV-951, was added as an alternative infusion set. The result of these mitigation measures seems reduced discontinuation rate, infusion site reactions/infections and treatment emergent AEs associated with product complains. It is understood that these mitigation measures are intended to be used with the commercial product. The Applicant agreed introduce additional risk minimization measures like educational material for patients.

In summary, the safety profile of ABBV-951 is based on very limited number of PD patients treated for relatively short time. However, no new safety findings were identified except the ones specifically related to infusion site reactions and infusion site infections. The relevant information provided in the SmPC related to these ADRs is expected to inform prescribers and patients to be cautious in noticing these ADRs and will help to manage them.

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to produodopa.

Safety specification

The Applicant provided updated Table of Safety Concerns:

Summary of Safety Concerns	
Important identified risks	Infusion site events (infusion site infections and serious infusion site reactions)
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include: Specific adverse reaction follow-up questionnaires for:

Important identified risk - Infusion site events (infusion site infections and serious infusion site reactions):

A targeted questionnaire will be utilized in the postmarketing setting to follow-up with treating health care professionals regarding infusion site infections and serious infusion site reactions (Annex 4). The objective is to collect comprehensive and structured information regarding infusion site events for meaningful assessment.

Other forms of routine pharmacovigilance activities for infusion site events (infusion site infections and serious infusion site reactions): Not applicable.

Additional Pharmacovigilance Activities

The Applicant has proposed a database study to evaluate the effectiveness of the educational material for patients (See aRMMs below). The study is summarised in Table 1 below.

Table 1 Summary of Additional Pharmacovigilance Activities

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Observational cohort study among individuals with advanced PD and use of ABBV-951 Planned	The objective of this study (a Category 3 PASS) is to assess the effectiveness of the additional measures proposed for ABBV-951 (patient education materials) utilizing an outcomes-based assessment of incidence rates of infusion site AEs, specifically infusion site infections and serious infusion site reactions, in patients with advanced Parkinson's Disease treated with ABBV-951.	The aim of this study is to evaluate the effectiveness of additional risk minimization measures (patient education materials) for infusion site AEs (including infusion infections and serious infusion site reactions) with ABBV-951.	ABBV-951 market availability[a] Date of registration in the EU PASS Register Start of data collection for secondary data use (date when data extraction starts)[b] End of data collection for secondary data use (date when analytical data set is available) Final study report	Q2 2023 30 calendar days post-protocol approval Estimated Q1 2024 Estimated Q1 2027 Estimated Q1 2028

It will be a descriptive prospective cohort study of individuals with PD residing in two or more EU countries who have a prescription for ABBV-951. The study will utilize secondary fit-for-purpose sources of data in evaluating ABBV-951 prescriptions and incidence rates of infusion site infections

and serious infusion site reactions. Sources of data include one or more national health registers, specialty electronic medical records (EMRs), and/or administrative data sources. It is a descriptive study, aimed at capturing as many new users of ABBV-951 as are available in the identified fit-for-purpose data source within at least 2 EU countries.

Although the planned study is only shortly described, the overall aim, and the use of existing data sources are endorsed. Overall, the study can be agreed as a category 3 study in the PhV plan.

Risk minimisation measures

The Table below shows an overview of the routine risk minimisation measures in place.

Safety Concern	Routine Risk Minimization Activities
Infusion site events (infusion site infections and serious infusion site reactions)	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use identifies the risk of infusion site events due to subcutaneous administration of ABBV-951 using the drug delivery system and guidance to mitigate them. SmPC Section 4.8 Undesirable effects describes infusion site events in clinical trials and recommends specific measures to reduce the risk. PL Section 2 What you need to know before you use ABBV-951: infusion site infections; skin changes at the infusion site and recommends specific measures to reduce the risk. Routine risk minimization activities recommending specific clinical measures to address the risk: A recommendation for patients to follow aseptic techniques and to frequently rotate the infusion site while using ABBV-951 to reduce the risk of infusion site infections is included in the SmPC Section 4.4. Skin changes at the infusion site should be monitored and infusion sites should be rotated frequently and should be at least 2.5 cm from sites used within the previous 12 days. - SmPC Section 4.8. Patients are instructed to inform their doctor if they notice any skin changes at the infusion site and to follow aseptic techniques and to regularly change infusion sites (at least every 3rd day) using a new infusion set. - PL Section 2. Other routine risk minimization measures: The SmPC and PL will contain adequate guidance on the proper use of ABBV-951, including aseptic techniques. Additionally, device IFUs will be shared with the patients and HCPs, and the references to these IFUs will be provided in the SmPC and PL.

IFUs = instructions for use; PL = Package Leaflet; SmPC = Summary of Product Characteristics

Additional risk minimisation measures

To address the identified important risks of *Infusion site events (infusion site infections and serious infusion site reactions)*, the additional RMMs are introduced; namely a patient educational material (patient guide). The objectives of this educational material are to enhance patient awareness of the risks of infusion site events and to educate patients on measures they should take to help mitigate these risks. In summary, the patient educational material contains 6 sections.

Section 1:
Awareness (why the patient guide was developed and why patients/care givers should read it). This section reminds patients/care givers of the indication of ABBV-951, how it is administered and about the 2 risks of concern that are infusion site infections and infusion site reactions.

Sections 2 to 5:
Education: In these sections, the patients and caregivers are educated on

- How patients should choose their infusion site
- How to recognize infusion site infection or reaction
- What patients can do to reduce the chance of getting infusion site infection or reaction
- What patients can do if they have infusion site infection or reaction to avoid a worst outcome
- Where patients can find more information about ABBV-951 (including how to report side effects)

Evaluation of effectiveness of the additional risk minimization measure

Implementation Plan including Target Audience and Planned Distribution Path:
The target audience for the patient guide is patients treated for advanced Parkinson's disease with foslevodopa/foscarbidopa.

Depending on local legislation, the patient guide will be distributed to patients via patient support programs and/or HCPs or other methods as agreed with local regulatory authorities. The patient guide will be made available as a print version where possible. The print version will be distributed by mail, courier, or in person etc. as determined at national level. In addition, the patient guide may be available in electronic format (pdf) or on digital platforms (websites) where permitted.

Where distribution to patients is not via treating HCPs, copies of the patient guide may also be distributed to HCPs for their awareness via the methods described above.

Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	**Risk Minimization Measures**	**Pharmacovigilance Activities**
Infusion site events (infusion site infections and serious infusion site reactions)	Routine risk minimization measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you use ABBV-951: The SmPC and PL provide reference to device IFUs. Device IFUs will be provided to patients and HCPs. Additional risk minimization measures: Patient Educational Material (Annex 6)	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Targeted questionnaire Additional pharmacovigilance activities: Observational cohort study among individuals with PD and use of ABBV-951

Summary of the RMP
The submitted Risk Management Plan, version 1.2 signed May 2022 is considered acceptable.

An updated RMP should be submitted:
- At the request of the RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was English.
The results 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Benefits

The application is based upon PK comparability of ABBV-951 to Duodopa (LCIG) from Study M17-220 and is further supported by a long-term open-label safety and tolerability study of ABBV-951 (Study M15-741) in subjects with aPD. The ABBV-951 is the first product for advanced PD applying LD/CD ratio 20:1 and administered subcutaneously. The subcutaneous administration could constitute clinical benefit for patients with aPD as an alternative to Duodopa treatment.

The clinical benefits were extrapolated from the Duodopa data based on established PK bridge between ABBV-951 and Duodopa. In addition, the clinical efficacy endpoints were evaluated as secondary endpoints in a Phase 3, 52-week, open-label study (Study M15-741). The study design allows no firm efficacy conclusions. Concerning both safety and efficacy (secondary objective), analyses were descriptive, and no hypothesis testing was planned.

As expected from the experience with Duodopa, the product used to for bridging the clinical efficacy, treatment with produodopa resulted in the “off” time reduction compared to the baseline and “on” time without troublesome dyskinesia increase compared to the baseline. The described changes of MDS-UPDRS, PDSS-2 scores, changes of scores on instruments evaluating quality of life from baseline until treatment end are acknowledged. However, interpretation of these results is difficult in the absence of control group and taking into account absence of randomisation and the open label nature of the study.

Currently, efficacy outcomes are presented in the SmPC (section 5.1). The data from MK15-741 open label study could be considered as supportive but addition of these data to 5.1 section from still on-going study based on small proportion of patients could be considered premature.

In addition, the subcutaneous administration of ABBV-951 could be considered as benefit compared to need for surgical intervention and PEG for Duodopa.

Risks

The safety profile of ABBV-951 is characterized on relatively small number of patients from study M15-741/M15-737 Analysis set (n=223) treated for rather short period of time. Also, some specific safety findings related to LD/CD could be assumed to be similar to the ones observed with Duodopa, since comparable PK profiles were established between Duodopa and ABBV-951.

Most patients experienced AEs (92.4%) and the majority of patients experienced infusion site reactions (78.5%). Infusion site infection including infusion site cellulitis and infusion site abscess were most common AEs. The information regarding infusion site reactions and infusion site infection is provided in the ADR Table section 4.8 and as warning in section 4.4. The type of infusion site reaction (erythema, oedema, nodule, pain, bruising, papule, extravasation, haematoma, haemorrhage,

induration, pruritus, exfoliation, rash, swelling, and inflammation) and infection (infusion site cellulitis and infusion site abscess) is also described in the ADR Table in section 4.8.

Other ADRs observed in M15-741 study like falls, somnolence, dizziness, postural dizziness, orthostatic hypotension, weight loss, hallucinations, delusion, psychotic disorders and paranoia listed in the ADR Table in section 4.8 are known from other LD/CD products including Duodopa.

Since higher frequency of hallucinations was also observed in concomitant dopamine agonists users (30.9%, 43/139) than in non-users (13.1%, 11/84) in study M15-741, a warning for concomitant use of dopamine agonists is included in the proposed SmPC.

In addition, Duodopa SmPC has polyneuropathy and syncope listed as a common ADRs in the ADR Table in section 4.8. Polyneuropathy and Syncope, particularly in the high dose group, were also observed in the M15-741 study. Both are added ADRs in the ADR Table in section 4.8 with frequency common.

Furthermore, Duodopa SmPC contains warning for the melanoma. It is considered that PD patients has higher risk to develop melanoma compared to general population. The effect of LD/CD on the development of melanoma in PD patients is unclear. Recommendation regularly check the skin of PD patients for melanoma is present in the Duodopa SmPC and is considered as class warning, and is added to section 4.4 of the produodopa SmPC.

In summary, the safety profile of ABBV-951 is based on very limited number of aPD patients treated for relatively short time. However, no new safety findings were identified except the ones specifically related to infusion site reactions and infusion site infections. The known safety findings identified for Duodopa and related to LD/CD, but not procedure itself, are presented in the proposed SmPC of produodopa. The relevant information provided in the SmPC related to these ADRs as well as ADRs specific for subcutaneous infusion, is expected to inform prescribers and patients to be cautious in noticing these ADRs early and will help to manage them appropriately.

Regarding hydrazine exposure, most patients will be exposed to hydrazine levels above the lifetime AI of 39 µg/day as outlined in ICH M7 (R1) and some patients may also be exposed to levels above a less-than-lifetime (10 years) adjusted AI of 273 µg/day indicating a potential risk to the patients.

Benefit/Risk balance

The benefits of ABBV-951 in treatment of aPD patients are primarily extrapolated from Duodopa, since PK bridge between duodopa and ABBV-951 was established. In addition, the subcutaneous administration of ABBV-951 could be considered as benefit compared to need for surgical intervention and PEG for Duodopa. The data from MK15-741 open label study with ABBV-951 could be considered as supportive but addition of these data to 5.1 section from still on-going study could be considered premature.

The safety profile related to ABBV-951 due to active substances essentially is similar to the known safety profile of Duodopa and could be managed by providing already established warnings and information on ADRs in the SmPC. The risks related to subcutaneous ABBV-941 administration are identified in a relatively small number of patients over relatively short treatment period. Since studies M15-741/M15737 are still ongoing it is expected that limited information on these risks available today will be complemented with additional data after completion of these studies. Also, the appropriate information provided in the SmPC and adequate risk minimization measures could allow manage known safety concerns.

The benefit/risk balance is considered positive.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Description	Due date
In vitro studies investigating the potential of foslevodopa to inhibit OATP1B1, OATP1B3, OCT1, OAT1, OAT3, OCT2, MATE1 and MATE2K	Q1 2023
Quality: AbbVie intends to submit the optional process for recovering the by-product LDP3 monosodium salt from the primary process for conversion to the final intermediate LDP3 Crude as a Type II variation.	Q2 2024
Quality: AbbVie intends to submit the sonication technology as an alternative to wet milling for both LDP3 mono-sodium salt crystallization and LDP4 Crude crystallization as a Type IB variation.	Q2 2024

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**
  The educational material consists of a patient educational material in the form of a guide to address the important identified risks of *infusion site events (infusion site infections and serious infusion site reactions).* The following key elements are addressed:

Section 1: Awareness (why the patient guide was developed and why patients/care givers should read it).

● This section reminds patients/care givers of the indication of ABBV-951, how it is administered and about the 2 risks of concern that are infusion site infections and infusion site reactions.

Sections 2 to 5: Education: In these sections, the patients and caregivers are educated on

● How patients should choose their infusion site
● How to recognize infusion site infection or reaction
● What patients can do to reduce the chance of getting infusion site infection or reaction
● What patients can do if they have infusion site infection or reaction to avoid a worst outcome
● Where patients can find more information about ABBV-951 (including how to report side effects)

VII. APPROVAL

The decentralised procedure for Produodopa, 240 mg/ml + 12 mg/ml, solution for infusion, was positively finalised on 2022-07-27.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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