



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 April 2016
EMA/343011/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ongentys

International non-proprietary name: opicapone

Procedure No. EMEA/H/C/002790/0000

Note

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



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List of abbreviations

AS	Active substance
API	Active Pharmaceutical Ingredient
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CVMP	Committee for Medicinal Products for Veterinary use
CFU	Colony Forming Units
CoA	Certificate of Analysis
CPP	Critical process parameter
CQA	Critical Quality Attribute
CRS	Chemical Reference Substance (official standard)
DoE	Design of experiments
EC	European Commission
EP	European Pharmacopoeia
GC	Gas Chromatography
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
IC	Ion chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
IU	International Units
IUPAC	International Union of Pure and Applied Chemistry
KF	Karl Fischer titration
LDPE	Low density polyethylene
LOD	Loss on drying
LoD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
LT	Less than
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OOS	Out of Specifications
PAR	Proven Acceptable Range
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PP	Polypropylene
PVDC	Polyvinylidene chloride
QbD	Quality by design
RH	Relative Humidity
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
USP	United States Pharmacopoeia
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bial - Portela & C^a, S.A. submitted on 25 November 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ongentys, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 July 2012.

The applicant applied for the following indication:

Ongentys is indicated as adjunctive therapy to preparations of levodopa/benserazide or levodopa/carbidopa in adult patients with Parkinson's disease and motor fluctuations.

The legal basis for this application refers to:

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

The applicant indicated that opicapone was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

The application contained a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal product Duodopa. However, as the orphan market exclusivity of Duodopa expired on 18 November 2015, it was considered unnecessary for the CHMP to conclude on possible similarity with Duodopa.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance opicapone contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 January 2012 and 18 October 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Greg Markey Co-Rapporteur: Martina Weise

- The application was received by the EMA on 25 November 2014.
- The procedure started on 24 December 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2015.
- PRAC Rapporteur assessment report circulated on 23 March 2015.
- PRAC RMP advice and assessment overview adopted by PRAC on 10 April 2015.
- During the meeting on 23 April 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 July 2015.
- The following GCP inspection was requested by the CHMP and its outcome taken into consideration as part of the Safety and Efficacy assessment of the product:
 - A GCP inspection at two clinical investigator sites in India was conducted in March 2015. The integrated inspection report of the inspections carried out was issued on 8 May 2015.
- PRAC Rapporteur assessment report circulated on 24 August 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 September 2015.
- PRAC RMP advice and assessment overview adopted by PRAC on 10 September 2015 (Annex 8).
- During the CHMP meeting on 24 September 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant, including a request for a critical report addressing the possible similarity with an authorised orphan medicinal product (Duodopa).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 October 2015, including a similarity report.
- PRAC Rapporteur assessment report circulated on 26 October 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 October 2015.
- PRAC RMP advice and assessment overview adopted by PRAC on 6 November 2015.
- During the CHMP meeting on 19 November 2015, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 25 January 2016.
- PRAC Rapporteur assessment report circulated on 1 February 2016.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 4 February 2016.
- During the CHMP meeting on 23 February 2016, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 25 February 2016, the CHMP agreed on a 3rd list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 28 March 2016.
- PRAC Rapporteur assessment report circulated on 4 April 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 3rd List of Outstanding Issues to all CHMP members on 7 April 2016.
- During the meeting on 28 April 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ongentys. In the context of the Duodopa's market exclusivity expiry on 18 November 2015, concluding the similarity assessment was no longer applicable at the time of the CHMP Opinion.

2. Scientific discussion

2.1. Introduction

Parkinson's disease is a neurological disorder with loss of dopamine generating neurons in the substantia nigra region of the mid brain and significant decrease in brain dopamine levels which result in typical Parkinson's symptoms. It is a degenerative disease that begins later in life: it is rare before 50 years of age, with a mean age of onset of about 60 years. The overall prevalence of Parkinson's disease for subjects aged 65 years or older is 1.6%. Prevalence increases with age, from 0.6% in the 65 to 69 years age group up to 3.5% in the 85 to 89 years age group.

The main features of Parkinson's disease are bradykinesia, tremor and rigidity, disturbances of movement, and problems with posture. Bradykinesia is the most disabling motor manifestation of Parkinson's disease, characterized by difficulty in initiating, and slowness in executing movements. The tremor occurs in the limbs while at rest and disappears on movement and during sleep. Rigidity refers to a resistance to passive movement and is often of a jerky or cogwheel nature. Other common symptoms of the disease are autonomic disturbances (sialorrhoea, seborrhoea, constipation, micturition disturbances, sexual functioning, orthostatic hypotension, hyperhidrosis), sleep disturbances, and disturbances in the sense of smell or sense of temperature. Depression and cognitive dysfunction is also common in Parkinson's disease patients.

L-DOPA is the most effective symptomatic treatment of Parkinson's disease. Progression of the disease requires gradual increases in L-DOPA dosage to achieve adequate motor control, which in turn leads to development of motor complications such as motor fluctuations and dyskinesias. Orally administered L-DOPA is predominantly metabolised in the periphery by aromatic L-amino acid decarboxylase, also called dopa decarboxylase, to dopamine, which can cause side effects such as emesis, orthostatic hypotension, and cardiac arrhythmia. To minimise the formation of dopamine in the periphery, L-DOPA is usually administered in combination with a peripheral DDCI (benserazide or carbidopa). However, when administered together with such inhibitors, only a relatively small amount of an oral dose of L-DOPA reaches the brain because COMT becomes the major metabolising enzyme for L-DOPA, and a considerable amount of the drug undergoes O-methylation to 3-O-methyl-levodopa (3-OMD) in the brain and periphery.

COMT inhibitors are thus also used as part of the treatment regimen to inhibit the O-methylation of L-DOPA to 3-OMD. COMT inhibition slows elimination of L-DOPA from the plasma by increasing its plasma half-life ($t_{1/2}$) and area under the curve (AUC) of plasma concentrations vs. time. The COMT inhibitors marketed to date are tolcapone and entacapone. They have demonstrated beneficial effects both in experimental models of parkinsonism and in Parkinson's disease patients.

Tolcapone is a more potent inhibitor of COMT than entacapone, both in the periphery and central nervous system. However, due to an increased risk of hepatic toxicity with tolcapone, its use is limited to fluctuating patients who have failed other therapies or are intolerant to entacapone. Entacapone, on the other hand, acts only in the periphery and is safer than tolcapone, but has limited efficacy as well as low to moderate oral bioavailability which requires frequent dosing.

It has been proposed that COMT inhibitors with limited access to the brain may serve as effective adjunctive therapy for Parkinson's disease, while avoiding potential undesired central side effects. As a result, although it is less efficacious than tolcapone, entacapone is currently the standard COMT inhibitor used in the treatment of Parkinson's disease. This constitutes an unmet need for new COMT inhibitors that can offer a better therapeutic profile than entacapone without an increased safety risk.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 25 or 50 mg of opicapone as active substance.

Other ingredients are:

- for the capsule content: lactose monohydrate, sodium starch glycolate, type A, maize starch, pregelatinised and magnesium stearate.
- for the capsule shell: gelatin, indigo carmine aluminium lake (E132), erythrosine (E127), titanium dioxide (E171)
- for the printing ink of the 25 mg capsules: shellac, propylene glycol, ammonia, indigo carmine aluminium (E132)
- for the printing ink of the 50 mg capsules: shellac, titanium dioxide (E171), propylene glycol, ammonia, simethicone

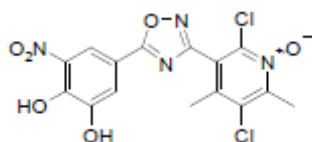
The product is available in white high density polyethylene (HDPE) bottles with polypropylene (PP) child resistant closures and in OPA/Al/PVC//Al blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of opicapone is

2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine-1-oxide corresponding to the molecular formula $C_{15}H_{10}Cl_2N_4O_6$. It has a relative molecular mass of 413.17 g/mol and the following structure:



The active substance is a non-hygroscopic yellow powder. Critical properties of the active substance relevant to product development, manufacture and performance are its solubility – it is insoluble in aqueous solutions at low pHs, very slightly soluble at higher pHs – and poor flow properties.

The molecule has no chiral centres. Polymorphism has been observed for the active substance. During development 6 solid forms were observed, representing different crystalline forms, hydrates or solvates; of these, form A was shown to be the most stable and is the form consistently produced by manufacture for development studies and for commercial use. Polymorphism is controlled by a XRPD identification test in the active substance specifications.

Manufacture, characterisation and process controls

The active substance is sourced from one supplier using one manufacturing site and another site for micronisation. Two processes for the synthesis of the active substance are described in full, both of which are proposed for commercial manufacture. The chemistry of both processes is similar with slight

differences in work-up operations. The active substance is synthesized in six or seven main steps using commercially available well-defined starting materials with acceptable specifications.

The first two steps are identical in the standard process and in the optimised process.

Critical process parameters were identified for each step and proven acceptable ranges (PARs) have been defined. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediates, starting materials and reagents have been presented. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. The outlined in-process controls, process parameters and proposed control strategy are acceptable. Process validation has demonstrated both processes to be capable of consistently and reproducibly producing material of the required quality.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Several changes have been introduced during the development of the manufacturing process. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The chemical structure of opicapone was elucidated by elemental analysis, infrared spectroscopy, ¹H-NMR spectroscopy and ¹³C-NMR spectroscopy, mass spectrometry, single crystal X-ray diffraction and UV spectroscopy. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The active substance is packaged in two LDPE bags which comply with Ph. Eur. and EC requirements. The secondary packaging consists of high density polyethylene drums.

Specification

The active substance specification includes tests for appearance, identification (IR, HPLC, XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC, HPLC, ion chromatography), water content (KF), heavy metals (USP), residue on ignition (Ph. Eur.), microbiological quality (Ph. Eur.), particle size distribution (optical microscopy).

Potential impurities and their origin have been discussed in detail, and adequate assurance has been provided that these are removed or controlled to suitably low levels by the commercial process. All possible impurities have been tested for their genotoxic potential.

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

Batch analysis data are provided for eleven production scale batches of the active substance using both manufacturing processes proposed. The results are within the specifications and consistent from batch to batch. Batch analysis data are also provided for batches of drug substance manufactured using the different synthetic processes that were used during development.

Stability

Stability data were provided for six production scale batches of active substance from the proposed manufacturer using both proposed manufacturing processes. Batches were stored in a container closure system simulating the packaging intended for market for up to 36 months under long term conditions at 25 °C / 60% RH and 30 °C / 65% RH and for up to 6 months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines. The samples stored at 25 °C were only analysed if the 30 °C samples showed an out of trend or out of specification result. The parameters tested are the same as for release. The analytical methods used were the same as for release and are stability indicating.

All tested parameters were within the specifications and no significant changes or trends were observed over time.

Photostability testing following the ICH guideline Q1B was performed on one batch of non-micronised active substance and one batch of micronised active substance. Results demonstrate that both are sensitive to light and must be stored in an opaque external container to prevent photodegradation.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months when packed in double polyethylene bags packed in HDPE drums with the following storage precaution "Keep the polyethylene bag inside the outer HDPE drum in order to protect from light".

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

For convenience of administration and precision of dosage, the hard gelatin capsule was selected as the dosage form. Due to the colour of opicapone, the selection of an opaque gelatine capsule was also critical during the clinical development program, allowing an easy and adequate blinding between strengths and between active and placebo. In addition, the opaque capsule provides good protection from light.

As opicapone has a very low aqueous solubility, a micronisation step was included in the manufacturing process and the particle size distribution of micronised opicapone is controlled by a 3 level specification.

Due to opicapone's poor flow properties, direct filling of capsules is not feasible. Also, dry granulation was not tested because it was considered challenging to scale-up and a less than robust method. Therefore, wet granulation was the selected manufacturing process to obtain the final granules for capsule filling. Water was used as granulation liquid, in order to avoid any possible environmental risks associated with the drug product development/ manufacture, and also to avoid any potential organic solvent uptake by the drug product. Opicapone is an anhydrous and non-hygroscopic substance. This supports the absence of overages during the manufacturing process and allows the use of a wet granulation process with purified water. The stability of opicapone in water at 70 °C supports the use of a water-based wet granulation process. Opicapone active substance has a melting point around 240 °C and has been shown to be thermostable in its solid form, since no degradation was observed when stored at 90 °C for 4 weeks. This supports the use of a fluid bed drying process without impacting the physicochemical properties of the drug substance.

Polymorphic screening shows that the most stable polymorphic form of opicapone is Form A. X-ray powder diffraction (XRPD) studies have shown that no effect on the crystal structure is induced by wet granulation or sieving.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Results from excipient level optimisation studies support the quantitative formulation.

During pharmaceutical development three different formulations were developed: one for Phase I and II clinical trials, one for Phase III clinical trials (also used in late phase I clinical trials) and the formulation proposed for commercial use. A detailed account of the development of the formulation is presented with clear explanations provided for the adjustments made at each point.

The three formulations were shown to have comparable dissolution characteristics in vitro. However, given that the lubricant was changed for the proposed commercial formulation and that this could impact

bioavailability, an in vivo bioequivalence study was carried out. The phase III and proposed commercial formulations were shown to be bioequivalent.

The development of the dissolution test method has been discussed. In view of the poor aqueous solubility of the active substance, the addition of a surfactant to the dissolution medium is considered to be justified. The discriminatory capability of the combination of the applied dissolution test conditions and proposed dissolution specification to eliminate batches of product at risk of poor *in vivo* performance has been demonstrated through experiments examining dissolution performance of batches prepared varying the active substance particle size, granule size and disintegrant content.

The primary packaging is white high density polyethylene (HDPE) bottles with polypropylene (PP) child resistant closures and OPA/Al/PVC//Al blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 8 main steps: pre-mixture, wetting, granulation, drying, calibration, final blend, capsule filling and packaging. The process is considered to be a standard manufacturing process. The in-process controls are adequate for this type of manufacturing process.

A commitment has been given to perform process validation on three consecutive process validation batches according to the process validation scheme provided before commercialisation. The commitment is accepted.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description; uniformity of dosage units (Ph. Eur.); dissolution (Ph. Eur.); water content (KF); identification (HPLC); assay (HPLC); degradation products (HPLC); microbiological attributes (Ph. Eur.).

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

Batch analysis results are provided for three production scale batches of the 25 and 50 mg strength and for several batches with a previous formulation used in pivotal phase III clinical trials confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. No significant differences were observed any of the measured parameters between the formulation used in the clinical development program and the proposed commercial formulation.

Stability of the product

Stability data were provided for three production scale batches of the finished product for the 25 mg and 50 mg strengths. Batches were stored for up to 36 months (HDPE bottles) and for up to 18 months (OPA/Al/PVC//Al blisters) under long term conditions at 25 °C / 60% RH and 30°C / 65% RH and for up to 6 months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines. The batches of medicinal product are identical to those proposed for marketing and were packed in both of the primary packaging presentations proposed for marketing.

Supportive stability were also provided for batches of finished product for a 5 mg strength, packed in HDPE bottles and OPA/Al/PVC//Al blisters, as well as batches of all three strengths packed in thermoform blisters (PVDC/Al).

Samples were tested for description, water, dissolution, assay, related substances and microbiological purity according to the shelf-life specification presented in previous section. The analytical methods used were the same as for release and are stability indicating.

In the supportive studies and under accelerated storage conditions, for capsules packaged in the PVDC/Al blisters, out of specification results were observed for dissolution and capsule appearance. No significant changes have been observed for opicapone 25 mg and 50 mg capsules, packaged in both of the primary packaging presentations proposed for marketing. Full compliance with the proposed specification is confirmed for all batches stored in the proposed commercial packaging presentations at all time-points and under all storage conditions.

For in-use stability assessment, two batches of opicapone 5 and 50 mg capsules packaged in white HDPE bottles containing 90 capsules, were studied. The protocol is to start the study with bottles stored unopened for 0, 24 and 48 months. The bottles will then be opened and closed repeatedly simulating patient use over a 90 day period. The study using the bottles stored for 0 months has been complete. Results showed no changes or trends in the stability behaviour of the product after repeated opening and closing of the bottles to simulate the use over time.

The holding time for bulk opicapone capsules was assessed on three batches (one batch of each strength) packaged into double-lined polyethylene bags inside fibre drums, and stored at controlled warehouse conditions: 20 – 25 °C and NMT 75% RH. 24 Months' data are available and all the results obtained complied with the specifications for all batches tested. No significant changes or trends were observed. The proposed bulk holding time (24 months when stored below 30 °C and packed in double-lined polyethylene bags inside either a fibre drum or an HDPE drum) is considered justified.

In addition, two batches of capsules of the 25 and 50 mg strength of the proposed formulation were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Supportive photostability data were also provided for different formulations of finished product including 5 mg capsules, 25 and 50 mg capsules with the phase III clinical formulation and for two strengths of opicapone granules (5 mg and 50 mg). The results for opicapone granules confirm that the non-capsulated product is slightly sensitive to light. Opicapone 5 mg capsules with the proposed commercial formulation had degradation products slightly above the specification limits. However the results demonstrate that opicapone 25 mg and 50 mg capsules (clinical formulation and to be marketed formulation) are photostable.

Based on available stability data, the proposed shelf-life of 3 years for the HDPE bottle and 2 years for the OPA/Al/PVC//Al blister and the storage conditions "Store in the original blister in order to protect from moisture" and "Keep the bottle tightly closed in order to protect from moisture" as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatin obtained from bovine sources is used in the product. Valid TSE CEPs from the suppliers of the gelatin used in the manufacture are provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The finished product is presented as hard capsules containing 25 and 50 mg of the new active substance opicapone. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

None

2.3. Non-clinical aspects

2.3.1. Pharmacology

Primary pharmacology

Some primary pharmacology information is derived from scientific publications generated by the applicant, rather than internal reports covering these studies. The original and published data provided fulfil all of the requirements of Annex I to Directive 2001/83/EC as amended for Module IV. These references are considered to be important for the appreciation of the primary activity of Opicapone and their inclusion as pivotal references is considered justified.

Bonifácio et al., 2007 reported that Opicapone behaved as long-acting COMT inhibitor that markedly increased systemic and central levodopa bioavailability.

In a series of in vitro and in vivo experiments Opicapone was examined for its mechanism of action, i.e. binding affinities to peripheral COMT and effect on levodopa availability after concomitant use with levodopa and DDCI. Experiments were done using computer simulations, in vitro studies with recombinant human soluble COMT (S-COMT) and in vivo experiments in rats and monkeys.

In monkeys it was demonstrated that combination L-DOPA/Benserazide therapy is effective at reducing MPTP-induced Parkinson's-like behaviour and its efficacy is increased by Opicapone treatment.

The opicapone metabolites BIA 9-1079, BIA 9-1103 and BIA 9-1104 were also shown to actively inhibit rat liver S COMT, whereas BIA 9-1100 and BIA 9-3752 were completely inactive. From the dose-response curves, IC₅₀ values for rat liver S-COMT inhibition of 224 nM (0.09 µg/ml), 429 nM (0.17 µg/ml) and 128 nM (0.05 µg/ml) were determined for opicapone, BIA 9 1079 and BIA 9-1104, respectively. For the metabolite BIA 9-1103, an IC₅₀ value of 1021 nM (0.6 µg/ml) was calculated, which was mainly attributed to the contamination of the batch with 9 % opicapone. In contrast to the IC₅₀ determinations, however, a three-fold lower inhibition constant Ki was calculated for rat liver S-COMT inhibition of opicapone (0.2

nM) compared to BIA 9-1104 (0.6 nM). These different inhibitory constants in rats and humans can most probably be related to species-specific differences, because this is also indicated by other analyses in rat and human erythrocytes studying the time-dependency of the inhibitory effect.

The chronic administration of Opicapone (3 mg/kg) to rats results in significant inhibition of liver and erythrocyte COMT, with no cumulative inhibitory effect. Hepatic enzyme activity was fully recovered only after a 7-day washout period, while the erythrocyte enzyme activity was recovered after a 1-day washout period.

Daily administration of 3 mg/kg or 30 mg/kg Opicapone for a period of 5 days did not induce changes in COMT protein or RNA levels supporting the proposed chronic treatment regimen.

These results support the rationale for the development of Opicapone in the proposed indication.

Secondary pharmacology

The activity of Opicapone and that of the major human metabolite BIA 9-1103 to other target has been explored in screening assays. Significant inhibition activity to Opicapone was only shown for serine/threonine phosphatase (PP2A), tyrosine kinase ZAP70 and Mitochondrial Translocator Protein (TSPO) at a concentration of 4.13 µg/ml (IC_{50} = 7.18 – 18.54 µg/ml). For the metabolite BIA 9-1103, this was shown to have potential to inhibit TSPO and phosphodiesterase (PDE5A1) activity at a concentration of 5.72 µg/ml (IC_{50} = 3.6 µg/ml). It is noted that these levels are in excess to levels expected in human exposure (C_{max} of 1.55 µg/ml), so these findings are of limited clinical relevance.

Safety pharmacology

A full battery of GLP safety pharmacology studies have been completed with Opicapone and the primary animal metabolite, BIA 9-1079.

Central nervous system (CNS) effect, gastrointestinal effects, renal effects and respiratory effects were all examined in the rat. No changes were seen in renal system or gastrointestinal function in rats up to an oral dose of 1000 mg/kg with opicapone. For metabolite BIA 9-1079 the only findings of note were of reduced sodium excretion and increased potassium/creatinine clearance at 1000 mg/kg. In the respiratory system study there was an indication of depressant effects at doses greater than 300 mg/kg for both Opicapone and BIA 9-1079.

Central nervous system effects were observed at dose levels of 300 mg/kg and above for both the parent compound and the major animal metabolite. These changes included sedative effects, defecation/diarrhoea, and at the highest dose included decreased respiration and nasal bleeding.

Cardiovascular parameters were measured in hERG assay, dog Purkinje fibres and in telemetered dogs with no significant adverse effects observed in dosing of up to 600 mg/kg. No significant effects were seen in the dogs for any examined cardiovascular parameters for Opicapone or BIA 9-1079, with the exception of slight shortening in the QT interval observed at 600 mg/kg with Opicapone. Effects on action potential parameters were not seen and are unlikely to have any impact given the expected clinical exposure levels. Opicapone inhibited hERG current with an IC_{50} of 388.9 µM. BIA 9-1079 had an IC_{50} 121.1 µM in the hERG assay. Both levels of compound that may lead to inhibition are well in excess of anticipated clinical exposure.

No obvious concerns are raised in terms of safety pharmacology for Opicapone and the major animal metabolite, BIA 9-1079.

Following CHMP advice given, further characterisation of the major human metabolite, BIA 9-1103 was requested. The applicant presented only in vitro cardiovascular data with BIA 9-1103 to evaluate the effects on the respiratory and central nervous systems. The in vitro work was limited to hERG and action potential parameters, in which indicates that at high enough dose levels (10 µg/ml) BIA 9-1103 can weakly effect potassium and calcium channels. With the anticipated exposure levels in the clinic well below these, these findings are unlikely to pose significant concern. Additionally the human trials with Opicapone have failed to identify issues for QT and cardiac repolarisation.

Concerning the lack of discussion for respiratory, gastrointestinal, renal and central nervous system parameters, the applicant reviewed the toxicokinetics from the 13 week rat study (Study No: D38007) to determine exposure to metabolite, BIA 9-1103, where a dose of 1000 mg/kg of Opicapone gave a C_{max} of 10.60 µg/mL and an AUC_{0-t} of 90.90 µg•h/mL for BIA 9-1103 on Day 1. This compares to clinical exposure levels of C_{max} 0.74 µg/mL and AUC₀₋₂₄ value of 17.71 µg•h/mL. The argument is that animals treated with Opicapone in the 13 week study were exposed to higher levels of Opicapone and its major metabolite than those in patients at 50 mg/day. Specific discussion on whether these parameters have been reviewed in Study No D38007 was not provided, as this is limited to only cardiac effects. The applicant has used BIA 9-1103 exposure data generated in the 13-week rat bridging study, conducted using comparable dose levels, to extrapolate assumed BIA 9-1103 exposure in the opicapone rat safety pharmacology studies. Exposure to BIA 9-1103 in the rat safety pharmacology studies are assumed to have been significantly higher than those observed in humans, and therefore utilising a similar risk assessment as that for opicapone, any effects shown in rats (e.g. central nervous system and respiratory) are not likely to occur in humans. In addition, *in vitro* cardiovascular safety pharmacology studies conducted with BIA 9-1103 did not show potential for pro-arrhythmic risk at doses >100 fold higher than anticipated clinical C_{max}.

Pharmacodynamic drug interactions

No studies have been conducted however there is some consideration of potential pharmacodynamic interactions discussed in the pharmacology studies with Opicapone. The possible interactions in a levodopa/DDC inhibitor combination reflecting the situation in clinical use has been examined in a 13-week combination repeat-dose study in rats. Opicapone at a dose of 1000 mg/kg/day was combined with levodopa/carbidopa at dose levels of 20/5, 50/12.5 and 120/30 mg/kg/day. As was expected, co-administration with Opicapone was shown to increase the levels of circulating levodopa.

2.3.2. Pharmacokinetics

The pharmacokinetics of Opicapone and its metabolites was investigated using in vitro and in vivo studies in the mouse, rat, dog, monkey and humans.

The bioanalytical methods were adequately validated to determine the plasma, urine, faecal and bile concentrations of Opicapone and its potential metabolites in all non-clinical species (mouse, rat, rabbit, dog and monkey) and humans.

Absorption of Opicapone was examined in single dose pharmacokinetic studies in mice, rats, dogs and monkeys. Opicapone was rapidly and extensively absorbed following oral administration, T_{max} across species was less than 4 hours. The applicant measured exposure of the parent compound as well as exposure to the active metabolite BIA 9-1079 across species, however measurement of the major human metabolite, BIA 9-1103 was not done, this was mainly due to a lack of understanding of the metabolism profile in humans, although the applicant has sought to rectify this by completing bridging studies in order to obtain a viable exposure profile for BIA 9-1103 in non-clinical species. Exposure to Opicapone was in

the main similar across gender in all species except for higher levels in female mice than male mice, and on repeated administration there was no evidence of accumulation.

Exposure to levels of the BIA 9-1079 metabolite were also confirmed, in mice and rats exposure to Opicapone was higher than that for BIA 9-1079. In monkeys exposure levels of BIA 9-1079 was slightly higher than of the parent compound.

Exposure to BIA 9-1103 in male and female mice and rats showed gender differences with less exposure in female rats as compared to male rats and the opposite effect was seen in mice. This has been attributed to differences in metabolism of Opicapone via sulphation.

Both in vitro and in vivo distribution studies have been completed encompassing whole body distribution in rats and more specific distribution to liver and brain in mice and rats. Distribution was predominantly to liver and kidney, but was seen to distribute to most tissues rapidly following administration. Distribution to the brain was relatively limited.

Plasma protein binding was high, >99.7% with no indication of a concentration-dependent effect. Binding to red blood cells is low, 0% in humans and up to 2.4 % in rats. Binding to primate blood was higher, up to 18.6% and this level of binding decreased with increasing concentration of Opicapone.

No data has been provided to detail potential placental transfer and excretion into milk, although given the target population it is understandable why this has not been investigated. Adequate warnings are summarised in the proposed SmPC.

Opicapone is rapidly absorbed and is extensively metabolised. The proposed metabolic pathway has been observed to be different across species. In animals Opicapone biotransformation is mainly via conjugation (sulphation, glucuronidation and methylation). Opicapone undergoes N-oxide reduction to BIA 9-1079, an active metabolite, and this is the main metabolite in monkeys, less significant in rats and mice however. In humans however this metabolite is not detectable. In contrast human metabolism reveals an inactive metabolite BIA 9-1103, the result of 3-O-sulphation, and BIA 9-1104, the result of 4-O-methylation. BIA 9-1103 has been detected in mouse, rat and monkey samples, and BIA 9-1104 detected in trace amounts in mini-pig, rat and mouse samples, and so no unique human metabolites are present and all can be detected in at least one of the non-clinical species. Two have been examined with significance, BIA 9-1079 and BIA 9-1103.

Opicapone was not considered to be an inducer of CYP450 enzymes, was a mild inhibitor of CYP1A2 and CYP3A4, a moderate inhibitor of CYP2B6 and significant inhibitor of CYP2C9 and CYP2C8. Metabolite BIA 9-1079 exhibited very similar characteristics to the parent compound, and more significantly BIA 9-1103 also inhibited CYP2C9 and CYP2C8. It is likely that possible interactions may exist between Opicapone (and BIA 9-1103) with CYP2C9 substrates and CYP2C8 substrates as well as other drugs metabolised through sulphation. This has been explored in more detail clinically and this is addressed in the SmPC.

The excretion of Opicapone has been evaluated following single dosing via intravenous and oral administration to male rats and monkeys. Excretion was predominantly via faeces, urinary excretion was at least 15-fold (oral) or at least 9-fold (i.v.) lower when compared to faecal excretion.

Pharmacokinetic drug-drug interactions were explored for Opicapone. Opicapone and one of its active metabolites in animals BIA 9-1079 and its major human inactive metabolite have been shown to be significant inhibitors of CYP2C8 and 2C9, and moderate inhibitors of CYP2B6.

Additional microsomal binding data has been used to recalculate IC₅₀ and K_i values for CYP2C8 and CYP2C9 with Opicapone and BIA 9-1103. For Opicapone, inhibition of CYP2C8 in vivo could not be excluded and a clinical interaction study with repaglinide concluded that an inhibition of CYP2C8 is likely. A clinical interaction with warfarin determined that inhibition of CYP2C9 could be excluded. Given the low

levels of free BIA 9-1103 in plasma, potential interactions of CYP2C8 and 2C9 with BIA 9-1103 could also be excluded. Opicapone (and BIA 9-1079 and BIA 9-1103) did not induce any CYP enzymes or have effects on multidrug resistance protein (MDR) 1, pregnane X receptor (PXR), constitutive androstane receptor (CAR) and aryl hydrocarbon receptor (AhR).

A number of in vitro study reports were provided to address the potential for effects of opicapone and the major human metabolite, BIA 9-1103, on various drug transporters, in line with CPMP/EWP/560/95/Rev. 1 Corr. Opicapone was shown to be transported by P-gp and BCRP, whereas BIA 9-1103 was transported by OATP1B1 and OATP1B3. In addition, opicapone inhibited OAT1, OAT3, OATP1B1 and B3, BSEP and MATE2-K in vitro. BIA 9-1103 was shown to inhibit OAT1, OAT3, OATP1B1 and B3 and BSEP, although in each case there is a substantial safety to the anticipated clinical exposure at 50 mg/kg.

In some in vivo studies with rats and mice the potential interactions of Opicapone and its metabolites with rifampicin, rosuvastatin and acetaminophen (paracetamol) was examined. Rifampicin caused a significant increase in levels of BIA 9-1103, suggesting an interaction with its metabolism and/or elimination. Paracetamol resulted in a significant decrease in Opicapone sulphation and therefore reduced levels of BIA 9-1103.

2.3.3. Toxicology

The programme of toxicology studies undertaken with Opicapone comprised of single- and repeat-dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity, together with supplementary studies with specific metabolites and impurities. Review of the major animal metabolite, BIA 9-1079 was routinely undertaken in the development programme; however the human metabolite BIA 9-1103 was not routinely monitored and has only been reviewed in later studies completed with Opicapone. Bridging studies have been completed to estimation exposure levels of BIA 9-1103 in the overall programme.

During the course of the conduct of the non-clinical and clinical development the formulation of opicapone constantly evolved, i.e. from Phase I/II, Phase II and to the to-be-marketed formulation. In terms of the conduct of the non-clinical studies the applicant has supplied sufficient evidence that the batches of opicapone product used to conduct pivotal non-clinical studies are representative of the to-be-marketed opicapone product.

Single dose toxicity

Single dose toxicity was completed in mice and rats for both Opicapone and also for the metabolite, BIA 9-1079.

For Opicapone, oral dosing was tolerated in mice and in rats up to 100 mg/kg in mice and 2000 mg/kg in rats. One death was observed in a female mouse treated orally with Opicapone at 2000 mg/kg, and this dose level was also associated with hunched appearance and piloerection. Red staining of urine and the vaginal area was seen at a dose of 10 mg/kg. Other effects included subdued behaviour, hunched appearance, laboured breathing, staggering, increased breathing rate with convulsions and prostration.

For BIA 9-1079, no deaths were observed after oral doses of 2000 mg/kg in mice and rats but one female rat after an intravenous dose of 8 mg/kg was found dead. A similar red staining in urine was observed in all treated and untreated animals.

The finding of red staining urine (both for Opicapone and BIA 9-1079) and of the vaginal area (Opicapone only) has been attributed to DMSO used in the formulation, however this was difficult to determine from the studies as vehicle only control animals were not included in either of the i.v. studies.

Repeated dose toxicity

Repeat-dose toxicity studies were conducted in mice (28 and 90 days), rats (28 and 90 days, 13 weeks, 13 weeks (with combination levodopa/carbidopa) and 26 weeks), dogs (maximum tolerated dose and 4 weeks), monkeys (maximum tolerated dose and 4, 13 and 52 weeks) and minipigs (maximum tolerated dose). Opicapone was found to be well tolerated orally in all species tested, with minimal adverse effects with the exception of discoloured stools attributed to the excretion of Opicapone and its metabolites. NOAELs were determined to be 1000 mg/kg/day in all studies in mice, rats and monkeys, apart from the 26-week rat study where effects were seen at the top dose including haematological and hepatic changes and a more cautious NOAEL was determined as 500 mg/kg/day.

Toxicokinetics

Toxicokinetics has been provided for the parent compound and the main active metabolite, BIA 9-1079. Extrapolations of exposure due to BIA 9-1103 have also been made using bridging toxicokinetic studies. Comparison of the toxicokinetic data for Opicapone in the repeat dose studies in mice, rats and monkeys with the expected AUC in humans shows there to be several fold margin of safety in terms of exposure (AUC). In the mouse this was 7.1-8.8-fold, the rat 6.8-30.5-fold, and in the monkey this was 4.1-5.2-fold.

BIA 9-1079 levels were also far in excess of those in the clinic, although impact of this metabolite is limited as in humans this is mainly below the limit of quantification.

Although not measured routinely in the toxicology studies levels of the main human metabolite BIA 9-1103 have been estimated using levels of BIA 9-1103 in the 13 week toxicokinetic study in rats (Study No. D38007), and single dose studies completed in mice (Study No. SRAL110222) and monkeys (Study No. SRAL070509). Exposure in rats (AUC_{0-t} values of 182 and 35.3 µg•h/mL) is well in excess to the human AUC of 17.71 µg•h/mL. Exposure of BIA 9-1103 in mice and monkeys however is below that expected in humans, and considering that BIA 9-1103 is a minor metabolite in these species and is generally well tolerated, this is considered adequately investigated.

Genotoxicity/carcinogenicity

A full battery of GLP genotoxicity tests were completed for Opicapone and for the major animal metabolite, BIA 9-1079. Both in vitro (bacterial mutation assay and clastogenicity assay) and in vivo (mouse micronucleus assay) assays were negative for genotoxicity.

In addition an in vitro bacterial mutation assay and in vitro clastogenicity assay was conducted with BIA 9-1103. BIA 9-1103 was negative for mutagenicity in these in vitro screens. No dedicated in vivo mouse micronucleus study was completed for this metabolite, however the applicant measured a level of BIA 9-1103 from the metabolite profile of Opicapone used in a TK study conducted in mice. These mice were exposed to the same level of Opicapone (and thus its metabolites) as that administered to the animals in the in vivo micronucleus study completed for opicapone (two doses of 1800 mg/kg of Opicapone 24 hours apart). BIA 9-1103 was present at low levels in the mouse, although exposure to BIA 9-1103 ranged from 0.311 to 1.14 µg/mL in these mice compared to a human C_{max} of 0.74 µg/mL. BIA 9-1103 is considered to be negative for genotoxicity.

Two long term carcinogenicity studies have been completed with Opicapone. Mice were dosed with oral opicapone at 100, 500/375 and 1000/500 mg/kg/day and rats were dosed with 100, 500 and 1000 mg/kg/day). Exposure to the metabolites BIA 9-1079 and BIA 9-1103 have also been reviewed, BIA 9-1079 levels were measured in plasma samples from both studies although sampling of BIA 9-1103 was

not. Exposure to BIA 9-1079 in these studies give sufficient safety margins to that expected from clinical dosing (50 mg/day) and provides adequate cover. Although no sampling of BIA 9-1103 was undertaken, the applicant has sought to address this by extrapolating the expected level of BIA 9-1103 in mice and rats using metabolite exposures observed in other completed TK studies. Relative exposures in mice look on the low side (AUC_{0-t} of 2.81 µg•h/mL at 1000 mg/kg in single dose study), however in the rat (AUC_{0-t} of 35.3 to 182 µg•h/mL) this has a adequate margin of safety compared to the expected human AUC_{0-t} of 4.00 µg•h/mL. In the end, the toxicological cover for the major human metabolite can be accepted.

In the mouse study the mid and high doses were poorly tolerated resulting in increased mortality and poor conditioning and so the doses were reduced to 375 and 750 mg/kg/day in week 10. Unfortunately deaths continued until it was determined that the particle size of Opicapone used in the mouse carcinogenicity study may be the cause of the increased sensitivity in these animals. The first batch of Opicapone used (batch 39129-1-5) had a large particle size (≤ 195.3 µm) and this was replaced on day 136 of the study with 5 further batches of Opicapone with smaller particle sizes (range of ≤ 19 to ≤ 69.92 µm). Opicapone was better tolerated after this and the study continued although the findings in the mid- to high dose groups are somewhat confounded with the poorly tolerated earlier batch of Opicapone. Major adverse clinical findings in the mid- to high dose groups were mainly related to poor tolerability of Opicapone, including death, weakness, hunched posture, ruffled fur, breathing noises, laboured breathing, swelling of abdomen, pallor, visible weight loss, reduced body temperature and distension of the gastrointestinal tract. In terms of development of neoplastic lesions the only findings of significance were that of two benign luteomas of the ovaries found in females treated with 500/375 mg/kg/day Opicapone, none were observed at the high dose. A benign pheochromocytoma was observed in one female treated with 500/375 mg/kg/day and in one animal treated with 1000/750 mg/kg/day. Due to the low incidence of these findings the significance is minimal and it is agreed that this is unlikely to be treatment related.

In rats the highest level of mortality was observed in the mid- to high doses. No repeat of the poor tolerability seen in the mouse study was observed and as a result there was no reduction in treatment dose. Mortality was associated with regurgitation/aspiration of Opicapone/vehicle that is attributed more to the high administration volume rather than any toxic effect due to Opicapone. There was no significant increase in incidence of neoplastic or non-neoplastic findings in the treated animals, changes are well within that expected as background incidence in Wistar rats.

Overall the findings from the rodent studies can conclude that there is no increased risk for carcinogenicity due to treatment with opicapone.

Reproductive and developmental toxicity

No adverse effects on male or female fertility were identified in the definitive fertility and early embryonic development study completed in the rat. The NOAEL for fertility, early embryonic development and F1 generation survival and growth was the highest dose tested at 1000 mg/kg/day. This provides an adequate safety margin of 16 to 17-fold to the anticipated clinical AUC_{0-t} of 4.00 µg•h/mL. The findings are adequately described in the SmPC under section 4.6.

Definitive developmental and embryo-fetal toxicity studies were completed in female rats and rabbits. There was no evidence of teratogenicity in either species, at any dose level. Minor variations were detected in both rats and rabbits however these were in line with background incidence in both species so are not likely to be of impact in humans. In pregnant rabbits maternal toxicity was evident already at exposure levels far below the human exposure at the recommended daily dose of 50 mg (AUC), while embryo-fetal development was not negatively influenced up to an AUC in the range of the human exposure, resulting in no safety margin either for the does (<1 time) or for the offspring (<1 to 1 time). Therefore, the results of the embryo-fetal development study in rabbits were not suitable for any risk

assessment and the applicant was requested to discuss the higher sensitivity of rabbits to low opicapone dosages compared to other species and to determine the predictive value of the results of the embryo-fetal development study in rabbits in terms of human risk assessment including the wording for section 5.3 of the SmPC. Due to the fact that opicapone is indicated as adjunctive therapy only to preparations of levodopa/benserazide or levodopa/carbidopa, all products with restricted use during pregnancy ("should not be used during pregnancy without using contraception measures"), or in female patients without childbearing potential, the deficiency of the rabbit study was agreed to be of minor concern and the issue was considered resolved.

It is also considered that any findings related to reproductive toxicity and their potential impact on clinical use would be somewhat limited, Opicapone is to be given to Parkinson's disease patients and the concern for use in women of childbearing potential or use during pregnancy is reduced. For this reason the applicant has not evaluated the potential transfer of Opicapone and/or its metabolites to the placenta and breast milk. As a result the reproductive toxicity findings and subsequent warnings are adequately reflected in the SmPC.

Pre and post-natal development was studied in pregnant rats. Mated rats were treated with Opicapone at 0, 150, 375, or 1000 mg/kg/day at GD6 through to LD20. In the F0 generation there were no changes seen in duration of gestation or parturition, or on the number of animals that became pregnant. Although 2 male pups were premature in the main development of pups was unaffected by treatment, no effect on learning, auditory acuity or co-ordination. The NOAELs for the F0 generation was the highest dose, 1000 mg/kg/day. Due to the incidence of premature pups, the NOEL for the F1 generation was the mid dose – 375 mg/kg/day.

No juvenile, local tolerance, immunotoxicology or dependence studies have been conducted with Opicapone. The absence of these studies has been adequately justified.

Other toxicity studies

A number of metabolites of Opicapone have been identified during the development programme. The initial focus of the development was on the major pharmacologically active, BIA 9-1079 and this was reviewed in the majority of pivotal toxicity studies with Opicapone. Levels of this metabolite in humans however are negligible, and in fact the more relevant metabolite was actually BIA 9-1103, the major human metabolite, but inactive pharmacologically. As detailed above, the applicant has sought to characterise the impact of BIA 9-1103 by extrapolating potential exposure levels in some of the completed toxicological studies retrospectively with the help of a 13 week toxicokinetic bridging study in rats.

A detailed examination of potential impurities has been undertaken by the applicant. 14 impurities were identified in the opicapone drug substance and tested for toxicity-related structural alert with three different in silico tools. For 13 of the impurities, alerts for genotoxicity were found and all 14 impurities were tested in a screening gene mutation test in bacteria. Two impurities, BIA 9-2995 and BIA 9-2997, were identified as mutagenic and further investigated in an in vitro clastogenicity test and an in vivo mouse micronucleus test to clarify the relevance of the effects in bacteria. These additional tests were negative. However, these tests are not regarded as sufficient to disqualify the relevance of a positive gene mutation assay. The current CHMP guideline on "The limits of genotoxic impurities in pharmaceuticals" does not recommend an in vivo micronucleus assay as an appropriate follow-up assay of a substance inducing gene mutations in an AMES assay. As outlined in the ICH M7 guideline, the appropriate follow-up for an AMES positive substance would be a gene mutation assay in vivo. Therefore, the impurities BIAL 9-2995 and BIAL 9-2997 are still regarded as mutagenic impurities. Accordingly, it was agreed to control both impurities at the TTC of NMT 30 ppm.

Opicapone showed photodegradation during light exposure. Although not required by the absorption spectrum and the prevailing ICH S10 guideline, the absence of a phototoxic and photoallergenic potential was confirmed in BALB/c 3T3 cells and in guinea pigs, respectively.

2.3.4. Ecotoxicity/environmental risk assessment

An environmental risk assessment (ERA) has been submitted. Phase I calculation of PEC surfacewater using the default $F_{pen}=0.01$ resulted in a value of 0.25 µg/L. This is above the action limit of 0.01 µg/L, triggering a Phase II environmental effect analysis. The applicant presented a Phase II assessment. As none of the PEC/PNEC ratios calculated for surfacewater, groundwater and microorganisms are above the trigger level it is not necessary to further evaluate the fate and effects of Ongentys in the aquatic environment and on microorganisms in Tier B studies. The ERA study data is summarised in the tables below.

Table 1 Summary of main study results – ERA

Substance (INN/Invented Name): Ongentys			
CAS-number (if available): 923287-50-7			
PBT screening		Result	Conclusion
Bioaccumulation potential- log D _{ow}	QSAR (MarvinSketch version 6.3.1)	1.16 (pH 7.4)	Potential PBT (N)
PBT-assessment			
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	Value	Unit	Conclusion
PEC _{surfacewater} , default or refined (e.g. prevalence, literature)	0.25	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	Test protocol	Results	Remarks
Adsorption-Desorption, BIA 9-1067	OECD 121	Koc-soil < 17.8 Koc.sludge < 33.1	<10,000 L/kg
Ready Biodegradability Test, D 73805	OECD 301 B	0 %/ 28d, not readily biodegradable k_{STP} = 0/h	Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems, D73862	OECD 308	River: Loamy Sand: DT _{50 water,20°C} = 0.30 d Mineralisation: 9.6 % NER _{max} =50.9 % at d 25 NER _{test end}) =45.5 % at d 40 Partitioning to sediment: 78% on day 11 Transformation products>10%: no information available for sediment Pond: Silt Loam DT _{50 water,20°C} = 0.46 d Mineralisation: 7.3 % NER _{max} =56.9 % at d 40 NER _{test end}) =56.9 % at d 40 Partitioning to sediment: 82% on day 11 Transformation products>10%: no information available for sediment	Shift to sediment by readily transform to many metabolites. The trigger value of 10% exceeded – a sediment-water Chironomid Toxicity Test according to OECD 219 should be conducted.
Phase IIa Effect studies			

Substance (INN/Invented Name): Ongentys					
CAS-number (if available): 923287-50-7					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/ <i>Pseudokirchneriella subcapitata</i> , D73816	OECD 201	NOEC	0.24	mg/L	
<i>Daphnia</i> sp. Reproduction Test, D73827	OECD 211	NOEC	8.8	mg/L	
Fish, Early Life Stage Toxicity Test/ <i>Danio rerio</i> , D73838	OECD 210	NOEC	3.6	mg/L	
Activated Sludge, Respiration Inhibition Test, D73840	OECD 209 (2010)	NOEC	≥ 100	mg/L	

Table 2 Risk characterisation Phase II Tier A

PEC	NOEC [mg/L]	AF	PNEC [µg/L]	PEC/PNEC	Trigger value	Conclusion Risk/no risk
Surfacewater* [µg/L] 0.25	Algae 0.24	10	24	1.0 E-02	1	no risk
	Daphnia 8.8	10	880	2.8 E-04	1	no risk
	Fish 3.6	10	360	6.9 E-04	1	no risk
Groundwater [µg/L] 0.0625	Daphnia 8.8	10	880	7.1 E-05	1	no risk
Sewage water = Surfacewater [µg/L] 0.25	Microorganism 100	10	 10000	 2.5 E-05	0.1	 no risk

*use PEC_{refined}, if available

Nevertheless, the ERA of Ongentys cannot be finalised. Within the conducted water sediment study, the applicant tried to analyse the sediment extracts for the parent substance, but a table on degradation pattern in river/pond sediment for all sampling days has not been included. The results of OECD 308 showed a significant shifting of the substance to sediment. Thus, a sediment-water Chironomid Toxicity Test according to OECD 219 should be conducted as post-approval commitment with the report being submitted until December 2016.

2.3.5. Discussion on non-clinical aspects

The non-clinical toxicology program is large but conventional and includes numerous studies i.e.: single and repeat-dose toxicity studies in mice, rats (main tox species), dogs and monkeys (main tox species), a battery of in vitro and in vivo mutagenicity tests, carcinogenicity bioassays in rats and mice; reproductive toxicity studies in rats and rabbits and mechanistic studies to investigate the in vitro cytotoxic effects on hepatocytes and other cell populations, in comparison to those of the approved COMT inhibitors: tolcapone and entacapone. Studies with major metabolite BIA 9-1079 and BIA-9-1103 have also been performed (i.e. genotoxicity and general toxicity). The oral route of administration (gavage) with a once daily regimen was used in the toxicology studies as this is the intended human therapeutic route. Combination studies with levodopa plus a DDC inhibitor (Benserazide and carbidopa) were included in both the pharmacology and toxicology programmes. The rat and the monkey were selected for the toxicological assessment.

Some primary pharmacology information is derived from scientific publications generated by the applicant rather than internal reports covering these studies. Opicapone has been demonstrated to bind to peripheral COMT and have an effect on levodopa availability after concomitant use with levodopa and DDCI in models of disease in rats and monkeys. The Applicant clarified that the different inhibitory constants of opicapone determined for rat and human S COMT can most probably be attributed to species-specific differences, because this is also indicated by other analyses in rat and human erythrocytes studying the time-dependency of the inhibitory effect. The resulting proposal for section 5.1 of the SmPC is regarded acceptable.

The safety pharmacology of Opicapone and its metabolite BIA 9-1079 has been reviewed in a full battery of GLP safety pharmacology studies. No in vivo assessment of the Opicapone metabolite BIA 9-1103 has been supplied, however the applicant has now provided a detailed discussion on the potential effects of metabolite, BIA 9-1103 on parameters in the respiratory, gastrointestinal, renal and central nervous systems, demonstrated by reviewing the findings in the completed toxicological studies. No effects on safety pharmacology parameters are expected given the anticipated clinical exposure to Opicapone and BIA 9-1103.

The pharmacokinetics of Opicapone and its metabolites was investigated using in vitro and in vivo studies in the mouse, rat, dog, monkey and humans. Absorption of Opicapone is rapid and extensive following oral administration. Distribution is predominantly to liver and kidney, and plasma protein binding was high >99.7%. The primary routes of Opicapone metabolism in humans were consistent with the principal metabolic routes in non-clinical species, leading to the same metabolism-derived products, despite some quantitative differences. Excretion is mainly via faeces followed to a lesser extent via urine. In terms for potential drug-drug interactions, Opicapone and its metabolites are not substrates for P-gp, nor were seen to induce CYP enzymes or xenobiotic receptors. There was significant inhibition of CYP2C8 and 2C9, and moderate inhibition of CYP2B6. Additional microsomal binding data has been used to recalculate IC₅₀ and K_i values for CYP2C8 and CYP2C9 with Opicapone and BIA 9-1103. For Opicapone, inhibition of CYP2C8 in vivo could not be excluded and a clinical interaction study with repaglinide concluded that an inhibition of CYP2C8 is likely. A clinical interaction with warfarin determined that inhibition of CYP2C9 could be excluded. Given the low levels of free BIA 9-1103 in plasma, potential interactions of CYP2C8 and 2C9 with BIA 9-1103 could also be excluded. The applicant has provided a number of in vitro study reports to address the potential for effects of opicapone and the major human metabolite, BIA 9-1103, on various drug transporters, in line with CPMP/EWP/560/95/Rev. 1 Corr*. Opicapone was shown to be transported by P-gp and BCRP, whereas BIA 9-1103 was transported by OATP1B1 and OATP1B3. In addition, opicapone inhibited OAT1, OAT3, OATP1B1 and B3, BSEP and MATE2-K in vitro. BIA 9-1103 was shown to inhibit OAT1, OAT3, OATP1B1 and B3 and BSEP.

The programme of toxicology studies undertaken with Opicapone comprises single- and repeat-dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity, together with supplementary studies with specific metabolites and impurities. The applicant has supplied sufficient evidence that the batches of opicapone product used to conduct pivotal non-clinical studies are representative of the to-be-marketed opicapone product. Review of the major animal metabolite, BIA 9-1079 was routinely undertaken during the course of the development programme; however the importance of the human metabolite BIA 9-1103 only came to light late in development. As a consequence BIA 9-1103 was not routinely monitored and have only been reviewed in the later studies completed. Bridging studies have also been used to allow for estimation of exposure levels of BIA 9-1103 in the overall programme. Opicapone was found to be well tolerated orally in all species tested, with minimal adverse effects with the exception of discoloured stools attributed to the excretion of Opicapone and its metabolites. Opicapone and its metabolites were found to be non-genotoxic and not carcinogenic. Studies completed for reproductive and developmental toxicity indicates that Opicapone is not teratogenic and has no effect on fertility or embryo-fetal

development. The rabbit tolerated substantially lower doses of opicapone in embryo-foetal development studies than all other species in toxicity investigations. Due to this particular sensitivity and the low predictive value of the embryo-fetal development study in rabbits, amendments of sections 4.6 and 5.3 of the SmPC are now acceptable.

Numerous impurities were identified in the manufacturing process and have been comprehensively evaluated from a toxicological perspective. The Applicant aimed to supersede the mutagenic potential, which was identified for the two impurities BIA 9-2995 and BIA 9-2997 in Ames tests, by a negative in vivo micronucleus study in bone marrow of mice. However, this in vivo study is not regarded suitable to disqualify the previous mutagenic response of BIA 9-2995 and BIA 9-2997, because of the different study endpoints (gene mutation in vitro vs. chromosome aberrations in vivo). For this reason, the Applicant agreed to control both mutagenic impurities BIA 9 2995 and BIA 9 2997 at the TTC level (NMT 30 ppm).

In terms of the environmental risk assessment, Opicapone and its metabolites does not pose a risk to aquatic life and the microbial community. However the available data does not allow for a definitive decision on the potential environmental risk of opicapone, because the potential risk to sediment organisms needs to be evaluated.

2.3.6. Conclusion on the non-clinical aspects

From a non-clinical point of view with the exception of the outstanding ERA issue that needs to be resolved post-approval, the applicant has adequately addressed all the other concerns. The CHMP felt that the following post-authorization measures were needed: The applicant should perform a sediment-water Chironomid Toxicity Test according to OECD 219, post-approval, with the report being submitted by December 2016.

2.4. Clinical aspects

2.4.1. Introduction

Opicapone is a peripheral, selective and reversible COMT inhibitor. It was designed as a hydrophilic 1,2,4-oxadiazole analogue with a pyridine N-oxide residue at position 3 to provide high COMT inhibitory potency and avoid cell toxicity. It has a high binding affinity for COMT that translates into a slow complex dissociation rate constant and a long duration of action in vivo. As a result, Opicapone is a selective and reversible COMT inhibitor that increases L-DOPA plasma levels when used concomitantly with L-DOPA/DDCI. In animals, Opicapone has been shown to have limited access to the brain. In humans, the effects of Opicapone on central COMT activity have not yet been studied. In the periphery, Opicapone causes a dose-dependent, marked and long-lasting COMT inhibition which reflects an underlying kinetic process that is consistent with the dissociation rate constant of the COMT-Opicapone complex. The sustained COMT inhibition by Opicapone, far beyond the observable point of clearance of circulating drug, is due to the long residence time of the reversible COMT-Opicapone complex.

The Opicapone clinical development programme comprised 27 Phase 1 studies, 2 Phase 2 studies, and 2 Phase 3 studies which in applicant's opinion provide data to support the proposed use of Opicapone as adjunctive therapy to L-DOPA plus a DDCI in patients with Parkinson's disease who have motor fluctuations. In the completed studies, Opicapone was administered at any dose to a total of 1651 subjects: 859 healthy subjects and 792 subjects with Parkinson's disease. In addition, at the cut-off date of 30 Jun 2014, a further 99 subjects had been exposed to Opicapone in the open-label part of the Phase

3 Study BIA-91067-301, which was the only study in the clinical programme that was still ongoing at that date. All doses of Opicapone were given orally in the clinical studies, as capsules.

GCP

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

2.4.2. Pharmacokinetics

Opicapone is a new active substance with a pKa of 8.1 (weak acid) with pH-dependent solubility, showing very low solubility below pH 4.5. A series of in vitro and 27 Phase 1 studies were included in the clinical pharmacology programme. The drug does not contain any chiral centres.

Absorption

The absolute bioavailability of Opicapone has not been determined. Based on in vitro studies in Caco-2 and MDCK cells, Opicapone is highly permeable. After oral dosing, the t_{max} ranges from 1 to 4 hours. Probably due to the drug's poor solubility, the bioavailability of Opicapone is highly dependent on particle size. The micronised formulation used in the phase 3 study was shown to have approximately twice the exposure of the non-micronised drug used in the vast majority of the phase 1 and in the phase 2 study programme. Food was shown to have a large impact on the non-micronised formulation with a 68%, 53% and 51% decrease in C_{max}, AUC_{0-t} and AUC_{0-∞}, respectively, however there is no significant impact on efficacy.

The transporter organic anion-transporting polypeptide B (OATP-B) may be involved in Opicapone uptake, and the multidrug resistance-associated protein (MRP) and breast cancer resistance protein (BCRP) transporters may be involved in Opicapone transport.

Distribution

The drug is highly protein bound and reported to be concentration-independent up to a concentration of 30 µg/mL. Binding was unaffected by warfarin, diazepam, digoxin, and tolbutamide, and the binding of these drugs was unaffected by Opicapone. Information regarding the binding of the major (inactive) metabolite and BIA 9-1079, the minor (active) metabolite was provided. It can be concluded that the active metabolite does not contribute to the in vivo effect of the drug. There was minimal association of Opicapone-associated radioactivity with red blood cells, with blood to plasma ratios ranging between 0.48 and 0.54.

The apparent volume of distribution was approximately 30 L following the micronised API and to-be-marketed formulations.

Elimination

Opicapone $t_{1/2}$ ranged between 0.7 to 3.2 hours following single doses of 5 to 1200 mg and between 0.7 and 2.3 hours following 5 to 50 mg QD administration. BIA 9-1103 $t_{1/2}$ ranged between 94 to 122 hours following 5 to 30 mg QD administration in a healthy subject multiple ascending dose study. As a consequence of its long $t_{1/2}$, BIA 9-1103 had a high accumulation ratio in plasma, with values of up to 6.6.

Excretion

Opicapone is predominantly eliminated as metabolites in faeces. There were two excretion balance studies conducted. The first (103) was poorly conducted (low recovery, low radioactivity, short study period) and there are a number of concerns/questions about the second study (122). The conclusion that the kidney is not a primary route of Opicapone excretion is supported. A different formulation was used for the radiolabelled drug therefore the extent of absorption of unchanged drug and appearance of active metabolite in faeces was different for radiolabelled compared to the unlabelled drug.

Metabolism

Sulphation is the major metabolic pathway of Opicapone, yielding the major metabolite BIA 9-1103 (Opicapone sulphate). Other metabolic pathways include reduction, methylation, and glucuronidation. The active, but minor, BIA 9-1079 metabolite is formed by reduction of Opicapone. The complete effect of polymorphisms in the SUT1A1 enzyme are unknown.

The most abundant peaks in plasma are metabolites BIA 9-1103 (sulphate) and BIA 9-1104, 67.1 and 20.5% of radioactive AUC respectively, followed by BIA 9-1100, BIA 9-1106, and BIA 9-1079 (active) in order of abundance. In urine 8% of administered radioactivity was excreted until 144 hours. No unchanged drug was excreted and BIA 9-1106 was the most abundant metabolite, accounting for 3% of administered radioactivity. In faeces, 55% of radioactivity was excreted until 216 hours. The most abundant, accounting for 9% of administered radioactivity was BIA 9-3752. Expired air accounted for 10-23% of elimination of administered radioactivity. Two metabolites were quantified in a selection of the clinical pharmacology studies for Opicapone, BIA 9-1079, an active but minor metabolite and BIA 9-1103, an inactive but major metabolite circulating in plasma. The active metabolite BIA 9-1079 was below the limit of quantification following multiple doses of up to 30 mg QD Opicapone in Parkinson's disease patients. While the parent drug has a short $t_{1/2}$ (1-2 hours), the metabolite BIA 9-1103 had a mean $t_{1/2}$ of 143 hours and accumulated (up to 6.6-fold) after daily dosing.

An additional circulating metabolite, M10, was identified late in the procedure. This metabolite only appeared post 72 h and over the 504 hour time period of the ADME study this metabolite accounted for a possible 32% of radioactivity however time points were very limited. As no mass could be assigned to this metabolite in the ADME study, absolute identification was not possible. However, based on the analysis using two distinct chromatographic conditions and the pattern of human metabolism in general, it is considered highly likely that M10 represents the hydroxylated sulphate metabolite BIA 9-4588, a possible secondary metabolite of BIA 9-1103. Additional studies in rats showed that this metabolite is present in the rat and thus this metabolite has been qualified in toxicology studies. In addition, re-analysis of samples from clinical studies suggests that this is not a major metabolite at steady state dosing in humans. It is recommended that the Applicant provide further analytical data showing that M10 is below the limit of detection (10 ng/mL) in patients treated once daily for more than 6 months, using a validated analytical method.

Dose proportionality

The parent drug shows less than proportional changes in C_{max} and AUC after doses ranging from 10 to 1200 mg of the non-micronised formulation, but was roughly dose-proportional between doses of 10 and 50 mg for both non-micronised and micronised formulations.

There is no accumulation of drug on multiple dosing.

Inter- and intra-subject variability

Inter- and intra-subject variability is high.

Special populations

There was no study of Opicapone in renal impairment. An analysis based on exposure of the major metabolite BIA 9-1103 shows no effect of renal impairment as judged by serum creatinine <60 ml/min on the PK of the metabolite. There is no data in subject considered to have severe renal impairment.

Opicapone pharmacokinetics was studied in patients with moderate hepatic impairment (Child Pugh Class B), with C_{max}, AUC_{0-t} and AUC_{0-∞} found to be almost 2-fold higher compared to matched healthy volunteers. Gender was shown to have no impact on Opicapone pharmacokinetics.

The pharmacokinetics and pharmacodynamics of Opicapone were similar between Japanese, Blacks and Caucasians.

There is no relationship between weight and exposure over the studied range of 40- 100 kg.

The incidence of treatment emergent adverse effects appears to be related to body weight. No evaluation of the relationship between body weight and Opicapone pharmacokinetics could be found within the dossier and should be provided.

Opicapone 30 mg QD was studied in 12 healthy elderly subjects and when compared to control healthy volunteers showed an increase in C_{max} (18%) and AUC (33%) and half-life. In addition in a spate analysis of all data, there was no relationship with exposure and age. However there is no data in those over 85 years of age.

No data are available in children.

Interactions

The potential for Opicapone, the active metabolite, BIA 9-1079, and the inactive metabolite, BIA 9-1103, to induce or inhibit CYP isozymes or other metabolic biomarkers was investigated in vitro. Opicapone and both metabolites were found to inhibit CYP2C8 and 2C9. For Opicapone K_i values of 0.9 µg/mL (2C8) and 18 µg/mL (2C9) were estimated, while values of 0.19 µg/mL (2C8) and 1.47 µg/mL (2C9) were estimated for BIA 9-1079 and IC₅₀ values of 6.70 µg/mL (2C8) and 20.7 µg/mL (2C9) were found for BIA 9-1103.

CYP2C19 is induced by Opicapone in vitro, however it appears unlikely this will translate to in vivo interaction BIA 9-1079 and BIA 9-1103. Opicapone, BIA 9-1079 and BIA 9-1103 do not appear to induce CYP1A2, 2B6, 2C9, or 3A4 and do not transcriptionally activate or repress any of the following metabolic biomarkers: CYP1A1, 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4; MDR1; PXR; CAR; or AHR. BIA 9-1103 is not an inhibitor of CYP2B6, 2C19, and 3A4; causes minor inhibition of CYP1A2, 2A6, 2D6, and 3A4; causes moderate inhibition of CYP2E1.

In a single dose study with co-administration of 25 mg Opicapone, Opicapone (CYP2C8 inhibitor) increased the rate (maximum observed plasma concentration [C_{max}]) of repaglinide (CYP2C8 substrate) exposure by 1.3-fold in a healthy subject drug-drug interaction study following 25 mg Opicapone. The study is not considered adequate as it was single dose (without accumulation of metabolites that also inhibit CYP2C8) and utilised half the recommended therapeutic dose of the drug. However as co-administration with CYP2C8 substrates, at C_{max} for opicapone is unlikely, a warning is judged to be sufficient for the SmPC.

In a single-dose, healthy subject drug-drug interaction study with the CYP2C9 substrate warfarin, no effect of Opicapone (CYP2C9 inhibitor) on S- and R-warfarin exposure was observed, while in a multiple-dose, healthy subject drug-drug interaction study, no effect to slight reductions in S- and R-warfarin exposure (13% to 15%), which were not considered clinically relevant, were observed. Opicapone does not inhibit OCT1, OCT2, MATE1, BCRP and Pgp. It is a weak inhibitor of OATP1B1, 1B3, and OAT1 and OAT3. Based on the in vitro data, in vivo interactions would not be expected with the exception of inhibition of OATP1B1 which cannot be ruled out. A clinical study or a statement to prevent co-administration of substrates is required.

From data captured with co-administered drugs in phase 3 study patients there was no evidence of interaction of Opicapone with commonly utilised drugs in these patients: rasagiline and other MAO inhibitors, dopamine agonists, amantidine.

2.4.3. Pharmacodynamics

The primary pharmacodynamics of Opicapone is well described in the dossier. As part of the investigation of the secondary pharmacodynamics effects on cardiac function have been investigated during the phase III efficacy studies.

Primary Pharmacodynamics

Primary PD of Opicapone has been investigated in healthy volunteers and patients with Parkinson's disease.

Studies in healthy subjects indicated that when Opicapone is administered alone, concomitantly with levodopa/DDCI, or 1 to 12 hours before levodopa/DDCI, S-COMT activity is strongly inhibited in an Opicapone dose-dependent manner. Doses of 15- to 75-mg QD Opicapone appeared to be more effective at inhibiting S-COMT activity than 200mg TID entacapone.

In placebo-controlled studies, S-COMT activity was significantly inhibited following Opicapone administration relative to following placebo administration. These findings are in line with the increased exposure to levodopa and decreased exposure to the 3-OMD metabolite of levodopa observed following administration of Opicapone concomitantly with or before levodopa/DDCI in healthy subjects.

Studies in subjects with Parkinson's disease indicated that when Opicapone is administered with levodopa/DDCI, S-COMT activity is markedly inhibited relative to when placebo is administered with levodopa/DDCI. These findings are in line with the increased exposure to levodopa and decreased exposure to the 3-OMD metabolite observed following administration of Opicapone concomitantly with levodopa/DDCI in subjects with Parkinson's disease.

Improvements of motor performance were also observed following both single and multiple doses of Opicapone, but none of the studies were powered to reliably confirm these observations.

The expected effect on inhibition of COMT has been confirmed in the clinical studies and there is generally trend of dose dependence. The results from healthy subjects and those from patients are congruent and it can be accepted that there are no significant primary pharmacodynamic differences between the healthy individuals and patients with Parkinson's disease.

Secondary Pharmacodynamics

The effect on cardiac function has been investigated as part of the two primary efficacy trials and in dedicated cardiac repolarisation study.

An integrated electrocardiogram analysis of the Phase 3 studies BIA-91067-301 and -302 was performed using the treatment groups that were common to both studies: 25- and 50-mg Opicapone (243 and 266 subjects, respectively) and placebo (263 subjects) (refer to Integrated ECG Report_BIA-91067-301 and 302).

The mean placebo-adjusted change from baseline for QTcF decreased by 0.6 ms (90% upper confidence limit [UCL] 2.1 ms) in the 25-mg treatment group and increased by 0.6 ms (90% UCL 3.3 ms) in the 50-mg treatment group. The mean placebo-adjusted change from baseline for QTcB increased by 0.4 ms (90% UCL 3.5 ms) in the 25-mg treatment group and increased by 0.9 ms (90% UCL 4.0 ms) in the 50-mg treatment group. These changes were not statistically significant. The 90% UCL of QTcF and QTcB change from baseline did not exceed the threshold of 10 ms at post-dose time-point Visit 7.

Following single doses of 50- and 800-mg Opicapone, Opicapone did not have a QT-prolonging effect, and no relationship was observed between plasma concentrations of Opicapone and time-matched changes in QTcI (refer to Section 2.7.2.2.6.1). Similarly, there was no relationship between plasma concentrations of any of the detected metabolites (BIA 9-1079, BIA 9-1103, BIA 9-1106) and changes in QTcI.

Study BIA-91067-111 was a Phase 1, randomised, double-blind, placebo-controlled and open-label active controlled, 4-way crossover study to investigate the effect of therapeutic (50 mg) and supratherapeutic (800 mg) doses of opicapone (FAAF 25- and FAAE 100-mg capsules [nonmicronised API formulation]) on the placebo-corrected time-matched change from baseline using individually corrected QT interval (QTcI) durations in healthy subjects. The study population consisted of 64 healthy adult male and female subjects.

In 4 consecutive treatment periods, subjects were randomly assigned to receive a single therapeutic (50 mg) opicapone dose, a single supratherapeutic (800 mg) opicapone dose, a single placebo dose, or a single 400 mg moxifloxacin dose (positive control). Each subject was to receive each of the 4 treatments in random sequence. Treatments were separated by washout periods of at least 7 days.

All medications were administered following an overnight fast, and the fasting state continued for 2 hours post-dose.

Following administration of 50- and 800-mg opicapone, mean C_{max} values for opicapone were attained at 1.5 to 2.0 hours post-dose (t_{max}). The mean AUC values were increased by approximately 8.5-fold following administration of 800-mg opicapone relative to the 50-mg dose; thus, the dose was less than dose proportional (a 16-fold increase in dose). Opicapone PK parameters were in good agreement with those seen in other clinical studies.

The hypotheses tested implied that, if at all time points, the upper bound of the 1-sided 95% CI was below 10ms, there was sufficient evidence that opicapone did not have a QT-prolonging effect. All the upper bounds of the 1-sided 95% CI were below 10ms. The highest upper bounds were observed at 30 minutes post-dose for both 50- and 800-mg opicapone as follows:

50-mg opicapone: 3.46 ms, corresponding to a mean (standard error) estimated change in QTcI difference between opicapone and placebo of 1.23 (1.35) ms;

800-mg opicapone: 3.58 ms, corresponding to a mean (standard error) estimated change in QTcI difference between opicapone and placebo of 1.32 (1.37) ms.

No relationship was observed between plasma concentrations of opicapone and time-matched changes in QTcI. Similarly there was no relationship between plasma concentrations of any of the detected metabolites (BIA 9-1079, BIA 9-1103, BIA 9-1106) and changes in QTcI.

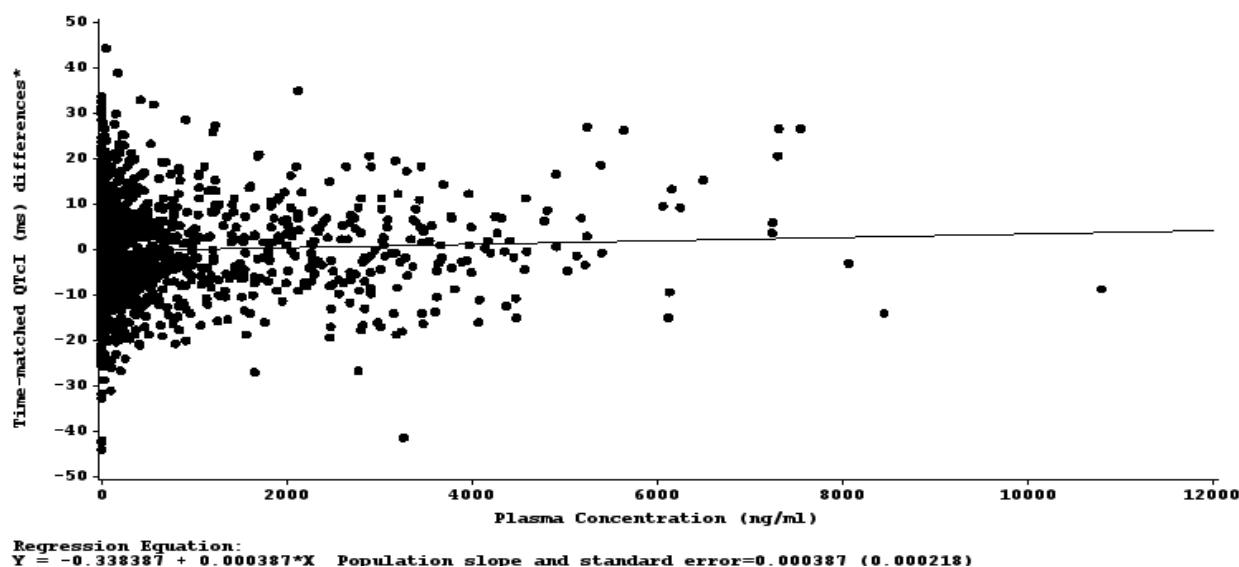


Figure 1 QTcI versus time-matched opicapone plasma concentrations in the overall population (Study BIA-91067-111; QTcI = individually corrected QT interval)

The applicant will be asked to provide the systematic overview of the available information on secondary pharmacology.

Opicapone was also assessed for other pharmacological activity through screening in a panel of 226 enzyme and radio-ligand binding assays, and indications of activity were followed up in a subsequent specific study. A concentration of 10 μ M (equivalent to 4.13 μ g/mL) was used in the screening assay.

In the screening assay, the only significant activity shown by opicapone was inhibition of serine/threonine phosphatase (PP2A), tyrosine kinase ZAP70 and mitochondrial translocator protein (TSPO) by 76.66%, 49.00%, and 82.15%, respectively (Report 11 8004), and subsequent determinations gave IC₅₀ values of 44.88 μ M (18.54 μ g/mL) and 17.38 μ M (7.18 μ g/mL) for PP2A and ZAP70, respectively (Report 11-8354).

The short half-life of opicapone precluded measurement of its levels during the Phase 3 studies, and data on its exposure in humans come from a Phase 1 study involving 10 days of once-daily administration of the 50 mg dose, which resulted in a C_{max} of 1.55 μ g/mL (Study BIA-91067-126). The activities shown in the secondary pharmacology studies are at concentrations in excess of the opicapone C_{max} value observed in humans and are therefore unlikely to have any consequence for clinical use of opicapone. Moreover, this is based on comparisons to the total levels of opicapone and consideration of the impact of protein binding (99.9% for opicapone [Study ZNA42782.001]) provides further reassurance. The maximal opicapone unbound fraction is 0.002 μ g/mL at the opicapone C_{max} in humans, which is 775 fold lower than the value of 1.55 μ g/mL.

Genetic Variation in PD Response

COMT genotype can be divided into low (COMTL/L), intermediate (COMTL/H), and high (COMTH/H) activity alleles. This polymorphism has ethnic differences; the low COMT activity allele is more common in Caucasians than in Asians and Africans. This was investigated in a study comparing Caucasian and Japanese subjects. Data indicated good correlation between the primary analyses (entire population integrated) and when the populations were separated based on COMT genotype. The observed PK and PD differences when the populations were separated based on their COMT-genotype were minor and could

have been related to inherent variability of Opicapone. The differences observed in PD are unlikely to cause clinically relevant consequences.

2.4.4. Discussion and conclusions on clinical pharmacology

Mechanism of action of Opicapone is well known and both primary and secondary pharmacodynamics are well described in the dossier. Clinical relevance of action on secondary binding sites is seen as very unlikely.

The Applicant has conducted an extensive clinical pharmacology programme to characterise the pharmacokinetics of Opicapone in healthy volunteers and Parkinson's disease patients. The drug has a very short half-life (between 1 and 2 hours), but can be administered once daily because of its long duration of inhibition of plasma COMT. The drug has low solubility at pH values less than 4.5-6.8. Absorption is dependent on particle size, with micronized material showing two-fold that of the non-micronised formulation.

2.5. Clinical efficacy

In support of their application the company have conducted two controlled phase III studies duration 14-15 weeks and one open label extension with duration up to one year. In addition, two phase II studies were presented in the dossier as supportive evidence of efficacy.

Table 3 Clinical studies provided the information on efficacy

Study	Number of subjects randomised	Objectives	Study design	Treatment regimen
<i>Phase 3 controlled</i>				
BIA-91067-301 Part I	600	To investigate the efficacy, safety, and tolerability of 3 doses of OPC compared to entacapone or placebo when administered in combination with L-DOPA/DDCI in subjects with Parkinson's disease and motor fluctuations.	Phase 3, multicentre, DB, randomised, placebo- and active-controlled study with 5 parallel treatment arms during the DB period: - 2-week screening period - 14- to 15-week DB period	OPC group: OPC 5 mg, 25 mg, or 50 mg QD at least 1 hour after the last daily dose of L-DOPA/DDCI and placebo concomitantly with each daytime L-DOPA/DDCI dose (3 to 8 times daily) ENT group: 200 mg ENT concomitantly with each daytime L-DOPA/DDCI dose (3 to 8 times daily) and placebo 1 hour after the last daily dose of L-DOPA/DDCI
BIA-91067-302 Part I	427	To investigate the efficacy, safety, and tolerability of 2 doses of OPC in comparison to placebo, when administered in combination with L-DOPA/DDCI in subjects with Parkinson's disease and motor fluctuations.	Phase 3, multicentre, DB, randomised, placebo-controlled study with 3 parallel treatment arms: - 2-week screening period - 14- to 15-week DB period	Placebo or OPC (25 mg or 50 mg) QD at least 1 hour after the last daily dose of L-DOPA/DDCI
<i>Phase 3 uncontrolled</i>				
BIA-91067-302 Part II	367	To investigate the long-term efficacy, safety, and tolerability of OPC when administered in combination with L-DOPA/DDCI in subjects with Parkinson's disease and motor fluctuations.	Phase 3, multicentre, uncontrolled, open-label, 1-year extension of Part I	Start at 25 mg OPC with flexible dosing according to clinical response (25 or 50 mg OPC)
<i>Phase 2 controlled</i>				
BIA-91067-201	10	To investigate the effect of 3 doses of OPC on L-DOPA pharmacokinetics, and to investigate the tolerability, safety, effects on motor response and S-COMT activity, and pharmacokinetics of OPC when administered in combination with immediate release 100 mg/25 mg L-DOPA/DDCI in Parkinson's disease subjects (30 to 75 years).	Phase 2, 3-centre, DB, randomised, placebo-controlled, crossover study with 4 consecutive single-dose treatment periods.	Immediate-release 100/25 mg L-DOPA/DDCI alone on Days 2 and 4 and concomitantly with OPC or placebo on Day 3
BIA-91067-202	40	To investigate the effect of repeat dosing of OPC on L-DOPA pharmacokinetics, and the tolerability, safety, effects on motor response and S-COMT activity, and pharmacokinetics of OPC in comparison to placebo in Parkinson's disease subjects with motor fluctuations (≥ 30 years).	Phase 2, multicentre, DB, randomised, placebo-controlled study with 4 parallel treatment arms during the maintenance phase: - 4-week screening period - 1- to 3-week baseline period - 3- to 4-week maintenance phase	Placebo or OPC (5 mg, 15 mg, or 30 mg) QD for 21 to 28 days with morning doses of L-DOPA/DDCI 1 hour later

DB = double-blind; DDCI = dopa decarboxylase inhibitor; L-DOPA = levodopa; OPC = opicapone; S-COMT = soluble catechol-O-methyltransferase

2.5.1. Dose response and main clinical study(ies)

2.5.2. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 4 Summary of efficacy for trial BIA-91067-301

Title: Efficacy and safety of BIA 9-1067 in idiopathic Parkinson’s disease patients with “wearing-off” phenomenon treated with levodopa plus a dopa decarboxylase inhibitor (DDCI): a double-blind, randomised, placebo- and active-controlled, parallel-group, multicentre clinical study.		
Study identifier	BIA 9-1067	
Design	This was a Phase III, multicentre, DB, randomised, placebo- and active-controlled, parallel group study conducted in adults diagnosed with idiopathic PD.	
	Duration of Screening period:	up to 2 weeks
	Duration of Double-Blind Period:	14 to 15 weeks
	Duration of Open Label Extension Phase:	1 year
	Duration of Follow-up Period:	approximately 2 weeks
Hypothesis	Superiority to Placebo and Non-inferiority to active comparator	
Treatments groups	Opicapone 5mg [OPC5]	Opicapone 5mg + L-DOPA + DDCI 122 Patients randomised
	Opicapone 25mg [OPC25]	Opicapone 25mg + L-DOPA + DDCI 119 Patients randomised
	Opicapone 50mg [OPC50]	Opicapone 50mg + L-DOPA + DDCI 116 Patients randomised
	Entacapone 200mg [ETC200]	Entacapone 200mg + L-DOPA + DDCI 122 Patients randomised
	Placebo [PLC]	Placebo 5mg + L-DOPA + DDCI 121 Patients randomised
Endpoints and definitions	The primary efficacy variable was the change in absolute OFF-time from baseline to the end of the DB period (endpoint), measured as the average absolute OFF-time reported in subject’s Hauser diaries in the 3-day period preceding each visit.	
	The key secondary efficacy variables were: OFF-time responders: 1 hour or more reduction in absolute OFF-time from baseline to endpoint. ON-time responders: 1 hour or more increase in absolute ON-time from baseline to endpoint.	
	Other secondary efficacy variables were: *Absolute OFF-time at the different visits of the DB period and change from baseline until endpoint. *Percentage OFF-time at the different visits of the DB period and change from baseline until endpoint (calculated as the sum in minutes from 30-minute periods classified as OFF divided by the total time awake). *Absolute and Percentage ON-time at the different visits of the DB period and change from baseline until endpoint, for the following ON-time categories: - Total ON - ON-time without dyskinesia. - ON-time with non-troublesome dyskinesia. - ON-time with troublesome dyskinesia. - ON-time without troublesome dyskinesia (ON-time with non-troublesome dyskinesia + ON-time without dyskinesia). *Frequency of OFF-time responders at the different visits of the DB period until endpoint.	
Database lock	28-Apr-2014	
Results and Analysis		
Analysis description	Primary Analysis	

Analysis population and time point description	Full analysis set (FAS2) – all randomised and treated patients with the worst of the baseline or last observation used to impute missing data					
Descriptive statistics and estimate variability	Treatment group	OPC5	OPC25	OPC50	ETC200	PLC
	Number of subject	122	119	115	122	121
	Absolute OFF-time change from baseline [LS mean]	-77.6	-73.2	-103.6	-78.7	-48.3
	SE	13.39	13.67	14.08	13.38	13.46
Effect estimate per comparison	Absolute OFF-time change from baseline – Test for Superiority	Comparison groups		OPC 5 mg – Placebo		
		LS mean		-29.3		
		SE		18.41		
		P-value		0.1117		
	Absolute OFF-time change from baseline – Test for Superiority	Comparison groups		OPC 25 mg – Placebo		
		LS mean		-25.0		
		SE		18.60		
		P-value		0.1803		
	Absolute OFF-time change from baseline – Test for Superiority	Comparison groups		OPC 50 mg – Placebo		
		LS mean		-55.3		
		SE		18.68		
		P-value (1-sided)		0.0032		
	Absolute OFF-time change from baseline – Test for Non-Inferiority	Comparison groups		OPC 5 mg – Entacapone		
		LS mean		-4.5 (PP), 1.1 (FAS)		
		SE		19.14 (PP), 18.32 (FAS)		
		P-value (1-sided)		0.0358 (PP), 0.0578 (FAS)		
	Absolute OFF-time change from baseline – Test for Non-Inferiority	Comparison groups		OPC 25 mg – Entacapone		
		LS mean		-7.3 (PP), 5.5 (FAS)		
		SE		19.36 (PP), 18.48 (FAS)		
		P-value (1-sided)		0.0275, 0.0927 (FAS)		
	Absolute OFF-time change from baseline – Test for Non-Inferiority	Comparison groups		OPC 50 mg – Entacapone		
		LS mean		-26.3 (PP), -24.8 (FAS)		
		SE		19.35 (PP), 18.63 (FAS)		
		P-value (1-sided)		0.0019 (PP), 0.0017 (FAS)		
Notes	All secondary efficacy measures were consistent with the primary analysis. Different UPDRS subscales, PDQ-39, NMSS and PDSS improved in a similar manner across all treatment groups in both studies without an apparent advantage of OPC with respect to these scales over placebo.					

Table 5 Summary of efficacy for trial BIA-91067-302

Title: Efficacy and Safety of BIA 9-1067 in Idiopathic Parkinson's Disease Patients with "Wearing-Off" Phenomenon treated with Levodopa plus a Dopa Decarboxylase Inhibitor (DDCI): a Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, Multicentre Clinical Study		
Study identifier	BIA-91067-302 (BIPARK II)	
Design	<p>This was a multicenter, DB, randomized, placebo controlled, parallel group study to investigate two different doses of OPC, given orally for 14 to 15 weeks, in comparison with matching placebo, in subjects with idiopathic PD who were already receiving L-DOPA/DDCI therapy. After a screening period of up to two weeks, subjects entered a 14- to 15-week DB period, followed by an additional one year OL extension period in which all subjects were treated with OPC. Eligible subjects were randomly assigned to one of the three treatments at Visit (V2) using a 1:1:1 ratio. Study medication was administered in combination with existing treatment of L-DOPA/ DDCI. From V2 to V4 of the DB period (first 2-3 weeks of DB period), the Investigator could decrease the daily dose of L-DOPA (keeping the number of daily intakes unchanged), according to subject response. If needed, the L-DOPA dose could be increased again up to the baseline dose level. The dosage of L-DOPA was not to be changed during the study from V4 through to the end of the DB period. After completion of this maintenance period, subjects who did not enter the OL period were to have a post-study visit in 14 days. No new anti-PD drug was to be started during the study and any that were ongoing at the start of the study were to be kept at a stable dose for at least four weeks before screening and throughout the study.</p>	
	Duration of main phase:	14-15 weeks
	Duration of Run-in phase:	Up to 14 days
	Duration of Extension phase:	1 year
Hypothesis	Superiority	
Treatments groups	OPC 25mg	Opicapone 25mg o.d. 14-15 weeks, 125 patients randomised (excluding site 1703)
	OPC 50mg	Opicapone 50mg o.d. 14-15 weeks, 151 patients randomised (excluding site 1703)
	Placebo	Placebo 14-15 weeks, 136 patients randomised (excluding site 1703)
Endpoints and definitions	<p>The primary efficacy parameter, change from baseline in absolute OFF-time at the end of the DB period (V7), was analyzed using an analysis of covariance (ANCOVA) model with treatment group and pooled country as fixed effects and baseline OFF-time as a covariate. Differences between each OPC dose group (25 mg and 50 mg) and the placebo group were estimated from the model.</p>	
	<p>An ANCOVA similar to that used for analysing the primary efficacy variable was used for all relevant secondary efficacy variables in the DB period. Responder rates were compared between the different treatment groups in the DB period, using a Cochran-Mantel-Haenszel test with pooled country as strata. A non-parametric van Elteren's test for treatment effect, stratified by pooled country, was performed for the analysis of the Investigator's and Subject's global assessment of change scores at the end of the DB period.</p>	

	All safety parameters were presented by descriptive statistics for each treatment group. The analyses focused on treatment-emergent AEs (TEAEs) and were categorized by System Organ Class (SOC) and Preferred Term (PT). Serious TEAEs, TEAEs leading to death and TEAEs resulting in discontinuation of IMP were tabulated using frequency tables. For laboratory parameters, descriptive analyses at each time point and of changes from baseline to each post-baseline time point were presented by treatment group. Values of vital signs and 12-lead ECGs, including changes from baseline were summarized. Frequency tables and subject listings were to be presented for markedly abnormal values. Shift tables were to be presented according to the reference ranges (low, normal or high).			
Database lock	15 October 2012			
<u>Results and Analysis</u>				
Analysis description	Primary Analysis			
Analysis population and time point description	Full analysis set (FAS2 - BOCF) – all patients randomised and treated excluding site 1703. Worst of baseline or last observation used to impute missing data			
Descriptive statistics and estimate variability	Treatment group	OPC 25mg	OPC 50mg	Placebo
	Number of subject	125	150	136
	Change from Baseline in Absolute OFF-time (Minutes)	-93.2	-107.0	-54.6
	SE	14.81	13.57	14.26
Effect estimate per comparison	Change from Baseline in Absolute OFF-time (Minutes) - ANCOVA Analysis	Comparison groups	OPC25mg - Placebo	
		Difference in LS Mean	-38.5	
		SE	19.57	
		P-value	0.0496 (not significant after adjustment for multiplicity)	
	Change from Baseline in Absolute OFF-time (Minutes) - ANCOVA Analysis	Comparison groups	OPC50mg - Placebo	
		Difference in LS Mean	-52.4	
		SE	18.68	
		P-value (Dunnett adjusted for multiplicity)	0.0053	
Notes	All secondary efficacy measures were consistent with the primary analysis. Except from a minimum numerical worsening in modified Hoehn and Yahr stage (UPDRS V) of the same magnitude in the placebo and OPC 50 mg group in study 302, UPDRS subscales, PDQ-39, NMSS and PDSS improved in a similar manner across all treatment groups in both studies without an apparent advantage of OPC with respect to these scales over placebo.			

2.5.3. Dose response studies

Study BIA-91067-101 was a Phase 1, first-in-man, randomised, double-blind, placebo-controlled study to investigate the safety and tolerability of single oral ascending doses of Opicapone, administered as the FAAD 5-, FAAF 25-, and FAAE 100-mg capsules (non-micronised active pharmaceutical ingredient [API] formulation). The study population consisted of 64 healthy male subjects divided into 8 successive groups of 8 subjects each. Within each group, 6 subjects were randomised to receive opicapone and 2 subjects were randomised to receive placebo. Single oral doses of placebo or 10, 25, 50, 100, 200, 400, 800, and 1200mg opicapone were administered in 8 sequential treatment periods. Administration followed an overnight fast of 10 hours. Dose escalation was performed only after evaluation of safety and tolerability in the previous group.

Inhibition of S-COMT activity increased across the dose range of 10 to 1200mg Opicapone in a roughly dose-dependent manner. Percent inhibition ranged between 26.07% (10-mg Opicapone) and 75.62% (800-mg Opicapone) at 24 hours post-dose and between 5.90% (10-mg Opicapone) and 54.62% (800-mg Opicapone) at 72 hours post-dose. S-COMT Emax was statistically significantly greater than placebo ($p < 0.05$) at all doses of opicapone.

The study methodology was acceptable. The mean maximum inhibition of activity (Emax) of S-COMT increased with dose between 10 and 200mg Opicapone, however, from 200mg opicapone, Emax was 100.00%.

In the healthy subject single-ascending dose study BIA-91067-101, following single doses of 10 to 1200mg Opicapone, a dose-dependent and long-lasting S-COMT inhibitory effect was observed. Percent inhibition ranged between 26% (10-mg Opicapone) and 76% (800-mg Opicapone) at 24 hours post-dose and between 5.9% (10-mg Opicapone) and 55% (800-mg Opicapone) at 72 hours post-dose. The mean S-COMT Emax increased with dose between 10- and 200-mg Opicapone; between 200- and 1200-mg Opicapone, Emax was 100%. Dose-effect proportionality with single doses of the to-be-marketed formulation (25 and 50 mg) was also assessed in Study BIA-91067-121; the extent (AUEC) of S-COMT activity inhibition increased in a less than dose-proportional manner between 25 and 50mg Opicapone (approximately 1.2- to 1.3-fold increase) (refer to Study BIA-91067-121).

Study BIA-91067-121 was a Phase 1 randomised, single-dose, open-label, 2-sequence, 2-way crossover study to investigate the bioequivalence between 5 x 5-mg FACP and 1 x 25-mg FACQ capsules, and between 2 x 25-mg FACQ and 1 x 50-mg FACR capsules, all of which used the to-be-marketed formulation. The study population consisted of 56 healthy subjects.

In 2 consecutive treatment periods, subjects received single oral doses of either 1 x 25-mg opicapone (Group 1: 5 x 5-mg and 1 x 25-mg capsules in random sequence) or single oral doses of 1 x 50-mg opicapone (Group 2: 2 x 25-mg and 1 x 50-mg capsules in random sequence). Treatments were separated by a washout period of 10 to 14 days or more, and administration of opicapone followed an overnight fast of at least 8 hours. Subjects participated in either Group 1 or Group 2, not both.

Because single doses 25-mg opicapone already presented an S-COMT inhibition (% Emax) of approximately 70%, and because repeated administration of opicapone may enhance COMT inhibition, 5- to 30-mg QD opicapone was the dose range chosen for the healthy subject multiple-ascending dose study BIA-91067-102. Following multiple ascending doses of 5- to 30-mg QD opicapone, a dose-dependent and long-lasting S-COMT inhibitory effect was observed, sustainable to a QD regimen. Percent inhibition ranged between 43% (5-mg opicapone) and 65% (30-mg opicapone) at 24 hours post-dose and between 16% (5-mg opicapone) and 31% (20-mg opicapone) at 144 hours post-dose. The tEmax was not influenced by the dose, as the median tEmax was similar between dose groups.

Study BIA-91067-102 was a Phase 1, randomised, double-blind, placebo-controlled study to investigate the tolerability of multiple oral ascending doses of opicapone, administered as the FAAD 5-mg capsule (non-micronised API formulation). The study population consisted of 34 healthy male subjects divided into 4 groups of at least 8 subjects each. Within each group, at least 6 subjects were randomised to receive opicapone and at least 2 subjects were randomised to receive placebo. Multiple oral doses of placebo or 5-, 10-, 20-, or 30-mg QD opicapone were administered for 8 days in 4 successive treatment periods. Progression to the next dose level occurred only if the previous dose level was considered safe and well tolerated. No subject was a member of more than 1 dose group. Administration followed an overnight fast of at least 10 hours on Days 1 and 8 and a fast of at least 8 hours on all other days. Dose escalation was performed only after evaluation of safety and tolerability in the previous group.

Although a clear linearity between the dose and response was not observed in this study, it was evident that such relationship was more likely at lower doses such as the ones used in this study than with the higher doses.

Dose-effect proportionality with multiple doses of the Phase 3 micronised API formulation (5, 25, and 50 mg QD) was assessed in 1 study (Study BIA-91067-126) in healthy Japanese and Caucasian subjects; maximum S-COMT inhibition (E_{max}) ranged between 75.0% and 100%, with no apparent differences between 25- and 50-mg QD Opicapone.

In a pooled analysis BIA-91067-PKPD001 of several studies in which single doses of the non-micronised API formulation of opicapone were administered, S-COMT activity inhibition increased with dose for single doses of between 10 and 100 mg, reaching an E_{max} of nearly 100% at 100-mg opicapone.

Table 6 Dose ratio and pooled mean E_{max} and AUEC for S-COMT activity inhibition and correspondent ratio for up to 100-mg opicapone in single-dose studies with the non-micronised API formulation (Study BIA-91067-PKPD001)

Parameter	Pooled Mean					
	10 mg	20 mg	25 mg	30 mg	50 mg	100 mg
N	12	6	6	18	6	6
Dose ratio (versus 10 mg)	1	2	2.5	3	5	10
E_{max} , %	39.25	48.0	71.74	81.4	93.8	96.3
E_{max} ratio	-	1.2	1.8	2.2	2.4	2.5
AUEC, %h	689.5	1047	1258	1250	1576	1749
AUEC ratio	-	1.5	1.8	1.8	2.3	2.5

Source data: [Study BIA-91067-PKPD001](#), [Table 12](#), and [Table 13](#)

API = active pharmaceutical ingredient; AUEC = area under the effect-time curve; E_{max} = maximum inhibition of activity; N = number of subjects; S-COMT = soluble catechol-*O*-methyltransferase

In a pooled analysis of studies BIA-91067-102 and -105 in which multiple QD doses of the non-micronised API formulation of opicapone were administered, S-COMT activity inhibition increased in a less than dose-proportional manner with opicapone dose for multiple doses of between 5- and 30-mg QD opicapone

Table 7 Pooled mean Emax and AUEC data for S-COMT activity inhibition after multiple doses of 5- to 30-mg QD opicapone with the non-micronised API formulation (BIA-91067-PKPD001)

Parameter	Pooled Mean			
	5 mg QD	10 mg QD	20 mg QD	30 mg QD
N	6	6	6	18
Dose ratio (versus 5 mg)	1	2	4	6
E _{max} , %	60.0	72.8	80.0	86.5
E _{max} ratio	-	1.2	1.3	1.4
AUEC _{0-t} , pmol/mg Hb/h.h	1213.4	1485.5	1652.8	1768.7
AUEC _{0-t} ratio	-	1.2	1.4	1.5
AUEC _{0-120/144} , pmol/mg Hb/h.h	3974.7	5142.4	6363.9	5835.6
AUEC _{0-120/144} ratio	-	1.3	1.6	1.5

Source data: Study BIA-91067-PKPD001, Table 15, and Table 16

API = active pharmaceutical ingredient; AUEC = area under the effect-time curve; E_{max} = maximum inhibition of activity; Hb = haemoglobin; N = number of subjects; QD = once daily; S-COMT = soluble catechol-O-methyltransferase

The pooled analyses demonstrate the effect of maximum enzyme inhibition being reached between the doses 100mg and 200mg and therefore the loss of effect of increase in dose on the inhibition with higher doses.

Healthy subjects - Administration of Opicapone with levodopa/DDCI

The effect of single doses of opicapone on S-COMT activity when opicapone was administered with single doses of 100/25-mg levodopa/DDCI was assessed in Studies BIA-91067-107, -108, -109, and -110. In Studies BIA-91067-107 and -108, opicapone was co-administered with immediate-release levodopa/benserazide (BIA-91067-107) and immediate-release levodopa/carbidopa (BIA-91067-108). In Studies BIA-91067-109 and -110, opicapone was coadministered with controlled-release levodopa/benserazide (BIA-91067-109) and controlled release levodopa/carbidopa (BIA-91067-110).

In general, when single doses of opicapone were co-administered with single doses of levodopa/DDCI, opicapone significantly inhibited the peak (Emax) and extent (AUEC0-8 and AUEC0-24) of S-COMT activity relative to placebo, and inhibition increased with opicapone dose. The % Emax increased with opicapone dose, ranging between 66% (25 mg) and 99% (100 mg).

Table 8 Point estimates (90% CIs) of S-COMT PD parameters after single doses of opicapone versus placebo, both co-administered with single doses of 100/25-mg levodopa/DDCI in healthy subjects

Parameter	Opicapone/placebo GMR point estimate (90% CI)			
	Immediate-release levodopa		Controlled-release levodopa	
	Study 107 ^a	Study 108 ^b	Study 109 ^a	Study 110 ^b
<u>25-mg opicapone</u>				
E _{max}	35.56 (21.21; 49.91)	45.92 (33.02; 58.82)	38.03 (29.52; 46.54)	42.15 (30.92; 53.38)
AUEC _{0-t} ^c	44.42 (35.22; 56.03)	53.06 (45.24; 62.23)	53.19 (48.97; 57.77)	50.30 (41.12; 61.53)
AUEC ₀₋₇₂	59.98 (54.35; 66.20)	67.98 (61.24; 75.47)	69.95 (64.97; 71.07)	64.97 (59.34; 71.14)
<u>50-mg opicapone</u>				
E _{max}	10.62 (-3.73; 24.97)	12.76 (-0.04; 25.56)	13.00 (4.49; 21.51)	22.38 (10.79; 33.98)
AUEC _{0-t} ^c	33.66 (26.69; 42.46)	34.27 (29.24; 40.15)	36.56 (33.66; 39.72)	36.34 (29.52; 44.75)
AUEC ₀₋₇₂	53.27 (48.27; 58.79)	52.92 (47.70; 58.71)	57.50 (54.98; 60.14)	58.55 (53.31; 64.30)
<u>100-mg opicapone</u>				
E _{max}	3.85 (-11.23; 18.93)	8.86 (-4.04; 21.76)	2.03 (-6.48; 10.54)	8.03 (-3.21; 19.26)
AUEC _{0-t} ^c	19.59 (15.34; 25.01)	25.63 (21.85; 30.06)	27.08 (24.93; 29.41)	27.57 (22.53; 33.72)
AUEC ₀₋₇₂	46.85 (41.85; 51.52)	49.23 (44.35; 54.65)	50.58 (48.37; 52.90)	50.22 (45.87; 54.99)

Source data: [Study BIA-91067-107, Table M](#); [Study BIA-91067-108, Table M](#); [Study BIA-91067-109, Table K](#); [Study BIA-91067-110, Table M](#)

AUEC = area under the effect-time curve; CI = confidence interval; DDCI = DOPA decarboxylase inhibitor; E_{max} = maximum inhibition of activity; GMR = geometric mean ratio; Hb = haemoglobin; S-COMT = soluble catechol-*O*-methyltransferase

^a Levodopa/benserazide.

^b Levodopa/carbidopa.

^c Levodopa/carbidopa AUC₀₋₂₄ for Studies BIA-91067-107 and -109.

The observed effects are generally similar to those seen when Opicapone was administered alone.

Two studies assessed the effect of opicapone on S-COMT activity when multiple doses of 5-, 15-, or 30-mg QD opicapone were administered 1 hour before single doses of immediate release 100/25-mg levodopa/DDCI (Studies BIA-91067-114 and -118).

Study BIA-91067-114 was a Phase 1, double-blind, randomised, placebo- and active-controlled, parallel-group study to investigate the effect of multiple oral doses of opicapone (FAAD 5- and FAAF 25-mg capsules [non-micronised API formulation]), compared with placebo and entacapone (positive control), on the PK of levodopa administered as immediate-release 100/25-mg levodopa/carbidopa (Sinemet® 100/25 tablets). The study population consisted of 82 healthy male and female subjects.

Study BIA-91067-118 was a Phase 1, double-blind, randomised, placebo-controlled study to investigate the effect of steady-state opicapone (FAAD 5- and FAAF 25-mg capsule formulations [nonmicronised API formulation]) on the PK of levodopa administered as immediate-release 100/25-mg levodopa/carbidopa (Sinemet® 100/25 tablets) or immediate-release 100/25-mg levodopa/benserazide (Prolopa® 100/25 tablets). The study population consisted of 52 healthy male and female subjects.

In Studies BIA-91067-114 and -118, the % E_{max} of S-COMT activity increased in an opicapone dose dependent manner, ranging between 56% (5 mg QD) and 91% (30 mg QD) for Study BIA-91067-114 and between 55% (5 mg QD) and 93% (30 mg QD) for study BIA-91067-118.

Across both studies, opicapone significantly inhibited the peak (Emax) and extent (AUEC0-8 and AUEC0-24) of S-COMT activity relative to placebo, and inhibition increased with opicapone dose. In Study BIA-91067-114, relative to 200-mg TID entacapone, 15- and 30-mg QD opicapone significantly inhibited the extent (AUEC0-8 and AUEC0-24), but not peak (Emax), of S-COMT activity.

In these two studies the applicant tested the effects of multiple doses. Dose-response effect was observed and 30mg showed the highest inhibition of the S-COMT activity.

Study BIA-91067-123 assessed the effect of opicapone on S-COMT activity when multiple doses of opicapone (5, 15, or 50 mg QD) were administered 12 hours before single doses of immediate-release 100/25-mg levodopa/carbidopa or immediate-release 100/25-mg levodopa/benserazide.

This was a Phase 1, double-blind, randomised, placebo-controlled study to investigate the effect of steady-state opicapone (FAAD 5- and FAAF 25-mg capsules [non-micronised API formulation]) versus placebo on the PK of levodopa administered as immediate-release 100/25-mg levodopa/carbidopa (Sinemet® 100/25 tablets) or immediate-release 100/25-mg levodopa/benserazide (Madopar® 100/25 tablets) when opicapone was administered 12 hours before levodopa/DDCI. The study population consisted of 74 healthy male and female subjects.

In this study, Opicapone significantly inhibited the peak (Emax) and extent (AUEC0-24) of S-COMT activity relative to placebo. S-COMT activity inhibition was dose dependent, with % Emax ranging between 58% following 5-mg opicapone to 99% following 50-mg QD opicapone. Dose dependency has been demonstrated in this study. Dose 50mg already approached the maximum inhibition.

Study BIA-91067-124 assessed the effect of steady-state opicapone (25, 50, or 75 mg QD) on S-COMT activity when opicapone was administered approximately 10 hours before the first of 3 daily doses of immediate-release 100/25-mg levodopa/carbidopa.

This was a Phase 1, double-blind, randomised, placebo-controlled study to investigate the effect of steady-state opicapone (FABA 25- and FABB 50-mg capsules [Phase 3 micronised API formulation]) versus placebo and 200-mg entacapone (Comtan®, a positive control) on the PK of levodopa administered as immediate-release 100/25-mg levodopa/carbidopa (Sinemet® 100/25 tablets) TID, 5 hours apart. Levodopa/carbidopa was administered approximately 10 hours after opicapone. The study population consisted of 80 healthy male and female subjects.

In this study, opicapone significantly inhibited the peak (Emax) and extent (AUEC0-5) of S-COMT activity relative to placebo. Inhibition was generally dose dependent, with the exception of following the third dose of levodopa/carbidopa, where the highest % Emax occurred following 50-mg QD opicapone administration. Following the second and third doses of levodopa/carbidopa, % Emax was higher with all doses of Opicapone compared with 200-mg TID entacapone; following the first dose, % Emax was higher with 50- and 75-mg QD opicapone compared with 200-mg TID entacapone.

Subjects with Parkinson's disease - Administration of Opicapone with levodopa/DDCI

Study BIA-91067-201 assessed the effect of single doses of 25-, 50-, and 100-mg opicapone on S-COMT activity and motor performance when co-administered with immediate-release 100/25-mg levodopa/carbidopa or levodopa/benserazide in subjects with Parkinson's disease. This was a Phase 2, randomised, double-blind, placebo-controlled, crossover study to investigate the effect of single oral doses of 25-, 50-, and 100-mg opicapone (administered as FAAF 25- or FAAE 100-mg capsules [non-micronised API formulation]) on the PK of levodopa when administered as immediate-release 100/25-mg levodopa/carbidopa (Sinemet® 25/100) or 100/25-mg levodopa/benserazide (Madopar®/Restex® 125) in subjects with Parkinson's disease. The study population consisted of 10 subjects with Parkinson's disease. In 4 separate treatment periods, each subject was to receive, in

random sequence, doses of 25-, 50-, and 100-mg opicapone or placebo co-administered with levodopa/carbidopa or levodopa/benserazide.

Following opicapone administration, the % Emax of S-COMT activity ranged between 68% and 100% (excluding 2 unexpected S-COMT profiles; with these 2 subjects, % Emax ranged between 68% and 87%). Relative to placebo, both the peak (Emax) and extent (AUEC) of S-COMT activity were markedly inhibited following opicapone administration, and inhibition occurred in an opicapone dose-dependent manner.

Concomitant administration of opicapone with levodopa/DDCI improved motor performance to some extent in Study BIA-91067-201, despite being a short and single-dose treatment study, and therefore, not a study in which relevant changes were expected. Relative to placebo, time to ON (onset latency) was markedly decreased with 100-mg opicapone, and time to best ON (peak latency) was markedly decreased following administration of 50- and 100-mg opicapone.

The results of this study do not contradict the results observed in other studies. The results of both analyses, including and excluding the subjects designated as outliers, show the same trend.

Study BIA-91067-202 assessed the effect of multiple doses of 5-, 15-, and 30-mg QD opicapone on S-COMT activity and motor performance when administered with immediate-release 100/25-mg levodopa/carbidopa or levodopa/benserazide in subjects with Parkinson's disease. This was a Phase 2, randomised, double-blind, placebo-controlled study in 4 parallel groups to investigate the effect of multiple oral doses of 5-, 15-, and 30-mg QD opicapone (administered as the FAAD 5- or FAAF 25-mg capsules [non-micronised API formulation]) on the PK of levodopa when administered as immediate-release 100/25-mg levodopa/carbidopa (Sinemet® 25/100) or 100/25-mg levodopa/benserazide (Madopar®/Restex® 125) in subjects with Parkinson's disease with motor fluctuations. The study population consisted of 40 subjects with Parkinson's disease. In 4 separate treatment groups, each subject was to receive 5-, 15-, or 30-mg opicapone or placebo co-administered with levodopa/carbidopa or levodopa/benserazide.

Following opicapone administration, the % Emax of S-COMT activity ranged between 52% and 80%. Relative to placebo, both the peak (Emax) and extent (AUEC) of S-COMT activity were markedly inhibited following opicapone administration, and inhibition occurred in an opicapone dose-dependent manner.

While Study BIA-91067-202 was not designed to detect any significant differences in motor performance, an exploratory analysis performed showed improvement in various motor outcomes, including an opicapone dose-dependent increase in ON time and a dose-dependent decrease in time to ON. Additionally, daily OFF time was decreased with opicapone relative to placebo. Results were highly consistent across the multiple analyses performed and showed that 30-mg opicapone tended to be the most efficacious treatment tested, followed by 15-mg opicapone.

The results show statistical significance over placebo in size of inhibition. There is a clear dose dependence trend between the three investigated doses. The study was not powered to detect the difference in motor performance, but the improvements have been observed.

2.5.4. Main studies

2.5.4.1. Study BIA-91067-301

"Efficacy and safety of BIA 9-1067 in idiopathic parkinson's disease patients with "wearing-off" phenomenon treated with levodopa plus a dopa decarboxylase inhibitor (DDCI): a double-blind, randomised, placebo- and active-controlled, parallel-group, multicentre clinical study"

Methods

• Objectives

Primary objective was to investigate the efficacy of 3 different doses of opicapone (5 mg, 25 mg, and 50 mg) administered once daily (QD), compared with placebo or 200 mg of entacapone, when administered with the existing treatment of L-DOPA plus a DDCI, in patients with PD and end-of-dose motor fluctuations.

Secondary objectives were to investigate the safety and tolerability of the combined treatment of L-DOPA/DDCI plus opicapone, entacapone, or placebo.

• Study Design

This was a Phase III, multicentre, double-blind (DB), randomised, placebo- and active-controlled, parallel-group study conducted in adults diagnosed with idiopathic PD and motor fluctuations. The study was conducted in estimated 130 sites in approximately 20 European countries.

After a Screening period of up to 2 weeks (14 days), subjects entered a DB period of 14 to 15 weeks (98 to 105 days). At the end of the DB period, subjects could enter an additional 1-year, open-label extension period (OL period) in which all subjects were to be treated with opicapone.

The DB period of the study had 5 treatment arms: 3 opicapone groups, each receiving 1 of 3 different doses (5 mg, 25 mg, or 50 mg); an active comparator group receiving 200 mg of entacapone with each L-DOPA/DDCI intake; and a placebo group. At Visit 2 (V2), eligible subjects were randomly assigned to treatments using a 1:1:1:1:1 ratio.

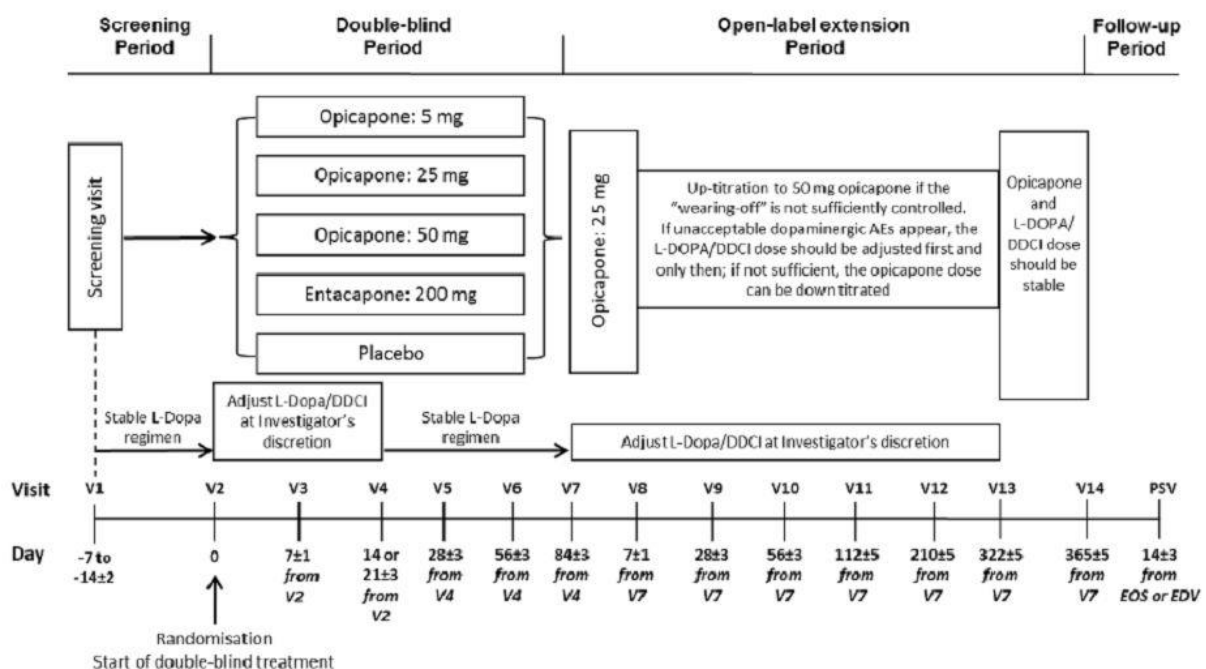


Figure 2 Overview of study design

The safety data from the study was monitored on a regular basis by an independent DSMB. The safety revision was to include summaries of AEs, summaries of laboratory data, summaries of relevant ECG and vital sign abnormalities and population status (including reasons for withdrawals).

Study days were defined as calendar days relative to the day of first IMP intake, which was set to Day 1. The day of randomisation was then usually set to Day -1, except for those subjects with a delayed first intake of IMP.

Table 9 Study Assessments Flow Chart

Activity	Screening		Double-blind Period							Open-label Period							Follow-up
Visit	V1	Pre-V2	V2	V3	Pre-V4	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	PSV
Day	-7 or -14±2	-7±1	0	7±1 of V2	14±3 of V2	14 or 21±3 of V2	28±3 of V4	56±3 of V4	84±3 of V4	7±1 of V7	28±3 of V7	56±3 of V7	112±5 of V7	210±5 of V7	322±5 of V7	365±5 of V7	14±3 of EOS or EDV
Informed consent	X																
Demographic characteristics	X																
Medical/neurological history	X																
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Skin examination ^b			X						X							X	
Physical (height at V1 only) and neurological exams	X		X						X				X			X	X
12-lead ECG	X		X ^c						X				X		X	X	X
Pregnancy test ^d	X ^e	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f
Safety laboratory tests ^g	X ^h		X			X	X	X	X ^h	X	X	X	X ^h	X	X	X ^h	X ^h
Review of subject eligibility	X	X	X														
Randomisation			X														
Record adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IMP			X	X	X	X	X	X	X ⁱ	X	X	X	X	X	X	X	X ⁱ
Medication accountability				X	X	X	X	X	X	X	X	X	X	X	X	X	
Record L-DOPA/DDCI dose	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Instruct on use of, and issue, diary	X	X	X	X	X	X	X	X	X ⁱ	X	X	X	X	X	X	X ⁱ	
Review and record diary charts		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
UPDRS I (ON)	X		X						X							X	X
UPDRS III, IV, and V (ON)	X		X			X	X	X	X	X	X	X	X	X	X	X	
UPDRS II and VI (ON+OFF)	X		X			X	X	X	X	X	X	X	X	X	X	X	
PDQ-39, PDSS, NMSS, mMIDI, C-SSRS			X			X ^j	X	X ^j	X		X ^j	X ^j	X	X ^j	X	X	
Blood sampling for PK assay			X				X		X						X	X	
Investigator and subject assessments of change						X	X	X	X	X	X	X	X	X	X	X	

C-SSRS=Columbia Suicide Severity Rating Scale; DDCI=dopa decarboxylase inhibitor; ECG=electrocardiogram; EDV=Early Discontinuation Visit; EOS=End-of-study Visit; IMP=investigational medicinal product; L-DOPA=levodopa; NMSS=Non-Motor Symptoms Scale; mMIDI=modified Minnesota Impulsive Disorders Interview; PDQ-39=Parkinson's Disease Questionnaire; PDSS=Parkinson's Disease Sleep Scale; PSV=Post-study Visit; PK=pharmacokinetic; UPDRS=Unified Parkinson's Disease Rating Scale; V=visit.

^a Blood pressure and pulse measured as a set of 3 measurements; ^b Skin examinations assessed by a dermatologist to screen for melanoma between V1-V2, if needed up to V3, at V7±7 days (up to PSV in case the subject does not participate in the open label phase), and between V14-PSV; ^c 12-lead ECG reading in triplicate; ^d Only in females of child-bearing potential and can be more often if required by local law; ^e Serum β-human chorionic gonadotropin; ^f Urine pregnancy test; ^g Blood and urine for haematology, biochemistry, and urinalysis; ^h Including coagulation; ⁱ Only if subject continues into subsequent extension and OL medication intake should start on the evening of this visit; ^j Only C-SSRS.

• Study participants

Key inclusion criteria for this study and for the study 302 were defined as follows.

At screening:

- Male and female subjects aged 30 to 83 years.
- Diagnosed with idiopathic Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria for at least 3 years.
- Disease severity Stages I-III (modified Hoehn & Yahr staging) at ON.
- Treated with L-DOPA/DDCI for at least 1 year with clear clinical improvement.
- On a stable regimen of L-DOPA/DDCI (3 to 8 daily doses) and other anti-Parkinson's disease drugs for at least 4 weeks before screening.
- Signs of "wearing-off" phenomenon (end-of-dose deterioration) for a minimum of 4 weeks before screening, with average total daily OFF-time while awake of at least 1.5 hours, excluding the early morning pre-first dose OFF period, despite "optimal" anti-Parkinson's disease therapy (based on the Investigator's judgment).
- Able to keep reliable diaries of motor fluctuations.

At randomisation:

- Have filled-in self-rating diary charts in the 3 days preceding Visit (V) 2 in accordance with the diary chart instructions and with ≤ 3 errors per day.
- At least 1.5 OFF hours per day, excluding the early morning pre-first dose OFF period, as recorded in the self-rating diary for at least 2 of the 3 days preceding randomisation.

Key exclusion criteria for both studies were defined as follows.

At screening:

- Non-idiopathic parkinsonism (atypical parkinsonism, acquired or symptomatic parkinsonism, Parkinson-plus syndrome).
- Dyskinesia disability score >3 in the Unified Parkinson's Disease Rating Scale (UPDRS) Sub-section IV A, Item 33.
- Severe and/or unpredictable OFF periods.
- Any investigational medicinal product (IMP) within the 3 months (or within 5 half-lives, whichever is longer) before screening.

At randomisation:

- Inadequate compliance to concomitant L-DOPA/DDCI and other anti-Parkinson's disease drugs during screening (based on the Investigator's judgment).

- ***Treatments***

The IMPs to be tested in this study were opicapone as the research therapy and entacapone and placebo as the reference therapies. Opicapone was supplied in capsules of 5mg, 25mg and 50 mg. Entacapone was supplied in 200mg tablets. Placebo capsules were identical capsules with filler.

To ensure blinding during the DB period, the opicapone capsules and entacapone tablets were identically over-encapsulated and taken orally. The placebo capsules were prepared by filling identical capsules with filler (also used as back-filling).

During the DB period, subjects were to take 1 capsule of IMP concomitantly with each LDOPA/DDCI dose (3 to 8 daily doses). An additional IMP bedtime dose was to be administered at least 1 hour after the last daily dose of L-DOPA/DDCI. The investigational medicinal product (IMP) was administered with existing treatment of L-DOPA/DDCI. From V2 to V4 of the DB period (first 2 to 3 weeks [14 to 21 days] of DB period), the Investigator could decrease the daily dose of L-DOPA/DDCI (keeping the number of daily intakes unchanged), according to subject response. The dose could be increased again but was not to exceed the baseline dose level. The dosage of L-DOPA/DDCI was not to be changed from V4 through the end of the DB period.

Prior anti-PD drug usage since diagnosis or taken in the last 2 years before entry to the study (whichever is shorter) were to be documented.

All medications being taken by the subjects on entry to the study or at any time during the study in addition to the IMP were regarded as concomitant medication and were to be documented. Concomitant medications were to remain stable during the study and to be recorded in the subject's file. However, the Investigator could start new medications or change the background regimen if these were considered necessary for the subject's welfare and were unlikely to interfere with the IMP.

Because of its mechanism of action, opicapone and entacapone could interfere with the metabolism of drugs containing a catechol group that are metabolised by COMT and could potentiate the effect of such drugs. Treatment with catechol-structured drugs (e.g. rimiterole, isoprenaline, adrenaline, noradrenaline, dopamine, dopexamine, dobutamide, paroxetine) was allowed, but the Investigator was to carefully monitor a subject treated with these drugs.

The potential for drug interactions between opicapone and hormonal contraceptives had not been assessed at the time of this study's design. Therefore, women of childbearing potential were to agree to use reliable nonhormonal contraception. Female subjects who requested to continue with oral contraceptives were to be informed that additional nonhormonal methods of contraception were to be used.

Entacapone can form chelates with iron in the gastrointestinal tract. Therefore, iron preparations were to be taken at least 2-3 hours apart from the IMP.

Subjects were prohibited from receiving the following medications prior to the study:

- Tolcapone, neuroleptics, venlafaxine, apomorphine, reserpine, alpha-methyldopa, MAO inhibitors (except selegiline up to 10 mg/day in oral formulation or 1.25 mg/day in buccal absorption formulation or rasagiline up to 1 mg/day), or anti-emetics (except domperidone) within the month before Screening.
- Entacapone.

Subjects were prohibited from receiving the following medications during the study:

- Apomorphine or tolcapone.
- Any entacapone other than that supplied by the Investigator for the study.
- Neuroleptics.

- Venlafaxine.
- MAO inhibitors, except:
 - o Selegiline up to 10 mg/day in oral formulation or 1.25 mg/day in buccal absorption formulation OR
 - o Rasagiline up to 1 mg/day.
- Alpha-methyldopa or reserpine.
- Anti-emetics with anti-dopaminergic action (domperidone allowed).
- Any other drugs with anti-dopaminergic action.
- Other experimental or investigational drugs.

Subjects were prohibited from receiving the following non-drug therapies during the study:

- Deep brain stimulation (during the entire study duration, including the OL period).
- Stereotactic surgery (e.g. pallidotomy, thalamotomy) for PD.

● **Randomisation**

The randomisation numbers were grouped in blocks. Blocking technique was used to facilitate attainment of homogeneous, by-centre distribution of treatment groups.

● **Blinding (masking)**

Study treatments were blinded and the randomisation schedule and the allocation to treatment groups was not to be known to the Investigator, the sponsor or any other person involved in the conduct of the study, except in case of an emergency. If the code was broken, the subject was to be removed from the study.

Subjects with a suspected unexpected serious adverse reaction (SUSAR) were to be unblinded by the Pharmacovigilance team for reporting purposes in accordance to the legislation in force.

The drug supplier/manufacturer was independent from the study team and was never to disclose the randomisation schedule.

The data reports reviewed by the DSMB were presented in a partially unblinded fashion. The data reports were generated by an unblinded biostatistician of the CRO independent of the study team. The DSMB was to ensure that the study team was not inappropriately exposed to confidential information contained within the safety reports. Only DSMB members could be present during the closed sessions of data review. An exception was the unblinded biostatistician, who could participate should questions arise during the sessions. The DSMB members could elect to fully unblind the data report if considered necessary.

● **Outcomes/endpoints**

The primary efficacy variable was the change in absolute OFF-time from baseline to the end of the DB period (endpoint).

The average OFF-time of the diaries completed on the last 3 days prior to V2 was to be considered as the baseline value. The average OFF-time of diaries completed on the last 3 days under treatment in the DB period prior to V7 or EDV was to be considered as the endpoint value.

If only diary data from less than these 3 days were available for either baseline or endpoint, the mean of the data from the available days were to be used. If the primary variable was missing at endpoint, it was to be replaced by the last available post-baseline observation until endpoint (LOCF).

Following the advice of the CHMP regarding study design and planned statistical analysis, the following endpoints were considered as key secondary endpoints in this study:

- OFF-time responders: 1 hour or more reduction in absolute OFF-time from baseline to endpoint.
- ON-time responders: 1 hour or more increase in absolute ON-time from baseline to endpoint.

Other Secondary Efficacy Variables

Subject Diary Data

The following variables, based on subject's diary data at the different visits of the DB period and at endpoint, were defined as other secondary efficacy variables:

- Absolute OFF-time.
- Change from baseline in absolute OFF-time.
- Percentage OFF-time.
- Change from baseline in percentage OFF-time.
- Absolute and Percentage ON-time at the different visits of the DB period and change from baseline until endpoint, for the following ON-time categories:
 - o Total ON
 - o ON-time without dyskinesia.
 - o ON-time with non-troublesome dyskinesia.
 - o ON-time with troublesome dyskinesia.
 - o ON-time without troublesome dyskinesia (ON-time with non-troublesome dyskinesia + ON-time without dyskinesia).
- Frequency of OFF-time responders.

Additional other secondary endpoints were based on the following questionnaires. If questionnaire items were missing, imputation was to be performed as specified in Section 4.1.10.3 of the SAP.

- Unified Parkinson's Disease Rating Scale
- Parkinson's Disease Sleep Scale
- Parkinson's Disease Questionnaire
- Non-motor Symptoms Scale
- Investigator's and Subject's Global Assessment of Change

● **Statistical methods**

The sample size calculation was based on the primary efficacy variable (change from baseline to endpoint in absolute OFF-time). 100 subjects per treatment group would ensure a disjunctive power of more than 97% to confirm a treatment effect in at least 1 opicapone dose group, assuming that the mean reductions in OFF-time of the doses are 75, 90, and 105 minutes and 30 minutes for placebo. These mean reductions

in OFF-time were based on previous studies on COMT inhibitors, which reported a mean reduction in OFF-time of between approximately 60 and 145 minutes. The power calculation used a common SD of 130 minutes.

Further, assuming that the mean reduction in OFF-time for entacapone is 75 minutes, and with a non-inferiority margin of 30 minutes, 100 subjects per treatment group would ensure a disjunctive power of 84% for at least 1 significant result in the non-inferiority tests. As the non-inferiority tests were to be performed on the PP set, the number of subjects randomised was adjusted for potential major protocol violators. Assuming a 10% rate of subjects with major protocol violations, 110 subjects were to be randomised to each group (550 subjects total).

If not stated otherwise, all statistical analyses based on the Randomised set, the Full Analysis Set (FAS), or the Per-protocol (PP) Set, are displayed by the treatment that subjects were randomised to receive during the DB period, whereas all statistical analyses based on the Safety set are displayed by the treatment that subjects actually received.

Continuous data are summarised by using descriptive statistics, i.e. generally displaying number of subjects, mean, median, standard deviation (SD), quartiles, minimum and maximum, and number of missing data. Categorical variables are summarised by using frequency counts and percentages; missing data are counted in a separate category. If not explicitly stated otherwise, for all analyses, the subject is the statistical unit.

The number and percentages of subjects in each analysis set are presented overall and by treatment, region, country, and site. Number and percentages of reasons for exclusion from any of the analysis sets are presented by treatment group and overall. Additionally, subject listings including the reason for exclusion are provided for all subjects excluded from any of the analysis sets.

The following analysis sets were defined:

- Enrolled set: all subjects screened and enrolled (i.e. all subjects who provided informed consent).
- Randomised set: all randomised subjects, irrespective of whether they received IMP.
- Safety set: all subjects who received at least 1 dose of IMP after randomisation.
- FAS: all randomised subjects, treated with at least 1 dose of IMP after randomisation and with at least 1 post-baseline OFF-time efficacy assessment. This is equivalent to the intention-to-treat population. Treatment assignment was as randomised.
- PP set: all subjects of the FAS without any major protocol deviations. Subjects were included in the PP set if they fulfilled all of the following criteria:
 - Fulfilled all relevant eligibility criteria.
 - Treated with IMP according to the randomisation plan.
 - Had sufficient compliance.
 - Received no L-DOPA dose higher than baseline during the study from V4 through the end of the DB period.
 - Not identified as a major protocol violator for other reasons during a blind data review meeting.

Identification of subjects for exclusion from the different analysis sets was done before unblinding and was documented in the blind data review meeting report. All subjects excluded from one of the analysis sets are listed with the reason for exclusion.

The primary efficacy analysis focused on identification of at least 1 efficacious dose of opicapone and its subsequent comparison with the active control, entacapone, with regard to the primary variable, as defined in Section 9.5.11.1. Multiple 1-sided tests based on an analysis of covariance (ANCOVA) were used to test superiority vs. placebo in the FAS and non-inferiority vs. entacapone in the PP set.

In order to control for multiplicity, a sequential gatekeeping procedure was used [Bretz 2009, Dmitrienko 2007]. The family-wise error rate (joint level of significance of all tests) was 0.025 (corresponding to 0.05 for 2-sided tests). For an illustration of the testing procedure to be performed, see Figure below.

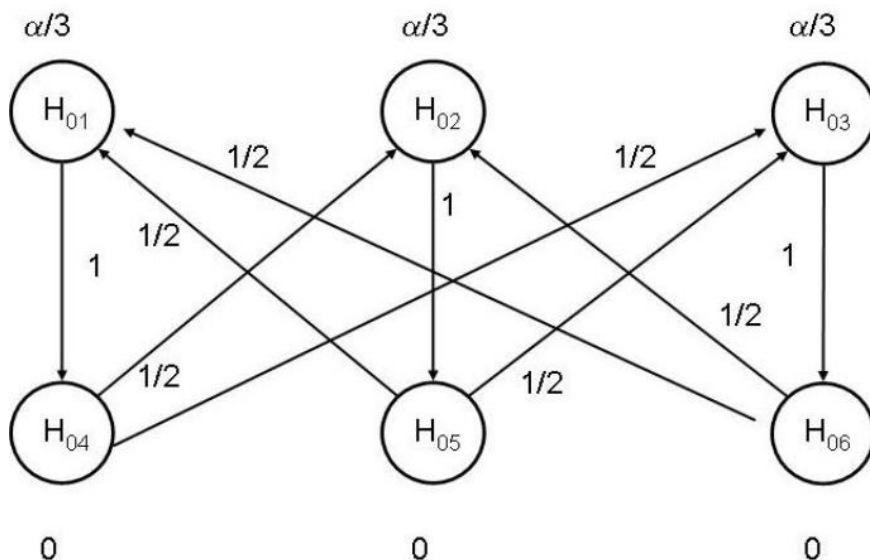


Figure 3 The stepwise gatekeeping procedure with hierarchical tests of opicapone vs. placebo (upper row) and entacapone (lower row).

Each dose of opicapone was compared with placebo using three 1-sided tests for superiority in the FAS set. This corresponds to the following 3 null hypotheses against the respective alternative hypotheses:

- $H_{01}: \mu_{5 \text{ mg}} = \mu_{\text{Plac}}$ vs. $H_{11}: \mu_{5 \text{ mg}} > \mu_{\text{Plac}}$
- $H_{02}: \mu_{25 \text{ mg}} = \mu_{\text{Plac}}$ vs. $H_{12}: \mu_{25 \text{ mg}} > \mu_{\text{Plac}}$
- $H_{03}: \mu_{50 \text{ mg}} = \mu_{\text{Plac}}$ vs. $H_{13}: \mu_{50 \text{ mg}} > \mu_{\text{Plac}}$

where μ denotes the mean reduction in OFF-time from baseline to end of the DB period.

A Bonferroni-adjustment was used to adjust the levels of significance for the 3 tests to ensure that the family-wise error rate and all comparisons vs. placebo were treated equally. If 1 or more of these tests yielded a significant difference to placebo, the significance levels of the other tests were adjusted according to the algorithm described by Bretz et al. [Bretz 2009].

For each dose of opicapone, non-inferiority vs. entacapone was tested only if the efficacy of opicapone vs. placebo had been established, i.e. if at least 1 of the null hypothesis H_{01} to H_{03} could be rejected. The non-inferiority comparisons correspond to the following family of null and alternative hypotheses:

- $H_{04}: \mu_{5 \text{ mg}} \leq \mu_{\text{entacapone}} - \delta$ vs. $H_{14}: \mu_{5 \text{ mg}} > \mu_{\text{entacapone}} - \delta$
- $H_{05}: \mu_{25 \text{ mg}} \leq \mu_{\text{entacapone}} - \delta$ vs. $H_{15}: \mu_{25 \text{ mg}} > \mu_{\text{entacapone}} - \delta$
- $H_{06}: \mu_{50 \text{ mg}} \leq \mu_{\text{entacapone}} - \delta$ vs. $H_{16}: \mu_{50 \text{ mg}} > \mu_{\text{entacapone}} - \delta$

where μ denotes the mean reduction in OFF-time from baseline to end of the DB period, and δ denotes the shift parameter or non-inferiority margin for mean reduction in OFF-time and was set to $\delta=30$ minutes (i.e. differences below 30 minutes were considered as irrelevant).

Three 1-sided t-tests against a shifted null-hypothesis were used to assess non-inferiority. The non-inferiority tests were done for the PP set of Part I.

For both the superiority and non-inferiority tests, an ANCOVA model with a common error variance was used to generate adjusted estimates and test statistics. The model included treatment group and region as fixed effects and baseline OFF-time as a covariate. All group comparisons from the ANCOVA model were based on Type III sums of squares.

The stepwise results of the above described testing procedure were summarised using the R package gMCP [Bretz 2011, Rohmeyer 2013]. For each hypothesis, the estimated treatment group difference, the nominal and adjusted p-values, the final significance level used for the test decision, and the compatible 1-sided simultaneous CIs according to Strassburger and Bretz (2008) [Strassburger 2008] are presented in a summary table.

The purpose of the secondary analyses was to support the primary efficacy analysis and to present additional efficacy data in an exploratory way. As far as statistical tests applied to secondary efficacy analyses, p-values and CIs were interpreted as descriptive measures of treatment group differences. If not stated otherwise, results are presented for the FAS and the PP population.

Subgroup analyses were performed to evaluate the consistency of results across pre-defined subgroups. The following subgroups were evaluated:

- Age (<70 years/ \geq 70 years).
- Gender.
- UPDRS Part V (modified Hoehn and Yahr staging) at baseline (<2.5/ \geq 2.5).
- Disease duration (time since PD diagnosis) at study entry (<8 years/ \geq 8 years).
- L-DOPA mean daily dose at baseline (<700 mg/day/ \geq 700 mg/day).
- L-DOPA formulation (IR, CR, or IR and CR) at baseline.
- Region.
- Concurrent usage of dopamine agonists as identified at baseline (yes/no).
- Concurrent usage of MAO inhibitors and dopamine agonists as identified at baseline (yes/no).

Subgroup analyses were performed via an ANCOVA that models the change in absolute OFF-time from baseline to the end of the DB period as a linear fixed-effect model of treatment, region, the respective subgroup variable, and subgroup*treatment interaction in the FAS. Two-sided 95% CIs and matching (2-sided) p-values are presented for the LS mean estimates and their differences because no directional tests could be pre-specified. Forest plots are presented to visually assess the presence of treatment by region interaction.

Results

● **Participant Flow**

Of 679 subjects screened for eligibility to participate in the study, 600 were randomised to treatment at 106 sites in 19 countries: Austria (n=3), Bosnia-Herzegovina (n=16), Bulgaria (n=50), Croatia (n=14), Czech Republic (n=51), France (n=15), Germany (n=35), Hungary (n=10), Italy (n=14), Latvia (n=7),

Lithuania (n=15), Poland (n=90), Portugal (n=22), Romania (n=53), Russia (n=34), Serbia (n=36), Slovakia (n=19), Spain (n=37), Ukraine (n=79) (Table below). The number of subjects randomised by region and treatment group was well balanced across the treatment groups both within region and overall. All subjects were treated as randomised.

Table 10 Number of subjects by region (Randomised set)

Region	Placebo	Entacapone	OPC 5 mg	OPC 25 mg	OPC 50 mg
Western Europe <i>Austria and Germany</i>	10	9	9	7	3
Southern Europe <i>France, Italy, Portugal, Spain</i>	16	18	18	18	18
North Eastern Europe <i>Croatia, Czech Republic, Slovakia, Poland, Latvia, Lithuania</i>	40	39	40	38	39
Russia and Ukraine	22	23	23	22	23
South Eastern Europe <i>Serbia, Bosnia and Herzegovina, Bulgaria, Hungary, Romania</i>	33	33	32	34	33
TOTAL	121	122	122	119	116

Source: Table 14.2.1

IMP=investigational medicinal product; OPC=opicapone

Of the 600 subjects randomised, 599 were treated (1 subject randomized to opicapone 50 mg did not start treatment), and 542 completed the study, with a similar proportion of subjects in each of the treatment groups. The 2 most common primary reasons for screening failures were ineligibility (37 subjects [5.4%]) and withdrawal of consent (28 subjects [4.1%]); any other reason occurred in ≤ 4 subjects.

Subjects were randomised in a 1:1:1:1:1 ratio across the treatment groups: 121 subjects for placebo, 122 for entacapone, 122 for opicapone 5 mg, 119 for opicapone 25 mg, and 116 for opicapone 50 mg. The completion rate was high and comparable across all treatment groups: 90.9% for placebo, 87.7% for entacapone, and between 90.2% and 92.2% for the 3 opicapone doses. The 2 most common reasons for discontinuation were AEs (6.6% for placebo, 6.6% for entacapone, 5.7% for opicapone 5 mg, 6.7% for opicapone 25 mg, and 4.3% for opicapone 50 mg) and withdrawal of consent (3.3% for placebo, 4.9% for entacapone, 2.5% for opicapone 5 mg, 3.4% for opicapone 25 mg, and 3.4% for Opicapone 50 mg).

Table 11 Reasons for discontinuation (Randomised set)

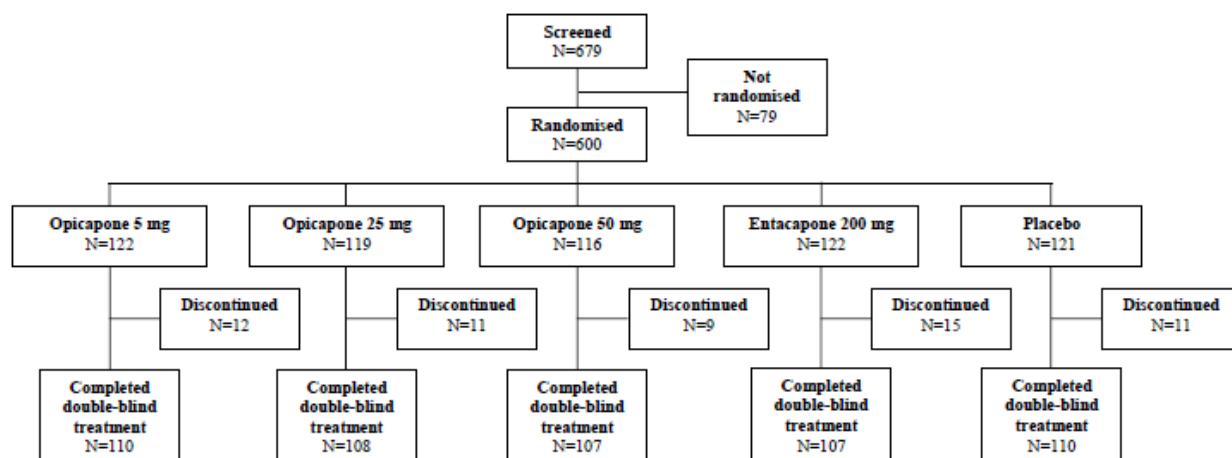
Discontinuation	Statistic	Placebo (N=121)	Entacapone (N=122)	OPC 5 mg (N=122)	OPC 25 mg (N=119)	OPC 50 mg (N=116)	Total OPC (N=357)
Total number of subjects who completed the study	n (%)	110 (90.9%)	107 (87.7%)	110 (90.2%)	108 (90.8%)	107 (92.2%)	325 (91.0%)
Total number of subjects who discontinued the study prematurely	n (%)	11 (9.1%)	15 (12.3%)	12 (9.8%)	11 (9.2%)	9 (7.8%)	32 (9.0%)
Reasons for discontinuation:							
Withdrawal of Consent	n (%)	4 (3.3%)	6 (4.9%)	3 (2.5%)	4 (3.4%)	4 (3.4%)	11 (3.1%)
Subject's Non-Compliance	n (%)	-	2 (1.6%)	1 (0.8%)	1 (0.8%)	-	2 (0.6%)
Protocol Violations	n (%)	1 (0.8%)	-	-	-	-	-
Adverse Events	n (%)	8 (6.6%)	8 (6.6%)	7 (5.7%)	8 (6.7%)	5 (4.3%)	20 (5.6%)
Deaths	n (%)	-	-	-	-	-	-
Safety or Ethical Reasons	n (%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.9%)	3 (0.8%)
Hypersensitivity Reactions	n (%)	1 (0.8%)	-	-	-	-	-
Sponsor's Discretion	n (%)	-	1 (0.8%)	1 (0.8%)	-	1 (0.9%)	2 (0.6%)
Ineligibility	n (%)	2 (1.7%)	2 (1.6%)	-	-	1 (0.9%)	1 (0.3%)
Pregnancy	n (%)	-	-	-	-	-	-
Unblinding of the IMP	n (%)	-	-	-	-	-	-
Other Reasons	n (%)	-	1 (0.8%)	3 (2.5%)	-	-	3 (0.8%)

Source: Table 14.1.2 and Listing 14.12.19

IMP=investigational medicinal product; OPC=opicapone

Notes: Percentages are based on the number of subjects in the Randomised set. Multiple reasons for discontinuation could be specified for a given subject.

The time course of drop-outs was comparable across all groups. Approximately half of the discontinuations occurred during the first month of treatment.

**Figure 4 Flow chart of subject disposition**

• Conduct of the study

There was no unblinding by Investigators during the DB period.

There was 1 request for an unblinding by the DSMB, in the case of a placebo subject who met Hy's Law criteria. The incidence of major protocol violations was generally similar across treatment groups (6.6% for placebo, 7.4% for opicapone 5 mg, 9.2% for opicapone 25 mg, and 7.8% for opicapone 50 mg), but was slightly higher in the entacapone group (13.1%) (Table below). This difference was due to a higher

incidence of subjects in the entacapone group with inadequate IMP compliance and changes in the L-DOPA/DDCI regimen, which according to protocol was to be kept stable between V4 and V7.

Table 12 Summary of major protocol violations (Randomised set)

Type of violation	Number (%) of subjects					
	Placebo (N=121)	Entacapone (N=122)	OPC 5 mg (N=122)	OPC 25 mg (N=119)	OPC 50 mg (N=116)	Total OPC (N=357)
Subjects with a Major Protocol Violation	8 (6.6%)	16 (13.1%)	9 (7.4%)	11 (9.2%)	9 (7.8%)	29 (8.1%)
Inclusion Criterion Deviation	5 (4.1%)	4 (3.3%)	2 (1.6%)	3 (2.5%)	2 (1.7%)	7 (2.0%)
IMP Treatment Compliance out of Interval [70% - 130%]	-	6 (4.9%)	4 (3.3%)	2 (1.7%)	1 (0.9%)	7 (2.0%)
Premature Termination the Study After Randomisation	-	2 (1.6%)	5 (4.1%)	1 (0.8%)	-	6 (1.7%)
Daily Dose of L-DOPA/DDCI Changes from V2 to V7	1 (0.8%)	5 (4.1%)	1 (0.8%)	2 (1.7%)	1 (0.9%)	4 (1.1%)
Prohibited Concomitant Medications Usage	-	-	-	2 (1.7%)	3 (2.6%)	5 (1.4%)
Exclusion Criterion Deviation	1 (0.8%)	-	-	1 (0.8%)	3 (2.6%)	4 (1.1%)
Other than L-DOPA/DDCI Anti-PD Medications Changes	1 (0.8%)	1 (0.8%)	2 (1.6%)	1 (0.8%)	-	3 (0.8%)
Partially Unblinded	-	-	-	2 (1.7%)	-	2 (0.6%)
Adherence of Last Available Diaries is <80%	-	1 (0.8%)	-	1 (0.8%)	-	1 (0.3%)
Unstable L-DOPA/DDCI According to the Subject Diaries	-	4 (3.3%)	-	-	-	-

Source: [Table 14.2.2](#)

DDCI=dopa decarboxylase inhibitor; IMP=investigational medicinal product; L-DOPA=levodopa; OPC=opicapone;
PD=Parkinson's disease; V=Visit

Note: Percentages are based on the number of subjects in the Randomised set.

No relevant differences were observed compared to the baseline L-DOPA medications for any of the 5 treatment groups, indicating that the vast majority of subjects kept the same LDOPA formulations throughout the DB treatment period.

At V4, the dose of L-DOPA had decreased relative to baseline in 4.2% of the placebo subjects compared to 8.3% of the entacapone, 12.6% of the opicapone 5 mg, 11.2% of the opicapone 25 mg, and 13.0% of the opicapone 50 mg subjects. Between V4 and endpoint, as required per protocol, very few subjects had changes in their L-DOPA dose. At endpoint, the mean L-DOPA reduction from baseline was similar in all active treatment groups (-25.5 mg in the entacapone group, -20.8 mg in the opicapone 5 mg group, -22.2 mg in the opicapone 25 mg group, and -33.2 mg in the opicapone 50 mg group) and higher than in placebo (-5.8 mg).

The incidence of concomitant anti-PD medications, excluding L-DOPA, that were used during the study in the FAS was almost identical to the incidence of those reported at baseline.

More than 65% of the subjects across the treatment groups used at least 1 concomitant non-anti-PD medication (78.5% of subjects in placebo, 75.4% of subjects in entacapone, 73.0% of subjects in the opicapone 5 mg, 76.5% of subjects in the opicapone 25 mg, and 68.7% of subjects in the opicapone 50 mg groups). The most common non-anti-PD medications by preferred drug name was acetylsalicylic acid, with a slightly higher incidence in the opicapone 25 mg group compared with the other treatment groups: 17.4% for placebo, 12.3% for entacapone, 11.5% for opicapone 5 mg, 22.7% for opicapone 25 mg, and 11.3% for opicapone 50 mg.

The majority of subjects ($\geq 91\%$) in all the treatment groups had a treatment compliance of between 80% and 120% at the daytime and the bedtime doses. There were 2 subjects in the entacapone group whose

daytime compliance was much greater than 120%. One subject had a compliance of 177% and had taken 2 capsules per intake instead of 1 for 3 visits. The other subject had a compliance of 149% which was due to losing 143 capsules over the period of several visits.

● **Numbers analysed**

Of the 600 subjects in the Randomised set, 599 subjects (99.8%) were included in the Safety set, 590 subjects (98.3%) in the FAS, and 537 subjects (89.5%) in the PP set (Table below). The efficacy analyses were made on the FAS and PP sets, while the safety analyses were made on the Safety set.

Table 13 Number of subjects per analysis set and reasons for exclusion from analysis sets (Randomised set)

	Statistic	Placebo (N=121)	Entacapone (N=122)	OPC 5 mg (N=122)	OPC 25 mg (N=119)	OPC 50 mg (N=116)	Total OPC (N=357)
Safety set ^a	n (%)	121 (100%)	122 (100%)	122 (100%)	119 (100%)	115 (99.1%)	356 (99.7%)
Number of Subjects Excluded From the Safety set	n (%)	-	-	-	-	1 (0.9%)	1 (0.3%)
Reasons for Exclusion from Safety set:							
Did Not Receive at Least One Dose of IMP	n (%)	-	-	-	-	1 (0.9%)	1 (0.3%)
Full Analysis set ^b	n (%)	120 (99.2%)	120 (98.4%)	119 (97.5%)	116 (97.5%)	115 (99.1%)	350 (98.0%)
Number of Subjects Excluded From the Full Analysis Set	n (%)	1 (0.8%)	2 (1.6%)	3 (2.5%)	3 (2.5%)	1 (0.9%)	7 (2.0%)
Reasons for Exclusion from Full Analysis Set:							
Did Not Receive at Least One Dose of IMP	n (%)	-	-	-	-	1 (0.9%)	1 (0.3%)
No post-baseline ON/OFF-time efficacy assessment	n (%)	1 (0.8%)	2 (1.6%)	3 (2.5%)	3 (2.5%)	-	6 (1.7%)
Per-protocol set ^c	n (%)	112 (92.6%)	104 (85.2%)	110 (90.2%)	105 (88.2%)	106 (91.4%)	321 (89.9%)
Number of Subjects Excluded From the Per-protocol Set	n (%)	9 (7.4%)	18 (14.8%)	12 (9.8%)	14 (11.8%)	10 (8.6%)	36 (10.1%)
Reasons for Exclusion from Per-protocol Analysis Set:							
Not in Full Analysis Set	n (%)	1 (0.8%)	2 (1.6%)	3 (2.5%)	3 (2.5%)	1 (0.9%)	7 (2.0%)
Major protocol violation	n (%)	8 (6.6%)	16 (13.1%)	9 (7.4%)	11 (9.2%)	9 (7.8%)	29 (8.1%)

Source: [Table 14.2.2](#).

IMP=investigational medicinal product; OPC=opicapone

a All randomised subjects who received at least 1 dose of investigational medicinal product.

b All randomised subjects who received at least 1 dose of investigational medicinal product and with at least 1 OFF-time efficacy assessment (Full Analysis set).

c All subjects in the Full Analysis set without major protocol deviations (Per-protocol set).

● **Baseline data**

The demographic characteristics at baseline were similar across the treatment groups in the Safety set, the FAS, and the PP set. In the Safety set, roughly 60% of subjects in all treatment groups were male, the mean age was between 63.5 years and 64.4 years, roughly 70% were younger than 70 years, and all subjects were Caucasian. The mean BMI ranged from 26.4 kg/m² to 27.1 kg/m².

Baseline PD characteristics did not differ significantly between the treatment groups for most characteristics (Table below). The mean duration of PD ranged between 6.99 and 7.71 years across the

treatment groups, and the onset of motor fluctuations began a mean of 2.16 to 2.32 years before subjects were included in the study.

Table 14 Baseline Parkinson's disease characteristics (FAS)

Characteristic	Statistics	Placebo (N=120)	Entacapone (N=120)	OPC 5 mg (N=119)	OPC 25 mg (N=116)	OPC 50 mg (N=115)
Time since PD diagnosis (years)	Mean (SD)	7.7 (4.19)	7.1 (4.12)	7.5 (3.59)	7.2 (4.14)	7.0 (3.84)
Time since start of motor fluctuations (years)	Mean (SD)	2.2 (1.87)	2.2 (2.13)	2.3 (2.32)	2.3 (2.51)	2.2 (2.29)
Incidence of dyskinesia ^a	n (%)	50 (41.7%)	51 (42.5%)	56 (47.1%)	49 (42.2%)	51 (44.3%)
OFF-time						
Absolute time (hours) ^b	Mean (SD)	6.2 (1.78)	6.5 (2.17)	6.7 (2.14)	6.9 (2.20)	6.2 (1.78)
% of total awake time	Mean (SD)	38.2 (10.84)	40.2 (12.89)	40.9 (12.25)	42.2 (12.94)	38.7 (10.45)
Total ON-time						
Absolute time (hours) ^b	Mean (SD)	10.0 (2.01)	9.6 (2.15)	9.7 (2.28)	9.4 (2.26)	9.9 (2.05)
% of total awake time	Mean (SD)	61.8 (10.84)	59.8 (12.89)	59.1 (12.25)	57.8 (12.94)	61.3 (10.45)
ON-time with non-troublesome dyskinesia						
Absolute time (hours) ^b	Mean (SD)	1.1 (1.76)	1.1 (1.66)	1.1 (1.95)	0.9 (1.82)	1.0 (1.91)
% of total awake time	Mean (SD)	6.8	6.8	6.8	5.3	6.2
ON-time with troublesome dyskinesia						
Absolute time (hours) ^b	Mean (SD)	0.4 (1.10)	0.3 (0.92)	0.4 (1.18)	0.3 (0.79)	0.3 (0.98)
% of total awake time	Mean (SD)	2.5 (6.72)	1.9 (6.52)	2.5 (6.99)	1.6 (4.86)	1.9 (5.91)
Total UPDRS (Part I, II [ON], III [ON])	Mean (SD)	37.6 (16.56)	35.4 (19.98)	38.2 (16.16)	40.1 (18.56)	38.8 (18.99)
UPDRS Part II (OFF)	Mean (SD)	18.6 (7.02)	18.0 (7.88)	17.8 (6.22)	18.5 (7.30)	18.9 (6.61)
UPDRS Part III (ON)	Mean (SD)	27.6 (11.68)	25.8 (13.80)	28.5 (11.90)	29.0 (12.93)	28.4 (13.74)
Modified H&Y (ON)	Mean (SD)	2.4 (0.51)	2.3 (0.55)	2.4 (0.42)	2.4 (0.52)	2.4 (0.52)
Schwab and England (ON)	Mean (SD)	82.6 (11.31)	82.5 (11.97)	82.9 (10.36)	81.9 (12.01)	82.9 (11.90)

Source: [Tables 14.4.2, 14.9.10, 14.11.1.5, 14.11.1.11, 14.11.1.23b, 14.11.1.29b, 14.11.1.17, 14.11.1.35, 14.11.1.41, 14.11.2.16, 14.11.2.1, 14.11.2.5, 14.11.2.8b, and 14.11.2.45.](#)

FAS=Full Analysis Set; H&Y=Hoehn and Yahr; OPC=opicapone; PD=Parkinson's disease; SD=standard deviation; UPDRS=Unified Parkinson's Disease Rating Scale

^a From Unified Parkinson's Disease Rating Scale question 32 at Visit 2: any subjects above >0

^b Converted to hours for better perception

The mean time since the start of L-DOPA treatment was similar across the treatment groups (ranging from 5.3 to 5.9 years) (Table below). While the majority of subjects in the FAS had a treatment duration of L-DOPA/DDCI of at least 1 year, the duration across the treatment groups ranged from 0.4 to 24.0 years. The minimum treatment duration of <1 year was due to 4 subjects who were major protocol violators because of this, but for 3 of these subjects, the Investigator explained that treatment had been >1 year with interruptions. The mean L-DOPA daily dose at baseline ranged from 642 mg/day to 695 mg/day across the treatment groups.

Table 15 Baseline anti-Parkinson's disease medications (FAS)

Characteristic	Statistic	Placebo (N=120)	Entacapone (N=120)	OPC 5 mg (N=119)	OPC 25 mg (N=116)	OPC 50 mg (N=115)
Time since start of L-DOPA (years)	Mean (SD)	5.8 (3.69)	5.6 (4.10)	5.8 (3.46)	5.9 (3.91)	5.3 (3.81)
L-DOPA mean daily dose (mg/day)	Mean (SD)	675 (302.1)	645 (329.7)	642 (310.3)	654 (324.3)	695 (337.5)
Subjects taking carbidopa with L-DOPA	n (%)	66 (55.0%)	64 (53.3%)	55 (46.2%)	59 (50.9%)	61 (53.0%)
Subjects taking benserazide with L-DOPA	n (%)	66 (55.0%)	61 (50.8%)	73 (61.3%)	62 (53.4%)	59 (51.3%)
Subjects taking both carbidopa and benserazide with L-DOPA	n (%)	12 (10.0%)	5 (4.2%)	9 (7.6%)	5 (4.3%)	5 (4.3%)
Subjects taking IR L-DOPA formulations	n (%)	114 (95.0%)	116 (96.7%)	111 (93.3%)	110 (94.8%)	112 (97.4%)
Subjects taking CR L-DOPA formulations	n (%)	44 (36.7%)	34 (28.3%)	44 (37.0%)	36 (31.0%)	34 (29.6%)
Subjects taking both IR and CR L-DOPA formulations	n (%)	38 (31.7%)	30 (25.0%)	36 (30.3%)	30 (25.9%)	31 (27.0%)
Subjects taking dopamine agonists	n (%)	88 (73.3%)	84 (70.0%)	69 (58.0%)	78 (67.2%)	79 (68.7%)
Subjects taking MAO inhibitors	n (%)	23 (19.2%)	28 (23.3%)	20 (16.8%)	24 (20.7%)	25 (21.7%)
Subjects taking anticholinergics	n (%)	7 (5.8%)	6 (5.0%)	3 (2.5%)	8 (6.9%)	8 (7.0%)
Subjects taking amantadine	n (%)	28 (23.3%)	29 (24.2%)	21 (17.6%)	29 (25.0%)	26 (22.6%)

Source: [Tables 14.5.8](#), [14.4.2](#), and [14.6.5](#).

CR=controlled release; FAS=Full Analysis Set; IR=immediate release; L-DOPA=levodopa; MAO=monoamine oxidase; SD=standard deviation

Table 16 Baseline anti-Parkinson's disease medications by descending frequency, other than L-DOPA (FAS)

ATC 2nd Level Subgroup	Number (%) of subjects					
	Placebo (N=120)	Entacapone (N=120)	OPC 5 mg (N=119)	OPC 25 mg (N=116)	OPC 50 mg (N=115)	Total OPC (N=350)
Subjects with Any Anti-PD Medication at baseline	99 (82.5)	96 (80.0)	83 (69.7)	95 (81.9)	94 (81.7)	272 (77.7)
N04 ANTI-PARKINSON DRUGS	99 (82.5)	96 (80.0)	83 (69.7)	95 (81.9)	94 (81.7)	272 (77.7)
PRAMIPEXOLE	43 (35.8)	29 (24.2)	34 (28.6)	35 (30.2)	39 (33.9)	108 (30.9)
ROPINIROLE	35 (29.2)	40 (33.3)	26 (21.8)	34 (29.3)	34 (29.6)	94 (26.9)
AMANTADINE	28 (23.3)	29 (24.2)	21 (17.6)	29 (25.0)	26 (22.6)	76 (21.7)
RASAGILINE	14 (11.7)	22 (18.3)	12 (10.1)	16 (13.8)	17 (14.8)	45 (12.9)
SELEGILINE	9 (7.5)	6 (5.0)	8 (6.7)	8 (6.9)	8 (7.0)	24 (6.9)
PIRIBEDIL	4 (3.3)	6 (5.0)	4 (3.4)	5 (4.3)	4 (3.5)	13 (3.7)
BIPERIDEN	4 (3.3)	5 (4.2)	2 (1.7)	4 (3.4)	5 (4.3)	11 (3.1)
ROTIGOTINE	4 (3.3)	10 (8.3)	7 (5.9)	2 (1.7)	2 (1.7)	11 (3.1)
TRIHENYPHENIDYL	3 (2.5)	1 (0.8)	1 (0.8)	3 (2.6)	3 (2.6)	7 (2.0)
BROMOCRIPTINE	2 (1.7)	1 (0.8)	-	1 (0.9)	-	1 (0.3)
CABERGOLINE	1 (0.8)	-	-	1 (0.9)	-	1 (0.3)
METIXENE	-	-	-	1 (0.9)	-	1 (0.3)
BUDIPINE	1 (0.8)	-	-	-	-	-

Source: Table 14.5.11a.

ATC=Anatomical Therapeutic Chemical Classification System; FAS=Full Analysis Set; L-DOPA=levodopa; OPC=opicapone; PD=Parkinson's disease

Notes: Medications were classified according to "primary" 2nd level ATC codes. Table excludes medications with substance name containing levodopa or melevodopa.

The highest incidence of ongoing medical conditions was reported in the SOC Vascular Disorders for all treatment groups: 50.4% for placebo, 52.5% for entacapone, 54.9% for opicapone 5 mg, 52.1% for opicapone 25 mg, and 47.0% for opicapone 50 mg. The most frequently reported medical conditions for all treatment groups were obesity (19.0% for placebo, 16.4% for entacapone, 14.8% for opicapone 5 mg, 18.5% for opicapone 25 mg, and 18.3% for opicapone 50 mg) and hypertension (39.7% for placebo, 45.9% for entacapone, 45.1% for opicapone 5 mg, 47.1% for opicapone 25 mg, and 32.2% for opicapone 50 mg).

The most commonly used anti-PD medications prior to enrolling in the study (stopped in the study and excluding LDOPA) were pramipexole, ropinirole, and amantadine in all treatment groups.

No subject was reported to have prior use of entacapone or tolcapone.

The highest incidence of ongoing medical conditions was reported in the SOC Vascular Disorders for all treatment groups: 50.4% for placebo, 52.5% for entacapone, 54.9% for opicapone 5 mg, 52.1% for opicapone 25 mg, and 47.0% for opicapone 50 mg. The most frequently reported medical conditions for all treatment groups were obesity (19.0% for placebo, 16.4% for entacapone, 14.8% for opicapone 5 mg, 18.5% for opicapone 25 mg, and 18.3% for opicapone 50 mg) and hypertension (39.7% for placebo, 45.9% for entacapone, 45.1% for opicapone 5 mg, 47.1% for opicapone 25 mg, and 32.2% for opicapone 50 mg).

● **Primary Efficacy Measure**

The estimated mean change (LS means) from baseline in absolute OFF-time at endpoint was largest in the opicapone 50 mg group (-116.8 minutes), followed by entacapone (-96.3 minutes), opicapone 5 mg (-91.3 minutes) and opicapone 25 mg (-85.9 minutes) groups, and was smallest in the placebo group (-56.0 minutes) in the FAS. Similar results were seen in the PP set.

Table 17 Absolute OFF-time (minutes): summary of primary analyses for change from baseline to endpoint

Treatment comparison	N	LS mean (SE)	95% CI	p-value*	critical value
Placebo	120	-56.0 (13.38)	(-83.0, -29.4)		
OPC 5mg	119	-91.3 (13.46)	(-119.7, -65.6)		
OPC 25mg	116	-85.9 (13.69)	(-121.6, -66.0)		
OPC 50mg	115	-116.8 (13.97)	(-143.8, -87.5)		
Entacapone 200mg	120	-96.3 (13.40)	(-117.5, -61.3)		
Test for superiority					
OPC 5mg vs. placebo		-35.2 (18.38)	(-71.4, 0.9)	0.059	0.025
OPC 25mg vs. placebo		-29.9 (18.54)	(-66.3, 6.5)	0.107	0.025
OPC 50mg vs. placebo		-60.8 (18.52)	(-97.2, -24.4)	0.001	0.0167
Test for non-inferiority (FAS)					
OPC 5mg vs. placebo		5.0 (18.32)	(-31.0, 41.0)	0.173	N/A
OPC 25mg vs. placebo		10.3 (18.46)	(-25.9, 46.6)	0.287	N/A
OPC 50mg vs. placebo		-20.5 (18.51)	(-56.9, 15.8)	0.007	0.0167
Test for non-inferiority (PP)					
OPC 5mg vs. placebo		-3.2 (18.92)	(-40.4, 33.9)	0.080	N/A
OPC 25mg vs. placebo		-4.4 (19.15)	(-42.0, 33.2)	0.073	N/A
OPC 50mg vs. placebo		-26.2 (19.13)	(-63.8, 11.4)	0.003	0.0167

* 2-sided p-values obtained by doubling the 1-sided values provided by the company

The results of the gatekeeping procedure in each sequence of tests were as follows:

Step 1: As the smallest p-value was observed for the comparison of opicapone 50 mg vs. placebo in the FAS, the procedure started with this comparison. The p-value was $p=0.001$ (2-sided) which was less than the threshold of $p=0.167$ so superiority of opicapone 50mg over placebo has been demonstrated

Step 2: The next primary test in the sequential procedure was the non-inferiority comparison of opicapone 50 mg vs. entacapone. The non-inferiority margin was 30 minutes. The company planned that non-inferiority tests should be done in the per-protocol (PP) set, however they should be done for both the FAS and the PP set, with similar conclusions needing seen for both analyses. In both populations the

p-value was less than the threshold of 0.0167, so non-inferiority of opicapone 50mg to entacapone 200mg has been shown. The estimates of the difference (-26.2 minutes (PP) and -20.5 (FAS)) indicates a tendency for greater OFF-time reductions compared to entacapone.

Step 3: The next step was the comparison of opicapone 5 mg vs. placebo in the FAS. The critical value for this test was 2-sided 0.025, but the p-value was 0.059 so superiority was not shown.

Step 4: Simultaneously, the superiority of opicapone 25 mg vs. placebo was tested in the FAS. Similarly the p-value of 0.107 was not smaller than the threshold of 0.025 so superiority was not shown.

Step 5: As Step 3 and 4 are not significant, the remaining 2 non-inferiority hypotheses of opicapone 5 and 25 mg vs. entacapone could not be tested in the gatekeeping procedure.

The ANCOVA in the FAS and the PP set shows significant differences between regions (FAS: $p=0.0012$, PP: $p=0.0044$) and a strong dependencies of outcomes on baseline OFF time ($p<0.0001$ each).

Sensitivity and Subgroup Analyses

In all of the exploratory ANCOVA models performed to test the robustness of the primary analysis, the results were comparable in terms of the direction and magnitude of effect sizes to the primary analysis, and collectively support its results:

If the primary analysis model is repeated without adjustment for baseline OFF-time, the change in LS mean OFF-time was superior to placebo in all 3 opicapone treatment groups ($p<0.007$ in the FAS, $p<0.006$ in the PP set) and was non-inferior to entacapone in the 50 mg opicapone group in the FAS (upper bound of 95% CI <30 minutes) and in the 50 mg and the 25 mg opicapone groups in the PP set.

If, in addition to the effects and covariates in the primary model, age and BMI were used as covariates, the change in LS mean OFF-time was superior to placebo in the Opicapone 50 mg and 5 mg groups ($p \leq 0.0223$ in the FAS) and in all 3 opicapone groups in the PP set ($p<0.03$) and was non-inferior to entacapone in the opicapone 50 mg group (upper bound of 95% CI <30 minutes) in the FAS and the PP set.

If country was added instead of region to the primary analysis model, the change in LS mean OFF-time was superior to placebo in the opicapone 50 mg group ($p=0.0015$ in the FAS, $p=0.0018$ in the PP set) and was non-inferior to entacapone in the 50 mg Opicapone group (upper bound of 95% CI <30 minutes) in the FAS and the PP set.

The mean change from baseline to endpoint in absolute OFF-time provides a further crude estimate of the treatment effect in each group.

Table 18 Absolute OFF-time (minutes): summary statistics for change from baseline to endpoint (Full Analysis Set)

Characteristic	Statistic	Placebo (N=120)	Entacapone (N=120)	OPC 5 mg (N=119)	OPC 25 mg (N=116)	OPC 50 mg (N=115)
Baseline	Mean	370.1	387.6	403.2	411.2	372.2
	SD	106.72	130.47	128.10	132.29	106.95
Change from Baseline to Endpoint	Mean	-44.8	-93.5	-96.0	-94.5	-106.8
	SD	160.76	155.55	149.09	162.02	134.20

Source: Table 14.9.10

OPC=opicapone; SD=standard deviation

Sensitivity analyses were performed on the primary endpoint using MMRM to account for missing data and early discontinuations in both the FAS and the PP set. As expected due to the low number of dropouts,

in all of the different MMRM analyses in both the FAS and the PP set, results were comparable and consistent with the primary LOCF analysis.

There were 408 subjects who were <70 years old and 182 subjects who were ≥ 70 years old in the FAS. Although there was a strong placebo response in subjects ≥ 70 years (LS mean change in OFF-time at endpoint -42.4 minutes in subjects <70 years compared to -81.5 minutes in subjects ≥ 70 years), the relative difference between treatment groups in the change from baseline to endpoint in absolute OFF-time was similar in both elderly and non-elderly subjects and consistent with the results in the overall FAS. The greatest decrease in both subgroups was in the opicapone 50 mg group.

There were 346 male subjects and 244 female subjects in the FAS assessed for change in absolute OFF-time. Although the change from baseline to endpoint in absolute OFF-time was consistently higher in most of the active treatment groups in females (LS mean difference ranged from -81.8 minutes in opicapone 5 mg group to -136.3 minutes in the opicapone 50 mg group) than in males (LS mean difference ranged from -65.7 minutes in opicapone 25 mg group to -102.9 minutes in the opicapone 50 mg group), the relative difference between treatment groups was similar in both genders and consistent with the results in the overall FAS.

There were 244 subjects whose UPDRS Part V score was <2.5 at baseline and 346 subjects whose score was ≥ 2.5 . Although there was a strong placebo response in subjects whose UPDRS V status was ≥ 2.5 (LS mean change in OFF-time at endpoint -29.6 minutes in subjects <2.5 compared to -77.7 minutes in subjects ≥ 2.5), the relative difference between treatment groups in the change from baseline to endpoint in absolute OFF-time was similar in both subgroups and consistent with the results in the overall FAS and the greatest decrease in both subgroups was in the opicapone 50 mg group.

There were 381 subjects whose disease duration was <8 years and 209 subjects whose disease duration was ≥ 8 years. Although there was a strong placebo response in subjects whose disease duration was ≥ 8 years (LS mean change in OFF-time at endpoint -34.4 minutes in subjects <8 years compared to -90.5 minutes in subjects ≥ 8 years), the relative difference between treatment groups in the change from baseline to endpoint in absolute OFF-time was similar in both subgroups and consistent with the results in the overall FAS and the greatest decrease in both subgroups was in the opicapone 50 mg group.

There were 355 subjects whose mean L-DOPA daily dose at baseline was <700 mg/day and 235 subjects for whom it was ≥ 700 mg/day. Except for the placebo group in the <700 mg group, which had a smaller decrease than in the overall population, the change from baseline to endpoint in absolute OFF-time was similar across treatment groups in both subgroups and consistent with the results in the overall FAS and the greatest decrease in both subgroups was in the opicapone 50 mg group.

There were 398 subjects who were using the IR formulation of L-DOPA at baseline, 27 subjects using the CR formulation, and 165 subjects using a combination of the IR and CR formulations. The relative difference between treatment groups in the change from baseline to endpoint in absolute OFF-time was similar in all 3 subgroups for L-DOPA formulation (IR, CR, and IR plus CR) and consistent with the results in the overall FAS, with the greatest decrease seen in the opicapone 50 mg group.

There were 398 subjects who had concurrent use of dopamine agonists at baseline and 192 subjects who did not. Although the change from baseline to endpoint in absolute OFF-time was unusually high in the opicapone 5 mg group of subjects who had concurrent use of dopamine agonists at baseline (LS mean change -116.2 minutes vs. -54.9 minutes in subjects without dopamine agonists at baseline), in all of the other treatment groups, the relative difference between treatment groups was similar in both subgroups and consistent with the results in the overall FAS and the greatest decrease in both subgroups was in the opicapone 50 mg group in the IR and the IR plus CR subgroups.

There were 97 subjects who had concurrent use with MAO inhibitors and dopamine agonists at baseline and 493 subjects who did not. All of the opicapone treatment groups in the subgroup of subjects who were using MAO inhibitors and dopamine agonists at baseline had a smaller change from baseline to endpoint in absolute OFF-time (LS mean change -66.4 minutes for opicapone 5 mg, -38.1 minutes for opicapone 25 mg, and -85.7 minutes for opicapone 50 mg) than in the subgroup of subjects who were not using MAO inhibitors and dopamine agonists (LS mean change -95.6 minutes for opicapone 5 mg, -94.9 minutes for opicapone 25 mg, and -124.3 minutes for opicapone 50 mg). In contrast, the change was higher in the entacapone group in subjects who were using MAO inhibitors and dopamine agonists at baseline (-114.7 minutes) than in those who were not using MAO inhibitors and dopamine agonists at baseline (-92.5 minutes). In the placebo groups, the change was similar in both subgroups. Nonetheless, the statistical model assessing the use of MAO inhibitors and dopamine agonists at baseline showed that there was neither an effect of the using these ($p=0.2057$) nor an interaction for concurrent use with MAO inhibitors and dopamine agonists with treatment ($p=0.5137$). The sample size of the subgroup of subjects who were using MAO inhibitors and dopamine agonists at baseline is small, and these differences need to be interpreted with caution.

There were 36 subjects in the subgroup of Western Europe, 88 subjects in the subgroup of Southern Europe, 192 subjects in the subgroup of North Eastern Europe, 112 subjects in the subgroup of Russia and the Ukraine, and 162 subjects in the subgroup of South Eastern Europe. The sample size of some of the regional subgroups (i.e. Western Europe and Southern Europe) were thus very small and preclude a clear interpretation of the regional differences by subgroup. Although there was a regional effect ($p=0.0012$), this was probably due to the small subgroup of Western Europe, as the other regions were generally consistent with each other. However, in general the relative difference between treatment groups in the change from baseline to endpoint in absolute OFF-time was consistent with the results in the overall FAS.

- **Assay Sensitivity**

Assay sensitivity of the study is demonstrated by the comparison of entacapone to placebo. Entacapone was also superior to placebo, with a treatment difference of -40.3 minutes ($p=0.0141$, an exploratory, unadjusted, 1-sided t-test at a 2.5% level of significance).

- **Other Analyses**

Proportion of OFF-time and ON-time Responders at Endpoint

An OFF-time responder was defined as a subject who had a reduction of at least 1 hour in absolute OFF-time from baseline to endpoint. An ON-time responder was defined as a subject who had an increase of at least 1 hour in absolute total ON-time. Compared to placebo (47.5%), the proportion of OFF-time responders in the FAS was significantly higher in the opicapone 25 mg group (60.3%, $p=0.0464$) and the opicapone 50 mg group (69.6%, $p=0.0011$). Likewise, the proportion of ON-time responders was significantly higher in the opicapone 50 mg group than in the placebo group (65.2% vs 45.8%, $p=0.0028$).

Table 19 OFF- and ON-time responder rates at endpoint (Full Analysis Set)

Characteristic	Statistic	Placebo (N=120)	Entacapone (N=120)	OPC 5 mg (N=119)	OPC 25 mg (N=116)	OPC 50 mg (N=115)
OFF-time Reduction						
Responders	n (%)	57 (47.5%)	70 (58.3%)	71 (59.7%)	70 (60.3%)	80 (69.6%)
Non-responders	n (%)	63 (52.5%)	50 (41.7%)	48 (40.3%)	46 (39.7%)	35 (30.4%)
Missing	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Difference with placebo						
CMH-test vs. Placebo	p-value	-	0.0938	0.0650	0.0464	0.0011
Breslow-Day test	p-value	-	0.6600	0.7738	0.0789	0.8330
Difference with entacapone						
CMH test vs. Entacapone	p-value	-	-	0.8206	0.7386	0.0626
Breslow-Day test	p-value	-	-	0.7951	0.2284	0.8134
ON-time Increase						
Responders	n (%)	55 (45.8%)	69 (57.5%)	65 (54.6%)	66 (56.9%)	75 (65.2%)
Non-responders	n (%)	65 (54.2%)	51 (42.5%)	54 (45.4%)	50 (43.1%)	40 (34.8%)
Missing	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Difference with placebo						
CMH-test vs. Placebo	p-value	-	0.0672	0.1690	0.0947	0.0028
Breslow-Day test	p-value	-	0.5320	0.7654	0.5339	0.4686
Difference with entacapone						
CMH test vs. Entacapone	p-value	-	-	0.6587	0.9293	0.1479
Breslow-Day test	p-value	-	-	0.6973	0.3315	0.7515

Source: [Table 14.11.1.1](#).

CMH=Cochran-Mantel-Haenszel-test, stratified by region; OPC=opicapone

Similar findings were observed in the PP set.

Change from Baseline to Endpoint of the Different ON-time States (Absolute Values)

The LS mean change at endpoint of total ON-time (sum of all ON-times) was highest in the opicapone 50 mg group (119.0 minutes), was similar in the entacapone (99.7 minutes) and the opicapone 5 mg (90.3 minutes) and 25 mg groups (86.1 minutes), and was lowest in the placebo group (47.1 minutes). This difference to placebo was statistically significant for all 3 opicapone groups ($p < 0.05$). The difference between the opicapone and entacapone groups was not statistically significant.

Table 20 Change from baseline to endpoint of the different ON-time states (absolute changes - minutes): statistical analysis (LOCF) (Full Analysis Set)

Parameter	Placebo (N=120)	Entacapone (N=120)	OPC 5 mg (N=119)	OPC 25 mg (N=116)	OPC 50 mg (N=115)
Total ON-time (Sum of All ON-times)					
Summary Statistics					
Mean	35.6	98.8	86.9	90.3	110.7
Median	50.0	100.0	75.0	75.0	100.0
Min/Max	-440/470	-360/505	-340/460	-495/670	-210/440
ANCOVA analysis					
LS Mean	47.1	99.7	90.3	86.1	119.0
Difference with placebo					
LS Mean	-	52.6	43.2	39.0	71.9
95% CI	-	(16.1, 89.1)	(6.7, 79.8)	(2.1, 75.9)	(35.0, 108.8)
p-value	-	0.0048	0.0205	0.0383	0.0001
Difference with entacapone					
LS Mean	-	-	-9.4	-13.6	19.3
95% CI	-	-	(-45.9, 27.1)	(-50.4, 23.1)	(-17.6, 56.2)
ON-time Without Troublesome Dyskinesia					
Summary Statistics					
Mean	35.0	93.3	82.3	88.8	100.5
Median	40.0	90.0	70.0	75.0	100.0
Min/Max	-440/510	-360/505	-470/460	-495/670	-400/425
ANCOVA analysis					
LS Mean	46.5	94.1	85.9	84.7	109.1
Difference with placebo					
LS Mean	-	47.6	39.4	38.2	62.6
95% CI	-	(9.3, 86.0)	(1.0, 77.8)	(-0.6, 77.0)	(23.8, 101.4)
p-value	-	0.0150	0.0442	0.0535	0.0016
Difference with entacapone					
LS Mean	-	-	-8.2	-9.4	15.0
95% CI	-	-	(-46.6, 30.1)	(-48.0, 29.1)	(-23.8, 53.7)
ON-time With Troublesome Dyskinesia					
Summary Statistics					
Mean	0.6	5.5	4.7	1.4	10.2
Median	0.0	0.0	0.0	0.0	0.0
Min/Max	-405/560	-410/240	-240/255	-270/355	-205/480
ANCOVA analysis					
LS Mean	0.6	5.6	4.4	1.4	9.9
Difference with placebo					
LS Mean	-	5.0	3.8	0.8	9.3
95% CI	-	(-11.2, 21.2)	(-12.4, 20.0)	(-15.5, 17.2)	(-7.0, 25.7)
p-value	-	0.5436	0.6436	0.9219	0.2635
Difference with entacapone					
LS Mean	-	-	-1.2	-4.2	4.3
95% CI	-	-	(-17.4, 15.0)	(-20.5, 12.1)	(-12.0, 20.7)

Source: Tables 14.11.1.13, 14.11.1.15, 14.11.1.25, 14.11.1.27, 14.11.1.37, and Table 14.11.1.39.

ANCOVA=analysis of covariance; CI=confidence interval; LOCF=last post-baseline observation carried forward; LS=least squares; Max=maximum; Min=minimum; OPC=opicapone

The results seen in the PP analyses were generally similar to those observed in the FAS analysis.

ON-time Changes from Baseline by Study Visit

The by-visit changes in absolute total ON-time (sum of all ON-times) reflect the inverse trends of those seen for absolute OFF-time. In the opicapone 50 mg and the entacapone groups in the FAS, the mean absolute ON-time continued to increase after baseline until V4, after which it remained relatively constant. In the opicapone 5 mg and 25 mg groups, the mean absolute ON-time continued to increase

until V5, after which it remained relatively constant. The placebo group had a minor increase initially, and then remained relatively constant for the rest of the study. Similar results were seen in the PP set.

The change by visit in ON-time without troublesome dyskinesia (the sum of ON without dyskinesia and with non-troublesome dyskinesia) and ON-time without dyskinesia was similar to the pattern seen for the sum of all ON-times. For ON-time with non-troublesome dyskinesia, the mean change by visit was variable across the treatment groups. In the opicapone 50 mg group the mean change ranged between 16.3 and 31.4 minutes across all visits, with a change at endpoint of 18.4 minutes. In the entacapone group the mean change was between 13.0 and 20.4 minutes at most visits, with a change at endpoint of 11.0 minutes.

Change in Percentage OFF- and ON-time

OFF- and ON-time percentages were calculated as the percentage of each time state in relation to total awake time, based on subject's diaries. The LS means were highest for the opicapone 50 mg group (-12.1%), followed by entacapone (-10.3%), opicapone 5 mg (-9.1%), opicapone 25 mg (-8.8%), and lowest for placebo (-5.6%). The difference for the comparison with placebo was statistically significant for the opicapone 50 mg group (p-value = 0.0007) and entacapone (p-value = 0.013).

Table 21 Change from baseline in percentage of OFF-time (relative to total awake time) at endpoint: statistical analysis (LOCF) (Full Analysis Set)

Parameter	Placebo (N=120)	Entacapone (N=120)	OPC 5 mg (N=119)	OPC 25 mg (N=116)	OPC 50 mg (N=115)
Summary Statistics					
Mean	-4.6	-10.0	-9.4	-9.5	-11.1
Median	-3.7	-9.4	-8.9	-7.7	-11.4
Min/Max	-51/42	-54/50	-54/27	-58/51	-57/19
ANCOVA analysis					
LS Mean	-5.6	-10.3	-9.1	-8.8	-12.1
Difference with placebo					
LS Mean	-	-4.7	-3.4	-3.2	-6.5
95% CI	-	(-8.3, -1.0)	(-7.1, 0.2)	(-6.9, 0.5)	(-10.2, -2.7)
p-value	-	0.0130	0.0675	0.0940	0.0007
Difference with entacapone					
LS Mean	-	-	1.2	1.5	-1.8
95% CI	-	-	(-2.5, 4.9)	(-2.2, 5.2)	(-5.5, 1.9)

Source: [Table 14.11.1.7](#) and [14.11.1.9](#).

ANCOVA=analysis of covariance; CI=confidence interval; LOCF=last post-baseline observation carried forward; LS=least squares; Max=maximum; Min=minimum; OPC=opicapone

The ANCOVA results for the sum of percentage total ON-time were generally consistent with the analyses using absolute values.

Similar results were seen for the percentage of ON-time without troublesome dyskinesia and ON-time without dyskinesia

UPDRS

The UPDRS was only analysed in the FAS.

The mean decreases from baseline to endpoint in total UPDRS were similar across all treatment groups, with LS means of -5.4 for placebo, -6.1 for entacapone, -7.3 for opicapone 5 mg, -7.0 for opicapone 25 mg, and -6.1 for opicapone 50 mg. None of the differences between active groups and placebo were statistically significant.

The changes from baseline to endpoint in UPDRS Part I were small and similar across all treatment groups, with LS means of -0.2 for placebo, -0.3 for entacapone, -0.3 for Opicapone 5 mg, -0.4 for opicapone 25 mg, and -0.1 for opicapone 50 mg. None of the differences between active groups and placebo were statistically significant.

The changes from baseline to endpoint in UPDRS Part II (OFF) were small and similar across all treatment groups, with LS means of -2.4 for placebo, -3.1 for entacapone, -2.8 for opicapone 5 mg, -3.1 for opicapone 25 mg, and -3.0 for opicapone 50 mg.

The changes from baseline to endpoint in UPDRS Part II + III (ON) were similar across all treatment groups, with LS means of -5.1 for placebo, -5.8 for entacapone, -7.0 for Opicapone 5 mg, -6.9 for opicapone 25 mg, and -6.0 for opicapone 50 mg. None of the differences between active groups and placebo were statistically significant.

The changes from baseline to endpoint in UPDRS Part II (ON) were similar across all treatment groups, with LS means of -1.4 for placebo, -1.5 for entacapone, -1.5 for Opicapone 5 mg, -1.9 for opicapone 25 mg, and -1.6 for opicapone 50 mg. None of the differences between active groups and placebo were statistically significant.

The changes from baseline to endpoint in UPDRS Part III (ON) were similar across all treatment groups, with LS means of -3.7 for placebo, -4.4 for entacapone, -5.5 for Opicapone 5 mg, -5.0 for opicapone 25 mg, and -4.5 for opicapone 50 mg. The p-value for the comparison between opicapone 5 mg and placebo was statistically significant ($p=0.0497$). None of the differences between other active groups and placebo were statistically significant.

UPDRS Dyskinesia, Tremor, Rigidity, Bradykinesia, Postural Instability and Gait Disturbance, and Freezing Subscores - No relevant differences were observed between the opicapone groups and placebo or entacapone. None of the differences between groups were statistically significant.

UPDRS Part V (ON, Modified Hoehn and Yahr) - The majority of subjects in all treatment groups had a score of between 2 and 3 at baseline and at endpoint.

UPDRS Part VI (Schwab and England Activities of Daily Living) - The changes from baseline to endpoint in UPDRS Part VI were small and similar across all treatment groups. None of the differences between groups were statistically significant.

Parkinson's Disease Sleep Scale (PDSS)

The post-baseline PDSS total scores improved across all groups with greater changes observed for the opicapone (2.89 in the 50 mg, 5.51 in the 25 mg, and 5.19 in the 5 mg groups) and entacapone groups (2.86) compared to placebo (1.04), however, there were no statistically significant differences between any of the groups them.

Parkinson's Disease Quality of Life Questionnaire (PDQ-39)

The post-baseline PDQ-39 total scores decreased in all groups, indicating a better perceived health status. At endpoint, LS mean changes from baseline were -4.1 for the opicapone 5 mg treatment group, -2.5 for opicapone 25 mg, -2.8 for opicapone 50 mg, and -4.0 for entacapone, and -2.6 for placebo. No significant differences between treatment groups were observed.

Non-Motor Symptoms Scale (NMSS)

The post-baseline NMSS total scores decreased in all treatment groups, indicating less disability in non-motor domains. At endpoint, LS mean changes from baseline were -5.6 for the opicapone 5 mg

treatment group, -4.2 for opicapone 25 mg, -2.0 for opicapone 50 mg, -4.7 for entacapone, and -5.7 for placebo. No significant differences between treatment groups were observed.

Investigator's Global Assessment of Change

A higher proportion of opicapone-treated subjects was assessed as having improved at endpoint (73.0% opicapone 50 mg, 60.3% opicapone 25 mg and 62.2% opicapone 5 mg) compared to entacapone (50.9%) and placebo (49.9%). The p-values for the comparisons to placebo indicate a significant difference for the opicapone 25 mg ($p=0.0339$) and 50 mg groups ($p=0.0005$). The p-values for the comparisons between opicapone and entacapone indicate a significant difference favouring the opicapone 50 mg group ($p=0.0070$).

Subject's Global Assessment of Change

A higher proportion of opicapone-treated subjects was assessed as having improved (comprising minimally, much, and very much improved) at endpoint (72.1% opicapone 50 mg, 63.7% opicapone 25 mg and 64.7% opicapone 5 mg) compared to entacapone (52.5%) and placebo (50.9%). The p-values for the comparisons to placebo indicate a significant difference for all 3 opicapone groups ($p=0.0177$ for 5 mg, $p=0.0055$ for 25 mg, and $p=0.0008$ for 50 mg). The p-values for the comparisons between opicapone and entacapone indicate a significant difference favouring the opicapone 25 mg ($p=0.0370$) and 50 mg groups ($p=0.0091$).

2.5.4.2. Study BIA-91067-302

"Efficacy and Safety of BIA 9-1067 in Idiopathic Parkinson's Disease Patients with "Wearing-Off" Phenomenon treated with Levodopa plus a Dopa Decarboxylase Inhibitor (DDCI): a Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, Multicentre Clinical Study"

Methods

● **Objectives**

The primary objective was to investigate the efficacy of two different doses (25 mg and 50 mg) of OPC, administered once a day, compared with placebo, when administered with the existing treatment of L-DOPA plus a DDCI, in subjects with PD and end-of-dose motor fluctuations.

The secondary objective was to investigate the safety and tolerability of OPC in comparison to placebo when administered with the existing treatment of L-DOPA/DDCI.

Study Design

The study was designed to include two periods, a double-blind (DB) period and an open-label (OL) period. This part of the assessment covers only the DB phase of the study.

This was a multicentre, DB, randomized, placebo-controlled, parallel-group Phase III study of OPC as an adjunctive treatment to L-DOPA/DDCI, conducted in adults diagnosed with idiopathic PD (Part I of the study).

The study was conducted at 71 sites globally located in 12 countries.

The study consisted of a screening period of one to two weeks, after which subjects were to enter a 14- to 15-week DB period. At the end of the DB period, as applicable, subjects could then enter an additional one year, OL extension period in which all subjects were treated with OPC. The total duration of treatment for an individual subject in this study was therefore up to 67 weeks.

The diagram illustrates the study timeline, divided into three main phases: Screening Period, Double-blind Period, and Open-label extension Period.

- Screening Period:** Includes the SCR Visit at Visit 1 (V1).
- Double-blind Period:**
 - Randomization occurs at Visit 2 (V2, Day 0).
 - Treatment groups are assigned: BIA 9-1067 25 mg, BIA 9-1067 50 mg, or Placebo.
 - Stable L-Dopa regimen is maintained from V2 to V4.
 - Adjustment of L-Dopa/DOPA at Investigator's discretion occurs between V4 and V7.
 - Stable L-Dopa regimen is maintained from V7 to V10.
 - Adjustment of L-Dopa/DOPA at Investigator's discretion occurs between V10 and V14.
- Open-label extension Period:**
 - Up-titration to 50 mg BIA 9-1067 if the "wearing-off" is not sufficiently controlled if unacceptable dopaminergic AEs appear, the L-DOPA dose should be adjusted first and only then, if not sufficient, the BIA 9-1067 dose can be down titrated.
 - Stable BIA 9-1067 and L-Dopa dose should be stable from V14 onwards.

Visits and corresponding days are marked along the timeline:

- V1: Day 0
- V2: Day 0
- V3: Day 7 ± 1 of V2
- V4: Day 21 ± 3 of V2
- V5: Day 28 ± 3 of V4
- V6: Day 56 ± 3 of V4
- V7: Day 84 ± 3 of V4
- V8: Day 7 ± 1 of V7
- V9: Day 28 ± 3 of V7
- V10: Day 56 ± 3 of V7
- V11: Day 112 ± 5 of V7
- V12: Day 210 ± 5 of V7
- V13: Day 322 ± 5 of V7
- V14: Day 365 ± 5 of V7

The DB period was to last from 14 to 15 weeks and the last visit in the DB period was V7, which was to take place 12 weeks after V4.

Following are the inclusion criteria which were confirmed at two points in the study.

V1 (screening, up to 14 days before V2)

1. Able to comprehend and willing to sign an ICF.

2. Male and female subjects between 30 and 83 years old, inclusive (see Section 9.8.1.3).
3. Diagnosed with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria for at least three years.
4. Disease severity Stages I-III (modified Hoehn &Yahr staging) at ON.
5. Treated with L-DOPA/DDCI for at least one year with clear clinical improvement.
6. Treated with three to eight daily doses of L-DOPA/DDCI, which could include a slow-release formulation.
7. On a stable regimen of L-DOPA/DDCI and other anti-PD drugs for at least four weeks before screening.
8. Signs of "wearing-off" phenomenon (end-of-dose deterioration) for a minimum of four weeks before screening with average total daily OFF time while awake of at least 1.5 hours, excluding the early morning pre-first dose OFF, despite optimal anti-PD therapy (based on the Investigator's judgment).
9. Able to distinguish their own motor states and able to keep reliable diaries of motor fluctuations, alone or with family/caregiver assistance (based on the Investigator's judgment).
10. Amenorrheic for at least one year or surgically sterile for at least six months before screening. Females of childbearing potential had to be using an effective non-hormonal contraceptive method.

11. Had filled-in self-rating diary charts in accordance with the diary chart instructions and with ≤ 3 errors per day, in three days preceding V2.

12. With at least 1.5 OFF hours per day, excluding the early morning pre-first dose OFF period (i.e. the time between wake-up and response to the first L-DOPA/DDCI dosage), as recorded in two of the three-day self-rating diary charts for the three days preceding V2.

13. Results of the screening laboratory tests were considered acceptable by the Investigator (i.e. not clinically relevant for the well-being of the subject or for the purpose of the study).

Key exclusion criteria for both studies, 301 and 302, were defined as follows.

At screening:

- Non-idiopathic parkinsonism (atypical parkinsonism, acquired or symptomatic parkinsonism, Parkinson-plus syndrome).
- Dyskinesia disability score >3 in the Unified Parkinson's Disease Rating Scale (UPDRS) Sub-section IV A, Item 33.
- Severe and/or unpredictable OFF periods.
- Any investigational medicinal product (IMP) within the 3 months (or within 5 half-lives, whichever is longer) before screening.

At randomisation:

- Inadequate compliance to concomitant L-DOPA/DDCI and other anti-Parkinson's disease drugs during screening (based on the Investigator's judgment).

Treatments

The IMP to be tested in this study were OPC as the research therapy and matching placebo as the reference therapy, to be administered orally as capsules. OPC was available in capsules of 25 mg and 50 mg. The applicant justifies the selection of the doses with the favourable safety and efficacy results in earlier phases of the research.

Subjects were to be assigned to one of three treatment groups as follows:

- OPC group: 25 mg QD
- OPC group: 50 mg QD
- Placebo group: placebo

In the event that the subject missed a dose due to illness, forgetfulness or if the subject vomited soon after taking a dose of the study medication, then they were to take the dose as scheduled the following evening. No additional tablets were to be taken.

Anti-PD medication used since diagnosis was to be documented on the appropriate pages of the eCRF. Any other previous medication used in the last three months prior to screening was to be recorded with start and stop dates on the appropriate pages of the eCRF.

All medications being taken by the subjects on entry to the study or at any time during the study in addition to the IMP were to be regarded as concomitant therapies and were documented on the appropriate pages of the eCRF.

No new anti-PD drug was to be started during the study. Any anti-PD drugs that were ongoing at the start of the study were to be kept at a stable dose throughout the study.

Concomitant therapies were to remain stable during the study.

Because of its mechanism of action, OPC could interfere with the metabolism of drugs containing a catechol group that are metabolized by COMT and could potentiate the effect of such drugs. Treatment with catechol-structured drugs (e.g. rimiterole, isoprenaline, adrenaline, noradrenaline, dopamine, dopexamine or dobutamide) was allowed, but the Investigator was to carefully monitor a subject being treated with these drugs because their effects could be potentiated by OPC.

The potential for drug interactions between OPC and hormonal contraceptives had not yet been assessed at the time of this study's design. Therefore, women of childbearing potential were to agree to use reliable contraception.

Subjects were prohibited from receiving the following medications prior to the study:

- Treatment with tolcapone, entacapone, neuroleptics, venlafaxine, MAO inhibitors (except selegiline up to 10 mg/day in oral formulation or 1.25 mg/day in buccal absorption formulation or rasagiline up to 1 mg/day), or antiemetics (except domperidone) within the month before screening
- Treatment with apomorphine within the month before screening

Subjects were prohibited from receiving the following medications during the study:

- Apomorphine, entacapone or tolcapone
- Neuroleptics
- Venlafaxine
- MAO inhibitors, except:
 - Selegiline up to 10 mg/day in oral formulation or 1.25 mg/day in buccal absorption formulation OR
 - Rasagiline up to 1 mg/day.
- Alpha-methyldopa or reserpine.
- Antiemetics with anti-dopaminergic action (domperidone allowed).
- Any other drugs with anti-dopaminergic action.
- Other experimental or investigational drugs.

No new anti-PD drug was to be started during the study. Any anti-PD drugs that were ongoing at the start of the study were to be kept at a stable dose throughout the study.

From V2 to V4 of the DB period, the Investigator could decrease the daily dose of L-DOPA/DDCI (keeping the number of daily intakes unchanged), according to subject response. If judged necessary by the Investigator, the dose could be increased again up to the baseline dose level.

The dosage of L-DOPA/DDCI was not to be changed during the study from V4 through the end of the DB period.

Randomisation

On Day 0 at V2, subjects who met the selection criteria were randomly assigned to one of three groups. Assignment to the groups was performed by Interactive Response Technologies (IRT). Each subject was to be given only the IMP related to their randomization sequence. The randomization schedule(s) were generated using a validated program that automated the random assignment of treatments to randomization numbers. The randomization schedule linked sequential numbers to treatment codes allocated at random with a 1:1:1 randomization ratio. The randomization blocks were generated by pooling countries of a similar region. Countries were pooled based principally on geography to try and

achieve a relatively uniform distribution of subjects across regions, with Belgium, UK, and Israel in Region 1, Estonia, Czech Republic, and Russia in Region 2, South Africa, Australia, and South Korea in Region 3, India in Region 4, and Argentina and Chile in Region 5. A block size larger than the largest expected number of subjects in any region was applied. This was estimated to be 150 subjects. A maximum consecutive allowable repetition of 50 within a block was also applied. Given the large number of subjects expected in each region, it was anticipated that adequate balance within region would be achieved.

Blinding (masking)

Study treatments were blinded and the randomization schedule and allocation to treatment groups was not to be known to the Investigator, the Sponsor or any other person involved in the conduct of the study, except in case of an emergency (if knowledge of the IMP was necessary to provide optimal treatment to the subject in an emergency situation).

The safety data from the study was monitored on a regular basis by an independent DSMB.

The data reports reviewed by the DSMB were presented in a partially unblinded fashion. The data reports were generated by an unblinded biostatistician of the CRO independent of the study team. The DSMB was to ensure that the study team was not inappropriately exposed to confidential information contained within the safety reports. Only DSMB members could be present during the Closed Sessions of data review. An exception was the unblinded biostatistician, who could participate should questions arise during the sessions. The DSMB members could elect to fully unblind the data report if considered necessary.

Outcomes/endpoints

The primary efficacy variable of the study was the change from baseline in absolute OFF-time at the end of the DB period (V7).

Absolute OFF-time was to be calculated in minutes as the average over the three days preceding each visit of the total daily sum of 30-minute periods classified as OFF in the subject's diary. If the primary variable at V7 was missing it was to be replaced by the last available observation (last post-baseline observation carried forward [LOCF]).

The key secondary variables (first to be tested per prespecified hierarchical procedure) were the proportion of OFF- and ON-time responders at the end of the DB period, change from baseline at the end of the DB period for UPDRS III (ON state) score, change from baseline at the end of the DB period of absolute total ON-time and change from baseline at the end of the DB period of percentage OFF-time.

Analysis of efficacy was to be performed on:

- Subject diary charts for ON/OFF periods, including ON-time without, with nontroublesome and with troublesome dyskinesia
- UPDRS Sections I (ON), II (ON and OFF) and III (ON)
- Complications of therapy (UPDRS IV)
- Modified Hoehn & Yahr staging (ON) (UPDRS V)
- Schwab and England scale (ON and OFF) (UPDRS VI)
- Change in L-DOPA/DDCI dose
- Investigator's and subject's assessments of change
- Parkinson's Disease Sleep Scale (PDSS)

- Parkinson's Disease Questionnaire (PDQ-39)
- Non-motor Symptoms Scale (NMSS)

For each 30-minute period during the day, subjects (with the help of a member of the family or other caregiver) were to rate their mobility as:

- OFF: poor mobility or complete immobility (You can move only slowly, or not at all)
- ON with troublesome dyskinesia: limited mobility (You are able to move around despite presence of troublesome dyskinesia)
- ON with non-troublesome dyskinesia: good mobility (You are able to move around relatively well despite presence of dyskinesia)
- ON without dyskinesia: excellent mobility (You are able to move around well)
- Asleep

The subjects were to complete the diaries on the 3 days preceding each study visit. For each 30-minute period the subject was trained to identify whether the majority of the period was spent as either ON or OFF (e.g. 20 minutes at OFF and 10 minutes at ON was to be rated as OFF).

The average ON/OFF times of the three diary charts completed before V2 (randomization) and V7/EDV (end of DB) were to be considered as the baseline and endpoint values, respectively.

Blood samples for measurement of BIA 9-1103 and anti-PD drugs levels were also obtained.

Plasma concentrations of anti-PD drugs were to be included in an integrated PK analysis (pooled with similar data from other studies) to explore potential drug-drug interaction effects. The details and results of the PK analysis are presented in a separate report.

Statistical methods

Power calculations were done for two different scenarios assuming 90- and 105-minute mean reductions in OFF-time for the OPC doses and of 30 minutes for placebo. These power considerations did not assume a monotone dose-response relationship.

Assuming that the mean reductions in OFF-time were 90- and 105-minutes for the two OPC doses and 30 minutes for the placebo, a sample size of 135 subjects per treatment group in the FAS would ensure a marginal power of more than 95% to confirm a treatment effect in the most efficacious group and a marginal power of about 85% to confirm a treatment effect in the less efficacious dose.

Therefore 405 subjects were to be randomized in order to have 135 subjects in each treatment group.

The following populations were defined:

- Enrolled Set: All subjects screened and enrolled into this study
- Randomized Set: All subjects in the Enrolled Set who were randomized to IMP irrespective of whether they received IMP or not
- Safety Set (SS): All subjects in the Randomized Set who received at least one dose of IMP and were not from site 1703 (see Section 9.8.2)
- Full Analysis Set (FAS): All subjects in the SS with at least one post-baseline OFF-time efficacy assessment. This was equivalent to the intention-to-treat population
- Per-protocol (PP) Set: All subjects in the FAS without any major protocol deviations.

The assignment of subjects to each set was discussed at the blind data review meeting. The reasons for exclusion from any of the analysis sets were documented in the minutes of this meeting.

The safety set will be used for the analysis of the safety and tolerance data. The primary population for efficacy analyses will be performed on the full analysis set (FAS). The per-protocol (PP) set will be defined through blind data review and will be the secondary efficacy population. An 'Enrolled Set' and 'Randomised Set' will further characterise the subjects.

All efficacy analysis will be based on the FAS and PP set. Where an analysis of covariance (ANCOVA) model is used, differences between each OPC dose group (25 mg/day and 50 mg/day) and the placebo group will be estimated from the final ANCOVA model using Dunnett's adjustment for multiple mean comparisons. 95% confidence intervals will be presented for the treatment effect estimates along with p-values for differences in treatment means. A two-sided significance level of 0.05 will be used.

The assumptions of the parametric ANCOVA models will be checked at the final evaluation by visual inspection of the residuals. In case the underlying assumptions are clearly not met, nonparametric ANCOVA will be performed.

To allow for the examination of treatment by country effects, the statistical analyses of the efficacy variables were performed using pooled country as a factor. Countries were pooled to match the pooling used in the randomization plan. This primary pooling was decided prior to unblinding and was used for any analyses in which the country effect was examined.

Table 22 Country pooling scheme as agreed following the EMA advice

Region	Countries
1	Belgium/UK
2	Estonia/Czech Republic/Russia
3	South Africa/Australia
4	India
5	Argentina/Chile
6	South Korea
7	Israel

Three different sensitivity analyses will also be performed on the primary endpoint to account for missing data. These are done to cater for the non-conservative estimates for missing data that the LOCF method provides.

The primary endpoint analysis was undertaken on the FAS population with an analysis of covariance (ANCOVA) and a LOCF approach. The model included treatment group and pooled country as factors and baseline OFF-time as a covariate. A Dunnett's alpha level adjustment was used for the comparison of each active dose group with placebo. The comparisons were based on Type III sums of squares. A two-sided significance level of 0.05 was used.

The adjusted treatment means (least squares mean [LS mean]) are presented together with their standard errors (SEs). The differences between the LS means for group comparisons are presented together with associated 95% CIs and P-values. Descriptive statistics for non-transformed values are also presented.

Different subgroup analyses were performed to investigate the consistency of the treatment effects for different groups of subjects. The following subgroups were defined:

- Age (categorized as <70 years, \geq 70 years)
- Gender
- Use of anti-PD medication on Day 1 other than L-DOPA: Yes/No
- Previous use of entacapone/tolcapone: Yes/No
- Hoehn and Yahr stage: <2.5, \geq 2.5
- Disease duration: <8 years, \geq 8 years
- L-DOPA daily dose at baseline: <700mg/day, \geq 700mg/day
- Concurrent use of MAO inhibitors (Rasagiline and Selegiline) at any time during the study: Yes/No
- Concurrent use of dopamine agonists at any time during the study: Yes/No
- Concurrent use of both MAO inhibitors and dopamine agonists at any time during the study: Yes/No
- Concurrent use of either MAO inhibitors or dopamine agonists at any time during the study: Yes/No
- L-DOPA formulation (Immediate Release/Controlled Release). Subjects taking the majority (> 50%) of their formulations as a controlled-release formulation were included in the controlled release group and subjects taking the majority of their formulations as immediate release were included in the immediate release group.

Results

• **Participant flow**

A total of 485 subjects were screened for eligibility to participate in the study. Of these, there were 72 subjects screened in Argentina, 38 in Australia, 23 in Belgium, 78 in Chile, 8 in the Czech Republic, 19 in Estonia, 63 in India, 21 in Israel, 57 in South Korea, 36 in Russia, 57 in South Africa and 13 in the United Kingdom.

A total of 427 subjects were randomized into the DB period in a 1:1:1 ratio across the treatment groups: 129 subjects to OPC 25 mg, 154 subjects to OPC 50 mg. and 144 subjects to placebo.

The number of subjects randomized by region is provided in Table below.

Table 23 Number of Subjects Randomized by Region

Region	OPC 25 mg	OPC 50 mg	Placebo
Argentina/Chile	36	50	46
Belgium/UK/Israel	16	20	14
Estonia/Czech Republic/Russia	14	20	19
India	16	16	21
South Africa/Australia/South Korea	47	48	44
TOTAL	129	154	144

Source: Table 14.1.2.1

A total of 376 (88.1%) subjects completed the DB treatment period: 118 (91.5%) subjects in the OPC 25 mg group, 128 (83.1%) subjects in the OPC 50 mg group, and 130 (90.3%) subjects in the placebo group.

The most common reason for premature discontinuation of the DB period was AEs for all three treatment groups, with a larger proportion in the OPC 50 mg group (11.0% of subjects) compared to the OPC 25 mg group (3.9%) and placebo group (6.3%).

Other reasons for premature termination were lack of efficacy, non-compliance and withdrawal of consent.

Conduct of the study

Major protocol violations for the FAS are presented in Table below.

Table 24 Major Protocol Violations (FAS)

	OPC 25 mg N = 125 n (%)	OPC 50 mg N = 147 n (%)	Placebo N = 135 n (%)
Subjects with at Least One Major Protocol Violation	11 (8.8%)	20 (13.6%)	15 (11.1%)
<i>Category of Major Protocol Violation:</i>			
Concomitant Medications	3 (2.4%)	3 (2.0%)	6 (4.4%)
Diary Cards	2 (1.6%)	1 (0.7%)	0
Inclusion Criteria	2 (1.6%)	4 (2.7%)	3 (2.2%)
Treatment Compliance	4 (3.2%)	5 (3.4%)	5 (3.7%)
Treatment Schedule	0	2 (1.4%)	0
Other	1 (0.8%)	5 (3.4%)	3 (2.2%)

Source: Table 14.1.3

Note: Subjects can be included in more than one category.

There was no unblinding by Investigators during the DB period. There were no unblinding requests by the DSMB. There was no requirement for rescue medication in this study.

Subjects with a suspected unexpected serious adverse reaction (SUSAR) were unblinded by the Pharmacovigilance department for reporting purposes in accordance to the legislation in force. For one SUSAR report an email containing unblinded information was sent to the incorrect distribution list, resulting in the unblinding of this subject to the Sponsor's study team. It was determined not to exclude the subject from the trial, and that all decisions about this subject and his/her inclusion or exclusion in the various analysis sets were to be taken by the blinded CRO team.

Numbers analysed

Following table shows the data sets analysed.

Table 25 Subject Samples

Subject Samples	OPC 25 mg n (%)	OPC 50 mg n (%)	Placebo n (%)
Randomized Set	129 (100%)	154 (100%)	144 (100%)
Safety Set (SS)	125 (96.9%)	150 (97.4%)	136 (94.4%)
Full Analysis Set (FAS)	125 (96.9%)	147 (95.5%)	135 (93.8%)
Per Protocol Set (PP)	114 (88.4%)	127 (82.5%)	120 (83.3%)

Source: [Table 14.1.2](#)

Note: Percentages are based on the number of subjects in the randomized set

The SS was used for the analysis of safety variables. Of the 427 subjects randomized to treatment, 411 were included in the SS (125 subjects in the OPC 25 mg group, 150 subjects in the OPC 50 mg group and 136 subjects in the placebo group). Fifteen subjects from site 1703 (see Section in the study report 9.8.2) and one subject in the OPC 50 mg group who did not take any dose of IMP were excluded from the SS.

Efficacy was analysed for the FAS. An additional four subjects who had no post-baseline OFF-time efficacy assessment were excluded from the FAS: three (1.9%) subjects in the OPC 50 mg group and one (0.7%) subject in the placebo group. Thus, 407 subjects were included in the FAS (125 subjects in the OPC 25 mg group, 147 subjects in the OPC 50 mg group and 135 subjects in the placebo group).

A further 46 subjects were excluded from the PP Set as a result of major protocol violations.

Baseline data

Demography data are summarised in Table below. Subjects in the OPC 25 mg group and OPC 50 mg group had similar mean ages (62.5 years and 65.5 years, respectively) and the majority in both treatment groups were male (65.6% and 60.5%, respectively) and White (72.0% and 78.2%), with Asians being the second most commonly represented race (23.2% and 21.1%). Subjects in the placebo group had a comparable mean age (61.5 years) to that of the active treatment groups, but the proportion of male subjects was lower than in the active treatment groups (52.6%) and the racial composition was also slightly different with fewer Whites (65.9%) and more Asians (31.1%). No Black/African American subjects were included in any group.

Table 26 Demographics (FAS)

	OPC 25 mg N = 125	OPC 50 mg N = 147	Placebo N = 135
Age, years			
Mean (SD)	62.5 (8.50)	65.5 (8.41)	61.5 (8.87)
Min/Max	43/82	44/83	36/81
Age, n (%)			
<70 years	96 (76.8%)	96 (65.3%)	107 (79.3%)
≥70 years	29 (23.2%)	51 (34.7%)	28 (20.7%)
Gender, n (%)			
Male	82 (65.6%)	89 (60.5%)	71 (52.6%)
Female	43 (34.4%)	58 (39.5%)	64 (47.4%)
Race, n (%)			
White	90 (72.0%)	115 (78.2%)	89 (65.9%)
Asian	29 (23.2%)	31 (21.1%)	42 (31.1%)
American Indian/Alaska Native	0	0	0
Black or African American	0	0	0
Native Hawaiian/Pacific Islander	0	0	0
Other	6 (4.8%)	1 (0.7%)	3 (2.2%)
Weight, kg			
Mean (SD)	75.35 (16.794)	71.61 (15.100)	72.12 (16.989)
Min/Max	44.5/147.6	41.0/118.0	39.4/133.8
Height, m			
Mean (SD)	1.67 (0.102)	1.66 (0.101)	1.65 (0.103)*
Min/Max	1.4/2.0	1.4/1.9	1.4/1.9*
BMI, kg/m²			
Mean (SD)	26.79 (4.903)	25.79 (4.342)	26.45 (5.175)*
Min/Max	17.1/52.8	15.8/37.9	15.6/49.2*

SD = standard deviation; *N=134

Source: Tables 14.1.4 and 14.1.5

Baseline PD characteristics did not differ significantly between the treatment groups. The mean duration of PD ranged between 7.7 and 8.5 years in the three treatment groups, and the onset of motor fluctuations had begun a mean of 3.0 to 3.2 years before subjects were included in the study.

Baseline absolute OFF-time ranged between 6.12 hours (placebo) and 6.32 hours (OPC 50 mg). Dyskinesia was present in more than 50% of the subjects in all three treatment groups and the mean ON-time with troublesome dyskinesia ranged between 0.53 (OPC 50 mg) and 0.58 hours (OPC 25 mg).

Part III UPDRS scores at ON state ranged between 21.5 and 22.5 points, while total UPDRS ranged between 30.8 and 31.7 points. Mean Hoehn and Yahr stage ranged between 2.3 and 2.4.

Table 27 Summary of Baseline Parkinson's Disease Characteristics (FAS)

	OPC 25 mg N = 125	OPC 50 mg N = 147	Placebo N = 135
Time since PD diagnosis, years Mean (SD)	8.54 (4.417)	8.20 (4.543)	7.73 (3.685)
Time since start of motor fluctuations, years Mean (SD)	3.22 (2.752)*	3.21 (3.255)*	3.02 (2.338)*
OFF-time Absolute time, hours Mean (SD)	6.21 (2.24)	6.32 (2.22)	6.12 (2.32)
Percentage of Total Awake Time, % Mean (SD)	38.8 (13.24)	38.9 (12.81)	37.5 (13.82)
ON-time without or with non-troublesome dyskinesia Absolute time, hours Mean (SD)	9.20 (2.32)	9.37 (2.22)	9.61 (2.40)
Percentage of Total Awake Time, % Mean (SD)	57.4 (12.91)	57.9 (12.99)	59.0 (14.48)
ON-time with troublesome dyskinesia Absolute time, hours Mean (SD)	0.58 (1.25)	0.53 (1.21)	0.57 (1.40)
Percentage of Total Awake Time, % Mean (SD)	3.8 (8.53)	3.2 (7.14)	3.5 (8.69)
Total UPDRS (Part I, II [ON] and III) Mean (SD)	30.8 (16.88)	31.7 (17.55)	31.5 (17.00)
UPDRS Part II (OFF) Mean (SD)	17.1 (6.75)	17.3 (7.49)	17.4 (7.08)
UPDRS Part III (ON) Mean (SD)	21.5 (11.95)	22.5 (12.26)	22.5 (11.96)
Modified Hoehn and Yahr (ON) Mean (SD)	2.3 (0.67)	2.4 (0.53)	2.4 (0.61)
Schwab and England ADL (ON) Mean (SD)	84.7 (10.05)	82.8 (11.57)	83.1 (11.62)
Incidence of Dyskinesia (UPDRS item 32) n (%)	65 (52.0%)	80 (54.4%)	72 (53.3%)

ADL = activities of daily living; SD = standard deviation; UPDRS = United Parkinson's Disease Rating Scale.

*N=110, 131 and 123 for OPC 25 mg, 50 mg and Placebo, respectively

Source: [Tables 14.1.5, 14.2.1.1, 14.2.1.2, 14.2.1.4, 14.2.6.1, 14.2.6.2, 14.2.6.4, 14.2.9, 14.2.13, 14.2.17, 14.2.31, and 14.2.33.](#)

A summary of baseline anti-PD medications is provided in the Table below. The mean time since the start of L-DOPA treatment was comparable across all three treatment groups (7.22 years in the OPC 25 mg group, 7.10 years in the OPC 50 mg group and 6.77 years in the placebo group).

The mean L-DOPA daily dose at baseline was 805.6 mg in the OPC 25 mg group, 700.3 mg in the OPC 50 mg group and 713.7 mg in the placebo group. The average number of daily intakes ranged between 4.8 and 4.9 in the three treatment groups. The majority of subjects received L-DOPA/carbidopa rather than L-DOPA/benserazide, with more than 2/3 of subjects across all three treatment groups using that combination. A minority of subjects were taking a regimen of both carbidopa and benserazide formulations. The vast majority of subjects (more than 90% of the subjects across all treatment groups) predominantly used immediate release (IR) formulations rather than controlled release (CR) formulations. The proportion of subjects receiving predominantly CR formulations ranged between 18.4%

and 21.5% in the three treatment groups. The majority of these CR formulations were taken in combined regimens with IR formulations (14.3% to 15.6% across the three treatment groups).

The use of anti-PD medications other than levodopa was also comparable across the three treatment groups. More than 2/3 of the subjects were taking dopamine agonists (66.4% to 72.6%), followed by MAO inhibitors (18.4% to 21.8%), amantadine (19.0% to 23.2%) and anticholinergics (9.5% to 16.0%). Individually, the most common anti-PD medications were pramipexole, ropinirole, amantadine, rasagiline, trihexyphenidyl and selegiline.

Two subjects were taking COMT inhibitors at baseline in deviation to the protocol: one subject in the placebo group was taking levodopa/carbidopa/entacapone and was discontinued for this reason on Day 46; one subject in the OPC 25 mg group received concomitantly entacapone up to Day 15, which was only discovered after the subject had already completed the DB period. Both subjects were excluded from the PP set.

Table 28 Summary of Baseline Anti-PD Characteristics (FAS)

Parameter	OPC 25 mg N = 125	OPC 50 mg N = 147	Placebo N = 135
Time since start of L-DOPA, years Mean (SD)	7.22 (4.302)	7.10 (4.667)	6.77 (3.610)
L-DOPA mean daily dose, mg/day Mean (SD)	805.6 (398.18)	700.3 (311.93)	713.7 (337.54)
Number of L-DOPA intakes Mean (SD)	4.76 (1.567)	4.86 (1.709)	4.85 (1.431)
Subjects taking carbidopa/L-DOPA n (%)	87 (69.6%)	91 (61.9%)	83 (61.5%)
Subjects taking benserazide/L-DOPA n (%)	43 (34.4%)	65 (44.2%)	60 (44.4%)
Subjects taking both carbidopa and benserazide formulations n (%)	5 (4.0%)	9 (6.1%)	9 (6.7%)
Subjects taking IR formulations n (%)	118 (94.4%)	141 (95.9%)	126 (93.3%)
Subjects taking CR formulations n (%)	26 (20.8%)	27 (18.4%)	29 (21.5%)
Subjects taking both IR and CR formulations n (%)	19 (15.2%)	21 (14.3%)	21 (15.6%)
Subjects taking COMT inhibitors n (%)	1 (0.8%)	0	1 (0.7%)
Subjects taking MAO inhibitors n (%)	23 (18.4%)	32 (21.8%)	26 (19.3%)
Subjects taking Dopamine Agonists n (%)	83 (66.4%)	102 (69.4%)	98 (72.6%)
Subjects taking Anticholinergics n (%)	20 (16.0%)	14 (9.5%)	13 (9.6%)
Subjects taking Amantadine n (%)	29 (23.2%)	28 (19.0%)	29 (21.5%)

Notes: Dopamine Agonists include bromocriptine, cabergoline, pergolide, pramipexole, pramipexole, ropinirole; MAO inhibitors include rasagiline, selegiline. Anticholinergics: benztropine, biperiden, procyclidine, trihexyphenidyl; IR = Immediate Release L-Dopa, CR = Controlled Release L-Dopa; SD = standard deviation. Subjects can be counted in more than one category.

Source: [Table 14.1.5](#), [Table 14.1.5.1](#), [Table 14.2.55](#), [Table 14.2.108](#), [Table 14.3.6.13](#).

Table 29 Baseline Anti-PD Medications by Descending Frequency, excluding L-DOPA (FAS)

ATC 2 nd Level Subgroup Active Ingredient – Generic Name	OPC 25 mg N = 125 n (%)	OPC 50 mg N = 147 n (%)	Placebo N = 135 n (%)
N04 Anti Parkinson Drugs	107 (85.6%)	122 (83.0%)	112 (83.0%)
Pramipexole	43 (34.4%)	57 (38.8%)	51 (37.8%)
Ropinirole	31 (24.8%)	33 (22.4%)	36 (26.7%)
Amantadine	29 (23.2%)	28 (19.0%)	29 (21.5%)
Rasagiline	10 (8.0%)	22 (15.0%)	16 (11.9%)
Trihexyphenidyl	18 (14.4%)	11 (7.5%)	11 (8.1%)
Selegiline	13 (10.4%)	10 (6.8%)	10 (7.4%)
Piribedil	6 (4.8%)	11 (7.5%)	11 (8.1%)
Cabergoline	3 (2.4%)	1 (0.7%)	1 (0.7%)
Rotigotine	1 (0.8%)	3 (2.0%)	0
Procyclidine	0	2 (1.4%)	0
Bromocriptine	1 (0.8%)	1 (0.7%)	0
Biperiden	0	1 (0.7%)	1 (0.7%)
Benzatropine	1 (0.8%)	0	0
Entacapone	1 (0.8%)	0	0
Orphenadrine	1 (0.8%)	0	0
Pergolide	0	1 (0.7%)	0
Carbidopa w/entacapone/levodopa	0	0	1 (0.7%)

Source: [Table 14.3.6.13](#)

Note: Excluded medications include benserazide w/levodopa and carbidopa w/levodopa.

Across all three treatment groups, in the medical and neurological history, the most frequently reported findings were in the SOCs vascular disorders (45.5%), psychiatric disorders (44.5%), musculoskeletal and connective tissue disorders (40.8%), GI disorders (34.4%) and metabolism and nutrition disorders (25.8%). The most commonly reported PTs overall were hypertension (37.6%), insomnia (19.7%), constipation (17.7%), depression (15.5%), osteoarthritis (10.8%) and anxiety (9.6%).

Conditions of interest commonly associated with PD (medical and neurological histories) are summarized in the Table below, and included sleep disorders such as insomnia (19.7%), rapid eyes movements sleep abnormal (4.7%), constipation (17.7%), depression (15.5%), hallucinations (1.3%), orthostatic hypotension (1.0%) and malignant melanoma (0.7%).

Table 30 Summary of Medical Conditions Commonly Associated with PD (FAS)

Primary SOC PT	OPC 25 mg N = 125 n (%)	OPC 50 mg N = 147 n (%)	Placebo N = 135 n (%)
Gastrointestinal disorders	45 (36.0%)	41 (27.9%)	54 (40.0%)
Constipation	27 (21.6%)	19 (12.9%)	26 (19.3%)
Psychiatric disorders	60 (48.0%)	65 (44.2%)	56 (41.5%)
Insomnia	22 (17.6%)	33 (22.4%)	25 (18.5%)
Depression	20 (16.0%)	24 (16.3%)	19 (14.1%)
REM sleep abnormal	8 (6.4%)	4 (2.7%)	7 (5.2%)
Sleep disorder	5 (4.0%)	0	3 (2.2%)
Hallucination	2 (1.6%)	2 (1.4%)	1 (0.7%)
Major depression	1 (0.8%)	0	1 (0.7%)
Sleep attacks	1 (0.8%)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	15 (12.0%)	31 (21.1%)	13 (9.6%)
Malignant melanoma	1 (0.8%)	0	1 (0.7%)
Malignant melanoma of eyelid	0	1 (0.7%)	0
Vascular disorders	65 (52.0%)	67 (45.6%)	53 (39.3%)
Orthostatic hypotension	0	2 (1.4%)	2 (1.5%)

PT = preferred term; REM = rapid eye movement; SOC = system organ class.

Source: [Table 14.3.6.7](#)

The most commonly used anti-PD medications prior to enrolling in the study in descending order of frequency were pramipexole (23.1%), ropinirole (18.9%), amantadine (11.1%), trihexyphenidyl and selegiline (both 8.8%). Previous treatment with COMT inhibitors was reported for few subjects and their use was comparable across all three treatment groups. Entacapone was used by 7.2%, 4.1% and 5.2% and carbidopa w/entacapone/L-DOPA by 4.8%, 4.1% and 3.7% of the subjects in the OPC 25 mg, OPC 50 mg and placebo groups, respectively. No subject was reported to have used tolcapone.

Per protocol, the L-DOPA regimen had to remain stable during the study, except from V2 (randomization) to V4 (first 2-3 weeks) of the DB period, when the daily dose of L-DOPA/DDCI could be adjusted according to subject response, keeping the number of daily intakes unchanged, and not exceeding the baseline dose level. From V4 onwards the L-DOPA dose was to remain stable. No relevant differences were observed compared to the baseline L-DOPA medications for any of the three treatment groups, indicating that the vast majority of subjects kept the same L-DOPA formulations throughout the DB treatment period.

Primary Efficacy Measure

Following Table presents the results of the ANCOVA analysis for the change from baseline in absolute OFF-time at V7 (LOCF) in the FAS population.

Table 31 Change from Baseline in Absolute OFF-time (Minutes) at Visit 7 – Statistical Analysis - LOCF (FAS)

	Placebo N = 125	OPC 25 mg N = 147	OPC 50 mg N = 135
Summary Statistics			
Mean (SD)	-64.5 (155.35)	-102.8 (159.42)	-124.0 (178.23)
ANCOVA Analysis			
LS Mean (SE)	-64.46 (14.35)	-101.67 (14.86)	-118.77 (13.81)
Difference in LS Mean (SE) with Placebo	-	-37.21 (19.64)	-54.31 (18.86)
95% CI for Difference with Placebo	-	(-80.82, 6.40)	(-96.18, -12.44)
Adjusted P-value for pairwise comparison with Placebo	-	0.1061	0.0081

ANCOVA = analysis of covariance, LOCF = last post-baseline observation carried forward, LS = least square, SD = standard deviation, SE = standard error

Note: Statistical analysis is based on an ANCOVA model with treatment group and pooled country as factors and baseline OFF-time as a covariate. Dunnett's alpha level adjustment is used for the comparison of each active dose group with placebo.

Source: [Tables 14.2.1.1](#) and [14.2.3.1](#)

The LS means were -64.46 mins for the placebo group, -101.67 for the OPC 25 mg and -118.77 mins for the OPC 50 mg groups. A Dunnett's alpha level adjustment was used for the comparison of each active dose group with placebo. The difference was -37.21 (adjusted P = 0.1061) for the comparison between the OPC 25 mg group and placebo, and -54.31 (adjusted P = 0.0081) for the comparison between the OPC 50 mg group and placebo. Based on the P-values, the difference from placebo was statistically significant for the OPC 50 mg group but did not reach statistical significance for the OPC 25 mg group.

The analysis of the primary endpoint in the PP Set is shown in the Table below. Results were similar to the FAS, with LS means of -67.58 for placebo, -98.06 for OPC 25 mg and -128.17 mins for OPC 50 mg. The adjusted P-values for the comparison with placebo were P = 0.2506 for the OPC 25 mg group and P = 0.0062 for the OPC 50 mg group.

Table 32 Change from Baseline in Absolute OFF-time (Minutes) at Visit 7 – Statistical Analysis - LOCF (PP Set)

	Placebo N = 125	OPC 25 mg N = 147	OPC 50 mg N = 135
Summary Statistics			
Mean (SD)	-66.0 (153.65)	-98.2 (161.33)	-134.0 (185.35)
ANCOVA Analysis			
LS Mean (SE)	-67.58 (15.61)	-98.06 (15.77)	-128.17 (15.27)
Difference in LS Mean (SE) with Placebo	-	-30.48 (20.95)	-60.60 (20.42)
95% CI for Difference with Placebo	-	(-77.00, 16.04)	(-105.94, -15.26)
Adjusted P-value for pairwise comparison with Placebo	-	0.2506	0.0062

ANCOVA = analysis of covariance, CI = confidence interval, LOCF = last post-baseline observation carried forward, LS = least square, PP = per protocol, SD = standard deviation, SE = standard error

Note: Statistical analysis is based on an ANCOVA model with treatment group and pooled country as factors and baseline OFF time as a covariate. Dunnett's alpha level adjustment is used for the comparison of each active dose group with placebo.

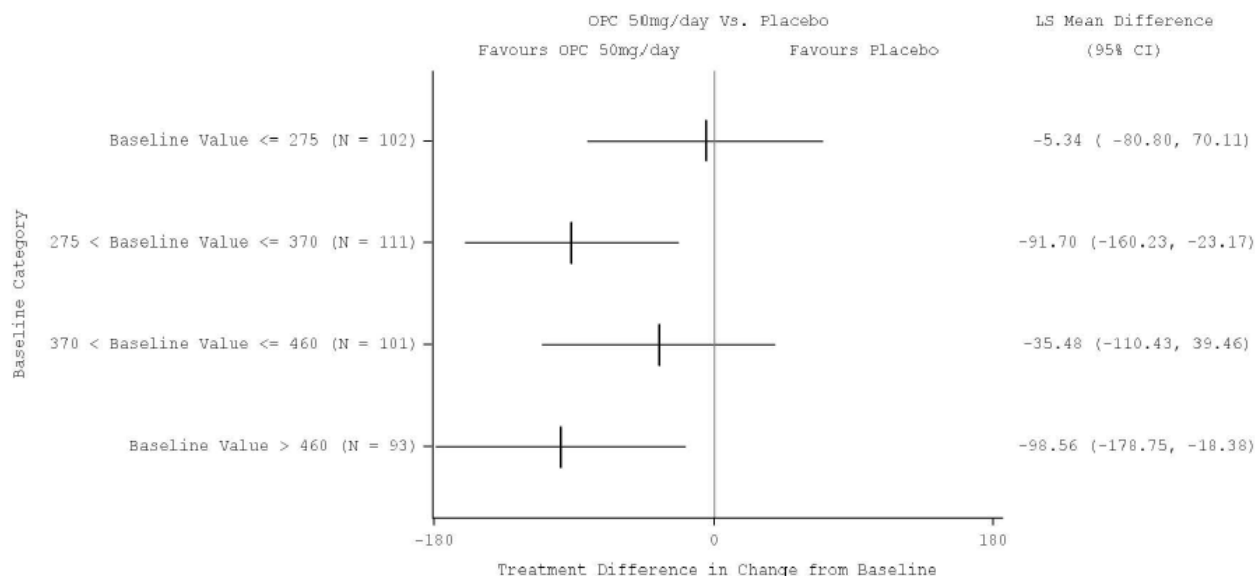
Source: [Tables 14.2.51.1](#) and [14.2.53.1.1](#)

In the analysis of the primary endpoint using an alternative pooling of countries as a factor in the FAS, comparable results to the primary analysis were observed with LS means of -65.17 mins for placebo, -103.56 for OPC 25 mg and -120.36 mins for OPC 50 mg. The adjusted P-values for the difference from placebo were P = 0.0978 for OPC 25 mg and P = 0.0075 for OPC 50 mg.

The analysis of the primary endpoint was also carried out using country as a fixed effect in place of pooled country. This analysis was performed in the FAS. The results were consistent with the primary analysis for all comparisons.

There is no indication of a treatment by pooled country interaction, with the estimated mean differences in each of the five regions favouring the OPC treatment group.

A Forest Plot for the estimate of mean difference in OFF time between OPC 50mg and placebo groups and its 95% CI by category of baseline OFF-time (≤ 275 , $275 \leq 370$, $370 \leq 460$, and >460 mins) is presented in the Figure below.



Note(s): Statistical analysis is based on an ANOVA model which includes treatment group, pooled country, baseline category and treatment by baseline category interaction as fixed effects.
Baseline category is defined as Baseline Value ≤ first quartile, first quartile < Baseline Value ≤ median, median < Baseline Value ≤ third quartile or Baseline Value > third quartile.

Figure 6 Forest Plot of Treatment x Baseline Category Interaction in Change from Baseline of Absolute OFF Time

There is no indication of an interaction, with the estimated mean differences in each of the five regions favouring the OPC treatment group.

A separate analysis of the primary endpoint was conducted on the PP Set excluding subjects enrolled at Site 1709. The results were similar to those observed in the primary analysis that included this site. Analysis of the Primary Endpoint Including Site 1703 In addition, an analysis of the primary endpoint was conducted on the PP Set including subjects enrolled at Site 1703. The results were similar to those observed in the primary analysis that excluded this site.

Sensitivity Analysis

Three different sensitivity analyses were performed on the primary endpoint to account for missing data and early discontinuations.

Mixed Model Repeated Measures (MMRM)

Table below presents the analysis of the primary endpoint performed on observed case data using a MMRM with treatment, visit pooled country, and treatment by visit interaction as factors and baseline OFF-time as a covariate in the FAS. A similar trend to the primary analysis was observed with LS means of -66.82 for placebo, -102.23 for OPC 25 mg and -122.53 mins for OPC 50 mg, with slightly higher SEs reported. The adjusted P-values for the difference from placebo were >0.05 for the OPC 25 mg group and 0.0498 for the OPC 50 mg group.

Table 33 Change from Baseline in Absolute OFF Time at Visit 7 (Minutes) - Statistical Analysis – MMRM – Sensitivity Analysis

FULL ANALYSIS SET

	Treatment/Treatment Comparison	LS Mean	Standard Error	P-value	95% CI
Change from Baseline To Visit 7	OPC 25mg/day	-102.23	14.75		
	OPC 50mg/day	-122.53	13.84		
	Placebo	-66.82	14.28		
	OPC 25mg/day - OPC 50mg/day	20.30	19.77	0.3054	(-18.58, 59.17)
	OPC 25mg/day - Placebo	-35.41	20.08	0.5321	(-92.99, 22.17)
	OPC 50mg/day - Placebo	-55.71	19.42	0.0498	(-111.39, -0.02)

The same analysis was performed adjusting OFF time to a 16-hour waking day in the FAS and in the PP Set. Both confirm the results of the primary analysis with higher (and dose dependent) LS means in the OPC groups than in the placebo group. For the OPC 25 mg group, the adjusted P-values for pairwise comparison with placebo were P = 0.3064 (FAS) and P = 0.8113 (PP set), and for comparison with the OPC 50 mg group were P = 0.0405 (FAS) and P = 0.0325 (PP set).

Multiple Imputation (Using a MNAR Assumption)

The second sensitivity analysis used multiple imputation for missing data using a missing not at random (MNAR) model. The MNAR assumption was achieved by assuming that the trajectory of withdrawal from the OPC arms was as bad as that for placebo subjects. This analysis was performed in the FAS, in the FAS adjusting OFF-time to a 16-hour waking day, and in the PP Set. Results were similar in the three sets and comparable to the primary LOCF analysis. For the OPC 25 mg group, the adjusted P-values for pairwise comparison with placebo were P = 0.0748 (FAS), P = 0.0375 (FAS adjusted to a 16-hour waking day) and P = 0.1735 (PP set), and for comparison with the OPC 50 mg group were P = 0.0061 (FAS), P = 0.0058 (FAS adjusted to a 16-hour waking day) and P = 0.0039 (PP set).

Repeat of Primary Analysis, Including Wake Time as a Covariate

The third sensitivity analysis was a repeat of the primary analysis, but including wake time (at the last post-baseline visit) as a covariate. The analysis was performed in the FAS. The results were consistent with the primary analysis for all comparisons.

Other Analyses

Proportion of Responders

An OFF-time responder was defined as a subject who had a reduction of at least one hour in absolute OFF-time from baseline to endpoint. An ON-time responder was defined as a subject who had an increase of at least one hour in absolute total ON-time.

Frequency counts and statistical analyses of OFF- and ON-time responders at the end of DB period in the FAS are presented in Table below.

The proportion of OFF-time responders were 50.4% in the placebo group, 62.4% in the OPC 25 mg group, and 66.0% in the OPC 50 mg group, while the proportion of ON-time responders were 45.2%, 63.2%, and 61.9%, respectively. The P-values for the differences between OPC groups and placebo were P < 0.05 for all comparisons.

Similar findings were observed in the PP Set.

Table 34 OFF- and ON-time Responders at Visit 7 – Statistical Analysis – LOCF (FAS)

	Placebo N = 135	OPC 25 mg N = 125	OPC 50 mg N = 147
OFF-time Responders			
n (%)	68 (50.4%)	78 (62.4%)	97 (66.0%)
Odds Ratio (95%CI)	-	1.68 (1.02, 2.76)	1.91 (1.17, 3.09)
P-value	-	0.0405	0.0088
ON-time Responders			
n (%)	61 (45.2%)	79 (63.2%)	91 (61.9%)
Odds Ratio (95%CI)	-	2.07 (1.26, 3.41)	1.97 (1.21, 3.20)
P-value	-	0.0040	0.0061

CI = confidence interval; LOCF = last post-baseline observation carried forward

Source [Tables 14.2.43](#) and [14.2.44](#).

Change from Baseline at the End of DB period of the Different ON-time States (Absolute Values)

Table below presents the results of the ANCOVA analysis for the change from baseline to endpoint of the different ON-time states (absolute values) in the FAS population.

Table 35 Change from Baseline to Visit 7 of the Different ON-time States (Absolute Changes - Minutes) – Statistical Analysis – LOCF(FAS)

Parameter	Placebo N = 135	OPC 25 mg N = 125	OPC 50 mg N = 147
Total ON-time (Sum of All ON-times)			
Summary Statistics Mean (SD)	58.1 (143.21)	110.8 (164.93)	117.4 (177.13)
ANCOVA analysis LS Mean (SE)	58.67 (14.21)	104.09 (14.71)	111.26 (13.67)
Difference in LS Mean with Placebo (SE)	-	45.42 (19.51)	52.59 (18.69)
95% CI for difference with Placebo	-	(7.06,83.77)	(15.84, 89.34)
P-value for pairwise comparison with Placebo	-	0.0204	0.0051

Parameter	Placebo N = 135	OPC 25 mg N = 125	OPC 50 mg N = 147
ON-time Without Dyskinesia			
Summary Statistics Mean (SD)	49.4 (179.39)	46.4 (217.27)	48.6 (226.12)
ANCOVA analysis LS Mean (SE)	47.36 (18.43)	49.13 (19.09)	46.51 (17.77)
Difference in LS Mean with placebo (SE)	-	1.77 (25.27)	-0.85 (24.24)
95% CI for difference with Placebo	-	(-47.91, 51.45)	(-48.51, 46.81)
P-value for pairwise comparison with Placebo	-	0.9442	0.9721
ON-time With Non-troublesome Dyskinesia			
Summary Statistics Mean (SD)	0.4 (135.35)	49.0 (177.79)	45.7 (204.56)
ANCOVA analysis LS Mean (SE)	-2.24 (15.70)	37.31 (16.21)	38.60 (15.09)
Difference in LS Mean with placebo (SE)	-	39.55 (21.53)	40.84 (20.59)
95% CI for difference with Placebo	-	(-2.791, 81.88)	(0.35, 81.32)
P-value for pairwise comparison with Placebo	-	0.0670	0.0480
ON-time Without Dyskinesia or With Non-troublesome Dyskinesia			
Summary Statistics Mean (SD)	49.8 (164.76)	95.3 (177.10)	94.3 (187.70)
ANCOVA analysis LS Mean (SE)	48.16 (15.36)	84.11 (15.94)	85.59 (14.80)
Difference in LS Mean with Placebo (SE)	-	35.95 (21.13)	37.42 (20.23)
95% CI for difference with Placebo	-	(-5.59, 77.48)	(-2.35, 77.20)
P-value for pairwise comparison with Placebo	-	0.0897	0.0651

Parameter	Placebo N = 135	OPC 25 mg N = 125	OPC 50 mg N = 147
ON-time With Troublesome Dyskinesia			
Summary Statistics Mean (SD)	8.3 (96.12)	15.5 (109.67)	23.1 (89.95)
ANCOVA analysis LS Mean (SE)	11.20 (8.65)	19.40 (8.97)	25.61 (8.33)
Difference in LS Mean with Placebo (SE)	-	8.20 (11.86)	14.41 (11.38)
95% CI for difference with Placebo	-	(-15.11, 31.51)	(-7.96, 36.78)
P-value for pairwise comparison with Placebo	-	0.4898	0.2060

ANCOVA = analysis of covariance, CI = confidence interval, LOCF = last post-baseline observation carried forward, LS = least square, SD = standard deviation, SE = standard error
Source: [Tables 14.2.3.3 to 14.2.3.7](#) and [Tables 14.2.1.2 to 14.2.1.6](#).

The LS mean changes at endpoint of total ON-time were 58.57 mins for the placebo group, compared to 104.09 mins for the OPC 25 mg group and 111.26 mins for the OPC 50 mg group. The difference was 45.42 (P = 0.0204) for the comparison between the OPC 25 mg and placebo groups, and 52.59 (P = 0.0051) for the comparison between the OPC 50 mg and placebo groups.

The LS mean changes for ON-time without dyskinesia were 47.36 mins for placebo, 49.13 mins for the OPC 25 mg group, and 46.51 mins for the OPC 50 mg group. The P-values for the comparisons of each active treatment and placebo were >0.05.

For the ON-time with non-troublesome dyskinesia, the LS mean changes were -2.24 mins for the placebo group, compared to 37.31 mins for the OPC 25 mg group and 38.60 mins for OPC 50 mg group. The P-values for the comparisons to placebo were P = 0.0670 and P = 0.0480 for OPC 25 mg and OPC 50 mg groups, respectively.

The LS mean changes for ON-time without dyskinesia or with non-troublesome dyskinesia were 48.16 mins for placebo, 84.11 mins for OPC 25 mg, and 85.59 mins for OPC 50 mg. The P-values for the comparisons of each active treatment and placebo were >0.05.

For the ON-time with troublesome dyskinesia, the LS mean changes from baseline were 11.20 mins for the placebo group, 19.40 mins for the OPC 25 mg group and 25.61 mins for the 50 mg OPC group. The differences were 8.20 and 14.41 mins for the comparisons of OPC 25 mg and OPC 50 mg to placebo, respectively, with P>0.05 for both comparisons.

OFF- and ON-time Changes from Baseline by Study Visit

Greater LS mean changes were observed in both OPC groups at all post-baseline visits compared to placebo from the first post-baseline visit (V3) with LS mean changes of -29.94 mins for placebo, -74.83 mins for OPC 25 mg and -74.45 mins for the OPC 50 mg group. LS mean reductions were greater in the next visit (V4) for all groups (-56.94, -99.41 and -105.23 mins for each group, respectively), and then continued to improve slightly to V7. A dose-related effect was observed at all timepoints after V3. The P-values for the pairwise comparison for both OPC groups with placebo was <0.05 at all timepoints except for OPC 25 mg at V5 (P = 0.1307) and V7 (P = 0.1061).

The by-visit LS mean changes of total ON-time were overall inversely proportional to the reduction of OFF-time, with greater LS mean increases observed in both OPC groups at all post-baseline visits

compared to placebo. The P-values for the pairwise comparison for both OPC groups with placebo was <0.05 at all timepoints except for OPC 25 mg at V5 (p=0.1446) and OPC 50 mg at V3 (p=0.0595). The profile for ON-time was maximally optimized at V4 for both OPC groups, with greater LS mean increases from baseline observed for ON without dyskinesia (44.62 and 32.55 mins [OPC 25 mg and OPC 50 mg vs. placebo, respectively]), compared to ON with non-troublesome dyskinesia (9.11 and 17.62 mins) and ON with troublesome dyskinesia (-1.57 and 1.59 mins). The ON time without dyskinesia decreased in the following visits for the OPC groups compared to placebo, while the ON time with dyskinesia increased.

At V7 the LS mean changes from baseline were greater for the ON-time with non-troublesome dyskinesia (39.55 and 40.84 mins) compared to the ON-time without dyskinesia (1.77 and -0.85 mins) and the ON-time with troublesome dyskinesia (8.20 and 14.41 mins). The L-DOPA dose could not be adjusted after V4 per protocol, which may have contributed to this observation.

Table 36 Absolute OFF-time Change from Baseline (Minutes) per Visit – Statistical Analysis - LOCF (FAS)

	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Placebo					
LS Mean (SE)	-29.94 (10.57)	-56.94 (12.46)	-69.26 (13.27)	-61.94 (13.65)	-64.46 (14.35)
OPC 25 mg					
LS Mean (SE)	-74.83 (10.95)	-99.41 (12.80)	-96.68 (13.62)	-115.60 (14.15)	-101.67 (14.86)
Difference in LS Mean with Placebo (SE)	-44.89 (14.48)	-42.47 (16.99)	-27.42 (18.11)	-53.67 (18.69)	-37.21 (19.64)
95% CI for difference with Placebo	(-73.37, -16.42)	(-75.88, -9.06)	(-63.02, 8.18)	(-90.41, -16.93)	(-80.82, 6.40)
P-value for pairwise comparison with Placebo	0.0021	0.0129	0.1307	0.0043	0.1061
OPC 50 mg					
LS Mean (SE)	-74.45 (10.24)	-105.23 (12.10)	-130.14 (12.87)	-116.51 (13.27)	-118.77 (13.81)
Difference in LS Mean with Placebo (SE)	-44.51 (13.94)	-48.28 (16.43)	-60.88 (17.50)	-54.58 (18.02)	-54.31 (18.86)
95% CI for difference with Placebo	(-71.91, -17.11)	(-80.59, -15.98)	(-95.29, -26.46)	(-90.01, -19.15)	(-96.18, -12.44)
P-value for pairwise comparison with Placebo	0.0015	0.0035	0.0006	0.0026	0.0081

CI = confidence interval, LOCF = last post-baseline observation carried forward, LS = least square, SE = standard error
Source: Tables 14.2.3.1 and 14.2.3.2

For the PP Set, summary statistics for the change from baseline by visit for the different motor states are similar to the results observed in the FAS.

OFF- and ON-time Changes from End of L-DOPA Adjustment Period (Visit 4) at the End of DB period

Most of the OFF-time improvements were seen in the first weeks of treatment (V3 and V4) and only slightly improved thereafter. For the different ON-states, there was a decrease in the ON-time without dyskinesia for both OPC groups compared to placebo (-28.12 and -10.40 mins, OPC 25 mg and OPC 50 mg, respectively), while the ON-time with dyskinesia increased in both OPC groups compared to placebo (30.19 and 26.47 mins for ON with non-troublesome dyskinesia; and 8.75 and 11.69 mins for ON with troublesome dyskinesia, respectively). The L-DOPA dose could not be adjusted after V4 per protocol, which may have contributed to this observation.

The results in the PP Set were comparable.

Average Number of Daily ON to OFF Transitions

The average number of transitions was calculated as the average of the number of times a subject transitions from ON (any state) to OFF each day based on subject's diaries over the three day diary collection period preceding each visit. Table below summarises the results of the ANCOVA analysis at V7.

Table 37 Average Number of Daily Transitions from ON to OFF at V7 - ANCOVA Analysis (FAS)

Parameter	Placebo N = 125	OPC 25 mg N = 147	OPC 50 mg N = 135
Baseline – Summary Statistics			
Mean (SD)	3.02 (1.129)	3.03 (1.331)	2.98 (1.155)
Visit 7 – Summary Statistics			
Mean (SD)	2.43 (1.278)	1.95 (1.463)	2.01 (1.377)
Visit 7 – ANCOVA Analysis			
LS Mean	2.47	1.98	2.06
95% CI	(2.25, 2.69)	(1.75, 2.21)	(1.85, 2.28)

ANCOVA = analysis of covariance, CI = confidence interval, LS = least square, SD = standard deviation
Source: [Tables 14.2.6.6 and 14.2.8.6](#)

The OPC groups had fewer ON to OFF transitions over the course of treatment, compared to placebo. At V7, the LS means were 2.47 (95% CI 2.25-2.69) for the placebo group, 1.98 (95% CI 1.75-2.21) for the OPC 25 mg group and 2.07 (95% CI 1.86-2.28) for the OPC 50 mg group. This trend showing fewer transitions to OFF periods in OPC groups compared to placebo is complementary to the results of the other OFF- and ON-time analyses.

The results in the PP Set were comparable to the FAS.

Subject's with a decrease in L-DOPA dose from Baseline to V4

At V4, 21.6% of the subjects in OPC 25 mg and 19.0% in OPC 50 mg had a decrease in the L-DOPA dose compared to 8.9% of the subjects in the placebo group. Overall, between baseline and V4, the L-DOPA dose decreased by a mean of 47.2 mg in the OPC 25 mg and 29.3 mg in the OPC 50 mg groups, compared to 9.4 mg in the placebo group.

UPDRS

The different UPDRS scores and subscores analysed and respective score ranges were as follows: Total Score: 0–176 (sum of parts I, II ON, III); Part I: 0–16 (items 1-4); Part II: 0–52 (items 5-17); Part III: 0-108 (items 18-31); Dyskinesia: 0–12 (items 32-34); Tremor: 0–32 (items 16, 20, 21); Rigidity: 0-20 (item 22); Bradykinesia: 0-36 (items 23-26, 31); Postural Instability and Gait Disturbance (PIGD): 0-20 (items 13-15, 29, 30); Freezing: 0-4 (item 14); Modified Hoehn and Yahr: 0-5; and Schwab and England Activities of Daily Living: 0-100%.

The mean decreases from baseline to V7 in Total UPDRS were small and similar across all three treatment groups, with LS means of -3.51 for placebo, -4.39 for OPC 25 mg and -2.80 for OPC 50 mg. The P-values were >0.05 for the comparisons between the OPC groups and placebo.

The changes from baseline to V7 in UPDRS Part I were small and similar across all three treatment groups, with LS means of -0.25 for placebo, -0.07 for OPC 25 mg and -0.24 for OPC 50 mg. The p-values were >0.05 for the comparisons between the OPC groups and placebo.

The changes from baseline to V7 in UPDRS Part II (OFF) were small and similar across all three treatment groups, with LS means of -1.90 for placebo, -2.48 for OPC 25 mg and -2.18 for OPC 50 mg. The P-values were >0.05 for the comparisons between OPC groups and placebo.

The changes from baseline to V7 in UPDRS Part II (ON) were small and similar across all three treatment groups, with LS means of -0.98 for placebo, -1.11 for OPC 25 mg and -0.54 for OPC 50 mg. The P-values were >0.05 for the comparisons between the OPC groups and placebo.

The changes from baseline to V7 in UPDRS Part III were small and similar across all three treatment groups, with LS means of -2.12 for placebo, -2.94 for OPC 25 mg and -1.95 for OPC 50 mg. The p-values were >0.05 for the comparisons between the OPC groups and placebo.

Post-baseline UPDRS Dyskinesia scores increased in the two OPC groups compared to the placebo group. At V7, the LS mean changes from baseline were -0.19 for placebo, 0.36 for OPC 25 mg, and 0.23 for OPC 50 mg. The P-values for the comparisons of OPC 25 mg and OPC 50 mg with placebo were 0.0007 and 0.0061, respectively.

The dyskinesia scores in the OPC groups increased, whether dyskinesia was present or not at baseline, compared to placebo. For all other subscores, no relevant differences were observed between the OPC groups and placebo.

UPDRS Part V (ON) the LS means minimally changed compared to baseline across the three treatment groups, ranging from -0.07 for OPC 25 mg to 0.02 for OPC 50 mg and placebo.

UPDRS Part VI (Schwab and England Activities of Daily Living) the changes from baseline to V7 were small and similar across all three treatment groups, with LS means of -4.4 for placebo, -2.2 for OPC 25 mg and -4.1 for OPC 50 mg.

Parkinson's Disease Sleep Scale (PDSS)

Post-baseline PDSS total scores improved slightly across all groups, with no significant differences between them. At V7, the LS mean changes from baseline were 5.10, 2.49 and 2.26 for the placebo, OPC 25 mg and OPC 50 mg groups, respectively. The P-values were >0.05 for the comparisons between the OPC groups and placebo.

For the PP set the results were comparable to the FAS.

Of note, the sleep time as assessed by subjects' diaries was similar at baseline and V7 for the three treatment groups, ranging between 7.70 hours (placebo) to 8.02 hours (OPC 25 mg) at baseline, and 7.80 (placebo) to 7.90 hours (OPC 50 mg) at V7.

Parkinson's Disease Quality of Life Questionnaire (PDQ-39)

Post-baseline PDQ-39 total scores showed slight improvements across all groups with no significant differences between them. At V7, the LS mean changes from baseline were -4.65, -2.38 and -4.18 for the placebo, OPC 25 mg and OPC 50 mg groups, respectively. The P-values were >0.05 for the comparisons between the OPC groups and placebo.

For the PP set the results were comparable to the FAS.

Non-Motor Symptoms Scale (NMSS)

Post-baseline NMSS total scores showed slight improvements across all groups with no significant differences between them. At V7, the LS mean changes from baseline were -5.20, -2.02 and -4.90 for the placebo, OPC 25 mg and OPC 50 mg groups, respectively. The P-values were >0.05 for the comparisons between the OPC groups and placebo.

No worsening trends were observed for any individual domain. Mean post-baseline scores for cardiovascular, sleep/fatigue, mood/cognition, urinary, sexual function and miscellaneous slightly improved across the three treatment groups.

For the PP set the results were comparable to the FAS.

Investigators Global Assessment of Change

Table below presents the comparison for each OPC group to placebo for the Investigators Global Assessment of Change score at the end of DB period (V7) for the FAS. The means were similar across the three treatment groups, ranging between 3.2 and 3.5 and the P-values were >0.1 for the comparisons between the OPC groups and placebo.

However, a higher proportion of OPC-treated subjects were assessed as having much or very much improved (27.4% and 23.2% for the OPC 25 mg and OPC 50 mg groups, respectively), compared to 18.6% of placebo subjects.

Similar results were observed in the PP Set.

Table 38 Investigator's Global Assessment of Change (FAS)

Visit 7	Statistic	Placebo	OPC 25 mg	OPC 50 mg
	N	134	124	146
	Mean (SD)	3.4 (1.02)	3.2 (1.17)	3.5 (1.16)
Category				
(1) Very much improved	n (%)	3 (2.2%)	8 (6.4%)	4 (2.7%)
(2) Much improved	n (%)	22 (16.3%)	26 (20.8%)	30 (20.4%)
(3) Minimally improved	n (%)	40 (29.6%)	37 (29.6%)	38 (25.9%)
(4) No change	n (%)	57 (42.2%)	37 (29.6%)	49 (33.3%)
(5) Minimally worse	n (%)	8 (5.9%)	13 (10.4%)	20 (13.6%)
(6) Much worse	n (%)	3 (2.2%)	2 (1.6%)	4 (2.7%)
(7) Very much worse	n (%)	0	0	1 (0.7%)
(0) Not assessed	n (%)	1 (0.7%)	1 (0.8%)	0
	P-value vs. placebo*	-	0.1091	0.8310
*Van Elteren's test with pooled country as the stratification variable				

SD = standard deviation

Source: Tables 14.2.45 and 14.2.47

Subject's Global Assessment of Change

Table below presents the comparison for each OPC group to placebo for the Subject's Global Assessment of Change score at the end of the DB period (V7) for the FAS. The means were similar across the three treatment groups, ranging between 3.2 and 3.5. The P-values were >0.05 for the comparisons between OPC groups and placebo. However, a higher proportion of OPC-treated subjects had a change of much or very much improved (29.8% and 25.3% for OPC 25 mg and OPC 50 mg groups, respectively) compared to 20.1% of placebo subjects.

Similar results were observed in the PP Set.

Table 39 Subject's Global Assessment of Change (FAS)

Visit 7	Statistic	Placebo	OPC 25 mg	OPC 50 mg
	n	134	124	146
	Mean (SD)	3.4 (1.18)	3.2 (1.36)	3.5 (1.25)
Category				
(1) Very much improved	n (%)	6 (4.4%)	11 (8.8%)	8 (5.4%)
(2) Much improved	n (%)	21 (15.6%)	26 (20.8%)	29 (19.7%)
(3) Minimally improved	n (%)	42 (31.1%)	38 (30.4%)	34 (23.1%)
(4) No change	n (%)	47 (34.8%)	26 (20.8%)	44 (29.9%)
(5) Minimally worse	n (%)	11 (8.1%)	15 (12.0%)	25 (17.0%)
(6) Much worse	n (%)	5 (3.7%)	6 (4.8%)	6 (4.1%)
(7) Very much worse	n (%)	1 (0.7%)	1 (0.8%)	0
(0) Not assessed	n (%)	1 (0.7%)	1 (0.8%)	0
	P-value vs. placebo*	-	0.0835	0.8167
*Van Elteren's test with pooled country as the stratification variable				

SD = standard deviation

Source: Tables 14.2.46 and 14.2.48

2.5.4.3. Study BIA-91067-302 part II

"Efficacy and Safety of BIA 9-1067 in Idiopathic Parkinson's Disease Patients with "Wearing-Off" Phenomenon treated with Levodopa plus a Dopa Decarboxylase Inhibitor (DDCI): a Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, Multicentre Clinical Study (Part II – *Open-Label Extension Phase*)"

Methods

- Objectives**

The objective of Part II, the Open Label Extension Phase of the study, was to investigate the safety, tolerability and maintenance of therapeutic effect of opicapone (OPC) (25 mg QD or 50 mg QD) adjusted according to clinical response over 1 year of treatment, when administered with the existing treatment of levodopa (L-DOPA) plus a DDCI, in Parkinson's disease (PD) patients with end-of-dose motor fluctuations who completed the Part I Double Blind Phase of the study.

Study Design

The study was designed to include two periods, a double-blind (DB) period and an open-label (OL) period: only the OL period is described in this report. The results of the DB period are presented in a separate report.

After a screening period of up to two weeks, eligible subjects entered the DB treatment period and were randomly assigned to one of the three treatments (Placebo, OPC 25 mg, or OPC 50 mg) at Visit 2 (V2)

using a 1:1:1 ratio. Study medication was administered in combination with existing treatment of L-DOPA/ DDCI. From V2 to V4 of the DB period (first 2-3 weeks of the DB period), the Investigator could decrease the daily dose of L-DOPA dose (keeping the number of daily intakes unchanged), according to subject response. If needed, the L-DOPA dose could be increased again up to the baseline level. The dosage of L-DOPA was not to be changed during the study from V4 through to the end of the DB period. After completion, subjects who did not enter the OL period were to have a post-study visit within 14 days.

The OL period started on the day after V7 and ended at V14 (52 weeks). All subjects were to begin OL treatment at a dose of 25 mg/day OPC for the first week (until V8). If "wearing off" was not sufficiently controlled and tolerability allowed, the OPC dose could be adjusted by titrating up to 50 mg/day. If unacceptable dopaminergic adverse events (AEs) were seen, the L-DOPA dose was to be adjusted. If not sufficient to manage the AEs, the OPC dose could then be down titrated. For other AEs, the same titration procedure could be applied or OPC dose adjustments implemented. From V13 to V14 (6 weeks to the end of the OL period), L-DOPA and OPC doses were to remain stable.

Table 40 Schedule of Study Assessments

Activity	Screening		Double-blind Period							Open-label Period							Follow-up
Visit	V1	Pre-V2	V2	V3	Pre-V4	V4	V5	V6	V7 or EDV	V8	V9	V10	V11	V12	V13	V14 or EDV	PSV
Day	-14	-7	0	7±1 of V2	14±3 of V2	14 or 21±3 of V2	28±3 of V4	56±3 of V4	84±3 of V4	7±1 of V7	28±3 of V7	56±3 of V7	112±5 of V7	210±5 of V7	322±5 of V7	365±5 of 7	14±3 of EOS or EDV
Informed consent	X																
Demographic characteristics	X																
Medical/neurological history	X																
Previous/concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Physical (height at V1 only) and neurological exams	X ^c		X						X ^c				X			X ^c	X
12-lead ECG	X		X ^a						X				X		X	X	X
Serum β-hCG ^d	X																
Urine pregnancy test ^d		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests ^e	X ^f		X			X	X	X	X ^f	X	X	X	X ^f	X	X	X ^f	X ^f
Review of subject eligibility	X	X	X														
Randomization			X														
Record adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study treatment			X	X	X	X	X	X	X ^g	X	X	X	X	X	X		
Medication accountability				X	X	X	X	X	X	X	X	X	X	X	X	X	
Record L-DOPA dose	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Instruct on use of and issue diary	X	X	X	X	X	X	X	X	X ^g	X	X	X	X	X	X		
Review and record diary charts		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
UPDRS I	X		X						X						X	X	
UPDRS II to VI	X		X			X	X	X	X	X	X	X	X	X	X	X	
PDQ-39, PDSS, NMSS, mMIDI, C-SSRS			X			X ^h	X	X ^h	X		X ^h	X ^h	X	X ^h	X	X	
Investigator and subject assessments of change						X	X	X	X	X	X	X	X	X	X	X	
Blood sampling for PK assay			X				X		X						X	X	

C-SSRS: Columbia Suicide Severity Rating Scale; ECG: electrocardiogram; EDV: Early Discontinuation visit; EOS: End-of-Study visit; hCG = human chorionic gonadotropin; L-DOPA = Levodopa; mMIDI: modified Minnesota Impulsive Disorders Interview; NMSS = Non-Motor Symptoms Scale; PDQ-39 = Parkinson's Disease Questionnaire; PDSS = Parkinson's Disease Sleep Scale; PSV = Post-study visit; PK = pharmacokinetics; UPDRS = Unified Parkinson's Disease Rating Scale; V = visit.

^a Three sets of vital signs measurements (blood pressure [BP] and pulse rate, both supine and standing) and 12-lead ECG reading in triplicate; ^b One set of vital signs measurements (BP and pulse rate); ^c Includes a skin examination by dermatologist for screening of melanoma (between V1 and V3, at V7 and between V14 and the PSV); ^d Only in females of childbearing potential; ^e Blood and urine for hematology, biochemistry and urinalysis; ^f Including coagulation; ^g Only if subject continues into subsequent extension; ^h Only C-SSRS.

● Study participants

Male and female subjects between 30 and 83 years old, inclusive, who had a diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria for at least three years, with the presence of recognizable ON and OFF states (motor fluctuations) and an average total daily OFF-time while awake of at least 1.5 hours. The disease severity at ON had to be rated as Stage I-III using the modified Hoehn & Yahr staging of PD and subjects were to have been treated with L-DOPA/DDCI (three to eight daily doses, which could include a slow-release formulation) for at least one year with clear clinical improvement.

Subjects with a dyskinesia disability score of >3 in the Unified Parkinson's Disease Rating Scale (UPDRS) sub-section IV A item 33 were not permitted to enter the study, neither were subjects with severe and/or unpredictable OFF periods.

Subjects who remained on study treatment at V7 could enter the OL period.

● Treatments

25 mg OPC capsules for oral administration once daily.

50 mg OPC capsules for oral administration once daily.

The investigational medicinal product (IMP) was to be taken in the evening and administered at least one hour after the last daily dose of L-DOPA/DDCI. Subjects had to fast for one hour before and for at least one hour after intake of IMP.

● Outcomes/endpoints

Efficacy: Subject diary charts for ON/OFF periods; UPDRS; Investigator's and subject's assessments of change; Parkinson's Disease Sleep Scale (PDSS); Parkinson's Disease Questionnaire-39 (PDQ-39); Non-motor Symptoms Scale (NMSS).

Safety: Adverse events (AEs), laboratory safety tests, physical and neurological examinations, skin examination for melanoma, vital signs, electrocardiogram (ECG), Columbia Suicide Severity Rating Scale (C-SSRS) and modified Minnesota Impulsive Disorders Interview (mMIDI).

- **Statistical methods**

Efficacy analyses:

Efficacy data for the OL period were generally summarised using descriptive statistics for the different parameters at the different visits of the OL period and respective changes to DB and OL baselines.

Maintenance of treatment effect from the end of the DB period through to the end of the OL period was assessed by exploratory analysis of absolute OFF-time in subjects in the OL-FAS who were randomised to OPC in the DB period (excluding subjects who received placebo during the DB period). The difference in OFF-time between OL baseline and at V14 was estimated using a linear model with pooled country as a factor.

Exploratory analysis to assess dose effect on the absolute OFF-time was conducted. At each scheduled OL visit, each subject was assigned a dose (25 mg or 50 mg, depending on the dose dispensed at the visit immediately prior to the scheduled assessments). A linear model with mixed effects was fitted to the data with pooled country as a fixed effect, subject as a random effect and dose of OPC and OL baseline OFF-time as covariates.

Summary statistics were also presented by visit and treatment (OPC or Placebo) in the DB period, for change from OL baseline in absolute OFF-time and, ON-time with troublesome, non-troublesome and without dyskinesia.

Safety analyses:

All safety parameters were presented using descriptive statistics. The analyses focused on treatment-emergent AEs (TEAEs) and were categorized by System Organ Class (SOC) and Preferred Term (PT). Serious TEAEs, TEAEs leading to death and TEAEs resulting in discontinuation of study treatment were tabulated using frequency tables. For laboratory parameters, descriptive analyses at each time point and change from OL baseline to each post-baseline time point were presented. Values of vital signs and 12-lead ECGs, including change from baseline were summarized. Frequency tables and subject listings were presented for markedly abnormal values. Shift tables were presented according to reference ranges (low, normal or high).

Results

- **Participant flow**

It was planned to randomize 405 subjects to achieve 135 subjects in each of the three treatment groups.

Consented: 485 subjects.

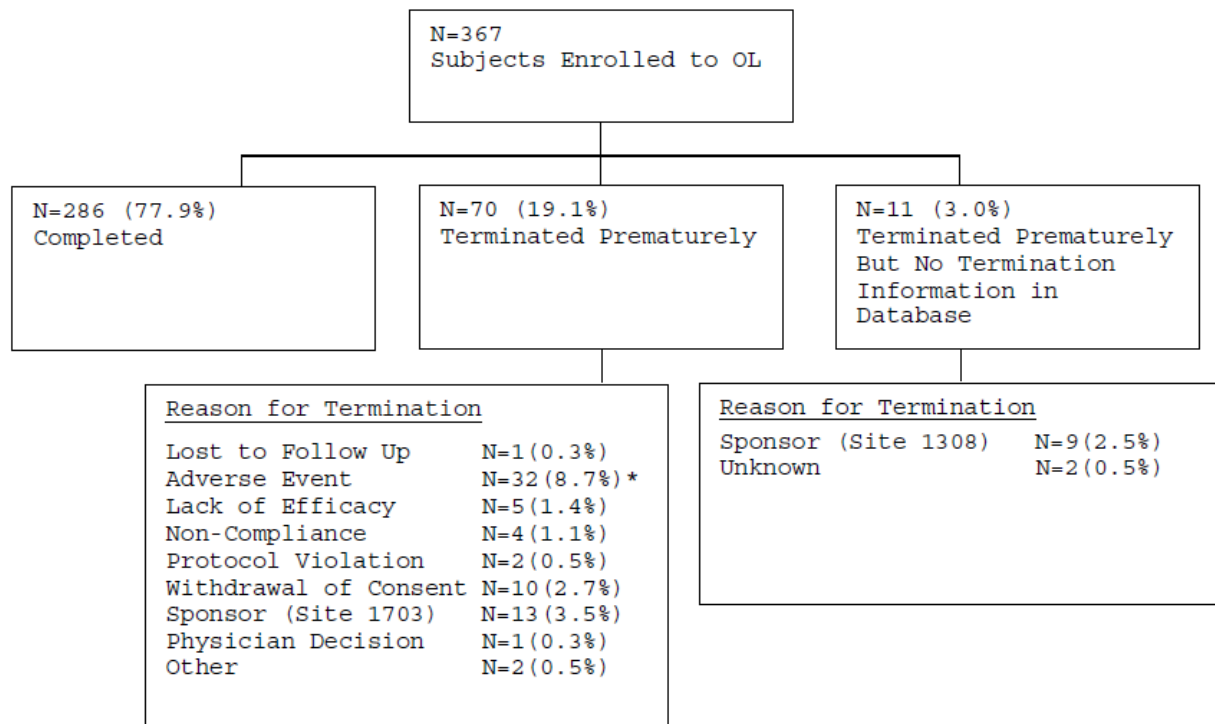
Randomized into the DB period: 427 subjects.

Enrolled into the OL period: 367 subjects.

OL Safety Set (SS): 353 subjects.

OL Full Analysis Set (OL-FAS): 339 subjects.

A total of 367 subjects were enrolled into the OL period. These included 365 subjects who completed the DB period and 2 subjects who terminated the DB period early due to a lack of DB study medication.



* Includes subjects #110504, #160203 and #170904 with non-treatment emergent AEs

Source: Table 14.1.1.

Figure 7 Flow Chart of Subject Disposition

- **Conduct of the study**

A total of 24 (7.1%) subjects were reported as having at least one major protocol violation in the OL period. The most common major protocol violations were the use of disallowed concomitant medication and non-adherence to the treatment schedule (both 5 [1.5%] subjects), followed by inadequate treatment compliance (4 [1.2%] subjects).

- **Baseline data**

Subjects had a mean age of 63.1 years and the majority were male (59.3%) and White (70.2%), with Asians being the second most commonly represented race (26.8%).

At OL baseline, mean absolute OFF-time was 4.48 hours and most of the ON-time was without or with non-troublesome dyskinesia (10.9 hours). Total UPDRS score was 27.9, UPDRS II OFF was 14.7 and UPDRS III ON was 19.9.

Table 41 Summary of Baseline Parkinson's Disease Characteristics (OL FAS)

	DB Baseline N = 339	OL Baseline N=339
OFF-time		
Absolute time, hours		
Mean (SD)	6.22 (2.22)	4.48 (2.98)
Percentage of Total Awake Time, %		
Mean (SD)	38.4 (13.15)	27.5 (17.87)
ON-time without dyskinesia or with non-troublesome dyskinesia		
Absolute time, hours		
Mean (SD)	9.39 (2.32)	10.90 (3.17)
Percentage of Total Awake Time, %		
Mean (SD)	58.1 (13.58)	67.9 (18.94)
ON-time with troublesome dyskinesia		
Absolute time, hours		
Mean (SD)	0.55 (1.30)	0.75 (1.76)
Percentage of Total Awake Time, %		
Mean (SD)	3.5 (8.26)	4.6 (10.71)
Total UPDRS (Part I, II [ON] and III)		
Mean (SD)	31.2 (17.75)*	27.9 (17.06)*
UPDRS Part II (OFF)		
Mean (SD)	17.4 (7.04)	14.7 (7.01)
UPDRS Part III (ON)		
Mean (SD)	22.2 (12.37)	19.9 (12.37)
Modified Hoehn and Yahr (ON)		
Mean (SD)	2.3 (0.61)	2.3 (0.61)
Schwab and England ADL (ON)		
Mean (SD)	84.0 (10.95)	86.2 (10.87)

ADL = Activities of Daily Living; DB = double-blind; OL = open-label; SD = standard deviation; UPDRS = United Parkinson's Disease Rating Scale

*N=302

Notes: OL baseline is defined as the last pre-OL treatment period assessment/value. DB baseline is defined as the last pre-DB treatment period assessment/value. Source data records time in minutes, which has been converted manually into hours

● **Efficacy Evaluation**

Tables below present summaries of OFF- and ON-time changes from OL and DB baseline at V14 (absolute values).

The OFF-time reduction was sustained over the OL period and even slightly improved compared to the end of the DB period. At V14 there was a decrease of -21.8 mins since OL baseline, corresponding to an OFF-time reduction of more than 2 hours (-126.3 mins) relative to the DB baseline.

Table 42 Change from Baseline in the Absolute Different ON-time States at Visit 14 (Minutes)
– Summary Statistics (LOCF) (Full Analysis Set)

Parameter	Change from OL Baseline (N = 339)	Change from DB Baseline (N = 339)
Absolute OFF-time (minutes)		
Mean (SD)	-21.8 (160.62)	-126.3 (177.31)
Median	-10.0	-130.0
Min/Max	-780/650	-690/575
Absolute ON-time (Sum of All ON-times) (minutes)		
Mean (SD)	24.9 (156.37)	127.3 (174.09)
Median	15.0	130.0
Min/Max	-710/820	-595/770
ON-time with troublesome dyskinesia (minutes)		
Mean (SD)	6.0 (129.05)	17.7 (110.94)
Median	0.0	0.0
Min/Max	-890/750	-270/750
ON-time with non-troublesome dyskinesia (minutes)		
Mean (SD)	-1.8 (166.01)	33.5 (207.00)
Median	0.0	0.0
Min/Max	-910/1000	-635/1060
ON-time without dyskinesia or with non-troublesome dyskinesia (minutes)		
Mean (SD)	18.8 (184.89)	109.6 (193.68)
Median	20.0	125.0
Min/Max	-765/930	-595/770
ON-time without dyskinesia (minutes)		
Mean (SD)	20.6 (230.99)	76.1 (244.71)
Median	10.0	70.0
Min/Max	-1105/930	-910/930

DB = double-blind; LOCF = last post-baseline observation carried forward; OL = open label; SD = standard deviation.

OL baseline is the last pre-OL treatment period assessment of Parkinson's symptoms as recorded in the subject diary. DB baseline is the last pre-DB treatment period assessment of Parkinson's symptoms as recorded in the subject diary.

Table 43 Change from OL Baseline in Absolute OFF/ON-time at Visit 14 (Minutes) by DB treatment – Summary Statistics (LOCF) (Full Analysis Set)

Mean (SD)	DB OPC (N = 222)	DB Placebo (N = 117)
Absolute OFF-time (minutes)		
OL Baseline	254.9 (179.02)	294.4 (176.96)
End of OL Period	240.3 (169.74)	258.9 (199.96)
Change from OL Baseline to End of OL Period	-14.6 (160.94)	-35.5 (159.79)
Absolute ON-time Without Dyskinesia (minutes)		
OL Baseline	498.1 (266.61)	479.1 (245.94)
End of OL Period	516.8 (269.23)	503.5 (273.59)
Change from OL Baseline to End of OL Period	18.7 (248.04)	24.4 (195.53)
Absolute ON-time With Non-Troublesome Dyskinesia (minutes)		
OL Baseline	170.7 (228.95)	147.4 (219.91)
End of OL Period	159.5 (224.08)	163.4 (239.60)
Change from OL Baseline to End of OL Period	-11.1 (179.73)	16.0 (135.19)
Absolute ON-time With Troublesome Dyskinesia (minutes)		
OL Baseline	45.2 (102.46)	44.1 (111.45)
End of OL Period	49.1 (120.08)	54.0 (118.44)
Change from OL Baseline to End of OL Period	4.0 (132.23)	9.9 (123.23)

DB = double-blind; LOCF = last post-baseline observation carried forward; OL = open label; OPC = Opicapone; SD = standard deviation

OL baseline is the last pre-OL treatment period assessment of Parkinson's symptoms as recorded in the subject diary.

At the end of the OL period, the proportion of OFF- and ON-time responders (relative to DB baseline) for the FAS was 68.4% and 65.8%, respectively, slightly above the rate observed at the end of the DB period.

The average number of ON to OFF transitions over the OL period ranged between 1.93 (V14) to 2.03 (V12), with 1 less transition compared to the DB baseline (3.03).

At the end of the OL period, the mean total UPDRS score was still slightly improved relative to the DB baseline (-3.3) with the decrease being similar to that observed at the end of the DB period. At the end of the OL period, the mean UPDRS Part I score was still slightly improved relative to the DB baseline (-0.1), with the decrease being similar to that observed at the end of the DB period.

The mean UPDRS Part II (OFF) score slightly improved up to OL Week 8 (V10). Thereafter the score started to slightly deteriorate, but at the end of the OL period was still improved relative to the DB baseline (-2.8), with the decrease being similar to that observed at the end of the DB period. The mean UPDRS Part II (ON) score slightly improved up to OL Week 8 (V10). Thereafter the score started to slightly deteriorate, but at the end of the OL period was still improved relative to the DB baseline (-0.8), with the

decrease being similar to that observed at the end of the DB period. The mean UPDRS Part III (ON) score slightly improved up to OL Week 8 (V10), with a mean improvement of -3.7 points compared to DB baseline. Thereafter the score started to slightly deteriorate, but at the end of the OL period was still improved relative to the DB baseline (-2.4), with the decrease being similar to that observed at the end of the DB period. The mean UPDRS Part VI score slightly improved up to OL Week 8 (V10). Thereafter the score started to slightly deteriorate, but at the end of the OL period was still improved relative to the DB baseline (1.2%).

The PDSS total score slightly worsened during the OL period (-3.51), but the change to the DB baseline was minimal (-0.51).

The PDQ-39 total score slightly worsened during the OL period (2.4), but some improvement was still observed relative to the DB baseline (-2.2). The dimension with greater changes during the OL was Mobility (4.5).

The total NMSS score slightly worsened during the OL period (1.9), but some improvement was still observed relative the DB baseline (-4.2). Mean post-baseline scores for cardiovascular, sleep/fatigue, mood/cognition, urinary, sexual function and miscellaneous generally remained stable when compared to the OL baseline and were still slightly improved when compared to the DB baseline.

Investigator's and Subject's Global Assessment of Change - The means were similar across the OL visits for the two scores, ranging between 2.9 and 3.2. The majority of the subjects (61.9% IGAC; 61.7% SGAC) had improvements in relation to study entry, slightly above the rate observed at the end of the DB period.

2.5.5. Clinical studies in special populations

No studies in special populations have been conducted. The population included in the phase III studies is representative of the age span of the target population with substantial numbers of patients aged above 70.

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

In the 2 Phase 3 studies, 1027 subjects were randomised in 30 countries. The population in the Phase 3 studies (301 and 302) was predominantly Caucasian (100% in Study 301 and 72.2% in Study 302), 59% male, with a mean age of <70 years and a mean BMI ranging from 25.8 to 27.2 kg/m² in the FAS.

Table 44 Demographics and other baseline characteristics (integrated Phase 3 studies, Full Analysis Set)

Characteristic	Placebo (N=255)	OPC 25 mg (N=241)	OPC 50 mg (N=262)
Age (years)			
n	255	241	262
Mean	62.9	63.4	64.6
SD	9.12	8.79	8.81
n (%) <70 years	186 (72.9)	175 (72.6)	176 (67.2)
n (%) ≥70 years	69 (27.1)	66 (27.4)	86 (32.8)
Gender (n [%])			
Male	141 (55.3)	147 (61.0)	158 (60.3)
Female	114 (44.7)	94 (39.0)	104 (39.7)
Ethnic group (n [%])^a			
Caucasian	209 (82.0)	206 (85.5)	230 (87.8)
Asian	42 (16.5)	29 (12.0)	31 (11.8)
Other	3 (1.2)	6 (2.5)	1 (0.4)
Body mass index (kg/m²)			
n	254	241	262
Mean	26.74	26.81	26.35
SD	4.722	4.628	4.497

Source data: [Table 2.7.3.B.1.5](#)

N = total number of subjects; n = number of subjects; OPC = opicapone; SD = standard deviation

a The ethnicity of 1 subject (0.4%) in the placebo treatment group was missing.

Baseline Parkinson's disease characteristics did not differ significantly between the treatment groups for most characteristics in the FAS in either Phase 3 study.

Table 45 Baseline Parkinson's disease characteristics (integrated Phase 3 studies, Full Analysis Set)

Characteristic	Placebo (N=255)	OPC 25 mg (N=241)	OPC 50 mg (N=262)
	Number (%) of subjects		
Incidence of dyskinesia ^a	122 (47.8)	114 (47.3)	131 (50.0)
	Mean (SD)		
Time since diagnosis of Parkinson's disease (years)	7.73 (3.923)	7.91 (4.327)	7.67 (4.285)
Time since start of motor fluctuations (years)	2.60 (2.159)	2.75 (2.662)	2.74 (2.884)
OFF-time			
Absolute time (hours) ^b	6.14 (2.083)	6.52 (2.242)	6.27 (2.039)
% of total awake time	37.80 (12.489)	40.43 (13.185)	38.81 (11.810)
Total ON-time			
Absolute time (hours) ^b	10.11 (2.201)	9.59 (2.259)	9.88 (2.161)
% of total awake time	62.20 (12.489)	59.57 (13.185)	61.19 (11.810)
ON-time with non-troublesome dyskinesia			
Absolute time (hours) ^b	1.77 (2.751)	1.31 (2.240)	1.61 (2.481)
% of total awake time	10.84 (16.663)	8.18 (13.939)	9.87 (15.300)
ON-time with troublesome dyskinesia			
Absolute time (hours) ^b	0.50 (1.268)	0.43 (1.065)	0.44 (1.116)
% of total awake time	3.06 (7.823)	2.78 (7.084)	2.61 (6.648)
Total UPDRS (Part I, II [ON], III)	34.4 (17.03)	35.3 (18.27)	34.8 (18.50)
UPDRS Part II (OFF)	18.0 (7.06)	17.8 (7.04)	18.0 (7.14)
UPDRS Part III (ON)	24.9 (12.07)	25.1 (12.95)	25.1 (13.23)
Modified H&Y (ON)	2.4 (0.56)	2.4 (0.60)	2.4 (0.53)
Schwab and England (ON)	82.9 (11.46)	83.4 (11.10)	82.8 (11.70)

Source data: [Table 2.7.3.B.2.5](#), [Table 2.7.3.B.3.5](#), [Table 2.7.3.B.4.5](#)

H&Y = Hoehn and Yahr; N = total number of subjects; OPC = opicapone; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale

^a From Unified Parkinson's Disease Rating Scale question 32 at Visit 2: any subjects above >0.

^b Converted to hours for better perception.

Subjects had to be treated with L-DOPA/DDCI for at least 1 year with clear clinical improvement prior to inclusion in either Phase 3 study. The mean time since the start of L-DOPA treatment was similar across the treatment groups in both studies in the FAS (ranging from 5.31 to 5.89 years in Study 301 and 6.77 to 7.22 years in Study 302). There were no clinically relevant differences in the baseline use of concomitant L-DOPA/DDCI between the individual treatment groups. In both Phase 3 studies, nearly all subjects (>88% in any treatment group) were taking IR L-DOPA/DDCI formulations and approximately half of each study population was taking L-DOPA/carbidopa and the other half was taking L-DOPA/benserazide.

In both Phase 3 studies, a similar proportion of subjects were taking anti-Parkinson's disease medications (other than L-DOPA/DDCI) at baseline (between 80.0% and 82.5% in Study 301 and between 83.0% and

84.8% in Study 302), except for a somewhat lower proportion of subjects in the opicapone 5 mg group (69.7%) in Study 301.

Table 46 Concomitant anti-Parkinson's disease medications at baseline (integrated Phase 3 studies, Full Analysis Set)

Characteristic	Placebo (N=255)	OPC 25 mg (N=241)	OPC 50 mg (N=262)
	Mean (SD)		
Time since start of L-DOPA (years)	6.31 (3.671)	6.58 (4.162)	6.32 (4.396)
L-DOPA daily dose (mg/day)	695.6 (321.32)	732.6 (371.61)	698.1 (322.77)
	Number (%) of subjects		
Subjects taking carbidopa with L-DOPA ^a	150 (58.8)	146 (60.6)	152 (58.0)
Subjects taking benserazide with L-DOPA	126 (49.4)	105 (43.6)	124 (47.3)
Subjects taking both carbidopa and entacapone with L-DOPA	1 (0.4)	0	0
Subjects taking IR L-DOPA formulations	230 (90.2)	222 (92.1)	244 (93.1)
Subjects taking CR L-DOPA formulations	24 (9.4)	18 (7.5)	18 (6.9)
Subjects taking COMT inhibitors ^b	1 (0.4)	1 (0.4)	0
Subjects taking dopamine agonists	186 (72.9)	161 (66.8)	181 (69.1)
Subjects taking MAO inhibitors	49 (19.2)	47 (19.5)	57 (21.8)
Subjects taking anticholinergics	20 (7.8)	28 (11.6)	22 (8.4)
Subjects taking amantadine	57 (22.4)	58 (24.1)	54 (20.6)

Source data: Table 2.7.3.M.7.5

COMT = catechol-O-methyltransferase; CR = controlled release; DDCI = dopa decarboxylase inhibitor;
 IR = immediate release; L-DOPA = levodopa; MAO = monoamine oxidase; N = total number of subjects;
 OPC = opicapone; SD = standard deviation

a Carbidopa with L-DOPA includes carbidopa with melevodopa and carbidopa with both entacapone and L-DOPA.

b With or without L-DOPA.

In the integrated Phase 3 population, there were no relevant differences in the proportion of subjects taking anti-Parkinson's disease medications (excluding L-DOPA/DDCI).

In both Study 301 and Study 302, the estimated mean change (LS means) from baseline in absolute OFF-time at endpoint in the FAS was largest in the opicapone 50 mg group (-116.8 minutes in Study 301 and -118.8 minutes in Study 302) with a statistically significant difference to placebo (Study 301: LS mean difference -60.8 minutes, $p=0.0015$; Study 302: LS mean difference -54.3 minutes, $p=0.0081$, demonstrating superiority of the opicapone 50 mg dose over placebo. Changes from baseline in the opicapone 25 mg groups (Study 301: -85.9 minutes; Study 302: -101.7 minutes) and the opicapone 5 mg group (Study 301 only: -91.3 minutes) were both greater than in placebo, but the differences were not statistically significant.

Table 47 Change in absolute OFF-time (minutes) from baseline to endpoint (integrated Phase 3 studies, Full Analysis Set)

Analysis Model Statistic	Placebo (N=255)	OPC 25 mg (N=241)	OPC 50 mg (N=262)
ANCOVA M3			
LS mean (SE)	-55.5 (10.90)	-92.9 (10.65)	-119.9 (10.54)
Difference in LS mean (SE) with placebo	--	-37.4 (15.25)	-64.4 (15.16)
95% CI for difference to placebo	--	(-67.4; -7.5)	(-94.2; -34.7)
p-value	--	0.0143	<0.0001
MMRM^a			
LS mean (SE)	-55.3 (10.24)	-93.2 (10.24)	-120.6 (10.02)
Difference in LS mean (SE) with placebo	--	-37.9 (14.48)	-65.3 (14.32)
95% CI for difference to placebo	--	(-66.3; -9.4)	(-93.4; -37.2)
p-value	--	0.0091	<0.0001

Source data: Table 2.7.3.P.2.1, Table 2.7.3.P.6.1

ANCOVA = analysis of covariance; CI = confidence interval; LS mean = least squares mean; N = total number of subjects; OPC = opicapone; SE = standard error

Note: Statistical analyses are based on the ANCOVA model M3 as specified in Table 3. p-values for treatment group differences are 2-sided, based on type III sums of squares, and not adjusted for multiplicity.

a Results are based on a mixed model for repeated measures, with the change from baseline to V7 presented.

The model included study, treatment group and region as fixed effects and baseline OFF-time as a covariate. The treatment × study, and treatment × region terms were also fitted.

In both Study 301 and Study 302, the proportion of OFF-time responders in the FAS was significantly higher in the opicapone 25 mg group (60 to 62%) and the opicapone 50 mg group (66 to 70%) compared to placebo (48 to 50%; $p < 0.05$). Likewise, the proportion of ON-time responders was significantly higher in the opicapone 50 mg group (62 to 65%) than in the placebo group (45 to 46%; $p < 0.05$); the proportion of ON-time responders in the opicapone 25 mg group (57 to 63%) was also higher than in the placebo group, but the difference was only statistically significant in Study 302 ($p = 0.0061$).

When the Phase 3 studies were integrated, the proportions of OFF- and ON-time responders were higher at endpoint for both the 25 mg and 50 mg opicapone treatment groups compared to placebo, with statistically significant differences for both opicapone doses.

To expand on this, an analysis was performed to look at increments of OFF-time reduction/ON-time increase beyond 1 hour. These analyses showed that a statistically significantly higher proportion of subjects had an OFF-time reduction/ON-time increase of at least 2.5 hours in the opicapone 50 mg group compared to placebo in the integrated Phase 3 population.

The vast majority of the gain in ON-time was due to an increase in ON-time without troublesome dyskinesia (the sum of ON without dyskinesia and with non-troublesome dyskinesia). As for the total ON-time, the LS mean change at endpoint in ON-time without troublesome dyskinesia was highest in the opicapone 50 mg group (Study 301: 109.1 minutes, Study 302: 85.6 minutes), and lowest in the placebo group (Study 301: 46.5 minutes, Study 302: 48.2 minutes). The difference to placebo was statistically significant for the opicapone 50 mg group in Study 301 ($p = 0.0016$) but not in Study 302 ($p = 0.0651$).

When the Phase 3 studies were integrated, the results supported those of the individual studies, and the ANCOVA analysis (M3) demonstrated consistent superiority of the opicapone 50 mg and 25 mg groups compared to placebo. All LS mean gains in ON-time (total ON-time, ON-time with troublesome dyskinesia, and ON-time without troublesome dyskinesia) were highest with opicapone 50 mg group and

lowest with placebo, with significant differences to placebo in both opicapone groups ($p < 0.01$) in total ON-time and ON-time without troublesome dyskinesia. Similar results were obtained when the ANCOVA was repeated using model M1. As observed in the individual studies, increases in ON-time with troublesome dyskinesia were minimal.

In both Study 301 and Study 302, the LS mean change at endpoint in percentage OFF-time was the highest in the opicapone 50 mg group (-12.1% in Study 301 and Study 302) and lowest in the placebo group (Study 301: -5.6%, Study 302: -6.7%), with a statistically significant difference between the opicapone 50 mg group and placebo. When the Phase 3 studies were integrated, the results supported those of the individual studies, and the ANCOVA analysis demonstrated superiority of the 25 mg and 50 mg opicapone treatment groups compared to placebo in the LS mean change at endpoint in percentage OFF-time).

In both Study 301 and Study 302, the changes from baseline to endpoint in UPDRS Part II (OFF) and UPDRS III (ON) showed slight improvements in all treatment groups. When the Phase 3 studies were integrated, the results were consistent with those of the individual studies, with no significant differences between the 25 mg and 50 mg opicapone groups and placebo or entacapone.

For the Investigator's Global Assessment of Change, a responder was defined for the integrated analysis as a subject whose score was much or very much improved from baseline to endpoint. Although responders were not defined in the individual studies, the definition for responders used for the integrated analysis was also applied to the individual studies for comparison. When the Phase 3 studies were integrated, the proportions of responders were higher at endpoint in the 25 mg and 50 mg opicapone treatment groups compared to placebo, consistent with the results of the individual studies. The comparison of entacapone to opicapone in Study 301 showed that entacapone had a lower proportion of responders at endpoint (19.2%) than opicapone 50 mg (27.8%), and the tendency for a better response in assessment scores was significant in the opicapone 50 mg group ($p = 0.0070$).

For the Subject's Global Assessment of Change, a responder was defined for the integrated analyses as a subject whose score was much or very much improved from baseline to endpoint. When the Phase 3 studies were integrated, the proportions of responders were higher at endpoint in the 25 mg and 50 mg opicapone treatment groups compared to placebo, and the difference to placebo was significant for both opicapone groups by the CMH test. The proportion of responders in the entacapone group in Study 301 was 20.0%, and comparisons between opicapone and entacapone indicate a tendency for a better response in assessment scores in the opicapone 50 mg group ($p = 0.0091$) and the 25 mg group (0.0370).

2.5.7. Supportive study(ies)

2.5.7.1. Study BIA-91067-201

Study 201 was a Phase 2, 3-centre, DB, randomised, placebo-controlled, crossover study with 4 consecutive single-dose treatment periods in subjects with Parkinson's disease and predictable signs of end-of-dose deterioration treated with IR 100 mg/25 mg L-DOPA/carbidopa or 100 mg/25 mg L-DOPA/benserazide. The washout period between doses was at least 10 days.

Methods

The primary objective was to investigate the effect of 3 single oral doses of opicapone (25 mg, 50 mg, and 100 mg) on the L-DOPA pharmacokinetics (PK) when administered in combination with IR 100 mg/25 mg L-DOPA/DDCI (carbidopa or benserazide) in Parkinson's disease subjects.

The secondary objectives were to investigate:

- The tolerability, safety and PK of opicapone (at 25 mg, 50 mg, and 100 mg) when co-administered with IR 100 mg/25 mg L-DOPA/DDCI (carbidopa or benserazide) in Parkinson's disease subjects.
- The dose effect of opicapone on the motor response to IR 100 mg/25 mg L-DOPA/DDCI (carbidopa or benserazide) in Parkinson's disease subjects.
- The dose effect of opicapone on the S-COMT activity when co-administered with IR 100 mg/25 mg L-DOPA/DDCI (carbidopa or benserazide) in Parkinson's disease subjects.

Key inclusion criteria were defined as follows.

- Male and female subjects of non-childbearing potential aged 30 to 75 years.
- Subjects diagnosed with Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank diagnostic criteria.
- Predictable signs of end-of-dose deterioration despite "optimal" L-DOPA/DDCI (carbidopa or benserazide) therapy.
- Stable regimen of 3 to 8 doses of IR 100 mg/25 mg L-DOPA/DDCI (carbidopa or benserazide) per day within at least 1 week prior to randomisation.
- Modified Hoehn and Yahr stage <5 in the OFF state; mean duration of OFF stage \geq 1.5 hours during waking hours.
- Concomitant anti-Parkinson's medication (other than apomorphine, entacapone, or tolcapone) in stable doses for at least 4 weeks prior to randomisation; results of clinical laboratory tests acceptable by the Investigator.

This study consisted of 4 consecutive, single-dose treatment periods for the 4 different treatments: 25 mg, 50 mg, and 100 mg opicapone, or placebo. On admission to the first treatment period, subjects were given a randomisation number to define the treatment sequence (the order by which the subject would receive the opicapone/placebo treatments). Each subject received each of the 3 opicapone doses and placebo in a random sequence with a 3:1 ratio (opicapone:placebo) per treatment period.

Each treatment period was 5 days long. The opicapone/placebo dose was only co-administered with L-DOPA on Day 3 of each 5-day period. On all other treatment days, subjects were only given their normal morning dose of 100 mg/25 mg L-DOPA/DDCI (carbidopa or benserazide). Efficacy (S-COMT activity) and PK assessments (L-DOPA, 3-OMD, and opicapone levels) were made both prior to and after the morning L-DOPA dose on Days 2, 3, and 4. S-COMT activity was also measured on Day 5 at discharge (48 hours after receiving the opicapone/placebo dose). ON/OFF times were recorded between admission to and discharge from each period.

The primary efficacy variable was the L-DOPA PK. This was considered an appropriate surrogate marker for clinical efficacy, as the therapeutic action of catechol-O-methyltransferase (COMT) inhibitors is exerted mainly via an increase in the systemic exposure to L-DOPA.

Secondary efficacy variables included pharmacodynamic (PD) measurements based on S-COMT activity and on motor response (including ON duration, time to ON and time to best ON).

Results

Compared to placebo, opicapone increase the rate (C_{max}) and systemic exposure to L-DOPA (AUC_{0-6}) in a dose dependent manner on both Days 3 and 4 (post-dose). On Day 3, there was an increase in L-DOPA C_{max} of 8.26% with 50 mg opicapone (mean opicapone/placebo ratio [90% CI]=108.26 [88.45; 132.52]) and 29.05% with 100 mg opicapone (mean opicapone/placebo ratio=129.05 [105.71;

157.53]). There was no increase in C_{max} with 25 mg opicapone. There was an increase in L-DOPA AUC₀₋₆ of 3.74% with 25 mg opicapone (mean opicapone/placebo ratio=103.74 [83.30; 129.20]) to 34.83% with 100 mg opicapone (opicapone/placebo ratio=134.83 [108.46; 167.62]). No statistical differences were found for t_{max} between any opicapone doses and placebo. On Day 4, similar results were seen, with a greater increase in AUC compared to Day 2 (pre-dose) in the 25 mg and 50 mg opicapone groups than was seen on Day 3. A marked decrease in both rate (C_{max}) and extent of systemic exposure (AUC) to 3-OMD occurred with 100 mg opicapone in comparison to placebo. No statistical differences were found in the rate or extent to 3-OMD when comparing Days 3 and 4 to Day 2. Both rate (C_{max}) and extent (AUC) of systemic exposure to opicapone increased in a dose-dependent manner. Plasma concentrations of BIA 9-1079 could only be quantified following opicapone administration at doses of 50 mg and 100 mg, for which both rate and extent of systemic exposure to BIA 9-1079 increased in a dose-dependent manner. No statistical difference was found for t_{max} between any of the opicapone doses and placebo.

All opicapone treatments markedly inhibited both peak and extent of S-COMT activity in a dose-dependent manner when compared to placebo. E_{max} occurred (tE_{max}) between 1.9 hours (100 mg opicapone) and 4.65 hours (25 mg opicapone) post-dose compared to 12.4 hours with placebo, and ranged from 67.8% (25 mg opicapone) to 80.0% (100 mg opicapone) compared to 15.4% with placebo.

PD assessments based on motor response did not show consistent dose-dependence in relation to time to ON and time to best ON following administration of opicapone. Increases in total ON-time and mean total ON-time without dyskinesias were observed following administration of 25 and 50 mg opicapone, but differences between active treatments and placebo did not attain statistical significance.

In conclusion, this short, single-dose study, showed that opicapone, administered concomitantly with IR 100 mg/25 mg L-DOPA/carbidopa or 100 mg/25 mg L-DOPA/benserazide, increased the extent of systemic exposure to L-DOPA, decreased exposure to 3-OMD, decreased S-COMT activity, and improved to some extent the subject's motor performance.

2.5.7.2. Study BIA-91067-202

Study BIA-91067-202 was a Phase 2, multicentre, DB, randomised, placebo-controlled, multiple-dose study in 4 parallel groups of Parkinson's disease subjects with motor fluctuations ("wearing-off" phenomenon) treated with CR 100 mg/25 mg L-DOPA/DDCI (carbidopa or benserazide).

Methods

The primary objective was to investigate the effect of repeated dosing of opicapone (5 mg, 15 mg and 30 mg, QD) on the L-DOPA PK, in comparison to placebo, in Parkinson's disease subjects with motor fluctuations.

The secondary objectives were to investigate

- The tolerability, safety, and PK of repeated dosing of opicapone (at 5 mg, 15 mg, and 30 mg).
- The effect of repeated dosing of opicapone on the motor response to CR 100 mg/25 mg L-DOPA/carbidopa or 100 mg/25 mg L-DOPA/benserazide.
- The effect of repeated dosing of opicapone on S-COMT activity in Parkinson's disease subjects with motor fluctuations.

Key inclusion criteria were defined as follows. At screening (admission to the baseline period):

- Male and female subjects of non-childbearing potential ≥ 30 years old.

- Subjects diagnosed with Parkinson's disease according to the United Kingdom (UK) Parkinson's Disease Society Brain Bank diagnostic criteria.
- Predictable signs of end-of-dose deterioration despite "optimal" L-DOPA/carbidopa or L-DOPA/benserazide therapy.
- Modified Hoehn and Yahr stage <5 in the OFF state; mean duration of OFF stage \geq 1.5 hours during waking hours.

At randomisation (completion of the baseline period):

- Treated with a stable regimen of 3 to 8 daily doses of IR 100 mg/25 mg L-DOPA/carbidopa or 100 mg/25 mg L-DOPA/benserazide within at least 1 week prior to randomisation.
- Mean duration of OFF state \geq 1.5 hours during waking hours (average of recordings of last 3 evaluable days on subject's diary).
- Concomitant anti-Parkinson's disease medication (other than apomorphine, entacapone, or tolcapone) in stable doses for at least 4 weeks prior to randomisation; results of clinical laboratory tests acceptable by the Investigator.

At admission to the baseline period, the L-DOPA/carbidopa or L-DOPA/benserazide formulation used by the subjects prior to admission was replaced by the CR L-DOPA/carbidopa or L-DOPA/benserazide branded formulations Sinemet® 100 mg/25 mg or Madopar®/Restex® 100 mg/25 mg. A stable regimen of 3 to 8 daily doses of these formulations was established and maintained for at least 1 week prior to randomisation.

After the baseline period, subjects were randomised in a 1:1:1:1 ratio to the 4 treatment groups: placebo, 5 mg, 15 mg, or 30 mg QD opicapone. Two L-DOPA test doses were used to measure several efficacy and PK variables before and after opicapone/placebo treatment during the maintenance period. Each of the L-DOPA tests required subject admission to the research facility.

The first L-DOPA test was given on Day 1 of the maintenance period, prior to the start of opicapone/placebo treatment. The L-DOPA test was a single dose of CR 100 mg/25 mg L-DOPA/carbidopa or 100 mg/25 mg L-DOPA/benserazide. After a minimum of 6 hours post-dose, subsequent doses of L-DOPA/carbidopa or L-DOPA/benserazide were administered respectively as subjects were newly OFF. Twelve hours after L-DOPA test procedures, subjects could leave the research facility.

From Day 2 through the end of maintenance (up to 21 to 28 days), opicapone/placebo treatments were administered in addition to each subject's baseline-established L-DOPA/carbidopa or L-DOPA/benserazide regimen. Opicapone/placebo was administered orally in the morning, after waking-up, with approximately 200 mL of water and in fasting. Subjects were to remain fasted until at least 1.5 hours post-dose. The morning dose of 100 mg/25 mg L-DOPA/carbidopa or 100 mg/25 mg L-DOPA/benserazide was administered 1 hours after the opicapone/placebo dose.

The second L-DOPA test was given at the end of the maintenance period. Treatments and procedures followed those for the first L-DOPA test.

As for Study 201, the primary efficacy variable in Study 202 was also the L-DOPA PK. This was considered an appropriate surrogate marker for clinical efficacy, as the therapeutic action of COMT inhibitors is exerted mainly via an increase in the systemic exposure to L-DOPA.

Secondary efficacy variables included PD measurements based on S-COMT activity, and several variables derived from the following assessments:

- Motor response to the L-DOPA tests (time to ON, time to best-ON, onset of “wearing-off” after the L-DOPA/DDCI dose, modified Abnormal Involuntary Movement Scale and UPDRS III responses before L-DOPA/DDCI dose and at best-ON).
- Subject’s diary (ON/OFF periods and times of L-DOPA/DDCI and IMP medications).
- Investigator’s and Subject’s Global Assessment of Change.
- UPDRS - Sections I, II, and III, IV, and VI (baseline scores, endpoint scores, and changes from baseline).

Results

A total of 46 subjects were enrolled in the study, 40 were randomised to 1 of the 4 treatment groups, and 36 completed the study. The population had a mean age of 68 years (range: 49 to 88 years), was 100% Caucasian and 50% male, with no relevant differences between treatment groups.

At the end of the maintenance phase (second L-DOPA test), the extent of exposure to L-DOPA as measured by AUC₀₋₆ increased in a dose-dependent manner, with significant increases for the 15 mg and 30 mg opicapone treatment groups compared to baseline (first L-DOPA test): 53.93% increase with 15 mg opicapone (second L-DOPA test/baseline mean [90% CI]=153.93 [104.43; 226.89]); and 65.61% increase with 30 mg opicapone (165.61 [125.64; 218.29]). The mean increase in L-DOPA C_{max} ranged from 8.11% with 15 mg opicapone (second L-DOPA test/baseline mean [90% CI]=108.11 [77.78; 150.26]) to 48.25% with 30 mg opicapone (148.25 [104.38; 210.56]). No statistical difference was found for t_{max} between any of the opicapone doses and placebo.

A marked and dose-dependent decrease in both rate (C_{max}) and extent of exposure (AUC₀₋₆) to 3-OMD occurred with all opicapone doses compared to baseline. The mean decrease in 3-OMD AUC₀₋₆ ranged from 37.06% with 5 mg opicapone (second L-DOPA test/baseline mean [90% CI]=62.94 [50.29; 78.80]) to 71.58% with 30 mg opicapone (28.42 [19.63; 41.16]). The mean decrease in 3-OMD C_{max} ranged from 41.78% with 5 mg opicapone (second L-DOPA test/baseline mean [90% CI]=58.22 [46.11; 73.53]) to 72.18% with 30 mg opicapone (second L-DOPA test/baseline mean [90% CI]=27.82 [19.16; 40.41]).

Mean C_{max} levels of opicapone, attained at 2 hours post-dose, were 2-fold higher in the 30 mg treatment group than in the 5 mg and 15 mg treatment groups (similar C_{max} values), suggesting a degree of interaction between opicapone and L-DOPA/DDCI during the absorption phase. Plasma concentrations of BIA 9-1079 were below the limit of quantification for all opicapone dose levels.

All opicapone treatments markedly inhibited both peak and extent of S-COMT activity in a dose-dependent manner in comparison to placebo. The average values of maximum S-COMT inhibition (E_{max}) occurred between 0.89 hours (30 mg opicapone) and 2.57 hours (15 mg opicapone) post-dose (tE_{max}) compared to 3.00 hours with placebo, and ranged from 52.0% inhibition (5 mg opicapone) to 79.8% inhibition (30 mg opicapone) compared to 15.1% with placebo.

During the maintenance phase, motor response based on subject diaries significantly improved for the 15 mg and 30 mg opicapone treatment groups, as assessed by OFF-time responder rates (subjects with a reduction of at least 1 hour in absolute OFF-time since baseline) and ON-time responder rates (subjects with an increase of at least 1 hour in absolute total ON-time since baseline). OFF-time responder rates increased 87.5% from baseline (p=0.0024) in the 15 mg opicapone group and 66.7% from baseline (p=0.0090) in the 30 mg opicapone group. ON-time responder rates increased 87.5% in the 15 mg opicapone group (p=0.0203) and 77.8% in the 30 mg opicapone group (p=0.0323). Other secondary variables demonstrated similar improvements in the opicapone treatment groups compared to placebo, but none reached statistical significance.

This Phase 2 study in Parkinson's disease subjects with "wearing-off" phenomenon showed that all opicapone doses (5, 15, and 30 mg QD), administered for up to 28 days with CR 100 mg/25 mg L-DOPA/DDCI, increased the extent of systemic exposure to L-DOPA, decreased exposure to 3-OMD and decreased S-COMT activity. The study was not designed to detect any significant differences in motor performance, but exploratory analyses showed improvement in various motor outcomes, including a dose-dependent change in absolute OFF-time. Results were highly consistent across the multiple analyses performed and showed that 30 mg opicapone tended to be the most efficacious treatment tested, followed by 15 mg opicapone.

2.5.8. Discussion on clinical efficacy

Design and conduct of clinical studies

In the 2 Phase 3 DB studies, 1027 subjects were randomised in 30 countries (22 European countries, and Russia, Argentina, Australia, Chile, India, Israel, South Africa, and South Korea), and 1010 began treatment. Efficacy analyses were performed on the Full Analysis Set (FAS) and/or the Per Protocol (PP) Set of the individual studies or the combined study populations. For Study 302, all 15 subjects from Site 1703 were excluded from the Safety Set, the FAS, and the PP Set for the individual study and the combined study populations, due to questionable data validity.

The demographic characteristics were similar across treatment groups for most characteristics in the integrated population and in the individual Phase 3 studies. The population was predominantly Caucasian (100% in Study 301 and 72.2% in Study 302), 59% male, with a mean age of <70 years and a mean body mass index (BMI) ranging from 26.4 to 26.7 kg/m² in the FAS.

Baseline Parkinson's disease characteristics did not differ significantly between the treatment groups for most characteristics in the integrated population or in the individual studies. The mean duration of Parkinson's disease was slightly shorter in Study 301 compared to Study 302 (from 6.99 to 7.71 years across the treatment groups in Study 301 and from 7.73 to 8.54 years in Study 302), as was the mean duration since the onset of motor fluctuations (from 2.16 to 2.32 years before subjects were included in Study 301 and from 3.02 to 3.22 years before inclusion in Study 302). The mean time since the start of L-DOPA treatment was similar across the treatment groups in both studies in the FAS (ranging from 5.31 to 5.89 years in Study 301 and 6.77 to 7.22 years in Study 302).

Baseline absolute OFF-time ranged from 6.1 hours to 6.9 hours in both studies. Dyskinesia was present at baseline in 41.7% to 47.1% of subjects across the treatment groups in Study 301 and 52.0% to 54.4% of subjects in Study 302. In both studies, most of the dyskinesia at baseline was non-troublesome and lasted for a mean of 0.88 to 1.1 hours in Study 301 and 1.7 to 2.4 hours in Study 302.

Unified Parkinson's Disease Rating Scale (UPDRS) scores were slightly higher at baseline in Study 301 compared to Study 302 for Part III UPDRS scores at ON state (between 25.8 and 29.0 points in Study 301 vs. 21.5 and 22.5 in Study 302), total UPDRS scores (between 35.4 and 40.1 points in Study 301 vs. 30.8 and 31.7 points in Study 302) and the mean Schwab and England scores (between 81.9 and 82.9% in Study 301 vs. 82.8% and 84.7% in Study 302).

The mean Hoehn and Yahr scores (ranging from 2.3 to 2.4) were similar across all treatment groups in both studies.

Subjects had to be treated with L-DOPA/DDCI for at least 1 year with clear clinical improvement prior to inclusion in either Phase 3 study. The mean time since the start of L-DOPA treatment was similar across the treatment groups in both studies in the FAS (ranging from 5.31 to 5.89 years in Study 301 and 6.77

to 7.22 years in Study 302). In both Phase 3 studies, nearly all subjects (>88% in any treatment group) were taking immediate-release L-DOPA/DDCI formulations and approximately half of each study population was taking L-DOPA/carbidopa and the other half was taking L-DOPA/benserazide.

In the placebo and Opicapone 25 mg and 50 mg groups in both Study 301 and 302, roughly 2/3 of the subjects were taking dopamine agonists, roughly 20% were taking MAO inhibitors, close to 10% were taking anticholinergics, and close to 1/4 were taking amantadine (22.6% to 25.0%). In both Phase 3 studies, the most commonly used anti-Parkinson's disease medications at baseline (>10% in any treatment group) were pramipexole, ropinirole, amantadine, and rasagiline.

Efficacy data and additional analyses

The primary efficacy variable in the Phase 3 studies was the change in absolute OFF-time from baseline to the end of the DB period (endpoint), where the baseline value was the average OFF-time of the diaries completed on the last 3 days prior to V2, and the endpoint value was the average OFF-time of diaries completed on the last 3 days under treatment in the DB period prior to V7. In an additional requested analysis all patients randomised and treated were included (FAS2) and modified BOCF was used to impute missing data (where the worst of the baseline or last observation is used to impute missing data). If diary data were available from <3 days for either baseline or endpoint, the mean of the data from the available days was used.

Since the primary efficacy variable was the same in both studies, it was possible to perform a series of statistical analyses to evaluate the consistency and robustness of results across the 2 studies and when the studies were combined. Six different analyses of covariance (ANCOVA) were used to model the change in absolute OFF-time from baseline to endpoint (i.e. while on treatment) for the combined study results. In addition, subgroup analyses were done on the primary efficacy variable to evaluate the consistency of results across pre-defined intrinsic factors (age, gender, race, BMI, UPDRS V score at baseline and disease duration at study entry) and extrinsic factors (L-DOPA daily dose and L-DOPA formulation at baseline, concurrent usage of dopamine agonists at baseline, and concurrent usage of MAO inhibitors at baseline), and the different geographical areas and countries.

Secondary efficacy variables included proportion of OFF-time and ON-time responders, ON-time increase from baseline to endpoint (with and without troublesome dyskinesia), and the change in percentage OFF- and ON-time from baseline to endpoint, all of which were based on subject diary data. Other secondary efficacy variables were based on the following questionnaires: UPDRS, Parkinson's Disease Sleep Scale (PDSS), Parkinson's Disease Questionnaire (PDQ-39), Non-motor Symptoms Scale (NMSS), and the Investigator's and Subject's Global Assessment of Change.

In both Study 301 and Study 302, the estimated mean change (LS means) from baseline in absolute OFF-time at endpoint was largest in the Opicapone 50 mg group (-103.6 minutes in Study 301 and -107.0 minutes in Study 302) with a statistically significant difference to placebo (Study 301: LS mean difference -55.3 minutes, $p=0.0032$, Study 302: LS mean difference -52.4 minutes, $p=0.0053$, demonstrating superiority of the Opicapone 50 mg dose over placebo. Changes from baseline in the Opicapone 25 mg groups (Study 301: -73.2 minutes; Study 302: -93.2 minutes) and the Opicapone 5 mg group (Study 301 only: -77.6 minutes) were both greater than in placebo, but the differences were not statistically significant.

Table 48 Change in absolute OFF-time (minutes) from baseline to endpoint (BOCF) – ANCOVA with region as factor and baseline OFF-time as covariate (Study 301)

Treatment comparison	N	LS mean (SE)	95% CI	2-sided p-value	1-sided p-value
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Treatment comparison	N	LS mean (SE)	95% CI	2-sided p-value	1-sided p-value
FAS2					
Placebo	121	-48.3 (13.46)	-74.7, -21.8	--	--
OPC 5 mg	122	-77.6 (13.39)	-103.9, -51.3	--	--
OPC 25 mg	119	-73.2 (13.67)	-100.1, -46.4	--	--
OPC 50 mg	115	-103.6 (14.08)	-131.2, -75.9	--	--
Entacapone	122	-78.7 (13.38)	-105.0, -52.4	--	--
Test for superiority					
OPC 5 mg – Placebo	--	-29.3 (18.41)	-65.5, 6.8	0.1117	0.0558
OPC 25 mg – Placebo	--	-25.0 (18.60)	-61.5, 11.6	0.1803	0.0902
OPC 50 mg – Placebo	--	-55.3 (18.68)	-92.0, -18.6	0.0032	0.0016
Test for non-inferiority					
OPC 5 mg – Entacapone	--	1.1 (18.32)	-34.9, 37.1	--	0.0578
OPC 25 mg – Entacapone	--	5.5 (18.48)	-30.8, 41.8	--	0.0927
OPC 50 mg – Entacapone	--	-24.8 (18.63)	-61.4, 11.8	--	0.0017
Per Protocol					
Placebo	112	-52.2 (13.79)	-79.3, -25.1	--	--
OPC 5 mg	110	-84.4 (13.91)	-111.7, -57.0	--	--
OPC 25 mg	105	-87.1 (14.33)	-115.2, -58.9	--	--
OPC 50 mg	106	-106.1 (14.49)	-134.6, -77.6	--	--
Entacapone	104	-79.8 (14.47)	-108.2, -51.4	--	--
Test for superiority					
OPC 5 mg – Placebo	--	-32.2 (18.86)	-69.2, 4.9	0.0885	0.0443
OPC 25 mg – Placebo	--	-34.9 (19.11)	-72.4, 2.6	0.0684	0.0342
OPC 50 mg – Placebo	--	-53.9 (18.99)	-91.2, -16.6	0.0047	0.0024
Test for non-inferiority					
OPC 5 mg – Entacapone	--	-4.5 (19.14)	-42.1, 33.0	--	0.0358
OPC 25 mg – Entacapone	--	-7.3 (19.36)	-45.3, 30.8	--	0.0275
OPC 50 mg – Entacapone	--	-26.3 (19.35)	-64.3, 11.7	--	0.0019

BOCF = baseline observation carried forward for subjects who discontinued IMP before Day 81 and have improved otherwise the last observation under treatment; Non-inferiority margin = 30 minutes.

Table 49 Change in absolute OFF-time (minutes) from baseline to endpoint (BOCF) – ANCOVA with region as factor and baseline OFF-time as covariate (FAS2, Study 302)

Treatment comparison	N	LS mean (SE)	95% CI	2-sided p-value
Placebo	136	-54.6 (14.26)	-82.7, -26.6	--
OPC 25 mg	125	-93.2 (14.81)	-122.3, -64.0	--
OPC 50 mg	150	-107.0 (13.57)	-133.7, -80.4	--
OPC 25 mg – Entacapone	--	-38.5 (19.57)	-77.0, -0.1	0.0496
OPC 50 mg – Entacapone	--	-52.4 (18.68)	-89.1, -15.7	0.0053

BOCF = baseline observation carried forward for subjects who discontinued IMP before Day 81 and have improved otherwise the last observation under treatment

The integrated analyses of the Phase 3 studies confirmed those of the individual studies and consistently demonstrated superiority of the 50 mg and 25 mg Opicapone doses over placebo in all models tested, with significant differences for both Opicapone doses in the LS mean difference to placebo for the change from baseline in absolute OFF-time at endpoint. The discussion below focusses on models M3, because it is as close as possible to the models specified for the primary analysis in the individual studies using a harmonized definition of regional geographical areas across studies.

Table 50

Change in absolute OFF-time (minutes) from baseline to endpoint using ANCOVA model M3 (integrated Phase 3 studies, Full Analysis Set)

ANCOVA Model Statistic	Placebo (N=255)	OPC 25 mg (N=241)	OPC 50 mg (N=262)
ANCOVA M3			
LS mean (SE)	-55.5 (10.90)	-92.9 (10.65)	-119.9 (10.54)
Difference in LS mean (SE) with Placebo	--	-37.4 (15.25)	-64.4 (15.16)
95% CI for Difference with Placebo	--	(-67.4; -7.5)	(-94.2; -34.7)
p-value	--	0.0143	<0.0001

Source data: [Table 2.7.3.P.2.1](#), [Table 2.7.3.P.6.1](#)

ANCOVA = analysis of covariance; CI = confidence interval; LS mean = least squares mean; MMRM = mixed model for repeated measures; N = total number of subjects; OPC = opicapone; SE = standard error

Note: Statistical analyses are based on the ANCOVA model specified in [Module 2.7.3](#), [Table 3](#). p-values for treatment group differences are 2-sided, based on type III sums of squares, and not adjusted for multiplicity.

The model included study, treatment group and region as fixed effects and baseline OFF-time as a covariate. The treatment × study, and treatment × region terms were also fitted. All group comparisons from the ANCOVA model were based on Type III sums of squares.

The robustness of these results was confirmed in a series of supportive ANCOVA that repeated the primary model using a variety of different factors and covariates.

Furthermore, none of the subgroup analyses showed an interaction with the subgroup tested, indicating that the findings are consistent across all subgroups evaluated. In particular, neither a treatment by study nor a treatment by geographical region interaction was observed (p-value >0.8 throughout) indicating a consistent treatment effect across the 2 studies and geographical areas, and the positive effect of Opicapone was seen with both immediate-release and controlled-release formulations of L-DOPA. The change in OFF-time and the treatment effects were consistent across both studies, as seen by the p-values associated with the factor study and the p-values associated with the factor treatment by study.

Subjects in the Phase 3 studies were allowed to take the selective MAO inhibitors rasagiline (up to 1 mg/day) and selegiline (up to 10 mg/day in oral formulation or 1.25 mg/day in buccal formulation) concomitantly with their Opicapone treatment. Those subjects who had concurrent use of these selective MAO inhibitors at baseline had a smaller change from baseline to endpoint in absolute OFF-time in all treatment groups (placebo and Opicapone) compared to subjects who did not have concurrent use of MAO inhibitors. However, the relative difference between treatment groups was similar in both subgroups and consistent with the results in the overall FAS, and the greatest decrease in both subgroups was in the Opicapone 50 mg group in the integrated Phase 3 population. Statistical model assessing the use of MAO inhibitors at baseline confirmed there was neither an effect of the using these (p=0.1269) nor an interaction for concurrent use with MAO inhibitors with treatment (p=0.8558).

Comparison of Opicapone to entacapone in Study 301 showed that the decrease in the estimated mean change (LS means) from baseline in absolute OFF-time at endpoint in the FAS2 (BOCF) was greater in the

Opicapone 50 mg group (-106.1 minutes) than in the entacapone group (-79.8 minutes). The Opicapone 50 mg group was shown to be non-inferior to entacapone and the estimates of the difference (-26.3 minutes) indicate a tendency for greater OFF-time reductions with Opicapone 50 mg compared to entacapone.

Analysis of the secondary efficacy variables demonstrated consistent efficacy in the Opicapone 50 mg group to that seen for the primary efficacy variable.

When Opicapone was compared to entacapone in Study 301, Opicapone was as good as or better than entacapone for several efficacy variables. Higher OFF- and ON-time responder rates were observed in the Opicapone 50 mg group (OFF-time responders: 75/115 (65.2%) Opicapone 50 mg vs. 66/122 (54.1%) entacapone; ON-time responders: 670/115 (60.9%) Opicapone 50 mg vs. 65/122 (53.3%) entacapone. Likewise, for all ON-times, the LS mean change at endpoint (LOCF) was consistently greater in the Opicapone 50 mg group than in the entacapone group (LS mean gain of 19.3 minutes for total ON-time, 15.0 minutes for ON-time without troublesome dyskinesia, 4.3 minutes for ON-time with troublesome dyskinesia. The differences in percentage OFF- or ON-time were similar in the Opicapone and entacapone groups.

However, for both Investigator's Global Assessment of Change and Subject's Global Assessment of Change there was a statistically significant difference compared to entacapone, indicating a tendency for a better response with Opicapone. For the Investigator's Global Assessment of Change, entacapone had a lower proportion of subjects with an assessment of much improved or very much improved at endpoint (19.2%) than Opicapone 50 mg (27.8%), and the tendency for a better response in assessment scores was statistically significant for the Opicapone 50 mg group ($p=0.0070$). For Subject's Global Assessment of Change, more Opicapone subjects had an assessment of much improved or very much improved compared to entacapone subjects, and the tendency for a better response in assessment scores was statistically significant for both the Opicapone 50 mg group ($p=0.0091$) and the 25 mg group (0.0370).

The efficacy of Opicapone achieved during the initial 14 to 15 weeks of treatment in the Phase 3 controlled, DB studies appeared to be maintained, and even improved slightly, over the course of a subsequent year of treatment in the 1-year, OL extension of Study 302. At the end of the 1-year OL extension study, OFF-time had decreased by a further 21.8 minutes relative to the OL baseline, corresponding to an OFF-time reduction of more than 2 hours (-126.3 minutes) relative to the original DB baseline. Similarly, total ON-time had increased by 24.9 minutes from OL baseline (127.3 minutes compared to DB baseline). A draft report of the OL extension of Study 301 showed generally similar results.

The changes in OFF- and ON-time based on the prior treatment during the DB period (either DB Opicapone or DB placebo) showed that, although both groups had further decreases in OFF-time and increases in ON-time compared to the OL baseline, the changes were greater in those subjects previously treated with placebo. At the end of the OL period, 68.4% of subjects were OFF-time responders and 65.8% were ON-time responders (relative to DB baseline) in the FAS, which was slightly higher than that observed at the end of the DB period.

Furthermore, the positive benefits of Opicapone treatment perceived by subjects and investigators at the end of the DB period were maintained after 1 year of treatment in the OL extension. About 60% of the subjects at the end of the OL period were assessed by investigators and subjects as having improved (i.e. much or very much improved) relative to the DB baseline, which was slightly above the rate observed at the end of the DB period.

Efficacy in the 2 supportive Phase 2 studies was assessed based on L-DOPA PK and measures of changes in motor response, including ON duration (defined as the interval between ON onset and the onset of

wearing-OFF after the morning dose of L DOPA on Days 2, 3, and 4), time to ON, time to best ON, number of doses of 100 mg/25 mg L-DOPA/carbidopa or 100 mg/25 mg L DOPA/benserazide per day, and subject responses to UPDRS Part III. The L-DOPA tests in Study 202 were performed at the start and the end of the maintenance period.

In both Study 201 and in Study 202, there was an increase in both the rate (C_{max}) and extent (AUC₀₋₆) of L-DOPA exposure with increasing dose of Opicapone. In both Study 201 and Study 202, all Opicapone treatments markedly inhibited both peak and extent of S-COMT activity in a dose-dependent manner compared to placebo.

Consistent with this, in the multiple-dose Study 202, after up to 28 days of treatment at the second L-DOPA test, Opicapone generally increased mean ON-time and decreased mean time to ON in motor tests, increased the mean change in absolute OFF-time and the percentage of ON-time without troublesome dyskinesia relative to baseline while decreasing the percentage OFF-time based on subject diary data, and increased the proportion of subjects who improved according to the Investigator's and Subject's Global Assessment of Change. These changes increased with increasing dose of Opicapone, and the differences in the higher Opicapone groups were greater than in the placebo group, although the differences were generally not statistically significant. The mean UPDRS scores for Parts I, II, and III were also consistently lower following administration of all doses of Opicapone compared to placebo, although these differences were not major.

In Study 201, despite being a single-dose study, and therefore unlikely to produce relevant changes in efficacy, the effects of Opicapone on motor responses were generally greater than for placebo, and in some cases the differences to placebo were quite notable. Mean UPDRS Part III scores were also lower (indicating less disability) following administration of 25 mg, 50 mg, and 100 mg Opicapone compared to placebo.

2.5.9. Conclusions on the clinical efficacy

Clinical efficacy has been evaluated in two appropriately designed and well executed phase III clinical studies. The chosen efficacy endpoints are appropriate and acceptable. The results support the claim of efficacy in up to 15 weeks demonstrating superiority to placebo and non-inferiority to entacapone, a marketed drug of similar mechanism of action. Clear dose-response relationship was not established, but daily dose of 50mg has proven to be consistently efficacious. A number of issues for clarification have been raised regarding the conduct of the phase III studies, all of which were subsequently adequately addressed.

The long term efficacy has been examined in an open label extension lasting approximately one year. There was no loss of efficacy and the subjects who entered OL extension after receiving placebo in the DB phase showed the largest improvement. While in absolute terms the subjects who were on Opicapone longer (those who received Opicapone in DB) exhibited larger overall improvement, the lack of control and limitations of the open label methodology preclude from making a reliable conclusion that there is an additional benefit in using Opicapone early.

Supportive evidence of clinical efficacy has been provided in two phase 2 PK studies. In these studies plasma L-DOPA exposure was considered a surrogate marker of efficacy. The studies showed an expected dose dependent raise in L-DOPA exposure with Opicapone. The L-DOPA exposure can be accepted as a surrogate efficacy marker in principle, but the lack of clear correlation with the observed efficacy makes the results of these studies only suitable as an additional support to the results seen in the main efficacy studies.

In summary, the efficacy can be regarded as proven.

2.6. Clinical safety

Patient exposure

In the completed studies, Opicapone was administered at any dose (single or multiple) to a total of 1651 subjects: 859 healthy subjects and 792 subjects with Parkinson's disease (Table below).

All subjects who received any amount of study medication were included in the analysis of safety (Safety set) except for 15 subjects from site 1703 in Study 302, who were excluded from all analyses due to questionable validity of their data.

This includes 631 subjects with Parkinson's disease in the DB part of the Phase 3 studies taking up to 50 mg Opicapone QD for 14 to 15 weeks, plus a further 121 subjects newly exposed to Opicapone (having received placebo in the DB part) in the 1-year OL extension of Study 302.

In the Phase 2 studies, 40 subjects with Parkinson's disease received Opicapone doses up to 30 mg QD for 21 to 28 days. In the Phase 1 studies, 859 subjects were treated with Opicapone: 524 subjects who received single doses up to 1200 mg and 335 subjects with multiple doses up to 75 mg QD for 11 days.

In addition, at the cut-off date of 30 Jun 2014, a further 99 subjects had been exposed to Opicapone in the open-label part of the Phase 3 Study BIA-91067-301, which was the only study in the clinical programme that was still ongoing at that date. All doses of Opicapone were given orally in the clinical studies, as capsules. The data from the completed OL extension of Study 302 are also presented alongside the DB results, to give the long-term perspective of Opicapone safety.

The highest dose of Opicapone tested concomitantly with L-DOPA/DDCI was 100 mg in single-dose studies with healthy subjects (Studies 107, 108, 109, and 110). In drug-drug interaction studies, single doses of 50 mg Opicapone were tested with rasagiline (Study 112 and 113) and paracetamol (Study 125), 25 mg Opicapone with repaglinide (Study 115), and 25 mg Opicapone with warfarin (Study 116) and multiple doses of 50 mg Opicapone were tested with warfarin (Study 127).

Entacapone was used as active comparator in study 301.

Table 51 Patient exposure

	<i>Placebo</i>	<i>Opicapone</i>	<i>Entacapone</i>	<i>Total</i>
Phase I (27 studies) Healthy subjects	27	859	32	1013
Phase II (2 studies) Patients with PD and motor fluctuations	19	40	None	50
Phase III-DB (2 studies) Patients with PD and motor fluctuations	257	631	122	1010
Phase III-OL (1 study) Patients with PD and motor fluctuations	None	353 (121 newly treated)	None	353 (121 newly treated)
Total in completed Clinical studies	519	1651	154	2194

Adverse events

Data collected from the Phase 1, 2 and 3 studies show that the most affected SOC's are the Nervous system(dyskinesia ,headache, somnolence, dizziness, worsening of Parkinson's disease, and tremor), gastrointestinal system(nausea, upper abdominal pain, diarrhoea), skin and subcutaneous tissue disorders(hyperhidrosis and seborrheic dermatitis)and vascular system(hypertension).

In Phase 3 studies dyskinesia was the most frequently reported TEAE in all treatment groups in both studies. The incidence of dyskinesia was higher in the treatment groups when compared to placebo and slightly higher than entacapone.

In study 302 the incidence of dyskinesia was much higher for Opicapone 25mg (23.2%) and 50mg (23.3%) when compared with placebo (8.1%). The incidence of dyskinesia didn't seem to be dose related since no difference in incidence was noted between the 25mg and 50 mg in study 302.

In study 301 the 5mg (13.1%) and 50mg (14.8%) strengths had similar incidence and the 25mg (7.6%) seems to be lower.

The incidence of dyskinesia seems to decrease with time (after visit 4) in both Phase III studies and in all treatment and placebo: Opicapone 50 mg group (from 12.2% up to Visit 4 to 4.3% after Visit 4), 5 mg group (from 12.3% up to Visit 4 to 1.6% after Visit 4), and 25 mg group (from 6.7% up to Visit 4 to 3.4% after Visit 4); in the placebo group dyskinesia decreased from 3.3% to 0.8% and in the entacapone group from 5.7% to 4.1%(Study 301).

Study 302.Dyskinesia decreased for both total Opicapone (from 13.9% to 6.9%) and placebo (from 5.1% to 1.6%).

The incidence of related dizziness was similar in the entacapone (3.3%) and Opicapone groups (ranging from 1.6% with 5 mg to 3.4% with 25 mg) and higher than with placebo (0.8%).

Other related TEAEs reported more frequently in the Opicapone groups compared to placebo included dry mouth, constipation, and increased blood CPK.

In both Phase 3 studies, most TEAEs were mild or moderate in severity for all treatment groups.

In the integrated population, the results were consistent with the individual studies. The only severe TEAEs reported by more than 1% of subjects were dyskinesia with 1.2% in the Opicapone 25 mg group and 1.1% in the Opicapone 50 mg group and nausea with 1.1% in the Opicapone 50 mg group.

Treatment-emergent adverse events I

Study 301. At the cut-off date, 62.2% of subjects had experienced at least 1 TEAE, 9.5% of which had a TESAE and 5.1% had a TEAE leading to discontinuation.

Study 302. Three quarters of subjects experienced at least 1 TEAE in the OL phase compared to two thirds of subjects in the DB phase of which 46.6% were considered to be related to Opicapone by the investigators

Table 52 Incidence of treatment emergent adverse events for at least 3% of subjects in any treatment group – individual Phase 3 studies (Safety Set)

Preferred Term	Number (%) of subjects							
	Study 301					Study 302		
	Placebo N=121	Entacapone N=122	OPC 5 mg N=122	OPC 25 mg N=119	OPC 50 mg N=115	Placebo N=136	OPC 25 mg N=125	OPC 50 mg N=150
Dyskinesia	5 (4.1)	10 (8.2)	17 (13.9)	9 (7.6)	18 (15.7)	11 (8.1)	30 (24.0)	36 (24.0)
Constipation	3 (2.5)	5 (4.1)	4 (3.3)	0	7 (6.1)	2 (1.5)	12 (9.6)	10 (6.7)
Insomnia	1 (0.8)	7 (5.7)	2 (1.6)	7 (5.9)	7 (6.1)	3 (2.2)	10 (8.0)	2 (1.3)
Dry mouth	2 (1.7)	2 (1.6)	2 (1.6)	3 (2.5)	2 (1.7)	1 (0.7)	13 (10.4)	6 (4.0)
Increased blood creatine phosphokinase	0	1 (0.8)	2 (1.6)	2 (1.7)	1 (0.9)	5 (3.7)	5 (4.0)	12 (8.0)
Hypertension	3 (2.5)	2 (1.6)	4 (3.3)	2 (1.7)	2 (1.7)	3 (2.2)	8 (6.4)	6 (4.0)
Dizziness	1 (0.8)	5 (4.1)	2 (1.6)	6 (5.0)	3 (2.6)	2 (1.5)	4 (3.2)	6 (4.0)
Fall	3 (2.5)	5 (4.1)	2 (1.6)	4 (3.4)	1 (0.9)	9 (6.6)	7 (5.6)	7 (4.7)
Nausea	2 (1.7)	8 (6.6)	2 (1.6)	3 (2.5)	3 (2.6)	8 (5.9)	8 (6.4)	5 (3.3)
Headache	3 (2.5)	3 (2.5)	1 (0.8)	2 (1.7)	4 (3.5)	9 (6.6)	6 (4.8)	6 (4.0)
Parkinson's disease	1 (0.8)	0	1 (0.8)	2 (1.7)	0	7 (5.1)	9 (7.2)	6 (4.0)
Somnolence	2 (1.7)	0	1 (0.8)	4 (3.4)	2 (1.7)	3 (2.2)	6 (4.8)	3 (2.0)
Urinary tract infection	0	2 (1.6)	2 (1.6)	1 (0.8)	1 (0.9)	2 (1.5)	3 (2.4)	9 (6.0)
Nasopharyngitis	5 (4.1)	2 (1.6)	4 (3.3)	2 (1.7)	1 (0.9)	1 (0.7)	4 (3.2)	4 (2.7)
Arthralgia	2 (1.7)	1 (0.8)	3 (2.5)	0	0	1 (0.7)	5 (4.0)	4 (2.7)
Back pain	6 (5.0)	1 (0.8)	4 (3.3)	3 (2.5)	0	1 (0.7)	2 (1.6)	3 (2.0)
Pain in extremity	2 (1.7)	0	2 (1.6)	0	0	2 (1.5)	6 (4.8)	4 (2.7)
Weight decreased	0	2 (1.6)	1 (0.8)	0	4 (3.5)	0	1 (0.8)	6 (4.0)
Anxiety	4 (3.3)	2 (1.6)	1 (0.8)	2 (1.7)	2 (1.7)	0	3 (2.4)	2 (1.3)
Diarrhoea	2 (1.7)	3 (2.5)	0	1 (0.8)	1 (0.9)	3 (2.2)	3 (2.4)	5 (3.3)
Hallucination	1 (0.8)	1 (0.8)	1 (0.8)	6 (5.0)	1 (0.9)	0	0	2 (1.3)
Hypotension	0	3 (2.5)	2 (1.6)	2 (1.7)	0	1 (0.7)	0	5 (3.3)
Muscle spasms	1 (0.8)	1 (0.8)	1 (0.8)	4 (3.4)	1 (0.9)	2 (1.5)	0	3 (2.0)

Table 53 Frequency of adverse reaction – integrated Phase 3 DB studies (Safety Set)

System Organ Class	Preferred terms		
	Very common	Common	Uncommon
Cardiac disorders	None	None	Palpitations
Ear and Labyrinth disorders	None	None	Ear congestion
Eye disorders	None	None	Dry eye
Gastrointestinal disorders	None	Constipation, Dry mouth, Vomiting	Abdominal distention, Abdominal pain, Abdominal pain upper, Dyspepsia
Investigations	None	Blood CPK increased	Weight decreased
Metabolism and nutrition disorders	None	None	Decreased appetite, Hypertriglyceridaemia
Musculoskeletal and connective tissue disorders	None	Muscle spasms	Muscle twitching, Musculoskeletal stiffness, Myalgia, Pain in extremity
Nervous system disorders	Dyskinesia	Dizziness, Headache, Somnolence	Dysgeusia, Hyperkinesia, Syncope, Tremor
Psychiatric disorders	None	Abnormal dreams, Hallucination, Hallucination visual, Insomnia	Anxiety, Depression, Hallucination auditory, Nightmare, Sleep disorder
Renal and urinary disorders	None	None	Chromaturia, Nocturia
Respiratory, thoracic and mediastinal disorders	None	None	Dyspnoea
Vascular disorders	None	Orthostatic hypotension	Hypertension, Hypotension

Source data: [Table 2.7.4.AE4.2](#)

CPK = creatine phosphokinase; DB = double-blind

Serious adverse events and deaths

In Phase 1 studies only one TESAE was reported (spontaneous abortion) and considered possibly related to the study medication. There were no TESAEs in Phase 2 studies.

Phase 3. Study 301: the number of TESAEs was higher for Entacapone (6.6%) and placebo(5.0%) than for Opicapone 5mg(3.3%), 25mg(0.8%) and 50mg(3.5%).The only TESAE reported for >1 subject in any treatment group was fall, with 2 subjects (1.6%) in the entacapone group.

Study 302: TESAEs were 3.2% for Opicapone 25 mg, 6.0% in Opicapone 50 mg, and 3.7% in placebo. No TESAE was reported for >1 subject in any treatment group.

In the integrated Phase 3 population, the incidence of TESAEs was similar across the total Opicapone (3.5%) and placebo (4.3%) groups .The only TESAE reported for >1 subject was dyskinesia (2 subjects [0.4%]; 1 subject in the Opicapone 25 mg and 1 subject in the Opicapone 50 mg group).

Fifteen deaths were reported in the Phase 3 studies: 1 in the Double blinded (75 years old man in the placebo group died of pneumonia), 5 in the Open label phase of study 302 and 9 in the OL phase of Study 301. The 9 deaths in OL Study 301, 2 cases were related to underlined cancer,(prostate and spine), one due to myocardial infarction, two were post-surgery related, three cases due to consequences of influenza, lung disorder and pneumonia and one sudden death . In all cases the subjects were on a stable dose of the study medication. The “unknown” death happened 1 month after the last dose; therefore unlikely to be caused by the administered drug.

The 5 deaths in OL Study 302 were caused by: brain haemorrhage in 2 cases, small lung cancer in one case, septic shock and unknown cause the other two. In all cases the patient were taking a stable dose of Opicapone (25mg or 50mg).The sudden death happened to a subject with obesity and hypertension which suggests being due to cardiovascular causes.

Laboratory findings

Chemistry

In the phase 3 studies the main laboratory finding was a markedly abnormal CPK levels, defined as elevations $\geq 3 \times \text{ULN}$. Results from the integrated population showed a higher incidence of subjects having markedly abnormal levels in the Opicapone 50 mg group (5.3%) compared to the 25 mg (1.6%) and placebo (1.9%). These differences were particularly evident in study 302.

In the Open Label study CPK elevations $> 3 \times \text{ULN}$, at each OL visit ranged between 0.8% and 1.7%, comparable to the incidence at baseline (1.1%). This was lower than the incidence of markedly abnormal CPK levels during the DB period of the study (between 1.6% and 8.0%).

The fact that CPK increase was lower during the OL phase is reassuring. However, a further discussion is needed on the changes of these abnormal values observed during the studies.

In Study 301, total bilirubin $\geq 2 \times \text{ULN}$ was reported for 2 subjects in the Opicapone 5 mg group compared to 1 subject in placebo, and ALT $\geq 3 \times \text{ULN}$ was reported for 1 subject in the Opicapone 25 mg group compared to 2 subjects in the placebo group. One subject in the placebo group reported acute hepatitis and pancreatitis, with liver function test abnormalities meeting Hy's law criteria.

In the open label phase 1 subject had an ALT elevation $\geq 3 \times \text{ULN}$ at Visit 11 and 1 subject had total bilirubin $\geq 2 \times \text{ULN}$ at Visit 8. No subjects had any AEs within 1 week of elevated AST or ALT $> 2 \times \text{ULN}$ and no Hy's law cases were identified for the OL.

Haematology

In both studies a slightly greater proportion of subjects in the active treatment groups exhibited post-baseline haemoglobin levels meeting the sponsor's markedly abnormal criteria ($\leq 115 \text{ g/L}$ male or $\leq 95 \text{ g/L}$ female) compared to placebo. In Study 301, the incidence of subjects meeting the sponsor's criteria was 4.9% in entacapone, 2.5% in Opicapone 5 mg, 5.0% in Opicapone 25 mg, 7.0% in Opicapone 50 mg, and 2.5% in placebo). However, that the incidence of shifts from normal haemoglobin values at baseline to low values at endpoint was low and similar across all groups. In Study 302, the incidence of subjects meeting the sponsor's criteria was 4.0% in Opicapone 25 mg, 4.0% in Opicapone 50 mg, and 2.2% in placebo. The results for haematocrit confirmed this observation. This trend was also observed in the integrated population with a higher incidence of subjects in the total Opicapone group (4.9%) meeting the sponsor's markedly abnormal criteria, compared to placebo (2.3%).

In the Open Label phase the incidence of markedly abnormal haemoglobin levels ($\leq 115 \text{ g/L}$ male or $\leq 95 \text{ g/L}$ female) at each OL visit ranged between 0.6% and 2.0%, which was also comparable to the incidence at baseline (0.8%) and was slightly lower than during the DB period of the study (between 2.2% and 4%). The incidence of haemoglobin decreases $> 30 \text{ g/L}$ during the study was low and no trend was observed related to the long-term exposure to Opicapone.

The applicant was asked to explain the shift in haemoglobin values as well as the decrease in haematocrit. In response to the Day 120 LoQs, the applicant declared that shifts from normal haemoglobin were seen only in Study 302 which were low and similar to placebo in all treatment groups with no further clinically relevant changes. As well for the shifts in haematocrit to below the normal range, there was not an increased incidence of clinically relevant (i.e. markedly abnormal or possibly related) changes. The Applicant's response was considered adequate.

Vital signs

Vital signs and neurological examination did not identify any clinically important safety signals.

Impulse control disorders were assessed with the Modified Minnesota Impulsive Disorders interview.

In study 301 the incidence of treatment-emergent impulse control disorders was higher in active treatment groups (8.2% entacapone, 6.2% Opicapone) than placebo (4.1%). No dose-relationship was noted in the Opicapone groups. The most commonly reported impulse control disorder was "buying disorder (3.3% in the placebo group and 7.4% in the entacapone group).

In Study 302, only 3 subjects in the Opicapone 50 mg and 2 subjects in the placebo group reported post-baseline impulsive disorders. During the OL phase 14 subjects reported clinically significant impulse disorders (4/0%): compulsive sexual behaviour (2.5%), pathological gambling (1.4%) and buying disorder (0.3%). Impulse control TEAEs (including PTs of pathological gambling, compulsive shopping, hypersexuality, and impulsive behaviour) were observed for 1.4% of subjects.

Section 4.4 of the SmPC includes a warning on the potential impulse control disorders in patients treated with dopamine agonists and /or other dopaminergic treatments. This was considered acceptable.

Cardiovascular finding

Cardiac safety was assessed based on the results of the ECG conducted during Phase I, II and III studies. Overall, no clinical relevant changes were observed in the electrocardiogram parameters (12-lead ECGs). Opicapone is regarded not to have a clinically relevant arrhythmogenic potential which is substantiated by the lack of QT prolongations following single doses of 50 and 800 mg opicapone in healthy human subjects (Thorough QT study no BIA-91067-111).

The incidence of cardiovascular or cerebrovascular TESAEs was similar between Opicapone, entacapone and placebo groups in Study 301. There were no cases of myocardial infarction in either study and no cardiovascular or cerebrovascular SAEs were reported.

In their safety overview the Applicant stated that in the integrated Phase 3 population, the incidence of subjects with ischaemic heart disease as found in the SMQs (Standardised MedDRA query) was higher in the total Opicapone group (4.1%) compared to placebo (2.3%), and appeared to be dose-dependent (2.9% for 25 mg and 5.3% for 50 mg Opicapone). Of the 21 subjects identified in the SMQs search, 20 had an increase in CPK levels and 1 had coronary artery disease. The higher CPK could have been responsible of the inclusion of these patients in the "ischaemic heart disease "category but requires further explanation.

The Applicant was requested to further discuss the dose-related higher incidence of ischaemic heart disease and CPK and their possible correlation. The summary of the TEAEs and the ECG changes have shown no correlation between the increased CPK and ischaemic heart disease. Analysis of the incidence of TEAEs correlated to ischaemic heart disease (coronary artery disease and myocardial ischaemia) in the individual double blind study results was comparable between opicapone (1 subject with coronary artery disease. 0.9%), Placebo (1 subject with myocardial ischaemia.0.8%) and Entacapone (1 subject with myocardial ischaemia. 0.8%) groups.

Assessment of Suicidality and depression

There were no cases of committed suicide reported during the studies. Few cases of mild suicidal ideation were reported in study 301 and 302. Only one case in study 302 (visit 7) was considered to be possibly related to Opicapone.

However, since in Study 301(25mg and 50mg groups) and in the integrated population analysis a higher proportion of subjects in the Opicapone showed TEAEs of depression/self-injury.

The incidence of TEAEs from the safety set of the combined phase 3 safety studies shows a no-dose related higher incidence of Psychosis and psychotic disorders in the Opicapone group and the higher

incidence of "hallucinations" seem to be responsible for these results. Hallucination is recognised as a class effect and is included in the RMP. This was considered acceptable.

The incidence of depression alone was comparable between the 3 groups (0.4% for all). There is a 1.4% higher incidence in the 25mg Opicapone group when depression and suicide/self-injury are combined together. The incidence of self-injuries should be discussed separately from depression. The Applicant was invited to consider adding this finding to the SmPC. Following the further clarification, the justification that there is no clear signal was accepted and no additional information has been added to the product information. The ongoing post-marketing pharmacovigilance activities should address this issue in future.

Safety in special populations

Race

The incidences of subjects with TEAEs was similar in the Asian and Caucasian sub-populations in the total Opicapone group (Asian: 53.2%, Caucasian: 64.5%) and the placebo group (Asian: 52.4%, Caucasian: 58.3%), suggesting that the races represented in the population had no major effect on the incidence of TEAEs. There were no specific trends related to race for the most frequently occurring TEAEs. No race differences in the incidence of TEAEs between Asians and Caucasians were noted in the total Opicapone groups.

Gender

No gender differences in the incidence of TEAEs were noted in the total Opicapone groups.

Body mass index

The incidence of TEAEs was almost 10% higher with Opicapone compared to placebo in subjects with a BMI 18 to 30 kg/m² (64.5% total Opicapone vs 55.5% placebo) whereas it was similar between groups in subjects with a BMI >30 kg/m² (57.3% of total Opicapone vs 63.0% of placebo), suggesting subjects with a lower BMI may be more inclined to have a TEAE during treatment with Opicapone. No meaningful comparison was possible for subjects whose BMI was <18 kg/m² due to the low number of these subjects (N<10). There were no specific trends related to BMI for the most frequently occurring TEAEs.

Subjects with a lower BMI >30 kg/m² (18 to 30 kg/m²) may be more inclined to have a TEAE during treatment with Opicapone (64.5% total Opicapone vs 55.5% placebo) compared with subject with a BMI >30 kg/m² (57.3% of total Opicapone vs 63.0% of placebo).

The Applicant was asked to elaborate further on these finding and discuss whether a lower incidence of TEAEs in patients with a BMI >30 kg/m² is not an indication of lower response due to a lower total exposure (AUC) in obese due to a larger volume of distribution. In the answer provided the Applicant demonstrated that the different BMI do not affect the PK of Opicapone and C_{max} and AUC are comparable in subjects with BMI ≥24 and <24 kg/m² following a single oral dose of 50 mg opicapone administered alone. Therefore, similar safety profiles are expected in the two different patients groups.

Age

Opicapone was dosed at 30mg single-doses for 7 days in 12 healthy elderly subjects (>65) and 12 control healthy volunteers.

No difference between elderly and young volunteers was noted for the PK parameters at day 1. However, at Day 7, the elderly showed an increase in C_{max} (19%) and AUC-24 (28%) with a statistical difference for AUC_{0-∞} (33%). The clearance/ F also decreased (35%) in the elderly leading to a slight increase of T_{1/2}.

No age differences in the incidence of TEAEs were noted in the total Opicapone groups.

The SmPC doesn't recommend any dose adjustment for the elderly. The Applicant stated that the higher exposure observed in the elderly after 7 days of dosing are not of clinical relevance. The Applicant was requested to provide a table to record the frequency of ADRs (MedDRA terms) which may be of special concern in the elderly (age groups up to ≥ 85) as part of the answers to the day 120 LoQ.

The Applicant provided the requested tables representing the incidence of related TEAEs in the elderly. It was shown, that for the overall integrated population, in the elderly subgroup the incidence of related TEAEs was higher in the opicapone groups than the placebo group but no dose-related increases were noted. However, considering that PD affects predominately the older population (especially age groups up to ≥ 85) the SmPC has been amended to reflect that data in this age category are limited and precautions should be taken.

Paediatric Patients

There is no information on paediatric patients.

Hepatic Impairment

Opicapone exposure was increased by almost 2-fold in subjects with moderate hepatic impairment (Child-Pugh B) relative to matched healthy subjects.

The Applicant states that due to its short half-life and complete clearance from systemic circulation before the subsequent dose, no dose adjustment for Opicapone needs to be considered.

Study BIA-91067-106 included only 8 patients with moderate hepatic impairment (Child-Pugh B). Since the bioavailability of Opicapone was almost doubled compared to healthy volunteers, it is expected to achieve a similar response with a lower dose than the standard 50 mg. On the contrary, a higher exposure could cause an increase in adverse events.

The SmPC has been amended to reflect the data from this group and that caution and dose adjustment may be necessary in patients with moderate hepatic impairment.

There is no clinical experience in patients with severe hepatic impairment (Child-Pugh C). Opicapone is therefore not recommended in these patients.

Renal Impairment

There are no data from the use of Opicapone in subjects with renal impairment. However, kidney (12.8%) is not a primary route of Opicapone excretion and renal impairment is likely to have little impact on Opicapone pharmacokinetics. The Applicant's proposal that dose adjustment is unnecessary in patients with mild, moderate or severe renal impairment was supported.

Pregnancy and Lactation

Studies in animals have not shown a teratogenic effect. If women receiving Opicapone become pregnant or plan to become pregnant, the use of Opicapone should be carefully re-evaluated.

It is unknown whether Opicapone is excreted in human milk. Animal studies on excretion of Opicapone in breast milk were not conducted. As a risk to the breast-fed child cannot be excluded breast-feeding should be discontinued during treatment with Opicapone.

The use of Opicapone should be discontinued during pregnancy and breast feeding.

The SmPC contains a warning and this was considered acceptable.

Immunological events

No specific studies were conducted.

Safety related to drug-drug interactions and other interactions

Dopamine agonists

In the integrated Phase 3 studies, use of dopamine agonists appears to have reduced the safety risk associated with Opicapone treatment. The incidence of TEAEs was lower in subjects using dopamine agonists across all treatment groups (placebo 56.1%, Opicapone 25 mg 59.7%, Opicapone 50 mg 59.4%) than for subjects not using dopamine agonists (placebo 60.0%, Opicapone 25 mg 67.1%, Opicapone 50 mg 74.1%). Furthermore, the incidence of TEAEs in subjects not using dopamine agonists increased with increasing Opicapone dose. The lower overall incidence of TEAEs in subjects using dopamine agonists compared to those not using dopamine agonists is partially due to a lower incidence of constipation (4.1% vs 8.8% in the total Opicapone group) and insomnia (3.8% vs 7.6% in the total Opicapone group), while the incidence in the placebo groups was similar in the 2 subgroups for both TEAEs. Dyskinesia was the most frequently reported event in all Opicapone groups in both subgroups, with a higher incidence in the Opicapone groups compared to placebo, but which was generally similar between subgroups.

The concomitant use of dopamine seemed to reduce the incidence of TEAEs across all treatment groups (placebo 56.1%, Opicapone 25 mg 59.7%, Opicapone 50 mg 59.4%) than for subjects not using dopamine agonists (placebo 60.0%, Opicapone 25 mg 67.1%, Opicapone 50 mg 74.1%).

MAO inhibitors

In the integrated Phase 3 studies, use of MAO inhibitors was associated with a somewhat higher safety risk in general, but this was not associated with Opicapone treatment. The higher incidence of TEAEs in subjects using MAO inhibitors (placebo 71.4%, total Opicapone 73.3%) compared to subjects not using MAO inhibitors (placebo 53.8%, total Opicapone 60.6%) was seen in all treatment groups including placebo.

The use of MAO inhibitors was associated with a higher safety risk in all groups, including placebo.

Discontinuation due to AES

In the Phase 3 studies, the discontinuation rate due to AEs was marginally higher in patients receiving Opicapone 50mg (8.7%) compared to those on 25mg (5.3%) and placebo (7.0%).

Dyskinesia had the highest incidence in the Opicapone 50mg group (3.0%) compared to placebo (0.4%) and the 25mg Opicapone group (0.8%).

Vomiting was also slightly higher in the Opicapone 50mg group (1.1%) when compared to the 25 mg group and placebo (0.4%). The other reasons for discontinuation had similar incidence in the different groups.

2.6.1. Discussion on clinical safety

Opicapone was administered at any dose (single or multiple) to a total of 1651 subjects: 859 healthy subjects and 792 subjects with Parkinson's disease.

This includes 631 subjects with Parkinson's disease in the DB part of the Phase 3 studies taking up to 50 mg Opicapone QD for 14 to 15 weeks, plus a further 121 subjects newly exposed to Opicapone (having received placebo in the DB part) in the 1-year OL extension of Study 302.

The highest dose of Opicapone tested concomitantly with L-DOPA/DDCI was 100 mg in single-dose studies with healthy subjects. In drug-drug interaction studies, single doses of 50 mg Opicapone were tested with rasagiline and paracetamol, 25 mg Opicapone with repaglinide and 25 mg Opicapone with warfarin and multiple doses of 50 mg Opicapone were tested with warfarin.

The most common TEAEs reported in the Opicapone group compared to placebo were dyskinesia, constipation, insomnia, dry mouth, increased CPK, and dizziness. A possible dose relationship in the incidence of individual TEAEs (difference of at least 2%) was seen for dyskinesia, increased CPK, urinary tract infection, and decreased weight. The incidence of most of these TEAEs remained similar during the Open label phase of study 302.

Differences in BMI seem to affect the frequency of adverse events. Subjects with a lower BMI >30 kg/m² (18 to 30 kg/m²) may be more inclined to have a TEAE during treatment with Opicapone (64.5% total Opicapone vs 55.5% placebo) compared with subject with a BMI >30 kg/m² (57.3% of total Opicapone vs 63.0% of placebo). Furthermore, the clinical studies didn't include the frail elderly population with lower BMI. In the responses provided to the Day 120 LoQs, the Applicant demonstrated that the different BMI do not affect the PK of Opicapone and C_{max} and AUC are comparable in subjects with BMI ≥24 and <24 kg/m² following a single oral dose of 50 mg opicapone administered alone. Therefore, similar safety profiles are expected in the two different patients groups.

Fifteen deaths occurred during the Phase III studies. Only two of these deaths were of unknown causes. However, based on the individual cases reports it seems that the causes of these deaths could be of cardiovascular origins in one subject with history of obesity and hypertension and the other happened one month after the last dose of the study medication. It is unlikely that those two deaths could be related to the study medication. The sudden death in the subject affected by obesity and hypertension was considered related to a cardiovascular reason. However, no post-mortem was available therefore a final conclusion was not possible.

Overall, the causes of death described are in line with the leading causes of deaths for person of 65 years of age or older in the general population. No specific trends were noted that can cause concern.

The main laboratory finding was a markedly abnormal CPK levels from the integrated population which showed a higher incidence in the Opicapone 50 mg group (5.3%) compared to the 25 mg (1.6%) and placebo (1.9%). These differences were particularly evident in study 302. The Applicant justifies these results with the higher incidence of dyskinesia in this study. From the description of the single cases that manifested an increase in CPK, a part of subject 180702 who complained of unpleasant sensation in the heart region, the other 13 subjects didn't complain of any cardiac pain or muscle pain that could indicate rhabdomyolysis or cardiac infarction. The Safety set table of the combined double-blind studies shows that after an increase between week 1 and 3, there is a progressive reduction of the CPK levels in all groups. Increased CPK is listed as common adverse reaction in Section 4.8 of the SmPC.

Vital signs were also investigated for safety related issues and no signals were identified.

Cardiac safety was assessed based on the results of the ECG conducted during Phase II and III studies. Overall, no clinical relevant changes were observed in the ECG parameters.

In Study 301, the incidence of cardiovascular or cerebrovascular TSEAEs was not different in active and placebo groups. No cases of myocardial infarction were reported. No cardiovascular or cerebrovascular SAEs were reported in Study 302. However, in their safety overview the Applicant states that in the integrated Phase 3 population, the incidence of subjects with ischaemic heart disease as found in the SMQs (Standardised MedDRA query) was higher in the total Opicapone group (4.1%) compared to placebo (2.3%), and appeared to be dose-dependent (2.9% for 25 mg and 5.3% for 50 mg Opicapone). Of the 21 subjects identified in the SMQs search, 20 had an increase in CPK levels and 1 had coronary artery

disease. The higher CPK could have been responsible of the inclusion of these patients in the "ischaemic heart disease" category but requires further explanation. In Study 301 and in the integrated population analysis a higher proportion of subjects in the Opicapone showed TEAEs of depression/self-injury and this has been further elaborated but no clear signal has been identified at this time.

In the investigation of safety in special populations, it appears that moderate liver impairment and the elderly may require change in posology. Study BIA-91067-106 included only 8 patients with moderate hepatic impairment (Child-Pugh B). Since the bioavailability of Opicapone was almost doubled compared to healthy volunteers, it is expected to achieve a similar response with a lower dose than the standard 50 mg. On the contrary, a higher exposure could cause an increase in adverse events.

The SmPC has been amended to reflect the data from this group and that caution and dose adjustment may be necessary in patients with moderate hepatic impairment.

2.6.2. Conclusions on the clinical safety

Safety and tolerability of Opicapone is generally good and the majority of adverse events are comparable to other COMT inhibitors. During the procedure a number of issues have been identified and resolved, some of them resulting in amendment of the product information.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3 with the following content:

Safety concerns:

Summary of safety concerns	
Important identified risks	
	Dyskinesia
	Hallucinations
Important potential risks	
	Ischaemic heart disease
	Neuroleptic malignant syndrome
	Impulse control disorders and other related behaviours
	Drug-related hepatic injury
	Interactions with drugs metabolised by CYP2C8 (e.g. hypoglycaemia risk with repaglinide)
Missing information	
	Use in patients with moderate/severe hepatic impairment
	Use in pregnancy and lactation
	Long-term safety
	Very elderly population

Pharmacovigilance plan

Routine pharmacovigilance activities are sufficient to monitor the safety concerns of the product. No category 1-3 studies are planned.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Dyskinesia	<p>SmPC section 4.2 provides instructions for reducing the levodopa dosage within the first days to first weeks after initiating Ogmentys treatment according to the clinical condition of the patient.</p> <p>SmPC section 4.4 includes a warning about levodopa-related dopaminergic adverse reactions (e.g. dyskinesia, hallucinations, nausea, vomiting and orthostatic hypotension).</p> <p>SmPC section 4.8 Undesirable effects Dyskinesia included as a very common ($\geq 1/10$) adverse reaction.</p>	None proposed.
Hallucinations	<p>SmPC section 4.2 provides instructions for reducing the levodopa dosage within the first days to first weeks after initiating Ogmentys treatment according to the clinical condition of the patient.</p> <p>SmPC section 4.4 includes a warning about levodopa-related dopaminergic adverse reactions (e.g. dyskinesia, hallucinations, nausea, vomiting and orthostatic hypotension).</p> <p>SmPC section 4.8 Undesirable effects Hallucination – common ($\geq 1/100$ to $< 1/10$) Hallucination visual – common ($\geq 1/100$ to $< 1/10$) Hallucination auditory – uncommon ($\geq 1/1,000$ to $< 1/100$)</p>	None proposed.
Ischaemic Heart Disease	None proposed	None proposed.
Neuroleptic malignant syndrome	SmPC section 4.3 includes a contra-indication for patients with a history of neuroleptic malignant syndrome and/or non-	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	traumatic rhabdomyolysis.	
Impulse control disorders and other related behaviours	SmPC section 4.4 contains a warning about impulse control disorders occurring in patients treated with dopamine agonists and/or other dopaminergic treatments. Advises that patients should be monitored regularly for the development of impulse control disorders and that treatment should be reviewed if symptoms develop.	None proposed.
Drug-related hepatic injury	SmPC section 4.4 warns that increases in liver enzymes were reported in studies with nitrocatechol COMT inhibitors. Advises that an evaluation of liver function should be considered in patients who experience progressive anorexia, asthenia and weight decrease within a relatively short period of time.	None proposed.
Interactions with drugs metabolised by CYP2C8 (e.g. hypoglycaemia risk with repaglinide)	SmPC Section 4.4 warn that concomitant use of opicapone may increase the blood glucose-lowering effect of repaglinide and thus increase the risk of severe hypoglycaemia. SmPC section 4.5 of the SmPC advises that concomitant use of medicinal products specifically metabolised by CYP2C8 must be avoided.	None proposed.
Use in patients with moderate/severe hepatic impairment	SmPC section 4.2 advises that no dose adjustment of Ongentys is necessary in patients with mild hepatic impairment. Caution must be exercised in patients with moderate hepatic impairment and dose adjustment may be necessary. Ongentys is not recommended in patients with severe hepatic impairment as there is no clinical experience.	None proposed.
Use in pregnancy and lactation	SmPC section 4.6 advises that there is no data from the use of opicapone in pregnant women and it is not known whether	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	opicapone or its metabolites are excreted in human milk. Therefore, it is preferable to avoid the use of Ongentys during pregnancy. Breast-feeding should be discontinued during treatment with Ongentys.	
Long-term safety	None proposed	None proposed
Very elderly population	SmPC section 4.2 advises that caution must be exercised in patients ≥ 85 years of age as there is limited experience in this age group.	None proposed.

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ongentys (opicapone) is included in the additional monitoring list as a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Opicapone has demonstrated clinical efficacy that is superior to placebo, both for the primary efficacy variable (reduction in OFF-time, which is a valid and clinically relevant measure of efficacy) and in most secondary variables in the main clinical trials performed.

The estimated mean change (LS means) from baseline in absolute OFF-time at endpoint in randomised and treated patients was largest in the Opicapone 50 mg group in both studies, with an LS mean difference to placebo of -53.9 min ($p=0.0047$) for Study 301 and -52.4 ($p=0.0053$) in Study 302, demonstrating superiority of the Opicapone 50 mg dose over placebo. Opicapone was also shown to be non-inferior to entacapone with a clear tendency to greater efficacy in Study 301.

When the results of the Phase 3 studies were combined, the LS means from baseline in absolute OFF-time at endpoint in the full analysis set (LOCF) was largest in the Opicapone 50 mg group (-119.9 minutes) with a statistically significant difference to placebo ($p<0.0001$), demonstrating superiority of the Opicapone 50 mg dose over placebo. This trend in the difference between the 50 mg and 25 mg groups compared to placebo was generally consistent across most of the secondary efficacy endpoints. In the integrated Phase 3 population, both the 50 mg and 25 mg QD doses of Opicapone had a statistically significant decrease in OFF-time, increase in ON-time (which was largely due to an increase in ON-time without dyskinesia), reduction in percentage OFF-time, and the proportion of OFF-time and ON-time responders. In fact, a statistically significantly higher proportion of subjects had an OFF-time reduction/ON-time increase of at least 2.5 hours in the Opicapone 50 mg group compared to placebo. The proportion of responders was also superior to placebo for both the Investigator's Global Assessment of Change and Subject's Global Assessment of Change.

Sensitivity analyses of the primary variable looking at the impact of missing values or various covariates and other parameters that might influence the outcomes demonstrated that the results are robust and consistent regardless of these factors. Furthermore, none of the subgroup analyses showed an interaction with the subgroup tested, indicating that the findings are consistent across all subgroups evaluated. In particular, a consistent treatment effect across the 2 studies and geographical areas was shown and the positive effect of Opicapone was seen with both immediate-release and controlled-release formulations of L-DOPA. Subgroup analyses to evaluate the effect of concurrent usage of approved MAO inhibitors for the treatment of Parkinson's disease, as identified at baseline, showed that Opicapone had similar efficacy when used alone or concomitantly with these MAO inhibitors.

Uncertainty in the knowledge about the beneficial effects

The applicant submitted the results of the completed OL part of pivotal study 301 which similarly to the results of the OL part of study 302 may be considered indicative of maintenance of effect. However on account of selection bias, open label extension studies should generally be interpreted with caution. Whereas for a daily dose of 25 mg OPC no convincing treatment effect could be demonstrated in the separate pivotal studies (DB part), which would allow for recommendation of 25 mg opicapone as a starting dose, it is generally possible, that some dyskinesia could potentially be managed by adjusting the opicapone dose. It was thus proposed, that respective information on possible L-DOPA and opicapone

dose adjustment allowed during open-extension parts of both pivotal studies be reflected the appropriate parts of the SmPC.

Although from the hitherto provided data regarding L-DOPA formulation, there is no indication, that efficacy of opicapone is restricted to IR formulation of L-DOPA/DDCI, adequate information in the product information (PI) was added indicating that the efficacy data of opicapone in combination with CR L-DOPA/DDCI are still limited.

Risks

Unfavourable effects

Based on the available data, no serious toxicity for opicapone has been identified so far.

The most common TEAEs reported in the Opicapone group compared to placebo were dyskinesia, constipation, insomnia, dry mouth, increased CPK and dizziness. A possible dose relationship in the incidence of individual TEAEs (difference of at least 2%) was seen for dyskinesia, increased CPK, urinary tract infection, and decreased weight. The majority of these adverse events are expected from the use of COMT inhibitors.

The main laboratory finding was a markedly abnormal CPK levels from the integrated population which showed a higher incidence in the Opicapone 50 mg group (5.3%) compared to the 25 mg (1.6%) and placebo (1.9%). The summary of the TEAEs and the ECG changes have shown no correlation between the increased CPK and ischaemic heart disease. Analysis of the incidence of TEAEs correlated to ischaemic heart disease (coronary artery disease and myocardial ischaemia) in the individual double blind study results was comparable between opicapone (1 subject with coronary artery disease. 0.9%), Placebo (1 subject with myocardial ischaemia.0.8%) and Entacapone (1 subject with myocardial ischaemia. 0.8%) groups.

A trend for decreases in haemoglobin, erythrocytes and haematocrit were observed consistently across the studies. However, the related anaemias were of mild or moderate intensity.

When depression and suicide/self-injury are combined together, there is a 1.4% higher incidence of this AE in the 25mg opicapone group. The incidence of self-injuries has been discussed separately from depression and no signal has been identified requiring change of product information.

Uncertainty in the knowledge about the unfavourable effects

From the safety data presented with the dossier, no adverse events were identified that raise major concern or require specific monitoring.

Cardiac safety was assessed based on the results of the ECG conducted during Phase II and III studies. Overall, no clinical relevant changes were observed in the ECG parameters. In Study 301, the incidence of cardiovascular or cerebrovascular TESAEs was not different in active and placebo groups. No cases of myocardial infarction were reported. No cardiovascular or cerebrovascular SAEs were reported in Study 302. However, in their safety overview the Applicant states that in the integrated Phase 3 population the incidence of subjects with ischaemic heart disease as found in the SMQs (Standardised MedDRA query) was higher in the total Opicapone group (4.1%) compared to placebo (2.3%), and appeared to be dose-dependent (2.9% for 25 mg and 5.3% for 50 mg Opicapone). Of the 21 subjects identified in the SMQs search, 20 had an increase in CPK levels and 1 had coronary artery disease.

For the overall integrated population, in the elderly subgroup the incidence of related TEAEs was higher in the opicapone groups than the placebo group but no dose-related increases were noted. Considering that

PD affects predominately the older population (especially age groups up to ≥ 85) the SmPC had to be amended to reflect that data in this age category are limited and precautions should be taken.

Study BIA-91067-106 included only 8 patients with moderate hepatic impairment (Child-Pugh B). Since the bioavailability of opicapone was almost doubled compared to healthy volunteers, it is expected to achieve a similar response with a lower dose than the standard 50 mg. On the contrary, a higher exposure could cause an increase in adverse events. The SmPC has been worded to reflect the data from this group and that caution and dose adjustment may be necessary in patients with moderate hepatic impairment.

Benefit-risk balance

Importance of favourable and unfavourable effects

The magnitude of effect of 50 mg OPC resulting from the European study 301 with a decrease in OFF-time of -55.3 min and an increase in ON-time without troublesome dyskinesia (i.e. ON-time which is qualitatively undoubtedly more valuable than OFF-time) of 62.6 min (LOCF) compared to placebo is considered clinically relevant and moderate. This conclusion is corroborated by the demonstration of non-inferiority of 50 mg OPC to the active comparator entacapone. The decrease in OFF-time (and increase in ON-time) was actually numerically higher in the OPC 50 mg group as compared to entacapone (-24.8 min), however superiority of 50 mg OPC to Entacapone was not demonstrated.

The relevance of the effect is further mirrored in a statistically significantly higher proportion of subjects in the 50 mg OPC compared to the placebo group with improvements in the Investigator's and Subject's Global Assessment of Change. During the course of study 301 only a very small percentage of overall awake time was ON-time with troublesome dyskinesia (≤ 3 percent at any visit).

The treatment effect of 50 mg OPC resulting from study 302 was somewhat lower as compared to study 301, e.g. the estimated treatment difference compared to placebo with respect to the primary efficacy parameter, mean change in total OFF-time, remained below one hour (-52.4 min), however, study results were generally similar to those of study 301 with a statistically significant effect with respect to the primary but also further diary derived secondary endpoints including OFF-and ON-time responder rates.

The safety profile of opicapone with respect to frequent adverse events is well characterised and no major safety concerns have been identified so far. Similarly no significant findings with regard to tolerability were reported.

Based on the present knowledge from all available sources the most important identified safety concerns associated with opicapone treatment are mainly dyskinesias which were reported in more than 10 % of patients receiving opicapone in the clinical studies. It may be necessary to decrease the dosage of levodopa within the first days to first weeks after starting treatment with opicapone in order to prevent severe dyskinesias.

Further common AEs reported during the opicapone clinical study program were increased CPK values, insomnia, dry mouth, dizziness, and constipation. The increased incidence of falls, depression, sleep disorder, and higher CPK levels probably is a consequence of the natural progression of the underlying disease and its comorbidities over a longer observation period.

At the moment there is no increased risk discernible for hepatic disorders, cardiac diseases or malignancies associated with opicapone treatment. Opicapone does not seem to cause any clinically significant changes in laboratory values, vital signs and ECG.

Based on the knowledge from all available clinical and non-clinical experiences no serious toxicity of opicapone has been identified so far.

Only minor safety concerns have been raised during the course of the application procedure and they were all adequately addressed.

Benefit-risk balance

Discussion on the benefit-risk balance

The extent of the knowledge about risks and benefits is generally good. While a new compound, the mechanism of action of Opicapone is well understood and the beneficial effects are in line with what is expected of a drug with such a mechanism.

Gaps in understanding of the PK of the product are evident and they introduce a level of uncertainty especially in the group of elderly patients expected to receive the drug.

The currently available COMT inhibitor entacapone has a moderate effect on decrease in OFF-time/increase in ON-time but shows low to moderate oral bioavailability and requires frequent dosing whereas the second available, more potent COMT inhibitor tolcapone is only indicated as second-line adjunctive treatment of Parkinson's disease, because of its hepatic toxicity potential.

In contrast to the available COMT inhibitors and in particular to entacapone the pharmacokinetic properties of opicapone allow for once daily dosing.

For 50 mg opicapone a treatment effect regarding decrease in OFF-time and increase in ON-time, respectively of approximately 1 hour each was found which is considered clinically relevant and non-inferiority of 50 mg OPC with entacapone could be demonstrated.

Compared to other anti-Parkinson medications, the occurrence of adverse events of opicapone appears low. No significant major safety issues like hepatic toxicity or cardiovascular ischaemic events have been raised with opicapone for the applied indication.

A once daily dose of 50 mg opicapone resulted according to the available data in a moderate and clinically relevant treatment effect without a notable worsening in the safety features, making the 50 mg dose the recommended dose and confirming that the benefit – risk balance is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Ongentys indicated as adjunctive therapy to preparations of levodopa/ DOPA decarboxylase inhibitors (DDCI) in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

Not applicable

- **Obligation to complete post-authorisation measures**

Not applicable

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

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that opicapone is qualified as a new active substance.