Bial - Portela & Cª, S.A.

CLINICAL TRIAL REPORT

(FULL VERSION FOR REGULATORY SUBMISSION)

Efficacy and safety of opicapone in clinical practice in Parkinson's Disease patients with wearing-off motor fluctuations

This was an open-label, uncontrolled, single-group, multi-centre trial.

Protocol Short Title	OPTIPARK
Product Name	Opicapone (BIA 9-1067)
Indication	Parkinson's Disease with wearing-off motor fluctuations
Protocol Number	BIA-OPC-401
EudraCT Number	2016-002391-27
Report Version	Final Version 1.0
Phase	IV
Date First Subject Entered	23-NOV-2016
Date Last Subject Completed	04-JUL-2018
Coordinating Investigator	Heinz Reichman Prof. Dr. University Hospital Carl Gustav Carus at the TU Dresden, Neurological University Clinic Fetscherstr. 74 01307 Dresden Germany
Name of Sponsor Signatory	Francisco Rocha Bial - Portela & Cª, S.A. À Av. da Siderurgia Nacional 4745-457 Coronado (S. Romão e S. Mamede), Portugal Phone: +351 229866100 Fax: +351 229866192
Report Issue Date	10-JUL-2019

This trial was performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents.

1. APPROVAL SIGNATURES / LIST OF AUTHORS

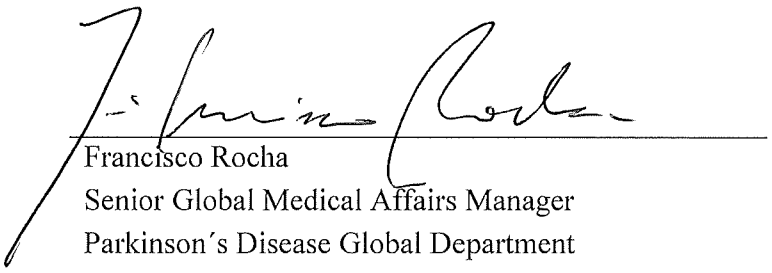
1.1 Sponsor Approval Signatures

TRIAL TITLE: Efficacy and safety of opicapone in clinical practice in Parkinson's Disease patients with wearing-off motor fluctuations

TRIAL NUMBER: BIA-OPC-401

I, the undersigned, have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the trial.

SIGNATURE: DATE:



18.07.2019

Francisco Rocha
Senior Global Medical Affairs Manager
Parkinson's Disease Global Department
BIAL - Portela & Ca, S.A.

1.2 Coordinating Investigator Approval Signature

TRIAL TITLE: Efficacy and safety of opicapone in clinical practice in Parkinson's Disease patients with wearing-off motor fluctuations

TRIAL NUMBER: BIA-OPC-401

I, the undersigned, have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the trial.

SIGNATURE: DATE: 19 JUL 2019

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2. SYNOPSIS

Name of Sponsor: Bial - Portela & Cª, S.A.	**Individual Trial Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of finished product: Opicapone (OPC)	**Volume:**	
Name of active ingredient: Opicapone	**Page:**	

Title of trial:

Efficacy and safety of opicapone in clinical practice in Parkinson's Disease patients with wearing-off motor fluctuations

Trial number: BIA-OPC-401

EudraCT number: 2016-002391-27

Sponsor details:

Francisco Rocha, Global Medical Affairs Manager
Parkinson´s Disease Global Department,
Bial - Portela & Cª, S.A., À Av. da Siderurgia Nacional, 4745-457 Coronado (S. Romão e S. Mamede), Portugal

Investigators: A total of 69 active centres

Coordinating Investigator:

Prof. Dr. Heinz Reichmann, University Hospital Carl Gustav Carus at the TU Dresden, Neurological University Clinic, Fetscherstr. 74, 01307 Dresden, Germany

Publication (reference):

None.

Studied period (years):

Date of first enrolment: 23-NOV-2016
Date of last subject completed: 04-JUL-2018

Reporting period:

This report includes the data of the final analysis stage. For the reporting period, please refer to the dates of studied period.

Phase of development: IV

Background and rationale:

Levodopa (L-dopa) is the most effective symptomatic treatment for Parkinson's Disease (PD). [4] Catechol-O-methyltransferase (COMT) inhibitors are indicated for the treatment of PD in combination with L-dopa and a peripheral dopa decarboxylase inhibitor (DDCI). Opicapone (OPC), a selective and reversible COMT inhibitor, has been developed by Bial to be used in combination with L-dopa/carbidopa or L-dopa/benserazide preparations in PD patients. In the two phase III trials (BIPARK I and II) subjects were treated for up to 15 weeks with OPC or entacapone. In both trials a reduction in OFF-time, without increasing ON-time with

troublesome dyskinesia could be shown at all tested OPC doses. In addition, 73% of OPC treated patients (50 mg) showed an improvement in the Investigator's Global Assessment of Change. In all performed trials, OPC was well tolerated by PD patients and most observed treatment emergent adverse events were of mild or moderate intensity. The outcome in these trials led to European marketing authorisation for 50 mg OPC once daily in June 2016 and was the rationale for the current trial. This trial was performed to evaluate the change in subject's condition after three and six months of treatment with 50 mg OPC once daily as adjunctive therapy in adult subjects with PD and wearing-off motor fluctuations in clinical practice i.e. after having received marketing authorisation.

Objectives:

Primary:

The primary objective was to evaluate the change in subject's condition according to the Investigator's Global Assessment of Change after three months of treatment with 50 mg opicapone once daily in a heterogeneous patient population reflecting daily clinical practice.

Secondary:

The secondary objectives were:

- To investigate the safety of opicapone 50 mg once daily in clinical practice.
- To investigate the efficacy of opicapone 50 mg once daily in clinical practice.
- To evaluate the influence of a 6-month treatment with opicapone 50 mg once daily on the health economic costs (only for the UK).

Methods:

This was a prospective open-label, uncontrolled, single-group, multi-centre trial in PD subjects with wearing-off motor fluctuations.

At screening/baseline (Visit 1, Day 1) all subjects were to start treatment with 50 mg OPC once daily for a 3-month period (in Germany) or a 6-month period (in the UK) in addition to their current treatment with L-dopa/DDCI.

In Germany, the investigator called the subject on Day 15 ±3 (Visit 2) to check if the L-dopa/DDCI dose needed to be reduced. In the UK, the investigator called the subject on Day 15 ±3 (Visit 2) to ask for adverse events (AE, e.g. dopaminergic AEs) and if required, to reduce the L-dopa/DDCI dose. In both countries, the investigator had the possibility to increase or decrease the total daily L-dopa/DDCI dose according to the subject's condition throughout the trial, except at Visit 1. At Visit 1 the L-dopa dose was not to be changed.

Further visits were to be performed on Day 30 ±4 (Visit 3) and on Day 90 ±4 (Visit 4) in Germany and on Day 30 ±4 (Visit 3), on Day 90 ±4 (Visit 4) and on Day 180 ±4 (Visit 5) in the UK.

Different treatment durations in Germany and the UK were based on the additional assessment of the influence of OPC treatment on the health economic costs caused by PD in the UK.

Number of subjects (planned and analysed):

Planned: 400-440 (in Germany) + 110-150 (in the UK)

Analysed:

	Overall	Without site 211
Enrolled	519	506
Screening failures	6	4
Allocated to treatment	513	502
Treated	506	495
Withdrawn	114	109
Completed	392	386
Safety set	506	495
Full analysis set	488	477
Per-protocol set	421	417

Enrolled Set

For site 211 a serious breach of GCP was reported to the Medicines & Healthcare products Regulatory Agency (MHRA). There were a number of issues relating to the quality of data at this site, including lack of PI oversight, data confidentiality/integrity, lack of source data and essential documents, incorrect SAE and AE reporting, protocol non-compliances and low return of IMP resulting in full IMP accountability not being possible. The sponsor excluded data of this site from all statistical analyses because the accuracy of data cannot be confirmed. Therefore, final analyses were performed once including site 211 data and once excluding site 211 data and only the analyses excluding site 211 were described in this report.

Diagnosis and main criteria for inclusion and exclusion:

Male and female subjects aged 30 years or older, diagnosed with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria and showing signs of "wearing-off" phenomenon according to the 9-Symptom Wearing-off Questionnaire (WOQ-9) were included in this trial. Disease severity was to be Stages I-IV (modified Hoehn &Yahr staging) at ON. In addition, the subjects were to be treated with three to seven daily doses of L-dopa/DDCI or L-dopa/DDCI/entacapone. Subjects with prior or concomitant use of tolcapone and/or OPC were excluded from the trial.

Paediatric regulatory details:

Not applicable

Measures of protection of subjects taken:

This trial was performed in specialised neurological centres and neurological private practices. The subjects were closely monitored during the trial. The investigator increased or decreased the total daily L-dopa/DDCI dose according to the subject's condition throughout the trial. Subjects who discontinued trial participation prematurely were asked to come to the site for an early discontinuation visit. The treatment duration of at least three months is in line with the requirement of the CHMP "Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease".

Test products, dose and mode of administration, batch number:

Opicapone (BIA 9-1067) 50 mg hard capsules. Oral administration, once daily at bedtime, at least one hour before or after the last daily dose of L-dopa/DDCI.

Batch numbers: 150285, 150286, 150287, 160661

Duration of treatment:

Total duration of trial participation and treatment: three months (Germany) or six months (the UK).

Reference therapy, dose and mode of administration, batch number:

Not applicable.

Endpoints:

Efficacy:

The primary efficacy endpoint of this trial was the Investigator's Global Assessment of Change at Visit 4.

The secondary efficacy endpoints of the trial were:

- Change in L-dopa total daily dose from baseline (Visit 1) to each on-site visit.
- Number and percentage of subjects with change in number of daily L-dopa doses from baseline (Visit 1) at each on-site visit.
- Number and percentage of subjects with change in L-dopa single dose from baseline (Visit 1) at each on-site visit.
- Number and percentage of subjects with stable L-dopa regimen between Visit 3 and Visit 4.
- Number and percentage of subjects with stable L-dopa regimen between Visit 3 and Visit 5 (only for the UK).
- Number and percentage of subjects for whom OPC will be prescribed further after trial completion.
- Number and percentage of subjects who stopped treatment with OPC before trial completion or at Visit 4 (for Germany) or Visit 5 (for the UK) due to:
  - AEs
  - Lack of efficacy
  - Other reasons
- Investigator's Global Assessment of Change at Visit 3 and Visit 5 (only for the UK).
- Subject's Global Assessment of Change at Visit 3, Visit 4 and Visit 5 (only for the UK).
- Number and percentage of subjects with each WOQ-9 symptom at each on-site visit.
- Absolute values and, if applicable, change from baseline to Visit 4 and change from baseline to Visit 5 (only for the UK):
  - UPDRS I mentation, behaviour, and mood at ON stage
  - UPDRS II (activities of daily living, ADL) at OFF stage
  - UPDRS II (ADL) plus III (motor function) during the ON stage
  - UPDRS IV at ON stage
  - PDQ-8
  - NMSS

During the development of the statistical analysis plan it was decided by the sponsor to evaluate also the following secondary efficacy endpoints in addition to the protocol:

- Change in L-dopa total daily dose from baseline (Visit 1) to each on-site visit in subjects who reported dopaminergic AEs (any of the following: dyskinesia, nausea, vomiting, orthostatic hypotension, any hallucination, illusion, delusion, disturbance in attention).
- Number and percentage of subjects with change in number of daily L-dopa doses from baseline (Visit 1) at each on-site visit in all subjects who reported dopaminergic AEs (any

of the following: dyskinesia, nausea, vomiting, orthostatic hypotension, any hallucination, illusion, delusion, disturbance in attention).

Safety:

- Incidence of AEs including SAEs.
- General safety information (vital signs, physical and neurological examinations).

With amendment no 4, UK, and protocol version 4.0 (20-SEP-2017):

- BIA 9-1103, BIA 9-4588 and potential other relevant OPC metabolites' plasma concentration at Visit 5, after 6-month treatment with OPC (only for the UK).

Secondary health economic costs endpoints (only for the UK):

- Absolute values and change from baseline to Visit 5.
- Number and percentage of subjects per service use at Visit 1 and Visit 5.
- Distribution of service costs (%) by categories at Visit 1 and Visit 5.
- Regression analysis of formal service costs at Visit 1 and Visit 5.
- Regression analysis of unpaid care costs at Visit 1 and Visit 5.

Statistical methods:

The final analyses were performed once including site 211 data and once excluding site 211 data.

The analysis of the primary efficacy endpoint was based on the full analysis set (FAS). Number and percentage of subjects in each category of Investigator's Global Assessment of Change at Visit 4 were presented. A missing value at Visit 4 was replaced by the last available observation (obtained at Visit 3 or EDV, Last Observation Carried Forward [LOCF]). Additionally, sensitivity analysis of Investigator's Global Assessment of Change at Visit 4 was summarised descriptively, using the per-protocol set (PPS). The primary efficacy endpoint was analysed by subgroups including age (<mean at baseline / ≥ mean at baseline), disease duration (< mean at baseline / ≥ mean at baseline), L-dopa mean daily dose (< mean at baseline / ≥ mean at baseline), usage of COMT inhibitors before first IMP intake (yes/no), concomitant usage of COMT inhibitors as identified at baseline (yes / no), concomitant usage of dopamine agonists as identified at baseline (yes / no) and concomitant usage of MAO-B inhibitors and dopamine agonists as identified at baseline (yes / no). Users of concomitant COMT inhibitors, dopamine agonists and MAO-B inhibitors at baseline were defined as subjects who used the respective treatment at baseline and at least one day thereafter or started to use them up to one day after baseline. Users of COMT inhibitors before first IMP intake were defined as subjects who have taken COMT inhibitors until one day before or until the same day of first IMP intake or who stopped COMT inhibitors 2 to 7 days before first IMP intake and used it for more than 4 days.

The analysis of secondary efficacy endpoints was based on FAS and PPS. All secondary efficacy endpoints were summarised descriptively.

The analysis of safety endpoints was based on the safety set (SS). All treatment-emergent AEs were summarised by calculating the number and percentage of subjects with AEs by preferred term (PT) and system organ class (SOC). Additionally, treatment-emergent AEs were summarised by severity (intensity) and relationship to treatment. The analyses of variables for vital signs parameters, physical examinations and neurological examinations focused on the

evaluation of the change from baseline to the scheduled time points after baseline. In addition, frequency tables were provided displaying the number and frequency of subjects with clinically significant values.

For the UK only (based on amendment no 4, UK, and protocol version 4.0, 20-SEP-2017): For quantification of OPC metabolites, only data from subjects of the safety set who completed the 6-month treatment were available. The concentration of each metabolite at Visit 5 (UK only) was summarised descriptively, presenting the number of subjects with data available, mean, median, standard deviation (SD), minimum, maximum, 25th percentile, 75th percentile.

The analysis of the health economic costs (the UK only) was based on FAS and PPS. The results were summarised descriptively. Additionally, regression analyses were performed for formal service costs and unpaid care costs.

For continuous variables, descriptive analysis (number of subjects, mean, median, SD, minimum, maximum, 25th percentile, 75th percentile) of the time course and of changes from baseline to each post-baseline time point are presented. Categorical variables were summarised by using frequency (counts) and percentages.

SUMMARY OF RESULTS

SUBJECT DISPOSITION AND BASELINE CHARACTERISTICS:

The following data are based on analyses excluding data from site 211 (i.e. excluding data of 11 subjects in the SS and FAS and of 4 subjects in the PPS).

Of 506 enrolled subjects in 68 active trial centres in Germany and the UK, 502 (99.2%) subjects were allocated to treatment with 50 mg OPC. A total of 495 (97.8%) subjects took at least one dose of IMP (SS). The FAS comprised 477 (94.3%) subjects and the PPS 417 (82.4%) subjects.

A total of 393 (79.4%) subjects of the SS completed Visit 4 of the trial. In the UK (SS), 95 subjects (72.0% of the UK population) completed also Visit 5.

All subjects of the SS were white and more male (63.6%) than female (36.2%) subjects were included in the trial. The subject's mean (SD) age was 67.7 (8.98) years, 65.7% of the subjects were aged between 65 and 84 years and 33.1% of the subjects between 18 and 64 years. The median duration of PD and motor fluctuations were 89.0 months and 15.0 months, respectively.

The most common ongoing medical conditions by preferred term apart from PD were hypertension (39.2%), constipation (21.8%), obesity (20.2%) and depression (20.0%).

As per study design, subjects had to be treated with three to seven daily doses of L dopa/DDCI or L-dopa/DDCI/entacapone, including a slow-release formulation prior to inclusion in study.

Regarding concomitant medications apart from L dopa/DDCI or L-dopa/DDCI/entacapone medications, other concomitant Anti-PD's medications were taken by 78.8% of the subjects (SS) and included the most common reported medications rasagiline (27.5%), pramipexole (24.8%), ropinirole (22.4%) and amantadine (21.2%). The most other common concomitant medications by ATC 2nd level subgroup were agents acting on the renin-angiotensin system (28.7%), followed by psychoanaleptic (28.3%), drugs for acid related disorders (24.8%) and antithrombotic agents (28.7%).

Compliance to IMP was high, the mean (SD) treatment compliance was 99.2 (8.14) % and for 475 (92.3%) subjects a compliance between 80% and 120% was reported.

The baseline characteristics between subjects in the UK and in Germany showed inhomogeneities. In the UK, the percentage of elderly subjects was slightly higher, the duration of PD and motor fluctuations was longer and the baseline UPDRS II, UPDRS II plus III scores and the total NMSS scores were higher compared to German subjects. The percentage of subjects who took other concomitant Anti-PD's medications apart from L-dopa/DDCI or L-dopa/DDCI/entacapone was lower compared to German subjects.

EFFICACY RESULTS:

The primary efficacy endpoint of this trial was defined as the **Investigator's Global Assessment of Change** at Visit 4/LOCF. An improvement was observed for 340 (71.3%) subjects (6.5% very much improved and 36.5% much improved). A worsening was observed for 46 (9.6%) subjects (3.1% much worse and 0.6% very much worse). No change was reported for 88 (18.4%) subjects. The results of the different subgroup analyses showed that for the majority of subjects an improvement was reported regardless of age, disease duration at study entry and L-dopa mean daily dose, concomitant usage of COMT inhibitors, usage of COMT inhibitors before first IMP intake, concomitant usage of dopamine agonists, concomitant usage of MAO-B inhibitors and dopamine agonists at baseline. Also at Visit 3 and Visit 5 (UK only), for the majority of subjects an improvement was observed.

Data of Visit 3 and Visit 4 are based on the total population including subjects from the UK and Germany whereas data of Visit 5 are based on the results of the UK population.

Regarding the **Subject's Global Assessment of Change**, the majority of subjects (> 70%) reported an improvement for all visits.

At baseline, a median **L-dopa** total daily **dose** of 525.0 mg was reported for the total FAS. A median change of 0.0 was observed from baseline to Visit 4 and Visit 5 (UK only). At Visit 3, Visit 4 and Visit 5 (UK only), the majority of the subjects reported no change in the number of daily doses from baseline and no change regarding the L-dopa single dose (Q1, median and Q3 change from baseline: 0.0 mg). At Visit 4 and Visit 5 (UK only), the majority of the subjects reported a stable total daily L-dopa dose compared to Visit 3.

A total of 80.9% subjects of the FAS completed the trial, for 69.9% of the subjects of the FAS, **OPC will be further prescribed**. A total of 19.1% subjects prematurely terminated the trial and stopped the OPC treatment, 15.9% due to an AE and only 0.6% due to lack of efficacy.

At Visit 3, Visit 4 and Visit 5 (UK only), all **WOQ-9 symptoms** were less frequently reported compared to baseline (for Visit 5 compared with baseline date of UK subjects). The majority of subjects reported an improvement of symptoms after the next dose of PD medication for all symptoms at these visits. At Visit 3 and Visit 4 the percentage of subjects who reported an improvement was lower compared to baseline whereas at Visit 5 an improvement was reported by a higher percentage of subjects compared to baseline for most symptoms.

For the **UPDRS** I (ON) score a median change from baseline of 0.0 was observed for Visit 4 and Visit 5 (UK only).
The UPDRS II (OFF), UPDRS II + III (ON) and UPDRS IV (ON) scores decreased from baseline to Visit 4 and Visit 5 (UK only). Statistically significant median decreases of 2.0 points and 5.0 points were observed for the UPDRS II and the UPDRS II + III score at Visit 4 and of 2.0 points and 3.0 points, respectively, at Visit 5 (UK only). For the UPDRS IV score a median decrease of 1.0 point was reported at Visit 4 and no median decrease at Visit 5 (UK only).

The **PDQ-8 and the NMSS scores** showed slight improvements. A median decrease from baseline of 3.125 points was observed for the PDQ-8 score at Visit 4 and Visit 5 (UK only). A median decrease of 5.0 points and 2.0 points from baseline was observed at Visit 4 and Visit

5, respectively, for the NMSS score. The changes from baseline to Visit 4 were statistically significant for both scores.

No relevant differences were observed between the PPS and the FAS regarding all efficacy endpoints.

SAFETY RESULTS:

The median treatment duration in Germany was 89.0 days ranging from 1 day to 134 days. In the UK, the median duration was 179.0 days, ranging from 1 day to 205 days.

Overall, 371 (74.9%) subjects experienced 1240 **TEAEs**. The most common individual TEAEs were dyskinesia (14.3%), constipation (8.7%), dry mouth (8.1%) and nausea (7.1%).

A total of 223 (45.1%) subjects experienced 507 **TEAEs assessed as at least possibly related to trial treatment**. The most common TEAEs by PT assessed as at least possibly related to trial treatment were dyskinesia (11.5%), dry mouth (6.5%), dizziness (4.8%), nausea (4.4%) and constipation (4.0%).

Overall 84 (17.0%) subjects experienced 136 **TEAEs leading to premature termination** of the trial. The most frequent individual TEAEs leading to withdrawal were nausea (2.0%), constipation (1.4%) and hallucination (1.2%).

The vast majority of TEAEs were assessed as mild or moderate. Overall, 65 **severe TEAEs** were reported for 46 (9.3%) subjects. The frequency of individual TEAEs assessed as severe was low, most of the severe TEAEs by PT occurred only in one subject. The most common TEAEs by PT assessed as severe were hallucination and constipation (0.6% each).

In this trial, one **death** due to endocarditis was reported, which was considered by the investigator to be severe and unlikely related to IMP.

The frequency of **SAEs** was low. Overall, 34 (6.9%) subjects experienced 46 treatment emergent SAEs (including the death). Treatment emergent SAEs by PT reported in more than one subject included urinary tract infection (0.6%), femoral neck fracture, hallucination (visual) and hypertension (0.4% each).

The related TESAEs femoral neck fracture and tachycardia were unexpected for OPC as per reference safety information, both TESAEs resolved.

Nine TESAEs experienced by eight (1.6%) subjects led to premature trial termination including anxiety, hypertension, tachycardia, breast cancer, hallucination (visual) (two events), volvulus, psychotic disorder and hypotension. The frequency of TESAEs judged to be as at least possibly related to IMP by the investigators was low and included eight TESAEs experienced by seven (1.4%) subjects including anxiety, hallucination (visual), psychotic disorder, hypertension, hypotension, tachycardia, femoral neck fracture and dizziness. Eighteen TESAEs (including the death) experienced by 16 subjects were of severe intensity. Four TESAEs did not resolve, the outcome of one TESAE (breast cancer) was unknown and one TESAE was fatal.

There were no relevant changes from baseline to Visit 4 or Visit 5 (UK only) in **vital signs, physical and neurological examinations**. The rate of TEAEs based on blood pressure and pulse rate changes was low. The number of subjects with physical and neurological examination findings assessed as clinically significant abnormal was low at baseline, Visit 4 and Visit 5.

Although 17.0% subjects experienced TEAEs leading to premature termination, the evaluation of SAEs and TEAEs reported for this study as well as the evaluation of physical and

neurological examinations and measurement of vital signs (blood pressure and pulse rate) did not raise any major safety concerns.

OTHER RESULTS:

Analysis of OPC Metabolites

BIA 9-1103, which is formed by sulphation of OPC, was found to be the major **OPC metabolite**. Low concentrations of metabolites BIA 9-4584 and BIA 9-5049 were observed. Metabolites BIA 9-4588 and BIA 9-5048 were not observed.

Health Economic Costs Assessment (only evaluated for the UK)

The median total **health economic costs** at baseline were 3875 UK-£ including 1127.04 UK-£ for formal service costs and 2506.00 UK-£ for unpaid care costs. The median total costs and the formal service costs decreased from baseline to Visit 5 (change of -344.81 UK-£ and -379.86 UK-£, respectively), whereas the median unpaid care costs increased (change of 14.00 UK-£) during the course of the trial. Regarding individual cost categories, a median change from baseline of 0.0 to Visit 5 was observed for the most individual categories except for the categories “primary and community care services” (change of -303.975 UK-£) and “informal care” (change of 648.000 UK-£).

At baseline and at Visit 5, all subjects used **any services**. The highest number of subjects was observed in the category “primary and community care services”, followed by “journeys” and “hospital and residential services” for both visits.

At baseline (n = 128), the total service costs were 284952.79 UK-£. The highest **percentage of service costs** were observed for the primary and community care doctor (36.3%) followed by the hospital doctor (18.8%) and prostheses/adaptations (9.4%). At Visit 5 (n = 95), the total service costs were 121280.83 UK-£. The highest percentage of service costs were observed for the hospital doctor (23.4%), followed by the primary and community care doctor (23.2%) and inpatient (20.0%). Mean service costs higher than 1000 UK-£ per subject were observed for residential care followed by social care, inpatient and primary and community care doctor at baseline compared to inpatient followed by residential care at Visit 5.

Statistically significant relationships for formal service costs and explanatory variables were observed only at baseline for UPDRS part I and part IV scores. The PPS supports these results, only for UPDRS part I scores at baseline no statistically significances were observed. Also the the sensitivity analysis (FAS) performed only for subjects with all model data available at both visits supported these results, only for UPDRS part IV scores at baseline no statistically significances were observed. These observations were confirmed in the PPS. The intercept values were statistically different from zero at baseline and at Visit 5 in all analyses and in all analyses sets.

S**tatistically significant relationships for unpaid care costs** and explanatory variables were observed for the duration of wearing-off motor fluctuations, UPDRS part I, UPDRS part II at OFF stage and part IV scores at baseline and for females and UPDRS part I at Visit 5. The PPS supported these results with the exception of the statistically non-significances for UPDRS part I scores at baseline but in addition statistically significances for UPDRS part I scores at Visit 5. The sensitivity analysis (FAS) also supported the results, only for UPDRS part I and part IV scores at baseline no statistical significances were observed. In the sensitivity analysis (PPS) statistically significant relationships were observed for the same variables as in the FAS and in addition for UPDRS part II scores at OFF stage at Visit 5. The intercept values were statistically different from zero at baseline and at Visit 5 in all analyses and in all analyses sets.

CONCLUSIONS:

- The primary efficacy endpoint of this trial defined as the Investigator's Global Assessment of Change at Visit 4/LOCF was assessed as improved for the majority of the subjects (71.3%).
- The results of the different subgroup analyses showed that for the majority of subjects an improvement was reported regardless of age, disease duration at study entry and L-dopa mean daily dose, usage of COMT inhibitors before first IMP intake, concomitant usage of COMT inhibitors, , concomitant usage of dopamine agonists, concomitant usage of MAO-B inhibitors and dopamine agonists at baseline.
- The Subject's Global Assessment of Change showed an improvement for the majority of subjects (> 70%) for all visits. For the majority of the subjects OPC will be further prescribed.
- The intake of 50 mg OPC seems to have no effect on the L-dopa total daily dose, the number of daily doses and the L-dopa single dose. The majority of the subjects reported a stable total daily L-dopa dose at Visit 4 and Visit 5 (UK only) compared to Visit 3.
- The UPDRS, WOQ-9, PDQ-8 and NMSS scores improved. Statistically significant median decreases were observed for the UPDRS II and the UPDRS II + III score at Visit 4 and at Visit 5 (UK only). The PDQ-8 changes as well as the NMSS changes from baseline to Visit 4 were statistically significant.
- The consistency of the results across the FAS and the PPS of this study demonstrate robust findings.
- The evaluation of TEAEs and SAEs reported for this study as well as the evaluation of physical and neurological examinations and measurement of vital signs (blood pressure and pulse rate) did not raise any major safety concerns.

Date of the report:

10-JUL-2019