SYNOPSIS

Title of study:

Randomised, double-blind, placebo-controlled, clinical study to evaluate the effect of opicapone 50 mg on Parkinson's disease patients with end-of-dose motor fluctuations and associated pain.

Protocol Short Title: Opi**C**apone **E**ffect on motor fluctuations and p**A**i**N** (**OCEAN**)

Study number: BIA-91067-404

EudraCT number: 2020-001175-32

Sponsor details:

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Investigators:

The study was conducted in 5 sites in the Czech Republic, 4 sites in Germany, 5 sites in Italy, 6 sites in Poland, 7 sites in Portugal, 7 sites in Spain and 10 sites in the United Kingdom.

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Chaudhuri KR, Odin P, Ferreira JJ, Antonini A, Rascol O, Kurtis MM, Storch A, Bannister K, Soares-da-Silva P, Costa R, Magalhães D, Rocha JF. Opicapone versus placebo in the treatment of Parkinson's disease patients with end-of-dose motor fluctuation-associated pain: rationale and design of the randomised, double-blind OCEAN (OpiCapone Effect on motor fluctuations and pAiN) trial. BMC Neurol. 2022 Mar 12;22(1):88. doi: 10.1186/s12883-022-02602-8. PMID: 35279112; PMCID: PMC8917369.

Studied period (years):

Date of first enrolment: 25-FEB-2021
Date of the last patient completed: 16-FEB-2024

Reporting period:

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

Phase of development:

Phase 3 or in countries where opicapone was already available on the market as Phase 4.

Background and rationale:

Parkinson's disease (PD) is a neurodegenerative disease of unknown aetiology with an estimated incidence of 4.5-16/100 000 persons/year. Analysis of worldwide data demonstrated a rising prevalence of PD with age and affects approximately 1.6% of people over the age of 65 years.

End-of-dose motor fluctuations and associated pain, sleep disorders or anxiety are commonly observed in PD patients under treatment with levodopa / DOPA decarboxylase inhibitors (L-DOPA/DDCI). They have a great impact on the quality of life and are significantly associated with reduced well-being.

Opicapone 50 mg is approved by the European Medicines Agency as adjunctive therapy to preparations of L-DOPA/DDCI in adult patients with PD and end-of-dose motor fluctuations who cannot be stabilised on those combinations.

The positive effect of opicapone in reducing the total daily OFF-time and improving the general well-being of patients as demonstrated in previous pivotal Phase 3 studies was also shown by a Phase 4 study (BIA-OPC-401) investigating the safety and efficacy of opicapone in over 3 months.

The aim of the current study was to evaluate the efficacy of opicapone 50 mg on Parkinson's disease patients with end-of-dose motor fluctuations and associated pain.

Objectives:

Primary:

The primary objective of this study was to investigate the efficacy of opicapone 50 mg when administered with the existing treatment of L-DOPA plus a DDCI, in PD patients with end-of-dose motor fluctuations and associated pain.

Secondary:

- To investigate the efficacy of opicapone 50 mg in reducing further symptoms.
- To investigate the safety and tolerability of opicapone 50 mg once daily.

Methods:

This was a randomised, double-blind, placebo-controlled, multi-centre, parallel group, interventional clinical study in PD patients with end-of-dose motor fluctuations and associated pain. The study consisted of a 1-week screening period, a 24-week double-blind treatment period and a 2-week follow-up period.

At Visit 1 (Day -7 ±2), the patient completed the King's Parkinson's Disease Pain Scale (KPPS). The patient was provided with a paper-based self-rating diary (Hauser's PD diary) and trained to complete it adequately.

Completion of diary entries was reviewed at Visit 2a (5 to 6 days after Visit 1) and in case the patient had completed the diary satisfactorily the investigator immediately continued with Visit 2b on the same day. If diary entries were non-compliant (i.e. ≥ 3 missing or incorrectly entries per day in the 3 days prior to Visit 2a), the patient was re-trained on correct use of the diary and Visit 2b was postponed for 3 to 4 days.

At Visit 2b (Day 1) and if eligibility was confirmed, the patient was randomised to opicapone 50 mg or placebo once daily (1:1) and started treatment in addition to the current treatment with L-DOPA/DDCI. *Rescue medication was dispensed to the patient as well and could be taken upon request.*

Since opicapone 50 mg enhances the effects of L-DOPA, patient's L-DOPA/DDCI dose could be changed by the investigator according to the patient's response up to Day 29 ± 2 (Visit 4). Changes included decreasing the dose and increasing it again up to the baseline dose level if the dose reduction was too much based on the investigator's opinion. *The use and dose adjustment of rescue medication had to be carefully monitored at regular visits and if needed during unscheduled visits.*

Further visits were performed on Day 85 ± 4 (Visit 5, after 12 weeks) and Day 169 ± 4 (Visit 6, after 24 weeks). A follow-up Visit was performed on Day 183 ± 4, approximately 2 weeks after the last intake of the investigational product (IP, opicapone 50 mg or placebo).

Note: The text in italics was only applicable in the Czech Republic, see clinical study protocol (CSP) Final Version 1.0, 19-SEP-2022 and CSP Final Version 2.0, 17-OCT-2022.

No global interruptions and re-starts occurred in this study.

The recruitment was terminated before reaching the estimated number of randomised patients. However, this had no impact on the analysis of data since the drop-out rate was less than 15% and thus the planned number of evaluable patients was reached.

Number of patients (planned and analysed)

Category	Number of Patients
Planned to screen	176
Planned to randomise	140
Planned to evaluate	120
Allocated to treatment	127
Withdrawn from the study	19
Completed	108
Analysed (efficacy)	122
Analysed (safety)	127

Diagnosis and main criteria for inclusion and exclusion:

Patients aged 30 years or older (in Germany only: patients aged 50 to 85 years, see CSP Final Version 1.0, 03-DEC-2020) diagnosed with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (2006) or according to MDS Clinical Diagnostic Criteria (2015) and disease severity Stages I to III (modified Hoehn & Yahr staging) at ON. Patients had to experience the "wearing-off" phenomenon (end-of-dose motor fluctuations) with an average total daily OFF-time while awake of at least 1.5 hours, excluding the early morning pre-first- dose OFF, despite 3 to 8 intakes per day of L-DOPA/DDCI (which could include a slow-release formulation) on a stable regimen for at least 4 weeks before Visit 1 (based on investigator's assessment). Additionally, they had to experience PD-associated pain for at least 4 weeks prior to Visit 1 and a Domain 3 score of the KPPS ≥ 12. There must have been no changes in chronic treatment regimen for pain within the last 4 weeks before Visit 1. This included medications (including but not limited to paracetamol, opioids, nonsteroidal anti-inflammatory drugs, antidepressants anticonvulsants and corticosteroids) and non-medication therapies (including but not limited to transcutaneous electrical nerve stimulation and bioelectrical therapy).

At Visit 2b, an OFF-time of at least 1.5 hours per day in at least 2 of the 3 days for the 3 days preceding Visit 2a/Visit 2b had to be confirmed via entries in the self-rating diary and the Domain 3 score of KPPS had to be ≥ 12.

Patients with non-idiopathic PD (atypical parkinsonism, secondary [acquired or symptomatic] parkinsonism, Parkinson-plus syndrome), severe or unpredictable OFF periods, according to the investigator's judgement or with major/prominent non-PD-related pain (e.g. due to malignant disease) were not eligible for this study.

Paediatric regulatory details:

Not applicable

Measures of protection of patients taken:

This study was performed in neurological centres and conducted in compliance with the study protocol, by the study personnel, who were qualified by education, training, and experienced in their roles. The patients were closely monitored during the study. Patients who discontinued study participation prematurely were asked to come to the site for an early discontinuation visit to exclude the possibility of an adverse event (AE) being the cause and otherwise to assess if the AE had any potential relationship to the study medication. Serious adverse events (SAEs) which were still ongoing after the patient's final visit were to be followed-up and follow-up information was to be recorded by the investigators. In case of SAEs detected after the end of the observation period, the investigator was instructed to contact the sponsor to determine how to document and report these SAEs.

In case of unusual symptoms or questions the patients could always contact the investigator and arrange an unscheduled visit. The planned study procedures, standard examinations and questionnaires, did not pose a risk to the patients other than those associated with assessments in general common clinical practice.

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

Test product: opicapone (BIA 9-1067), 50 mg

Bulk batch numbers: Lot 220754, Lot 190761, Lot 180220

Reference product: matching placebo

Bulk batch numbers: Lot 190770, Lot 190769, Lot 190767

Each patient took opicapone 50 mg or matching placebo once daily at bedtime, at least 1 hour before or after the last daily dose of L-DOPA/DDCI in accordance with the dosing instructions in the leaflet of the authorised product. The patients were instructed to swallow the capsule whole with a glass of water.

Auxiliary Medicinal Products:

The patients were allowed to use one of the following as rescue medication, upon request:

Paracetamol: 500 mg tablets; 4 g per day at maximum

In Germany only, 3 g per day at maximum, see CSP Final Version 2.0, 19-FEB 2021

In the Czech Republic only, 4 g per day [1 g per single dose] at maximum. During a long-term therapy (over 10 days), the daily dose should not exceed 2.5 g (5 tablets of paracetamol 500 mg), see CSP Final Version 1.0, 19-SEP-2022

Bulk batch numbers: Lot 23382, Lot PHX5FB7

OR

Tramadol: 50 mg capsules; 400 mg per day at maximum

Bulk batch numbers: Lot TK728, Lot TK790, Lot TK913

Duration of treatment:

Each patient received IP and rescue medication, if applicable for a duration of 24 weeks.

Endpoints:

Primary endpoint:

Change from baseline in Domain 3 (fluctuation-related pain) of KPPS

Secondary efficacy endpoints:

1. Change from baseline in Domain B (anxiety) of Movement Disorder Society-sponsored Non-motor Rating Scale (MDS-NMS)
2. Change from baseline in Domain A (depression) of MDS-NMS
3. Change from baseline in Domain K (sleep and wakefulness) of MDS-NMS
4. Change from baseline in total score of MDS-NMS
5. Change from baseline in Domain 4 (nocturnal pain) of KPPS
6. Change from baseline in total score of KPPS
7. Change from baseline in Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III and IV
8. Change from baseline in Parkinson's Disease Questionnaire (PDQ-8)
9. Clinical Global Impression of Change (CGIC)
10. Patient's Global Impression of Change (PGIC)
11. Change from baseline in functional status via Hauser's PD diary
12. Changes from baseline in morning dystonia
13. Frequency of use of rescue medication

Safety endpoints:

14. Incidence of AEs including SAEs
15. Changes from baseline in vital signs
16. Changes from baseline in physical and neurological examinations

17. Changes from baseline in routine laboratory parameters

Statistical methods:

The **enrolled set** was defined as all patients who signed informed consent.

The **randomised set** was defined as all randomised patients.

The **safety set** was defined as all patients who took at least one dose of IP. Patients were analysed according to actual treatment taken.

The **full analysis set (FAS)** was defined as all patients who were randomised and who had at least one post-baseline assessment of the primary efficacy measurement. Patients were analysed according to the randomised treatment.

The **per-protocol set (PPS)** was defined as all patients who were included into the FAS and had no major protocol deviations that could have an influence on the primary efficacy endpoint. Patients were analysed according to the randomised treatment.

The following statistical hypotheses were tested:

H_0: $\mu_T = \mu_C$

H_1: $\mu_T \neq \mu_C$

where μ_T was the mean change in the KPPS Domain 3 from baseline in the opicapone 50 mg group and μ_C was the mean change in the KPPS Domain 3 from baseline in the placebo group.

The analysis of the primary efficacy endpoint was based on the FAS (primary analysis population) and the PPS and was analysed using a two-sided alpha 0.05 using a mixed model for repeated measures (MMRM) assuming that unobserved data were missing at random (MAR). Only patients with no missing data at baseline were used for the primary analysis within the FAS.

The following subgroups were defined for the primary efficacy endpoint analysis:

- Age group: ≤ 65 years and > 65 years
- Modified Hoehn and Yahr Staging: 1 – 2 and 2.5 - 3
- PD duration: ≤ 5 years and > 5 years
- Motor-fluctuations (wearing-off) duration: < 2 years and ≥ 2 years
- L-DOPA total dose at baseline: < 600 mg and ≥ 600 mg.

The primary model was used for each subgroup analysis.

All secondary endpoints were analysed in an exploratory manner. No multiplicity adjustments were conducted. The same MMRM models with MAR assumptions as defined for the primary analysis were used as applicable. Statistical analyses including 95% confidence intervals and corresponding p-values (non-confirmatory) for each visit were presented.

Categorical data such as defined treatment emergent adverse event (TEAE) categories and terms, physical and neurological examination findings were summarised by default frequency tabulations (number and percentage of patients), while continuous data such as vital signs parameter were displayed by default summary statistics on absolute values and changes from baseline. All laboratory values were summarised by default frequency tabulations (number and

percentage of patients) and by default summary statistics. The analysis of all safety endpoints was based on the safety set.

SUMMARY OF RESULTS

PATIENT DISPOSITION:

A total of 144 patients were enrolled at 44 active sites in Europe. Of these, 127 (100.0%) patients were randomised and received at least 1 dose of IP. A total of 122 (96.1%) patients met the criteria for the FAS including 59 (92.2%) opicapone 50 mg and 63 (100.0%) placebo patients. The PPS comprised of 87 (68.5%) patients with a similar percentage of patients in the opicapone 50 mg and the placebo group (42 patients, 65.6% vs. 45 patients, 71.4%). Of the 40 (31.5%) patients excluded from the PPS, 8 patients in each treatment group (13.6% vs. 12.7%) were excluded due to L-DOPA/DDCI changes between Visit 4 and Visit 6/EDV or due to L-DOPA/DDCI dosage above the baseline dose level.

Of 127 (100%) patients in the safety set, 108 (85.0%) patients completed the study, specifically 53 (82.8%) opicapone 50 mg and 55 (87.3%) placebo patients.

A total of 19 (15.0%) patients prematurely terminated the study with similar percentages in the opicapone 50 mg and the placebo group (17.2% vs. 12.7%). The main reason for the premature study termination was adverse events (8 patients, 6.3%).

Most patients in the FAS were of white race (121 patients, 99.2%). In the opicapone 50 mg group, the proportion of males was higher than that of females (54.2% vs. 45.8%) whereas in the placebo group, similar proportions of males and females (50.8% vs. 49.2%) were reported. The patients' mean (SD) age in the total population was 66.2 (9.26) years and ranged from 44 to 85 years.

In total, the median time since PD diagnosis was 5.35 years ranging from 0.3 to 15.9 years and the median time since the first occurrence of wearing-off motor fluctuations was 1.00 year with a range of 0.1 to 10.0 years. No relevant differences were observed between the treatment groups.

At enrolment, most patients in total (81 patients, 66.4%) had a disease severity Stage 2 according to the modified Hoehn & Yahr staging at "ON". Relevant differences between the treatment groups were observed for Stage 2 (71.2% vs. 61.9%) and for Stage 2.5 (5.1% vs. 11.1%) with higher percentage of patients in the opicapone 50 mg group compared to the placebo group.

The time since the occurrence of PD-associated pain varied widely among the patients with a range from 0.1 to 15.3 years resulting in a median of 1.60 years. The median time was similar in both treatment groups.

The most common ongoing medical conditions by PT were pain (119 patients, 97.5%), hypertension (60 patients, 49.2%) and depression (33 patients, 27.0%).

The most frequently used concomitant medications besides anti-Parkinson drugs and analgesics by preferred name were atorvastatin (20 patients, 16.4%) and omeprazole and clonazepam (15 patients, 12.3% each).

At baseline, the patients' mean (SD) L-DOPA dose was similar in the opicapone 50 mg and the placebo group (633.6 [281.19]) mg/day vs. 611.5 [319.24] mg/day) and was most commonly divided into 4 or 5 daily doses (32 patients, 26.2% each). The mean total daily dose remained almost constant throughout the study in both groups.

A decrease in the L-DOPA/DDCI total daily dose compared to baseline was reported in a higher number of opicapone 50 mg than in placebo patients (4 patients, 6.8% vs. 0 patients from Visit 2b until Visit 4 and 6 patients, 10.2% vs. 1 patient, 1.6% from Visit 4 until Visit 6).

The median overall treatment duration in the safety set was 169.0 days ranging from 3 days to 194 days in the opicapone 50 mg group and 168.0 days ranging from 14 to 179 days in the placebo group. In both treatment groups, a similar actual treatment duration was reported.

The mean (SD) compliance to IP in the total population was 98.33% (5.195%) ranging between 73.3% and 110.1%. It was similar in both treatment groups.

EFFICACY RESULTS:

The primary efficacy endpoint was defined as the change from baseline in Domain 3 (fluctuation-related pain) of the KPPS.

The **KPPS Domain 3 score** decreased from baseline to the end of the study to a similar extent in the opicapone 50 mg and the placebo group. The statistical analysis of the changes from baseline showed no statistically significant treatment group difference at any visit with an LS mean (SE) difference of -0.62 (1.215) points, 95% CI: -3.03, 1.79 at Visit 4 ($p = 0.6106$), of -1.19 (1.091) points, 95% CI: -3.35, 0.98 at Visit 5 ($p = 0.2792$), and of 0.30 (1.139) points, 95% CI: -1.96, 2.55 at Visit 6 ($p = 0.7940$).

The results in the PPS confirmed the results in the FAS and the results of the sensitivity analysis supported the results of the primary analysis.

No statistically significant treatment group difference could be shown in any subgroup (FAS) except for the subgroup of patients with a modified Hoehn and Yahr Staging of 2.5 to 3 (Visit 6: LS mean difference [SE]: 5.47 [2.054] points, 95% CI: 1.27, 9.67; $p = 0.0124$ in favour of placebo) and for the subgroup of patients with an L-DOPA total dose ≥ 600 mg (Visit 5: LS mean difference [SE]: -3.68 [1.395] points, 95% CI: -6.47, -0.88; $p = 0.0108$ in favour of opicapone 50 mg).

Secondary endpoints

The mean (SD) **KPPS Domain 4 score (nocturnal pain)** decreased in the opicapone 50 mg group and the placebo group to a similar extent during the study resulting in a mean (SD) change from baseline to Visit 4 of -2.1 (4.52) points vs. -1.7 (4.73) points, to Visit 5 of -2.9 (6.08) points vs. -2.1 (4.69) points and to Visit 6 of -4.0 (6.33) points vs. -2.7 (4.87) points. No statistically significant group difference could be shown at any visit (Visit 4: $p = 0.8086$, Visit 5: $p = 0.3478$, Visit 6: $p = 0.1293$).

The mean (SD) **KPPS total score** decreased during the study in the opicapone 50 mg group and the placebo group. This resulted in a mean (SD) change from baseline to Visit 4 of -13.3 (17.88) points vs. -10.6 (15.58) points, to Visit 5 of -18.4 (17.60) points vs. -13.4 (15.05) points and to Visit 6 of -18.1 (19.46) points vs. 16.1 (16.42) points. No statistically significant group difference could be shown at any visit (Visit 4: $p = 0.6033$, Visit 5: $p = 0.11039$, Visit 6: $p = 0.7538$).

The mean (SD) **MDS-NMS Domain A (depression)**, **Domain B (anxiety)** and **Domain K (sleep and wakefulness) scores** remained almost constant from baseline to Visit 6 in the opicapone 50 mg and placebo group as shown by mean (SD) changes of -1.6 (10.78) points vs. -3.1 (10.31) points (Domain A), of -3.1 (7.29) points vs. -2.1 (7.50) points (Domain B) and of -2.9 (8.34) points vs. -2.8 (8.23) points (Domain K). The statistical analysis of the changes from baseline to Visit 6 showed no statistically significant treatment group difference in the

Domain A score (p = 0.4151), the Domain B score (p = 0.7464) and the Domain K score (p = 0.9185).

The mean (SD) and median **MDS-NMS total score** decreased from baseline to Visit 6 to a similar extent in the opicapone 50 mg and placebo group (-28.4 [49.34] points vs. (-27.1 [55.14] points and -10.0 points vs. -16.0 points, respectively). No statistically significant treatment group difference was reached at Visit 6 (p = 0.9391).

The **MDS-UPDRS Part III** and **Part IV total scores** remained almost constant from baseline to Visit 6 in the opicapone 50 mg and placebo group as shown by mean (SD) changes of -2.7 (9.93) points vs. -2.7 (9.38) points and of -1.2 (2.56) points vs. -1.8 (2.54) points, respectively. The statistical analysis of the changes from baseline to Visit 6 showed no statistically significant treatment group differences for the Part III total score (p = 0.6930, 95% CI of -4.11, 2.74) and the Part IV total score (p = 0.5474).

The **PDQ-8 index scores** decreased to a similar extent from baseline to Visit 6 in the opicapone 50 mg and placebo group (-5.719 (16.702) points vs. -3.807 (17.271) points). The statistical analysis of the changes from baseline to Visit 6 showed no statistically significant treatment group difference (p = 0.9276).

At Visit 6, the **CGIC** and **PGIC** in the overall status since the start of the study was categorised as improved for a lower proportion of patients in the opicapone 50 mg than in the placebo group (27 patients, 50.9% vs. 31 patients, 56.4% and 30 patients, 56.6% vs. 34 patients, 61.8%). These differences were not statistically significant (CGIC: p = 0.6997 and PGIC: p = 0.6957).

The results in the PPS regarding the KPPS Domain 4 and total score, MDS-NMS Domain A, Domain B, Domain K and total score, MDS-UPDRS Part III and Part IV total score, PDQ-8 index score and CGIC and PGIC confirmed the results in the FAS.

About half of the patients in each treatment group were **OFF-time responders** at Visit 6 (53.8% of the opicapone 50 mg patients vs. 49.1% of the placebo patients). The proportion of **ON-time responders** was higher in the opicapone 50 mg group than in the placebo group both in the FAS (51.9% vs. 43.6%) and in the PPS (55.3% vs. 42.9%, respectively).

At Visit 6, the proportion of patients with a shift from “yes” (with **morning dystonia**) to “no” (without morning dystonia) was higher in the opicapone 50 mg group than in the placebo group (27.1% vs. 17.5%). A shift from “no” to “yes” was reported by a similar proportion of patients in both treatment groups (8.5% vs. 6.3%). The results in the PPS confirmed the results in the FAS.

A similar proportion of patients in the opicapone 50 mg and the placebo group used paracetamol as rescue medication during the study (41 of 59 patients vs. 40 of 63 patients, respectively). The number of days on which paracetamol was taken was lower in the opicapone 50 mg group than in the placebo group; overall: 1653 days vs. 1811 days, from the first IP intake until Visit 4: 288 days vs. 369 days and from Visit 4 until Visit 5: 514 days vs. 606 days. At the end of the study (from Visit 5 until Visit 6), patients in the opicapone 50 mg and placebo group took paracetamol on a similar number of days (851 days vs. 836 days).

Overall, the mean (SD) number of daily taken paracetamol tablets was similar between the opicapone and placebo group (2.4 [1.81] tablets/day vs. 1.8 [1.31] tablets/day). Also, the mean (SD) number of daily taken paracetamol tablets for those patients completing the diary was similar between the opicapone and the placebo group in the period from Visit 5 until Visit 6 (2.6 [2.05] tablets/day vs. 1.9 [1.15] tablets/day).

The overall number of days with tramadol intake was lower in the opicapone 50 mg group compared with the placebo group (142 vs. 445 days) and also the mean (SD) number of daily

taken tramadol capsules during the treatment period was also lower in the opicapone 50 mg group compared to the placebo group: 1.1 (0.34) vs. 2.2 (1.49) capsules. Also, the mean (SD) number of tramadol capsules taken within 30 days before Visit 6 was lower in the opicapone 50 mg than in the placebo group (1.0 [0.00] capsules/day vs. 3.2 [2.10] capsules/day). Since the number of patients with tramadol intake was low (9 opicapone 50 mg patients and 10 placebo patients) the data should be interpreted with caution.

Usage frequency of rescue medication in the PPS was similar compared with the FAS.

SAFETY RESULTS:

Overall, 127 patients (64 opicapone 50 mg users and 63 placebo users) received at least one dose of IP and were included in the safety set.

Overall, 76 (59.8%) patients experienced a total of 245 **TEAEs** with a higher frequency of patients in the opicapone 50 mg (40 patients, 62.5%, 150 events) than in the placebo group (36 patients, 57.1%, 95 events).

The most frequently reported individual TEAEs in the total population were nausea (9.4%), anxiety and pain (6.3%, each) and dyskinesia (5.5%). The most frequent TEAEs in the opicapone 50 mg group were nausea (10.9%), anxiety (9.4%), constipation and pain (7.8%, each), whereas in the placebo group nausea (7.9%) and dyskinesia (6.3%) were most frequently reported.

The frequency of **TEAEs assessed as at least possibly related to IP** was comparable between the opicapone 50 mg (16 patients, 25.0%; 28 TEAEs) and the placebo (18 patients, 28.6%; 29 TEAEs) group. The most common TEAE assessed at least possibly related to IP by PT in the opicapone 50 mg group was nausea (6.3%), dyskinesia and decreased appetite (3.1%, each) and in the placebo group, nausea (6.3%) followed by dyskinesia, fatigue and musculoskeletal stiffness (3.2%, each).

The vast majority of TEAEs were mild or moderate in intensity. Overall, 8 **severe TEAEs** were reported for 5 (3.9%) patients: 5 TEAEs for 3 (4.7%) patients in the opicapone 50 mg group and 3 TEAEs for 2 (3.2%) patients in the placebo group. None of the individual TEAEs assessed as severe was reported for more than 1 patient in total.

No deaths were reported. Overall, 6 (4.7%) patients experienced 9 **serious TEAEs**, with a higher frequency of TESAEs in the opicapone 50 mg group (4 patients, 6.3%; 7 events) than in the placebo group (2 patients, 3.2%; 2 events). None of the individual TESAEs was reported for more than one patient in total and atrial fibrillation was the only TESAE reported twice for the same opicapone 50 mg patient. All TESAEs were considered to be unlikely or not related to the IP, except one case of possibly related faecaloma in the opicapone 50 mg group, which was assessed as severe and led to patient's withdrawal from the study. Faecaloma was unexpected for opicapone as per reference safety information. All TESAEs resolved.

Overall, 8 (6.3%) patients prematurely **terminated the study due to 14 TEAEs**, with similar frequency in the opicapone 50 mg (4 patients, 6.3%, 6 TEAEs: nausea, faecaloma, hallucinations, mixed; impulse-control disorder, nightmare and deep vein thrombosis) and the placebo (4 patients, 6.3%, 8 TEAEs: nausea, dyspepsia, anxiety, asthenia, fatigue, pain, musculoskeletal stiffness and non-small cell lung cancer) group. The incidence of TEAEs leading to withdrawal was low with no TEAEs by PT reported for more than 1 patient per treatment group. All TEAEs leading to discontinuation except one in each treatment group were considered at least possibly related to IP. All TEAEs leading to discontinuation resolved.

No relevant changes from baseline to Visit 6/EDV or differences between the treatment groups were observed for **vital signs, physical and neurological examination findings**. The incidence of TEAEs based on blood pressure or heart rate was low during the study. Changes from normal or not CS abnormal physical and neurological examination findings at Visit 1 to CS abnormal at Visit 6/EDV were reported for a few patients only.

No relevant changes from Visit 1 to Visit 6/EDV were observed for the **laboratory** variables investigated. The frequency of TEAEs based on abnormal laboratory values was low. Such TEAEs were reported for 2 patients in the opicapone 50 mg and 1 patient in the placebo group and none was reported as at least possibly related to IP.

OTHER RESULTS:

Not applicable.

CONCLUSION:

- The primary efficacy endpoint, defined as the change from baseline in KPPS Domain 3 (fluctuation-related pain), was not statistically met in this study. Both treatment groups demonstrated a similar improvement in the KPPS Domain 3 score from baseline to Visit 6, which may be attributed to a considerable placebo effect on pain. All patients participating in the study showed a meaningful improvement of the KPPS total score of greater magnitude than the minimum clinical improvement difference of 3 units, regardless of the treatment.
- The secondary efficacy endpoints, namely the change from baseline in KPPS Domain 4 and total score, MDS-NMS Domain A, Domain B, Domain K and total scores, MDS-UPDRS Part III and Part IV total scores as well as the change in the PDQ-8 index score and the CGIC and PGIC also showed no statistically significant treatment group difference.
- No relevant need to adjust L-DOPA/DDCI therapy and no frequent use of rescue medication was reported.
- Opicapone 50 mg was generally well tolerated. The observed safety findings as assessed by reported TEAEs, evaluation of physical and neurological examinations, measurement of vital signs (blood pressure and pulse rate) and laboratory parameters correlate to the safety profile presented in the SmPC/IB and did not reveal any new safety concern.
- Even with the use of validated PD pain- and non-motor-symptom specific scales detecting the possible effect of adjunctive opicapone 50 mg treatment is challenging. Investigating the effect of anti PD medications on the improvement of fluctuation-associated pain in PD patients with end-of-dose motor fluctuations requires further study.

Date of the report:

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