Bial - Portela & C[a], S.A.

CLINICAL STUDY PROTOCOL

Synopsis

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	**O**pi**C**apone **E**ffect on motor fluctuations and p**A**i**N** (**OCEAN**)
Protocol Number	BIA-91067-404
EudraCT Number	2020-001175-32
Phase	IV
Version	Final Version 1.0
Date	04-JUN-2020
Product Name	Opicapone
Indication	Parkinson´s Disease
Sponsor	Bial - Portela & C[a], S.A. À Av. da Siderurgia Nacional 4745-457 Coronado (S. Romão e S. Mamede), Portugal Phone: +351 229866100 Fax: +351 229866192 http://www.bial.com
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PROTOCOL SYNOPSIS

Name and address of sponsor/company: Bial - Portela & C[a], S.A.,
À Av. da Siderurgia Nacional, 4745-457 Coronado (S. Romão e S. Mamede), Portugal.

Name of active ingredient: Opicapone (BIA 9-1067)

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.

Study number: BIA-91067-404

EudraCT number: 2020-001175-32

Coordinating investigator: Prof. Kallol Ray Chaudhuri (King's College Hospital, London, United Kingdom).

Clinical study site(s): Approximately 50 sites in Germany, Italy, Portugal, Spain and the United Kingdom. (Other countries and additional sites may be added as needed.)

Planned duration of the study:
First patient first visit: August 2020

Last patient last visit: July 2022

Phase of development: Phase IV

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To investigate the efficacy of 50 mg opicapone when administered with the existing treatment of levodopa (L-dopa) plus a dopa decarboxylase inhibitor (DDCI), in Parkinson's disease (PD) patients with end-of-dose motor fluctuations and associated pain	Change from baseline in Domain 3 (fluctuation-related pain) of King's Parkinson's Disease Pain Scale (KPPS)
Secondary	
• To investigate the efficacy of opicapone 50 mg in reducing further symptoms	1. Change from baseline in Domain B (anxiety) of Movement Disorder Society-sponsored Non-motor Rating Scale (MDS-NMS) (Key secondary endpoint) 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
• To investigate the safety and tolerability of opicapone 50 mg once daily	14. Incidence of adverse events (AEs) including serious adverse events (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

Methods / study design: This is 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 consists of a 1-week screening period, a 24-week double-blind treatment period and 2 weeks of follow-up period.

At visit V1 (7 ± 2 days before V2b), the patient will complete specific questionnaires. The patient will be provided with a paper-based self-rating diary (Hauser's PD diary) and will be instructed how to complete it.

Completion of diary entries will be reviewed at V2a (5 to 6 days after V1). In case the patient completed the diary satisfactorily the investigator will immediately continue with V2b at the same day. If diary entries are non-compliant (i.e. more than 3 missing entries per day in the 3 days prior to V2a), the patient will be re-trained on correct use of the diary and V2b will be postponed for 3 to 4 days.

At V2b (Day 1) and if eligibility is confirmed, the patient will be randomised to 50 mg opicapone or placebo once daily (1:1) and start treatment in addition to current treatment with L-dopa/DDCI.

Opicapone enhances the effects of L-dopa. Hence, it may be necessary to reduce the patient's L-dopa/DDCI dose within the first days or weeks of opicapone treatment. Therefore, the investigator will call the patient on Day 8 ± 2 (V3) to ask for any changes in the medical condition. If dose decrease of L-dopa/DDCI is deemed necessary, it may be adjusted by phone at V3 or an unscheduled on-site visit may be performed at the investigator's discretion. In case of L-dopa/DDCI adjustment an unscheduled phone call should be repeated up to 7 days after dose adjustment or V4 (Day 29 ± 2) should be performed, whatever applies first. The investigator can decrease the daily dose of L-dopa/DDCI (but keeping the number of daily intakes unchanged) as required until V4. If the investigator finds that the dose reduction was

too much, it can be increased again up to the baseline dose level. The dosage of L-dopa/DDCI should not be changed from V4 through the end of the study. No new anti-PD drugs should be started during the study and any that are ongoing at the start of the study must be kept at a stable dose throughout the study. No new pain medication should be started during the study except the allowed rescue medication. Baseline dose of pain medication may be reduced throughout the study if required due to pain medication-related AEs. If the investigator finds that the dose reduction was too much, it can be increased again up to the baseline dose level.

Further visits will be performed on Day 85 ± 4 (V5, after 12 weeks) and Day 169 ± 4 (V6, after 24 weeks). The primary analysis will be performed on the data collected at V6. A follow-up Visit (FU) will be performed on Day 183 ± 4, approximately 2 weeks after last intake of the investigational product (IP; 50 mg opicapone or placebo).

Patients who discontinue study participation prematurely will be asked to come to the site for an early discontinuation visit (EDV).

At V6 (or EDV, if applicable) the investigator will arrange for the patient's subsequent treatment, i.e. either prescribe further opicapone or switch to another treatment.

Number of patients (planned):

Screened:	176
Randomised:	140
Evaluable:	120

Diagnosis: Parkinson's disease patients with wearing-off motor fluctuations and associated pain.

Inclusion criteria at Visit 1 (Screening):

1. Able to comprehend and willing to sign an informed consent form and to comply with all aspects of the study.
2. Male or female patients aged 30 years or older.
3. Experiencing PD associated pain for at least 4 weeks prior to V1.
4. 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).
5. Disease severity Stages I-III (modified Hoehn & Yahr staging) at ON.
6. Treated with 3 to 8 intakes per day of L-dopa/DDCI (which may include a slow-release formulation), on a stable regimen for at least 4 weeks before V1.
7. In case of any other anti-PD-treatment, it should be on a stable regimen for at least 4 weeks before V1, and not likely to need any adjustment until V6.
8. No changes in chronic treatment regimen for pain within the last 4 weeks before V1. This includes medication (including but not limited to paracetamol, opioids, nonsteroidal anti-inflammatory drugs [NSAIDS], antidepressants, anticonvulsants and corticosteroids) and non-medication therapies (including but not limited to transcutaneous electrical nerve stimulation and bioelectrical therapy).
9. Signs of "wearing-off" phenomenon (end-of-dose motor fluctuations) 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 investigator's assessment).

10. Domain 3 of KPPS ≥ 12.
11. For females: Postmenopausal for at least 2 years before V1, surgically sterile for at least 6 months before V1, or practicing effective contraception until V6. Female patients who request to continue with oral contraceptives must be willing to use non-hormonal methods of contraception in addition during the course of this study.
    For males: Male patients who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved method of highly effective contraception during the treatment period until V6.

Inclusion Criteria at V2b (Baseline):

12. Have filled-in self-rating diary in accordance with the diary instructions and with ≤ 3 missing entries per day, in the 3 days preceding V2a/V2b.
13. 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 at least 2 of the 3 days in the self-rating diary for the 3 days preceding V2a/V2b.
14. Results of the screening laboratory tests are considered acceptable by the investigator (i.e. not clinically relevant for the well-being of the patient or for the purpose of the study).
15. Domain 3 of KPPS ≥ 12.
16. Adequate compliance to relevant (PD and pain related) concomitant medication during the screening period (based on the investigator's judgment).

Exclusion criteria:

1. Non-idiopathic PD (atypical parkinsonism, secondary [acquired or symptomatic] parkinsonism, Parkinson-plus syndrome).
2. Severe and/or unpredictable OFF periods, according to investigator judgement.
3. Major/prominent non-PD-related pain (e.g. due to malignant disease).
4. Treatment with prohibited medication: entacapone, tolcapone, monoamine oxidase (MAO) inhibitors (except selegiline up to 10 mg/day in oral formulation or 1.25 mg/day in buccal absorption formulation, rasagiline up to 1 mg/day or safinamide up to 100 mg/day), or antiemetics with antidopaminergic action (except domperidone) within the last 4 weeks before V1.
5. Previous or planned (during the entire study duration) L-dopa/carbidopa intestinal gel infusion, deep brain stimulation or stereotactic surgery (e.g. pallidotomy, thalamotomy).
6. Treatment with apomorphine within the last 4 weeks before V1 or likely to be needed at any time until V6.
7. Previous or current use of opicapone.
8. Use of any other IP, currently or within the 3 months (or within 5 half-lives of the IP, whichever is longer) before V1.
9. Past (within the past year) or present history of suicidal ideation or suicide attempts.
10. Current or previous (within the past year) alcohol or substance abuse excluding caffeine or nicotine.
11. Phaeochromocytoma, paraganglioma, or other catecholamine secreting neoplasms.
12. Known hypersensitivity to the excipients of IP (including lactose intolerance, galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption) or of rescue medication.
13. History of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis.

14. History of severe hepatic impairment (Child-Pugh Class C).
15. Previous history of psychosis or psychiatric disorders, including severe major depression.
16. Any medical condition that might place the patient at increased risk or interfere with assessments.
17. For females: Pregnant or breastfeeding.
18. Employees of the investigator, study centre, sponsor, clinical research organisation and study consultants, when employees are directly involved in this study or other studies under the direction of this investigator or study centre, and their family members.
19. Persons committed to an institution by virtue of an order issued either by the judicial or other authorities.

Duration of treatment for the individual patient:

Twenty-four weeks

Test product, dose and mode of administration:

Opicapone (BIA 9-1067) 50 mg hard capsules. Oral administration, once daily, at least 1 hour before or after the last daily dose of L-dopa/DDCI.

Reference therapy, dose and mode of administration:

Matching placebo hard capsules. Oral administration, once daily, at least 1 hour before or after the last daily dose of L-dopa/DDCI.

Rescue medication, dose and mode of administration:

Paracetamol 500 mg tablets. Oral administration, upon request with maximum daily dose of 8 tablets (4 g).

Tramadol 50 mg hard capsules. Oral administration, upon request with maximum daily dose of 8 capsules (400 mg).

Paracetamol and tramadol are not allowed to be taken concomitantly.

Statistical methods:

The analyses of all efficacy endpoints will be based on the full analysis set (primary analysis population) and per-protocol set for sensitivity purpose.

The primary efficacy endpoint (change from baseline to V6 in the Domain 3 of KPPS) will be analysed using Analysis of Covariance (ANCOVA) with treatment as fixed factor and baseline KPPS as a covariate to demonstrate superiority of opicapone against placebo.

The key secondary endpoint (change from baseline in Domain B [anxiety] of MDS-NMS) as well as all other secondary efficacy endpoints will be analysed in an exploratory manner by treatment arm using appropriate parametric or non-parametric statistical methods. Descriptive statistics including 95%-confidence intervals will be presented per treatment arm. Potential sensitivity analyses will be specified in the *statistical analysis plan* (*SAP*).

The analyses of all safety endpoints will be based on the safety set.

All AEs will be summarised by number and percent of patients with AEs. Treatment-emergent AEs (TEAEs) will be summarised by calculating the number and percent of patients with AEs by preferred term (PT) and system organ class (SOC). TEAEs will also be summarised by severity and relationship to treatment. Number and percent of patients with serious TEAEs,

related serious TEAEs and TEAEs leading to discontinuation from study will be provided by SOC and PT. All AEs, SAEs and TEAEs leading to study termination will be listed.

Vital signs and laboratory parameters will be summarised by calculating summary statistics on the absolute values and on the change from baseline. Abnormal values will be assessed as clinically significant or not clinically significant.

Summary statistics and shift tables will be performed for physical examinations and, neurological examinations. Abnormal values will be assessed as clinically significant or not clinically significant.

Sample size:

For the primary endpoint (change from baseline in Domain 3 of KPPS), a difference to placebo of 3.0 is regarded as clinically meaningful and from a former study (Rascol O et al 2016; DOI: 10.1002/jcph.678) a standard deviation (SD) of 5.8 can be assumed. With a two-sided significance level α of 0.05, a power of 80%, a 1:1 treatment allocation ratio and with the abovementioned assumptions, 2 x 60 = 120 evaluable patients are required. A drop-out rate of 15% is assumed, therefore 140 patients need to be randomised.

Schedule of study procedures

Visit no./name	V1	V2a[1]	V2b	V3[2]	V4	V5	V6/ EDV[3]	FU
	Screening		Double-blind treatment period					Follow-up
			Baseline				End of Study	
Day	-7 (±2)	5-6 days after V1	1	8 (±2)	29 (±2)	85 (±4)	169 (±4)	183 (±4)
On-site visit ⊗ / telephone contact ☎	⊗		⊗	☎	⊗	⊗	⊗	⊗
Initiation procedures								
Informed consent	●							
Demographics	●							
Height and weight	●							
Medical/neurological history	●							
Previous medications/therapies	●							
In-/exclusion criteria	●		●					
Modified Hoehn & Yahr staging at ON	●							
Review of Hauser's PD diary		●	●[4]		●	●	●	
Instructions on use and delivery of Hauser's PD diary	●	●[4]	●		●	●		
Urine pregnancy test[6]	●		●			●	●	
Medication								
Concomitant medications/therapies	●		●	●	●	●	●	●
Record L-dopa/DDCI dose	●		●	●	●	●	●	●
Adjust L-dopa/DDCI dose, if necessary			●	●	●			
Randomisation (1:1)			●					
IP dispensing			●		●	●		
Dispensing rescue medication			●		●	●		
Instructions on use and dispensing of rescue medication diary.			●					
Review of rescue medication diary					●	●	●	
Drug accountability (IP and rescue medication)					●	●	●	
First IP administration[5]			●					
Efficacy								
KPPS	●		●		●	●	●	
MDS-NMS			●		●	●	●	
MDS-UPDRS Part I and II			●					
MDS-UPDRS Part III and IV			●		●	●	●	
PDQ-8			●		●	●	●	
Early morning dystonia			●		●	●	●	
CGIC					●	●	●	
PGIC					●	●	●	
Safety								
Record adverse events	●	●[4]	●	●	●	●	●	●
Vital signs (blood pressure, heart rate)	●		●		●	●	●	
Physical and neurological examinations	●					●	●	
Blood samples for routine laboratory	●						●	

CGIC: Clinical Global Impression of Change; DDCI: Dopa decarboxylase inhibitor; EDV: early discontinuation visit; FU: Follow-up; KPPS: King's Parkinson's Disease Pain Scale; L-dopa: levodopa; IP: investigational product; MDS-NMS: Movement Disorder Society-sponsored Non-motor Rating Scale; MDS-UPDRS: Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; PD: Parkinson's disease; PDQ-8: Parkinson's Disease Questionnaire; PGIC: Patient's Global Impression of Change.

1) If self-rating diary (Hauser's PD diary) entries are non-compliant, the patient will be re-trained on correct use of the diary and V2b will be postponed for 3 to 4 days. If the patient completed the diary satisfactorily, V2b is to be performed immediately, at the same day.
2) If L-dopa/DDCI adjustment is deemed necessary, an unscheduled on-site visit for dose adjustment may be performed at the investigator's discretion. After L-dopa/DDCI adjustment, either the phone call should be repeated up to 7 days after dose adjustment or V4 should be performed, whatever applies first.
3) An EDV should be performed as soon as possible (not exceeding 7 days) after early discontinuation.
4) Only to be performed if V2a and V2b will not take place on the same day.
5) The first intake of opicapone will take place on the day of V2b, at least 1 hour before or after the last daily dose of L-dopa/DDCI.
6) In females of childbearing potential.