



STUDY PROTOCOL

# Opicapone as an Add-on to Levodopa in Patients with Parkinson's Disease Without Motor Fluctuations: Rationale and Design of the Phase III, Double-Blind, Randomised, Placebo-Controlled EPSILON Trial

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## ABSTRACT

**Introduction:** Levodopa remains the cornerstone treatment for Parkinson's disease (PD) but its use is associated with the development of 'wearing-off' fluctuations and other motor and non-motor complications over time. Adding a catechol-O-methyltransferase (COMT) inhibitor to levodopa/dopa decarboxylase (DDC) inhibitor therapy reduces fluctuations in the profile of plasma levodopa levels following oral dosing, and can therefore be beneficial for the

management of motor complications. The objective of the EPSILON study is to investigate the efficacy of opicapone (OPC; a third-generation, once-daily COMT inhibitor) in enhancing the clinical benefit of levodopa in patients in earlier stages of PD, without end-of-dose motor fluctuations.

**Methods:** EPSILON is a phase III, double-blind, randomised, placebo-controlled and parallel-group study, designed to evaluate the efficacy and safety of OPC as add-on to levodopa/DDC inhibitor therapy in patients with early PD who

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do not exhibit signs of motor complications. Eligible patients will be randomised (1:1) to receive OPC 50 mg or placebo, in addition to their existing levodopa/DDC inhibitor therapy, over a 24-week, double-blind treatment period, after which they will have the option of entering an additional 1-year, open-label extension period, during which all patients will receive OPC 50 mg.

**Planned Outcomes:** The primary efficacy endpoints are change in Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III total score from baseline to the end of the double-blind period (double-blind phase) and change in MDS-UPDRS Part IV total score from open-label baseline to the end of the open-label period (open-label phase). Secondary outcomes during the double-blind phase will include other measures of PD symptoms, including quality of life, non-motor symptoms, and development of motor fluctuations. Safety assessments will include evaluation of treatment-emergent adverse events, laboratory safety parameters, suicidality and impulse control disorders.

**Trial Registration:** European Union Drug Regulating Authorities Clinical Trials Database (number 2020-005011-52).

**Keywords:** Catechol-O-methyltransferase inhibitor; Early Parkinson's disease; EPSILON; Levodopa; Motor fluctuations; Opicapone; Randomised controlled trial

### Key Summary Points

#### Why carry out this study?

Levodopa remains the cornerstone treatment for Parkinson's disease (PD) but its use is associated with the development of wearing-off fluctuations and other motor and non-motor complications.

The addition of a catechol-O-methyltransferase (COMT) inhibitor to levodopa therapy increases plasma levodopa levels and reduces fluctuations following oral dosing.

Opicapone (OPC; a third-generation, once-daily COMT inhibitor) ensures a substantial and prolonged inhibition of COMT over 24 h and increases the overall systemic exposure to levodopa.

EPSILON is a phase III, randomised, double-blind, placebo-controlled trial and open-label extension study that will evaluate the efficacy of OPC in enhancing the clinical benefit of levodopa in patients in the early stages of PD, without end-of-dose motor fluctuations.

#### What will be learned from the study?

EPSILON will evaluate the impact of adding OPC to levodopa therapy on motor symptoms in patients with early PD who do not exhibit signs of motor complications.

## INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder, presenting with a variety of motor and non-motor symptoms [1]. It is the second most common neurodegenerative disease (after Alzheimer's disease) [2], affecting an estimated 6 million people globally [3]. PD has a particularly debilitating effect on patients' health-related quality of life, with a significant impact on areas such as psychosocial functioning and mobility [4]. Thus, identification, diagnosis and effective treatment strategies in the early stages of the disease are essential.

Dopamine substitution is still the primary strategy for symptomatic treatment of PD [5], with levodopa remaining the cornerstone therapeutic agent [6]. While levodopa is well tolerated and efficacious, it is extensively metabolised in the periphery by dopa decarboxylase (DDC) and catechol-O-methyltransferase (COMT), and consequently only 1% of an oral dose of levodopa reaches the brain [7, 8]. In addition, with disease progression the duration of each levodopa dose becomes shorter, with use of levodopa being associated with the

development of motor complications (fluctuations of motor function and dyskinesias) and non-motor fluctuations [9]. Evidence suggests that the appearance of motor complications is associated with loss and decreased buffering capacity of striatal dopamine nerve terminals, as well as non-physiological, pulsatile stimulation of dopamine receptors, resulting from intermittent oral dosing with levodopa [10, 11]. A therapy providing a continuous delivery of levodopa ('continuous dopamine stimulation') might help restore dopamine at a more physiological level, thereby facilitating the management of motor complications, and this concept has been validated in advanced patients undergoing levodopa jejunal infusions [12]. Within this context, the addition of a COMT inhibitor to levodopa/DDC inhibitor therapy may help to reduce fluctuations in plasma levodopa levels following oral dosing and extend the benefit of each levodopa dose, without the necessity for increasing the dose or frequency of levodopa administration [10, 11, 13]. There has therefore been a long-standing debate regarding the potential role of COMT inhibitors as early adjunctive therapy to prevent or delay the development of wearing-off. Results of a meta-analysis of entacapone studies demonstrated that the use of the triple therapy of levodopa/carbidopa/entacapone resulted in significant improvements in Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III scores in patients with early PD (although associated with more adverse events [AEs] than levodopa/carbidopa alone) [14]. However, when levodopa/carbidopa/entacapone was compared with levodopa/carbidopa in non-fluctuating patients initiating levodopa therapy in the prospective STalevo Reduction In Dyskinesia Evaluation in PD (STRIDE-PD) study, it was associated with a shorter time to onset and increased frequency of dyskinesia, compared with levodopa/carbidopa alone [15]. Potential reasons for the failure of this study have been proposed: the dosing schedule used (four daily doses administered every 3.5 h) may not have provided stable and continuous levodopa plasma levels, despite administration with entacapone; compliance may not have been optimal in the early, non-fluctuating patients

enrolled in the study; and the daily levodopa load was higher in the levodopa/carbidopa/entacapone group than the levodopa/carbidopa group [16]. Further studies are therefore required in order to validate the use of a COMT inhibitor as an adjunctive therapy to levodopa plus a DDC inhibitor in early PD.

Opicapone (OPC) is a third-generation COMT inhibitor [7, 8, 17] which was developed to improve the toxicity limitations of other COMT inhibitors in a convenient, once-daily dosage regimen [17]. It was evaluated in two pivotal trials in patients with PD and end-of-dose motor fluctuations (BIPARK-I and II), and the results demonstrated an acceptable tolerability profile, combined with efficacy in reducing OFF-time [18, 19]. These studies led to the approval of OPC in the European Union, USA, Japan, Australia and other countries as adjunctive therapy to preparations of levodopa/DDC inhibitor in patients with PD and end-of-dose motor fluctuations [20] or OFF episodes [21]. In the recent guidelines from the Movement Disorders Society (MDS), OPC was deemed efficacious, with no safety concerns and no need for specialised monitoring [22], and it may, therefore, represent a suitable candidate for add-on COMT inhibition with levodopa/DDC inhibitor therapy in patients with early or stable PD. Although the mean disease duration of patients enrolled in the BIPARK studies was approximately 8 years and the mean duration of motor fluctuations was approximately 3 years [23], the studies did include patients with end-of-dose motor fluctuations in early stages of PD. Recently, a post hoc analysis of the BIPARK studies has demonstrated that OPC was efficacious over the entire course of motor fluctuation evolution in patients with PD, with enhanced efficacy in patients who were earlier, in comparison to later, in both their disease course and levodopa treatment pathway, supporting its use as an early adjunct to levodopa in PD [24].

Given the acceptable safety profile and encouraging efficacy observed in studies of OPC in patients with PD and end-of-dose motor fluctuations, including evidence demonstrating its specific efficacy in those who are relatively early in their disease course and levodopa treatment pathway, the EPSILON (Early Parkinson with Levodopa/DDC inhibitor and

Opicapone) study is a phase III, double-blind, randomised, placebo-controlled, parallel-group trial that has been designed to explore the potential of OPC to enhance the clinical benefit of levodopa in patients in the early stages of PD, without end-of-dose motor fluctuations.

## METHODS

### Study Design

EPSILON is a phase III, double-blind, randomised, placebo-controlled and parallel-group study to evaluate the efficacy and safety of OPC as add-on to levodopa and a DDC inhibitor in patients with early idiopathic PD who do not exhibit signs of any motor complication (consisting of fluctuations in the motor response and/or involuntary movements or dyskinesias). After a screening period of up to 4 weeks, eligible patients will be randomised in a 1:1 ratio to receive treatment with either OPC 50 mg or placebo, in addition to their existing levodopa/DDC inhibitor therapy, and enter a 24-week, double-blind treatment period (Fig. 1). At the end of the double-blind period, and at the discretion of both the investigator and patient, participants may enter an additional 1-year, open-label extension period, during which all patients will receive OPC 50 mg, irrespective of their prior treatment group. A post-study visit (PSV) will be performed approximately 2 weeks after the end-of-study visit (EOS) or early discontinuation visit (EDV). The study is registered on the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT; number 2020-005011-52).

### Treatment Allocation

Subjects will be centrally assigned to randomised study treatment using an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). Eligible patients will be randomly assigned (1:1) at baseline using a proprietary computer-generated scheme (IQVIA Holdings Inc. and its subsidiaries, USA) to once-daily OPC 50 mg or matching placebo, using a sequential, non-stratified, dummy block approach.

### Treatment Groups and Duration

The estimated duration of individual patient participation in the double-blind period is 28 weeks (including a 4-week screening period, and 24-week maintenance treatment period). An additional 2-week follow-up period will be performed if the patient does not enter the open-label period. The estimated duration of individual patient participation in the open-label period is 54 weeks (including a 52-week treatment period, and 2-week follow-up period).

### Dose Regimen

Study treatment (OPC or matching placebo) will be taken orally once daily in the evening at least 1 h after the last daily dose of levodopa/DDC inhibitor (considered the bedtime dose). There should be no change to the patient's levodopa/DDC inhibitor regimen throughout the double-blind period of the study, unless adjustment is necessary for patient safety. In the open-label period, levodopa/DDC inhibitor dose adjustments and new anti-PD drugs will be permitted, if necessary, for patient safety and/or to treat a worsening of the patient's condition; adjustments for any other reason are discouraged.

### Study Population

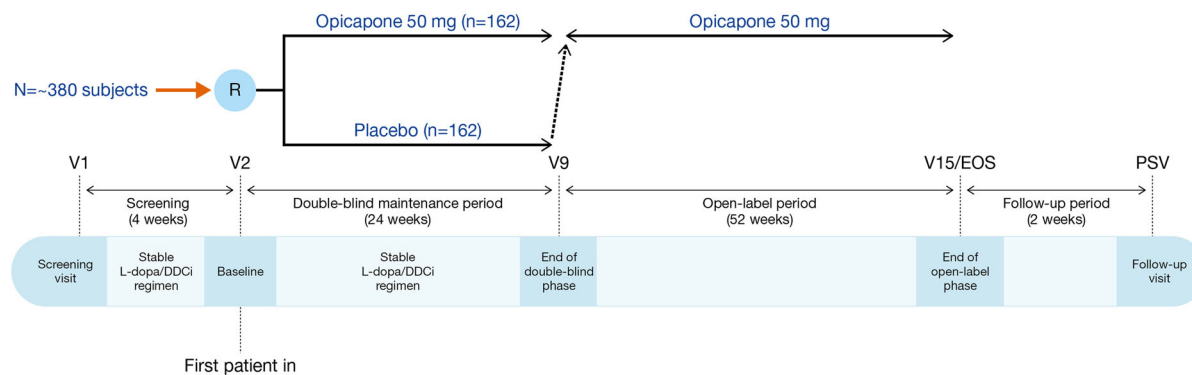
The study will be conducted in approximately 85 clinical sites in 13 countries (Belgium, Bulgaria, Czech Republic, France, Germany, Italy, Poland, Portugal, Serbia, Spain, Turkey, Ukraine, UK). Other countries and additional sites may be added, if required. Inclusion and exclusion criteria for the study population are outlined in Table 1.

### Study Assessments

All endpoint assessments are outlined in Table 2 and the timing of these assessments is outlined in Fig. 2.

### Efficacy Assessments

The primary efficacy endpoint for the double-blind phase of the study is the change in MDS-UPDRS Part III total score from baseline (visit



**Fig. 1** Study design. *DDCi* dopa decarboxylase inhibitor, *EOS* end-of-study, *L-dopa* levodopa, *PSV* post-study visit, *R* randomisation, *V* visit

[V] 2) to the end of the double-blind period (V9). The change in MDS-UPDRS Part IV total score is included as a secondary endpoint to evaluate all patients with PD who develop motor complications during the study. For this reason, for the open-label phase of the study, the primary endpoint is the change in MDS-UPDRS Part IV total score from open-label baseline (V9) to the end of the open-label period (V15). Secondary efficacy assessments, using other measures of PD symptoms, will be evaluated in both phases of the study, as outlined in Table 2.

The MDS-UPDRS is a revised version of the UPDRS, evaluating various aspects of PD in four parts [25]. Parts IA and IB cover the non-motor aspects of experiences of daily living, Part II addresses the motor aspects of experiences of daily living, Part III involves an examination of the motor symptoms, and Part IV covers motor complications. The Hoehn and Yahr scale, which is used to classify symptom progression in PD, was originally described in 1967 to include stages 1–5 [26], but was subsequently modified to include stages 1.5 and 2.5, in order to account for the intermediate course of PD [27]. The Schwab and England Activities of Daily Living (ADL) Scale assesses the difficulties patients experience completing activities of daily living, and rates a patient's functional ability on a scale from 0 (worst possible function) to 100 (no impairment) [28]. The PD Sleep Scale-2 (PDSS-2) is a visual analogue scale

developed to assess nocturnal disturbances and sleep disorders in patients with PD [29, 30]. The scale has a maximum value of 60 points, with a higher score indicating greater sleep disturbance, and a cutoff value of  $\geq 18$  distinguishing poor sleep quality ( $\geq 18$ ) from good sleep quality ( $< 18$ ) [31]. The Non-Motor Symptoms Scale (NMSS) assesses 30 non-motor symptoms of PD across nine dimensions (cardiovascular, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function, and miscellany [pain, smell, weight change, and hyperhidrosis]) [32]. The total score is quantified by multiplying severity (score 0–3) by frequency (score 1–4) for each question, giving a score range of 0–360. The PD Questionnaire-39 (PDQ-39) is a 39-item patient-reported outcome that assesses aspects of functioning and well-being that are usually adversely affected by PD across eight dimensions (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort) [33]. Each dimension score ranges from 0 ('never have difficulty') to 100 ('always have difficulty') and the overall score is the sum of the dimension scores divided by eight. The nine-item Wearing-Off Questionnaire (WOQ-9) is a screening tool for wearing-off symptoms in PD [34]. The Clinical Global Impression of Improvement (CGI-C) and Patient's Global Impression of Improvement (PGI-C) are, respectively, physician and patient assessments

**Table 1** Inclusion and exclusion criteria

Category of characteristic	Inclusion criteria	Exclusion criteria
Demographics	Male or female Aged 30–80 years	
Disease-related characteristics	Diagnosed with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria within the previous 5 years Disease severity stages 1–2.5 <sup>a</sup> Signs of treatable motor disability for $\geq 4$ weeks before screening, with minimum threshold with MDS-UPDRS Part III score of $\geq 20$ at both screening and V2, despite stable anti-PD therapy <sup>b</sup>	Non-idiopathic PD Signs of motor complications with a total score of MDS-UPDRS Part IV A + B + C greater than '0' (zero)
Anti-PD medication	Receiving treatment with L-DOPA/DDCI (either controlled-release, immediate-release or combined controlled/immediate-release) for $\geq 1$ year, and at a stable regimen for $\geq 4$ weeks prior to V2 at a daily dose of 300–500 mg, 3 to 4 times a day	Treatment with prohibited medication <sup>c</sup> within the 4 weeks prior to screening Previous or current use of COMTI (including OPC) Previous or planned (during the entire study duration) deep brain stimulation Previous stereotactic surgery (e.g. pallidotomy, thalamotomy) for PD or with planned stereotactic surgery during the study period Use of any other investigational product, currently or within 3 months (or 5 half-lives of the investigational product, whichever is longer) prior to screening
Compliance	Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the study protocol	

Table 1 continued

Category of characteristic	Inclusion criteria	Exclusion criteria
Safety	<p><i>For female patients:</i> not of childbearing potential, or of childbearing potential but agrees to follow contraceptive during the treatment period and until the PSV<sup>d</sup></p> <p><i>For male patients:</i> use of contraception during the treatment period and until the PSV, and refrain from donating sperm during this period</p>	<p>Current or past (within previous year) history of suicidal ideation or suicide attempts</p> <p>Clinically relevant electrocardiogram abnormality</p> <p>Current evidence of unstable cardiovascular disease<sup>e</sup></p> <p>Prior renal transplant or current renal dialysis</p> <p>Pheochromocytoma, paraganglioma or other catecholamine-secreting neoplasms</p> <p>Known hypersensitivity to the excipients of the investigation product<sup>f</sup> or rescue medication</p> <p>History of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis</p> <p>Current or past (within previous year) history of psychosis or psychiatric disorders, including severe major depression</p> <p>Malignancy within the past 5 years<sup>g</sup></p> <p>Unstable active narrow-angle or unstable wide-angle glaucoma</p> <p>Any medical condition that might place the patient at increased risk or interfere with assessments</p> <p><i>For female patients:</i> pregnant or breastfeeding</p>

Table 1 continued

Category of characteristic	Inclusion criteria	Exclusion criteria
Laboratory parameters	Acceptable results of screening laboratory tests (i.e. not clinically relevant for the well-being of the patient or for the purpose of the study according to investigator's judgment)	Any abnormality in ALT or AST > 2 times the ULN range, in the screening laboratory tests results Plasma sodium < 130 mmol/L, white blood cell count < 3000 cells/mm <sup>3</sup> , or any other relevant clinical laboratory abnormality that, in the investigator's opinion, may compromise the patient's safety

*ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *COMTI* catechol-*O*-methyltransferase inhibitor, *DDCI* dopa decarboxylase inhibitor, *L-DOPA* levodopa, *MDS-UPDRS* Movement Disorder Society Unified Parkinson's Disease Rating Scale, *OPC* opicapone, *PD* Parkinson's disease, *PSY* post-study visit, *ULN* upper limit of normal, *V* visit

<sup>a</sup>According to modified Hoehn & Yahr staging  
<sup>b</sup>Based on the investigator's judgment  
<sup>c</sup>Entacapone, tolcapone, antiemetics with antidopaminergic action (except domperidone) or Duopa<sup>TM</sup> (carbidopa/levodopa intestinal gel) within the 4 weeks before screening. Concomitant use of monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine and moclobemide) other than those for the treatment of PD  
<sup>d</sup>Female subjects of childbearing potential must use a highly effective non-hormonal contraception method until the post-study visit  
<sup>e</sup>Including, but not limited to, uncontrolled hypertension, myocardial infarction with important systolic or diastolic dysfunction, unstable angina, congestive heart failure (New York Heart Association Class ≥ III), and significant cardiac arrhythmia (Mobitz II 2nd or 3rd degree AV block or any other arrhythmia causing haemodynamic repercussions as symptomatic bradycardia or syncope)  
<sup>f</sup>Including lactose intolerance, galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption  
<sup>g</sup>Excluding cutaneous basal or squamous cell cancer resolved by excision



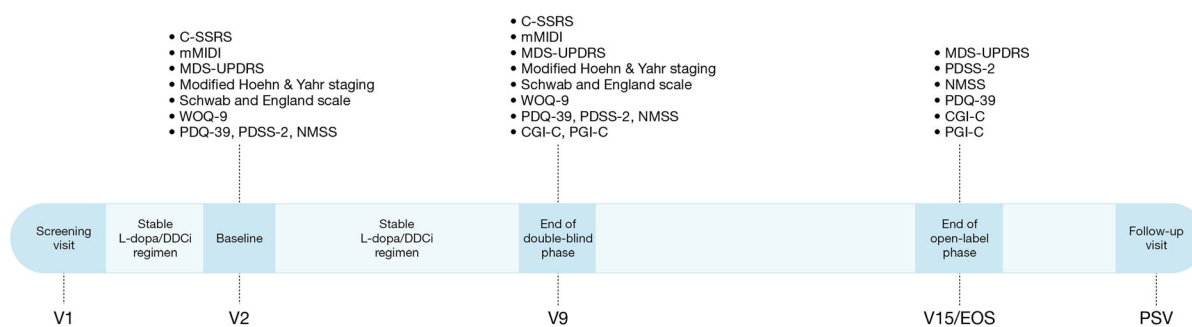
**Table 2** Study assessments

Double-blind period	
Primary endpoint	Change from baseline (V2) to the end of the double-blind period (V9) in MDS-UPDRS Part III total score
Secondary endpoints	Change from baseline (V2) to post-baseline visits during the double-blind period in: MDS-UPDRS total scores: Parts I, II, III and IV, and Part II + III Modified Hoehn & Yahr staging total score Schwab and England ADL scale score PDSS-2 total score NMSS total and subdomain scores PDQ-39 total and subdomain scores WOQ-9: Presence of wearing-off, total and subsection (motor and non-motor) scores Proportion of patients with an improvement from baseline (V2) in CGI-I total score at post-baseline visits during the double-blind period Proportion of patients with an improvement from baseline (V2) in PGI-I total score at post-baseline visits during the double-blind period
Open-label period	
Primary endpoint	Change from open-label baseline (V9) to the end of the open-label period (V15) in MDS-UPDRS Part IV total score
Secondary endpoints	Change from double-blind baseline (V2) and open-label baseline (V9) to post-baseline visits in: MDS-UPDRS total scores: Parts I, II, III and IV, and Part II + III Modified Hoehn & Yahr staging total score Schwab and England ADL scale score PDSS-2 total score NMSS total and subdomain scores PDQ-39 total and subdomain scores WOQ-9: Presence of wearing-off, total and subsection (motor and non-motor) scores Proportion of patients with an improvement from open-label baseline (V9) in CGI-I total score at post-baseline visits during the open-label period Proportion of patients with an improvement from open-label baseline (V9) in PGI-I total score at post-baseline visits during the open-label period

**Table 2** continued

Safety endpoints (both double-blind and open-label periods)	TEAEs including SAEs Laboratory safety tests (biochemistry, haematology, and urinalysis) Physical and neurological examinations Vital signs 12-lead ECG readings C-SSRS mMIDI
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*ADL* activities of daily living, *CGI-I* Clinical Global Impression of Improvement, *C-SSRS* Columbia-Suicide Severity Rating Scale, *ECG* electrocardiogram, *MDS-UPDRS* Movement Disorder Society-Unified Parkinson's Disease Rating Scale, *mMIDI* modified Minnesota Impulsive Disorders Interview, *NMSS* Non-Motor Symptoms Scale, *PDQ-39* 39-item Parkinson's Disease Questionnaire, *PGI-I* Patient's Global Impression of Improvement, *PDSS-2* Parkinson's Disease Sleep Scale 2, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event, *V* visit, *WOQ-9* 9-item Wearing-Off questionnaire



**Fig. 2** Timelines of study assessments. *CGI-C* Clinicians' Global Impression of Change, *C-SSRS* Columbia-Suicide Severity Rating Scale, *DDCi* dopa decarboxylase inhibitor, *EOS* end-of-study, *L-dopa* levodopa, *MDS-UPDRS* Movement Disorder Society-Unified Parkinson's Disease Rating Scale, *mMIDI* modified Minnesota Impulsive Disorders

Interview, *NMSS* Non-Motor Symptoms Scale, *PDQ-39* 39-item Parkinson's Disease Questionnaire, *PDSS-2* Parkinson's Disease Sleep Scale 2, *PGI-C* Patients' Global Impression of Change, *PSV* post-study visit, *V* visit, *WOQ-9* 9-item Wearing-Off Questionnaire

of how much a patient's overall status has improved or worsened since the start of the study, comprising a 7-point scale: (1, 'very much improved'; 2, 'much improved'; 3, 'minimally improved'; 4, 'no change'; 5, 'minimally worse'; 6, 'much worse'; 7, 'very much worse').

### Safety Assessments

The safety and tolerability of OPC 50 mg as add-on therapy to levodopa/DDC inhibitor will be

assessed as a secondary objective of the study. Assessments will include the incidence of treatment-emergent AEs (TEAEs), changes from baseline in vital signs, clinical and neurological examinations, 12-lead electrocardiogram readings, routine laboratory parameters, and the evaluation of suicidality (assessed using the Columbia-Suicide Severity Rating Scale [C-SSRS]) and impulse control disorders (assessed

using the modified Minnesota Impulse control Disorders Interview [mMIDI]) (Table 2).

The C-SSRS was designed to distinguish domains of suicidal ideation and suicidal behaviour, measured using four constructs (severity of ideation, intensity of ideation, behaviour, and lethality) [35]. The mMIDI is an instrument developed to diagnose impulse control disorders, including compulsive buying, kleptomania, trichotillomania, intermittent explosive disorder, pyromania, pathological gambling, compulsive sexual behaviour, skin-picking, and binge-eating [36].

### Sample Size Calculation

A minimum clinically relevant magnitude of effect in change from baseline of MDS-UPDRS Part III (primary endpoint) between treatment arms (OPC versus placebo) is expected to be at least 3 points. For the purpose of this evaluation, previous data were checked to understand the variability of an intended-to-treat population of patients with early PD. Results from the double-blind period of BIPARK-I and II studies [18, 19] showed a standard deviation (SD) for the change from baseline of UPDRS Part III equal to approximately 6.9 points for a group of patients with early fluctuations (< 1 year) and aged 80 years or younger (i.e. a population comparable as much as possible to patients with early PD). Following the conversion formula of Goetz et al. [25] to transform UPDRS Part III score to MDS-UPDRS Part III score, the SD for early PD subjects in change from baseline of MDS-UPDRS Part III is expected to be 8.3 points. Therefore, to determine the sample size, the following specifications and assumptions were applied: a two-sided 5% significance level; a power of 90%; a mean treatment effect (OPC versus placebo) of 3 points; and an SD of 8.3 points. It was also assumed that the primary endpoint would follow normal distribution and equal variance in both treatment groups. With these assumptions, a sample size of 162 patients in each treatment group is required. Approximately 382 patients will be screened to achieve a study population of approximately 324 patients (162 patients per treatment group),

assuming a dropout rate of 15%. It was also considered that patients without end-of-dose motor fluctuations might have lower baseline MDS-UPDRS Part III scores; therefore, in order to see a magnitude of effect, only subjects with MDS-UPDRS Part III score of at least 20 will be allowed to enter the study as indicated in Table 1.

### Blinding

Patients and study site personnel will remain blinded to individuals' double-blind treatment until the end of the open-label phase. Masking of randomisation will be maintained by use of identical OPC 50 mg and placebo capsules. Unblinding of the double-blind period will be performed after database lock for the purpose of data analyses. In the case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination.

### Statistical Methodology

The primary efficacy analysis will be performed after all patients have completed the double-blind period. Results of the open-label phase will be presented separately once the open-label period is completed. Unblinding of the double-blind period will be performed after database lock for the purpose of data analyses; however, patients and sites will remain blinded to their double-blind treatment until the end of the open-label phase. Efficacy assessments will be analysed for the full analysis set (FAS), defined as all patients who are randomised and who have at least one measurement of the primary efficacy assessment. Safety assessments will be analysed for the safety set, defined as all patients who take at least one dose of investigational product.

### Primary Efficacy Analysis

The primary efficacy parameter, change from baseline (V2) in MDS-UPDRS Part III total score at the end of the double-blind period (V9), will

be analysed for the double-blind FAS population, using a mixed model repeated measures (MMRM) approach, with fixed effects for baseline, centre, treatment, visit, treatment by visit interaction, and baseline by visit interaction, and patient as a random effect. Between-group differences (OPC versus placebo) will be estimated from the model.

### ***Secondary Efficacy Analysis***

An MMRM analysis will be used for relevant secondary efficacy endpoints in the double-blind period. The proportion of patients with an improvement from baseline in CGI-I and PGI-I scores, at 2 weeks after baseline and at the end of the double-blind period (V9), will be analysed using logistic regression, with treatment and baseline total score included in the model.

### ***Sensitivity Analysis***

A sensitivity analysis will be performed on the primary endpoint using an analysis of covariance (ANCOVA) approach, with fixed effects for baseline, centre and treatment. Missing data will be imputed using a multiple imputation method for the sensitivity analysis of the primary endpoint only.

### ***Safety Analyses***

TEAEs will be summarised with regard to the number and percentages of patients with TEAEs. Vital signs and laboratory parameters will be summarised using summary statistics of absolute values and changes from baseline. Summary statistics and shift tables will be presented for physical and neurological examinations. Demographic and baseline characteristics will be presented using descriptive statistics. C-SSRS and mMIDI results will be presented as incidence rates (overall and by visit) and shift tables.

## **STRENGTHS AND LIMITATIONS**

In early tolcapone and entacapone studies, adding a COMT inhibitor to the levodopa regimen in subgroups of stable patients with PD improved UPDRS scores. However, these studies

have not been viewed as unequivocally showing an effect in stable disease, and, as such, they have failed to make an impact on product labelling and use. The strengths of EPSILON are that it was designed as a pivotal study with a COMT inhibitor, OPC, to formally demonstrate an enhanced clinical benefit of levodopa therapy in patients in the early stages of PD, and that it will include a relatively large population of patients who will have the opportunity to be exposed to OPC 50 mg for an additional 1-year open-label extension.

## **ETHICS AND DISSEMINATION**

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Patients adopted by the General Assembly of the World Medical Association (2013); the applicable regulatory requirements of the participating countries; the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Guideline—integrated addendum to ICH E6(R1) Guideline for Good Clinical Practice E6(R2); and with the European Commission Directives 2001/20/EC and 2005/28/EC, and EU Regulation No. 536/2014. The protocol has been submitted to relevant institutional review boards (IRBs), namely National Regulatory Agencies and Central Ethics Committee, and when/if applicable to regional/local ethics committees; unconditional approval/favourable opinion must be obtained before the start of the study. All patients must provide written informed consent in order to participate in the study.

Protocol details are available at [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu) (EudraCT number 2020-005011-52). In line with European Federation of Pharmaceutical Industries and Associations (EFPIA) and Pharmaceutical Research and Manufacturers of America (PhRMA) guiding principles, the sponsor (BIAL – Portela & C<sup>a</sup> S.A.) undertakes to share, upon request, anonymised patient-level, study-level clinical trial data (analysable data sets), and other information (such as protocols) from clinical trials in

patients for medicines and indications approved in the USA and the European Union, to qualified researchers as necessary for conducting legitimate research. Results of the study will be published when available.

## CURRENT STATUS

The study has received approval in Belgium, Bulgaria, Czech Republic, France, Germany, Italy, Poland, Portugal, Spain, Turkey, the UK and Ukraine; approval is pending in Serbia. To date, around 280 patients have been screened and over 215 patients randomised.

## DISCUSSION

Effective symptomatic treatment of PD is critical in order to offer relief from both motor and non-motor features of the disease and maintain patients' quality of life. Degeneration of neurons in the nigrostriatal dopaminergic pathway and the resultant loss of dopamine is the primary cause of both the motor and non-motor features of PD; thus, maintenance of dopamine levels remains an important strategy to alleviate symptoms across the disease course [5, 37, 38]. Levodopa is the gold standard treatment for PD, but clinical response to levodopa decreases with time, as the duration of the benefits following a dose of levodopa shortens [39]. Use of adjunctive therapies to maximise levodopa bioavailability is a rational therapeutic approach [22].

Evidence supports the hypothesis that the development of motor complications is linked to the non-physiological, pulsatile stimulation of dopamine receptors [10, 11, 40]. However, studies have thus far failed to establish whether continuous dopamine stimulation in the early stages of PD, using either a controlled-release levodopa/DDI inhibitor or adjunctive therapy with entacapone, can prevent or delay the development of wearing-off motor complications over the longer term [15, 41]. Addition of OPC to levodopa therapy has been shown to be effective in reducing OFF-time in patients with PD and end-of-dose motor fluctuations, both in clinical trials [18, 19] and in the clinical practice

setting [42]. Moreover, evidence has shown that OPC has enhanced efficacy in patients with end-of-dose motor fluctuations who are relatively early in their disease course and levodopa treatment pathway [24], and data suggest that the addition of OPC to levodopa in patients with PD without end-of-dose motor fluctuations might also be beneficial [10]. Initiating OPC in early PD might improve current symptoms in these patients and additionally prevent or delay the development of motor fluctuations (although not the primary objective of this study). The NMSS will allow us to gain a better understanding of the evolution of non-motor symptoms in relation to motor fluctuations by assessing which non-motor symptoms develop before the onset of motor fluctuations, which non-motor symptoms fluctuate in those patients who develop motor fluctuations and by evaluating the severity of non-motor fluctuations before and after the onset of motor fluctuations.

Despite having a relatively short plasma half-life, OPC has been shown to inhibit peripheral COMT activity long after its plasma clearance, resulting in sustained COMT inhibition that endures over 24 h, allowing once-daily dosing [7, 43].

Given the lack of unequivocal evidence for the use of COMT inhibitors during the early stages of PD, the EPSILON study will provide valuable information on whether the use of adjunctive OPC 50 mg treatment can improve symptoms in patients with early PD, before end-of-dose motor fluctuations become clinically manifest.

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**Compliance with Ethics Guidelines.** The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Patients adopted by the General Assembly of the World Medical Association (2013); the applicable regulatory requirements of the participating countries; the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Guideline—integrated addendum to ICH E6(R1) Guideline for Good Clinical Practice E6(R2); and with the European Commission Directives 2001/20/EC and 2005/28/EC, and EU

Regulation No. 536/2014. The protocol will be submitted to national independent ethics committee(s) and competent authorities and unconditional approval/favourable opinion must be obtained before the start of the study. All patients must provide written informed consent in order to participate in the study.

**Data Availability.** Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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