


Please download and read the instructions before proceeding to the peer review

# Opicapone for the treatment of Parkinson's disease

| | |
|---|---|
| Journal: | *Expert Opinion On Pharmacotherapy* |
| Manuscript ID | EOOP-2016-0247 |
| Manuscript Type: | Drug Evaluation |
| Keywords: | Opicapone, Parkinson's disease, motor fluctuations, COMT inhibitor |
| | |

# Opicapone for the treatment of Parkinson's disease

## 3. Abbreviations

| | |
|---|---|
| AUC | Area under the curve |
| BIA 9-1067 | Opicapone (Ongentys®) |
| Cmax | Maximal concentration |
| COMT | Catechol-O-methyltransferase |
| L-dopa | Levodopa |
| MAO-B | Monoamine oxidase B |
| MCI | Mild cognitive impairment |
| NMSS | Non-Motor Symptom Scale |
| PD | Parkinson's disease |
| PDQ-39 | 39-item Parkinson's Disease Questionnaire |
| PDSS | Parkinson's Disease Sleep Scale |
| RBD | Rapid-eye movement behavioral sleep disorder |
| REM | Rapid-eye movement |
| UDP | Uridine 5'-diphospho |

## 4. Abstract

a. Introduction

Parkinson's disease (PD) is a relentless progressive neurodegenerative disease characterized by motor and non-motor symptoms. Unfortunately, at the present time, the only available treatment options have a symptomatic effect. Altough as the disease progresses almost all antiparkinsonian pharmacological classes are tried, the gold standard of pharmacological management is still L-dopa. Various strategies can be used to raise the dopaminergic tone among the basal ganglia. Catechol-O-methyltransferase (COMT) inhibitors attain this goal mainly by decreasing L-dopa peripheral metabolism.

b. Areas covered

Opicapone (Ongentys®) is a newly designed COMT inhibitor developed to fulfil the need for more potent, safer and longer acting COMT inhibitors. This review puts into context the use of COMT inhibitors, in particular opicapone's indications, its chemical and preclinical data, the pharmacodynamics and pharmacokinetic characteristics, and finally the efficacy and safety results delivered by clinical trials.

c. Expert opinion

Opicapone, also known as BIA 9-1067, is an efficacious COMT inhibitor. Its chemical, pharmacodynamics and pharmacokinetic proprieties make it adequate for a once a day oral dose regimen. It has proved to reduce the off-time and to increase the on-time without troublesome dyskinesias in PD patients with motor fluctuations. The reported adverse events suggest an overall safe and well-tolerated profile.

The most common adverse events were dyskinesia and there were no issues of concern for hepatotoxicity, severe diarrhoea or chromaturia.

## 5. Keywords

Opicapone, Parkinson's disease, motor fluctuations, COMT inhibitor

## 6. Introduction

Parkinson's disease (PD) is a multifaceted neurodegenerative condition with a relentless natural course and results from an intricate interplay between nature and nurture.[1] It affects each 3 in 1,000 people in the world[2] and is characterized by progressive motor and non-motor symptoms.

Intracellular aggregation of alfa-synuclein and consequent formation of Lewy bodies and Lewy neuritis throughout the nervous system is one of the pathological hallmarks of PD.[3]

The very particular result of this occurrence in basal ganglia is thought to lead to dopaminergic neuronal cell loss at substantia nigra *pars compacta* with a subsequent fall on cortical dopaminergic input.[4] This phenomenon is likely responsible for the detrimental classical parkisonian motor symptoms, including bradykinesia, rigidity and rest tremor.[5]

Still, neuronal loss is widespread along the nervous system and determines non-motor symptoms.[4] A great focus has been put on these symptoms due to their burden [6] and specific time course.[7] The premotor phase of the disease can be remarkable for constipation, rapid-eye movement (REM) behavioral sleep disorders (RBD), hyposmia and depression[8] whereas in the motor phase PD is also accompanied by further autonomic dysfunction – urinary incontinence or retention, orthostatic hypotension, sexual dysfunction, hyperhidrosis –, psychosis, cognitive impairment – such as mild cognitive impairment (MCI) followed by dementia –, skin disturbances, among others.[9]

The clinical management is purely symptomatic, since no therapeutic strategy – either pharmacologic or not – has proven to regress, halt or decelerate disease progression.[10, 11]

However, treatment of motor and non-motor symptoms can have a significant impact on patient health status. Direct and indirect dopamine enhancing agents are the mainstay of pharmacologic symptomatic therapy for motor symptoms. This group of drugs includes: L-dopa, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors and catechol-O-methyltransferase (COMT) inhibitors.[12] Furthermore, functional neurosurgery and specific physiotherapy interventions are also beneficial for a subset of patients.[12]

By means of reducing L-dopa metabolism, COMT inhibitors amplify L-dopa's half-life, and consequently its therapeutic effect duration. As such, they are only useful clinically as an add-on drug to L-dopa and never as a monotherapy.

This class of drugs has shown little benefit when treating parkinsonism in early stage PD patients and preventing motor complications [13, 14, 15, 16] but substantial improvement was attained in reducing the off-time in more advanced PD.[17, 18, 19, 20, 21, 22, 23]

Still, the only available COMT inhibitors for medical use – entacapone and tolcapone, both second generation COMT inhibitors – have some weaknesses: entacapone requires frequent administrations (with each L-dopa intake) and has mild potency, and tolcapone, although a more potent and longer acting COMT inhibitor, obliges repeated liver function monitoring due to the risk of hepatotoxicity.[23]

Opicapone (Ongentys®), a third generation COMT inhibitor, designed to cover the drawbacks of others compounds from the same group, was granted market authorization in June 2016 by the Committee for Medicinal Products for Human Use, European Medicines Agency.

The aim of this paper is to review the current evidence regarding opicapone's pharmacological proprieties, efficacy and safety for the treatment of PD.

a. Review criteria

All published studies on opicapone were included and hierarchised by grade of evidence. The references were retrieved from EMBASE, Medline and CENTRAL using the terms "opicapone" and "BIA 9-1067". Reference lists were cross-checked. The last search was conducted on February 2016. No language, time or quality restriction was applied.

## 7. Body of review

### a. Overview of the market

Nowadays' PD management is multidisciplinary and involves neurologists, psychiatrist, psychologists, neurosurgeons, nurses, physiotherapists, speech-language therapists, occupational therapists, social workers, nutritionists, sex therapists, among others.[24, 25]

In the early stage of this dopamine deficiency state, the best strategy for the beginning of the pharmacological treatment is hill defined, and disability, handicap and treatment objectives should be weighted. The first-line drug groups for motor symptoms are MAO-B inhibitors, L-dopa and dopamine agonists.[24] L-dopa is the most efficacious drug, but longstanding use is associated with motor and non-motor fluctuations and dyskinesia.[24]

As the disease advances, motor and non-motor symptoms evolve and aggravate, and other drug classes may have to be used, such as anti-psychotics, cholinesterase inhibitors.[25]

Although the vast drug armamentarium available for PD management, L-dopa – induced motor complications remain a key unmet need.[26] Indeed, about 40% of patients experience motor fluctuation after 4-6 years of L-dopa therapy.[27] Several strategies aiming to maintain a stable striatal dopaminergic tone over time are being develop, including new formulations and modes of delivery of L-dopa and apomorphine, adenosine antagonists, glutamatergic antagonists, and serotonergic drugs. [26]

Dopamine is the neurotransmitter critically involved in the physiology of motor symptoms: cortical loss of striatal tone. The exogenous replacement of this catecholamine is the mainstay of L-dopa treatment. This prodrug is the biological precursor of dopamine, but it is extensively metabolized in peripheral tissues before arriving to the brain, where it is transformed in dopamine by decarboxylation. As such, L-dopa is administrated together with a peripheral amino acid decarboxylase inhibitor – as carbidopa or benserazide -, preventing the breaking down of this catecholamine precursor[28] before trespassing the blood-brain barrier and increasing L-dopa bioavailability.

Furthermore, COMT is a ubiquitous intracellular enzyme also involved in the peripheral tissues' L-dopa catabolism. It mediates the transformation of L-dopa to 3-O-methyldopa - an agent known to aggravate parkinsonism[29] - by transferring a methyl group from *S*-adenosyl-L-methionine to catecholic substracts.[30] When this enzyme is inhibited by COMT inhibitors, it has been found that L-dopa delivery to and availability in the central nervous system are superior and more stable.[31, 32] Correspondingly, L-dopa plasma half-life increases.[31]

Currently there are two COMT inhibitors in the market: entacapone and tolcapone, both with practical limitations, as explained earlier.[23] This justified the research efforts put into the development of new, third generation, COMT inhibitor: nebicapone and opicapone. Nebicapone development program was discontinued due to safety concerns on hepatotoxicity.[33]

b. Introduction to the compound

Opicapone, also known as BIA 9-1067, is a hydrophilic, 1,2,4-oxadiazole analogue with a pyridine N-oxide residue at position 3. It is a competitive COMT inhibitor with

a long-acting inhibitory profile and its inhibitory effects are felt essentially in peripheral tissues, and in a reversible way. It was tailored-designed to be taken orally and once a day. [34]

Opicapone chemical name is 2,5-dichloro-3-[5-(3,4-dihydroxy-5-nitrophenyl]-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine-1-oxide (Figure 1).[33]

Its market name is Ongentys® and is currently licensed by the European Medication Agency. It has already been launched in the United Kingdom and Germany.

c. Chemistry and preclinical data

Opicapone is a heterocyclyl nitrocatechol derivative that evolved after structure-activity studies. The first COMT inhibitors posing heterocyclic rings at the meta-position relative to the nitro group were described in 1989.[35] Although having low toxicity in mice, their minor *in vivo* efficacy precluded clinical application. In 2010, Kiss et al. reported an optimization process for the former compounds.[34] Primarily, they substituted the trihydroxybenzene ring by a nitrocatechol subunit, generating a potent in vitro COMT inhibitor with less satisfactory *in vivo* characteristics. Then, a pyrazole ring was permuted by an oxadiazole ring, which provided a high *in vivo* potency to this molecule. Nonetheless, it was not sufficiently selective to peripheral tissue COMT and was vastly toxic. An extra replacement of the phenyl ring with heterocyclic rings produced meta-pyridyl-*N*-oxides with modest inhibitory potency and with little toxicity. Lastly, the pyridyl N-oxide ring was replaced by methyl and halogen, restoring the high potency and further dropping the toxicity, creating the opicapone molecule.[34]

Opicapone showed a high capacity of reducing COMT in rats and monkeys,[36, 37] and oral administration of opicapone in both animal models led to marked (>80%) but reversible inhibition of liver and kidney COMT without affecting COMT protein, RNA expression, or brain COMT.[36, 38, 39] The long-lasting effect of opicapone surpassed 24 hours and the enzymatic recovery took more than 28 hours.[37, 39] The maximal inhibitory effect was sustained over the first 8 hours.[40] Indeed, computational chemistry studies showed that opicapone has an exceptionally high-binding affinity to human COMT: opicapone is a slowly reacting COMT substrate and the determinants of its high-inhibition potency are the catalytic rate of the inhibitor's O-methylation rather than on the dissociation rate of the complex.[41]

In rats, opicapone has been shown capable of achieving maximal COMT inhibition after 3-4 hours of oral administration and the inhibitory potency was proportional to the oral dose of opicapone.[34, 39]

Comparing with tolcapone – the most potent COMT inhibitor used in clinical practice –, opicapone was found to be slightly more potent, and to increase by about 100% the L-dopa plasma levels and maintain these values for 24 hours.[34]

Rat brain and liver homogenate studies showed that opicapone exercises a stronger and more sustainable COMT inhibition than tolcapone or entacapone: 99%, 82% and 68% respectively after 1 hour of oral administration; and 91%, 16% and approximately zero after 9 hour of administration.[37]

Opicapone catabolism involves conjugation to opicacone 3-O-glucuronide and opicapone 3-O-sulfate. Theses reactions take place in the liver and intestine and the main role-players are UDP-glucuronosyltransferases 1A7 and 1A9, and sulfotransferase 1A1, respectively for glucuronidation and sulfation.[42, 43]

Non-human primate and rat studies revealed that brain and blood bioavailability of L-dopa duplicated after both single and chronic administration of opicapone, and 3-O-metyldopa shrank to less than half.[36, 39, 40] The same studies demonstrated increased exposure of L-dopa in the dorsal striatum, substantia nigra and prefrontal cortex, and to dopamine in the brain matter in general. These results were not at the expense of a higher Cmax but of a greater AUC.

In vitro human hepatocyte models compared opicapone, tolcapone and entacapone hepatotoxicity. Contrary to what was observed with tolcapone, opicapone did not compromised cell homeostasis and viability, an effect portrayed across growing doses.[44]

d. Clinical development plan

The clinical development plan of opicapone involved, so far, multiple phase I[45, 46, 47], two phase II [48, 49] and two phase III trials (table 1).[50, 51]

In 2013, Almeida L. and colleagues released the report of the first clinical study of opicapone in humans. This phase I dose-escalation and tolerability double-blind, randomized placebo-controlled clinical study intended to evaluate tolerability, pharmacokinetics and pharmadynamics after a single oral dose in healthy and young male individuals.[45]

The same group conducted a further phase I, multiple-dose, dose-escalation and tolerability, double-blind, randomized placebo-controlled clinical to appraised tolerability, pharmacokinetics and pharmadynamics in healthy and young individuals.[46]

Rocha and colleagues conducted a phase 1, double-blind, randomized placebo and entacapone controlled clinical trial performed in a gender balanced population of 80 healthy participants to study L-dopa opicapone-induced pharmacokinetics.[47]

Multiple other phase I trials were conducted to test selected pharmacodynamic, pharmacokinetic, safety and tolerability aspects of opicapone, both on healthy volunteers and in niche groups, such as people with hepatic impairment and people on specific medications.

The first phase II trial that tested opicapone was a multinational, multicenter, randomized, cross-over, double-blind, placebo-controlled trial of three single-dose regimens – 25, 50 and 100mg – on 10 patients with idiopathic PD on levodopa/carbidopa and with motor end-of-dose fluctuations. Pharmacokinetics was the primary outcome, but safety outcomes were also reported.[49]

A second four-arm phase II, multinational, multicenter, randomized, parallel-group, double-blind, placebo-controlled trial by Ferreira JJ and colleagues compared 5, 15 and 30mg of opicapone once daily with placebo during 28 day in 40 idiopathic PD patients on levodopa/carbidopa and with motor end-of-dose fluctuations. Pharmacokinetics was the primary outcome, but pharmacodynamics, efficacy, safety and tolerability were also studied.[48]

Two phase III, multinational, multicenter, randomized, parallel-group, double-blind, placebo- and active-controlled studies – BIPARK-I and BIPARK-II – were conducted to evaluate the efficacy and safety of a once-daily dose of opicapone in addition to L-dopa/carbidopa or L-dopa/benserazide in patients with end-of-dose motor fluctuations. Both studies included patients between 30 and 83 years-old with

idiopathic PD for at least 3 years, under 3-8 daily doses of L-dopa/DDCI and with end-of-dose wearing-off (end-of-dose deterioration).[50, 51]

In BIPARK-I 600 patients from 20 European countries were randomized to opicapone (5mg, 25 mg or 50mg), placebo or entacapone (200mg) during 14 to 15 weeks. The primary end-point of this study was change in absolute off-time between baseline and the end of the evaluation period. This trial was designed to power a superiority comparison against placebo and a non-inferiority comparison against entacapone.[51]

In BIPARK-II 407 patients from Europe, South America, Asia and Africa were randomized to opicapone (25 mg or 50mg) or placebo during 14 to 15 weeks. The primary end-point of this study was change in absolute off-time between baseline and the end of the evaluation period.[50, 52]

After the blind-phase of BIPARK-I and BIPARK-II, keen subjects were allowed to enter an additional 1 year (52 weeks) open-label period of treatment with opicapone titrated to the most efficacious dose up to 50 mg maximum.

e. Pharmacodynamics

Opicapone produces a marked and sustained COMT inhibition – as assessed using an erythrocyte COMT activity model.

The inhibitory capacity of opicapone varies from 50% (5mg) to 100% (200mg and higher doses) and is attained 1 to 8 hours after oral dosing.[45, 46, 47, 48]

This effect is long lasting and dose-dependent. Twenty-four hours after the last oral dose, the inhibition varied from 50% to 70% for opicapone doses ranging 5mg to 30mg.[46, 48] The duration of effect is independent of the dose and the half-life of COMT inhibition is superior to 60 hours.[45]

These effects can be explained by the high binding affinity of opicapone to COMT that translates into a slow complex dissociation rate constant.[41]

Ferreira et al. demonstrated that 5mg of opicapone were capable of a maximal COMT inhibition of 52%, while 30mg could raise the inhibition up to 80%.[48]

f. Pharmacokinetics and metabolism

Opicapone has a dose-proportional kinetics (first order kinetics).[45, 46]

The time to reach maximum plasma concentration after oral administration is approximately 1.5-4 hours.[45, 46] The maximum plasma concentration is proportional to the administered dose[45, 46, 48] and significantly decreases if dosing is preceded by a high-fat high-caloric meal.[45]

Studies in PD patients showed that 5, 15 and 30mg oral opicapone attain their maximal serum concentration at 2 hours and the its apparent half-life varies between 0.9 and 1.6 hours.[48]

Opicapone metabolism is entirely done via hepatic sulfation and elimination exclusively done by biliary excretion.[45, 46] No opicapone or its metabolites were ever quantified in urine.[45, 46]

L-dopa pharmacokinetic profile studies in healthy subjects showed a significant increase in L-dopa minimal concentration, mean concentration and AUC without an increase in maximal concentration comparing opicapone treated arms with placebo arm. The AUC of entacapone (200mg) arm was significantly inferior to the one of opicaponde arm (50 and 75mg), leading to the conclusion that opicapone is superior to placebo and entacapone regarding L-dopa bioavailability.[47] In PD patients, opicapone (5, 15 and 30mg) increased L-dopa's maximal concentration, area under the curve and half-life comparing with placebo.[48] The magnitude of AUC increase was 24,7%, 53,9% and 65,6% superior to placebo, respectively.[48]

Overall, these results point out that opicapone pharmacologic profile fits an orally formulation taken only once a day. They also suggest that dose adjustments have to be done in liver failure but not in kidney injury/disease.

g. Clinical efficacy

Opicapone showed to be efficacious, safe and well tolerated across clinical trials.

Ferreira et al., 2015 trial, although not designed or powered to detect differences in efficacy, showed a dose-dependent change in absolute off-time.[48] Patients on opicapone arm (5, 15 and 30mg) reported a decrease in off-time (16, 117 and 145 min per day, respectively) and an increase in on-time without troublesome dyskinesia (2, 12 and 16%, respectively).[48]

In BIPARK-I trial the mean change from baseline in off-time was -91.3 min for 5mg of opicapone, -85.9 min for 25 mg of opicapone, -116.8 min for 50mg of opicapone, -96.3 min for 200 mg of entacapone and -56.0 min for placebo, respectively. The higher dose of opicapone was significantly different from placebo. Furthermore, 5 mg and 50 mg of opicapone significantly increased the on-time without or with non-troublesome dyskinesia, and no dose increased on-time with troublesome dyskinesia comparing with placebo. The three opicapone doses generated a statistically significant difference in the patients global assessment of change comparing to placebo, and 50mg opicapone dose generated statistic difference comparing with entacapone. No changes were observed for Unified Parkinson's Disease Rating Scale (UPDRS) scores, 39-item Parkinson's Disease Questionnaire (PDQ-39), Parkinson's Disease Sleep Scale (PDSS) and Non-Motor Symptoms Scale (NMSS). Global assessment of change evaluated by the investigators showed a significant overall improvement for the 25mg and 50mg compared with placebo and, for the 50mg compared with entacapone.[51]

In BIPARK-II study both opicapone doses decreased the off-time comparing with placebo (1.7 hours for 25mg, 2.0 hour for 50mg and 1.1 hour for placebo) but only the

greater dose achieved statistical significance. Mean increase in absolute on-time without or with non-troublesome dyskinesia was considerably greater with either dose of opicapone comparing with placebo (1.4 hours for 25mg, 1.43 hours for 25 mg, 0.8 hours for placebo), although not statistically significant, as was the total daily on-time with troublesome dyskinesia. Comparing with placebo, the change from baseline in percentage reduction of off-time, the off-time responders and the on-time responders were statistically significant in both intervention arms. [52]

In the open label phase of BIPARK-II, where almost 98% of the patients randomized in the blinded-phase were included, similar motor and non-motor efficacy results were achieved.[53, 54]

The post-hoc pooled analysis of BIPARK I and II participants over 70 years old confirmed opicapone's efficacy in this subgroup of patients.[55] A further pooled analysis evaluated the effect of concomitant use of opicapone and dopamine agonists and Mao-B inhibitors. It was shown that these two classes of drug do not interfere with opicapone's efficacy.[56]

h. Safety and tolerability

Phase 1 studies disclosed no tolerability or safety issues among single or multiple doses of opicapone.[45, 46, 47] A further study showed that opicapone 50mg concentrations increase significantly in patients with moderate hepatic impairment (Child-Pug B) due to decrease clearance, but no significant adverse events were reported, leading to the conclusion that no dose adjustment is needed in this

population.[57] Opicapone does not increase QTc interval, neither in a therapeutic dose (50mg) nor in a supratherapeutic dose (800mg).[58]

Ferreira et al., 2015 trial did not bring up any tolerability or security issues [48].

In BIPARK-I, adverse events more frequent in opicapone arms that in placebo were dyskinesia (12.4% versus 4.1%), insomnia (4.5% versus 0.8%) and dizziness (3.1% versus 0.8%). Opicapone and entacapone had similar profiles, in exception to dyskinesia that was more common with opicapone (12.4% versus 8.2%) and to nausea and falls that were more common with entacapone (2.2% versus 6.6% and 2.0% versus 4.1%, respectively). For opicapone, there was no dose-response relation as far as adverse events were concerned.[51]

In BIPARK-II, 70.4% of subjects in 25mg opicapone, 69.3% of subjects in 50mg and 61.0% of subjects in placebo group reported at least one adverse event. The most frequent adverse events in the treatment arms were dyskinesia, dry mouth, insomnia, constipation and blood CPK increase, all significantly higher than in the placebo group. It is noteworthy that insomnia was only higher in the 25 mg arm and blood CPK increase in the 50mg arm.[52]. The proportion of withdrawals was superior in the 50 mg arm (17%), comparing with the 25 mg arm (8%) and the placebo arm (10%).

The open-phase of BIPARK II did not revealed any new or unexpected adverse events. Expected adverse events frequencies were consistent with what was found on the blinded-phase. The drop-outs rate was low and there was no association with liver dysfunction and diarrhea.[59]

The post-hoc pooled analysis of BIPARK I and II participants over 70 years old confirmed opicapone's safety. Nevertheless, the proportion of patients with hallucinations and weight loss slightly increased in this age group.[55] Another pooled analysis proved that no clinically relevant association can be drawn between opicapone and hepatobiliary dysfunction.[60] From a similar approach, it was also possible to determine that opicapone is not associated with electrocardiographic changes, including QT interval widening.[61]

i. Regulatory affairs

The proprietary of opicapone, BIAL, received market authorization in the European Union by the European Medication Agency in June 2016.

## 8. Conclusion

Opicapone (Ongentys®), a third generation COMT inhibitor also known as BIA 9-1067, was laboratory-tailored to attain a higher and longer inhibitory potency than tolcapone and entacapone. Clinical trials were able to prove opicapone's safety and superiority comparing to placebo.

Opicapone is a once a day, orally-administrated, peripheral acting, COMT inhibitor that yields a marked and sustained inhibitory effects. Has a first order kinetics, take 1.5-4 hours to reach peak plasma concentrations and a half-life of 0.9 to 1.6 hours. The duration of effect is independent of the plasma half-life and largely exceeds 24 hours. It is metabolized via hepatic sulfation and elimination is exclusively done by biliary excretion. Opicapone optimizes L-dopa pharmacokinetic profile to a larger extent than entacapone.

Phase II and III clinical trials showed that opicapone is safe and well tolerated, even after long-term administration and in older groups of patients, which effectively reduces the OFF-time when used as an add-on intervention to L-dopa in PD patients with motor fluctuations.

The most frequent adverse events are dyskinesia. No dose adjustment is need in liver and kidney failure.

## 9. Expert opinion

Before the opicapone development, there was a gap in the therapeutic option as far as COMT inhibitors were concerned. Entacapone is a mildly effective drug and requires multiple daily administrations and tolcapone, although more efficacious, it is reserved

as a second line drug due to its potentially severe side effects and need for frequent monitoring. Opicapone was designed to match available COMT inhibitors efficacy and safety profile.

In the completed clinical trials, 50mg of opicapone once daily achieved at least 1-hour OFF-time reduction compared to placebo. Results versus entacapone for both investigators and patients global assessment of change suggest also a tendency for a better response with opicapone.

Evidence is still lacking to draw conclusions on how opicapone compares to other non-COMT inhibitor options available in the market and licensed for motor fluctuations in PD patients. Only further head to head trials will respond to this question.

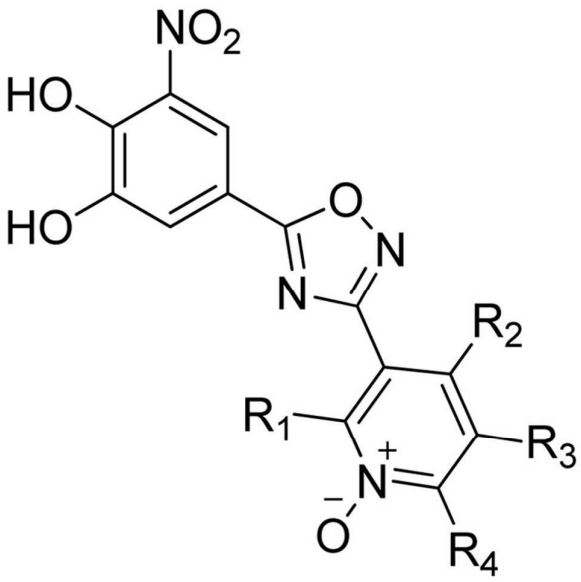
In the meantime, the use of this new compound is expected to expand the armamentarium to treat motor complications, due to its proven efficacy, safety profile and administration regimen.

## 10. Drug summary box

| | |
|---|---|
| Drug name (generic) | Opicapone |
| Phase (for indication under discussion) | Phase III |
| Indication (specific to discussion) | Parkinson's disease patients with motor fluctuations |
| Pharmacology description/mechanism of action | COMT inhibitor |
| Route of administration | Oral |
| Chemical structure | 2,5-dichloro-3-[5-(3,4-dihydroxy- 5-nitrophenyl]-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyri dine 1-oxide |
| Pivotal trial(s) | Ferreira et al., 2015, BIPARK-I and BIPARK-II trials |

## 11. Figures

Figure 1 – Opicapone



## 12. Tables

### Table 1 – Clinical studies

| Reference | Phase | Aims | Population | Intervention | Comparator | Duration | Centers | Country |
|---|---|---|---|---|---|---|---|---|
| Almeida et al., 2013 | I | Dose-escalation study (tolerability, safety, pharmacokinetics and pharmacodynamics) | 64 young healthy male volunteers | 10, 25, 50, 100, 200, 400, 800 and 1,200 mg opicapone single dose | Inactive placebo | 1 day | 1 | France |
| Almeida et al., 2013 | I | Food-effect study | 12 healthy male volunteers | 50mg opicapone | | 9 days | 1 | Canada |
| Rocha et al., 2013 | I | Dose-escalation, repeated dose study (tolerability, safety, pharmacokinetics and pharmacodynamics) | 34 young healthy male volunteers | 5, 10, 20 or 30mg of opicapone | Inactive placebo | 8 days | 1 | France |
| Rocha et al., 2014 | I | L-dopa pharmacokinetics | 80 healthy volunteers on levodopa | 25, 50 and 75 mg opicapone once daily | Inactive placebo or 200 mg entacapone | 12 days | 1 | France |
| NCT01568034 | II | Pharmacokinetics, tolerability and safety | 10 PD patients on levodopa and with motor flactuations | 25, 50, 100 mg opicapone single dose | Inactive placebo | 3 days | 3 | Portugal, Romania, Ukraine |
| Ferreira et al, 2015 (NCT02071810) | II | Tolerability, safety, pharmacokinetics, pharmacodynamics and efficacy | 35 PD patients on levodopa and with motor flactuations | 5, 15, 30 mg opicapone once daily | Inactive placebo | 28 days | 7 | Romania, Ukraine |
| BIPARK-I (NCT01568073) | III | Efficacy and safety (superiority vs. placebo and non-inferiority vs. entacapone) | 600 PD patients on levodopa and with end-of-dose motor flactuations | 5, 25 and 50 mg opicapone once daily | Inactive placebo or 200 mg entacapone | 14-15 weeks | 130 | Austria, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, France, Germany, Hungary, Italy, Latvia, Lithuania, Montenegro, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Spain, and Ukraine |
| BIPARK-II (NCT01227655) | III | Efficacy and safety | 427 PD patients on levodopa and with end-of-dose motor flactuations | 25 and 50 mg opicapone once daily | Inactive placebo | 14-15 weeks | 69 | Argentina, Australia, Belgium, Chile, Czech Republic, Estonia, India, Israel, Korea, Russia, South Africa and United Kingdom |

## 13. Annotated ~~biography~~


1. Kalia LV, Lang AE. Parkinson's disease. Lancet (London, England). 2015;386:896-912. Epub 2015/04/24.
2. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. The Lancet Neurology. 2006;5:525-35. Epub 2006/05/23.
3. Goedert M, Spillantini MG, Del Tredici K, Braak H. 100 years of Lewy pathology. Nature reviews Neurology. 2013;9:13-24. Epub 2012/11/28.
4. Dickson DW. Parkinson's disease and parkinsonism: neuropathology. Cold Spring Harbor perspectives in medicine. 2012;2. Epub 2012/08/22.
5. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. Journal of neurology, neurosurgery, and psychiatry. 1988;51:745-52. Epub 1988/06/01.
6. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR, Group NV. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2011;26:399-406. Epub 2011/01/26.
7. Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. Brain : a journal of neurology. 2010;133:1755-62. Epub 2010/04/08.
8. Postuma RB, Aarsland D, Barone P, Burn DJ, Hawkes CH, Oertel W, Ziemssen T. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2012;27:617-26. Epub 2012/04/18.
9. Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, Brown RG, Koller W, Barone P, MacPhee G, Kelly L, Rabey M, MacMahon D, Thomas S, Ondo W, Rye D, Forbes A, Tluk S, Dhawan V, Bowron A, Williams AJ, Olanow CW. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Movement disorders : official journal of the Movement Disorder Society. 2006;21:916-23. Epub 2006/03/21.
10. Suchowersky O, Gronseth G, Perlmutter J, Reich S, Zesiewicz T, Weiner WJ, Quality Standards Subcommittee of the American Academy of N. Practice Parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;66:976-82. Epub 2006/04/12.
11. Kalia LV, Kalia SK, Lang AE. Disease-modifying strategies for Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2015;30:1442-50. Epub 2015/07/25.
12. Ferreira JJ, Katzenschlager R, Bloem BR, Bonuccelli U, Burn D, Deuschl G, Dietrichs E, Fabbrini G, Friedman A, Kanovsky P, Kostic V, Nieuwboer A, Odin P, Poewe W, Rascol O, Sampaio C, Schupbach M, Tolosa E, Trenkwalder C, Schapira A, Berardelli A, Oertel WH. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. Eur J Neurol. 2013;20:5-15. Epub 2013/01/03.
13. Waters CH, Kurth M, Bailey P, Shulman LM, LeWitt P, Dorflinger E, Deptula D, Pedder S. Tolcapone in stable Parkinson's disease: efficacy and safety

of long-term treatment. Tolcapone Stable Study Group. Neurology. 1998;50:S39-45. Epub 1998/05/20.
14. Dupont E, Burgunder JM, Findley LJ, Olsson JE, Dorflinger E. Tolcapone added to levodopa in stable parkinsonian patients: a double-blind placebo-controlled study. Tolcapone in Parkinson's Disease Study Group II (TIPS II). Movement disorders : official journal of the Movement Disorder Society. 1997;12:928-34. Epub 1997/12/17.
15. Myllyla VV, Kultalahti ER, Haapaniemi H, Leinonen M, Group FS. Twelve-month safety of entacapone in patients with Parkinson's disease. Eur J Neurol. 2001;8:53-60. Epub 2001/08/18.
16. Brooks DJ, Sagar H, Group UK-IES. Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomised, placebo controlled, double blind, six month study. Journal of neurology, neurosurgery, and psychiatry. 2003;74:1071-9. Epub 2003/07/24.
17. Koller W, Lees A, Doder M, Hely M, Tolcapone/Pergolide Study G. Randomized trial of tolcapone versus pergolide as add-on to levodopa therapy in Parkinson's disease patients with motor fluctuations. Movement disorders : official journal of the Movement Disorder Society. 2001;16:858-66. Epub 2001/12/18.
18. Efficacy and tolerability of tolcapone compared with bromocriptine in levodopa-treated parkinsonian patients. Tolcapone Study Group. Movement disorders : official journal of the Movement Disorder Society. 1999;14:38-44. Epub 1999/01/26.
19. Adler CH, Singer C, O'Brien C, Hauser RA, Lew MF, Marek KL, Dorflinger E, Pedder S, Deptula D, Yoo K. Randomized, placebo-controlled study of tolcapone in patients with fluctuating Parkinson disease treated with levodopa-carbidopa. Tolcapone Fluctuator Study Group III. Archives of neurology. 1998;55:1089-95. Epub 1998/08/26.
20. Baas H, Beiske AG, Ghika J, Jackson M, Oertel WH, Poewe W, Ransmayr G. Catechol-O-methyltransferase inhibition with tolcapone reduces the "wearing off" phenomenon and levodopa requirements in fluctuating parkinsonian patients. Journal of neurology, neurosurgery, and psychiatry. 1997;63:421-8. Epub 1997/10/29.
21. Rajput AH, Martin W, Saint-Hilaire MH, Dorflinger E, Pedder S. Tolcapone improves motor function in parkinsonian patients with the "wearing-off" phenomenon: a double-blind, placebo-controlled, multicenter trial. Neurology. 1997;49:1066-71. Epub 1997/10/27.
22. Kurth MC, Adler CH, Hilaire MS, Singer C, Waters C, LeWitt P, Chernik DA, Dorflinger EE, Yoo K. Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomized, placebo-controlled trial. Tolcapone Fluctuator Study Group I. Neurology. 1997;48:81-7. Epub 1997/01/01.
23. Deane KH, Spieker S, Clarke CE. Catechol-O-methyltransferase inhibitors for levodopa-induced complications in Parkinson's disease. The Cochrane database of systematic reviews. 2004:CD004554. Epub 2004/10/21.
24. Oertel W, Berardelli A, Bloem B, Bonuccelli U, Burn D, Deuschl G, Dietrichs E, Fabbrini G, Ferreira J, Friedman A. Early (uncomplicated) Parkinson's disease. European handbook of neurological management. 2011;1:217-36.

25. Oertel W, Berardelli A, Bloem B, Bonuccelli U, Burn D, Deuschl G, Dietrichs E, Fabbrini G, Ferreira J, Friedman A. Late (complicated) Parkinson's disease. European handbook of neurological management. 2011;1:237-67.
26. Rascol O, Perez-Lloret S, Ferreira JJ. New treatments for levodopa-induced motor complications. Movement disorders : official journal of the Movement Disorder Society. 2015;30:1451-60. Epub 2015/08/22.
27. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Movement disorders : official journal of the Movement Disorder Society. 2001;16:448-58. Epub 2001/06/08.
28. Rinne UK, Molsa P. Levodopa with benserazide or carbidopa in Parkinson disease. Neurology. 1979;29:1584-9. Epub 1979/12/01.
29. Calne DB, Reid JL, Vakil SD. Parkinsonism treated with 3-O-methyldopa. Clinical pharmacology and therapeutics. 1973;14:386-9. Epub 1973/05/01.
30. Axelrod J, Senoh S, Witkop B. O-Methylation of catechol amines in vivo. The Journal of biological chemistry. 1958;233:697-701. Epub 1958/09/01.
31. Bonifati V, Meco G. New, selective catechol-O-methyltransferase inhibitors as therapeutic agents in Parkinson's disease. Pharmacology & therapeutics. 1999;81:1-36. Epub 1999/03/02.
32. Nutt JG, Fellman JH. Pharmacokinetics of levodopa. Clinical neuropharmacology. 1984;7:35-49. Epub 1984/01/01.
33. Kiss LE, Soares-da-Silva P. Medicinal chemistry of catechol O-methyltransferase (COMT) inhibitors and their therapeutic utility. J Med Chem. 2014;57:8692-717.
34. Kiss LE, Ferreira HS, Torrao L, Bonifacio MJ, Palma PN, Soares-da-Silva P, Learmonth DA. Discovery of a long-acting, peripherally selective inhibitor of catechol-O-methyltransferase. J Med Chem. 2010;53:3396-411.
35. Borgulya J, Bruderer H, Bernauer K, Zurcher G, Daprada M. Catechol-O-Methyltransferase-Inhibiting Pyrocatechol Derivatives - Synthesis and Structure-Activity Studies. Helvetica Chimica Acta. 1989;72:952-68.
36. Bonifacio MJ, Sutcliffe JS, Torrao L, Wright LC, Soares-da-Silva P. Brain and peripheral pharmacokinetics of levodopa in the cynomolgus monkey following administration of opicapone, a third generation nitrocatechol COMT inhibitor. Neuropharmacology. 2014;77:334-41.
37. Bonifacio MJ, Torrao L, Loureiro AI, Wright LC, Soares-Da- Silva P. Opicapone: Characterization of a novel peripheral long-acting catechol-O-methyltransferase inhibitor. Parkinsonism and Related Disorders. 2012;18:S125.
38. Bonifacio MT, Torrao L, Pinho MJ, Wright L, Soares-da-Silva P. COMT expression and activity after chronic administration of BIA 9-1067 to Wistar rats. Drug Metabolism Reviews. 2010;42:139-40.
39. Bonifácio MJ, Torrão L, Loureiro A, Fernandes-Lopes C, Wright LC, Soares-da-Silva P. Pharmacological Profile of Opicapone in Wistar rat. In: Eiden LE, editor. Catecholamine Research in the 21st Century. Boston: Academic Press; 2014. p. 83.
40. Bonifacio MJ, Torrao L, Loureiro AI, Palma PN, Wright LC, Soares-da-Silva P. Pharmacological profile of opicapone, a third-generation nitrocatechol catechol-O-methyl transferase inhibitor, in the rat. Br J Pharmacol. 2015;172:1739-52.

41. Palma PN, Bonifacio MJ, Loureiro AI, Soares-da-Silva P. Computation of the binding affinities of catechol-O-methyltransferase inhibitors: multisubstate relative free energy calculations. J Comput Chem. 2012;33:970-86. Epub 2012/01/27.
42. Loureiro A, Fernandes-Lopes C, Wright L, Soares-Da- Silva P. Glucuronidation of opicapone, a nitrocatechol-type COMT inhibitor, by recombinant UGTs and human microsomes. 2013.
43. Loureiro A, Fernandes-Lopes C, Wright L, Soares-Da- Silva P. Sulfation of opicapone, a nitrocatechol-type COMT inhibitor, by human recombinant SULTs and human S9 fraction. 2013.
44. Bonifacio M, Sousa F, Loureiro A, Wright L, Soares-Da- Silva P. Evaluation of potential mechanisms of cellular toxicity by nitrocatechol COMT inhibitors: opicapone, entacapone and tolcapone. 2013.
45. Almeida L, Rocha JF, Falcao A, Palma PN, Loureiro AI, Pinto R, Bonifacio MJ, Wright LC, Nunes T, Soares-da-Silva P. Pharmacokinetics, pharmacodynamics and tolerability of opicapone, a novel catechol-O-methyltransferase inhibitor, in healthy subjects: prediction of slow enzyme-inhibitor complex dissociation of a short-living and very long-acting inhibitor. Clin Pharmacokinet. 2013;52:139-51.
46. Rocha JF, Almeida L, Falcao A, Palma PN, Loureiro AI, Pinto R, Bonifacio MJ, Wright LC, Nunes T, Soares-da-Silva P. Opicapone: a short lived and very long acting novel catechol-O-methyltransferase inhibitor following multiple dose administration in healthy subjects. Br J Clin Pharmacol. 2013;76:763-75.
47. Rocha JF, Falcao A, Santos A, Pinto R, Lopes N, Nunes T, Wright LC, Vaz-da-Silva M, Soares-da-Silva P. Effect of opicapone and entacapone upon levodopa pharmacokinetics during three daily levodopa administrations. Eur J Clin Pharmacol. 2014;70:1059-71.
48. Ferreira JJ, Rocha JF, Falcao A, Santos A, Pinto R, Nunes T, Soares-da-Silva P. Effects of opicapone on levodopa pharmacokinetics, catechol-O-methyltransferase activity and motor fluctuations in patients with Parkinson's disease. Eur J Neurol. 2015;22:815-25, e56.
49. Bial - Portela CSA. A Study to Investigate the Tolerability and Effect of Three Single-dose Regimens of BIA 9-1067. 2010.
50. Lees A, Costa R, Oliveira C, Lopes N, Nunes T, Soares-da-Silva P. The design of a double-blind, placebo-controlled, multi-national phase-III trial in patients with Parkinson's disease and end-of-dose motor fluctuations: Opicapone superiority vs. placebo. Movement disorders : official journal of the Movement Disorder Society. 2012;27 Suppl 1:S1-639.
51. Ferreira JJ, Lees A, Rocha JF, Poewe W, Rascol O, Soares-da-Silva P. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial. The Lancet Neurology. 2015. Epub 2016/01/05.
52. Lees A, Ferreira JJ, Costa R, Rocha JF, Oliveira C, Lopes N, Nunes T, Soares-da-Silva P. Efficacy and safety of opicapone, a new COMT-inhibitor, for the treatment of motor fluctuations in Parkinson's Disease patients: BIPARK-II study. Journal of the Neurological Sciences. 2013;333:e116.
53. Oliveira C, Lees A, Ferreira J, Lopes N, Costa R, Pinto R, Nunes T, Rocha JF, Soares-Da-Silva P. Opicapone and non-motor symptoms in Parkinson's disease: Results from a double-blind, randomized, placebo-controlled study and open-label extension. Movement Disorders. 2015;30:S173.

54. Costa R, Oliveira C, Pinto R, Lopes N, Nunes T, Rocha JF, Soares-da-Silva P, Mamede S. One-year open label efficacy and safety of opicapone in Parkinson's disease BIPARK-II study. Movement Disorders. 2014;29:S233.
55. Lees A, Ferreira J, Lopes N, Costa R, Santos A, Oliveira C, Pinto R, Nunes T, Rocha JF, Soares-Da-Silva P. Efficacy and safety of opicapone in patients over 70 years with Parkinson's disease and motor fluctuations. Movement Disorders. 2015;30:S99.
56. Lopes N, Ferreira J, Lees A, Costa R, Santos A, Oliveira C, Pinto R, Nunes T, Rocha JF, Soares-Da-Silva P. Exploratory efficacy of opicapone in combination with dopamine agonists or MAO-B inhibitors on the treatment of motor fluctuations in Parkinson's disease. Movement Disorders. 2015;30:S101.
57. Rocha JF, Santos A, Falcao A, Lopes N, Nunes T, Pinto R, Soares-da-Silva P. Effect of moderate liver impairment on the pharmacokinetics of opicapone. Eur J Clin Pharmacol. 2014;70:279-86.
58. Pinto R, l'Hostis P, Patat A, Homery M-C, Falcão A, Nunes T, Rocha J-F, Soares-da-Silva P. Evaluation of opicapone on cardiac repolarization in a thorough QT/QTc study. Clinical Pharmacology in Drug Development. 2015:n/a-n/a.
59. Ferreira J, Lees A, Gama H, Lopes N, Santos A, Costa R, Oliveira C, Pinto R, Nunes T, Rocha JF, Soares-Da-Silva P. Safety and tolerability of opicapone in the treatment of Parkinson's disease and motor fluctuations: Analysis of pooled phase III studies. Movement Disorders. 2015;30:S86.
60. Lopes N, Ferreira J, Lees A, Gama H, Santos A, Oliveira C, Costa R, Nunes T, Rocha JF, Soares-Da-Silva P. Hepatic safety of opicapone in Parkinson's disease patients. Movement Disorders. 2015;30:S101.
61. Pinto R, Vaz-Da-Silva M, Lopes N, Ferreira J, Lees A, Gama H, Santos A, Oliveira C, Nunes T, Rocha JF, Soares-Da-Silva P. Cardiac safety of opicapone in patients with Parkinson's disease: Analysis of the centralized phase III ECG dataset. Movement Disorders. 2015;30:S112.