

## **Opicapone for the management of end-of-dose motor fluctuations in patients with Parkinson's disease treated with L-DOPA**

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## **Summary**

Introduction: Opicapone is a third generation, highly potent and effective catechol

*O*-methyltransferase (COMT) inhibitor that optimizes the pharmacokinetics and bioavailability of L-DOPA therapy.

Areas covered: In this review, we describe the preclinical and clinical development of opicapone. In PD patients with motor fluctuations, once daily opicapone administration was well-tolerated and consistently reduced OFF-time and increased ON-time without increasing the frequency of troublesome dyskinesia, and these benefits were maintained over at least a year of continued open-label therapy.

Expert commentary: With its convenient once-daily regimen, adjunct opicapone should be considered as an effective option for use in L-DOPA treated PD patients experiencing motor fluctuations.

## **Keywords**

Opicapone, L-DOPA, Parkinson's disease, wearing-off, motor fluctuations, COMT inhibition

## 1. Introduction

Parkinson's disease (PD) has a prevalence of 1 in 800 people, with advancing age being by far the greatest risk factor. It is predicted that the PD patient population will at least double by 2030 [1], and the associated increase in medical costs will be considerable [2]. Although the choice of initial therapy depends on age of onset of symptoms, disease severity, co-morbidities and patient preference, L-DOPA remains the most efficacious and widely used symptomatic treatment for PD [3] and almost all patients will eventually receive the drug at some stage during their illness [4].

The first few years of L-DOPA therapy are often referred to as the 'honeymoon phase' [5], but with longer disease duration and greater cumulative exposure to L-DOPA [6], most patients eventually experience L-DOPA-induced complications, including response fluctuations and dyskinesia. For many patients, the first sign of these is when they begin to notice a decline in the duration of therapeutic benefit from each L-DOPA dose, a phenomenon commonly termed 'wearing-off', which is defined as *"a generally predictable recurrence of motor or non-motor symptoms that precedes a scheduled dose and usually improves after the administration of antiparkinsonian medication"* [7]. A considerable literature exists on the possible pathophysiology and management of wearing-off fluctuations [7-12]. Up to 50% of patients can develop mild motor fluctuations within 2 years of initiating L-DOPA therapy [5, 6], with the ELLDOPA study reporting wearing-off within 5 to 6 months in some patients [7]. Up to 70% of patients receiving L-DOPA will have response fluctuations after 9 years of sustained treatment [13].

Response fluctuations lead to a deterioration of quality of life [14, 15], a recent survey of over 3000 PD patients found that over 90% of patients experience at least one OFF episode per day and 65% spend at least two hours per day in the OFF state [16].

## **2. L-DOPA related response fluctuations: overview of current treatment options**

### **2.1 L-DOPA adjustments**

Fragmentation of total daily L-DOPA intake into smaller and more frequent doses should theoretically provide more consistent plasma levodopa levels, and thus more consistent symptom control. However, the use of lower frequent doses can lead to dose failures and even more unpredictable motor responses in some cases [7]. Physicians may also consider increasing individual L-DOPA dose(s) at the times of the day when the patient finds wearing-off to be most troublesome, but while sometimes effective, this approach may increase the risk of dyskinesias [17]. Dietary protein restriction, treatment of constipation and dosing at least one hour before meals may all also be helpful in selected patients.

### **2.2 Adjunct therapies**

Current national and international treatment guidelines all consider dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors and catechol *O*-methyltransferase (COMT) Inhibitors, as efficacious for adjunct use with L-DOPA to reduce motor fluctuations [18, 19]. Although effective in the management of response fluctuations, the recognition of significant risks of developing impulse control disorders (ICDs) and other adverse effects [20] has led to a decline in the early use of dopamine agonists such as ropinirole and pramipexole [21]. MAO-B inhibitors, such as selegiline and rasagiline are effective in the treatment of mild end of dose deterioration [22], although there is less evidence for selegiline in this indication [19]. Recently, a 'third generation' MAO-B inhibitor safinamide has also received EU market approval as an adjunct to L-DOPA for PD patients experiencing response fluctuations [23].

The COMT inhibitor entacapone is a common first-line strategy for the management of wearing-off, but like the MAO-B inhibitors, reductions in daily OFF-time are moderate (mean of 41 minutes across clinical trials) and it has to be given with each L-DOPA dose [24]. Tolcapone is a more

efficacious COMT inhibitor than entacapone [24], but its practical utility is restricted by the potential risk of liver toxicity necessitating regular monitoring of liver function and is only indicated for patients who failed to respond to entacapone [19, 25]. There is therefore a need for a more effective COMT inhibitor that can be easily used in routine clinical practice [26].

### **2.3 New L-DOPA formulations**

Until recently, the available controlled release L-DOPA formulations such as Madopar CR and Sinemet CR have proved disappointing in the management of motor fluctuations and are now mainly used for the management of nighttime-akinesia. The last few years has seen considerable interest in the development of more efficacious L-DOPA formulations that address its pharmacokinetic limitations. The first of these new formulations to receive regulatory approval is IPX066 (Rytary/Numient) which is described as an extended-release L-DOPA capsule containing combined immediate- and sustained-release pellets of L-DOPA/carbidopa. IPX066 has been shown to provide a greater reduction of OFF time and a greater increase in ON time without troublesome dyskinesia when compared to standard immediate release (IR) L-DOPA therapy and the combined L-DOPA/carbidopa/entacapone (Stalevo) formulation [27, 28]. It remains to be seen whether these promising trial results will be borne out in clinical practice and it is currently unclear if this drug will be reimbursed in the EU at a level that would make its introduction into the market attractive from the business perspective.

Other L-DOPA formulations including a gastric-retentive (accordion pill) formulation [29], a sustained release formulation of a L-DOPA prodrug [30], a formulation for subcutaneous delivery [31] and an intrapulmonary delivery system [32] have reached clinical development.

### **3. Introduction to opicapone**

Opicapone (Ongentys, manufactured and marketed by BIAL -Portela & C<sup>a</sup>, S.A. Portugal) received

approval for Marketing Authorization from the European Commission in June 2016 as adjunctive therapy to preparations of L-DOPA/DOPA decarboxylase inhibitors (DDCIs) in adult patients with PD and end-of-dose motor fluctuations who cannot be stabilized on those combinations. Based on research into the structure and function of the COMT enzyme and using an analogue-based research approach, opicapone was designed and developed in-house by BIAL to reduce the risk of toxicity and improve tissue selectivity compared with other COMT inhibitors [33].

### **3.1 Chemistry**

Opicapone (2,5-dichloro-3-[5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl]-4,6-dimethylpyridine 1-oxide (previously known as BIA 9-1067) is a hydrophilic 1,2,4-oxadiazole analogue with a pyridine N-oxide residue at position 3 to provide high inhibitory potency and avoid cell toxicity (Figure 1) [34].

**[Figure 1 near here]**

Opicapone has been designed as a ‘tight-binding’, reversible COMT inhibitor which means it is a highly selective inhibitor of COMT versus the other enzymes involved in catecholamine metabolism. It has a high binding affinity (sub-picomolar K<sub>d</sub>) resulting in a long residence time of the reversible COMT–opicapone complex, and translating into a slow complex dissociation rate constant, suitable for once-daily administration [34, 35].

### **3.2 Pharmacodynamics**

*In vivo*, the duration of COMT inhibition by opicapone, extends far beyond the observable point of clearance of circulating drug, and reflects an underlying kinetic process that is consistent with the slow dissociation rate constant of the COMT-OPC complex [36]. In a time course experiment conducted in rats opicapone achieved the maximum inhibitory (99%) effect on COMT within 3 hours

of oral administration, which was continued by 80–90% inhibition for up to 9 hours and a gradual return to lower levels over the next 15 hours [33]. In liver and brain homogenates of rats given L-DOPA/benserazide and equivalent doses of COMT inhibitors via gastric tubes; opicapone demonstrated a stronger and more sustained COMT inhibitory effect than both entacapone and tolcapone. At 1-hour post-administration COMT inhibition was 99% with opicapone versus 82% with tolcapone and 68% with entacapone. At 9 hours post-administration the level of COMT inhibition remained at high levels (91%) with opicapone, but tolcapone only had residual effects (16% inhibition) and the COMT inhibitory effects of entacapone had worn off [37].

Opicapone does not cross the blood-brain barrier of rats [34] or monkeys [37]. Chronic administration of opicapone to cynomolgus monkeys doubled the bioavailability of systemic L-DOPA, by shifting T<sub>max</sub> later and without affecting C<sub>max</sub> values, and reduced both 3-O-methyldopa (3-OMD) exposure and C<sub>max</sub> values by 5-fold. These changes were accompanied by 76–84% reduction in erythrocyte COMT activity. Microdialysis revealed that opicapone increased L-DOPA exposure in the dorsal striatum by 170%, the substantia nigra by 140% and in the prefrontal cortex by 230% – all with concomitant reductions in 3-OMD exposure [37].

### **3.3 Pharmacokinetics and metabolism**

#### *3.3.1 Opicapone pharmacokinetics*

In healthy volunteers, pharmacokinetic dose-proportionality in terms of C<sub>max</sub> and AUC<sub>0-∞</sub> has been observed for opicapone (10-1200 mg) and its metabolites; the apparent terminal elimination half-life of opicapone was 0.8–3.2 hours [36].

The major metabolic pathway of opicapone is sulphation (resulting in the inactive metabolite BIA 9-1103) with other metabolic pathways including reduction, methylation, and glucuronidation. By contrast, the metabolite formed by reduction of the pyridine-N-oxide to pyridine ring (BIA 9-1079) is



active, but accounts for less than 15% of systemic exposure to opicapone and its contribution to the overall clinical effect is assumed to be of minor clinical relevance. Since urine levels of opicapone and its major metabolites remained below the limit of quantification in the opicapone dose range tested (10 to 1200 mg), it is thought that the biliary route is likely to be the main route of opicapone [36]. This is supported by a mass balance recovery study conducted in 6 healthy male volunteers, where the major route of excretion of [<sup>14</sup>C]-radioactivity was via feces (arithmetic mean = 67.2%). The remainder of [<sup>14</sup>C]-radioactivity was excreted in urine and via expired air (arithmetic mean = 12.8% and 15.9%, respectively). In this study, single doses of [<sup>14</sup>C]-opicapone 100mg were rapidly absorbed; the median t<sub>max</sub> for opicapone in plasma was 2.51 hours [38].

A high fat meal decreased the rate and extent of absorption of opicapone, with delayed peak plasma levels as compared to drug administration under fasting conditions [36]. It is recommended, therefore, that opicapone should not be taken with food – and a minimum interval of one hour can be recommended.

### 3.3.2 *Effect on COMT and L-DOPA pharmacokinetics*

In the tested dose range (10-1200 mg), single doses of opicapone had a dose-dependent inhibitory effect on erythrocyte soluble COMT activity with a maximum S-COMT inhibition (E<sub>max</sub>) ranging from 34.5% (with the 10 mg dose) to 100% (with doses >200mg), and an inhibition of 25.1 to 76.5% remained at 24-hours post-dosing [36]. This effect was independent of the dose taken, and the half-life of opicapone-induced COMT inhibition in human erythrocytes was 61.6 hours [36]. This long lasting effect is thought to reflect the slow dissociation of the tightly bound COMT-opicapone complex, and was replicated in repeat dose studies where the extent of S-COMT inhibition was shown to be significantly longer with opicapone (25-75mg doses) versus entacapone [39].

Age, gender, ethnicity (Caucasian versus Japanese), and COMT polymorphism have not been found

to exert relevant effects on the pharmacokinetics or pharmacodynamics (S-COMT inhibition) of opicapone that would warrant a dose adjustment in any patient subgroup [40]. Although opicapone exposure was increased in subjects with moderate hepatic impairment (Child-Pugh B) relative to matched healthy subjects, due to its short half-life and complete clearance from systemic circulation before the subsequent dose, no dose adjustment for opicapone needs to be considered [41]. Although there are no data in patients with renal impairment, since opicapone is not excreted by the kidney no dose adjustments are needed in patients with renal impairment [40].

**[Figure 2 near here]**

In healthy volunteers, once daily administration of opicapone (25–75mg) dose-dependently increased the minimum (trough) plasma concentrations ( $C_{min}$ ) of repeat doses of L-DOPA compared to placebo [39]. The 50mg opicapone dose increased L-DOPA trough levels by 260% (versus placebo) compared with a 190% increase with entacapone [39]. Peak L-DOPA values ( $C_{max}$ ) increased by 110 – 130% versus placebo at the second and third L-DOPA administrations with opicapone 50mg. Although L-DOPA peak levels were similar or even slightly lower with concomitant administration of entacapone 200mg, there was no statistical difference for L-DOPA  $C_{max}$  between the active treatments (opicapone and entacapone) and placebo [39]. In accordance with these changes, administration of 50 mg opicapone was associated with a statistically significant increase in the bioavailability of L-DOPA (as assessed by concentration-time curve (AUC)) versus placebo. By contrast, no statistical difference was found for L-DOPA AUC when entacapone was compared to placebo [39].

In PD patients experiencing motor fluctuations, administration of opicapone has been consistently shown to dose dependently increase L-DOPA bioavailability versus placebo [42, 43]. In one study, L-DOPA bioavailability increased by 16.4% with a single dose of opicapone 50mg and 34.8% with a

single dose of opicapone 100 mg [43]. Repeat dosing (over 28 days of maintenance dosing) showed a higher magnitude of effect of up to 65.6%, but the highest opicapone dose tested in this study was 30 mg [42].

### **3.4 Clinical efficacy**

#### **3.4.1. Phase II studies**

The Phase II clinical program focused on the effects of single and repeat dosing of opicapone on L-DOPA pharmacokinetics, including two clinical studies which evaluated the efficacy of opicapone in reducing OFF time and increasing ON time as exploratory outcomes [42, 43].

In a study of single opicapone doses, administration of opicapone 50 mg increased ON time by 25% compared with placebo. For this dose, ON time without dyskinesia increased by 73% versus placebo. Conversely, ON time with dyskinesia decreased by 34% [43]. This benefit was also observed in a study of repeat opicapone doses (once daily for 28 days), which showed a similar dose-dependent change in absolute OFF time (as assessed by patient diaries) corresponding to a percentage decrease of 4.16% (15.6 minutes,  $p>0.05$ ), 29.55% (116.9 minutes,  $p>0.05$ ) and 32.71% (145.0 minutes,  $p<0.05$ ) with 5, 15 and 30 mg opicapone, respectively [42]. The percentage of OFF time reduction was similar to the percentage increase of ON time without dyskinesia, with both 15 and 30 mg opicapone reaching a statistical difference to placebo for the ON time without dyskinesia ( $P = 0.0162$  and  $P = 0.0065$ , respectively) [42]. In this study, administration of opicapone was also reported to decrease the time to ON (interval between time of ON start after L-DOPA test dose and time of L-DOPA test dose intake), time to best-ON (interval between time of best-ON start after L-DOPA test dose and time of L-DOPA test dose intake) [42].

#### **3.4.2 Phase III studies**

The Phase III program was based on two large scale, multicenter, double-blind trials with their 1

year open label extensions [44, 45] in 1,027 randomized adult patients with PD treated with L-DOPA/DDCI (alone or in combination with other antiparkinsonian drugs) and end-of-dose motor fluctuations.

The first study, BIPARK I – was a randomized, double-blind, placebo-controlled and active-controlled trial of three doses of opicapone (5 mg, 25 mg, and 50 mg once daily) as an adjunct to L-DOPA in PD patients with end-of-dose motor fluctuations [44]. The active control was entacapone (200 mg with every L-DOPA intake), and the primary endpoint was the change from baseline to study-end in absolute OFF time. According to the hierarchical analysis, the opicapone 50 mg group had the most consistent efficacy and met the primary efficacy outcome of superiority compared with placebo and non-inferiority compared with entacapone in reducing OFF time [44]. The mean reduction of 60.8 minutes in OFF time versus placebo ( $p=0.0015$ ) has previously been established as clinically meaningful [46, 47], and the reductions in OFF time were accompanied by a corresponding increase in time in ON time without troublesome dyskinesia (62.6 minutes;  $p=0.002$ ). Importantly, the duration of ON time with troublesome dyskinesia did not change [44].

The inclusion of entacapone as an active control not only validated the findings of the trial (by showing expected efficacy of entacapone in this population of patients), but also helps understand the potential differences between opicapone and entacapone. Assessments of global health status using the Clinician's Global Impression of Change (CGI-C) and the Patient's Global Impression of Change (PGI-C) indicated clinically significant improvements for opicapone 50 mg versus both placebo (CGI-C,  $p=0.0005$ ; PGI-C,  $p=0.0070$ ) and entacapone (CGI-C,  $p=0.0008$ ; PGI-C,  $p=0.0091$ ), reflecting a better functioning or well-being of the patients versus entacapone (Figure 3). Likewise, responder rates for reductions in OFF time (patients with a reduction of  $\geq 1$  h in OFF time; 70% of patients) and increases in ON time (patients with an increase of  $\geq 1$  h in ON time;  $\leq 65\%$  of patients) were significantly higher for the opicapone 50 mg dose (OFF time,  $p=0.003$ ; ON time,  $p=0.0001$ ) than

for placebo, which was not the case for entacapone [44].

**[Figure 3 near here]**

The second study, BIPARK II – was also conducted as a multicenter, randomized, double-blind placebo-controlled study, without an active comparator [45]. As in the earlier study, opicapone 50mg significantly reduced OFF time by an average of 54 minutes versus placebo ( $p=0.0084$ ), and this was accompanied by corresponding improvements in absolute ON time. Once again, most of the gain of ON-time with opicapone was without troublesome dyskinesia and increases in ON-time with troublesome dyskinesia were not significantly different from placebo for both groups. Significantly more patients receiving 50 mg opicapone achieved the OFF time responder endpoint (patients with a reduction of  $\geq 1$  h in OFF time; 62.4%,  $p=0.0405$ ).

In this study, change from baseline in Unified Parkinson's Disease Rating Scales (UPDRS) Part III (motor) scores was included as the third secondary measure to be assessed in a hierarchical procedure. UPDRS motor scores were not improved versus placebo, and so it should be noted that the improvements in ON time as described above should be considered exploratory. Indeed, in both pivotal studies, changes in UPDRS motor function were small and similar across all groups [44]. It is thought this is probably because the patients were already receiving L-DOPA treatment for symptomatic control, and such small changes have been a feature of most previous COMT inhibitor trials [48].

The results of these two studies were reassuringly consistent, with the 50 mg dose providing the most consistent efficacy although therapeutic benefits with the 25 mg dose were also apparent in some patients. The similarity of trial design between the two large studies (similar designs, identical eligibility criteria and consistent assessment methods) permits a pooled analysis of OFF and ON time changes across the two studies [49]. When analyzed in this way, treatment both opicapone 25mg

(n=241) and 50mg (n=262) significantly reduced daily OFF-time (-37.4 min and -64.4 min vs. placebo (n=255);  $p<0.05$  and  $p<0.0001$ , respectively) and increased the ON-time without troublesome dyskinesia (42.7 min and 64.7 min vs. placebo;  $p<0.05$  and  $p<0.0001$ , respectively) (Figure 4) [49]. No significant differences were observed for the ON-time with troublesome dyskinesia.

**[Figure 4 near here]**

Results of the open-label phases of the pivotal trial indicate a maintenance of effect [50]. In both studies, OFF-time reductions from double-blind baseline were sustained (or even further improved) over the open-label phases and, as expected, these reductions were accompanied by increases in ON time (BIPARK II, Figure 3). Findings from the BIPARK II open-label extension appear to indicate a benefit of earlier initiation; results at the end of the open-label phase were numerically better for the patients in the original opicapone groups versus those who were originally assigned to placebo [45]. In the BIPARK I open-label extension, patients who switched from entacapone treatment in the double-blind phase to open-label treatment with opicapone experienced a further statistically significant reduction in OFF time of -39.3 minutes ( $p<0.05$ ) with a corresponding increase of ON-time without dyskinesia of 46 minutes ( $p=0.0148$ ). By the end of the one year open-label phase, the means for OFF time were similar, irrespective of original double-blind allocation [50] (Figure 5) [51].

**[Figure 5 near here]**

Further support for the benefits of long-term opicapone treatment comes from ratings of global function as perceived by patients and investigators. In both studies, improvements in global function at the end of the double-blind period were maintained after 1 year of treatment in the open-label extensions. Across the studies, about 60% of the subjects at the end of the open-label period were assessed by investigators and subjects as having improved (i.e. minimally, much or very much

improved) relative to the double-blind baseline, which was slightly above the rate observed at the end of the double-blind periods [38].

L-DOPA dosing is often used as a proxy of efficacy, and in a progressive disease maintenance of dosing and dosing frequency can be said to reflect sustained control of motor fluctuations over the long term. It is therefore of note that, in the BIPARK II study, almost two-thirds (63%) of patients were maintained on the same dose of L-DOPA, despite freedom adjust dosing according to clinical need [45]. The average number of daily L-DOPA intakes also remained stable during this phase, ranging from 4.69 to 4.76 over the course of the year.

**[Figure 6 near here]**

### **3.5 Safety and tolerability**

During the clinical development program, opicapone was administered (single or multiple doses) to a total of 1651 subjects: 859 healthy subjects and 792 subjects with PD [40]. In all studies, opicapone has been generally well tolerated with no apparent dose-relationship for the majority of treatment-emergent adverse events (TEAEs).

Studies in healthy volunteers have confirmed that the 50 mg dose of opicapone is not associated with a clinically significant effect on cardiac repolarization as measured by the QTc intervals [52] with no clinically significant out-of-range value in hematology, blood chemistry or urinalysis parameters, no clinically significant out-of-range value in vital signs or ECG parameters [38]. Other Phase I studies show that although co-administration of paracetamol causes a significant decrease in opicapone sulphation and therefore reduced levels of the BIA 9-1103 metabolite, it has no effect on opicapone exposure or tolerability profile in healthy volunteers [40].

This favorable tolerability profile in healthy volunteers has also been consistent in the Phase II and III studies conducted in patients with PD and motor fluctuations. Overall, the incidence of TEAEs and related TEAEs has been higher with opicapone than with placebo in the double-blind phases (Table 1) [53]. Across both studies, the percentage of patients who discontinued because of TEAEs was low and similar across the treatment groups. Few patients discontinued opicapone therapy due to TEAEs and the high retention of patients across the double-blind and open-label extension phases support the good tolerability of repeated treatment [45, 53].

Across both double-blind studies, the most common TEAEs reported in the opicapone group compared to placebo were the dopaminergic events of dyskinesia, constipation, insomnia, dry mouth and dizziness, as well as increased blood creatine phosphokinase (CPK). L-DOPA is frequently the drug of choice for older patients [4], and in this respect it is noteworthy that opicapone appears to be equally well tolerated in older PD patients over the age of 70 years (also with equivalent efficacy) [54]. When analyzed by age (<70 versus  $\geq$ 70 years old), TEAEs occurring more frequently in older versus younger patients included constipation (8.5% vs 4.5%); dizziness (7.2% vs 2.2%), visual hallucinations (5.2% vs. 0.6%), nausea (5.2% vs. 3.1% and weight decreased (4.6% vs. 1.1%) [54]. During open-label treatment the incidence of most of these TEAEs remained similar to the double-blind phases. In the extension of BIPARK II, there was an increased incidence of falls and depression, which is likely a reflection of the natural progression of the underlying disease and associated co-morbidities. In particular, increased blood CPK went from 4.9% of subjects in the opicapone 50 mg group to 7.4% of all subjects in the OL extension. As increased CPK levels are often associated with muscular lesions due to falls or accidents, dyskinesia, and PD in general, this increased incidence probably also reflects the natural incidence of associated co-morbidities of the underlying disease over a longer period of observation.

**[Table 1 near here]**



Dyskinesia was the most frequently reported TEAE considered related to the study drug, with a higher incidence in the combined opicapone groups (17.7%) than either placebo (6.2%) or entacapone (7.4%) groups. The higher level of dyskinesia with opicapone versus entacapone is in line with opicapone's more potent inhibition of COMT resulting in greater L-DOPA bioavailability. For reasons of data interpretation, both Phase III studies did not allow L-DOPA dose reductions during the last 12 weeks of the study, but this would not be an issue in clinical practice where L-DOPA dose reductions within the first days to first weeks after initiating treatment are recommended according to the clinical condition of the patient [55]. As demonstrated in the efficacy evaluations of ON time with and without troublesome dyskinesia, most dyskinesia was deemed non-troublesome by the patients. Of note, in the BIPARK I study, 47 (80%) of 59 treatment-emergent dyskinesia occurred in patients (in all groups) who were already experiencing dyskinesia at baseline [44]. Furthermore, when AEs are broken down by time frame, it becomes apparent that whereas the rates of dyskinesia AEs are higher for opicapone 50 mg vs entacapone 200 mg during the first 2 weeks of treatment (before Visit 4: 12.2% with opicapone versus 5.7% with entacapone), the rates of dyskinesia are actually very similar after this initial period (after Visit 4: 4.3% with opicapone versus 4.1% with entacapone) [38].

Another safety aspect of special interest to COMT inhibitors is hepatic safety, which has been the most important limitation of tolcapone [25] and other COMT inhibitors in development. It is therefore of importance that, across both pivotal studies, there was no apparent increase in hepatic disorders with opicapone. Indeed, the overall incidence of drug-related hepatic disorders was lower with opicapone compared to placebo (1.2% vs. 3.1%), there were no relevant differences between groups in the mean changes from baseline to endpoint for hepatic laboratory parameters and no severe hepatic events were reported with opicapone in the pivotal trials [56].

Likewise, the utility of entacapone can be limited in some patients by the development of gastrointestinal problems such as severe diarrhea. In the BIPARK I study, the most common TEAEs leading to discontinuation was diarrhea, but these patients came from the entacapone (n=2) and placebo (n=1) groups, and no patient in the opicapone groups discontinued due to diarrhea [44]. Opicapone is not associated with urine discoloration [44] or orange staining of teeth, hair or nails associated with entacapone administration [57]. Although not a serious medical problem, patients can find this staining embarrassing.

A pooled analysis of data collected with the modified Minnesota Impulsive Disorders Interview (mMIDI) found that opicapone, like all current dopaminergic PD medications, is associated with an increase in impulse control disorders. In the BIPARK I study (which excluded patients with current impulse control disorders, and where baseline medication use was broadly similar across groups) the overall incidence of treatment-emergent impulse control disorders (as identified by the mMIDI) was highest in the entacapone group (8.2%), followed by opicapone (6.2%) and then placebo (4.1%). There was no dose relationship in the opicapone groups [44]. The most common disorders seen in both studies were buying disorders and changes in sexuality (hypersexuality, sexual excitability, compulsive sexual behavior) [44].

Finally, it is important to note that most patients in this advanced group of PD patients are on multiple medications. Subgroup analyses to evaluate the effect of concurrent usage of MAO inhibitors and dopamine agonists for PD treatment, as identified at baseline, showed that opicapone presented similar efficacy when used alone or concomitantly [58]. Just as importantly, there were no differences in the incidence of TEAEs between opicapone patients treated with or without these adjunct agents, thereby supporting the role of opicapone in a polypharmacy approach.

### **3.6 Regulatory affairs**

On the 24<sup>th</sup> June 2016, Ongentys (opicapone) received a Marketing Authorization approval from the European Commission as adjunctive therapy to preparations of L-DOPA/DOPA decarboxylase inhibitors (DDCIs) in adult patients with PD and end-of-dose motor fluctuations who cannot be stabilized on those combinations [40]. The recommended dose is 50 mg, taken once a day at bedtime, at least one hour before or after L-DOPA combination medicines.

Ongentys is approved as 25mg and 50mg hard capsules in packs of 10, 30 or 90 capsules [40]. As a new active substance, opicapone is authorized in the European Union member states under the Anatomical therapeutic chemical (ATC) code of N04 (Anti-parkinson drugs), with additional monitoring in place. Following an exclusive license agreement, the Japanese company - Ono Pharmaceutical Co., Ltd. will develop opicapone for use in Japan. No plans have yet been announced for filing with the US Food and Drug Administration.

### **3.7 Conclusion**

Opicapone is a third generation, highly potent and effective COMT inhibitor that optimizes the pharmacokinetics of L-DOPA therapy, with the unique characteristic of once daily dosing. Across all clinical studies, opicapone consistently reduced OFF-time and increased ON-time without increasing the frequency of troublesome dyskinesia, and these benefits were maintained over at least a year of continued open-label therapy.

The impact of reducing OFF time and increasing ON time in patients with PD and motor fluctuations is well established and the efficacy of opicapone is further supported by the significant benefits in terms of clinician rated and patient rated global function. Although the BIPARK I study was not powered to compare opicapone with entacapone treatment, the results favored opicapone – indicating that opicapone may offer greater improvements in increasing ON time and decreasing

OFF time. Supporting these observations, patients receiving opicapone once-daily experienced statistically significant improvements in their functioning or well-being compared to entacapone (investigator rated  $P=0.007$ ; patient rated  $p=0.0091$ ).

### **3.8 Expert commentary**

Long-term studies have shown that starting treatment with either a dopamine agonist or a selective MAO-B inhibitor confer little or no long-term advantage compared to L-DOPA [59-61]. Together with concerns about dopamine agonist-induced impulse control disorders these studies have supported a general swing away from dopamine agonist monotherapy back to early L-DOPA treatment [61]. Nevertheless, higher cumulative doses (>400–600mg) of L-DOPA are strongly correlated with the earlier emergence of motor complications [6, 62], and the presence of wearing-off is associated with the earlier development of dyskinesia and *vice versa* [63]. Adjunct therapies to control motor fluctuations are high on the list of clinical need for patients on sustained L-DOPA treatment, and opicapone will take its place in the PD armamentarium as a novel and effective adjunctive option. Opicapone offers an important alternative to entacapone, with convenient once-daily dosing and potential efficacy advantages.

### **3.9 Five-year view**

Despite some exciting prospects of potentially disease-modifying activity of novel interventions that target the aggregation and propagation of toxic alpha-synuclein species, improved symptomatic therapies will likely dominate the PD drug market over the next five years. These will include innovations of L-DOPA formulation and delivery where a clinical development program of continuous subcutaneous infusions of L-DOPA/carbidopa has shown promising Phase II results in PD patients with L-DOPA related motor complications. This formulation has been reported to more reliably achieve L-DOPA plasma levels in the therapeutic range that are likely needed for patients with motor fluctuations when co-administered with entacapone [31], opening interesting

perspectives for the future use of once-daily COMT-inhibitors like opicapone. The efficacy of opicapone with the various extended release L-DOPA formulations coming to market (e.g. IPX066 and the gastric-retention formulation) will need to be evaluated, in particular if a combination of opicapone with extended-release L-DOPA from the outset of treatment can reduce the incidence and severity of motor complications. Other reformulations include the development of an inhaled L-DOPA and a novel sublingual apomorphine formulation, both of which are in Phase III clinical development. While these fast acting medications are unlikely to replace classical adjunct approaches, they would be expected to supplement oral regimens as rescue medication for intervening OFF-periods.

In the next five years, the role of opicapone in clinical practice will become clearer with routine use. Only clinical experience with opicapone will show if the efficacy benefits versus entacapone suggested by the BIPARK-I study will translate into routine practice. Further pharmacogenetics research involving COMT polymorphisms may allow pre-treatment determination of patients likely to respond well to opicapone.

### **Key issues**

- The effective management of motor fluctuations is key to the global health status and well-being of patients with PD.
- Opicapone is a third generation, potent and effective catechol *O*-methyltransferase (COMT) inhibitor that provides long-lasting COMT inhibition to optimize the pharmacokinetics and bioavailability of L-DOPA therapy.
- In PD patients with motor fluctuations, opicapone 50 mg given once-daily, consistently reduced OFF-time and increased ON-time without increasing the frequency of troublesome dyskinesia.

- The BIPARK I pivotal study included entacapone (200mg with each L-DOPA dose) as an active comparator. Patients receiving opicapone once-daily experienced greater improvements in their global health status (as assessed by both the Clinician's and Patient's Global Impression of Change) versus entacapone.
- The efficacy of opicapone on reducing OFF time and increasing ON time are maintained over at least a year of continued open-label therapy. During a 1-year open-label follow-up period, patients switching from entacapone to opicapone once-daily achieved additional increases in ON-time.
- Opicapone is generally well-tolerated. The most common treatment-related adverse events were dyskinesia, constipation, insomnia, dry mouth and dizziness. Treatment with opicapone has not been associated with the development of liver problems, diarrhea and urinary discoloration.

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## **Table legends**

**Table 1. Treatment-emergent adverse events in >3% of any treatment group, by decreasing frequency all completed Phase III double-blind studies (Safety Set)**

## **Figure legends**

**Figure 1: Opicapone chemical structure**

**Figure 2: Dose dependent COMT inhibition in (a) healthy volunteers and (b) PD patients with motor fluctuations [39, 43]**

*[Legend]: Figure 2a shows Mean S-COMT activity on Day 12 following once daily oral administration of 50mg opicapone or placebo for 11 days (Day 1 to 11) or co-administration of 200mg entacapone or placebo with each L-dopa/carbidopa dose (n=15)*

**Figure 3: Clinician's Global Impression of Change (CGI-C) and the Patient's Global Impression of Change (PGI-C) in the BIPARK-I study. Adapted from reference [44]**

*Legend: Improved includes patients 'minimally improved', much improved' and 'very much improved'.*

**Figure 4: Change from baseline in ON (upper part) and OFF (lower part) time (minutes)**

*[Legend]: Pooled analysis from the BIPARK I and BIPARK II studies*

**Figure 5: BIPARK-I study: OFF-time change from double-blind baseline to double-blind endpoint and open-label endpoint.**

*[Legend]: All patients switched to active treatment with opicapone at the start of the open-label phase. \*p<0.05 vs. pre-switch.*

**Figure 6: Change from double-blind baseline in (a) absolute OFF-time (b) absolute ON time without or with non-troublesome dyskinesia and (c) ON time with troublesome dyskinesia (BIPARK II study)**