CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212489Orig1s000

SUMMARY REVIEW

From	Gerald D. Podskalny, DO Eric Bastings, MD Billy Dunn, MD
Subject	Joint Summary Review
NDA/BLA # and Supplement#	NDA 212489
Applicant	Neurocrine Biosciences, Inc.
Date of Submission	04/26/2019
PDUFA Goal Date	04/26/2020
Proprietary Name	Ongentys
Established or Proper Name	Opicapone
Dosage Form(s)	25-mg and 50-mg capsules
Applicant Proposed Indication(s)/Population(s)	Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes
Applicant Proposed Dosing Regimen(s)	50 mg orally once daily at bedtime.
Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes.
Recommended Dosing Regimen(s) (if applicable)	50 mg orally once daily at bedtime.

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Parkinson's disease (PD) is the second most common neurodegenerative disease, with an estimated prevalence of 930,000 individuals in the United States. PD is caused by progressive loss of dopamine producing neurons in the substantia nigra located in the midbrain. The cardinal motor features of PD are bradykinesia, tremor, rigidity, and postural instability. As PD progresses, it causes increasing motor disability. Medications that replace or enhance the effects of dopamine, such as levodopa, treat the motor aspects of PD and remain the mainstay of treatment. About 5 years after starting treatment with levodopa, many patients develop motor fluctuations (dyskinesia and wearing-off). In advanced PD (approaching 10 years with PD and beyond), patients may develop cognitive impairment, neuropsychiatric symptoms (e.g., hallucinations and impulse control disorders) and impaired autonomic function (e.g., incontinence and orthostatic hypotension).

Levodopa is generally administered with medications that block its metabolism before it gets across the blood-brain barrier, e.g., carbidopa, a blocker of the most common peripheral path of levodopa degradation which uses the enzyme dopa decarboxylase. However, levodopa can still be metabolized by COMT, resulting in O-methylation in the periphery, which decreases the amount of levodopa available to enter the brain. Ongentys (opicapone) is a selective and reversible peripheral COMT inhibitor developed as adjunctive therapy to levodopa/carbidopa in patients with PD experiencing "OFF" episodes. Two other COMT inhibitors are currently marketed in the US: entacapone and tolcapone.

The applicant conducted two adequate and well controlled studies to establish the efficacy of opicapone (Study 301 and Study 302). Both had a similar randomized, double-blind, placebo-controlled, and multi-center design, and were conducted in patients diagnosed with PD experiencing at least 1.5 hours of OFF-time daily. Study 301 tested three dosages of opicapone (5, 25, and 50 mg per day), while Study 302 only tested the 25-mg and 50-mg dosages of opicapone. The primary efficacy variable in both studies was the change in OFF-time from baseline to the end of the double-blind period, based on 24-hour patient diaries. Secondary outcome measures included responder analyses of OFF-time and ON-time, and the change from baseline in ON-time without troublesome dyskinesia.

Both studies clearly met their primary endpoint for the 50-mg dosage of opicapone. In Study 301, patients treated with opicapone 50 mg had, on average, a 1.01-hour greater reduction in OFF-time that patients on placebo ($p=0.002$). In Study 302, patients treated with opicapone 50 mg had, on average, a 0.91-hour greater reduction in OFF-time that patients on placebo ($p=0.008$). The meaningfulness of the reduction in OFF-time was supported by the observed increases in ON-time without troublesome dyskinesia. Trends in favor of opicapone 25 mg were observed in Study 301 and 302, but the difference from placebo did not reach statistical significance. The benefit to patients observed with opicapone 50 mg for ON-time without troublesome dyskinesia, statistically significant in one study and trending similarly, though nominally, in the other, represents, in conjunction with the reduction in OFF-time, a clinically important improvement in the motor status (and daily life) of the advanced PD patient.

Because COMT inhibitors derive their therapeutic effect by blocking the peripheral catabolism of levodopa and increasing its bioavailability, it logically follows that drug-related adverse reactions are predictably related to this increase in central dopaminergic tone. This is what was observed in patients treated with opicapone. No unexpected adverse events were seen. The most common adverse reaction leading to discontinuation was dyskinesia, reported in 3% of patients treated with opicapone 50 mg, compared with 0.4% in patients who received placebo. The most common adverse reactions that occurred in $\geq 4\%$ of patients treated with opicapone 50 mg and were more frequent than on placebo were dyskinesia (20%), constipation (6%), blood creatinine kinase increased (5%), hypotension/syncope (5%), and weight decreased (4%). Opicapone compares favorably to the currently marketed COMT inhibitors, as it does not have the hepatic liability of tolcapone, and appears to have fewer intestinal adverse reactions than entacapone. Opicapone also has convenient once-daily dosing. Opicapone will be a useful addition to the Parkinson's disease drug armamentarium.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Parkinson's disease (PD) is a progressive degenerative disorder of the nervous system that affects one in 100 people above age 60. The risk for PD increases with age (until age 80). • PD is caused by progressive loss of dopamine producing neurons in the substantia nigra located in the midbrain resulting in progressive impairment of motor function. • This results in the cardinal motor symptoms of the disorder: slowness of movement, rigidity of muscles, and tremor. Postural instability and gait disorder occur as the illness progresses. • There are no treatments proven to slow the progression of PD. • The mainstay of PD pharmacotherapy for the last half century has been to compensate the loss of dopamine via the oral administration of levodopa. • While levodopa provides good relief of motor symptoms, the benefit from levodopa decreases as the illness progresses. Most PD patients will eventually develop the "on-off syndrome": the pharmacodynamic effect of levodopa becomes shorter in duration, and patients experience "OFF" episodes during which mobility is reduced, and develop a dyskinetic motor response that, while leaving the patient mobile, may itself become disabling. • In advanced PD (approaching 10 years with PD and beyond), patients may develop cognitive impairment, neuropsychiatric symptoms (e.g., hallucinations and impulse control disorders), and impaired autonomic function (e.g., incontinence and orthostatic hypotension).	Parkinson's disease is a progressive degenerative disorder of the nervous system that produces the symptoms of slowness of movement, rigidity of muscles, and tremor. In advanced disease, postural instability and gait disorder also occur as the illness progresses. Non-motor symptoms also occur in more advanced disease, with psychiatric and cognitive symptoms and autonomic dysfunction. As the illness progresses, available pharmacological treatment become less able to control the motor symptoms of the disorder and each dose of medication wears off, producing an "OFF" period during which the patient suffers increased motor impairment. Unpredictable "OFF" episodes may also occur. This results in significant disability and loss of life quality.
Current Treatment Options	• Several drug classes are currently available for the treatment of PD patients who experience "OFF" episodes. The mechanism of action is related to extending the action of levodopa itself, which suffers from poor absorption in the gut, poor transport into the brain, short duration of action, and excessive catabolism outside of the nervous system. This may be accomplished by using drugs that increase the amount of levodopa getting into the brain by preventing its breakdown (e.g., monoamine oxidase type B inhibitors and catechol-O-methyltransferase (COMT) inhibitors). Levodopa taken with a dopa decarboxylase inhibitor results in COMT becoming the major peripheral metabolizing enzyme for levodopa. COMT	Current pharmacological treatment for PD aims at restoring levels of dopamine in the brain. Levodopa, an oral precursor to dopamine, is generally administered with carbidopa, which inhibits its catabolism before it gets into the nervous system. Several drug classes are currently available for the treatment of PD patients who experience "OFF" episodes.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	inhibitors increase the amount of levodopa available for conversion to dopamine in the brain. • Two COMT inhibitor medications are currently approved. Tolcapone has a significant risk of hepatocellular toxicity and has even caused fulminant hepatic failure, requiring regular surveillance for liver injury. Entacapone must be taken with each levodopa dose up to six times a day and has been associated with colitis and diarrhea. • Istradefylline is an adenosine receptor antagonist that can also be used as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease experiencing "OFF" episodes. The precise mechanism by which istradefylline exerts its therapeutic effect in Parkinson disease is unknown. • Other treatment options include artificially stimulating dopamine receptors in the brain (dopamine agonists), a constant delivery of levodopa by parenteral administration, and other classes of adjunctive medications such as anticholinergic agents and amantadine. • Some drugs can also be used for the intermittent treatment of "OFF" episodes: levodopa through oral inhalation, and apomorphine (a non-ergoline dopamine) through subcutaneous injection. • Invasive techniques employing deep brain stimulators or ablative neurosurgery can be very effective at improving the motor state but are generally useful in only a limited population of PD patients.	Opicapone is a COMT inhibitor. Two COMT inhibitor medications are currently approved. Tolcapone has a significant risk of hepatocellular toxicity and has even caused fulminant hepatic failure, requiring regular surveillance for liver injury. Entacapone must be taken with each levodopa dose up to six times a day and has been associated with colitis and diarrhea.
Benefit	• The applicant conducted two adequate and well-controlled studies to establish the efficacy of opicapone (Study 301 and Study 302). • Both studies had a similar randomized, double-blind, placebo-controlled, and multi-center design, and were conducted in patients diagnosed with PD experiencing at least 1.5 hour of OFF-time daily. • Study 301 tested three dosages of opicapone (5, 25, and 50 mg per day), while Study 302 only tested the 25-mg and 50-mg dosages of opicapone. • The primary efficacy variable in both studies was the change in OFF-time from baseline to the end of the double-blind period, based on 24-hour patient diaries. • Secondary outcome measures included responder analyses of OFF-time and ON-time, and the change from baseline in ON-time without troublesome dyskinesia. • In Study 301, patients treated with opicapone 50 mg had, on average, a 1.01-hour greater reduction in OFF-time than patients on placebo (p=0.002). • In Study 302, patients treated with opicapone 50 mg had, on average, a 0.91-hour greater reduction in OFF-time than patients on placebo (p=0.008).	Opicapone was investigated in two studies in advanced PD patients who averaged over 6 hours of OFF time daily, as self-reported by diary. Both studies showed about a 1-hour greater reduction in OFF-time with opicapone 50 mg, compared with placebo. The meaningfulness of the reduction in OFF-time was supported by an increase in ON-time without troublesome dyskinesia. Opicapone 50 mg provides a clear and meaningful benefit to PD patients who experience "OFF" episodes.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The meaningfulness of the reduction in OFF-time was supported by an increase in ON-time without troublesome dyskinesia. • Trends in favor of opicapone 25 mg were observed in Study 301 and 302, but the difference with placebo did not reach statistical significance.	
Risk and Risk Management	• In the opicapone development program, 1021 PD patients received at least one dose of opicapone. Of these, 965 PD patients received opicapone in the Phase 3 program. • At the proposed dose for marketing (50 mg once a day), 263 patients were exposed for more than 6 months but less than 12 months, and 133 patients were exposed for a year or more. • The pattern of adverse drug reactions is consistent the mechanism of action of opicapone (increased central dopaminergic tone). • No deaths related to opicapone occurred in the development program. • The most common adverse reaction leading to discontinuation was dyskinesia, reported in 3% of patients treated with opicapone 50 mg, compared with 0.4% in patients who received placebo. • The most common adverse reactions that occurred in ≥ 4% of patients treated with opicapone 50 mg and were more frequent than on placebo were dyskinesia (20%), constipation (6%), blood creatinine kinase increased (5%), hypotension/syncope (5%), and weight decreased (4%). • The elevation of creatine phosphokinase (CPK), a muscle enzyme, is reversible and not clinically significant. • Opicapone compares favorably to the currently marketed COMT inhibitors, as it does not have the hepatic liability of tolcapone, and appears to have fewer intestinal adverse reactions than entacapone. • Opicapone has convenient once-daily dosing. • No postmarketing risk mitigation strategy is necessary at this time.	The adverse reactions associated with opicapone are consistent with the mechanism of action of increasing the central dopaminergic tone. Opicapone compares favorably to the currently marketed COMT inhibitors, as it does not have the hepatic liability of tolcapone, and appears to have fewer intestinal adverse reactions than entacapone. Opicapone has convenient once-daily dosing.

2. Background

Opicapone (Ongentys; OPC; BIA 9-1067) is a new molecular entity (NME) in the pharmaceutical class of catechol-O-methyltransferase (COMT) inhibitors. Levodopa (LD) taken with a DOPA decarboxylase inhibitor (DDCI) results in COMT becoming the major peripheral metabolizing enzyme for levodopa, catalyzing its conversion to 3-O-methyldopa (3-OMD). In humans, OPC inhibits COMT in peripheral tissues, resulting in an increase in overall exposure to levodopa and a decrease in exposure to 3-OMD. OPC was developed as adjunctive therapy to carbidopa/levodopa (CD/LD) in patients with Parkinson's disease (PD) experiencing "OFF" episodes.

In February 2017, Neurocrine Biosciences, Inc. (NBI) and the OPC innovator and study sponsor BIAL – Portela & Ca, S.A. (BIAL) entered into an exclusive licensing agreement for the development and commercialization of OPC in North America. In June 2016, BIAL received approval for OPC in the European Union as "adjunctive therapy to preparations of levodopa/ DOPA decarboxylase inhibitors (DDCI) in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations", under the proprietary name Ongentys.

Clinical development of OPC was conducted outside of a US IND. The important clinical efficacy and safety studies supporting the applicant's submission were conducted in sites in Europe, South America, and Asia.

3. Product Quality

General product quality considerations:

Ben Zhang, Ph.D., was the primary Drug Substance Reviewer, and Su Tran, Ph.D., completed the secondary review. Qun (Stephanie) Liang, Ph.D., was the primary Drug Product Manufacturing reviewer and Erin Kim, Ph.D., completed the secondary review. Dahlia Woody, M.S., was the OPQ Regulatory Business Process Manager. Martha Heimann, Ph.D., was the Application Technical Lead for this NDA.

The active pharmaceutical ingredient (API), opicapone (OPC), is manufactured by (b) (4) The applicant cross-referenced the Drug Master File (DMF) for the API held by Bial-Portela. The drug substance manufacturing process, controls, certificates of analysis, and analytical methods, including the reference standards and validation methods, were all deemed acceptable by the drug substance reviewer. The container closure information and stability data included in the review of the DMF are acceptable.

The final drug product is manufactured in 25-mg or 50-mg hard gelatin capsules. Several changes were made to the formulation original formulation used in early clinical studies to the registration batches. The (b) (4) used in the Phase 3 clinical batches were exchanged for (b) (4) in the registration and commercial batches. The only other difference between the registration and commercial batches was a change in the capsule color. The changes in

formulation are supported by bioequivalence studies. The change in the capsule color from the registration batches to the final commercial batch is supported by in vitro dissolution data. The drug product reviewer found the manufacturing process adequate. All excipients are compendial grade and are present at acceptable levels. The registration batches were manufactured at the same scale as the proposed commercial batches. The drug product reviewer recommends granting the applicant's proposal for a 60-month expiration dating for drug product stored below 30°C (86°F). All facilities that will be involved in the manufacture and testing of OPC are currently acceptable based on the previous inspection history.

Biopharmaceutics:

Gerlie Giesser, Ph.D., was the primary Biopharmaceutics reviewer, and Ta-Chen Wu, Ph.D., completed the secondary Biopharmaceutics review.

OPC has low aqueous solubility at low pH and it is only slight soluble at pH 6.8. The applicant's proposed dissolution method was shown to be discriminating for intentional formulation changes and changes in key process parameters. However, the dissolution method could not discriminate between non-bioequivalent drug product batches made using drug substance batches with differences in particle morphology. An alternative particle size test that reliably detects differences in particle morphology in the API was submitted to the DMF and was found to be acceptable.

Mariappan Chelliah, Ph.D., completed the primary drug product labeling review, and Julia Pinto, Ph.D., completed the secondary review. Agreement was reached on drug product labeling.

OPQ granted the applicant's claim for categorical exclusion under 21 CFR §25.31(b).

Recommendation

The Office of Product Quality review team recommends approval.

4. Nonclinical Pharmacology/Toxicology

Luann McKinney, DVM, DACVP, was the primary nonclinical Pharmacology/Toxicology reviewer, and Lois Freed, Ph.D., provided a supervisory review.

The nonclinical safety package includes safety pharmacology, toxicology, reproductive/ developmental, genetic toxicology and carcinogenicity studies. In most species, the maximum feasible dose of 1000 mg/kg/day was also the NOAEL. OPC 3-O-sulfate, the only major circulating metabolite in humans (metabolism is primarily through sulfation in humans), is inactive at therapeutic concentrations. Exposures to levels of OPC 3-O-sulfate that exceeded clinical exposure were achieved in a 13-week repeat-dose toxicology study in rats.

The applicant's AMES test and micronucleus assays did not show OPC to be clastogenic or mutagenic. Carcinogenicity studies lasting 104 weeks were completed in mice and rats. OPC was found to be non-carcinogenic.

OPC had no meaningful effects on hERG-mediated currents in HEK cells or isolated Purkinje fiber action potential and in vivo studies found no effects on electrocardiogram, respiratory function, or behavior.

The applicant's reproductive toxicology and embryo-fetal toxicology studies in rats and rabbits found no change in performance in males or females and no evidence of teratogenicity or developmental toxicity.

Results of a combination 13-week combination toxicology of OPC, carbidopa, levodopa, and carbidopa plus levodopa in rats revealed changes related to chronic administration of dopamine.

Recommendation:

The application is approvable from a nonclinical perspective. In her supervisory memorandum, Dr. Freed concluded that the nonclinical studies are adequate to support approval of opicapone for the proposed indication.

5. Clinical Pharmacology

Mariam Ahmed, Ph.D., was the primary Clinical Pharmacology reviewer. A secondary review was performed by Atul Bhattaram, Ph.D., and Sreedharan Sabarinath, Ph.D. Mehul Mehta, Ph.D., completed a supervisory review.

General clinical pharmacology considerations

Dr. Ahmed noted that the applicant did not determine the absolute oral bioavailability of OPC. Repeat daily dosing of OPC 50 mg with administration of carbidopa/levodopa every 3 or 4 hours increased levodopa C_{max} by 43-44% and AUC_{last} by 62-94%. The administration of OPC 50 mg with a high fat meal decreased the OPC C_{max} and AUC_{last} by 62% and 31%, respectively, and delayed the median T_{max} by 4 hours compared to OPC administration under fasted conditions. The Dosing and Administration section of the label will recommend patients not eat food for at least one hour before and after taking OPC.

The single-dose pharmacokinetic characteristics of OPC 25 mg and 50 mg in healthy subjects are shown in Table 1. Pharmacokinetics parameters are dose-proportional for the two proposed tablet strengths.

Table 1. Pharmacokinetic Characteristics of PC 25-mg and 50-mg Tablets

25 mg OPC	
T_{max}, h	2.00 (0.50-4.00)
C_{max}, ng/mL	424.5 (36.8)
AUC_{last}, ng h/mL	1137 (37.6)
AUC_{inf}, ng h/mL	1321 (25.0)
t½, h	0.97 (29.5)
50 mg OPC	
t_{max}, h	2.00 (1.00-4.00)
C_{max}, ng/mL	756.2 (38.4)
AUC_{last}, ng h/mL	2043 (45.7)
AUC_{inf}, ng h/mL	2244 (40.8)
t½, h	0.92 (30.6)

Source: Adapted from the Clinical Pharmacology Review

Dr. Ahmed noted that once absorbed, OPC is highly bound to plasma proteins (99.9%) and that there is no evidence of mutual displacement from plasma proteins when OPC is incubated with other extensively protein bound medications. In vitro and in vivo studies showed that sulfation produces the only circulating major human metabolite, OPC 3-O-sulfate, which is inactive. No binding interaction between OPC and OPC 3-O-sulfate was observed. OPC is mainly cleared through metabolism. Fecal excretion accounted for about 70% of the dose, while recovery from urine was about 5%.

Population PK assessments of the effect of differences in weight, race, age, and sex did not identify a meaningful impact on systemic exposure to OPC.

Special Populations

The applicant conducted studies to evaluate the effect of mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment on OPC exposure. In subjects with mild hepatic impairment, OPC C_{max} and AUC_{inf} increased by 34% and 35%, respectively, compared with healthy subjects. In subjects with moderate hepatic impairment, OPC C_{max} and AUC_{inf} increased by 89% and 84%, respectively, compared with healthy subjects. The effect on OPC pharmacokinetics has not been evaluated in patients with severe hepatic impairment. The recommended dose of OPC in patients with moderate hepatic impairment (Child-Pugh B) is 25 mg/day. Treatment with OPC is not recommended in patients with severe hepatic impairment (Child-Pugh C).

The applicant did not conduct a study to assess the effect of renal impairment on the pharmacokinetics of OPC. Instead, the applicant used population pharmacokinetic analyses, and found no clinically significant differences in the pharmacokinetics of opicapone in patients with mild or moderate renal impairment relative to those with normal renal function. Patients with severe renal impairment or end-stage renal disease have not been studied by the applicant. No dosage adjustment is required for patients with mild, moderate, or severe renal impairment. However, because of a potential for increased exposure of OPC, patients with severe renal impairment should be monitored for adverse reactions and OPC discontinued if tolerability

issues arise. Because of the potential for multiple physiologic functions to be affected in patients with end-stage renal disease, the use of OPC in patients with end-stage renal disease should be avoided.

Drug interactions

The clinical pharmacology review team reviewed the results of in vitro studies and analyses of pooled PK data from Phase 3 clinical studies and concluded that OPC and OPC 3-O-sulfate have a low potential risk for meaningful CYP or transporter-mediated drug interactions.

Exposure to carbidopa, rasagiline, selegiline, pramipexole, and ropinirole was not meaningfully altered following administration of OPC.

Formulation bridging

The applicant developed four formulations of OPC (non-micronized, micronized, registration, and commercial) of OPC. Appropriate bridging was provided between the various formulations.

Thorough QT study

The Interdisciplinary Review Team for QT (IRT-QT) studies found no significant QTc prolongation potential for OPC. The highest evaluated dose (800 mg) resulted in a Cmax 8.4 times greater than peak clinical therapeutic exposure, covering the worst-case clinical scenario. The largest upper bounds of the 2-sided 90% CI for the time-matched, mean difference between OPC (50 mg and 800 mg) and placebo were below 10 ms, the threshold for concern. Assay sensitivity was demonstrated for the moxifloxacin arm (active control) on the study.

Recommendation

The Office of Clinical Pharmacology review team recommends approval.

6. Clinical/Statistical- Efficacy

Minjeong Park, Ph.D., was the primary statistical reviewer for this application. Supervisory concurrence was provided by Kun Jin, Ph.D., (Team Leader) and H.M. James Hung, Ph.D., (Director, Division of Biometrics I). Kenneth Bergmann, MD, was the primary medical reviewer.

Study Design

The primary evidence of efficacy for OPC comes from Study BIA-91067-301 and Study BIA-91067-302, hereafter referred to as Study 301 and Study 302. Both studies were multicenter, double-blind, randomized, placebo-controlled, with parallel groups, and both started with a controlled phase lasting 14 to 15 weeks. After completing the controlled phase of the study, eligible patients could enter an open-label extension lasting an additional 52 weeks.

In both studies, patients were required to be between 30 and 83 years of age and have a diagnosis of idiopathic PD fulfilling the UK brain bank criteria. Patients were to have a minimum duration of PD of at least three years, and a Modified Hoehn and Yahr scale stages 1 to 3 during ON-state. Patients needed to have at least 1.5 hours of OFF-time per day and have been treated with levodopa and a dopa decarboxylase inhibitor (DDCI). Patients with a history of deep brain stimulation, pallidotomy, or thalamotomy were excluded.

After randomization, investigators could adjust the levodopa/DDCI dose over the first 2 to 3 weeks of the study; however, the number of daily doses of levodopa/DDCI had to remain the same. From Visit 4 (Day 21), the dose of levodopa/DDCI had to remain the same until the end of the double-blind phase (approximately 84 days). At the beginning of the open-label extension, all patients were started on OPC 25 mg once daily at night. The dose of OPC could be increased to 50 mg if wearing-off was not adequately controlled. Levodopa adjustments and OPC down titration were permitted throughout the open-label portion of the study.

Study 301

Study Population

In Study 301, patients were recruited from 19 countries in Eastern and Western Europe, with no centers in the United States, the rest of North America, or Asia. Overall, 600 patients were randomized in the same proportion to 5 mg, 25 mg, or 50 mg of OPC, placebo, or entacapone 200 mg, taken with each dose of levodopa. The mean age of patients was 63 to 64 years in each of the study arms. Males represented about 58% of population, and all patients were Caucasian. Patients averaged 6.2 to 6.9 hours of OFF-time at baseline. There were no meaningful differences in the baseline characteristics of patients in any of the randomized arms.

Study Endpoints

The primary efficacy variable was the change in absolute OFF-time from baseline to the end of the double-blind period (endpoint) assessed using the Parkinson's Disease Diary. The average OFF-time in the diaries completed during the last 3 days prior to Visit 2 (randomization) was used to establish the baseline value. The average OFF-time of diaries completed on the last 3 days prior to the end of the double-blind period (Visit 7) or prior to the End-of-Study Visit, was considered as the endpoint value. All efficacy analyses were performed on the Full Analysis Set (FAS), which included all randomized subjects treated with at least one dose of study medication after randomization and who had at least one post-baseline OFF-time efficacy assessment. The FAS was the same as the Intention to Treat (ITT) population.

The key secondary endpoints in Study 301 included: 1) Proportion of OFF-time responders, defined as having a 1-hour or more reduction in absolute OFF-time from baseline to endpoint; 2) Proportion of ON-time responders, defined as having a 1-hour or more increase in absolute ON-time from baseline to endpoint. The key secondary endpoints were analyzed using a Cochran-Mantel-Haenszel test stratified by region. Of note, the 1-hour OFF-time and ON-

time responder rates are closely related to each other and to the primary endpoint. They do not provide additional information about patients' ability to function in daily life.

ON-time without troublesome dyskinesia (ON-time with non-troublesome dyskinesia + ON-time without dyskinesia) was another secondary endpoint (not a key secondary endpoint in that it was not included in the statistical hierarchy) in Study 301. It is, however, a typical endpoint in late PD studies, and important to interpret the clinical meaningfulness of the reduction in OFF-time. The benefit associated with a reduction in absolute OFF-time must be balanced with a potential increase in ON-time with troublesome dyskinesia, which would not be desirable. Dr. Park conducted an exploratory analysis of ON-time without troublesome dyskinesia (in minutes) in the FAS population using an ANCOVA model with treatment and region as factors and baseline ON-time without troublesome dyskinesia as a covariate.

Efficacy Results

Of the 600 patients enrolled, 122 subjects were randomized to OPC 5 mg, 119 to OPC 25 mg, 116 to OPC 50 mg, 122 to entacapone 200 mg, and 121 to the placebo. Nine percent of patients withdrew during the double-blind phase of Study 301, with a similar rate across the treatment arms and placebo.

Dr. Park confirmed the results for the primary analysis of the primary endpoint using the prespecified ANCOVA model (which included treatment group and region as fixed effects, and baseline OFF-time as a covariate). The Last Observation Carried Forward (LOCF) was used to replace missing diary data at the endpoint visit. The applicant conducted additional sensitivity analyses to explore the effects of using the LOCF method of handling missing data. The applicant used a sequential gate-keeping procedure for one-sided comparisons of each dose of OPC to placebo at an error rate of 0.025.

The change from baseline at the end of the double-blind period in absolute OFF-time was significantly greater for OPC 50 mg than for placebo. Although the reduction in absolute OFF-time for the OPC 25-mg and 5-mg groups were not statistically greater than for placebo, the results showed a strong trend in favor of OPC (see Table 2).

Table 2. Change from Baseline to Endpoint in Absolute OFF-time (minutes) in Study 301

Treatment comparison	N	LS mean (SE)	Upper bound of CI [a]	Local p-value	Local significance level [b]	Adjusted p-value [b]
Full Analysis Set (FAS)						
Placebo	120	-56.0 (13.38)	-29.7	-	-	-
OPC 5 mg	119	-91.3 (13.46)	-64.8	-	-	-
OPC 25 mg	116	-85.9 (13.69)	-59.1	-	-	-
OPC 50 mg	115	-116.8 (13.97)	-89.4	-	-	-
Test for superiority (FAS):						
OPC 5 mg – Placebo		-35.2 (18.38)	0.9	0.0279	0.01250	0.0558
OPC 25 mg – Placebo		-29.9 (18.54)	6.5	0.0536	0.01250	0.0796
OPC 50 mg – Placebo		-60.8 (18.52)	-24.4	0.0005	0.00833	0.0015

Source: Table 14.9.1, 14.9.2, and Table 14.9.3
CI=confidence interval; FAS=Full Analysis set; LS mean=least squares mean; N=number of non-missing values; OPC=opicapone; PP=Per-protocol; SE=standard error
Note: p-values are 1-sided and based on Type III sums of squares.
a Upper bound of the 2-sided unadjusted 95% CI.
b Calculated using Graph Based Multiple Comparison Procedure gMCP (from CRAN, see Bretz 2011)

Source: FDA Statistical Review

Dr. Park confirmed the applicant's results for sensitivity analyses using the ANCOVA model with LOCF for the 50-mg dose using the Per-Protocol (PP) population, and a Mixed Model Repeated Measures (MMRM) analysis for the change from baseline in absolute OFF-time. Both of these sensitivity analyses supported the primary result. Dr. Park conducted additional analyses (replacing missing values in the 50-mg group with the mean endpoint value of placebo group or replacing missing values with the mean change for the OPC 50-mg group at the endpoint visit), which also supported the primary analysis.

The proportion of ON-time responders (OPC 50 mg=65% vs. placebo 46%; p=0.0028) and OFF-time responders (OPC 50 mg=70% vs. placebo=48%; p=0.0011) was nominally significantly greater for OPC 50 mg than for placebo (see Table 3).

Table 3. Proportion of OFF- and ON-time Responders in Study 301

Characteristic	Statistic	Placebo (N=120)	OPC 5 mg (N=119)	OPC 25 mg (N=116)	OPC 50 mg (N=115)
OFF-time Reduction					
Responders	n (%)	57 (47.5%)	71 (59.7%)	70 (60.3%)	80 (69.6%)
Non-responders	n (%)	63 (52.5%)	48 (40.3%)	46 (39.7%)	35 (30.4%)
Missing	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Difference with placebo					
CMH-test vs. Placebo	p-value	-	0.0650	0.0464	0.0011
Breslow-Day test	p-value	-	0.7738	0.0789	0.8330
ON-time Increase					
Responders	n (%)	55 (45.8%)	65 (54.6%)	66 (56.9%)	75 (65.2%)
Non-responders	n (%)	65 (54.2%)	54 (45.4%)	50 (43.1%)	40 (34.8%)
Missing	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Difference with placebo					
CMH-test vs. Placebo	p-value	-	0.1690	0.0947	0.0028
Breslow-Day test	p-value	-	0.7654	0.5339	0.4686

CMH=Cochran-Mantel-Haenszel-test, stratified by region; OPC=opicapone

Source: FDA Statistical review

The change from baseline to the end of the double-blind period in ON-time without troublesome dyskinesia was nominally significantly greater for all three doses of OPC than for placebo (see Table 4).

Table 4. Change from Baseline to Endpoint in ON-Time Without Troublesome Dyskinesia (minutes) in Study 301

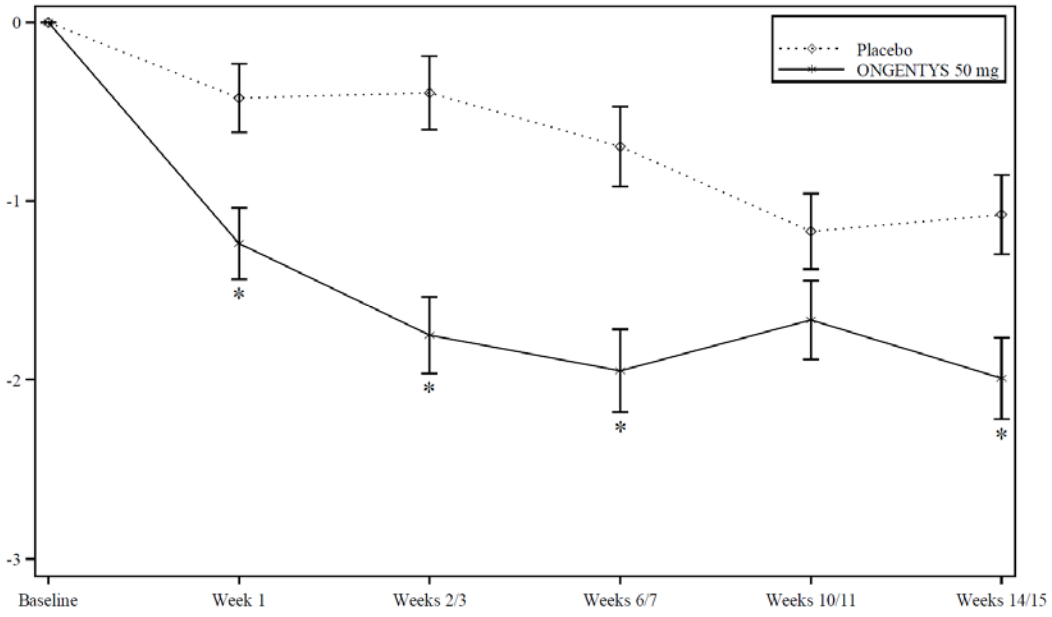
Parameter	Placebo	OPC 5 mg (N=119)	OPC 25 mg	OPC 50 mg (N=115)
Summary Statistics				
Mean (SD)	35.0 (165.7)	82.3 (174.5)	88.8 (170.0)	100.5 (134.3)
Median (Min/Max)	40.0 (-440/510)	70.0 (-470/460)	75.0 (-495/670)	100.0 (-400/425)
ANCOVA (Difference with Placebo)				
LS Mean	-	39.4	41.8	65.1
95% CI	-	(1.1, 77.6)	(3.3, 80.4)	(26.4, 103.7)
p-value	-	0.0437	0.0336	0.0010

ANCOVA=analysis of covariance; CI=confidence interval; LOCF=last post-baseline observation carried forward; LS=least squares; Max=maximum; OPC=opicapone. Note: Results are based on ANCOVA with treatment and region as factors and baseline ON-time without troublesome dyskinesia as a covariate. Source: FDA Statistical review.

Source: FDA Statistical Review

The time course of the change in OFF-time in Study 301 is displayed in Figure 1. A change favoring OPC 50 mg is present at Week 1 and continues throughout the double-blind phase of Study 301, with nominal significance at most timepoints.

Figure 1: Study 301- Absolute OFF-time Change from Baseline by Visit (Hours)



Placebo	120	117	114	112	110
Ongentys 50 mg	114	113	109	108	107

LS = Least Squares; SE = Standard Error; * = p value <0.05
Source: Applicant

Study 302

The design of Study 302 was identical to that of Study 301. Study 302 compared OPC 25 mg and OPC 50 mg to placebo, without an active comparator arm. The duration of the levodopa/DDCI adjustment and maintenance periods was the same as in Study 301. All eligible patients completing the double-blind phase of Study 302 were offered enrollment in a 52-week open-label extension.

Study Population

Patients were randomized at 69 centers in 12 countries, including South America, Europe, Russia, India, Australia, South Africa, Israel, and the United Kingdom. The FAS population (same as ITT) included 125 patients treated with OPC 25 mg, 147 treated with OPC 50 mg, and 135 treated with placebo. Overall, 12% of patients dropped out of the double-blind phase of the study. The highest number of dropouts was in the OPC 50-mg group (18%), compared with 9% in the OPC 25-mg group and 10% in the placebo group.

There were some minor differences in the baseline characteristics of patients enrolled in Study 302. On average, patients in the OPC 50-mg group were 4 years older than patients in the

placebo group. However, the average time from PD diagnosis was similar in all three treatment groups (8.5, 8.2 and 7.7 years in OPC 25 mg, OPC 50 mg and placebo group, respectively). The mean OFF-time at baseline ranged between 6.1 and 6.3 hours.

Efficacy Endpoints

The primary efficacy variable was the change in absolute OFF-time from baseline to the end of the double-blind period (endpoint) assessed using the Parkinson's Disease Diary. The primary analysis used an ANCOVA model with treatment group and pooled country as factors and baseline OFF-time as a covariate. Dunnett's alpha level adjustment was used for the comparison of each active dose group with placebo. As in Study 301, key secondary endpoints included the proportion of OFF-time responders and the proportion of ON-time responders.

Efficacy results

Dr. Park confirmed the sponsor's efficacy results showing that OPC 50 mg was statistically superior to placebo for the reduction from baseline to the end of the double-blind period in absolute OFF-time (primary endpoint), while the difference between OPC 25 mg and placebo did not reach statistical significance but trended in favor of OPC 25 mg (see Table 5).

Table 5. Change from Baseline to Endpoint in Absolute OFF-time (minutes) in Study 302

	Placebo N = 135	OPC 25 mg N = 125	OPC 50 mg N = 147
Summary Statistics			
Mean (SD)	-64.5 (155.35)	-102.8 (159.42)	-124.0 (178.23)
ANCOVA Analysis			
LS Mean (SE)	-64.46 (14.35)	-101.67 (14.86)	-118.77 (13.81)
Difference in LS Mean (SE) with Placebo		-37.21 (19.64)	-54.31 (18.86)
95% CI for Difference with Placebo		(-80.82, 6.40)	(-96.18, -12.44)
Adjusted P-value for pairwise comparison with Placebo		0.1061	0.0081

ANCOVA = analysis of covariance; CI = confidence interval; FAS = Full Analysis Set; LOCF = last post-baseline observation carried forward; LS = least square; OPC = opicapone; SD = standard deviation; SE = standard error.
Note: Statistical analysis is based on an ANCOVA model with treatment group and pooled country as factors and baseline OFF-time as a covariate. Dunnett's alpha level adjustment is used for the comparison of each active dose group with placebo.

Source: FDA Statistical Review

Dr. Park confirmed the result of three sensitivity analyses performed by the applicant (observed case data using a MMRM, a missing not at random model, and primary endpoint analysis using awake time at the last post-baseline visit as a covariate), which all supported the primary endpoint results.

The proportion of ON-time responders (OPC 50 mg=62% vs. placebo 45%; p=0.0061) and OFF-time responders (OPC 50 mg=66% vs. placebo=50%; p=0.0088) was nominally significantly greater for OPC 50 mg than for placebo (see Table 6).

Table 6. Proportion of OFF- and ON-time Responders in Study 302

	Placebo N = 135	OPC 25 mg N = 125	OPC 50 mg N = 147
OFF-time Responders			
n (%)	68 (50.4%)	78 (62.4%)	97 (66.0%)
Odds Ratio (95%CI)		1.68 (1.02, 2.76)	1.91 (1.17, 3.09)
P-value		0.0405	0.0088
ON-time Responders			
n (%)	61 (45.2%)	79 (63.2%)	91 (61.9%)
Odds Ratio (95%CI)		2.07 (1.26, 3.41)	1.97 (1.21, 3.20)
P-value		0.0040	0.0061

CI = confidence interval; FAS = Full Analysis Set; LOCF = last post-baseline observation carried forward; OPC = opicapone.

Source: FDA Statistical Review

The change from baseline to the end of the double-blind period in ON-time without troublesome dyskinesia was 37 minutes longer in the group treated with OPC 50 mg than for placebo (nominal p value 0.065) (see Table 7), with a similar result in the OPC 25 mg group .

Table 7. Change from Baseline to Endpoint in ON-Time Without Troublesome Dyskinesia (minutes) in Study 302

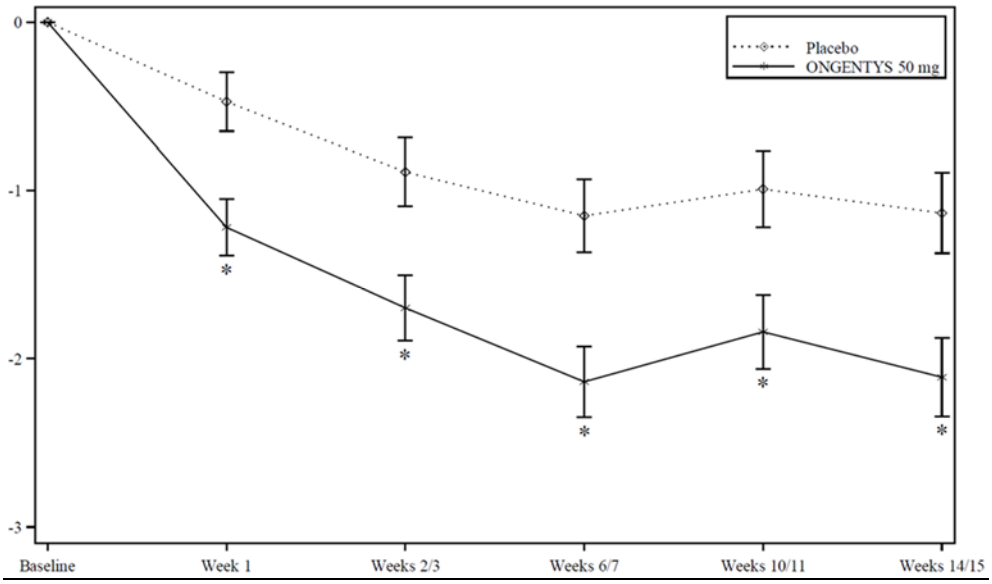
Parameter	Placebo (N=135)	OPC 25 mg (N=125)	OPC 50 mg (N=147)
Summary Statistics Mean (SD)	49.8 (164.8)	95.3 (177.1)	94.3 (187.7)
ANCOVA LS Mean (SE)	48.2 (15.4)	84.1 (15.9)	85.6 (14.8)
Difference in LS Mean with placebo (SE)	-	35.95 (21.13)	37.42 (20.23)
95% CI for difference with placebo	-	(-5.59, 77.48)	(-2.35, 77.20)
P-value for pairwise comparison with placebo	-	0.0897	0.0651

ANCOVA=analysis of covariance, CI=confidence interval, FAS=full analysis set, LOCF=last post-baseline observation carried forward, LS=lease square, OPC=opicapone, SD=standard deviation, SE=standard error

Source: FDA statistical review

The time course of the change in OFF-time in Study 302 is displayed in Figure 2. A change favoring OPC 50 mg is present at Week 1 and continues throughout the double-blind phase of Study 302, with nominal significance at all timepoints after Week 1.

Figure 2: Study 302- Absolute OFF-time Change from Baseline by Visit (Hours)



Placebo	135	133	129	124	122
Ongentys 50 mg	147	145	136	133	124

LS = Least Squares; SE = Standard Error; * = p value <0.05
Source: Applicant

Efficacy in subgroups

An analysis of efficacy by racial subgroups was not possible in Study 301, as 100% of the population was Caucasian. There was no meaningful difference in efficacy subgroups according to age (<65 vs ≥ 65 years), gender, or country.

In Study 302, a larger treatment effect was observed in males treated with OPC 50 mg (-76.3 minutes for males vs. -29 minutes for females). Otherwise, there were no meaningful differences in efficacy by racial, regional, or age-related subgroups.

Efficacy Conclusions

Study 301 and Study 302 both clearly met their primary endpoint for the 50-mg dosage of opicapone. Together, these two studies provide substantial evidence of effectiveness of opicapone 50 mg.

In Study 301, patients treated with opicapone 50 mg had, on average, a 1.01-hour greater reduction in OFF-time that patients on placebo (p=0.002). In Study 302, patients treated with opicapone 50 mg had, on average, a 0.91-hour greater reduction in OFF-time that patients on placebo (p=0.008). The opicapone effect on OFF-time was consistent throughout the double-blind study period. Various responder analyses and sensitivity analyses support the robustness of the findings.

Along with changes in OFF-time, it is critical to consider changes in ON-time without troublesome dyskinesia, which is the desired outcome in late PD patients (in contrast with ON-time with troublesome dyskinesia, which would be an unsatisfactory change in the patient functional status). The benefit to patients observed with opicapone 50 mg for ON-time without troublesome dyskinesia, statistically significant in one study and trending similarly, though nominally, in the other, represents, in conjunction with the reduction in OFF-time, a clinically important improvement in the motor status (and daily life) of the advanced PD patient.

Trends in favor of opicapone 25 mg were observed in Study 301 and 302, but the difference from placebo did not reach statistical significance, and the effect size was quite smaller than for opicapone 50 mg. Therefore, the recommended dosage of opicapone is 50 mg (and this dosage is acceptably safe, as discussed below).

7. Safety

Kenneth Bergmann, MD, was the primary clinical reviewer for this application.

Adequacy of the safety data

The safety analysis was conducted on data from the placebo-controlled and open-label portions of Study 301 and 302. The data integrity was acceptable. The coding of verbatim to MedDRA Preferred terms was acceptable, with minimal omissions or necessary corrections. The study reports and the Integrated Summary of Safety (ISS) were navigable, as were the related datasets.

Exposure

Long-term exposure came from patients enrolled in the open-label portion of Study 301 and 302. Long-term patient exposure exceeded the Division's recommendations for at least 100 patients treated continuously for one year, with at least half treated at the highest dose proposed for marketing. In the database, 396 patients were treated with OPC 50 mg for at least 180 days, and 133 for at least one year[1].

Disposition

Adverse events were the most common reason for withdrawal in all 3 treatment groups. In the OPC 50 mg group, 11% of patients withdrew because of an adverse event, compared with 4% in the OPC 25 mg group, and 6% in the placebo arm.

[1] 1-year defined by the applicant as 360 days. 108 patients were treated for 1-year defined as 365 days.

Adverse events

Deaths

Fifteen patients treated with opicapone died while taking part in Study 301 or 302, all in the open-label portion of the studies. Patients died from cardiovascular disease, cancer, infection and from injuries. Dr. Bergmann notes that the deaths did not appear to be related to study medication.

Nonfatal serious adverse events

Five percent of patients treated with OPC 50 mg experienced at least one serious adverse event (SAE) during the double-blind phase of Study 301 and 302, compared to 4% of patients on placebo. No SAE term was reported in more than one patient treated with OPC 50 mg.

Adverse dropouts

Eight percent of patients treated with OPC 50 mg discontinued because of an adverse event during the double-blind phase of Study 301 and 302. Among patients treated with OPC 50 mg, dyskinesia was the most common adverse event leading to discontinuation (3%), contrasting with no discontinuation for dyskinesia on placebo. Two percent of patients treated with OPC 50 mg discontinued because of nausea/vomiting, compared with 0.4% on placebo.

All adverse events

Dyskinesia and constipation were the most common adverse events (see Table 8). Dr. Bergmann found a dose-response for dyskinesia, constipation, and blood creatine phosphokinase increase reported as adverse reactions.

Table 8. Adverse Reactions reported in ≥ 2% of Patients Treated with OPC 50 mg and With an Incidence Higher Than Placebo, in the Controlled Phase of Study 301 and 302.

Adverse Reactions	OPC 50mg/day (N=265) %	Placebo (N=257) %
Nervous system disorders		
Dyskinesia	20	6
Dizziness	3	1
Gastrointestinal disorders		
Constipation	6	2
Dry mouth	3	1
Psychiatric disorders		
Hallucination[1]	3	1
Insomnia	3	2
Investigations		
Blood creatine phosphokinase increased	5	2
Weight decreased	4	0
Vascular disorders		
Hypertension	3	2
Hypotension/Syncope[2]	5	2

1 Includes: Hallucinations, Hallucinations visual, Hallucinations auditory, Hallucinations mixed
2 Includes: Hypotension, Orthostatic hypotension, Syncope, Presyncope
Source: CDTL

Vital signs and Electrocardiograms (ECG)

Few patients treated with OPC had an abnormal ECG finding. In the group treated with OPC 50 mg, 5.1% had an QTcF of > 480 msec, vs. 2.1% on placebo. The applicant conducted a thorough QT study, which did not show a meaningful QTc prolongation.

Dr. Bergmann's review of vital signs and ECG information for the double-blind and open-label studies did not identify any safety concerns.

Clinical laboratory

There were no meaningful changes in hematology parameters in the double-blind portion of Study 301 or 302. No patient in the OPC 50 mg group had elevated total bilirubin ≥2 X the ULN or higher, and no patient met Hy's Law criteria. Creatine kinase (CK) was elevated to ≥3 X ULN in 5.4 % of patients treated with OPC 50 mg, compared with 1.7% on placebo. Two patients treated with OPC (one with OPC 25 mg and one with OPC 50 mg) discontinued study participation because of CK elevation. There is insufficient information to determine whether OPC played a role in CK elevation in these patients.
Review of the open-label clinical laboratory information did not raise new safety concerns.

Safety in subgroups

In the pooled double-blind placebo-controlled trials, dyskinesia, constipation, urinary tract infection, headache, and dry mouth were more common in females and in patients 65 years of

age or older treated with OPC 50 mg. Elevated creatine kinase (CK) was observed more frequently in Asians than in Whites (9% vs. 4%), but the small number of Asian patients in the studies limits the interpretability of that observation.

Adverse reactions of special interest

In the placebo-controlled phase of Study 301 and 302, 2% of patients treated with OPC 50 mg developed an impulse control disorder (ICD) vs. no patient on placebo. All patients entering the open-label portion of both studies started on OPC 25 mg daily and increased to 50 mg daily if tolerated. Two percent of patients developed an impulse control disorder while treated open-label with OPC 25 mg daily, but only one patient treated with OPC 50 mg had an ICD-related event.

Dyskinesia was the most common adverse event of special interest (AESI) in the OPC 50 mg group (20%, vs. 6% on placebo). The incidence of sleep attacks and somnolence was not greater in patients treated with opicapone than on placebo. Melanoma was not reported in any patient treated with OPC in placebo-controlled studies. The incidence of falls and injuries was not greater in patients treated with opicapone than on placebo. Suicidality assessments did not show an increase from baseline in any group. The incidence of diarrhea was below 2% in all treatment groups.

The labeling for all dopaminergic products, including levodopa-containing products, includes a warning for somnolence. The risk for somnolence in patients taking OPC is difficult to determine in light of the concomitant use of levodopa and other dopaminergic medications. Although the incidence of somnolence was the same in patients treated with OPC 50 mg and in patients on placebo (1.9%), an increased risk cannot be ruled out, and class language for somnolence will be included in OPC labeling.

There were no reports of myocardial infarction or myocardial ischemia in patients treated with OPC in the controlled portion of Study 301 and 302. One patient experienced a myocardial infarction in the open-label portion of the studies, and 5 (0.6%) experienced myocardial ischemia. Four patients (0.1%) experienced a serious adverse related to cardiovascular disease during the open-label portion of Study 301 or 302. These rates are compatible with background risk in that population.

Prostate cancer was reported in one patient in the open-label portion of Study 302. No case of prostate cancer was reported in the double-blind portion of Studies 301 or 302. This rate is compatible with background risk in that population.

Open-label safety

Serious adverse events, including fatalities and those leading to early discontinuation, were discussed earlier in this review. No new safety concern was identified during open-label exposure.

Postmarketing safety information

Dr. Bergmann's review of (ex-US) postmarketing information did not identify any new safety concern.

Safety conclusions:

Overall, the safety profile of OPC is consistent with its mechanism of action, with adverse reactions mostly mediated by increased exposure to levodopa and dopamine. The safety profile is similar to that of approved COMT inhibitors (i.e., entacapone and tolcapone), but with fewer reports of diarrhea or colitis than with entacapone, and no identified significant hepatic toxicity, in contrast with tolcapone.

8. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because because this drug is not the first in its class, the safety profile is similar to that of other drugs approved for this indication, the clinical trial designs are acceptable, the efficacy findings are clear, and the safety profile is acceptable in light of the serious nature of the disease being treated.

9. Pediatrics

The NDA included an approved Initial Pediatric Study Plan that included a request for a drug specific waiver for all pediatric age groups. The Pediatric Research Committee (PeRC) agreed with granting a full waiver of studies in pediatric patients because studies are impossible or highly impracticable.

10. Other Relevant Regulatory Issues

Financial disclosures

The applicant met the requirements for obtaining financial disclosure information and demonstrated due diligence in attempts obtain the information.

Ethics and Good Clinical Practice (GCP)

The applicant attested to obtaining signed informed consent before all study-related procedures from all subjects in the covered studies. The informed consent and all appropriate study-related documents were reviewed and approved by an independent ethics committee (IEC)/institutional review board (IRB). The study conduct conformed with the principles of the Declaration of Helsinki and good clinical practice (GCP), as required by the International Conference on Harmonization.

Office of Scientific Investigations (OSI) audits

In Study 301, the applicant's site audit did not reveal protocol deviations that were likely to introduce bias, and no violations of GCP were found at any site. In Study 302, the applicant closed a single site because of concerns over data integrity. The Office of Scientific Investigations (OSI) conducted inspections in four high enrolling sites that participated in the controlled and open-label portions of both studies (two for Study 301 and two for Study 302). The official recommendation was "no action is indicated" (NAI) for all four inspections.

Controlled Substance Staff (CSS)

Alicja Lerner, M.D., Ph.D., is the primary clinical reviewer and Jovita Randall-Thompson, Ph.D., is the CSS Pharmacology reviewer. Dominic Chiapperino, Ph.D., Director, and Chad Reissig, Ph.D., provided supervisory concurrence.

OPC is not structurally related to substances of abuse. In vitro studies did not show significant binding of OPC to receptors associated with abuse related effects. The applicant did not conduct nonclinical studies to specifically assess abuse potential in animals.

CSS's review of the applicant's 8-factor analysis of abuse-related adverse events focused on analyses of psychiatric adverse events. In the placebo-controlled studies, there was a minor increase in hallucinations compared with placebo. Hallucinations are known to occur in patients with advanced PD. OPC and other medications that increase central nervous system dopamine increase the risk for hallucinations.

One patient in the placebo-controlled Phase 3 OPC studies was reported to have dopamine dysregulation syndrome (DDS). DDS is a rare complication usually seen in young-onset PD patients who take more levodopa than is needed to control motor function. The CSS reviewer recommends adding a Warning for DDS "similar to other dopamine enhancing drugs approved to treat PD." However, DDS is not described in any other dopaminergic product label. The Division and the Office of Safety and Epidemiology have reviewed DDS on more than one occasion and concluded there was insufficient information to add language about DDS to dopaminergic drug labels.

The CSS reviewer's assessment of gaps in returned medications is not adequate to infer patients were over-using OPC or had DDS. The paucity of information about DDS in this NDA is not sufficient to draw conclusions about the risk for DDS or to provide recommendations for labeling.

The CSS reviewer also recommended tapering OPC before discontinuing it. The review cites adverse event information from patients who discontinued open-label OPC after at least 4 weeks of treatment. Levodopa and most PD medications have an effective period of a few hours. After the effective period, the symptoms of PD return; this is a well described phenomenon called wearing off. The return of PD symptoms after discontinuing treatment is expected. If the symptoms of PD are masked for a prolonged period (e.g., 6 to 12 months) by symptomatic medications, PD will progress during that period and when unmasked, the

symptoms of PD may appear worse than they did previously. That worsening should not be mistaken for rebound or withdrawal from treatment.

CSS did not recommend scheduling for OPC and Section 9, Drug Abuse and Dependence, is not required in labeling.

Labeling for DDS, rebound, or withdrawal is not warranted at this time for the reasons stated above. The Division concurs with CSS that scheduling, and Section 9 of the label are not needed.

Pediatrics

The Pediatric Research Equity Act (PREA) is triggered for opicapone because it is a new ingredient. The Pediatric Research Committee (PeRC) concurred with the applicant's request for a full waiver from study requirement under PREA because studies in the pediatric population are highly impracticable.

11. Labeling

Proprietary name review

The proprietary name Ongentys is acceptable to the Office of Prescription Drug Promotion (OPDP) and by the Division of Medication Error Prevention and Analysis.

Carton and container labels

Chad Morris, PharmD, MPH, is the safety evaluator, and Briana Rider, PharmD, CPPS, is the Team Leader in the Division of Medication Error Prevention and Analysis (DMEPA) who provided comments about the proposed carton and container labels. DMEPA's comments were forwarded to the applicant and the applicant's revisions were adequate.

Prescribing Information

Dhara Shah, Pharm.D., and Aline Moukhtara, MPH, Team Leader in the Office of Prescription Drug Promotion (OPDP), completed the review of the Package Insert, the Patient Package Insert, and the carton and container labels.

Kelly Jackson, Pharm.D., Dhara Shah, Pharm.D.., Marcia Williams, Ph.D., Team Leader, Patient Labeling, and LaShawn Griffiths, MSHS-PH, BSN, RN, Associate Director for Patient Labeling, completed the Patient Labeling review of the patient pack.

See the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

12. Postmarketing Recommendations

Lindsey W. Crist, Pharm.D., BCPS, Primary Reviewer, Donella Fitzgerald, Pharm.D., Team Leader, and Jamie Wilkins, Pharm.D., Deputy Director of the Division of Risk Management (DRM), Office of Medication Error Prevention and Risk Management (OMEPRM), agree that a REMS is not necessary to ensure the benefits of opicapone outweigh its risks. The risks associated with opicapone can be communicated through labeling.

There are no recommendations for postmarketing commitments or requirements to further assess safety, and no recommendations for enhanced pharmacovigilance during the initial postmarketing period.

13. Recommended Comments to the Applicant

None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GERALD D PODSKALNY
04/24/2020 04:27:33 PM

ERIC P BASTINGS
04/24/2020 04:28:53 PM

WILLIAM H Dunn
04/24/2020 04:30:19 PM