CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505 (b)(1)
Application Number	212489
Priority or Standard	Standard
Submit Date	2019 April 26
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Division/Office	DN I, ON, OND
Reviewer Name	Kenneth Bergmann, MD
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Established/Proper Name	Opicapone
(Proposed) Trade Name	Ongentys™
Applicant	Neurocrine Biosciences, Inc
Dosage Form	Capsules: 25 and 50 mg
Applicant Proposed Dosing Regimen	50 mg taken orally, once daily at bedtime
Applicant Proposed Indication(s)/Population	Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "OFF" episodes.
Recommendation on Regulatory Action	Approvable
Recommended Indication/Population	Adults with Parkinson's disease and motor fluctuations in response to levodopa treatment.

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Glossary

AC	advisory committee
AE	adverse event
ADR	adverse drug reaction
ANCOVA	analysis of covariance
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COMT	catechol-O-methyltransferase
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DB	double-blinded period
DDCI	DOPA decarboxylase inhibitor
DMC	data monitoring committee
DNP	Division of Neurological Products
DNI	Division of Neurology I
ECG	electrocardiogram
eCTD	electronic common technical document
ENT	entacapone
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization

IMP	investigational medicinal product
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LOCF	last observation carried forward
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMRM	mixed model for repeated measures
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OLEX	open-label extension period
OPC	opicapone
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBO	Placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Parkinson's disease
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	system organ class
TEAE	treatment emergent adverse event
WOTD	without troublesome dyskinesia

1. Executive Summary

1.1. Product Introduction

Opicapone, with the proposed proprietary name of Ongentys™, is a peripheral catechol-O-methyltransferase (COMT) inhibitor. Its proposed indication is for use as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes.

Opicapone is a new molecular entity and has had marketing authorization for this same indication in the EU since June 2016.

The recommended dose of opicapone is 50 mg administered orally once daily at bedtime. Patients should not eat food for 1 hour before and for at least 1 hour after ingestion. Opicapone comes as a 50 mg capsule but is also available as a 25 mg capsule, for the purpose of titration upon initiation of treatment if needed but also for a reduced dosage in the case of severe renal impairment or moderate hepatic impairment.

1.2. Conclusions on the Substantial Evidence of Effectiveness

By submitting two positive adequate and well-controlled clinical trials in support of the proposed indication, the Applicant has provided the substantial evidence of effectiveness required by law to support approval.

Individually and in combination, both Phase 3 studies demonstrate a statistically valid reduction of OFF-time in PD patients treated with opicapone 50 mg once daily when compared to placebo treated patients. Importantly, this reduction in OFF-time was not associated with any significant increase in troublesome dyskinesia. It is evident that the benefit of increased ON-time with good function (i.e., without disabling dyskinesia), represents a clinically important improvement in the motor status (and daily life) of the advanced PD patient.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Opicapone is a COMT inhibitor designed to increase the availability of levodopa to the nervous system in patients with Parkinson's disease (PD). Because PD patients have times when their medication effect wears off, this action would reduce the amount of time when this decline takes place, thereby reducing the patients' OFF-time. Following assessment of the clinical data, Ongentys (opicapone) is found to be approvable as a safe and effective treatment indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes.

Parkinson's disease is a progressive degenerative disorder of the nervous system that affects one in 100 people above age 60. Its pathophysiologic basis is the loss of striatal dopaminergic cells via the toxic effects of abnormal aggregation of the alpha synuclein protein in these neurons. The neurotransmitter, dopamine, is replaced via the oral administration of levodopa, the mainstay of PD pharmacotherapy for the last half century. While levodopa provides good relief of motor symptoms, the benefit from levodopa changes as the illness progresses. Most PD patients will eventually develop the "on-off syndrome." The pharmacodynamic effect of levodopa becomes shorter in duration and the nervous system develops a dyskinetic motor response that, while leaving the patient mobile, may itself become disabling.

There are multiple pharmacological strategies using approved medications designed to increase the level of dopaminergic tone in the central nervous system. One method of doing so is to administer levodopa with medications that block its metabolism before it gets across the blood-brain barrier. Levodopa is most commonly prescribed in a combination product with carbidopa, a blocker of the most common peripheral path of levodopa degradation which uses the enzyme DOPA decarboxylase. The other major catabolic pathway is via metabolism by catechol-O-methyltransferase (COMT). This is the molecular target for pharmacological inhibition by Ongentys.

The sponsor has submitted two adequate and well-controlled clinical trials demonstrating substantial evidence of effectiveness in support of this indication. Studies 301 and 302 have core features in common that evaluate opicapone to ameliorate the amount of OFF-time in PD patients. Using an established patient-reported outcome employing patient-completed PD diaries, these studies compared opicapone 50 mg/d to placebo in double-blind and randomized fashion, investigating its ability to reduce the absolute OFF-time (average of the daily sum of OFF-time on the 3 days prior to visit) when evaluated at the end of the double-blind period (14 to 15 weeks following randomization). Secondary outcome measures supported this primary efficacy measure: responder analyses of the percent of those patients who reduced OFF-time by at least 1 hour and the percent of those patients who increased ON--time by at least 1 hour. Furthermore, the increase in ON-time had to come without the liability of increasing levodopa induced dyskinesia, a disabling phenomenon which may accompany increased dopaminergic tone from medication changes in advanced PD patients. Using appropriate methods of statistical analysis, both studies succeeded in this regard.

In both Phase 3 studies there is a statistically valid reduction of OFF-time in opicapone 50 mg/d treated patients, reducing the daily duration of a lack of beneficial medication effect for the PD patient as self-reported by diary. In Study 301, the opicapone 50 mg/d treated group reduced OFF time by an average of 107 minutes while, in Study 302, the opicapone treated group reduced their average OFF time by 124 minutes. This compares favorably to reductions in OFF time in the placebo treated groups of 45 and 65 minutes, respectively. Overall, about 2/3 of opicapone-treated patients had an hour or more of reduction in OFF-time.

More importantly, this reduction in OFF-time was not associated with troublesome dyskinesia. In Study 301, ON time without troublesome dyskinesia increased an average of 101 minutes in the opicapone 50 mg/d-treated arm compared to 35 minutes in the placebo arm. Likewise, in Study 302, ON time without troublesome dyskinesia increased by 45 minutes in the opicapone 50 mg/d-treated arm compared to 0.4 minutes in the placebo arm. Neither study revealed an important contribution to efficacy by subgroup analyses of age, gender, race, and disease characteristics.

On face, it is evident that the possibility of a benefit of this magnitude of increased ON-time with good function (i.e., without disabling dyskinesia), represents a clinically important improvement in the motor status (and daily life) of the advanced PD patient.

Ongentys would be the third approved COMT inhibitor in its pharmacological class after tolcapone and entacapone. 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 Ongentys. No new, novel, or unexpected adverse events were seen. The class of COMT inhibitors are associated with an elevation of CPK in some patients, however Ongentys does not appear to have the more specific adverse drug reactions associated with tolcapone (liver damage) or entacapone (colitis). The favorable safety profile is enhanced through the experience of its use in the European Union where this drug has had marketing authorization for 3 years.

The improvement of the functioning of PD patients by enhancing the action of their drug treatment regimens remains a pressing need for this patient population. Peripheral COMT inhibition is an established mechanism of drug action that assists in achieving this aim. Ongentys (opicapone) has been studied in adequate and well controlled trials that have established its efficacy in significantly reducing OFF-time. Its favorable safety profile and convenient once daily dosing compares favorably with currently available products of the same class. Ongentys will be a useful addition to the Parkinson's disease drug armamentarium and it is recommended that it be approved for the sought-after indication. Labelling will adequately describe its method of use, benefits, and risk, and at this time there is no need for further risk mitigation strategies.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Parkinson's disease is a well-characterized progressive degenerative disorder of the nervous system that affects one in 100 people above age 60. • Its pathophysiologic basis is the loss of striatal dopaminergic cells via the toxic effects of abnormal aggregation of the alpha synuclein protein in these neurons. • 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. • The neurotransmitter, dopamine, is replaced via the oral administration of levodopa, the mainstay of PD pharmacotherapy for the last half century. While levodopa provides good relief of motor symptoms, the benefit from levodopa changes as the illness progresses. • Most PD patients will eventually develop the "on-off syndrome." The pharmacodynamic effect of levodopa becomes shorter in duration and the abnormal nervous system develops a dyskinetic motor response that, while leaving the patient mobile, may itself become disabling. • Decreased motor ability results in the loss of quality of life, and when severe, can adversely affect the lifespan.	Parkinson's disease is a common, 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. This results in significant disability and loss of life quality.
Current Treatment Options	• When focusing upon the specific goal of increasing the duration of anti-parkinson therapeutic effect each day, treatments focus on extending the action of levodopa itself, which suffers from poor absorption in the gut, poor transport into the brain, short duration of	Current pharmacological treatment for PD aims at restoring levels of the neurotransmitter, dopamine, in the brain. Levodopa, an oral precursor to dopamine is

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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 (addition of a DOPA decarboxylase inhibitor and a COMT inhibitor), artificially stimulating dopamine receptors in the brain (dopamine agonists), constant delivery of levodopa by parenteral administration of a gel formulation, and other classes of adjunctive medications such as anticholinergic agents and amantadine. • 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. • 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.	administered with carbidopa which inhibits its catabolism before it gets into the nervous system. There are different classes of dopaminergic drugs which can prolonged the action of levodopa or artificially stimulate dopaminergic receptors in the brain. COMT inhibition outside the nervous system is another mechanism by which the amount of levodopa reaching the brain may be increased by blocking another peripheral pathway that degrades orally administered levodopa before it can act.
Benefit	• The sponsor has submitted two adequate and well-controlled clinical trials demonstrating substantial evidence of effectiveness in support of this indication. • Studies 301 and 302 have core features in common that evaluate opicapone to ameliorate the amount of OFF-time in PD patients. Using an established patient-reported outcome employing patient-completed PD diaries, these studies compared opicapone 50 mg/d to placebo in double-blind and randomized fashion. • The primary outcome is the ability to reduce the absolute OFF-time (average of the daily sum of OFF-time on the 3 days prior to visit) when evaluated at the end of the double-blind period (14 to 15 weeks	Ongentys was investigated in two studies of advanced PD patients who averaged over 6 hours of OFF time daily, the duration of a loss of beneficial medication effect as self-reported by diary. The patients who received 50 mg once daily were evaluated after 14 to 15 weeks of treatment. Both Phase 3 studies demonstrated a statistically significant reduction of OFF-time in opicapone treated patients. In Study 301

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	following randomization). • The secondary outcome measures in support of this primary efficacy measure are responder analyses: the percent of those patients who reduced OFF-time by at least 1 hour and the percent of those patients who increased ON--time by at least 1 hour. • Furthermore, the increase in ON-time had to come without the liability of increasing levodopa induced dyskinesia, a disabling phenomenon which may accompany increased dopaminergic tone from medication changes in advanced PD patients. • Using appropriate methods of statistical analysis, both studies succeeded in this regard. In Study 301, the opicapone 50 mg/d treated group reduced OFF time by an average of 107 minutes while, in Study 302, the opicapone treated group reduced their average OFF time by 124 minutes. This compares favorably to reductions in OFF time in the placebo treated groups of 45 and 65 minutes, respectively. • About 2/3 of opicapone-treated patients had an hour or more of reduction in OFF-time. • More importantly, this reduction in OFF-time was not associated with troublesome dyskinesia; In Study 301, ON time without troublesome dyskinesia increased an average of 101 minutes in the opicapone 50 mg/d-treated arm compared to 35 minutes in the placebo arm. Likewise, in Study 302, ON time without troublesome dyskinesia increased by 45 minutes in the opicapone 50 mg/d-treated arm compared to 0.4 minutes in the placebo arm. • On face, it is evident that the possibility of a benefit of this magnitude of increased ON-time with good function (i.e., without disabling dyskinesia), represents a clinically important improvement in the	patients treated with opicapone had, on average, 62 minutes less OFF time than the placebo treated patients, while in Study 302, opicapone treated patients had an average of 59 minutes less OFF time than the placebo group. Overall, about 2/3 of opicapone-treated patients had an hour or more reduction in OFF-time. More importantly, this reduction in OFF-time was not associated with the development of troublesome dyskinesia which may be seen when dopaminergic treatment is increased. Patients in Study 301 had, on average, 66 minutes more ON time without troublesome dyskinesia than placebo-treated patients while in Study 302, opicapone-treated patients had an average of 45 minutes more ON time without troublesome dyskinesia than the placebo arm. On face, it is evident that the possibility of a benefit of this magnitude of increased ON-time with good function (i.e., without disabling dyskinesia), represents a clinically important improvement in the motor status and daily functioning of the advanced PD patient.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	motor status (and daily life) of the advanced PD patient.	
Risk and Risk Management	• Because of a large development program and 3 years' experience after marketing authorization in the EU, a good deal is known about the clinical safety profile of opicapone. • 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. • The intended treatment dose is 50 mg once a day and 263 PD patients took this does for more than 6 but less than 12 months; 133 patients took this dose for a year or more. • The observed incidence and pattern of adverse drug reactions is consistent with a medication whose mechanism of action is to increase the amount of levodopa absorbed from a given dose administered to a patient with advanced PD and motor fluctuations. • These are dyskinesia, constipation, dry mouth, psychiatric and sleep disturbances, and orthostatic hypotension. A reversible elevation of creatine phosphokinase (CPK), a muscle enzyme, has been noted and this may be related to the class of COMT inhibitors. • In general, this is a well-tolerated drug and no deaths related to opicapone occurred in the development program. • Serious adverse events in the development program were mostly either unrelated or a consequence of interaction the underlying disease process and its treatment. • The safety profile of opicapone is consistent with its mechanism of	Ongentys would be the third approved COMT inhibitor in its pharmacological class after tolcapone and entacapone. 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 Ongentys. No new novel or unexpected adverse events were seen. The class of COMT inhibitors are associated with an elevation of CPK in some patients, however Ongentys does not appear to have the more specific adverse drug reactions associated with tolcapone (liver damage) or entacapone (colitis). The favorable safety profile is enhanced through the experience of its use in the European Union where this drug has had

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	action and it appears to lack the potential for hepatocellular injury or colitis that other members of this pharmacological class display. • It is possible to fully describe the adverse event profile in labelling and no postmarket mitigation strategies appear necessary at this time.	marketing authorization for 3 years.

1.4. Patient Experience Data

The primary efficacy outcome measure used in opicapone pivotal trials was the change from baseline in absolute OFF-time at the end of the double blind treatment period. The key secondary endpoints are OFF-time responders (1 hour or more reduction in absolute OFF-time from baseline to endpoint) and ON-time responders (1 hour or more increase in absolute ON-time from baseline to endpoint).

These outcomes are dependent upon the accurate reporting of the motor state at 30 minute intervals by the patient during waking hours using an accepted patient self-rating diary (Houser diary). Both site investigators and participants and caregivers were provided with training in order to perform this correctly.

The UPDRS Part II is a self-evaluation of the activities of daily life (ADLs) including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food. This secondary endpoint was analyzed outside of a pre-defined statistical hierarchy.

Table 1 Patient experience data relevant to this application

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		Sections 6.1.1 and 6.2.1, study endpoints
		X	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	X	Patient-focused drug development or other stakeholder meeting summary reports		Section 2.1 Analysis of Condition
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			

		□	Input informed from participation in meetings with patient stakeholders	
		X	Patient-focused drug development or other stakeholder meeting summary reports	Therapeutic Context, Current Treatment Options
		□	Observational survey studies designed to capture patient experience data	
		X	Other: (Please specify)	Reviewer's clinical experience
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Parkinson's disease (PD) is a chronic progressive degenerative disorder of the central nervous system, with slowly progressive degeneration of the nigrostriatal dopamine system. The predominant motor symptoms are tremor, increased muscle tone and bradykinesia, but non-motor symptoms also cause considerable disability. The underlying pathophysiology of the motor symptoms is a deficiency of dopamine in neuronal terminals in the striatum.

The estimated incidence of PD is 4.5 to 16 per 100.000 persons/year. The prevalence of PD is between 175 to 350 / 100,000 population in the US. Parkinson's disease is associated with eventual disability or death. Untreated PD had a mortality rate of 80 % within 10 years of diagnosis, but even successfully treated PD patients without dementia still experience a shortened life span.

Parkinson's disease as a clinical syndrome is likely the final clinical result of a variety of brain pathologies, some acquired and some with a genetic contribution. PD has been described in every population, race and ethnic group and in both sexes.

The diagnosis is made clinically, using established criteria derived from the presence of the major motor symptoms of the disease: bradykinesia, rigidity and tremor. More recently, imaging studies with ligands that demonstrate dopaminergic function in the striatum have been a technology used to help support the clinical diagnosis.

Non-motor symptoms generally occur during the illness and can antedate the development of the motor signs. These are often more troublesome than the motor symptoms for which a range of pharmacological and surgical treatments exist.

A public FDA patient-focused drug development meeting (in which this reviewer participated)

was held on September 22, 2015.[1] The meeting assembled the perspectives of patients, caretakers and other patient representatives on the most significant effects of their disease, its impact on daily life, and their experiences with currently available therapies. The key themes the report of the meeting emphasized included symptoms and their management.

- Parkinson's disease is a progressive, devastating disease. Participants emphasized the difficulty of living with the unexpected onset and progression of symptoms. Many described living with daily motor symptoms which included bradykinesia, dyskinesia, tremor and dystonia. In addition to motor symptoms, participants also highlighted sleep disturbances, cognitive impairment, fatigue, and constipation.
- The meeting reiterated the complexity of Parkinson's disease management. Participants described the burden of selecting the best available treatments to address their symptoms, the complexity of managing proper timing of medications in addition to pill burden (number and frequency of pills taken throughout the day), and the need for adjustment of their medication regimen because of unpredictable symptoms, changes in daily demands leading to increases in symptoms, as well as disease progression.

Among the motor symptoms, the bradykinesia of PD and the dyskinesia resulting from its treatment were rated most problematic. Freezing of gait was also disturbing. Motoric fluctuations are often eclipsed by more troublesome symptoms for which there are few or no treatment options: freezing, imbalance, cognitive impairment, sleep disturbance, orthostatic hypotension, and depression. However, the periodic loss of medication effect on mobility remains problematic for many patients.

- Participants expressed frustration with periods of "off-time," which was described as unpredictable exacerbation of symptoms during which medications were less effective. A few described the daily unpredictability that off-time brought into their lives. One participant shared, "[symptoms] can vary not only from day to day, but from hour to hour." This comment resonated with many participants. One participant stated, "the various off-and-on states, is what makes this disease so hard to live with." Another participant described experiencing "several months of good on-time, and then off-time where I can't even stabilize myself with a walker."

Several perspectives were provided on ideal treatments for Parkinson's disease. The top three aspects of ideal treatment desired by commenters included *medications with less "off" time, better symptom control, and fewer side effects* [emphasis added].

2.2. Analysis of Current Treatment Options

Levodopa (L-dihydroxyphenylalanine or L-dopa) is a dopamine precursor which is

[1] https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM498266.pdf

decarboxylated in the brain to become dopamine. It is combined with carbidopa, a dopa-decarboxylase (DDC) inhibitor, so that this conversion takes place mostly within the central nervous system. This remains an effective symptomatic therapy of PD motor symptoms four decades following its introduction. However, with each passing year of levodopa treatment, more fluctuations in motor control occur. These often become disabling. Motor complications involve fluctuations, erratic or unstable responses to medications (e.g. wearing-off phenomena) and dyskinesia or involuntary movements.

Current scientific concepts suggest that the waning of the therapeutic effect of levodopa at intervals ("off" states) during the day is closely related to waning levels of levodopa in the blood and dopamine in the brain (related to the short plasma half-life levodopa). Treatments have been developed to extend the action of levodopa. These include extended release formulations and drugs that reduce the catabolism of levodopa peripherally before it gets to the brain (catechol-o-methyl transferase inhibitors) as well as after it has been converted to dopamine in the central nervous system (monoamine oxidase B inhibitors). Artificial dopamine receptor agonists have also been developed to directly act upon the central dopamine receptors. These have served to generally extend dopaminergic tone in the CNS from dose to dose and often allow for some reduction of levodopa dose which may result in lessened dyskinesia. Some agents that affect other neurotransmitter systems are also used, particularly for tremor reduction (anticholinergics) or reduction of dyskinesia (amantadine). Finally, apomorphine, an injectable non-selective dopamine agonist is approved in the US for episodic use in treating "off" states that occur as drug effects wear off. Beginning with the approval of levodopa (NDA 16912) in 1970, there are now over two dozen drug products approved for PD based upon their effectiveness on alleviating the motor symptoms of the disorder.

Table 2 Types of currently available anti-parkinson medication

Dopamine precursor	levodopa		Catabolic inhibitors:	
			DOPA decarboxylase	carbidopa
Dopamine agonist	apomorphine			
	bromocriptine		COMT	entacapone
	pramipexole			tolcapone
	ropinirole			
			MAO-B	selegiline
Anticholinergic	amantadine			rasagiline
	trihexyphenidyl			
	benztropine		Antiglutamatergic	amantadine

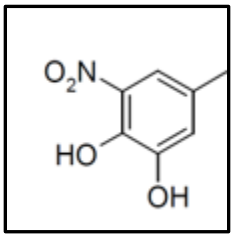
Direct electrical stimulation or ablative lesions of the basal ganglia outflow (thalamus, pallidum, or subthalamic nucleus) have also been effective in alleviating the motor symptoms of PD in a

selected group of patients. There are also other classes of drugs that assist in the treatment of non-motor symptoms of PD but those are not touched upon here.

Currently marketed COMT Inhibitors

There are two currently marketed COMT inhibitors in the US: entacapone (Comtan, NDA 20796) approved October 19, 1999 and tolcapone (Tasmar, NDA 20697) approved January 29, 1998. Opicapone, entacapone, and tolcapone are all nitrocatechol-structured compounds, each having a different side structure. While they all share a common adverse event profile consistent with their mechanism of action (e.g., dyskinesia, nausea and vomiting, diarrhea, orthostatic hypotension, anorexia, sleep disorder, somnolence, hallucination), the side structures unique to each product are likely responsible for their differing pharmacokinetic characteristics, but also compound-specific adverse event profiles.

Figure 1 Common nitrocatechol core of COMT inhibitors.



In its prescribing information, tolcapone carries a boxed warning due to hepatocellular injury and cases of fulminant liver failure. A program of periodic laboratory monitoring for hepatocellular injury is recommended with treatment cessation if the ALT (SGPT) or AST (SGOT) two times the ULN or if clinical symptoms of hepatic dysfunction develop. It is administered three times daily with levodopa dosing.

Entacapone is taken orally with each carbidopa/levodopa dose up to eight time daily. In clinical studies, diarrhea was noted, at times severe. Postmarketing experience has shown that the diarrhea may be a sign of drug-induced microscopic colitis, primarily lymphocytic in nature. In these cases, diarrhea has usually been moderate to severe, watery, and non-bloody, at times associated with dehydration, abdominal pain, weight loss, and hypokalemia. It remits with drug cessation but recurs with rechallenge.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Opicapone is a new molecular entity, but two other moieties that inhibit COMT are approved in

the US: tolcapone and entacapone. This drug is seeking approval for the same indication. Opicapone has been approved in the European Union since June 2016 under the name Ongentys. The clinical trials development program was performed exclusively outside the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

The following list represent the clinically-relevant regulatory interactions with the sponsor during the clinical development program.

2009 April 30
- Development International Birth Date

2011 June 27
- IND 104380 is allowed to proceed.

2016 June 24
- International Birth Date (EU Marketing Authorization)

2017 November 27
- Proprietary name request is provisionally accepted.

2018 January 18 – End of Phase 2 Meeting (minutes of February 18, 2018)
- It appeared that, on face, the Phase 3 pivotal studies demonstrated a statistically significant change in the primary endpoint for the target PD population. It was noted that adequacy of efficacy and safety information would be evaluated during review.
- As the clinical data proposed to support the NDA was of foreign origin, the Division affirmed the need for the Sponsor to demonstrate compliance with regulations found in 21 CFR 314.106 Foreign Data and 21 CFR 312.120 Foreign Clinical Studies Not Conducted Under an IND.
- The Division provided guidance on the number of subjects required to fulfill ICH E1A Extent of Population Exposure long-term safety database requirements (100 subjects treated continuously for at least a year with dosages of opicapone intended for clinical use with at least half of these having received the highest recommended dose of opicapone for the year).
- The sponsor was told to provide an analysis of the effect of amantadine (an anti-dyskinesia drug used by 20-25% of the pivotal study population) on the efficacy result.
- The Division also provided recommendations on the analyses required to support an abuse potential assessment.

2018 June 26 – Type C Meeting (written responses)
- The Division agreed with the proposed study data standardization plan and the proposed strategy for assessment of clinical laboratory and thresholds for vital signs changes of

potentially clinically significant thresholds.

2018 July 17

- Initial Pediatric Study Plan Agreement (full waiver for PD to be requested)

2018 September 6 – Type B Pre-NDA Meeting (preliminary responses)
Following review of the Division's preliminary responses, the sponsor did not feel the need to meet. Agreement on the following was communicated in the preliminary correspondence:

- The Summary of Clinical Efficacy (SCE) could serve as the narrative portion of the Integrated Summary of Efficacy (ISE), with supportive appendices and datasets located in Module 5.
- The Division requested the integrated Phase 3 double-blind (DB) period data and datasets be analyzed and presented separately from the open-label (OLEX) period within the SCE, ISE and Integrated Summary of Safety (ISS).
- The Division agreed with the proposed integrated data pooling and data presentation strategies for the SCE and ISS.
- The Division requested the following additional information for the ISS: supplemental summaries of subject exposure (by actual dose, by actual days on dose, by formulation), inclusion of diarrhea as an AESI, and coding of adverse event data using a single version of the Medical Dictionary for Regulatory Activities (MedDRA).

3.3. Foreign Regulatory Actions and Marketing History

The sponsor has submitted annual Development Safety Update Reports to the IND. The last DSUR (#7) covered the year ending April 30, 2018. Opicapone is authorized for marketing in 32 countries under the proprietary name Ongentys. However, opicapone was only being distributed in Germany, UK and Spain as of the date of the DSUR. At the end of that reporting period, (b) (4) capsules had been sold, representing 12,360 patient-years. The events that were reported to be adverse drug reactions for this reporting period were reviewed. There were no new, unusual or unexpected events when compared to the trial experience reviewed below. The important risks identified from postmarket reporting are dyskinesia and hallucinations.

No actions related to safety have been mandated by any regulatory agency or were undertaken by the sponsor.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

In preliminary review of this application, there were no specific efficacy or safety concerns raised by the submitted safety and efficacy data. The findings of the financial disclosures, sponsor's audits, and efforts to assure Good Clinical Practices were reviewed. Evaluating the data revealed no patterns that might indicate fraudulent activity or omission of important safety information. In collaboration with the Division of Good Clinical Compliance, Office of Scientific Investigations, four clinical sites were selected based on numbers of patients contributed to the pivotal studies. Of particular attention were the protection of human subjects, completeness and accuracy of the patient-completed PD diaries through which the efficacy outcome was determined, and adequacy of adverse event reporting especially regarding events leading to drug discontinuation.

Sites 3301 and 4201 (Study 301) and Sites 1904 and 2002 (Study 302) representing 59 patients in the Phase 3 safety population from Poland, Portugal, South Africa, and South Korea, respectively, were inspected. No objectionable conditions or practices were identified at any site and all received notice of no action indicated.

4.2. Product Quality

The applicant submitted adequate information for the assessment of chemistry, manufacturing, and controls (CMC), sterility, biopharmaceutics, and related facilities. Following review of the materials, the Office of Product Quality (OPQ) found an adequate basis to support a finding that the sponsor can consistently manufacture a product that is suitable for use by the intended patients. No special labeling recommendations were made.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

There were no toxicological findings that impacted the clinical assessment of opicapone, including carcinogenicity and reproductive toxicology studies.

4.5. Clinical Pharmacology

Mechanism of action:
Opicapone is a reversible inhibitor of peripheral catechol-O-methyl transferase (COMT). In the presence of a peripheral aromatic amino acid (DOPA) decarboxylase inhibitor (DDCI), COMT becomes the major peripheral metabolizing enzyme for levodopa, catalyzing its conversion to 3-O-methyl DOPA which can interfere with transport of levodopa across the blood brain barrier. In humans, opicapone inhibiting the COMT enzyme in peripheral tissues results in an increase in overall exposure to levodopa.

Pharmacokinetic characteristics:
A single oral dose of 50 mg (the intended dose for daily treatment) reached its C_{max} in about 2 hours. The PK of single doses is roughly dose proportional in the 25 to 50 mg dose range. Because absorption is reduced (lower AUC) and delayed (later T_{max}) opicapone should not be taken with food. Steady state is achieved in one day and there appears to be no accumulation after repeated once-a-day dosing.

Opicapone is highly bound to plasma proteins and is eliminated by metabolism via sulfate conjugation, glucuronidation, methylation, reduction and conjugation with glutathione. The elimination half-life is about 1 to 2 hours with most of the drug and its metabolites excreted fecally (70%). Approximately 20% of a dose is excreted unchanged. The exposure to a given dose appears to 15 to 20% higher in healthy Japanese volunteers compared to Caucasians, but no dose adjustment is recommended based upon demographic factors such as age, sex, race, and body weight.

Opicapone exposure is increased in patients with hepatic impairment. In moderate impairment the dose should be reduced to 25 mg/d and opicapone should be avoided in cases of sever hepatic impairment. No adjustment is needed for age. No dose adjustment is made for renal disease but it is not recommended for use in severe renal impairment.

At therapeutic exposures, based upon *in vitro* and *in vivo* studies, no specific recommendations concerning drug-drug interactions are made. However, PK studies of opicapone with chronic LD/DDCI treatment show that the exposure to levodopa is increased both in AUC and C_{max}. The prescribing information takes this observation into account, alerting the provider that the development of dyskinesia may necessitate reducing the patient's daily levodopa dosage or the dosage of another dopaminergic drug in order to mitigate dyskinesia. There are no other DDI of note with other drugs used to treat PD (dopamine agonists, MAO-B inhibitors, and amantadine).

Investigational to marketed product bridge:
The sponsor was required to perform a BA/BE study to bridge the formulation used in the Phase 3 clinical trials to the to-be-marketed medicinal product. This Phase I study, BIA-91067-119, was examined by the clinical pharmacology reviewer and found to be acceptable as the pivotal PK bridge between the investigational and marketed product. The Office of Study Integrity and Surveillance (OSIS) conducted a routine site inspection for the pivotal PK bridging study BIA-91067-119 for the bioanalytical and the clinical sites. While the bioanalytical site passed muster, the clinical site was faulted for not retaining samples of the test and reference products for confirmation. This likely was a result of lacking administrative oversight after the EU market authorization when the EU license holder, Bial, failed to consider the US regulatory needs of the US NDA applicant, Neurocrine. However, the clinical pharmacology review team considered the weight of available evidence and found the bridge to be acceptable. From the Office of Clinical Pharmacology review, page 44:

> "Considering the following facts: 1) The study protocol compliance was verified by the OSIS inspector, including the documentation of test and reference product administration. The only issue from the OSIS inspection is the non-availability of reserve sample for the test and reference products used in the study. , 2) A cross-study comparison using PK data from Phase 1 studies included in the NDA that used Phase 3 formulation and the registrational formulation suggests the results from study BIA-91067-119 as reliable, and 3) acceptance of the results from Study BIA- 91067-119 by EMA in 2016 to support marketing authorization for ONGENTYS in Europe, based on routine Biotrial site inspection and no specific inspection for this study, , the review team concluded that bridging results from Study BIA-91067-119 is acceptable."

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The opicapone clinical development program consists of 38 clinical studies: 34 Phase 1 studies, two Phase 2 studies, and two Phase 3 studies. Each of the two Phase 3 studies have a randomized, placebo controlled, double blind treatment period (DB) followed by an open label extension study (OLEX).

A tabular listing of all clinical studies is presented in Appendix 13.1. The table below constitutes the studies examined in detail in Sections 6 and 7 of this review for support of efficacy and safety.

Table 3 Phase 3 studies in support of efficacy and safety (source: sponsor, eCTD module 5.2)

Protocol No. Number of Centers	Study Periods	Treatment Duration	Treatment Dose, Route, Regimen	Diagnosis, Planned Number of Subjects	Study Objectives	Efficacy Endpoint
BIA-91067-301 106 sites (19 countries)	Randomized, placebo- and active-controlled, parallel-group, DB period	14-15 weeks	OPC 5 mg, OPC 25 mg or OPC 50 mg; oral; qd at bedtime PBO; oral; 3-8 daily daytime doses and/or a bedtime dose ENT 200 mg; oral; 3-8 daily daytime doses	Idiopathic PD and "wearing off" phenomenon 550 subjects (110 subjects per treatment group)	Efficacy, safety, and tolerability of OPC when administered with existing levodopa/DDCI treatment	CFB in absolute OFF-time at Visit 7 (end of DB period) based on subject PD diaries[a]
	OL period	52 weeks	OPC 5 mg, OPC 25 mg or OPC 50 mg; oral; qd[b]	Patients who completed the DB period	Safety, tolerability, and maintenance of therapeutic effect of OPC	Change in OFF-and ON-time at Visit 14 (end of OL period) relative to DB and OL baselines
BIA-91067-302 71 sites (12 countries)	Randomized, placebo-controlled, parallel-group, DB period	14-15 weeks	OPC 25 mg, OPC 50 mg, or PBO; oral; qd at bedtime	Idiopathic PD and "wearing off" phenomenon 405 subjects (135 per treatment group)	Efficacy, safety, and tolerability of OPC when administered with existing levodopa/DDCI treatment	CFB in absolute OFF-time at Visit 7 (end of DB period) based on subject PD diaries[a]
	OL period	52 weeks	OPC 25 mg or 50 mg; oral; qd at bedtime[b]	Patients who completed the DB period	Safety, tolerability, and maintenance of therapeutic effect of OPC	Change in OFF-and ON-time at Visit 14 (end of OL period) relative to DB and OL baselines

These two pivotal trials (hereinafter referred to as Study 301 and Study 302) were performed outside of the US. The sponsor has appended a Foreign Clinical Data Compliance Statement to both clinical study reports in compliance with 21 CFR 312.120.

The other studies listed in the appendix are reviewed for safety only. These include studies of drug-drug interaction (DDI) and a study of cardiac repolarization (Thorough QT Study) in healthy adults. The adequacy and results of the Thorough QT study and the DDI studies are reviewed by subject matter experts in these areas.

5.2. Review Strategy

The double blinded periods (DB) of Studies 301 and 302 provide the evidence for effectiveness. These are reviewed in depth in Section 6 and reference is made to the evaluation of the primary outcomes and related analyses by the biostatistics reviewer. These studies also provide the highest quality evidence of overall safety in the development program. The open label extension (OLEX) portions of these studies provide the bulk of the longer-term safety data in support of clinical use.

The timeframe in which the pivotal studies were performed permitted the sponsor to submit legacy datasets which approximate the domains used in SDTM and ADaM datasets. However,

the non-standard format and absence of metadata prevented the use of many analytic features of data standard-based FDA digital tools. As a result, this reviewer used the approach of employing datasets to manually confirm the sponsor's basic analyses such as demographics, use of concomitant medication, dropouts, adverse events and so forth. This laborious process made the creation of tables difficult. In some places in this review the sponsor's tables are used directly and in these cases the sponsor's numbers have been confirmed by the reviewer using the corresponding datasets.

The evaluation of Study BIA-91067-111, Thorough QT Study in healthy adults, relies heavily upon the opinion provided by our colleagues on the QT interdisciplinary review team (QT-IRT). Similarly, evaluation of the studies of drug-drug interaction, food effect, and bioavailability relies heavily upon the review provided by our clinical pharmacology colleagues.

Evaluation of safety by this reviewer will look at the entire clinical population in the development program to evaluate unexpected events, deaths, serious adverse events, AEs leading to dropping out from clinical studies, and AEs of increased severity or of special interest to this class of drug and the Parkinson's disease population.

At the time of the 120-day Safety Update, data through April 30, 2018 was submitted. This included a final report for Study BIA-OPC-401, a Phase 4 open-label single arm study of opicapone 50 mg daily in PD patients with motor fluctuations. Treatment lasted 3 months (Germany) or 6 months (UK) and 69 clinical centers took part, enrolling 519 patients. No datasets were submitted, and adverse event reporting consisted of line listings added to the NDA submission. The quality of data for this study is unknown. One site was reported to the Medicines and Healthcare Regulatory Agency for irregularities in safety reporting and pervasive failure to adhere to GCP. Neither a 21 CFR 312.120 Foreign Clinical Data Compliance Statement nor investigators' financial certification or disclosure was provided by the sponsor for this marketing study. For this reason, only safety data representing deaths, serious AEs, and AEs of special interest are included in this review.

Finally, the Periodic Safety Update Reports are discussed for this drug which has had market authorization in the EU since June 2016.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study BIA-91067-301 "Efficacy and Safety of BIA 9-1067 in Idiopathic Parkinson's Disease Patients with "Wearing-Off" Phenomenon Treated with Levodopa plus a DOPA decarboxylase inhibitor (DDCI): A Double-Blind, Randomized, Placebo- and Active-Controlled, Parallel- Group, Multicenter Clinical Study"

6.1.1. Study Design

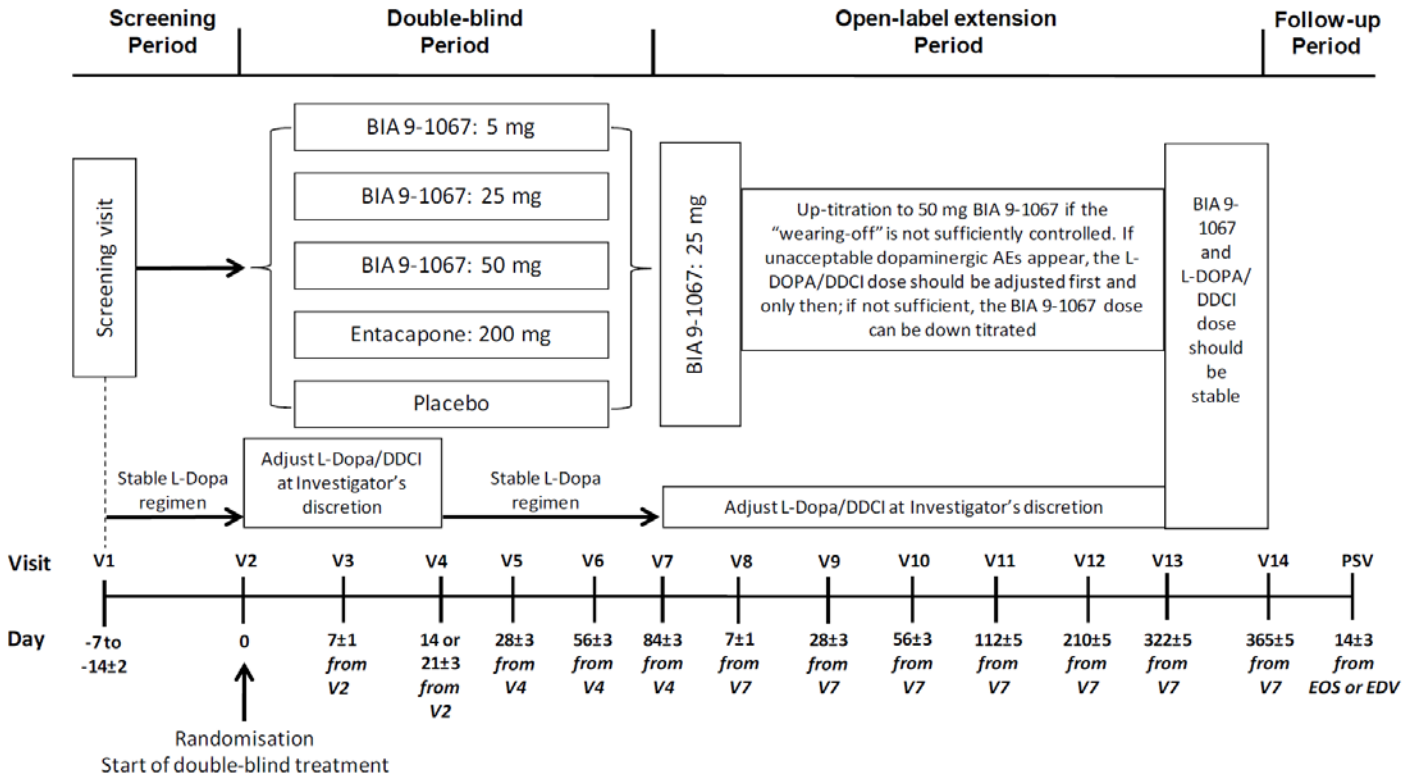
Overview and Objective

This study is designed to investigate the efficacy of 3 different doses of opicapone (5 mg, 25 mg, and 50 mg) administered once a day, compared with 200 mg of entacapone or placebo, when administered with the existing treatment of L-DOPA plus a DOPA decarboxylase inhibitor (DDCI), in patients with PD and end-of-dose wearing off. After efficacy assessment in a 14 to 15-week blinded treatment period, the safety of opicapone is assessed as an open-label treatment for up to a year in duration.

Trial Design

The trial design is a well-established, randomized, double-blinded, parallel treatment method used in evaluating the effect of adjunctive treatment on fluctuations in control of the motor state in advanced PD patient treated with oral levodopa and an oral DOPA decarboxylase inhibitor. In addition to a placebo treatment arm, this study has an active comparator arm as well, i.e., advanced PD treated with levodopa + DDCI + entacapone. Entacapone is an approved COMT inhibitor and co-administered with each daily dose of levodopa.

Figure 2 Study 301 design schema (source: sponsor's protocol, page 29)



EDV: Early Discontinuation visit; EOS visit: End-of-Study visit; PSV: Post-study visit.

Trial Location

This study was performed at outpatient clinical facilities in Europe, as well as Ukraine and Russia. The European population of PD patients historically has no discernable features or characteristics of drug response that differ from a US population of PD patients. Following the extensive clinical experience derived from other currently marketed PD medications, it is expected that results of this study would be generally applicable to an American population of like-PD patients.

Diagnostic Criteria

The criteria for patient selection was the standard UK PD Society Brain Bank Clinical Diagnostic Criteria. Patients had to have prior documented clinical improvement on levodopa treatment. Signs of "wearing-off" phenomenon (end-of-dose deterioration) must be consistent with an average total daily OFF time while awake of at least 1.5 hours despite optimal anti-PD therapy, excluding the early morning pre-first dose OFF time.

Key Inclusion and Exclusion Criteria

Inclusion

- PD patients aged 30 to 83.
- PD diagnosis at least 3 years duration.
- Hoehn and Yahr Stage I-III in ON period.
- Levodopa and DDCI treatment for at least 1 year with documented clinical improvement.
- 1.5 hours of wearing-off daily on optimal anti-PD treatment.
- Able to keep a reliable diary of the motor state (by self or with caregiver assistance).

Exclusion

- Clinical evidence of atypical parkinson syndrome.
- Dyskinesia score >3 on UPDRS Part 4A, Item 33.
- Severe or unpredictable OFF periods.
- Previous use of entacapone.
- Use of prohibited medication within month of screening: tolcapone, neuroleptics, venlafaxine, monoamine oxidase inhibitors (except selegiline up to 10 mg/day in oral formulation or 1.25 mg/day in buccal absorption formulation or rasagiline up to 1 mg/day), or antiemetics with antidopaminergic action (except domperidone).
- Treatment with apomorphine, alpha-methyldopa, or reserpine within the month before screening or likely to be needed at any time during the study.
- Dosage change of concomitant anti-PD medication within 4 weeks of screening.
- Previous or planned (during the entire study duration, including the OLEX period) deep brain stimulation.
- Previous stereotactic surgery (e.g. pallidotomy, thalamotomy) for PD or with planned stereotactic surgery during the study period.
- Past (within the past year) or present history of suicidal ideation or suicide attempts.
- Current or previous (within the past year) diagnosis of major depressive disorder, mania, bipolar disorder, psychosis, dysthymia, generalized anxiety disorder, alcohol or substance abuse excluding caffeine or nicotine, impulse control disorders (e.g. pathological gambling), dementia or eating disorders by DSM IV criteria.
- Clinically relevant abnormal electrocardiogram or evidence of unstable cardiovascular disease.
- Inadequate compliance with anti-PD medication.
- Abnormality in screening laboratory clinical testing of liver enzymes (alanine aminotransferase and/or aspartate aminotransferase) >2 times the upper limit of the normal range.

Dose Selection

The opicapone dosage range selected was based upon the experience derived from Phase 2 studies of COMT inhibition and pharmacokinetic parameters. Entacapone as an active comparator was administered to the patient with each dose of levodopa as labeled for use. Opicapone was administered 1 hour after the last daily dose of levodopa/DDCI.

Study Treatments

The study has five assigned treatment arms: 3 different doses of opicapone (5 mg, 25 mg, and 50 mg) administered once a day in the evening, compared with 200 mg of entacapone or placebo, administered with the patient's existing treatment of L-DOPA plus a DDCI.

Assignment to treatment was performed by an interactive response system using a block randomization schedule created by an outside vendor. The randomization ratio among the 4 arms was 1:1:1:1. The randomization codes were not held by the sponsor.

To ensure the blind, the opicapone capsules and entacapone tablets were identically over-encapsulated. The placebo capsules were manufactured by filling identical capsules with filler. A third-party contract drug supplier managed the packaging, labelling, and supply of investigational drugs.

Dose Modification and Concurrent Medication

Opicapone and entacapone are administered as fixed dosages, added to the patient's anti-PD drug regimen. Patients may be taking levodopa at 3 to 8 dose intervals daily. From Visit 2 to Visit 4 of the DB period (first 2-3 weeks), the investigator may decrease the daily dose of L-DOPA/DDCI (keeping the number of daily doses unchanged), according to patient response. After the initial adjustment period, the dosage of L-DOPA/DDCI is unchanged during the DB period.

During the OLEX period, all patients will begin treatment at a dose of 25 mg opicapone once daily at bedtime for the first week regardless of their prior treatment in the DB period. If the "wearing-off" is not sufficiently controlled, and tolerability allows, the opicapone dose can be adjusted by titrating up to 50 mg. During the OLEX period, the L-DOPA/DDCI dose may be adjusted at the investigator's discretion up to Visit 13 (Day 322) but remains unchanged through the end of the OLEX period (Visit 14, Day 365). No new anti-PD drug may be started during the study and any that were ongoing at the start of the study must be kept at a stable dose throughout the study.

Administrative Structure

This study was performed by a CRO with assignment of specific responsibilities and obligations by the sponsor. An electronic case report form (eCRF) system was used for data collection and investigator signature. At regular intervals throughout the study, the study sites were to be monitored by CRO personnel who were trained for this clinical study. They had access to all documents needed to verify the eCRF. No separate safety monitoring committee was created for this study.

Table 4 Study 301 flow chart of procedures and schedule of events (source: protocol, page 48).

Activity	Screening Period		Double-blind Period							Open-label Period							Follow-up Period
Visit	V1	Pre-V2	V2	V3	Pre-V4	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	PSV
Day	-7 or -14±2	-7±1	0	7±1 of V2	14±3 of V2	14 or 21±3 of V2	28±3 of V4	56±3 of V4	84±3 of V4	7±1 of V7	28±3 of V7	56±3 of V7	112±5 of V7	210±5 of V7	322±5 of V7	365±5 of V7	14±3 of EOS or EDV
Informed consent	X																
Demographic characteristics	X																
Medical/neurological history	X																
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical (height at V1 only) and neurological exams	X		X						X				X			X	X
12-lead ECG	X		X						X				X		X	X	X
Serum β-hCG[a]	X																
Urine pregnancy test[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests[b]	X[c]		X			X	X	X	X[c]	X	X	X	X[c]	X	X	X[c]	X[c]
Review of subject eligibility	X	X	X														
Randomisation			X														
Record adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IMP			X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]	
Medication accountability				X	X	X	X	X	X	X	X	X	X	X	X	X	
Record L-DOPA/DDCI dose	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Instruct on use of, and issue, diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]	
Review and record diary charts		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
UPDRS I (ON)	X		X						X						X	X	
UPDRS III, IV, and V (ON)	X		X			X	X	X	X	X	X	X	X	X	X	X	
UPDRS II and VI (ON+OFF)	X		X			X	X	X	X	X	X	X	X	X	X	X	
PDQ-39, PDSS, NMSS			X				X		X				X		X	X	
Blood sampling for PK assay			X				X		X						X	X	
Investigator and subject assessments of change			X			X	X	X	X	X	X	X	X	X	X	X	

Dietary Restrictions
There were no dietary restrictions nor rules regarding the administration of medication and meals.

Treatment Compliance
Compliance was determined by pill count. The study staff dispensed the appropriate amount of investigational drug for each patient and for each treatment window between visits. At each visit, patients brought back all unused dispensed investigational drug and empty packaging. Each subject's compliance with drug administration was to be assessed by interview and by counting the number of returned capsules. Compliance with treatment was also to be corroborated based on entries in the patient's diary. Compliance was considered acceptable if it was between 80 and 120% of expected use.

Rescue Medication
Use of rescue medication was not anticipated or planned.

Patient Completion, Discontinuation, or Withdrawal
Patients may withdraw or may be withdrawn at any time from the study due to withdrawal of consent, non-compliance, significant protocol violations, AEs (serious or not), or unblinding. Patients who withdraw are not replaced. The investigator is to notify the CRO as soon as possible if a subject has been discontinued. In all cases, the reason for and date of withdrawal is to be recorded in the electronic case report form.

Study Endpoints

Primary Efficacy Endpoint
The primary efficacy endpoint will be the change from baseline in absolute OFF-time at the end of the DB period. Absolute OFF-time will be calculated in minutes as the average of the daily sum of 30-minute periods classified as OFF in the patient's diary. For each 30-minute period during the day, patients (with the help of a member of the family or other caregiver, if needed) rate their mobility as: OFF, ON with troublesome dyskinesia, On with non-troublesome dyskinesia, ON without dyskinesia, or Asleep.

Patients and caregivers were instructed on how to keep a diary to record ON and OFF periods and times of administration of their L-DOPA/DDCI and investigational drugs. At the end of the 7-day screening period, the diary was evaluated for accuracy by the investigator and, if necessary, training extended. The patient (alone or with family/caregiver assistance) was instructed to record the ON/OFF times in his/her diary chart on the 3 days preceding the next visit. The average ON/OFF times of the 3 diaries completed before randomization at Visit 2 are considered as the baseline values.

Key Secondary Efficacy Endpoints

- OFF-time responders: 1 hour or more reduction in absolute OFF-time from baseline to endpoint.
- ON-time responders: 1 hour or more increase in absolute ON-time from baseline to endpoint.

Other Secondary Efficacy Endpoints

The protocol defines multiple secondary efficacy variables consisting of various permutations of measures derived from the diary or the UPDRS which consists of the following parts:

- UPDRS I evaluation of mentation, behavior, and mood
- UPDRS II self-evaluation of the activities of daily life (ADLs) including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food
- UPDRS III clinician-scored monitored motor evaluation
- TOTAL UPDRS score is the sum of Parts I, II and III scores. If one or two items in a scale are missing, they will be imputed with the mean of the non-missing items of that scale. Subscale items are rated 0 to 4, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe. The final cumulative score ranges from 0 (normal) to 199 (severe disability).
- UPDRS IV evaluation of complications of therapy

These secondary assessments include

- Absolute OFF-time.
- Change from baseline in absolute OFF-time.
- Percentage OFF-time.
- Change from baseline in percentage OFF-time.
- Change from baseline in the percentage ON time without troublesome dyskinesia.
- Frequency of OFF-time responders.
- Change from baseline of the various UPDRS Parts scores.

Other secondary assessments used the Parkinson's Disease Sleep Scale (PDSS), the Non-motor Symptoms Scale (NMSS) and the PDQ-36, a quality of life scale.

Safety Assessments

Analysis of safety includes evaluation of treatment emergent adverse events occurring during the study and up to 14 days following treatment cessation. Physical examination, vital signs, electrocardiogram and clinical laboratory measures will also be assessed.

Statistical Analysis Plan (SAP)

Study 301 enrolled its first patient on March 31, 2011. The last patient completed the DB period on November 30, 2013, and the last OLEX patient completed December 17, 2014. The SAP was finalized on April 7, 2014, following a final review of blinded data on March 26, 2014. No interim analysis was planned.

Based upon power calculations done for 3 different scenarios assuming 75-, 90-, and 105-minute mean reductions in OFF-time for the opicapone doses and of 30 minutes for placebo, the planned sample size was 550 patients (110 in each treatment arm).

The efficacy population consisted of the Full Analysis Set (FAS) containing all patients who received one dose of medication and had one post baseline OFF-time efficacy outcome assessment. This is the Intent-to-Treat (ITT) population. The Safety Population (SP) are all those who received at least one dose of investigational drug. The sponsor also performed efficacy analyses on a Per Protocol (PP) population of patients.

While this protocol was not governed by a Special Protocol Assessment (SPA) agreement, the general outcome measures reflecting on-and off time were agreeable to the Division as was indicated in minutes of the EOP2 meeting. The key secondary analysis of ON and OFF time responders was recommended to the sponsor by the EU Committee for Medicinal Products for Human Use (CHMP).

Endpoints are defined as the last available post baseline value during the double-blind period (last observation carried forward, LOCF). This applies if the absolute OFF-time value at endpoint is missing. If there are less than 3 days of diaries prior to a visit, the value will be the average of the diaries completed. Missing values of absolute ON or OFF time were not imputed, rather subject to last post treatment observation carried forward. In diaries, if two or more consecutive 30-minute periods are missing, these are set to missing and not imputed. If a single 30-minute period is missing, the value is imputed from the 30-minute periods before and after the missing half hour. A diary with less than 8 assessible hours of waking time is considered missing.

In the UPDRS if one or two items are missing in Parts I, II, or III, they will be imputed using the mean of the non-missing items in that Part. If three items or missing, the scale value is considered missing.

Planned Analyses
ANCOVA with baseline value as a covariate will be used for the primary outcome.

Step 1: Each dose of opicapone will be compared with placebo using 3 one-sided tests for superiority. A Bonferroni-adjustment will be used to adjust the levels of significance for the 3 tests to ensure the family-wise error rate and all comparisons vs. placebo are treated equally, i.e. all t-tests will be performed at a significance level of 0.025/3. If one or more of these tests are significant vs placebo, the remainder of the tests are adjusted accordingly.

Step 2: For each dose of BIA 9-1067, the non-inferiority vs. entacapone will be tested if and only if the efficacy of this dose vs. placebo has been established. A difference of 30 minutes or less

is considered to not be clinically significant. The basis for selection of 30 minutes ON time as the non-inferiority margin is unclear and the non-inferiority testing was to be performed on the Per Protocol population.

To check the robustness of the primary outcome analysis with respect to handling of missing data a mixed model for repeated measurements (MMRM), modelling the change from baseline in absolute OFF-time at each post baseline visit will be used to estimate and compare the Least Square Means by visit in the FAS. The model for this analysis will include the fixed, categorical effects of treatment, region, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline OFF- time.

Secondary analyses and comparisons are considered exploratory by the sponsor. Subgroup analyses consistent with CFR Section 314.50 requirements were planned.

Protocol Amendments

Two amendments were made to the protocol clarifying procedures and correcting small errors in the protocol after initiation of the trial. These included adding specific procedures to assess for impulse control disorder and vital signs. Five additional country-specific amendments were made to affect conduct of the protocol in Germany, France and Czech Republic. None of these affected the primary or key secondary measures or their analysis.

6.1.2. Study Results

Compliance with Good Clinical Practices

The sponsor has provided attestation that this study was conducted in accordance with the EU equivalents of the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (ICH E6 Guideline, 1996). Because this study was conducted solely outside the US, the study protocol, informed consent documents, and other appropriate study-related documents were reviewed and approved by an independent ethics committee (IEC)/institutional review board (IRB) in compliance with the requirements of 21 CFR 312.120 as it applies to foreign clinical studies not conducted under an IND. The sponsor also certified that it did not use the services of any persons debarred under Section 306(k) of the FDCA.

Financial Disclosure

In Study 301, financial disclosure was obtained prospectively on 419 of 427 investigators. Remediation procedures obtained the remaining disclosure information on all but 5 investigators. No significant conflicts of interest were identified that might compromise the integrity of this double blinded randomized trial.

Patient Disposition

Table 5 Study 301 study population by geographic region (source: CSR, page 80)

Region	Placebo	Entacapone	OPC 5 mg	OPC 25 mg	OPC 50 mg
Western Europe *Austria and Germany*	10	9	9	7	3
Southern Europe *France, Italy, Portugal, Spain*	16	18	18	18	18
North Eastern Europe *Croatia, Czech Republic, Slovakia, Poland, Latvia, Lithuania*	40	39	40	38	39
Russia and Ukraine	22	23	23	22	23
South Eastern Europe *Serbia, Bosnia and Herzegovina, Bulgaria, Hungary, Romania*	33	33	32	34	33
TOTAL	**121**	**122**	**122**	**119**	**116**

Figure 3 Study 301 disposition of DB study population (source: CSR, page 82)

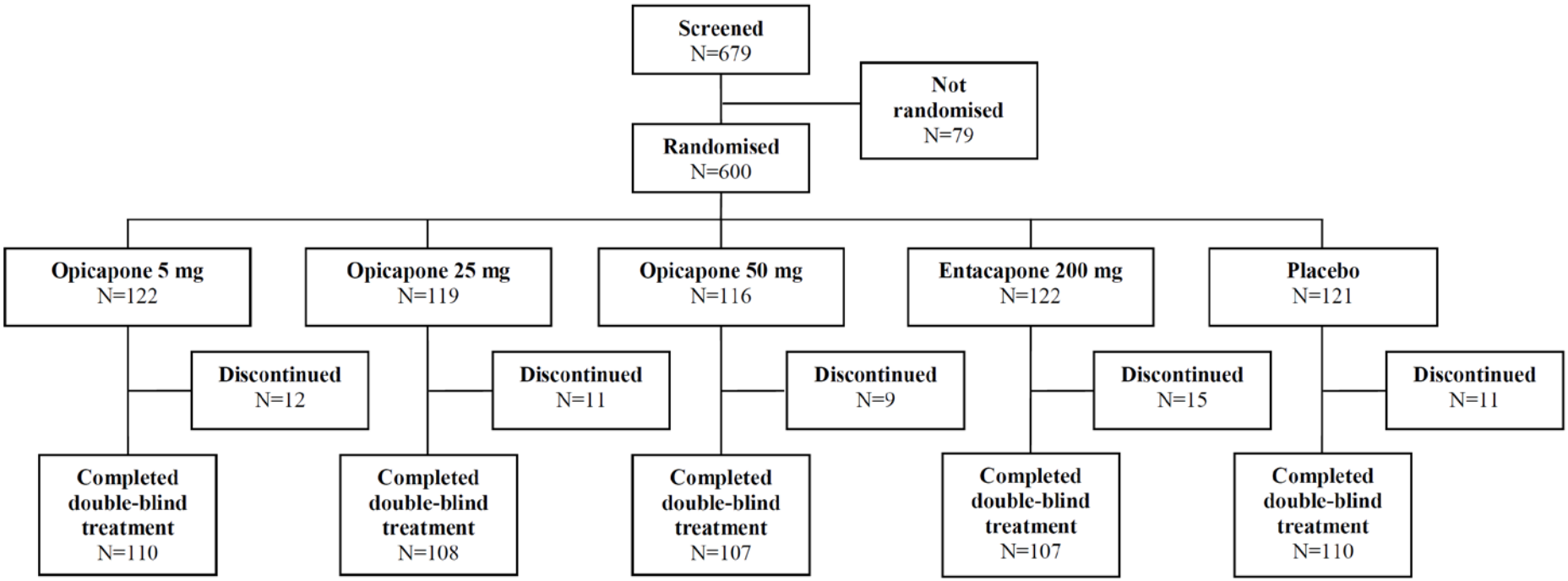
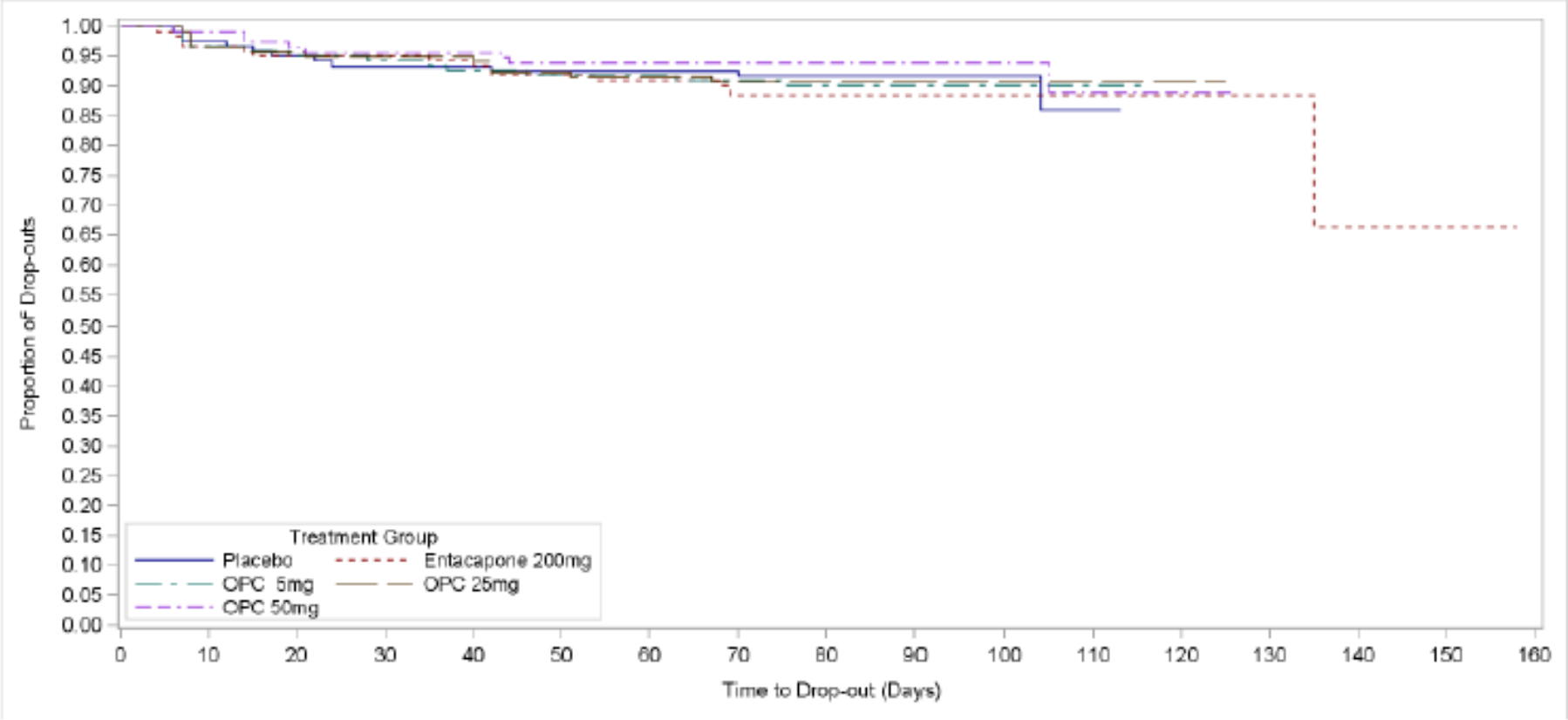


Table 6 Study 301 reasons for premature DB discontinuation (source: CSR, page 81)

Discontinuation	Statistic	Placebo (N=121)	Entacapone (N=122)	OPC 5 mg (N=122)	OPC 25 mg (N=119)	OPC 50 mg (N=116)	Total OPC (N=357)
Total number of subjects who completed the study	n (%)	110 (90.9%)	107 (87.7%)	110 (90.2%)	108 (90.8%)	107 (92.2%)	325 (91.0%)
Total number of subjects who discontinued the study prematurely	n (%)	11 (9.1%)	15 (12.3%)	12 (9.8%)	11 (9.2%)	9 (7.8%)	32 (9.0%)
Reasons for discontinuation:							
Withdrawal of Consent	n (%)	4 (3.3%)	6 (4.9%)	3 (2.5%)	4 (3.4%)	4 (3.4%)	11 (3.1%)
Subject's Non-Compliance	n (%)	-	2 (1.6%)	1 (0.8%)	1 (0.8%)	-	2 (0.6%)
Protocol Violations	n (%)	1 (0.8%)	-	-	-	-	-
Adverse Events	n (%)	8 (6.6%)	8 (6.6%)	7 (5.7%)	8 (6.7%)	5 (4.3%)	20 (5.6%)
Deaths	n (%)	-	-	-	-	-	-
Safety or Ethical Reasons [a]	n (%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.9%)	3 (0.8%)
Hypersensitivity Reactions	n (%)	1 (0.8%)	-	-	-	-	-
Sponsor's Discretion	n (%)	-	1 (0.8%)	1 (0.8%)	-	1 (0.9%)	2 (0.6%)
Ineligibility	n (%)	2 (1.7%)	2 (1.6%)	-	-	1 (0.9%)	1 (0.3%)
Pregnancy	n (%)	-	-	-	-	-	-
Unblinding of the IMP	n (%)	-	-	-	-	-	-
Other Reasons	n (%)	-	1 (0.8%)	3 (2.5%)	-	-	3 (0.8%)

Reviewer's Note: All 5 patients who discontinued for "Safety or Ethical Reasons" had AEs and these are discussed below as AEs that led to discontinuation.

Figure 4 Study 301 Kaplan-Meier plot of time course for DB study dropouts (source: CSR, page 484)



Early versus late appearing adverse events are discussed below in Section 8.4.5 TEAEs and Adverse Reactions.

Protocol Violations/Deviations

In the DB portion of the study, 53 of 600 patients (9%) had what were characterized as major protocol deviations. These were not associated in greater number with treatment arms except for an increased percentage in the entacapone arm due to non-compliance with their assigned treatment and changes in their levodopa/DDCI after initial adjustment. There were no observable systematic occurrences of major protocol deviations in any treatment arm or timepoint in the study. The 25 and 50 mg opicapone arms had good compliance with treatment and unchanged anti-PD medication. Lack of adherence to proper filling out the last available study diary only occurred in one entacapone and one opicapone patient. These findings suggest that the protocol procedures upon which the efficacy analysis is based were unaffected.

In the OLEX portion of the study 30 of 495 patients (6%) had major protocol violations. These were inconsequential to review of this portion of the study. Most occurred in the areas of insufficient treatment compliance, changing of the underlying anti-PD drug treatment, or premature discontinuation of participation due to non-compliance or sponsor's discretion (i.e., interruption of availability of investigational drug).

Table of Demographic Characteristics

Reviewer's note: a full discussion of the demography of the population enrolled in the efficacy studies is in the integrated review of safety, below.

Table 7 Study 301 demographic features of the DB study population (source: CSR, page 85)

Characteristic	Statistic	Placebo (N=121)	Entacapone (N=122)	OPC 5 mg (N=122)	OPC 25 mg (N=119)	OPC 50 mg (N=115)	Total OPC (N=356)
Age (years)	n	121	122	122	119	115	356
	Mean	64.3	63.7	63.6	64.4	63.5	63.8
	SD	9.25	8.78	9.30	8.98	9.22	9.15
	Min	39	42	34	41	36	34
	Max	83	83	82	82	82	82
Age group							
<70 years	n (%)	80 (66.1%)	84 (68.9%)	87 (71.3%)	81 (68.1%)	80 (69.6%)	248 (69.7%)
≥70 years	n (%)	41 (33.9%)	38 (31.1%)	35 (28.7%)	38 (31.9%)	35 (30.4%)	108 (30.3%)
Sex							
Male	n (%)	71 (58.7%)	76 (62.3%)	71 (58.2%)	67 (56.3%)	69 (60.0%)	207 (58.1%)
Female	n (%)	50 (41.3%)	46 (37.7%)	51 (41.8%)	52 (43.7%)	46 (40.0%)	149 (41.9%)
Race/Ethnicity							
Caucasian	n (%)	121 (100%)	122 (100%)	122 (100%)	119 (100%)	115 (100%)	356 (100%)
Weight (kg)	n	121	122	122	119	115	356
	Mean	76.0	76.7	75.0	75.7	76.2	75.6
	SD	13.30	15.02	12.11	14.09	14.46	13.54
Height (cm)	n	121	122	122	119	115	356
	Mean	167.3	167.9	168.8	167.8	167.7	168.1
	SD	9.60	9.28	9.25	8.38	9.65	9.09
Body Mass Index (kg/m^2)	n	121	122	122	119	115	356
	Mean	27.1	27.1	26.4	26.8	27.1	26.8
	SD	4.25	4.64	4.45	4.29	4.61	4.44
Body Mass Index Group							
<18 kg/m^2	n (%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	-	1 (0.9%)	2 (0.6%)
18 - 30 kg/m^2	n (%)	91 (75.2%)	100 (82.0%)	96 (78.7%)	91 (76.5%)	84 (73.0%)	271 (76.1%)
>30 kg/m^2	n (%)	29 (24.0%)	21 (17.2%)	25 (20.5%)	28 (23.5%)	30 (26.1%)	83 (23.3%)

Table 8 Study 301 population demographic characteristics of Parkinson's disease (source: CSR, page 86)

Characteristic	Statistics	Placebo (N=120)	Entacapone (N=120)	OPC 5 mg (N=119)	OPC 25 mg (N=116)	OPC 50 mg (N=115)
Time since PD diagnosis (years)	Mean (SD)	7.7 (4.19)	7.1 (4.12)	7.5 (3.59)	7.2 (4.14)	7.0 (3.84)
Time since start of motor fluctuations (years)	Mean (SD)	2.2 (1.87)	2.2 (2.13)	2.3 (2.32)	2.3 (2.51)	2.2 (2.29)
Incidence of dyskinesia [a]	n (%)	50 (41.7%)	51 (42.5%)	56 (47.1%)	49 (42.2%)	51 (44.3%)
OFF-time						
Absolute time (hours) [b]	Mean (SD)	6.2 (1.78)	6.5 (2.17)	6.7 (2.14)	6.9 (2.20)	6.2 (1.78)
% of total awake time	Mean (SD)	38.2 (10.84)	40.2 (12.89)	40.9 (12.25)	42.2 (12.94)	38.7 (10.45)
Total ON-time						
Absolute time (hours) [b]	Mean (SD)	10.0 (2.01)	9.6 (2.15)	9.7 (2.28)	9.4 (2.26)	9.9 (2.05)
% of total awake time	Mean (SD)	61.8 (10.84)	59.8 (12.89)	59.1 (12.25)	57.8 (12.94)	61.3 (10.45)
ON-time with non-troublesome dyskinesia						
Absolute time (hours) [b]	Mean (SD)	1.1 (1.76)	1.1 (1.66)	1.1 (1.95)	0.9 (1.82)	1.0 (1.91)
% of total awake time	Mean (SD)	6.8 (11.1)	6.8 (10.5)	6.8 (11.2)	5.3 (10.9)	6.2 (12.0)
ON-time with troublesome dyskinesia						
Absolute time (hours) [b]	Mean (SD)	0.4 (1.10)	0.3 (0.92)	0.4 (1.18)	0.3 (0.79)	0.3 (0.98)
% of total awake time	Mean (SD)	2.5 (6.72)	1.9 (6.52)	2.5 (6.99)	1.6 (4.86)	1.9 (5.91)
Total UPDRS (Part I, II [ON], III)	Mean (SD)	37.6 (16.56)	35.4 (19.98)	38.2 (16.16)	40.1 (18.56)	38.8 (18.99)
UPDRS Part II (OFF)	Mean (SD)	18.6 (7.02)	18.0 (7.88)	17.8 (6.22)	18.5 (7.30)	18.9 (6.61)
UPDRS Part III	Mean (SD)	27.6 (11.68)	25.8 (13.80)	28.5 (11.90)	29.0 (12.93)	28.4 (13.74)
Modified H&Y (ON)	Mean (SD)	2.4 (0.51)	2.3 (0.55)	2.4 (0.42)	2.4 (0.52)	2.4 (0.52)
Schwab and England (ON)	Mean (SD)	82.6 (11.31)	82.5 (11.97)	82.9 (10.36)	81.9 (12.01)	82.9 (11.90)

Notes on table: Incidence of dyskinesia is taken from UPDRS Question 32 and indicates all patients whose answers were not 0. All OFF-time and ON-time epochs were recorded as minutes but converted to hours for this table.

The use of anti-PD and concomitant medications are discussed in the integrated safety review below. There was no appreciable difference in mean mg of daily levodopa dose from baseline to the study's end across treatment arms. About ¾ of patients had at least one other anti-PD drug in addition.

Treatment Compliance

Over all treatment compliance was good, with greater than 96% of patients within acceptable use parameters across all treatment arms. There were only three instances of overuse of opicapone.

Data Quality and Integrity

In Study 301, there were 104 sites enrolling 600 patients in 19 countries. At 43 sites, 116 patients were audited in depth. In addition, participating vendors were audited:

- (b) (4) (Biostatistics)
- (b) (4) (Central Safety Lab, 2 audits)
- (b) (4) (IRT and EDC, 4 audits)
- (b) (4) (CRO Clinical Trial Services, 4 audits)
- (b) (4) (Medical Writing)

The study sponsor (BIAL) assured the quality of its clinical studies through a combination of investigational site audits, Trial Master File audits, vendor audits and oversight, and pharmacovigilance audits. However, the NDA sponsor (Neurocrine Biosciences) conducted quality audits 4-to 5 years following study completion to evaluate compliance with CFR requirements. This latter audit comprised 17% of patients in 22% of all clinical sites in 74% of participating countries.

The sponsor found that Site 3104 (Czech Republic) had inadequate control and oversight of the investigational medication. This apparently resulted from a shortage of investigational drug and an ongoing problem with the use of the interactive electronic system for dispensing. This resulted in some brief gaps in treatment for a few patients.

Reviewer's comment: This error would not bias the study toward a finding of greater efficacy.

OSI inspections were requested for two high enrolling clinical sites that participated in both the double blind and open-label portions of the study: Site 4201, n=10 treated (Portugal) and Site 3301, n=20 treated (Poland). A major aim of inspections was to verify of time in the patients' diaries, a metric upon which the primary outcome is based. OSI discovered no major data integrity issues.

Efficacy Results – Primary Endpoint

To recap, the analysis populations for Study 301 are as follows:

Table 9 Study 301 analysis populations (source: datasets and CSR, p 84)

Study 301	N		
Arm	Safety Set	Full Analysis Set	Per Protocol Set
Placebo	121	120	112
5 mg/d	122	119	110
25 mg/d	119	116	105
50 mg/d	116	115	106

The primary efficacy endpoint is the change from baseline in absolute OFF-time at the end of the DB period. Absolute OFF-time is calculated in minutes as the average of the daily sum of 30-minute periods classified as OFF in the patient's diary.

In Study 301, the opicapone 50 mg/d treated group reduced OFF time by an average of 107 minutes while the placebo treated groups reduced OFF time an average of 45 minutes.

The sponsor's primary ANCOVA analysis using the FAS demonstrated superiority of the 50 mg dose over placebo with a mean overall decrease of 62 minutes of OFF time. On face, this decrease is clinically meaningful for the patient. The 25 mg and 5 mg doses moved in the direction of efficacy, about a half-hour of decreased OFF time, though these arms did not achieve statistical significance.

Table 10 Study 301 Absolute OFF time (minutes) change from baseline to endpoint (FAS, from CSR Table 14.9.10, p 496)

Characteristic	Statistic	Placebo (N=120)	Entacapone 200mg (N=120)	OPC 5mg (N=119)	OPC 25mg (N=116)	OPC 50mg (N=115)
Change from Baseline to Endpoint						
	n	120	120	119	116	115
	nmiss	0	0	0	0	0
	Mean	-44.8	-93.5	-96.0	-94.5	-106.8
	SD	160.76	155.55	149.09	162.02	134.20
	Q1	-132.5	-190.0	-190.0	-157.5	-180.0
	Median	-50.0	-80.0	-90.0	-80.0	-110.0
	Q3	33.8	-10.0	5.0	0.0	-20.0
	Min	-465	-580	-550	-620	-445
	Max	453	630	300	345	300

Table 11 Study 301 Primary outcome analysis (FAS, from CSR Table 16, p 95)

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	-	-	-
Entacapone 200 mg	120	-96.3 (13.40)	-70.0	-	-	-
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

The sponsor performed sensitivity analyses for the effect of missing data but, as would be expected from the high rate of study completion, the results were comparable to the primary efficacy analyses. The analysis of the PPS mirrored the FAS, unsurprisingly considering the low dropout and high compliance rate of the study.

Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoints are OFF-time responders (1 hour or more reduction in absolute OFF-time from baseline to endpoint) and ON-time responders (1 hour or more increase in absolute ON-time from baseline to endpoint).

Compared to placebo, the proportion of OFF-time responders in the FAS was significantly higher in the opicapone 50 mg arm (47.5% vs 69.6%, p=0.0011).

Likewise, the proportion of ON-time responders was significantly higher in the opicapone 50 mg group than in the placebo group (65.2% vs 45.8%, p=0.0028).

Table 12 Study 301 OFF and ON time responders (FAS, from CSR Table 19, p 101)

Characteristic	Statistic	Placebo (N=120)	Entacapone (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%)	70 (58.3%)	71 (59.7%)	70 (60.3%)	80 (69.6%)
Non-responders	n (%)	63 (52.5%)	50 (41.7%)	48 (40.3%)	46 (39.7%)	35 (30.4%)
Missing	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Difference with placebo						
CMH-test vs. Placebo	p-value	-	0.0938	0.0650	0.0464	0.0011
Breslow-Day test	p-value	-	0.6600	0.7738	0.0789	0.8330
Difference with entacapone						
CMH test vs. Entacapone	p-value	-	-	0.8206	0.7386	0.0626
Breslow-Day test	p-value	-	-	0.7951	0.2284	0.8134
ON-time Increase						
Responders	n (%)	55 (45.8%)	69 (57.5%)	65 (54.6%)	66 (56.9%)	75 (65.2%)
Non-responders	n (%)	65 (54.2%)	51 (42.5%)	54 (45.4%)	50 (43.1%)	40 (34.8%)
Missing	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Difference with placebo						
CMH-test vs. Placebo	p-value	-	0.0672	0.1690	0.0947	0.0028
Breslow-Day test	p-value	-	0.5320	0.7654	0.5339	0.4686

Being derived primarily from the patient reported diaries, other secondary outcomes are in many cases variations on the above. These include absolute OFF-time, change from baseline in absolute OFF-time, percentage OFF-time, and change from baseline in percentage OFF-time.

Of greater importance are measures quantifying troublesome dyskinesia as it is clinically important that PD improvement not come at the expense of hyperkinesis. In this, the 50 mg arm was successful. Again, both the 5 mg and 25 mg arms moved equally well in the appropriate direction.

In Study 301, ON time without troublesome dyskinesia increased an average of 101 minutes in the opicapone 50 mg/d-treated arm compared to 35 minutes in the placebo arm.

Table 13 Study 301 ON time without troublesome dyskinesia (FAS, after Table 20, CSR p 102)

Parameter	Placebo (N=120)	Entacapone (N=120)	OPC 5 mg (N=119)	OPC 25 mg (N=116)	OPC 50 mg (N=115)
ON-time Without Troublesome Dyskinesia					
Summary Statistics					
Mean	35.0	93.3	82.3	88.8	100.5
Median	40.0	90.0	70.0	75.0	100.0
Min/Max	-440/510	-360/505	-470/460	-495/670	-400/425
ANCOVA analysis					
LS Mean	46.5	94.1	85.9	84.7	109.1
Difference with placebo					
LS Mean	-	47.6	39.4	38.2	62.6
95% CI	-	(9.3, 86.0)	(1.0, 77.8)	(-0.6, 77.0)	(23.8, 101.4)
p-value	-	0.0150	0.0442	0.0535	0.0016
Difference with entacapone					
LS Mean	-	-	-8.2	-9.4	15.0
95% CI	-	-	(-46.6, 30.1)	(-48.0, 29.1)	(-23.8, 53.7)

Multiple other secondary assessments were derived from the UPDRS Parts I-IV, looking at the total score, Part II + III (ON period), and Parts II and III separately. None of these analyses had a statistically significant result for the FAS. Other secondary assessments used the Parkinson's Disease Sleep Scale (PDSS), the Non-motor Symptoms Scale (NMSS) and the PDQ-36, a quality of life scale. None of these distinguished the treatment arms.

Dose/Dose Response

Only a single dose, 50 mg/d, was considered for full efficacy analysis. The lower dose of 25 mg/d did show about half the decrease of OFF time compared to the full dose. Given that the 5 mg/d arm also demonstrated this much effect, it brings into question the ability of the diary method to quantify small changes in OFF time accurately. The 5 mg/d dose is likely a homeopathic dose of opicapone.

Durability of Response

While the study does not have a controlled long duration design, the contribution of the open-label extension studies to our understanding of the durability of treatment effect is considered in the integrated discussion of efficacy, below.

Persistence of Effect

Persistence of effect of COMT inhibition after discontinuation was not evaluated in this study.

Additional Analyses Conducted on the Individual Trial

The sponsor performed subgroup analyses of the effect of age, gender, Parkinson disease duration, levodopa dose at baseline, concomitant anti-PD medications and geographic region.

Age (above and below 70) did not alter the treatment effect though it was noted that those older than 70 appeared to have a greater response to placebo treatment. Women appeared to have a greater reduction in OFF time than men on average (about 18 minutes) but this was not a statistically significant difference. Disease duration and anti-PD treatment did not appear to affect the efficacy outcome. Analysis by geographic region suffered from having numbers too small in some regions to allow for comparability.

Reviewer Comment: The findings above represent the sponsor's analyses for Study 301. The statistical reviewer in the Office of Biostatistics has reviewed the sponsor's findings and performed additional analyses. She has verified the primary efficacy endpoint, found that sensitivity analyses for missing data did not detract from the robustness of the result. The same is true for the key secondary endpoints and the analysis of ON time without troublesome dyskinesia.

6.2. BIA-91067-302 "Efficacy and safety of BIA 9-1067 in idiopathic Parkinson's disease patients with "wearing-off" phenomenon treated with levodopa plus a dopa decarboxylase inhibitor (DDCI): a double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical study."

6.2.1. Study Design

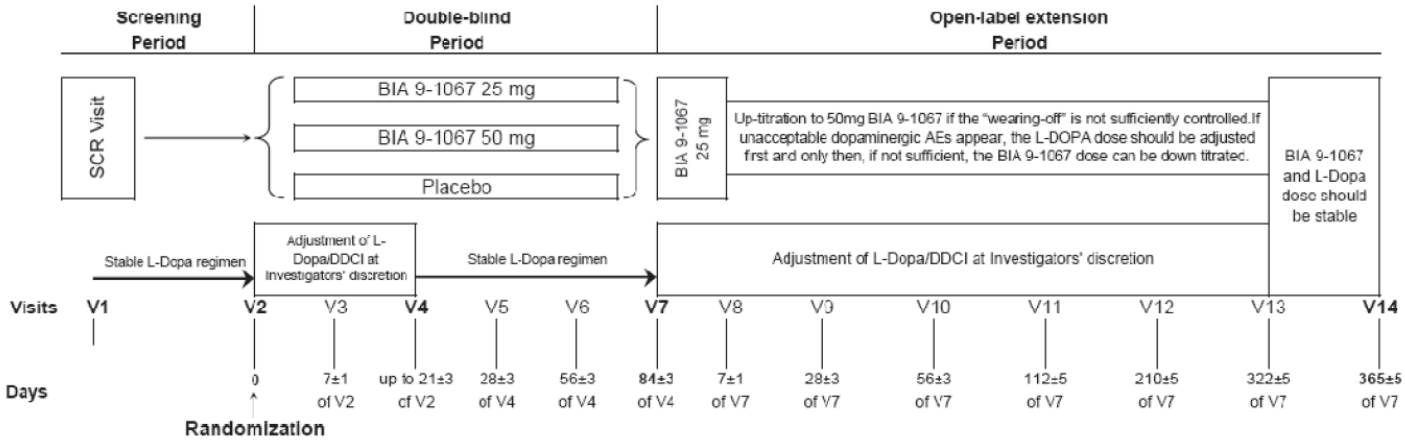
Overview and Objective

This study is designed to investigate the efficacy of 2 different doses of opicapone (25 mg and 50 mg) administered once a day, compared with placebo, when administered with the existing treatment of L-DOPA plus a DDCI, in patients with PD and end-of-dose motor fluctuations. After efficacy assessment in a 14 to 15-week blinded treatment period, the safety of opicapone is assessed as an open-label treatment for up to a year in duration.

Trial Design

This study is virtually identical to Study 301 in design and execution as described in Section 6.1, above. The only difference is that this study has three treatment arms and does not include low dose opicapone or an active comparator. The SAP also has some differences as described in the relevant section below.

Figure 5 Study 302 design schema (source: sponsor's protocol, page 27)



Trial Location
This study was performed in outpatient clinical facilities in Europe, UK, Israel, Australia, South Africa, South America, South Korea, and India.

The following protocol features are identical to that of Study 301:

- Diagnostic criteria
- Key Inclusion and Exclusion Criteria
- Dose Modification and Concurrent Medication
- Administrative Structure
- Dietary Restrictions
- Treatment Compliance
- Rescue Medication
- Patient Completion, Discontinuation, or Withdrawal

Study Treatments
The study has three assigned treatment arms: 2 different doses of opicapone 25 mg and 50 mg) administered once a day, and a placebo arm, administered with the patient's existing treatment of L-DOPA plus a DDCI.

Of note, while the investigational product is administered 1 hour after the last daily dose of levodopa/DDCI, the following additional instructions for administration are provided in Study 302: "Subjects should fast for 1 hour before and for at least 1 hour after the intake of the [investigational drug]." This was not explicitly specified in Study 301.

Table 14 Study 302 flow chart of procedures and schedule of events (source: protocol, page 46).

Activity	Screening Period		Double-blind Period							Open-label Period							Follow-up Period
Visit	V1	Pre-V2	V2	V3	Pre-V4	V4	V5	V6	V7 or EDV	V8	V9	V10	V11	V12	V13	V14 or EDV	PSV
Day	-14	-7	0	7±1 of V2	14±3 of V2	14 or 21±3 of V2	28±3 of V4	56±3 of V4	84±3 of V4	7±1 of V7	28±3 of V7	56±3 of V7	112±5 of V7	210±5 of V7	322±5 of V7	365±5 of 7	14±3 of EOS or EDV
Informed consent	X																
Demographic characteristics	X																
Medical/neurological history	X																
Previous/concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical (height at V1 only) and neurological exams	X		X						X				X			X	X
12-lead ECG	X		X						X				X		X	X	X
Serum β-hCG[a]	X																
Urine pregnancy test[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests[b]	X[c]		X			X	X	X	X[c]	X	X	X	X[c]	X	X	X[c]	X[c]
Review of subject eligibility	X	X	X														
Randomisation			X														
Record adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study treatment			X	X	X	X	X	X	X[d]	X	X	X	X	X	X		
Medication accountability				X	X	X	X	X	X	X	X	X	X	X	X	X	
Record L-DOPA dose	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Instruct on use of and issue diary	X	X	X	X	X	X	X	X	X[d]	X	X	X	X	X	X		
Review and record diary charts		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
UPDRS I	X		X						X						X	X	
UPDRS II to VI	X		X			X	X	X	X	X	X	X	X	X	X	X	
PDQ-39, PDSS, NMSS			X				X		X				X		X	X	
Investigator and subject assessments of change			X			X	X	X	X	X	X	X	X	X	X	X	
Blood sampling for PK assay			X				X		X						X	X	

Study Endpoints

The primary and key secondary efficacy endpoints remain identical to Study 301 and are assessed in identical manner:

The primary efficacy endpoint will be the change from baseline in absolute OFF-time at the end of the DB period.

The key secondary endpoints are OFF-time responders (1 hour or more reduction in absolute OFF-time from baseline to endpoint) and ON-time responders (1 hour or more increase in absolute ON-time from baseline to endpoint).

Safety assessment are the same as in Study 301.

Statistical Analysis Plan

Study 302 enrolled its first patient on March 18, 2011. The last patient completed the DB period on July 11, 2012, and the last OLEX patient completed June 25, 2013. The SAP was finalized on October 9, 2012. However, the database was reopened following its locking of the double-blind period (see below).

The definition of analysis populations and methods for the handling of data, including missing values, is the same as the SAP for Study 301.

The methods of statistical analysis for the primary and key secondary outcomes are also identical, including sensitivity analyses to account for missing data. No hierarchy is established for the analysis of the two opicapone dose levels compared to placebo for the primary outcome. The SAP states that differences between opicapone dose and the placebo arm will use methods to adjust for multiple comparisons. For the key secondary outcome, a hierarchy is established to test the higher dose first.

Changes in the Planned Analyses

A scheduled interim database lock and unblinding was performed after all patients completed the DB period. During the management of the OL part of the study, incomplete data entry and data discrepancies were identified and corrected at various times. As a result, the clinical review team and OSI made a detailed information request of the sponsor and the following was learned:

- First DB patient treated: 2011 March 18
- Last DB patient out: 2012 July 11
- Initial database lock 2012 Oct 15
- Database unblinding 2012 Oct 16
- Data inconsistencies found, queries generated.
- Database unlocked 2013 Aug 2, corrected

- Database relocked 2013 Nov 7
- Database unlocked 2013 Nov 13 "for one patient"
- Database relocked 2013 Nov 18

The analyses submitted in this NDA use this last database version. The Information Request to the sponsor from the review team revealed that only the CRO data team had full access to the database for corrections (though BIAL study personnel had "read only" access). While only one change to data that was part of the efficacy outcome measure was made (a subject with one baseline diary missing entry added), 736 entries for safety data, UPDRS, PDQ-36, and baseline features were also corrected.

Reviewer's comment: A line listing of all database changes following the initial lock was submitted by the sponsor. After review of the data discrepancies it was concluded that none of the information had any impact on subject eligibility and none of the corrected data discrepancies resulted in any significant change to the statistical output. While illustrative of very sloppy study conduct, there is no evidence of systematic errors that could ultimately affect the efficacy or safety assessment of the trial.

Protocol Amendments

Two amendments were made to the protocol clarifying procedures and correcting small errors in the protocol, two and five months after the start of the study respectively. Three additional country-specific amendments were made to affect conduct of the protocol Czech Republic. None of these affected the primary or key secondary measures or their analysis.

6.2.2. Study Results

Compliance with Good Clinical Practices

The sponsor has provided attestation that this study was conducted in accordance with the EU equivalents of the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (ICH E6 Guideline, 1996). Because this study was conducted solely outside the US, the study protocol, informed consent documents, and other appropriate study-related documents were reviewed and approved by an independent ethics committee (IEC)/institutional review board (IRB) in compliance with the requirements of 21 CFR 312.120 as it applies to foreign clinical studies not conducted under an IND. The sponsor also certified that it did not use the services of any persons debarred under Section 306(k) of the FDCA.

Financial Disclosure

In Study 302, financial disclosure was obtained prospectively on 306 of 310 investigators. Remediation procedures obtained the disclosure information on all but 2 investigators. No

significant conflicts of interest were identified that might compromise the integrity of this double blinded randomized trial.

Patient Disposition

Table 15 Study 302 study population by geographic region (source: CSR, page 85)

Region	Placebo	OPC 25 mg	OPC 50 mg
Argentina/Chile	46	36	50
Belgium/UK/Israel	14	16	20
Estonia/Czech Republic/Russia	19	14	20
India	21	16	16
South Africa/Australia/South Korea	44	47	48
TOTAL	144	129	154

Distinct from this study in which South Korea participated, Study 301 has no southeast Asia study sites.

Figure 6 Study 302 disposition of DB study population and reasons for termination (source: CSR, page 86)

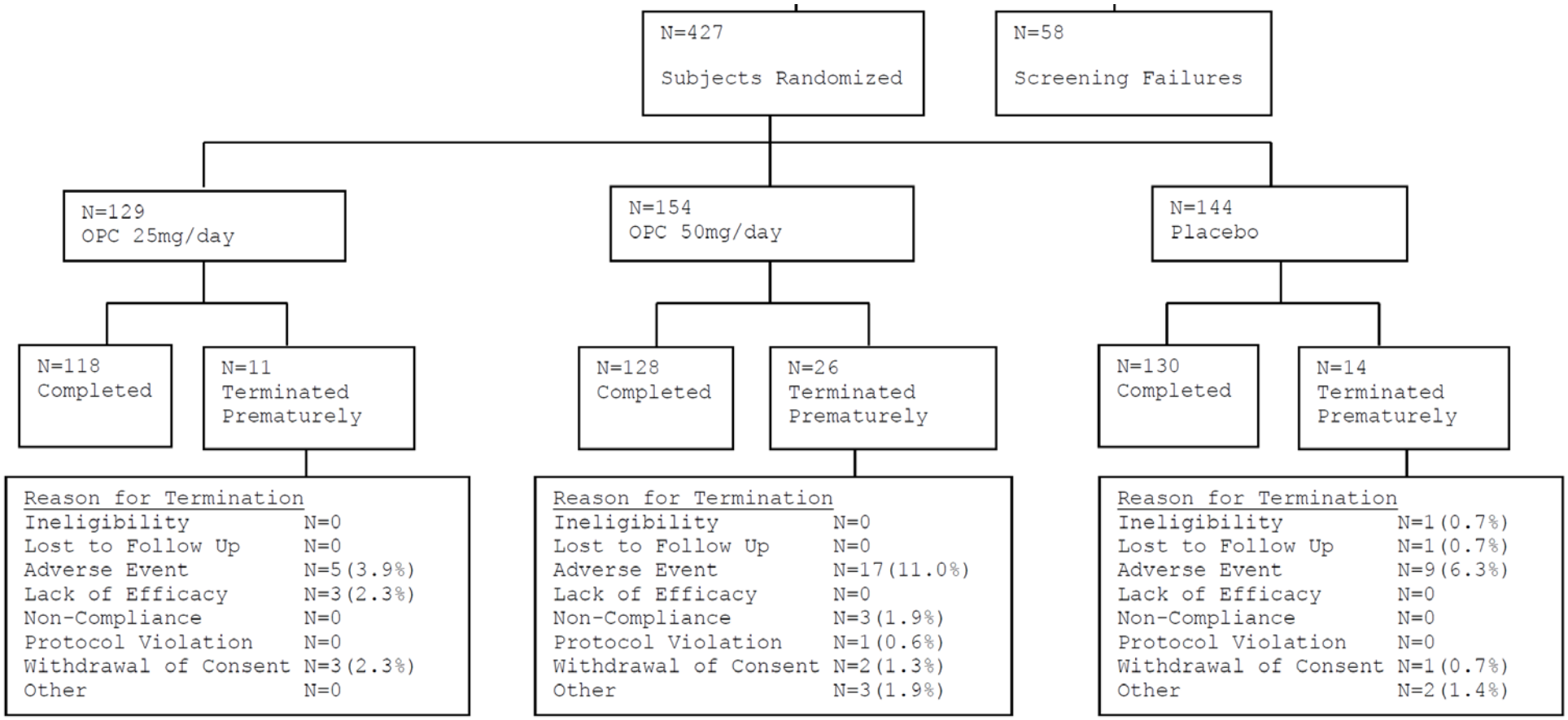
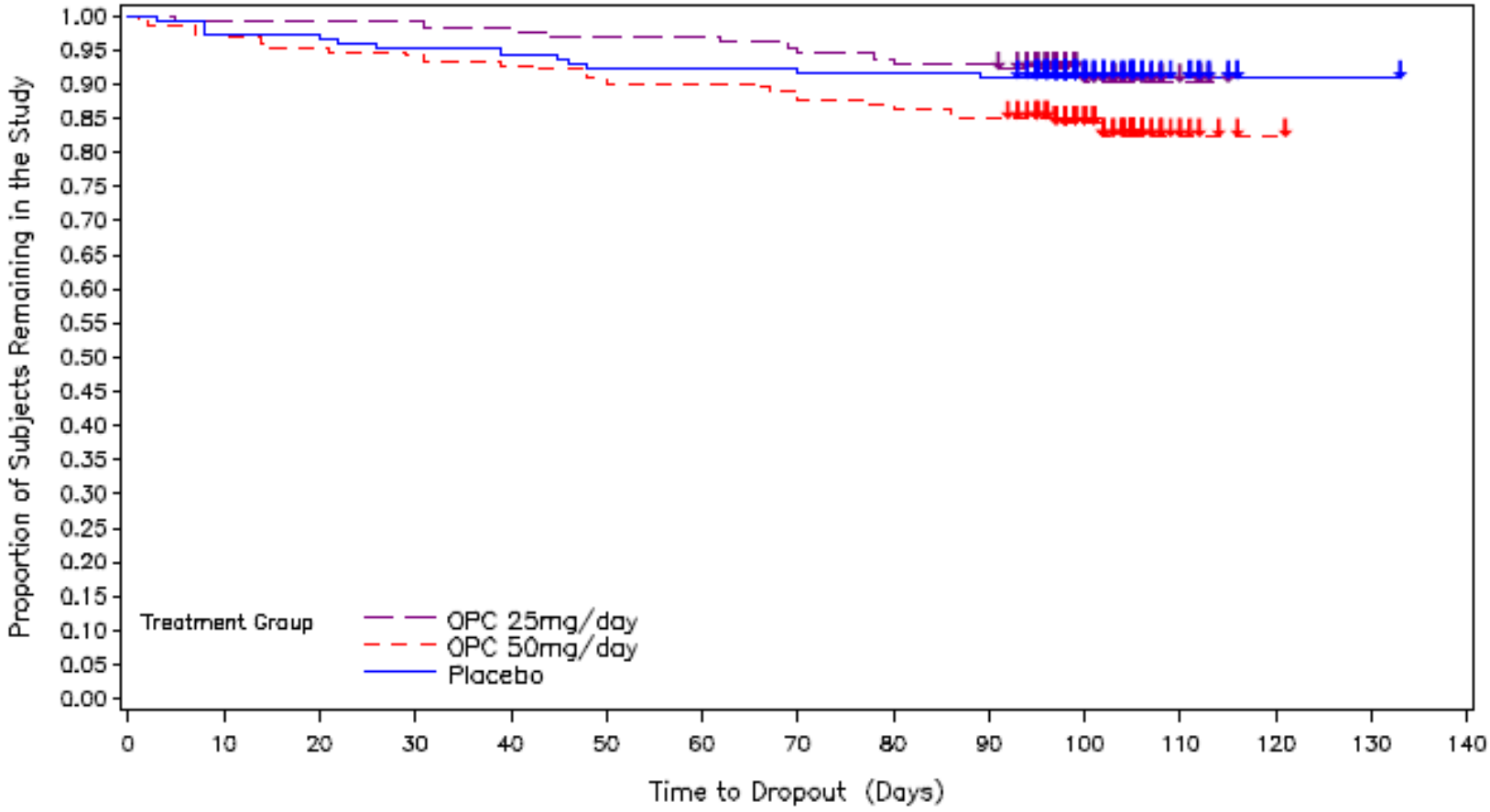


Figure 7 Study 302 Kaplan-Meier plot of time course for DB study dropouts (source: CSR, page 1811)



Early versus late appearing adverse events are discussed below in Section 8.4.5 TEAEs and Adverse Reactions.

Protocol Violations/Deviations

In the DB portion of the study, 53 of 407 patients (11%) had what were characterized as major protocol deviations. These were not associated in greater number with any treatment arm except for an increased percentage of non-compliance with changes in their levodopa/DDCI regimen in the placebo arm. Compliance with investigational treatment was the same across treatment arms and with adherence to diary reporting. There was no observable systematic occurrence of major protocol deviations in any treatment arm or timepoint in the study. Good compliance with investigation drug treatment is noted in all treatment arms. These findings suggest that the protocol procedures upon which the efficacy analysis is based were unaffected.

In the OLEX portion of the study 24 patients (7%) had major protocol violations. These were inconsequential to the review of this portion of the study. Most occurred in the areas of insufficient treatment compliance and changing of the underlying anti-PD drug treatment.

Of note, one instance of unintentional overdosing (> 50 mg/day) occurred.

- Patient (b) (6) accidentally took opicapone 50 mg twice daily for two months instead of the prescribed 50 mg once daily. The subject was discontinued from the study because of an AE of "overdose". The narrative pertaining to this 45-year-old woman reported that the patient was asymptomatic in this period and no findings were identified. However, the patient was removed from the study.

Table of Demographic Characteristics

Reviewer's note: a full discussion of the demography of the population enrolled in the efficacy studies is in the integrated review of safety, below.

Table 16 Study 302 demographic features of the DB study population (source: CSR, page 90)

	Placebo N = 135	OPC 25 mg N = 125	OPC 50 mg N = 147
Age, years			
Mean (SD)	61.5 (8.87)	62.5 (8.50)	65.5 (8.41)
Min/Max	36/81	43/82	44/83
Age, n (%)			
<70 years	107 (79.3%)	96 (76.8%)	96 (65.3%)
≥70 years	28 (20.7%)	29 (23.2%)	51 (34.7%)
Gender, n (%)			
Male	71 (52.6%)	82 (65.6%)	89 (60.5%)
Female	64 (47.4%)	43 (34.4%)	58 (39.5%)
Race, n (%)			
White	89 (65.9%)	90 (72.0%)	115 (78.2%)
Asian	42 (31.1%)	29 (23.2%)	31 (21.1%)
American Indian/Alaska Native	0	0	0
Black or African American	0	0	0
Native Hawaiian/Pacific Islander	0	0	0
Other	3 (2.2%)	6 (4.8%)	1 (0.7%)
Weight, kg			
Mean (SD)	72.12 (16.989)	75.35 (16.794)	71.61 (15.100)
Min/Max	39.4/133.8	44.5/147.6	41.0/118.0
Height, m			
Mean (SD)	1.65 (0.103)*	1.67 (0.102)	1.66 (0.101)
Min/Max	1.4/1.9*	1.4/2.0	1.4/1.9
BMI, kg/m^2			
Mean (SD)	26.45 (5.175)*	26.79 (4.903)	25.79 (4.342)
Min/Max	15.6/49.2*	17.1/52.8	15.8/37.9

Table 17 Study 302 population demographic characteristics of Parkinson's disease (source: CSR, page 92)

Parameter	Placebo N = 135	OPC 25 mg N = 125	OPC 50 mg N = 147
Time since PD diagnosis, years Mean (SD)	7.73 (3.685)	8.54 (4.417)	8.20 (4.543)
Time since start of motor fluctuations, years* Mean (SD)	3.02 (2.338)	3.22 (2.752)	3.21 (3.255)
OFF-time **Absolute time, hours** Mean (SD)	6.12 (2.33)	6.21 (2.24)	6.32 (2.22)
Percentage of Total Awake Time, % Mean (SD)	37.5 (13.82)	38.8 (13.24)	38.9 (12.81)
ON-time without or with non-troublesome dyskinesia **Absolute time, hours** Mean (SD)	9.61 (2.40)	9.20 (2.32)	9.37 (2.22)
Percentage of Total Awake Time, % Mean (SD)	59.0 (14.48)	57.4 (12.91)	57.9 (12.99)
ON-time with troublesome dyskinesia **Absolute time, hours** Mean (SD)	0.57 (1.40)	0.58 (1.25)	0.53 (1.21)
Percentage of Total Awake Time, % Mean (SD)	3.5 (8.69)	3.8 (8.53)	3.2 (7.14)
Total UPDRS (Part I, II [ON] and III) Mean (SD)	31.5 (17.00)	30.8 (16.88)	31.7 (17.55)
UPDRS Part II (OFF)** Mean (SD)	17.4 (7.08)	17.1 (6.75)	17.3 (7.49)
UPDRS Part III (ON) Mean (SD)	22.5 (11.96)	21.5 (11.95)	22.5 (12.26)
Modified Hoehn and Yahr (ON) Mean (SD)	2.4 (0.61)	2.3 (0.67)	2.4 (0.53)
Schwab and England ADL (ON) Mean (SD)	83.1 (11.62)	84.7 (10.05)	82.8 (11.57)
Incidence of Dyskinesia (UPDRS item 32) n (%)	72 (53.3%)	65 (52.0%)	80 (54.4%)

The use of anti-PD and concomitant medications are discussed in the integrated safety review below. There was no appreciable difference in mean mg of daily levodopa dose from baseline

to the study's end across treatment arms. About 84% of patients had at least one other anti-PD drug in addition to levodopa, slightly higher than in Study 301.

Treatment Compliance

Compliance with the investigational drug treatment regimen was over 90% and there were very few changes in concomitant anti-PD medication over the course of the DB epoch. There were only two instances of overuse of opicapone.

Data Quality and Integrity

In Study 302, there were 69 sites enrolling 427 patients in 12 countries. At 25 sites, 95 patients were audited in depth. In addition, as in Study 301, the participating vendors were audited.

The NDA sponsor (Neurocrine Biosciences) conducted quality audits 4-to 5 years following study completion to evaluate compliance with CFR requirements. This latter audit comprised 17% of patients in 20% of all clinical sites in two-thirds of participating countries.

Issues concerning source document availability were identified at two sites: Site 1006 (Argentina) had portions of the paper clinical records (source documents) missing. The informed consent document was present as were the original diaries upon which outcomes assessments were based. These may have been related to the clinical site being moved and were later satisfactorily resolved. Site 1308 (Chile) had ceased to be an active clinical trial center but provided site subject files for review.

More significant findings are described for the following trial sites:
Site 1703 (India): Central ECG review revealed that several ECGs for different subjects were found to have very similar characteristics and ECGs for the same subject taken at different visits showed remarkably different characteristics. For this reason, an independent For Cause Audit was performed, and the sponsor was unable to confirm the validity and integrity of the data. The site was terminated and decisions were made regarding the data: all site data were removed from both the Safety Set and Full Analysis Set prior to unblinding (n = 15). Adverse events were reviewed and a sensitivity analysis performed on both efficacy outcome. It revealed no effect on the overall study outcome.

Site 1709 (India): Suspected similarities in markings on the patient diaries at the randomization and final visits of the double-blind study prompted a For Cause Audit (n=13). Patient interviews confirmed the sources of the data. The Sponsor concluded that the efficacy and safety data from Site 1709 were considered valid and were to be included in the final analysis. The Drug Controller General [regulatory authorities] of India conducted a routine inspection of the site and no findings of note were reported.

There were investigational drug shortages during the DB period of Study 302 due to short expiry dates. As a result, Sites 1807 (Russia) and Sites 1703 and 1705 (India) were directed to put recruitment on hold until enough quantities of investigational drug were available. The shortages in Russia did not prevent subjects who had already been screened from being randomized. In India, five subjects had to be screen failed and re-screened under a new screening number since the site could not supply drug within the acceptable screening window. As a result of the shortage, a limited number of treatment interruptions were identified at sites in Chile, India and Russia based on study medication accountability data and review of other study source data. A total of 16 cases of treatment interruptions due to shortages or interactive voice response system (IVRS) issues were identified in 14 subjects (4 in the opicapone 50 mg group and 10 in the placebo group):

Table 18 Study 302 unplanned treatment interruption in the DB period (source: CSR Appendix 16.4, page 67)

Site[a]	Subject	Duration of Interruption (Days)	Treatment Group	Included in FAS/PP set?	Reason
1301	(b) (6)	2	OPC 50 mg	N/N	IVRS error
1304		1	Placebo	Y/Y	IMP not available on visit day
1703		29	Placebo	N/N	IMP shortage
		4	Placebo	N/N	Unable to confirm with site whether due to IMP shortage or IVRS issue
		18	Placebo	N/N	IMP shortage
		23	Placebo	N/N	IMP shortage
		6	Placebo	N/N	IMP shortage
		8	Placebo	N/N	IMP shortage
1705		2	OPC 50 mg	Y/Y	IVRS error
1807		2	Placebo	Y/N	IMP shortage
		1	Placebo	Y/Y	IMP shortage
		1	Placebo	Y/Y	IMP shortage
		6	Placebo	Y/Y	IMP shortage
		9	Placebo	Y/Y	IMP shortage
		5	OPC 50 mg	Y/N	IMP shortage
		2	OPC 50 mg	Y/N	IMP shortage

Excluding these patients in sensitivity analysis of efficacy did not affect the outcome result.

OSI inspections were requested for two high enrolling clinical sites that participated in both the double blind and open-label portions of the study: Site 2002, n=18 treated (Korea) and Site

1904, n=11 treated (South Africa). A major aim of inspections was to verify of time in the patients' diaries, a metric upon which the primary outcome is based. At Site 2002 no major issues with data integrity were found. At Site 1904, OSI discovered data discrepancies of a minor nature in four patients resulting from site monitors failing to collect all the diaries recorded by patients at the final visit in the open label portion of the study (Visit 14). This would not have affected the efficacy evaluation in the double blinded portion of the trial providing evidence of efficacy.

Efficacy Results – Primary Endpoint

To recap, the analysis populations for Study 302 are as follows:

Table 19 Study 302 study populations (source: datasets and CSR, p 88)

Study 302	N		
Arm	Safety Set	Full Analysis Set	Per Protocol Set
Placebo	136	135	120
25 mg/d	125	125	114
50 mg/d	150	147	127

The primary efficacy endpoint is the change from baseline in absolute OFF-time at the end of the DB period. Absolute OFF-time is calculated in minutes as the average of the daily sum of 30-minute periods classified as OFF in the patient's diary.

in Study 302, the opicapone 50 mg/d treated group reduced their average OFF time by 124 minutes. This compares favorably to a reduction in OFF time in the placebo treated groups of 65 minutes, respectively. The sponsor's primary ANCOVA analysis using the FAS demonstrated superiority of the 50 mg dose over placebo with a mean overall decrease of 59 minutes of OFF time when compared to placebo, similar to Study 301. On face, this decrease is clinically meaningful for the patient. The 25 mg dose also moved in the direction of efficacy but did not achieve statistical significance.

Table 20 Study 302 Absolute OFF time (minutes) change from baseline to endpoint (FAS, CSR Table 14, p 101)

	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

The sponsor performed sensitivity analyses for the effect of missing data and the results were comparable to the primary efficacy analyses. The analysis of the PPS closely mirrored the FAS.

Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoints are OFF-time responders (1 hour or more reduction in absolute OFF-time from baseline to endpoint) and ON-time responders (1 hour or more increase in absolute ON-time from baseline to endpoint). The study achieved statistical significance for both dose arms over placebo in both measures. The results closely parallel those of Study 301 for the 50 mg dose.

Table 21 Study 302 Proportion of OFF- and ON-time responders at week 12 (FAS, CSR Table 16, page 105)

	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

As in Study 301, other secondary outcomes are variations on the above. These include absolute

OFF-time, change from baseline in absolute OFF-time, percentage OFF-time, and change from baseline in percentage OFF-time.

Improvement in ON time did not come at the expense of troublesome dyskinesia, with a mean increase over placebo of 45 minutes (ANCOVA, LS Means p=0. 048) in the 50 mg arm. The 25 mg arm demonstrated a trend in the same direction of improvement.

As in Study 301, none of the secondary outcomes derived from the UPDRS or non-motor rating scales were able to distinguish among treatment arms.

Dose/Dose Response

No direct dose response comparison was made; however, the lower dose of 25 mg/d did show a lesser decrease of OFF time compared to the full dose but more than placebo.

Durability of Response

While the study does not have a controlled long duration design, the contribution of the open-label extension studies to our understanding of the durability of treatment effect is considered in the integrated discussion of efficacy, below.

Persistence of Effect

Persistence of effect of COMT inhibition after discontinuation was not evaluated in this study.

Additional Analyses Conducted on the Individual Trial

The sponsor performed subgroup analyses of the effect of age, gender, Parkinson disease duration, levodopa dose at baseline, concomitant anti-PD medications and geographic region.

It was noted that those older than 70 appeared to have a greater response to active treatment compared to younger patients (by a group mean of 14 minutes). Men appeared to have a greater reduction in OFF time than women on average but this appears to be a much greater response in the placebo arm rather than an actual difference in the achieved reduction in OFF time. Neither disease duration, anti-PD treatment, nor geographic region appeared to affect the efficacy outcome.

Reviewer Comment: The findings above represent my review of the sponsor's analyses for Study 302. The statistical reviewer in the Office of Biostatistics has reviewed the sponsor's findings and performed additional analyses. She has verified the primary and key secondary outcomes as well as the analysis of ON time without troublesome dyskinesia.

6.3. BIA-OPC-401 "Efficacy and safety of opicapone in clinical practice in Parkinson's Disease patients with wearing-off motor fluctuations."

6.3.1. Study Design

Overview and Objective

This is a Phase 4 post approval open-label study to evaluate the change in the patient's condition assessed by the Investigator's Global Assessment of Change after three months of treatment in Germany or 6 months of treatment in the United Kingdom with 50 mg opicapone once daily in a heterogeneous PD patient population reflecting daily clinical practice.

Reviewer's note: This study was submitted in its entirety as part of the 120-day Safety Update and not the original NDA application even though the last patient completed in February 2018, and the NDA application was submitted April 26, 2019. Line listings but no datasets were provided. Nevertheless, it is presented here in brief because, while uncontrolled and open-label, its size and duration of treatment provide additional safety information relevant to the evaluation of opicapone, with regards to the potential SAEs, severe adverse reactions and reason for leaving treatment. Because of the uncontrolled nature of the study, the efficacy measures are not reviewed.

Trial Design

After completing a screening/baseline visit (Day 1), patients started open-label treatment with opicapone 50 mg once daily in addition to their current treatment with levodopa/DDCI. Subjects treated with levodopa/DDCI/entacapone before study entry were to discontinue entacapone treatment on Day 1. The investigator could increase or decrease the total daily levodopa/DDCI dose according to the patient's clinical condition.

After enrolling, executing informed consent, and receiving the first administration of opicapone on Day 1, the patient had subsequent telephone contact on Day 15 and clinic visits on Day 30, Day 90 and, if in the UK, Day 180.

Trial Location
This study was performed in outpatient clinics in UK and Germany.

Key Inclusion and Exclusion Criteria

1. Diagnosed with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria.
2. Disease severity Stages I-IV (modified Hoehn &Yahr staging) at ON.
3. Treated with three to seven daily doses of L-dopa/DDCI or L-dopa/DDCI/entacapone, which can include a slow-release formulation.
4. Signs of "wearing-off" phenomenon despite optimal anti-PD therapy and the wearing-

off phenomenon must be confirmed clinically by the investigator.

Excluded if they are suspect for atypical parkinsonism or if OFF periods are severe or unpredictable.

Dose Modification and Concurrent Medication
The investigator could reduce the subject's L-dopa/DDCI dose within the first days or weeks of opicapone treatment by extending the dosing intervals and/or reducing the amount of L-dopa/DDCI per dose. The investigator was allowed increase or decrease the total daily L-dopa/DDCI dose according to the patient's condition throughout the trial.

Administrative Structure
The study was administered centrally by the sponsor and CRO without a drug safety monitoring board. Standard reporting of AEs was employed and the sponsor monitored the clinical sites for adherence to GCP.

Study Endpoints

The primary efficacy endpoint was an Investigator's Global Assessment of Change at Visit 4. Secondary endpoints included changes in the total daily dose of levodopa and number of daily doses needed. Safety endpoints included the incidence of AEs including SAEs and general safety information (vital signs, physical and neurological examinations).

Statistical Analysis Plan

The safety population was used for descriptive analyses of adverse events and safety. This population consisted of all enrolled patients who received at least one dose of opicapone.

Protocol Amendments

No amendments materially affected the conduct of this study.

6.3.2. Study Results

Compliance with Good Clinical Practices

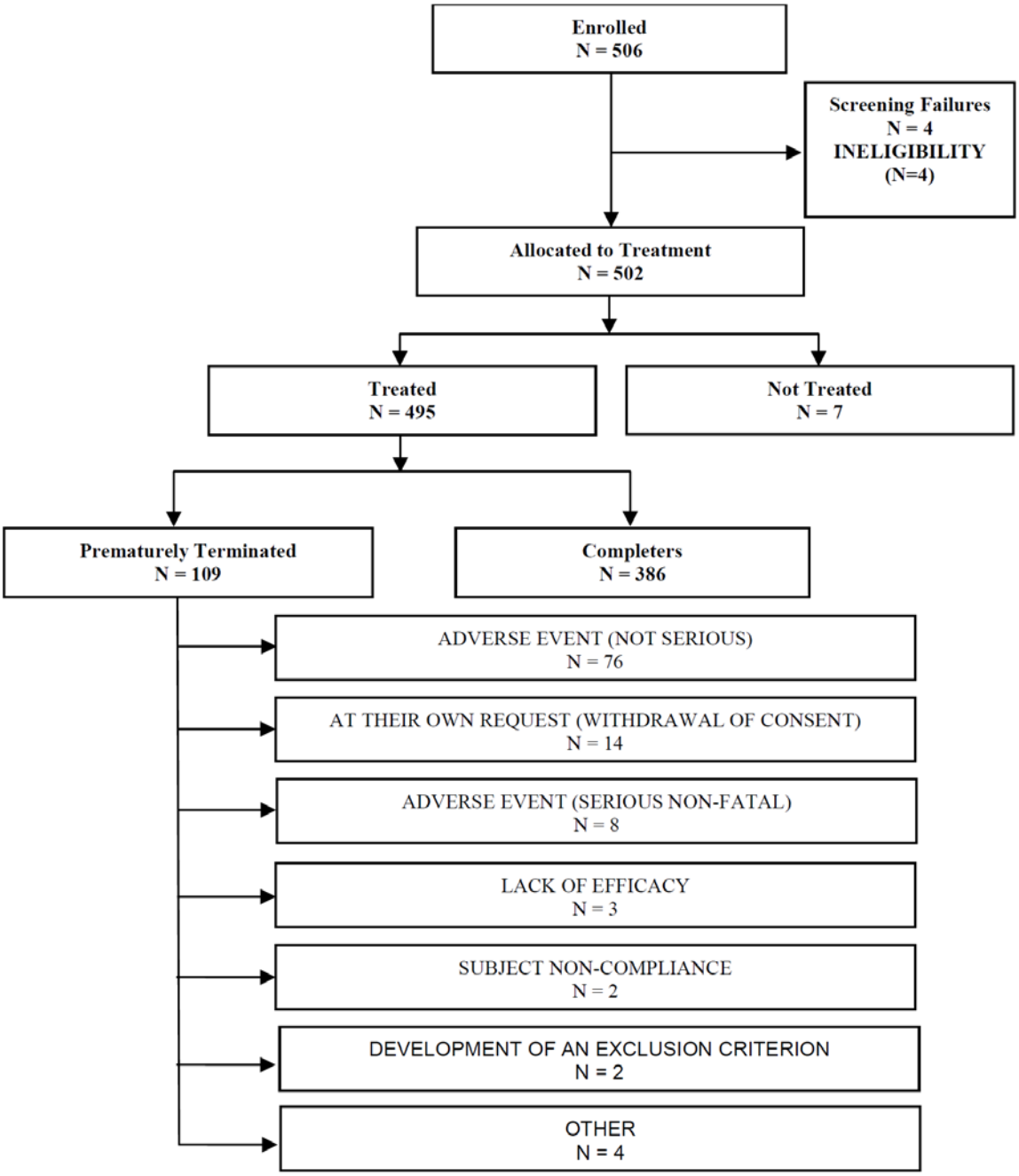
The sponsor has provided attestation that this study was conducted in accordance with the ICH Guideline for Good Clinical Practice (GCP) (E6), and with the Commission Directives 2001/20/EC, 2005/28/EC and 2001/83/EC. Because this study was conducted solely in the UK and Germany, the study protocol, informed consent documents, and other appropriate study-related documents were reviewed and approved by local independent ethics committees.

Financial Disclosure

No financial disclosure information was provided regarding the investigators used in this post EU-approval marketing study

Patient Disposition

Figure 8 Study 401 study population disposition and reasons for termination (source: CSR, page 52)



Protocol Violations/Deviations

In this study 63 of 495 patients (13%) had reports of major protocol violations. Half of these were related to poor compliance (outside of 80-120% use range) and most of the remainder were related to changes in underlying levodopa treatment.

Table of Demographic Characteristics

Table 22 Study 401 demographic characteristics of the safety population (source: CSR, page 60)

Parameter	Category	Statistic	Total N = 495
Age (years)		n	495
		nmiss	0
		Mean	67.7
		SD	8.98
		Min/Max	43/87
		Median	69.0
Age (years)	≥ 18 to < 65	n (%)	164 (33.1)
	≥ 65 to < 85	n (%)	325 (65.7)
	≥ 85	n (%)	6 (1.2)
Gender	Male	n (%)	315 (63.6)
	Female	n (%)	179 (36.2)
	Missing	n (%)	1 (0.2)
Race	White	n (%)	495 (100.0)

Table 23 Study 401 safety population baseline Parkinson's disease characteristics (source: CSR, page 61)

Parameter	Statistic	Total N = 495
Duration of Parkinson's disease (months)	n	495
	Mean	102.1
	SD	59.60
	Median	89.0
	Min/Max	5/420
Duration of wearing-off motor fluctuations (months)	n	493
	Missing	2
	Mean	30.1
	SD	37.97
	Median	15.0
	Min/Max	0/324

Almost 80% of the PD patients in this study reported taking at least one additional anti-PD medication in addition to the levodopa/DDCI. Most common were rasagiline (28%), pramipexole (25%), ropinirole (22%) and amantadine (21%). Treatment compliance with the IMP was estimated at 92%.

Efficacy Results

Individual patient efficacy data from this open and uncontrolled study were not submitted in reviewable form.

Data Quality and Integrity

The sponsor performed audits on 10 of 68 enrolling clinical sites using procedures in conformance with good clinical practice and usual sponsor oversight of the CRO and clinical trial sites. Overall, 495 patients received at least one dose of active treatment.

Site 211 (UK) with 11 patients receiving treatment was found to have troubling deviations from GCP. These included lack of investigator oversight, data confidentiality/integrity, lack of source data and essential documents, incorrect SAE and AE reporting, protocol non- compliances and low return of investigational drug resulting in full accountability not being possible. In a decision made prior to database lock, the sponsor has excluded this site's data from analysis.

Safety Results

Individual adverse data was not submitted for review. Reported safety events including deaths, serious adverse events and events leading to drug discontinuation are included in the

integrated review of safety below.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This assessment of efficacy across the two Phase 3 opicapone trials will be brief as both trials were similarly designed to evaluate the 50 mg/d dose against placebo, had identical endpoints, were performed in similar populations, had identical statistical analyses, and yielded similar results. The combined FAS of the two studies comprised 997 PD patients of whom 255 were assigned to placebo and 262 were taking 50 mg/d (the remainder in 5 mg/d, 25 mg/d or entacapone treatment arms). The placebo and 50 mg active treatment populations were comparable in their respective demographic characteristics.

Table 24 Phase 3 FAS demographic characteristics (source: datasets, ISE Table 1.1.1)

Characteristic	PBO N=255	Opicapone 50 mg N=262
Age (years)		
Mean (SD)	62.9 (9.12)	64.6 (8.81)
Median (min, max)	63.0 (36, 83)	65.0 (36, 83)
Age groups – n (%)		
<65 years	143 (56.1)	123 (46.9)
≥65 years	112 (43.9)	139 (53.1)
Age groups – n (%)		
<65 years	143 (56.1)	123 (46.9)
≥65 - <75 years	91 (35.7)	108 (41.2)
≥75 years	21 (8.2)	31 (11.8)
Sex – n (%)	255	262
Male	141 (55.3)	158 (60.3)
Female	114 (44.7)	104 (39.7)
Race – n (%)		
White	209 (82.0)	230 (87.8)
Black	0	0
Asian	42 (16.5)	31 (11.8)
Other	3 (1.2)	1 (0.4)
Missing	1 (0.4)	0
Geographic region - n (%)		
Western Europe[a]	40 (15.7)	41 (15.6)
ROW[b]	215 (84.3)	221 (84.4)
Weight (kg), n	255	262
Mean (SD)	73.81 (15.323)	73.63 (14.968)
Median (min, max)	72.60 (39.4, 133.8)	75.00 (43.0, 141.0)

Table 25 Phase 3 FAS PD characteristics (source: datasets, ISE Table 1.2)

Characteristic	PBO N=255	Opicapone 50 mg N=262
Time since PD diagnosis (years)		
Mean (SD)	7.73 (3.923)	7.67 (4.285)
Median (min, max)	6.70 (2.5, 24.0)	6.45 (3.0, 30.5)
Time since start of motor fluctuations (years), n	243	246
Mean (SD)	2.60 (2.159)	2.74 (2.884)
Median (min, max)	2.00 (0, 11.8)	1.71 (0, 21.5)
Presence of dyskinesia at DB baseline, n (%)		
Yes	122 (47.8)	131 (50.0)
No	133 (52.2)	131 (50.0)
Hoehn and Yahr staging during ON state at DB baseline, n (%)		
<2.5	113 (44.3)	113 (43.1)
≥2.5	142 (55.7)	149 (56.9)
UPDRS III during ON state at DB Baseline		
Mean (SD)	24.9 (12.07)	25.1 (13.23)
Median (min, max)	24.0 (2, 58)	23.0 (2, 73)
UPDRS III during ON state at DB Baseline, n (%)		
<24	117 (45.9)	132 (50.4)
≥24	138 (54.1)	130 (49.6)

Table 26 Phase 3 FAS anti-PD treatment regimen (source: datasets, ISE Table 1.2)

Treatment at DB Baseline	PBO N=255	50 mg N=262
Time since start of levodopa (years)		
Mean (SD)	6.31 (3.671)	6.32 (4.396)
Median (min, max)	5.63 (0.4, 18.2)	5.14 (1.1, 30.5)
Levodopa TDD (mg/day)		
Mean (SD)	695.60 (321.320)	698.08 (322.765)
Median (min, max)	625.00 (150.0, 2000.0)	600.0 (150.0, 2100.0)
Levodopa TDD (mg/day) groups, n (%)		
<700 mg/day	138 (54.1)	143 (54.6)
≥700 mg/day	117 (45.9)	119 (45.4)
DDCI treatment, n (%)		
Carbidopa only	129 (50.6)	138 (52.7)
Benserazide only	105 (41.2)	110 (42.0)
Both carbidopa and benserazide	21 (8.2)	14 (5.3)
≥1 Dopamine agonist, n (%)		
Yes	186 (72.9)	181 (69.1)
No	69 (27.1)	81 (30.9)
≥1 MAO-B inhibitor, n (%)		
Yes	49 (19.2)	57 (21.8)
No	206 (80.8)	205 (78.2)
Amantadine, n (%)		
Yes	57 (22.4)	54 (20.6)
No	198 (77.6)	208 (79.4)
≥1 Anticholinergic, n (%)		
Yes	20 (7.8)	22 (8.4)
No	235 (92.2)	240 (91.6)

At baseline, the two cohorts were also equivalent regarding daily OFF-time (6 hours) and ON-time without troublesome dyskinesia (about 9.5 hours).

7.1.1. Primary Endpoints

The primary endpoints of both trials were quantified by patients or caregivers using the PD diary in which they rated their mobility as OFF, ON with troublesome dyskinesia, ON with non-troublesome dyskinesia, ON without dyskinesia, or Asleep, for each 30-minute period during the day.

The primary efficacy endpoint in both studies was the change from baseline (CFB) in absolute OFF-time (average of the daily sum of OFF-time on the 3 days prior to visit) at the end of the DB treatment period (14 to 15 weeks following randomization).

Table 27 Phase 3 FAS Primary efficacy endpoint OFF time (hours) change from baseline (source: datasets, ISE Table 3.2)

Timepoint / Statistics	PBO N=255	Opicapone 50 mg N=262
Baseline, n	255	262
Mean (SE)	6.14 (0.130)	6.27 (0.126)
Visit 7, n	255	262
Mean (SE)	5.22 (0.183)	4.33 (0.165)
Mean CFB (SE)	–0.92 (0.165)	–1.94 (0.165)
LS mean CFB (SE)	–1.21 (0.172)	–2.17 (0.170)
95% CI	(–1.546, –0.872)	(–2.500, –1.834)
LS mean difference vs. placebo (SE)	–	–0.96 (0.219)
95% CI	–	(–1.387, 0.529)
Nominal p value	–	<0.001
ANCOVA treatment p value	0.001	

In both Studies 301 and 302, the treatment effect was established by the 3rd week after imitation and persisted through the final evaluation visit at week 14-15. The sponsor's mixed model for repeated measures revealed significant differences in OFF time reduction between 50 mg/d and placebo through the treatment periods.

Analysis of ON time without troublesome dyskinesia for the pooled FAS also supports that the finding of improvement in clinical status did not come at the expense of increasing levodopa induced dyskinesia.

Table 28 Phase 3 FAS Increase in ON time (hours) without troublesome dyskinesia (source: ISE Table 4.2)

Timepoint / Statistics	PBO N=255	Opicapone 50 mg N=262
Baseline, n[a]	255	262
Mean (SE)	9.61 (0.141)	9.44 (0.130)
Visit 7, n	255	262
Mean (SE)	10.32 (0.176)	11.06 (0.184)
Mean CFB (SE)	0.71 (0.172)	1.62 (0.171)
LS mean CFB (SE)	0.96 (0.182)	1.79 (0.180)
95% CI	(0.601, 1.315)	(1.441, 2.146)
LS mean difference vs. placebo (SE)	–	0.84 (0.232)
95% CI	–	(0.380, 1.291)
Nominal p value	–	<0.001

7.1.2. Secondary and Other Endpoints

The pre-specified key secondary outcomes were responder analyses: OFF-time responders (1 hour or more reduction in absolute OFF-time from baseline to endpoint) and ON-time responders (1 hour or more increase in absolute ON-time from baseline to endpoint).

Table 29 OFF and ON time FAS responder rates (source: CSR Studies 301 and 302)

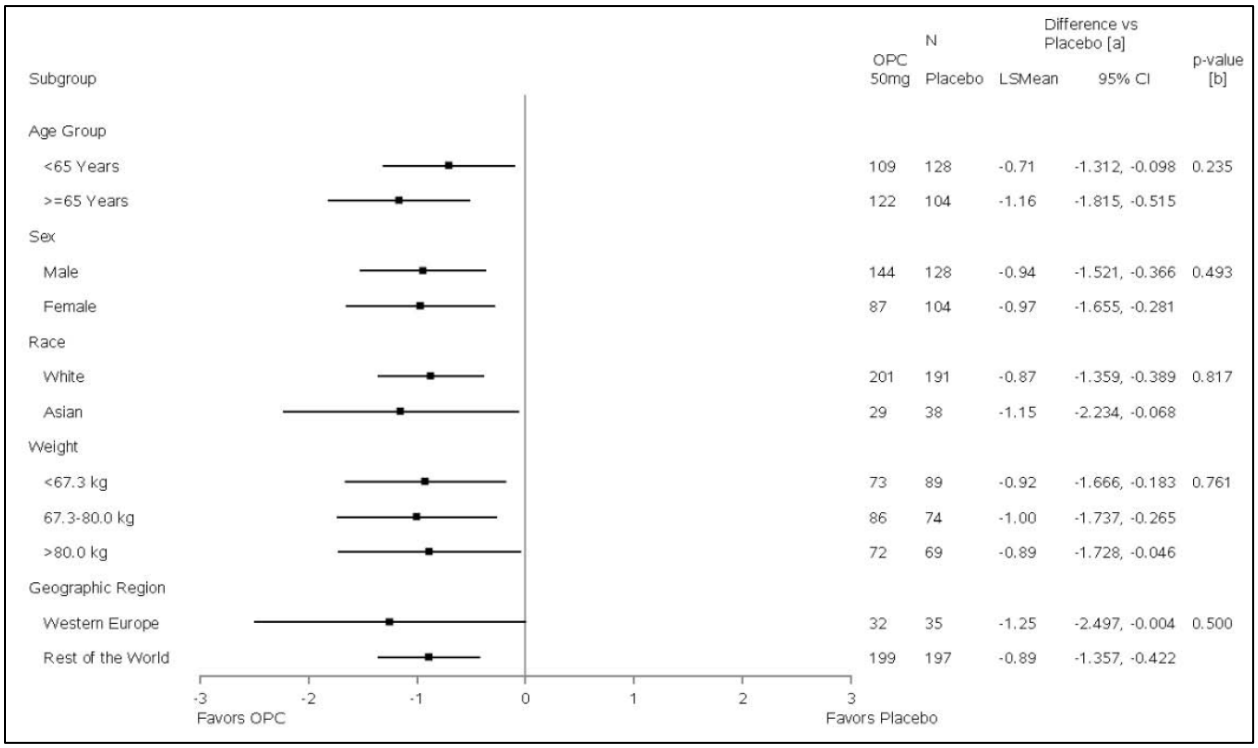
Responders	Study 301		Study 302	
	PBO N=120	50 mg N=115	PBO N=135	50 mg N=147
OFF-time, n (%)	57 (47.5)	80 (69.6)	68 (50.4)	97 (66.0)
p value (difference from placebo)	-	0.0011	-	0.0088
ON-time, n (%)	55 (45.8)	75 (65.2)	61 (45.2)	91 (61.9)
p value (difference from placebo)	-	0.0028	-	0.0061

In both pivotal studies, opicapone treatment resulted in a statistically significant increase in the number of patients with reduced OFF-time and increased ON-time (Cochran-Mantel-Haenszel non-parametric analysis). While the difference in the proportion of responders between active and placebo treatments were approximately the same in both studies, the effect of placebo on this outcome was more pronounced in Study 302.

7.1.3. Subpopulations

The results of the MMRM analysis of the primary efficacy endpoint of the change from baseline in absolute OFF-time at Visit 7 are presented for the pooled Phase 3 subgroups in the sponsor's table below. In all subgroups, while the treatment effect favored the opicapone-treated groups, there were no statistically significant treatment-by-subgroup interactions. No dosing modification (i.e. reduction to 25 mg/d due to adverse treatment effect) for any specific subgroups was identified.

Figure 9 Phase 3 FAS Forest Plot of Absolute Off time change from baseline by subgroup (source: SCE, p 69)



Similarly, there were no differential responses to active treatment when disease-related features were investigated: Hoehn and Yahr stage or UPDRS motor score at baseline, daily levodopa dose, and concurrent dopamine agonist, MAO-B inhibitor, anticholinergic, or amantadine therapy.

There were also no statistically significant or qualitative treatment-by-subgroup interactions for the key secondary measures.

7.1.4. Dose and Dose-Response

Only a single daily dose of opicapone was evaluated for use in the Phase 3 program.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The onset of the pharmacodynamic effect of opicapone in the Phase 3 studies was performed by the sponsor using repeated measures of the efficacy outcomes. This reveals that that full clinical improvement was largely evident by Visit 4 (week 2-3 of the titration period) in both Study 301 and 302 and remained level for the remainder of the visits.

Table 30 Phase 3 change from baseline in absolute OFF hours by study visit in the FAS (source: SCE p 57)

Timepoint / Statistics	OPC	
	25 mg N=241	50 mg N=262
Visit 3 LS mean difference vs. placebo (SE)	-0.63 (0.181)	-0.77 (0.177)
95% CI	(-0.989, -0.279)	(-1.117, -0.422)
Nominal p value	<0.001	<0.001
Visit 4 LS mean difference vs. placebo (SE)	-0.72 (0.202)	-1.06 (0.198)
95% CI	-1.116, -0.324	-1.444, -0.669
Nominal p value	<0.001	<0.001
Visit 5 LS mean difference vs. placebo (SE)	-0.52 (0.217)	-1.11 (0.214)
95% CI	(-0.944, -0.092)	(-1.528, -0.688)
Nominal p value	0.017	<0.001
Visit 6 LS mean difference vs. placebo (SE)	-0.70 (0.216)	-0.68 (0.213)
95% CI	(-1.127, -0.279)	(-1.093, -0.258)
Nominal p value	0.001	0.002
Visit 7 LS mean difference vs. placebo (SE)	-0.55 (0.227)	-0.94 (0.223)
95% CI	(-0.996, -0.106)	(-1.382, -0.504)
Nominal p value	0.015	<0.001

At the end of the DB periods of the Phase 3 studies, participants could enter an additional 1-year, OL period in which all patients were treated with opicapone, the majority with 50 mg/d day. (The OLEX for Study 301 extended the dose received by the patient in the DB period: 5 mg, 25 mg, or 50 mg daily). The total duration of opicapone treatment for an individual subject in these studies, including DB and OL, was up to 67 weeks. Efficacy data were summarized by the sponsor using descriptive statistics including changes from DB and OL baselines.

In the OLEX of Study 301, 495 patients enrolled and 87% completed (n=432). In Study 302, 367 enrolled in the OLEX and 78% completed (n=286). The sponsor's efficacy analysis of open label treatment included these completers as well as the last observation carried forward for non-completers. In Study 301, 84 patients received 50 mg/d in the DB study and received the same in the OLEX (and were not subject to initial treatment titrations). For this group, by the end of the OLEX period, there was little change in the primary and key secondary outcome measures from the start of the OLEX period. The sponsor's analysis for Study 302 did not discriminate whether the patient had been 25 or 50 mg/d in the double blind period but the treatment effect in the OLEX was also substantially maintained.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

No additional information on efficacy was derived from reports from the use of opicapone following marketing authorization in the EU.

7.3. Integrated Assessment of Effectiveness

The proposed indication for opicapone is a catechol-O-methyltransferase (COMT) inhibitor indicated as adjunctive treatment to levodopa/carbidopa (LD/CD) in patients with Parkinson's disease (PD) experiencing "OFF" episodes.

The sponsor has submitted two adequate and well-controlled clinical trials demonstrating substantial evidence of effectiveness in support of this indication. Studies 301 and 302 have core features in common that evaluate opicapone to ameliorate the amount of OFF-time in PD patients. Using an established patient-reported outcome employing patient-completed PD diaries, these studies compared opicapone 50 mg/d to placebo in double-blind and randomized fashion, investigating its ability to reduce the absolute OFF-time (average of the daily sum of OFF-time on the 3 days prior to visit) when evaluated at the end of the double-blind period (14 to 15 weeks following randomization). Secondary outcome measures supported this primary efficacy measure: responder analyses of the percent of those patients who reduced OFF-time by at least 1 hour and the percent of those patients who increased ON--time by at least 1 hour. Furthermore, the increase in ON-time had to come without the liability of increasing levodopa induced dyskinesia, a disabling phenomenon which may accompany increased dopaminergic tone from medication changes in advanced PD patients. Using appropriate methods of statistical analysis, both studies succeeded in this regard.

In Study 301, the placebo and 50 mg/d treatment arms both had 6.2 hours of OFF-time at baseline. The mean reduction in OFF-time at endpoint was 106.8 minutes in the 50 mg /d arm and 44.8 minutes in the placebo group (p=0.0005). A one hour decrease of OFF-time was achieved in 47.5% of placebo patients and 69.6% of opicapone 50 mg/d patients (p=0.0011). Likewise, the proportion of ON-time responders was significantly higher in the opicapone 50 mg/d arm than in the placebo group (65.2% vs 45.8%, p=0.0028). Finally, this improvement did not come at the expense of troublesome dyskinesia. Where placebo arm patients increased their ON-time without troublesome dyskinesia (WOTD) 35.0 minutes on average, patients receiving 50 mg/d had an average increase of 100.5 minutes. This difference of 65.5 minutes was significant (p=0.0016).

In Study 302, the placebo and 50 mg/d treatment arms had 6.12 and 6.32 hours of OFF-time at baseline, respectively. The mean reduction in OFF-time at endpoint was 124.0 minutes in the 50 mg /d arm and 64.5 minutes in the placebo group (p=0.0081). A one hour decrease of OFF-time was achieved in 50.4% of placebo patients and 66.0% of opicapone 50 mg/d patients (p=0.0088). Likewise, the proportion of ON-time responders was significantly higher in the opicapone 50 mg/d arm than in the placebo group (61.9% vs 45.2%, p=0.0061). This improvement was not accompanied by troublesome dyskinesia. Where placebo arm patients

increased their ON-time WOTD only 0.4 minutes on average, patients receiving 50 mg/d had an average increase of 45.7 minutes (p=0.048).

Neither study revealed an important contribution to efficacy by subgroup analyses of age, gender, race, and disease characteristics.

Combining both Phase 3 studies there is a statistically valid reduction of an average 1.94 hours of OFF-time in opicapone 50 mg/d treated patients, reducing the daily duration of a lack of beneficial medication effect for the PD patient as self-reported by diary. This compares favorably to a mean reduction of 1.02 hours of reduced OFF time in the placebo treated patients. More importantly, this reduction in OFF-time was not associated with troublesome dyskinesia; 50 mg/d patients had an average increase of 1.62 hours of ON-time WOTD, while the placebo arm increased 0.71 hours.

On face, it is evident that the possibility of a benefit of this magnitude of increased ON-time with good function (i.e., without disabling dyskinesia), represents a clinically important improvement in the motor status (and daily life) of the advanced PD patient.

8. Review of Safety

8.1. Safety Review Approach

The review of safety for opicapone includes all persons who received one or more doses of the medicinal product. The aim of this section was to determine the safety of the intend-to-market product, evaluating the drug dose and duration of exposure.

The drug is planned for daily use in advanced PD patients with an intended single evening dose of 50 mg. However, both pivotal trials included an arm of 25 mg, necessary by design in the case of unacceptable dyskinesia or other dose related adverse event requiring dose reduction. One of the studies had also comparison treatment arms with opicapone 5 mg/d once daily or entacapone 200 mg taken with each carbidopa/levodopa dose. The entacapone treatment arm is not reviewed in this application; the opicapone 5 mg/d dose is addressed if significant or serious adverse events may have occurred but not beyond this. On a practical level, the aligned designs of Studies 301 and 302 and the identical PD patient demographics allow these to be combined for analysis (hereinafter Phase 3 DB cohort). The individual adverse event profiles for each trial support using a single integrated analysis for these two studies. Similarly, the open label periods for Studies 301 and 302 are combined for analysis (Phase 3 OLEX cohort).

As noted above, there was difficulty in using usual FDA analytic tools for the legacy ISS datasets submitted. Datasets were only provided for the safety population of Studies 301 and 302. The

remainder of the data was provided by the sponsor in line listings and tabulations. Narratives were appropriately provided for serious adverse events, deaths and dropouts due to AEs. The verbatim description of AEs and Preferred Terms used in the equivalent of the ISS ADAE dataset were inspected for terms noted for being prone to split similar types of adverse events. This was important regarding adverse events of special interest. Where this reviewer's results differ from the sponsor's submission, both are shown. It should be noted that the sponsor's tabulations of AEs included only those considered treatment emergent (TEAE). This determination was based on the site investigator's judgment whether the event was treatment-related. In some cases, this judgement was likely a guess or an opinion rather than fact, especially, for example, in the case of dyskinesia or orthostatic hypotension which could be due to concomitant anti-PD drugs. My tabulations were created using the study and ISS datasets directly

For this review, while all early phase studies are examined for severe or serious events, the bulk of safety information comes from the Phase 3 Studies 301 and 302, constituting 94.5% of all PD patients (965 of 1021) in the development program.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

In the opicapone development program 2025 persons received at least one dose of opicapone. Of these, 988 were healthy volunteers, 16 were non-PD hepatically impaired subjects, and the remainder (1021) were PD patients. These numbers do not include the 495 PD patients treated in Phase IV Study 401 submitted in the 120 day Safety Update; these patients are not included in the verifiable exposure data provided by the Phase 3 datasets.

A variety of micronized and non-micronized formulations of opicapone were evaluated and accounted for the sizeable non-PD population. All non-PD patients had less than one month exposure to opicapone, and most only 1 or 2 days.

In Phase 1 studies, 16 PD patients had less than one month exposure, all receiving 50 mg/d. In Phase 2 studies, 40 PD patients were exposed to opicapone with only 10 reaching the 50 mg/d dose. All Phase 2 patients were also treated for 1 month or less.

The source of the controlled Phase 3 safety population is from the double blind trials. The table below indicated the number exposed in those studies and how they rolled over into the open label long term population in the extension studies.

Table 31 Sources of the Phase 3 safety population (source: sponsor's ISS datasets)

Study	DB OPC Arm	N treated		OL Extension*
301	5 mg/d	122	→	100
	25 mg/d	119	→	98
	50 mg/d	116	→	98
	From placebo or entacapone arms		→	199
302	25 mg/d	129	→	114
	50 mg/d	154	→	125
	From placebo arm		→	128

* Both open label extensions had variable treatment rules for treatment assignment. In Study 301, OL patients were started on their DB dose and adjusted as needed. Roughly 41% received 50 mg/d, 53% received 25 mg/d and less than 5% received 5 mg/d as their modal dose in the OLEX. In Study 302, OL patients were to begin at 25 mg and then increased to 50 mg.

When combined, these two studies yield blinded safety data on both the 50 mg/d (n=270) and 25 mg/d (n= 248) doses. Long term safety data that includes the DB and OLEX portions of these studies yields information on patients taking either 25 or 50 mg/d. The ISS indicates the following dose and duration exposure in Phase 3.

Table 32 Phase 3 opicapone dose and exposure (sponsor's table, ISS Report, page 59)

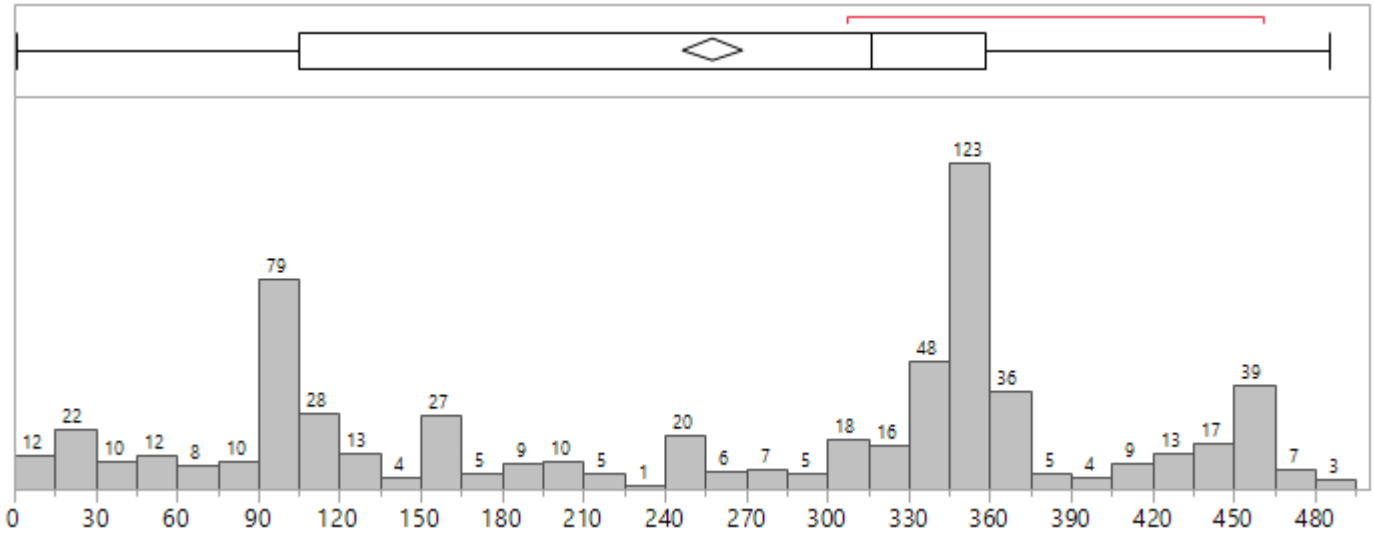
Phase 3 Duration of Exposure	Opicapone			
	<25 mg	25 mg	50 mg	Any Dose
At least 1 dose	157	897	631	965
1 day	1	2	1	2
2 days to <1 month	12	270	33	36
1 month to <3 months	10	74	40	39
3 months to <6 months	109	168	156	81
6 months to <12 months	18	127	268	108
12 months or greater	7	256	133	699

It is important to note that in this table the sponsor counts patients more than once for any given dose level, e.g. patients who received 25 mg and then 50 mg were counted in both of

those columns. However, they were counted only one in the "any dose" column. This is a direct result of the legacy dataset structure and this is reflected in the submitted ISS ADEX dataset covering the 1025 patients in the two Phase 3 studies, who are reported as 1685 patients taking the 3 dose levels of 5 mg, 25, mg, and 50 mg (n= 157, 897, and 631, respectively).

Because 50 mg/d will be the labeled dose for opicapone, I isolated those 631 patients who took 50 mg and tallied exposure for that dose alone. Note that this would not include exposure for a given patient at a lower dose, i.e. if a patient took 25 mg for 64 days and then 50 mg for 98 days, only the 98 days is reflected in the graph below.

Table 33 Phase 3 opicapone 50 mg/d duration of exposure in days (source: ISS ADEX dataset)



The mean exposure for the 50 mg dose was 258 days in Phase 3 (mean 95% CI 247 – 268 days). Using a standard month of 30 days, the following duration of exposure at 50 mg was calculated from the ISS ADEX dataset. This confirms the sponsor's calculation (ISS Table 1.7.1 p 247 and reveals adequate numbers of patients to judge the safety of the proposed dose:

Table 34 Sponsor's estimation of duration of exposure to 50 mg/d (source: ISS table 1.7.1., page 247)

Phase 3 Duration of Exposure	Studies 301 + 302 (DB+ OLEX)		
Opicapone 50 mg (N=631)			
0 to <3 months	3 months to <6 months	6 months to <12 months	≥12 months
74	156	268	133

8.2.2. Relevant characteristics of the safety population:

Demographic Characteristics
Using the ISS ADSL dataset, I removed the treatment arms for entacapone 200 mg and opicapone 5 mg. (These did not provide useful information for understanding the comparative safety of the two dosages of opicapone.) The resulting n of 781 did not demonstrate any important demographic differences:

Table 35 Phase 3 safety population demographic features (source: ISS ADSL dataset)

Phase 3 Safety Population (n=781)	Placebo	OPC 25 mg	OPC 50 mg
Demographic Parameters	n = 265 (34%)	n = 248 (32%)	n = 268 (34%)
Sex			
Male	149 (56%)	153 (62%)	162 (60%)
Female	116 (44%)	95 (38%)	106 (40%)
Age			
Mean years (SD)	62.7 (9.2)	63.4 (8.7)	64.4 (8.2)
Median (years)	63	63.5	65
Min, max (years)	36-83	41-82	36-83
Age Group			
< 65 years	151 (57%)	136 (55%)	129 (48%)
≥ 65 years	114 (43%)	112 (45%)	139 (52%)
> 65 - < 75 years	92 (35%)	84 (34%)	108 (40%)
≥ 75 years	22 (8%)	28 (11%)	31 (12%)
Race			
White	211 (81%)	209 (86%)	231 (87%)
Black or African American	0	0	0
Asian	50 (19%)	33 (14%)	36 (13%)
Missing	4	6	1

Disease Characteristics and Anti-Parkinson Medication Use
Similarly, there were no important differences in the duration or character of the PD syndrome nor treatments being taken by the patients across treatment arms. The mean duration since PD diagnosis was 7.6 years and the mean length of time since the appearance of motor fluctuations was 2.6 years prior to enrollment. Most patients (57%) had at least moderate Parkinson's disease, as indicated by modified Hoehn and Yahr stage ≥2.5 (i.e., bilateral symptoms and signs of disease with some balance impairment) and mean UPDRS Part III motor score of 25.6, in the ON state.

At baseline, 47% of the subjects had dyskinesia (based on response to the single UPDRS item)

and the mean daily dose of levodopa was 692 mg in divided doses. Most patients were on concurrent treatment with a dopamine agonist (68%), while fewer were on a MAO-B inhibitor (20%), amantadine (22%), or anticholinergic (8%) treatment.

Domperidone, an antiemetic not approved for use in the US, was taken by 5.4% of the opicapone safety population, the same proportion regardless of dose. Of interest, 7.8% of the placebo population received domperidone, reflecting the observation that most dopaminergic antiparkinson drugs are capable of inducing nausea in susceptible individuals.

About 16% of the safety population used anti-depressant medication for the control of psychiatric symptoms. Anxiolytic mediation, mostly of the benzodiazepine class, was used by 23% of the safety population. Use of both these two groups of medication were well balanced across treatment arms. A few patients (n=18) were treated with neuroleptics, all but one with quetiapine.

Table 36 Phase 3 safety population Parkinson's disease characteristics (source: ISS ADSL dataset)

Phase 3 Safety Population (n=781)	Placebo	OPC 25 mg	OPC 50 mg
	n = 265 (34%)	n = 248 (32%)	n = 268 (34%)
PD characteristics (mean, SD)			
Years of PD	7.6 (3.9)	7.8 (4.3)	7.6 (4.2)
Baseline UPDRS Part III	25 (12)	25 (13)	25 (13)
Years of motor fluctuation	2.6 (2.2)	2.7 (2.7)	2.7 (2.9)
Years of L-DOPA treatment	6.3 (3.6)	6.5 (4.1)	6.3 (4.4)
Percent with dyskinesia at baseline	46%	46%	50%
Baseline PD treatment:			
L-DOPA mg/d at baseline	685 mg (321 mg)	727 mg (369 mg)	695 mg (322 mg)
Percent taking amantadine	23%	24%	21%
Percent taking dopamine agonist	73%	67%	69%
Percent taking MAO-B inhibitor	20%	21%	22%

8.2.3. Adequacy of the safety database:

The size of the safety population is adequate and usual for a drug intended for chronic use in advanced PD patients. The demographic and disease-related characteristics, medical histories, and concomitant medications are also typical of the advanced PD population with motor fluctuations. The population was, in the main, a group comprised of European Caucasian patients and there is no evidence in the scientific literature or in the experience of this reviewer

than they would respond differently to the medication compared to the intended population in the US.

The measures of compliance employed in the pivotal trials to quantify compliance with administered medication and the method of assessment of the efficacy outcome support the adequacy of the submission. The querying for AEs, their assessment, and reporting appear to be adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no issues of significance identified prior to or during the review period that fueled concern regarding the integrity or quality of the NDA submission. Issues of quality occurring at individual sites were adequately discovered and addressed by the sponsor. No irregularities were discovered that would materially affect the assessment of the efficacy or safety of opicapone. Investigations performed by OSI did not uncover any need for further action.

8.3.2. Categorization of Adverse Events

All AEs in the ISS were coded (or re-coded, where necessary) using MedDRA version 20.0.

The trial protocols addressed the recording and categorization of adverse events in a generally standard fashion giving definitions of severity, seriousness, duration, relatedness to the investigational drug, and actions to be taken. Querying the patient about the occurrence of AEs was actively addressed in the conduct of the studies.

TEAEs were defined as all AEs with onset or worsening after the first intake of opicapone (or equivalent study drug dictated by treatment arm) until 14 days after the last intake of study drug. The exception to this was an SAE considered related to opicapone which was followed through resolution. Unless a patient came in unexpectedly or called, TEAEs were recorded at the next scheduled outpatient visit.

Reviewer comment: In the Study 301 and 302 protocols, the sponsor states that "TEAEs and possibly related TEAEs (i.e. any possibly, probably, or definitely related TEAEs) will be summarized and tabulated according to primary system organ class and preferred term." The term "TEAE" as used in the sponsor's tabulations does not always make plain when tables use all AEs occurring during treatment or just those TEAEs where the causality to opicapone is suspected. In these cases, the reviewer repeated the analyses and noted differences where they occur.

8.3.3. Routine Clinical Tests

Vital signs (systolic and diastolic blood pressure, pulse rate) and weight were determined at every visit. Blood pressure was measured twice: in the sitting position after the subject rested in a quiet room for at least 3 minutes and in standing position after 2 minutes.

Reviewer's comment: This method was suggested by the Division upon opening the IND. The Phase 3 studies had already begun by that time and this method was added to the protocols by amendment.

A central laboratory performed all clinical tests. The following were measured at most visits (see Schedule of Events, above):

Biochemistry: sodium, potassium, chloride, calcium, phosphate, glucose, creatinine, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, CPK, lactic dehydrogenase, albumin, total protein, total cholesterol, low- and high-density lipoprotein cholesterol, triglycerides, total bilirubin and direct/indirect bilirubin. Serum pregnancy test was only taken as a screening measure.

Hematology: red blood cell count, hematocrit, hemoglobin, white blood cell count (total and differential), and platelet count.

Coagulation: prothrombin time (INR and activated partial thromboplastin time).

Urine was assessed for pH, specific gravity, protein, blood, glucose, ketones, bilirubin, urobilinogen (dipstick). Microscopy and other tests (as needed) were to be performed by the central laboratory if dipstick testing indicated any significant abnormality.

Electrocardiogram: A 12-lead resting ECG was obtained at baseline, five subsequent visits and at the end of the study visit. Each 12-lead ECG copy was printed locally and sent to the sponsor's data management center for evaluation.

8.4. Safety Results

8.4.1. Deaths

There were 18 deaths in the opicapone development program, all occurring in the Phase 3 studies. Of these, one death occurred before treatment was administered and 1 occurred in a person taking placebo in the blinded period. A third death occurred 1 month after treatment cessation. Two deaths occurred while receiving entacapone as the active treatment. The remaining 13 deaths occurred during open-label treatment.

Table 37 Deaths in the opicapone development program (source: sponsor's ISS Report, p. 61)

Subject ID	Age/Sex	DB Treatment	Last Treatment Before Event	Study Day at Onset/ Days Since First OPC Exposure	Preferred Term
BIA-91067-301 OL					
(b) (6)	79/M	25 mg	OPC 50 mg	411 / 411	Pneumonia
	73/M	Entacapone	OPC 50 mg	470 / 370	Lung disorder
	61/M	50 mg	OPC 50 mg	410 / 410	Multiple organ dysfunction syndrome
	66/M	Entacapone	OPC 50 mg	419 / 322	Sudden death
	75/M	5 mg	OPC 50 mg	190 / 190	Myocardial infarction
	66/F	5 mg	OPC 50 mg	418 / 418	Death
	65/M	50 mg	OPC 50 mg	328 / 328	Small cell lung cancer
	70/F	5 mg	OPC 25 mg	359 / 359	Embolism
	57/M	50 mg	OPC 50 mg	363 / 363	Metastases to spine
	62/M	50 mg	OPC 25 mg	424 / 424	Pulmonary embolism
	73/M	Placebo	OPC 25 mg	392 / 301	Cardiovascular insufficiency
BIA-91067-302 Pretreatment					
(b) (6)	67/M	Pretreatment	Pretreatment	--	Myocardial infarction
BIA-91067-302 DB					
(b) (6)	75/M	Placebo	Placebo	27 / 0	Pneumonia
BIA-91067-302 OL					
(b) (6)	57/F	50 mg	OPC 50 mg	195 / 195	Septic shock
	63/M	25 mg	OPC 25 mg	161 / 161	Death
	70/M	25 mg	OPC 25 mg	310 / 310	Skull fractured base
				310 / 310	Cerebral haemorrhage
				310 / 310	Craniocerebral injury
	57/M	50 mg	OPC 50 mg	194 / 194	Cerebral haemorrhage
	60/M	25 mg	OPC 50 mg	239 / 239	Small cell lung cancer

Following review of all narratives, it is apparent that the deaths resulted from complications of cancer, infection, cardiovascular disease, hypertension, or the consequences of advanced Parkinson's disease (e.g., head trauma). In this last case (ID (b) (6)) the contribution of opicapone to the AE cannot be ruled out. (Please see the discussion in Section 8.5.7 Injuries and Falls.) One additional death (ID (b) (6)) occurred in Study 401 and was reported in the 120-day Safety Update. This 69 year old man was on 50 mg opicapone for one month before being hospitalized after a week of fever, chills, backpain, and confusional state. He was discovered to

have endocarditis and during treatment progressed to pneumonia (likely nosocomial in nature) and died as a result.

8.4.2. Serious Adverse Events

The following review of SAEs excludes the deaths noted above.

Phase 1 and 2
In Phase 1 and 2 of the opicapone development program there were 8 SAEs, all in healthy volunteers, one occurring before the patient in Study 124 was enrolled. Three others occurred while on placebo.

Table 38 Phase 1 and 2 SAEs (source: sponsor's ISS Report, page 174)

Study	Subject ID	Age/Sex	Treatment at Onset	Preferred Term	Severity	Outcome
BIA-91067-101	(b) (6)	21/M	Placebo	Spastic paraplegia	Severe	Recovered
BIA-91067-102		21/M	Placebo	Hemiparesis	Moderate	Recovered
BIA-91067-114		29/F	OPC 15 mg	Abortion spontaneous	Severe	Resolved without sequelae
BIA-91067-119		25/M	OPC 25 mg	Joint dislocation	Severe	Recovered/resolved
BIA-91067-123		38/F	Placebo	Facial palsy	Moderate	Recovered/resolved
BIA-91067-124[a]		31/M	NA	Post-traumatic stress	Mild	Resolved without sequelae
BIA-91067-127		33/F	OPC 50 mg + warfarin 25 mg	Tonsillitis	Severe	Recovered/resolved
BIA-91067-129		51/M	OPC 50 mg	Gastroenteritis	Severe	Recovered/resolved

Study 114, Subject ID (b) (6): A 29 year old woman on 15 mg opicapone for 8 days. Her last menses were December 24, 2009. Her pregnancy test was negative on January 4 and January 14, 2010 (screening and admission visits, respectively). Her first dose of drug was January 15, 2010 and she took daily opicapone until January 22, 2010. At post treatment follow-up on February 5, 2010 she had a positive urine pregnancy test confirmed by plasma HCG. On (b) (6) she was seen by her obstetrician presenting with vaginal bleeding. Transvaginal echo indicated no pregnancy at that time and when seen on (b) (6), she had a normal plasma HCG. The diagnosis was probable pregnancy with spontaneous abortion. A relationship of the abortion to opicapone could not be ruled out.

Study 119, Subject ID (b) (6): A 25 year old man dislocated his elbow after hitting a dog on his bicycle.

Study 127, Subject ID (b) (6): A 33 year old woman in this drug interaction study (i.e. warfarin) had severe pustular tonsillitis toward the end of the study. This was diagnosed clinically by fever, positive strep test with elevated leukocytes and neutrophils. She did complete the study but was hospitalized for intravenous antibiotics and recovered completely.

Study 129, Subject ID (b) (6): A 51 year old man, 25 days after a single oral dose of 50 mg opicapone, developed gastroenteritis (diarrhea and vomiting) requiring hospitalization and resolved after two days of non-specific treatment. The clinical examination and laboratory data were normal. The subject dropped out and did not participate in the second part of the study.

Phase 3 Double Blind Period

In the double-blind epochs of Studies 301 and 302, 35 patients in treatment arms receiving opicapone had 43 SAEs reported. The numbers of patients with SAEs in combined opicapone and placebo treatment arms were approximately the same (3.6% vs 4.7%, respectively). As taken from the ISS ADAE dataset, these occurred in the following distribution. The sponsor considered the SAEs as tallied in the last row of the table to be related to treatment (ISS, p 73).

Table 39 Phase 3 DB SAEs (source: ADAE dataset)

Phase 3 DB Treatment Arm	Placebo	OPC 25mg	OPC 50 mg	OPC 5 mg
N	257	244	265	122
Patients having SAE: N (%)	12 (4.7%)	6 (2.4%)	13 (4.9%)	4 (3.3%)
Number of SAEs reported	18	6	15	4
Patient considered to be TEAE	11	5	13	4

The narratives for all SAEs are reviewed. The table below reflects those that occurred in patients who were in active drug treatment arms. As may be obvious from the Preferred Term describing the event, most are not likely to be related to opicapone. Events considered by the reviewer as likely related are shown in **bold font: hepatic enzyme elevation, dyskinesia, orthostatic hypotension, and nausea/vomiting**. All events resolved. Additional explanatory comments follow the table.

Table 40 Phase 3 DB Epoch SAEs (source: ISS ADAE dataset)

USUBJID	AGE	SEX	Dose	Preferred Terms	Began (Study Day)	Duration (Days)	Severity	Dose Change
(b) (6)	72	F	OPC 25mg/day	Bowen's disease	115	1	SEVERE	N/A
	70	F	OPC 5mg/day	Wrist fracture	38	44	MOD	No
	72	M	OPC 50mg/day	Coronary artery disease	60	3	MILD	No
	63	M	OPC 5mg/day	Basal cell carcinoma	95	11	MILD	N/A
	55	M	OPC 50mg/day	Inguinal hernia	110	4	MOD	No
	66	F	OPC 5mg/day	Pain in extremity	86	10	MILD	No
	59	**M**	**OPC 5mg/day**	**Hepatic enzyme increased**	**33**	**19**	**MOD**	**DISCONTINUED**
	70	**F**	**OPC 50mg/day**	**Dyskinesia**	**3**	**2**	**SEVERE**	**INTERRUPTED**
	75	F	OPC 50mg/day	Constipation	91	5	MOD	No
	75	M	OPC 25mg/day	Acute kidney injury	85	4	MOD	No
	48	F	OPC 50mg/day	Pulmonary embolism	100	41	SEVERE	DISCONTINUED
	73	M	OPC 25mg/day	Osteoarthritis	18	19	MILD	INTERRUPTED
	61	**F**	**OPC 50mg/day**	**Fall, Head Injury**	**55**	**14**	**MILD**	**No**
	72	**M**	**OPC 50mg/day**	**Nausea**	**51**	**5**	**SEVERE**	**DISCONTINUED**
	69	M	OPC 50mg/day	Cholecystitis acute *(duct stone)*	98	17	SEVERE	DISCONTINUED
	63	M	OPC 25 mg/day	Hyponatraemia	-26	4	SEVERE	N/A
	73	**M**	**OPC 25mg/day**	**Dyskinesia**	**31**	**125**	**SEVERE**	**INTERRUPTED**
	55	F	OPC 50mg/day	Pyelonephritis acute	18	9	MOD	No
	62	M	OPC 50mg/day	Biopsy prostate	51	2	MOD	No
	64	M	OPC 25mg/day	Urinary retention	1	2	SEVERE	N/A
	75	M	OPC 50mg/day	Pleural effusion, Delirium febrile	6	6	MOD	DISCONTINUED
	75	F	OPC 50mg/day	Cystocele	72	239	MOD	No
	72	M	OPC 50mg/day	Basal cell carcinoma	93	76	MILD	No

Comments: Study 301 SAEs

Patient (b) (6) had an elevation of hepatic enzymes beginning 16 days after starting opicapone 5 mg/d. Drug was stopped on Day 23 after the enzymes continued to climb. The reached a maximum elevation of AST 2xULN, ALT 1.6xULN, and ALP 1.2xULN. The enzymes returned to normal in the weeks following drug cessation. The patient was asymptomatic. Liver ultrasound was normal. Other medications included levodopa, trihexyphenidyl and ropinirole. This reaction was likely related to drug.

Patient (b) (6) was in her 12th year of PD and 5th year of motor fluctuation. At baseline she was treated with L-DOPA (1200 mg/day in 6 divided doses), trihexyphenidyl, topiramate, escitalopram, primidone, and zolpidem. She experienced severe dyskinesia 3 days after

beginning opicapone 50 mg. Drug was briefly stopped and her L-DOPA adjusted downward to 825 mg/d. She resumed treatment and had a satisfactory response with no further dyskinesia as an adverse event. Of interest, the patient also had the AE of Dopamine Dysregulation Syndrome beginning Day 35 through Day 100. These were both likely opicapone related.

Patients (b) (6) both had skin cancers treated in the observation period after they had received their last dose of opicapone. The site investigator for Patient (b) (6) considered the skin cancer possibly related to opicapone given a theoretical relationship of PD to skin cancer. The sponsor considered it unrelated.

Patient (b) (6) stumbled and fell suffering a broken wrist which required splinting. She also suffered from spinal stenosis and was being treated with gabapentin. No symptoms of orthostasis were elicited.

Patient (b) (6) underwent shoulder surgery to treat a pre-existing injury.

Comments: Study 302 SAEs

Patient (b) (6) developed acute renal insufficiency due to obstruction from an exacerbation of chronic prostate disease. It resolved with medical treatment of the prostate. The patient subsequently withdrew consent and left the study.

Patient (b) (6) underwent an elective knee replacement and treatment was interrupted for 5 days during the perioperative period. He resumed medication and completed the study.

Patient (b) (6) gardening, tripped on a stone hitting her head and requiring sutures. She did have a past medical history of hypotension and orthostatic hypotension was described for this patient and it worsened over the course of the study. She suffered another fall considered "mild" on Day 88. She completed the study. It is likely that treatment with opicapone exacerbated her orthostasis as her previous history of falls was "rare". From the patient's narrative:

Table 41 Orthostatic BP in Patient ID (b) (6) (source: SAE narrative)

	V1 (day -8)	V2 (day 1)	V3 (day 7)	V4 (day 14)	V5 (day 27)	V6 (day 62)	V7 (day 97)
BP sitting or supine	142/95	150/100	125/91	104/71	139/92	100/55	114/76
BP standing	127/91	128/92	101/69	100/70	117/76	95/55	102/63
Rate	73	79	72	70	67	75	69

Patient (b) (6) developed nausea beginning 4 days following initiation of opicapone 50 mg/d. It did not resolve with domperidone 10 mg TID. On day 48, the patient developed moderate dyskinesia and severe nausea / vomiting and stopped the medication. Three days later (day 51) he required hospitalization and was treated medically. Dyskinesia resolved on day 52 and the nausea lessened by day 56. It finally resolved by day 73.

Patient (b) (6), after signing consent but before treatment, developed a viral upper respiratory tract infection with associated hyponatremia. He was hospitalized and treated and, after resolution, initiated treatment with opicapone and completed the trial.

Patient (b) (6) had a 7 year history of PD with previous mild disabling dyskinesia. Assigned to the 25 mg arm, he developed severe dyskinesia on day 31 of the study. Medication was stopped on day 33 and the patient was treated with clonazepam 0.5 mg/d. At an unscheduled visit on day 38, dyskinesia had improved but was not yet to baseline levels. Opicapone was restarted on day 58. The L-DOPA dose was reported as being unchanged during the events.

Patient (b) (6) consented to the study but had a day of urinary retention prior to receiving study medication. Possible urinary tract infection was diagnosed. It resolved overnight after his anticholinergic (orphenadrine) was discontinued. He received a course of oral antibiotics as well.

Phase 3 Open-label treatment in Studies 301 and 302

During open label treatment in Phase 3, 166 SAEs occurred in 91 patients, about 10% of patients. Excluding the 18 deaths described above, 148 SAEs occurred in 85 patients. Most patients (60%) were taking 50 mg/d. Of the SAEs, 64 were considered severe (43%), while 50 (34%) were moderate and 34 (23%) mild. The sponsor considered 19 SAEs in 15 patients to be probably or possibly related to opicapone and 129 (87%) either unlikely or not related.

The narratives for all open label SAEs are reviewed. The table below, derived from the ISS ADAE dataset, reflects those that were considered by site investigators as probably or possibly related to opicapone during open label treatment. All events resolved except those that are disease related (e.g., dementia). Most are self-explanatory but some additional comments follow the table.

Table 42 Phase 3 OLEX Epoch SAEs (source: ISS ADAE dataset)

USUBJID	AGE	SEX	Dose	Preferred Term	Began (OL Study Day)	Duration (Days)	Severity	Dose Change
(b) (6)	70	M	OPC 25mg/day	Superficial spreading melanoma	-93	284	MILD	Discontinued
	72	M	OPC 50mg/day	Malignant melanoma in situ	93	295	MILD	Unchanged
	63	M	OPC 50mg/day	Basal cell carcinoma	-3	11	MILD	Unchanged
	69	F	OPC 25mg/day	Malignant melanoma	56	71	SEVERE	Discontinued
	52	M	OPC 25mg/day	Jealous delusion	75	508	SEVERE	Discontinued
	56	F	OPC 50mg/day	Epilepsy, Wrist fracture	39	1	SEVERE	Unchanged
	63	M	OPC 50mg/day	Aggression, Dementia	278 / 315	38	SEVERE	Unchanged
	62	M	OPC 50mg/day	Head injury	178	62	SEVERE	Discontinued
	80	M	OPC 50mg/day	Atrioventricular block complete	327	19	MILD	Discontinued
	75	M	OPC 50mg/day	Diarrhoea, Orthostatic hypotension	350 / 367	3	MILD	Unchanged
	61	F	OPC 50mg/day	Depression	223	10	MILD	Dose reduced
	63	M	OPC 50mg/day	Abnormal behaviour	104	44	SEVERE	Discontinued
	61	M	OPC 50mg/day	Hallucination, auditory	83	50	SEVERE	Interrupted
	70	M	OPC 25mg/day	Confusional state, Dyskinesia	189	19	SEVERE	Reduced
	57	F	OPC 50mg/day	Agitated depression	51	3	SEVERE	Reduced

Patient (b) (6) was a 52 year old man with a history of anxiety, depression and REM behavior disorder. Concomitant medications included levodopa, ropinirole 20 mg/d, selegiline 1.25 mg/d, trihexyphenidyl, clonazepam and amitriptyline. Beginning around study day 75, while on opicapone 25 mg/d, the patient began to express jealousy and physical threats but would not let his spouse report it. Medication was increased to 50 mg/d on study day 113. Associated non-serious AEs starting around day 75 included other impulse control disorders of moderate intensity (buying disorder and compulsive sexual behavior) and moderate insomnia. Opicapone and ropinirole were both discontinued on study day 329 and the syndrome was considered resolved when the patient was seen 8 months later.

Patient (b) (6) was a 56 year old woman who had a fall preceded by vertigo and syncope with urinary incontinence. She regained consciousness with amnesia for the event and disorientation. The wrist fracture was the result of the fall. This occurred after 5 months of opicapone treatment but she had had an increase in dose 3 weeks prior. The patient had a second, "less serious" spell and suffered several other falls. No orthostatic hypotension was

documented. The patient had a medical history of heart failure, hypertension, and panic attacks and medication included levodopa, ropinirole, tramadol, phenobarbital (prn) and bromisoval (a bromine containing hypnotic/sedative).

Patient (b) (6) was a 63 year old man who on study day 278 was hospitalized for aggressive behavior towards his family. He had been on a stable dose of opicapone since study day 8. While there was no prior diagnosis of dementia, at examination for this episode the patient was diagnosed as dementia with confusion in time and place, disinhibition, delusions, and denial of illness. By study day 325, opicapone was discontinued, the aggression had resolved but the patient remained institutionalized.

Patient (b) (6) was a 62 year old with a medical history of hypertension taking amlodipine, enalapril, valsartan in addition to levodopa and pramipexole. The patient fell on study day 178, resulting in facial and cranial trauma with a left periorbital hematoma, and the subject was hospitalized. The patient suffered from freezing gait but had no prior history of falls. He also had "sleep attacks" for which the pramipexole dose was reduced and opicapone interrupted and then stopped on study day 190.

Patient (b) (6) was an 80 year-old man who had been on a stable opicapone dose up to discontinuing the study on day 329 when he developed complete heart block. He was asymptomatic and this was discovered by electrocardiogram at a routine study visit. A pacemaker was implanted and the patient left the study.

Patient (b) (6) was 75 year old man who had a diarrheal illness with dehydration that does not appear related to medication. However shortly thereafter he had recurrence of diarrhea which was then associated with orthostasis. He was treated medically and the symptoms resolved. Opicapone dose was unchanged.

Patient (b) (6) was a 61 year old woman with the SAE of depression but this was likely related to worsening orthostatic hypotension beginning study day 85, requiring the initiation of midodrine, desmopressin, and fludrocortisone. The opicapone dose was not changed at this time. She also suffered from falls, and postural instability. On day 223 she had recurrence of depression, was admitted to the hospital, and opicapone dose reduced to 25 mg. She continued this to the end of the study on day 355.

Patient (b) (6) was a 63 year old man on levodopa, selegiline and pramipexole and opicapone 50 mg/d. Prior to starting the study, he was noted to have some behavior problems of "lesser intensity" not considered to be of "clinical relevance." On study day 104, the patient was reported to behave abnormally with several episodes where he undressed in public, showed aggressive behavior towards his partner and had an "abnormal craving for candy." He withdrew from the study on day 138, began quetiapine, and the symptoms resolved by day 147.

Patient (b) (6) was a 621 year old man with no prior history of hallucinations. He was on stable opicapone treatment 50 mg/d. Beginning study day 83, he developed auditory hallucinations of a morbid and sexual nature of severe intensity. He was on pramipexole which was stopped on study day 123 and opicapone treatment interrupted on day 124. The hallucinations resolved and opicapone was restarted on study day 133 with no recurrence.

Patient (b) (6) was a 70 year old man with a 10 year history of PD and disabling dyskinesia. On opicapone 50 mg/d, the patient reported severe dyskinesia associated with confusion on study 189. In retrospect the confusion had begun on study day 120. He was hospitalized but details of the hospitalization were not available. His opicapone dose was reduced to 25 mg/d on study day 120, and his levodopa dose had been reduced. Dyskinesia was lessened by day 204 and the confusion resolved by day 207.

Patient (b) (6) was a 57 year old woman who developed agitated depression. She had been on 25 mg in the double-blind portion of the study. On open-label study day 33, opicapone was increased to 50 mg/d. On study day 51 the patient developed increased agitation, restlessness, confusion and tearfulness. She was admitted to hospital the following day with thought disorder and abnormal mouthing movements. She was begun on alprazolam and fluoxetine. The opicapone dose was reduced to 25 mg/d on study day 53, she improved clinically, and was on this dose until termination at study day 362.

Inspection of the remainder of the SAEs in the open label cohort that were judged not related to opicapone occurred only sporadically and are, on face, related to other intercurrent illness, such as pneumonia, cancer, atherosclerotic vascular disease, and so forth.

SAEs suggesting an adverse event of special interest (AESI) such as orthostasis or falls and fractures are considered separately below, regardless of their severity.

Study 401 Open-label Treatment
Of the 506 patients in the safety population for this open-label study, 35 (7%) suffered an SAE. Narratives and datasets were not submitted and as a result, these findings and their outcomes are not in a reviewable format. A review of the line listings suggest falls and fractures, exacerbation of underlying features of PD such as dementia and orthostasis, and unrelated intercurrent illness.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The sponsor performed no meaningful analysis of patients who discontinued the pivotal trials, providing instead only line listings. My analyses below used the ISS ADSL, ADEX and ADAE datasets. The entacapone arm in Study 301 was not considered and most of the discussion is focused upon the 50 mg dose which the dose intended for efficacy.

The non-completers in placebo and opicapone arms were inspected for termination due to AE versus non-treatment related reasons, e.g., withdrawal of consent, non-compliance, protocol violation, etc.

Phase 3 Double Blind Period
For the double blind epoch, the study termination date of the non-completers was matched to the AE dataset to look for AEs that might be proximate to the time of patients leaving the study. There were no patients with a non-drug related reason for termination that had an AE close to the last study day.

In the placebo arm, 25 patients left the study due to an AE while 67 opicapone-treated patients did so. Half of the opicapone patients who left with an AE were on 50 mg/d. Excluding deaths and SAEs described above, there were 22 patients on opicapone 50 mg/d who left the study for AEs. In the ADSL dataset, the reason for discontinuation was not given beyond "adverse event." It was only possible to approximately match AEs leading to discontinuation in ADAE using the study day of occurrence in ADAE to the end of study day in ADSL. On average, the age of a patient in this group was older than the mean age of participants. The sample was too small to make an accurate assessment of sex or race or the role of anti-PD polypharmacy. Of note, the events reflected the most common events associated with opicapone: abdominal discomfort, dyskinesia, orthostatic hypotension and falls.

Two patients, only one of whom appears in the table below, bear mentioning and are discussed in Section 8.4.6 Laboratory Findings below. Patient (b) (6) was discontinued for the AE of moderate dyskinesia. However, a mild elevation of CPK also occurred at this time, beginning 4 days after the dyskinesia was noted and resolving 2 days before the dyskinesia did.

Another patient, (b) (6), taking 25 mg/d, also had a moderate elevation of CPK which resolved after 10 days.

Table 43 Phase 3 DB on 50 mg/d patient discontinuations due to AE but not SAE or death. (source: ADSL, ADAE datasets)

USUBJID	AGE	SEX	RACE	DB Duration (Days)	Preferred Term
(b) (6)	80	F	WHITE	43	Abdominal pain, Vomiting
	80	M	ASIAN	91	Muscle spasms
	79	M	WHITE	19	Dyspepsia
	75	M	WHITE	24	Focal dyscognitive seizures
	74	F	WHITE	35	Palpitations, Tachycardia, Dyskinesia
	73	M	WHITE	48	Auditory hallucination, Orthostatic hypotesnion
	73	F	WHITE	101	Dizziness, Dyskinesia Fall
	72	M	WHITE	62	dyskinesia
	72	F	WHITE	57	Dyskinesia
	71	F	WHITE	45	Dyskinesia, Vomiting, Abdominal pain
	70	F	WHITE	64	Dizziness, Fall, Influenza
	70	F	WHITE	21	Nausea, Vomiting
	69	M	WHITE	111	Endoscopic procedure
	63	F	WHITE	53	Dyskinesia
	63	M	ASIAN	21	Dyskinesia
	62	F	WHITE	24	Visual hallucination
	62	F	WHITE	62	Dyskinesia
	62	F	ASIAN	16	Loss of consciousness
	57	M	WHITE	28	Dyskinesia, Fall
	50	F	WHITE	96	Dysgeusia
	48	F	WHITE	116	Myalgia, Dystonia, Fall
	45	F	WHITE	80	Dyskinesia

Phase 3 Open Label Treatment

Adverse events leading to discontinuation in OLEX occurred in 56 of 848 (7%) of patients. According to the sponsor, the most common reasons were “dyskinesia” in 6 patients, “Parkinson’s disease” in 4 and “hallucinations” in 3. Using the ISS ADSL dataset, the sponsor’s tally was confirmed; 144 patients in the open-label safety population did not complete the OLEX epoch, all but the 56 for non-treatment related reasons. While most AEs leading to discontinuation occurred as unique events in individual patients, perusal by SOC reveals a clearer pattern. Psychiatric disturbances let to discontinuation in 13 (1.5%) with related

behavioral symptoms: hallucination, delusion, violence, impulse dyscontrol, etc. Nervous system related symptoms, e.g., dyskinesia, Parkinson's disease, dystonia, and stroke occurred in 18 (2.1%) of patients.

AEs that led to temporary interruption of opicapone treatment were reported in two subjects each: dyskinesia and influenza. TEAEs that led to dose reduction of opicapone in three or more patients in the OLEX were tallied by the sponsor.

Table 44 Phase 3 TEAEs occurring in more than 3 patients that led to dose reduction (source: sponsor's ISS report, page 111)

Preferred Term	OL All OPC N=848
	n (%)
Number of subjects with at least 1 TEAE leading to dose reduction	68 (8.0)
Dyskinesia	24 (2.8)
Parkinson's disease	7 (0.8)
Nightmare	4 (0.5)
Anxiety	3 (0.4)
Hallucination, visual	3 (0.4)
Orthostatic hypotension	3 (0.4)

Study 401

Summary comments for Study 401 were provided in the 120 day Safety Update. In Study 401, 86 subjects (17%) had an AE leading to study drug discontinuation. The most frequently reported TEAEs leading to study drug discontinuation were nausea (10 subjects; 2%), constipation (7 subjects; 1.4%), hallucination and dizziness (6 subjects each; 1%), and dyskinesia (5 subjects; 1%).

8.4.4. Significant Adverse Events

In the Phase 3 trials double -blind epochs, 46 of 1266 AEs (3.6%) reported in the opicapone treatment arms were rated as severe. Of these 46 severe events, 72% occurred in the age group 65 or older, 57% were on the 50 mg/d dose, and 33 of 46 (72%) were considered either possible, probable, or related to study drug. These events were mostly represented by dyskinesia (8) and nausea or vomiting (6), with the remainder being closely aligned with the underlying disease process (PD symptoms, weakness, spasms, psychiatric symptoms and falls).

In the open label epoch of Studies 301 and 302, 160 of 2704 AEs (5.9%) were considered severe in nature. Of these 160 severe events, 48% occurred in the age group 65 or older, 62% were on

the 50 mg/d dose, and 54 of 160 (34%) were considered either possible, probable, or related to study drug. As in the double blinded population, these events were mostly represented by dyskinesia (16 reports) with most of the remainder being closely aligned with the underlying disease process (PD symptoms, poor therapeutic response, weakness, spasms, psychiatric symptoms). Of note, no nausea or vomiting of a severe nature was reported in this population. It is worth recalling that all patients in the OLEX came from the blinded portions of these trials and it is possible that those susceptible to severe nausea or vomiting were no longer participating.

No new, novel, or unexpected AEs of any unusual severity occurred.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The sponsor listed the following Adverse Drug Reactions occurring in the safety population for blinded epochs in Studies 301 and 302. These reactions were selected by potential causal relationship, frequency **> 1% of the 50 mg** treatment arm, and event rate higher than placebo. (Whether the event could have been caused by other anti-parkinson drugs alone or in combination with opicapone was ignored.)

Table 45 Phase 3 DB population: ADRs selected for causal relationship, > 1% of the cohort and rate higher than placebo (source: ISS Report, page 78).

Preferred Term	Placebo N=257	OPC 5 mg N=122	OPC 25 mg N=244	OPC 50 mg N=265	All OPC N=631
	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 TEAE	147 (57.2)	63 (51.6)	152 (62.3)	170 (64.2)	385 (61.0)
Dyskinesia	16 (6.2)	17 (13.9)	39 (16.0)	54 (20.4)	110 (17.4)
Constipation	5 (1.9)	4 (3.3)	12 (4.9)	17 (6.4)	33 (5.2)
Insomnia	4 (1.6)	2 (1.6)	17 (7.0)	9 (3.4)	28 (4.4)
Dry mouth	3 (1.2)	2 (1.6)	16 (6.6)	8 (3.0)	26 (4.1)
Blood creatine phosphokinase increased	5 (1.9)	2 (1.6)	7 (2.9)	13 (4.9)	22 (3.5)
Hallucinations	3 (1.2)	2 (1.6)	11 (4.5)	9 (3.4)	22 (3.5)
Hypertension	6 (2.3)	4 (3.3)	10 (4.1)	8 (3.0)	22 (3.5)
Dizziness	3 (1.2)	2 (1.6)	10 (4.1)	9 (3.4)	21 (3.3)
Abdominal pain	1 (0.4)	2 (1.6)	4 (1.6)	6 (2.3)	12 (1.9)
Weight decreased	0	1 (0.8)	1 (0.4)	10 (3.8)	12 (1.9)
Dyspepsia	1 (0.4)	0	5 (2.0)	4 (1.5)	9 (1.4)
Hypotension	1 (0.4)	2 (1.6)	2 (0.8)	5 (1.9)	9 (1.4)
Muscle spasms	3 (1.2)	1 (0.8)	4 (1.6)	4 (1.5)	9 (1.4)
Dyspnoea	0	2 (1.6)	3 (1.2)	3 (1.1)	8 (1.3)
Decreased appetite	0	1 (0.8)	3 (1.2)	3 (1.1)	7 (1.1)
Orthostatic hypotension	0	0	2 (0.8)	4 (1.5)	6 (1.0)
Sleep disorder	1 (0.4)	1 (0.8)	1 (0.4)	3 (1.1)	5 (0.8)
Dysgeusia	0	1 (0.8)	0	3 (1.1)	4 (0.6)
Syncope	1 (0.4)	0	0	3 (1.1)	3 (0.5)

This analysis was confirmed by the reviewer analyzing the unedited ADAE dataset using the MedDRA Adverse Event Diagnosis (MAED) Tool. Because there was some observed splitting of adverse events among several related Preferred Terms, the ADAE dataset was critically reviewed and Preferred Terms edited when analyzing the Adverse Events of Special Interest in Section 8.5, below.

AEs considered by the sponsor to be treatment emergent (TEAEs) occurring in **3% or more** of patients are listed below:

Table 46 Phase 3 population: TEAEs in > 3% of cohort (source: sponsor's ISS, page 76).

Preferred Term	Placebo N=257	OPC 5 mg N=122	OPC 25 mg N=244	OPC 50 mg N=265	All OPC N=631
	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 TEAE	147 (57.2)	63 (51.6)	152 (62.3)	170 (64.2)	385 (61.0)
Dyskinesia	16 (6.2)	17 (13.9)	39 (16.0)	54 (20.4)	110 (17.4)
Constipation	5 (1.9)	4 (3.3)	12 (4.9)	17 (6.4)	33 (5.2)
Insomnia	4 (1.6)	2 (1.6)	17 (7.0)	9 (3.4)	28 (4.4)
Dry mouth	3 (1.2)	2 (1.6)	16 (6.6)	8 (3.0)	26 (4.1)
Blood creatine phosphokinase increased	5 (1.9)	2 (1.6)	7 (2.9)	13 (4.9)	22 (3.5)
Hypertension	6 (2.3)	4 (3.3)	10 (4.1)	8 (3.0)	22 (3.5)
Dizziness	3 (1.2)	2 (1.6)	10 (4.1)	9 (3.4)	21 (3.3)
Nausea	10 (3.9)	2 (1.6)	11 (4.5)	8 (3.0)	21 (3.3)
Parkinson's disease	8 (3.1)	1 (0.8)	11 (4.5)	6 (2.3)	18 (2.9)
Somnolence	5 (1.9)	1 (0.8)	10 (4.1)	5 (1.9)	16 (2.5)
Urinary tract infection	2 (0.8)	2 (1.6)	4 (1.6)	10 (3.8)	16 (2.5)
Viral upper respiratory tract infection	6 (2.3)	4 (3.3)	6 (2.5)	5 (1.9)	15 (2.4)
Weight decreased	0	1 (0.8)	1 (0.4)	10 (3.8)	12 (1.9)
Back pain	7 (2.7)	4 (3.3)	5 (2.0)	3 (1.1)	12 (1.9)

There is no important difference between the sponsor's lists of AEs considered to be treatment emergent versus adverse drug reactions to opicapone, suggesting that there was not a great deal of uncertainty about the relatedness of observed adverse events to treatment. However, as is considered in in the review of AESI, below, this assessment was not always considered accurate or complete by the reviewer. The individual listing of AEs in Studies 301 and 302 are also well aligned. When the 3% cut off was used in listing TEAEs, 11 of the frequent events appeared in AE lists from both studies. Those events that are listed for just one of the studies below were not unique; they did not have sufficient numbers of events in the other study to achieve the 3% cut-off level for the table.

Table 47 Between study comparison of TEAEs in > 3% of DB cohort (source: ADSL and ADAE datasets).

≥ 3% in Studies 301 and 302	≥ 3% only in Study 301	≥ 3% only in Study 302
Dyskinesia	Hallucination	Dry mouth
Constipation	Back pain	Blood CPK increased
Falls	Muscle spasms	Parkinson's disease
Hypertension	Anxiety	Urinary tract infection
Nausea	Hyperhydrosis	Pain in extremity
Headache		Arthralgia
Insomnia		Diarrhea
Dizziness		Abnormal dreams
Somnolence		Hypotension
Nasopharyngitis		
Weight decreased		

Prescribing Information 6.1 Clinical Trials Experience

Following interaction with the sponsor, the proposed Adverse Reactions list in Prescribing Information 6.1 will approximate the following table which illustrates the adverse drug reactions with an incidence of at least 2% of patients treated with opicapone and occurring at a rate greater than placebo for the double-blind safety population in Studies 301 and 302:

Table 48 Proposed Adverse Reactions table in Prescribing Information 6.1 Clinical Trials Experience.

Adverse Reactions	ONGENTYS 50 mg 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 kinase increased	5	2
Weight decreased	4	0
Vascular disorders		
Hypotension/syncope[2]	5	1
Hypertension	3	2

[1] Includes hallucinations, hallucinations visual, hallucinations auditory, and hallucinations mixed
[2] Includes hypotension, orthostatic hypotension, syncope, and presyncope

TEAEs by time of occurrence:
As suggested by the Kaplan-Meier curves showing the cumulative occurrence of drop-outs over time in Study 301 **Figure 4** and Study 302 **Figure 7**, the rate of adverse events does not cluster in any particular time period during the course of the studies. During the first 2 to 3 weeks of the DB period the start of assigned treatment in the Phase 3 studies (i.e., before Visit 4), each participants' s levodopa dose could be adjusted.

In general, for AEs of special interest, the incidence of TEAEs after Visit 4 was similar to the incidence before Visit 4. The notable exception is dyskinesia and this is expected due to the effect of COMT inhibitors on levodopa PK. Among the placebo assigned patients in Studies 301 and 302, 12 of 257 (4.6%) patients had the first occurrence of dyskinesia as an AE within the first 14 days of treatment. For the remainder of the studies only 4 additional placebo patients developed dyskinesia as an AE. This contrasts with those assigned to the 50 mg/d treatment where 38 of 256 (14.8%) had the first occurrence of the AE of dyskinesia within the first two weeks with 16 additional new patients so listed during the remainder of the DB period (source: ISS Table 2.1.10, pp 710-735).

8.4.6. Laboratory Findings

The sponsor analyzed clinical laboratory tests in all phases of opicapone development but the results from Studies 301 and 302 represent the chronic exposure to the drug.

Laboratory findings were analyzed as mean results over time for the Phase 3 study populations but shift tables were also created for hematology and chemistry tests to observe the change from baseline values to the worst post treatment value.

Other than creatine phosphokinase (CPK), there were no clinically important differences between groups and no consistent trends were observed over time for chemistry and hematology clinical laboratory data. Most patients did not shift outside the normal range and where there were shifts from normal to low or high values, the events were relatively similar between the placebo and the opicapone treated group.

CPK

Studies 301 and 302 had different central laboratories for clinical analyses, (b) (4) respectively. The laboratory reference range of normal for CPK varied slightly between the Phase 3 Studies:

Study 301: Female 38-176; Male 52-336
Study 302: Female 24-170; Male 24-195

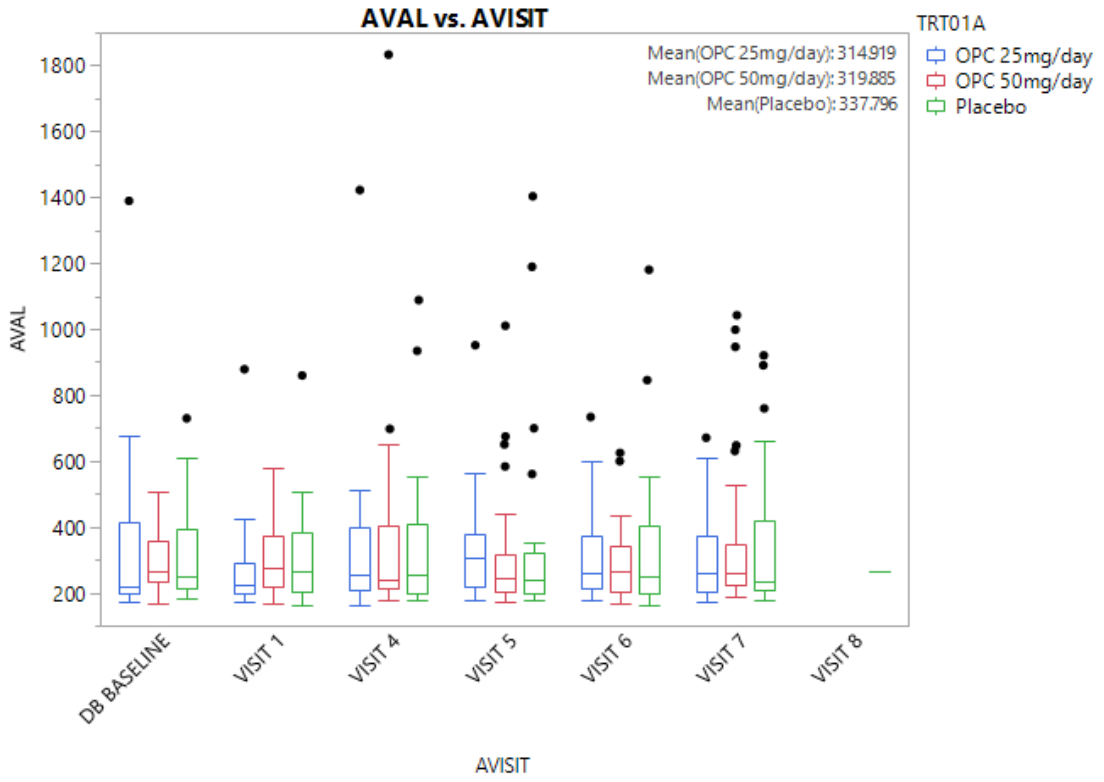
In Phase 3, there were 67 instances of the PT "Blood CPK increased" in 46 patients (taking 25 mg/d [n=18], 50 mg /day [n=29], and placebo [n=5]). Inspecting the measurement of CPK from the ADLB dataset, over all Phase 3 patients on treatments of opicapone 25 or 50 mg/d or placebo (N= 781), at all visits, there were 350 patients (45%) who had at least one elevation of CPK above the ULN. Of these 207 patients had elevations on one or two occasions only.

There was a greater increase in mean creatine phosphokinase (CPK) in the opicapone 50 mg group compared to placebo. The mean change from baseline ranged 11.5 to 37.0 U/L for opicapone 50 mg and 2.8 to 8.1 U/L for placebo. A similar percentage of subjects had shifts in CPK from normal to high in the OPC 25 and 50 mg groups compared to placebo (18.9%, 21.5%, and 18.3%, respectively). This was confirmed by looking at the CPK subset of the ADLB dataset. For 988 Phase 3 patients, 9643 CPK values were obtained for patients taking opicapone 50 mg/d, 25 mg/d, or placebo. Due to constraints of dataset structure these were separated in the DB and OLEX study phases. The patients whose CPK measures for baseline values became higher values above the laboratory reference range for the ULN were then selected. In the DB population, this resulted in 76/248 (30.6%) taking 25 mg/d, 86/270 (31.9%) taking 50 mg/d, and 72/265 (27.2%) of placebo patients having CPK values that became abnormally high. The OLEX added 116 more patients whose CPK moved from the normal range to higher in that portion of the study including both placebo patients who rolled over to denovo opicapone treatment and those coming from an active treatment arm but had no previous abnormal CPK.

However, the use of measures of central tendency (i.e., means) obscures the more important cases of patients who had much higher abnormal values. This is evident in the graph below of CPK values (AVAL) in patients who exceeded the ULN from baseline by DB arm and visit.

Derived from the ISS ADLB dataset, the upper "whisker" of the box plot represents CPK values that exceeded the 3rd quartile upper boundary + 1.5 x the interquartile range.

Figure 10 Phase 3 DB population: box plot of CPK values above ULN by treatment arm and visit (source: ADLB dataset).



Most patients in this group of select patients had similar elevations in all 3 arms regardless of treatment. Outliers (black dots) from the boxplot were extracted: 33 outlying values occurred in 26 patients. Most (22 of the 26 patients) of these events were single occurrences for that patient. Two patients with 3 and 4 occurrences of outlier elevations were in the placebo arm. The other two patients each had two outlier events and taking 25mg/d and 50 mg/d, respectively. These outlier events did not favor a race category (Caucasian, n=14 and Asian, n=4) on active treatment. These patients were also inspected in the ADAE dataset to see if they had other AEs that could explain the elevated CPK, i.e. falls, muscle weakness, bruises, excessive dyskinesia, and so forth. There were none.

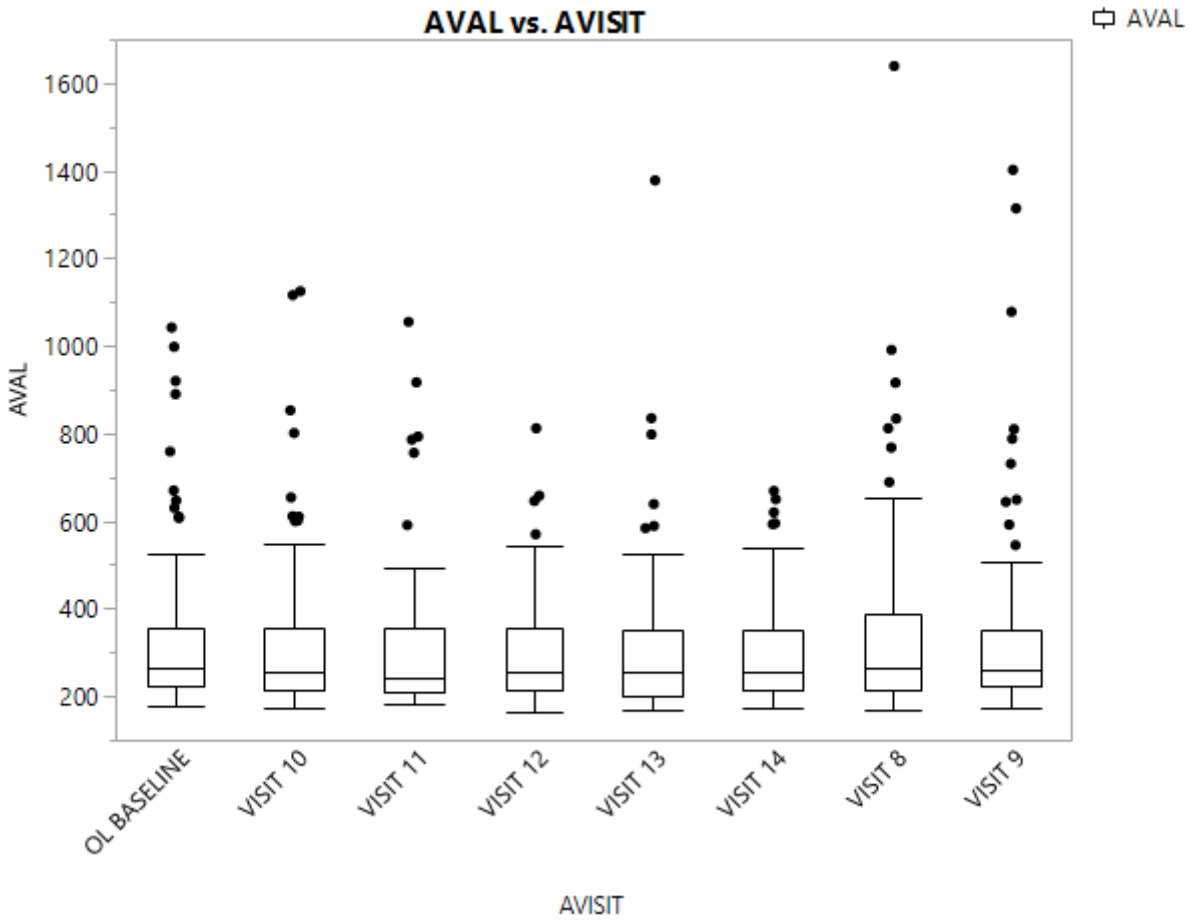
The number of AEs related to elevated CPK were investigated by race. The numbers are small and, in my estimate, inconclusive. On those patients taking 50 mg/d, the percentage of Asian patients is twice that of white patients. However, elevations were noted on placebo and, likely by chance, were much higher by percentage in the Asian sub-group. Overall, in those patients taking opicapone the percentages by race of increased CPK as an AE were roughly equivalent.

Table 49 Phase 3 AE PT Increased CPK by race (source: after ISS Table 2.1.3.3, p 484 and 499)

Clinical Laboratory - Increased CPK	Placebo	All OPC	OPC 5mg	OPC 25 mg	OPC 50 mg
White (n by arm)	211 (81%)	562 (90%)	122	209	231
n with increased CPK	2 (0.9%)	18 (3.2%)	2	6	10 (4.3%)
Asian (n by arm)	42 (19%)	62 (10%)	0	29	33
n with increased CPK	2 (4.8%)	3 (4.8%)	0	0	3 (9.1%)

In the OLEX population (25 mg/d and 50 mg/d patients combined), the same analysis was performed. A box plot like that seen in the DB epoch was the result with remarkable similarity in the variance of the measured results.

Figure 11 Phase 3 OLEX population, box plot of CPK values above ULN by visit (source: ADLB dataset).



The outliers (57 events in 39 patients) were extracted for a closer look. Only nine of these had more than one high measurement. One very high value at Visit 13 was retested and was subsequently in the normal range. The very high measurement at Visit 8 was that patient's last

laboratory measurement. Again, there was no corresponding AE to explain these lab results. The outliers were represented by both Asian (n=10) and Caucasian (n=28) patients.

Reviewer's comment: It is difficult to interpret the meaning of these CPK elevations. The proportion of elevations of CPK above the ULN posited by both clinical laboratories, even for the placebo group, is remarkable. Notable is the wide range of values by box plot suggesting that the stated lab reference values may not have been representative of the population at hand and/or the quality of the measurements varied. However, there wasn't any difference in the range of values between the two central laboratories. It is possible that local storage and shipping was related to the observations: CPK is greatly affected by poor specimen preparation and hemolysis. There does not seem to be a clear relationship of the lab result to dose or duration of exposure.

Adverse events related to laboratory tests other than CPK are listed below as derived in MAED. Excluded are results related to an underlying concomitant medical ailment responsible for an abnormal laboratory result, e.g. iron deficiency anemia, leukocytosis with infection. The paucity of events corroborates the sponsor's numerical analyses of laboratory test analysis.

Double Blind Epoch lab abnormalities reported as AEs

Table 50 Phase 3 DB: Laboratory tests reported as AEs (source: ADLB and ADAE datasets).

MedDRA	*25mg/day (N = 248)*			*50mg/day (N = 270)*			*Placebo (N = 265)*		
High Level Term	*Events*	*Head Count*	*%*	*Events*	*Head Count*	*%*	*Events*	*Head Count*	*%*
Urinalysis NEC	2	1	0.4	9	5	1.9	1	1	0.4
Leukopenias NEC	0	0	0.0	6	4	1.5	1	1	0.4
Liver function analyses	5	3	1.2	5	4	1.5	12	6	2.3
Anaemias NEC	2	2	0.8	3	3	1.1	1	1	0.4
White blood cell analyses	3	2	0.8	4	3	1.1	5	3	1.1
Elevated cholesterol	0	0	0.0	2	2	0.7	1	1	0.4
Elevated triglycerides	2	2	0.8	3	2	0.7	0	0	0.0
Renal function analyses	2	2	0.8	3	2	0.7	3	3	1.1
Triglyceride analyses	0	0	0.0	2	2	0.7	4	4	1.5
Hyperlipidaemias NEC	0	0	0.0	1	1	0.4	0	0	0.0
Leukocytoses NEC	0	0	0.0	1	1	0.4	3	3	1.1
Neutropenias	1	1	0.4	2	1	0.4	1	1	0.4

Open Label Epoch lab abnormalities reported as AEs

Table 51 Phase 3 OLEX: Laboratory tests reported as AEs (source: ADLB and ADAE datasets).

MedDRA	*50mg/day (N = 270)*			*25mg/day (N = 248)*		
Higher Level Term	*Events*	*Head Count*	*%*	*Events*	*Head Count*	*%*
Anaemias NEC	8	8	3.0	4	4	1.6
Elevated cholesterol	2	2	0.7	1	1	0.4
Elevated triglycerides	3	3	1.1	8	4	1.6
Leukocytoses NEC	1	1	0.4	1	1	0.4
Leukopenias NEC	2	2	0.7	2	2	0.8
Neutropenias	0	0	0.0	1	1	0.4
Red blood cell abnormal findings NEC	2	1	0.4	0	0	0.0
Thrombocytopenias	1	1	0.4	1	1	0.4

Liver test abnormalities are addressed as an AESI in 8.5.9 Hepatotoxicity, below.

8.4.7. Vital Signs

The Phase 3 protocols were amended after their start to include orthostatic vital sign assessment to include a change from supine to standing rather than sitting to standing. Mean decreases in systolic and diastolic blood pressure (SBP, DBP) taken sitting and standing were greater in the OPC 50 mg group compared to placebo. In general, the reduction in blood pressure was greater with higher OPC doses, but the magnitude of reduction was small. Orthostatic blood pressure drops were common, as illustrated by the Phase 3 blinded cohort: roughly 35% of patients in both the placebo and opicapone arms had orthostasis as defined by a decrease of SBP ≥20 mmHg from sitting/supine to standing OR decrease of DBP ≥10 mmHg from siting/supine to standing. The clinical relevance of such a finding is assessed through the production of symptoms related to orthostatic drops in blood pressure. Few of these patients developed orthostatic symptoms sufficient to be identified as an AE. See Section 8.5.3 below for a discussion the AESI of hypotension and syncope.

8.4.8. Electrocardiograms (ECGs)

ECGs were collected in Studies 301 and 302 in both the double-blind and OLEX epochs. The sponsor provided descriptive statistics of the observed value and change from baseline for heart rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval [Bazett's (QTcB) and Fridericia's (QTcF) formulae]. Post baseline analysis was performed categorically for patients whose QT values lengthened and were greater than 450, 480, and 500 msec. A second analysis was performed looking at change from baseline ≥ 30 or 60 msec.

In the double blind safety population no clinically important changes were observed in QTcF, QTcB, or other ECG parameters with opicapone treatment. QTcF values >450 msec were observed in 5.1% of subjects in the opicapone 50 mg group compared to 2.6% of patients in the placebo group. Of these, 3 patients had QTcF >480 msec (1 subject each in the opicapone 5 mg, 50 mg, and placebo groups) and none had values >500 msec. A similar result was obtained with Bazett's correction and none had a CFB >60 msec. There was no observed relationship of ECG changes in these indices related to opicapone dose.

Similarly, in the OLEX portion of the Phase 3 studies no clinically important mean changes from baseline for ECG parameters were reported during the OL period with OPC treatment. During the OL period, mean QTcF CFB ranged from -0.9 to 0.4 msec. Seven subjects (0.9%) had a QTcF value >480 msec and 2 subjects (0.3%) had a QTcF >500 msec. Both subjects with QTcF >500 msec (Subjects (b) (6) in Study 301) had a high QTcF at baseline (488 and 479 msec, respectively) and the highest value during the OL period was 503 msec.

Few ECG-related TEAEs were reported in the safety population. These are discussed as AESI below.

8.4.9. QT

Reviewer's note: I rely heavily upon the review performed by the QT Interdisciplinary Review Team (QTIRT). This section closely follows their review and indicated portions are cited verbatim. The interested reader is referred to their careful review for details.

The sponsor performed a Thorough QT Study, BIA-91067-111, to evaluate the effect of the proposed therapeutic opicapone dose (50 mg) and supra-therapeutic (800 mg) doses of opicapone on cardiac repolarization in healthy subjects. The study is a randomized, double-blind, placebo-controlled, open-label active controlled, 4-period crossover trial. A total of 64 subjects were randomized to the study and 61 subjects were in the per protocol analysis set. Volunteers were randomly assigned to receive in each period either a single dose of 50 mg opicapone, 800 mg opicapone, placebo or 400 mg moxifloxacin (positive control). There was a wash-out period of at least 7 days between dose administrations.

> "The sponsor used QTcI for the primary analysis. The results for QTcF were presented as secondary analysis in the sponsor's report. The sponsor's choices of QT/RR correction methods are acceptable.
>
> The reviewers used QTcF as the primary endpoint because no significant increases or decreases in heart rate were observed (i.e., absolute mean change in HR <10 bpm).

The final assessment from the QTIRT review is that there was no evidence for significant QTc

prolongation effect of opicapone detected. The QTIRT's opinion was that the TQT study alone is adequate to characterize drug effect on the QTc interval. As a consequence, in their opinion, the ECG data from Studies 301 and 302 were not felt to provide additional data to support any label recommendation.

Proposed label wording from the QTIRT review:

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

(b) (4) At a dose (b) (4) (b) (4) ONGENTYS (b) (4) not prolong the (b) (4) interval to any clinically relevant extent.

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

Reviewer's comment: *We agree with the QT-IRT description of Study 111, their analysis, and findings.*

8.4.10. Immunogenicity

Immune reactions were not anticipated for this small molecule. None resulted in an SAE or in a patient leaving the trial in either the blinded or open label portions of the Phase 3 trials. The adverse events from the blinded portion of the Phase 3 studies were analyzed using Broad SMQ for allergy mediated adverse events and revealed the events in the table below. They occurred roughly equally in active and placebo control exposure for the double blind epoch. Of note, when more constrained criteria were used in a Narrow SMQ, these findings were eliminated.

Table 52 Phase 3 DB: MAED SMQ for allergy mediated AEs (source: ADAE)

	50mg/day (N = 270)			*25mg/day (N = 248)*			*5mg/day (N = 122)*			*Placebo (N = 265)*		
SMQ Broad Search	*Events*	*Head count*	*%*	*Events*	*Head count*	*%*	*Events*	*Head count*	*%*	*Events*	*Head count*	*%*
Severe cutaneous adverse	2	2	0.7	2	2	0.8	1	1	0.8	1	1	0.4
Anaphylactic reaction	15	14	5.2	13	11	4.4	7	6	4.9	14	13	4.9
Angioedema	3	3	1.1	4	4	1.6	4	4	3.3	4	4	1.5
Asthma/bronchospasm	0	0	0.0	0	0	0.0	1	1	0.8	1	1	0.4
Eosinophilic pneumonia	5	4	1.5	4	4	1.6	3	2	1.6	10	7	2.6
Hypersensitivity	10	8	3.0	8	8	3.2	5	3	2.5	16	14	5.3
Drug reaction with eosinophilia and systemic symptoms	38	26	9.6	25	22	8.9	9	5	4.1	46	28	10.6
SMQ Narrow Search												
Severe cutaneous adverse	0	0	0	0	0	0	0	0	0.0	1	1	0.4
Angioedema	0	0	0	0	0	0	1	1	0.8	0	0	0.0
Asthma/bronchospasm	0	0	0	0	0	0	1	1	0.8	1	1	0.4
Oropharyngeal disorders	0	0	0	0	0	0	1	1	0.8	0	0	0.0

8.5. Analysis of Submission-Specific Safety Issues

AESIs were selected by the sponsor based upon known or previously reported potential safety risks with other medications in the COMT inhibitor class (i.e., hepatotoxicity with tolcapone; prostate cancer with entacapone; diarrhea), known adverse effects associated with levodopa or other dopaminergic medications (i.e., psychosis/hallucinations, dyskinesia, hypotension and syncope, impulse control disorders, sleep attacks and excessive somnolence, withdrawal-emergent pyrexia and confusion), or associated with other CNS medications (i.e., suicidality, injuries and falls).

Each AESIs was addressed using a Standardized MedDRA Query (SMQ) if a relevant one exists for the AESI and/or additional relevant AE terms. If a scale was used to asses an AESI, that is indicated as well. A discussion of the AEs pertinent to each AESI category follows below.

Reviewer's Note: The findings and results of analyses in this section support the inclusion of the following WARNINGS ANDS PRECAUTIONS in the Prescribing Information for Ongentys:

- *5.1 Falling Asleep During Activities of Daily Living and Somnolence*
- *5.2 Hypotension/Syncope*
- *5.3 Dyskinesia*
- *5.4 Hallucinations*

5.5 Impulse Control/Compulsive Behavior and Psychosis

The following are included as warnings generally applicable to this class:

5.6 Withdrawal-Emergent Hyperpyrexia and Confusion

(There were no reports of this syndrome occurring during the opicapone development program.)

5.7 [redacted] (b) (4) Concomitant Use of Drugs Metabolized by Catechol-O-Methyltransferase (COMT)

8.5.1. Dyskinesia

Dyskinesia is known to be related to increased systemic levodopa exposure, an expected effect of COMT inhibition by opicapone. However, the full therapeutic effect of opicapone is tied to the notion that increase in functional time (ON time) must not come at the expense of an increase in troublesome dyskinesia as rated by the patient. In addition, dyskinesia could be an event counted as a TEAE using the Preferred Term, dyskinesia.

As seen above, dyskinesia was on occasion an SAE and/or a reason for the participant to leave their study (opicapone treatment 3% vs placebo 0.4%). From a mechanistic point of view this is not surprising as opicapone increases not only the AUC of a levodopa dose but also the C_{max}. This section includes those events and look as at all dyskinesia reported as an AE.

Table 53 Phase 3 DB: dyskinesia reported as an AE (source: ADAE).

Double Blind	25mg/day (N = 244)		50mg/day (N = 265)		All Opicapone (N=631)		Placebo (N = 257)	
PT	N	%	N	%	N	%	N	%
Dyskinesia	39	16	54	20.4	110	17.4	16	6.2

In both Studies 301 and 302, the levodopa dose could be decreased in the first 2 to 3 weeks of the DB period (baseline to Visit 4) based on clinical response. The mean change in the daily levodopa dose from baseline to Visit 4 was greater in the opicapone 50 mg/d cohort than placebo (-30.05 mg vs -7.53 mg) and similar results were seen from baseline to Visit 7 (end of study or early termination (-29.19 mg and -6.13 in the opicapone 50 mg/d and placebo groups, respectively). Reduction of levodopa can be used in medical practice to reduce troublesome dyskinesia but in the development of opicapone it does not appear to have been a common treatment strategy.

In the OLEX epoch of the studies, 148 of 848 participants or 17.5% reported dyskinesia as an AE at some point during their treatment. In both epochs, the onset of dyskinesia TEAEs occurred

most frequently during the initial 2 to 3 weeks of treatment, during which levodopa could be adjusted. This is common for the class of COMT inhibitors. In the OLEX, 0.7% of patients discontinued due to dyskinesia while 3% of patients had dose reductions.

Subgroup analysis reveals that, for the double-blind epoch, the occurrence of dyskinesia was similar within the age and sex, subgroups. The incidence was modestly lower among Asians in the double blind epoch, while higher in the OLEX. These numbers are largely artifactual due to the small sample size. Baseline disease status however appears to influence dyskinesia.

- The UPDRS motor score below 24 in the ON state had a larger percent of dyskinesia AE than those with a motor score greater than 24 (23% vs 12%).
- Total daily levodopa dose higher than 700 mg had a higher rate of dyskinesia AEs than less than 700 mg/d (24.6% vs 11.7%)
- Concurrent treatment with amantadine appeared to have no effect on the reporting of dyskinesia as a TEAE. Dyskinesia was reported by 18.5% of patients taking amantadine, (19% of all opicapone patients) while it was reported as a TEAE in 17% of patients not taking amantadine.

8.5.2. Nausea and Vomiting

While not addressed as an AESI by the sponsor, vomiting was the second most common reasons for discontinuation (1.1%) of study drug in the Phase 3 studies (after dyskinesia). When it occurred, it was often rated as "severe." Because nausea and vomiting often occurred in the same patient, they were calculated together:

Table 54 Phase 3 DB: combined nausea and vomiting reported as an AE (source: ADAE)

DB	OPC 25mg/day (N = 248)			OPC 50mg/day (N = 268)			Placebo (N = 265)		
PT	Events	Count	%	Events	Count	%	Events	Count	%
Nausea and/or vomiting	14	14	5.6	17	10	3.7	17	15	5.7

In the DB population the occurrence was roughly equal in the opicapone 25 mg, 50 mg and placebo arms. Nausea accounted for about 3/4 of the events reported as an AE. It should be noted that domperidone, an antiemetic not approved for use in the US, was given concomitantly to 5.4% of all opicapone patients and 7.8% of placebo patients in the DB epoch. It was not possible to link concomitant medication use to these events with the datasets provided.

In the OLEX population the occurrence was about the same as in the DB population (initial titration of opicapone occurred in the OLEX). Vomiting accounted for about 30% of the reported events.

Table 55 Phase 3 OLEX: combined nausea and vomiting reported as an AE (source: ADAE)

OLEX	OPC 50mg/day (N = 270)			OPC 25mg/day (N = 248)		
PT	Events	N	%	Events	N	%
Nausea and or vomiting	13	11	4.1	24	14	5.6

8.5.3. Hypotension and Syncope

The sponsor used the following selected Preferred Terms to search for the AESI of hypotension and syncope:

Table 56 Preferred Terms used by sponsor to query AESI hypotension or syncope (source: ISS Report)

Orthostatic hypotension
Dizziness postural
Syncope
Blood pressure decreased
Presyncope
Blood pressure orthostatic decreased
Blood pressure systolic decreased

The sponsor's analysis found that, overall, the incidence in the hypotension and syncope AESI was similar between the Phase 3 opicapone 50 mg group (2.6%) and the placebo group (2.3%). The most commonly reported event was orthostatic hypotension, which was reported at a higher incidence in the opicapone 50 mg group (1.5%) than in the placebo group (0%). No important differences were observed between the opicapone 25 mg and 50 mg groups. Most events were mild or moderate in severity and 1 event (presyncope) was severe. In the OLEX using the same collection of terms, 49 of 848 (5.8%) patients developed this AESI.

The sponsor's analysis was flawed due to lack of inclusion of other Preferred Terms likely related to the AESI. For example, the verbatim of "worsening hypotension" was coded as the PT "Hypotension" yet this was not included in the sponsor's analysis (presumably because its presence was not viewed as "treatment emergent.") I reviewed the verbatim descriptions of the ADAE dataset to look for descriptions combining symptoms with change in posture that would suggest orthostasis. Dizziness, in particular, was closely reviewed. As examples, the verbatim descriptions of "dizziness on standing," "orthostatic dizziness," and "lightheadedness on standing" received PT related to dizziness and were not counted as orthostasis. This review process added 36 additional events to the sponsor's count of 20 for the Phase 3 DB study populations:

Table 57 Preferred Terms from ADAE where the verbatim description suggests exacerbation by postural change.

Preferred Term	50 mg/ d	25 mg/d	Placebo
Asthenia	1		
Blood Pressure Decreased		1	
Dizziness	10	10	2
Dizziness postural		4	4
Hypotension	5		1
Loss of consciousness	1		
Orthostatic hypotension	4	2	
Presyncope	1		
Syncope	4		1
Vertigo		4	1
Total Event Count (56)	26 (46%)	21 (38%)	9 (16%)

Reanalysis using the above events as a "custom SMQ" resulted in what I consider to be more representative assessment of the occurrence of symptomatic orthostasis resulting from increased levodopa availability, a total of 43 patients from the DB population.

Table 58 Phase 3 DB: Reviewer's "custom SMQ" for orthostasis (see text for explanation).

Phase 3 Double Blind	25mg/day (N = 248)			50mg/day (N = 270)			Placebo (N = 265)		
	Events	N	%	Events	N	%	Events	N	%
"Custom" SMQ	21	17	6.9	26	17	6.3	9	9	3.4

The sponsor's assessment using their criteria found that 49 of 848 patients (5.8%) in the OLEX pool had an event described by one of the PT. A review of verbatim descriptions of events in the AE dataset was not performed for the OLEX population.

Subgroup analysis should be considered in a *post hoc* light due to the small group size. However, the increased incidence in the ≥ 65 age group is logical and consistent with other studies.

Table 59 Phase 3 DB: Demographic features of patients with AEs suggesting orthostasis (source: ADAE, ADSL).

	N (%) of Subgroup		Subgroup N (%) of Phase 3 Population (N=781)	
Age	**< 65**	**≥ 65**	**< 65**	**≥ 65**
	17 (4.1%)	26 (7.1%)	416 (53.2%)	365 (46.7%)
Sex	**Male**	**Female**	**Male**	**Female**
	21 (4.5%)	22 (6.9%)	(464) 59.4%	317 (40.6%)
Race*	**Asian**	**Caucasian**	**Asian**	**Caucasian**
	8 (6.7%)	35 (5.4%)	119 (15.5%)	651 (84.5)
	* Race not entered (N=11)			

8.5.4. Falling Asleep During Activities of Daily Living and Somnolence

Using MAED Preferred Terms suggesting an increased tendency to sleepiness (hypersomnia, sudden onset of sleep, sleep attacks, somnolence) were analyzed for the double blind and OLEX study populations:

Table 60 Phase 3 DB: PTs suggesting increased daytime sleepiness (source: ADAE).

DB	OPC 25mg/day (N = 248)			OPC 50mg/day (N = 270)			Placebo (N = 265)		
HLT	Events	N	%	Events	N	%	Events	N	%
Somnolence	10	10	4.03	5	5	1.85	5	5	1.89
Hypersomnia	0	0	0	0	0	0	2	2	0.75
Sleep attacks	1	1	0.4	0	0	0	2	2	0.75

Table 61 Phase 3 OLEX: PTs suggesting increased daytime sleepiness (source: ADAE).

OLEX	OPC 50mg/day (N = 270)			OPC 25mg/day (N = 248)		
HLT	Events	N	%	Events	N	%
Somnolence	1	1	0.37	5	4	1.61
Sleep attacks	1	1	0.37	0	0	0

The incidence of events suggesting increased daytime sleepiness in all treatment arms likely reflects the fact that all anti-PD drug treatments are associated with this phenomenon. The effect of anti-PD polypharmacy cannot be accounted for.

The Parkinson's Disease Sleep Scale (PDSS) did not elicit any differences among the treatment groups. The clustering of scores at the top end of the scale suggested that it was an insensitive instrument (all opicapone mean score 101.3, SD±24.6 vs. placebo mean 102, SD ± 27.3).

8.5.5. Psychosis and Hallucinations

The sponsor analyzed psychosis using the narrow SMQ: Psychosis and psychotic disorders. TEAE listings were reviewed for additional terms related to hallucinations and illusions. This analysis specifically excluded behaviors related to Impulse Control Disorder (see below). Overall, the incidence of psychosis and related AEs was higher than placebo for all doses of opicapone (4% overall vs. 1.2%). Delusional or frank psychotic behavior was rare and the bulk of the difference was due to the occurrence of hallucinations (mostly visual) in both DB and OLEX epochs. In six cases it did lead to drug discontinuation. The incidence of psychotic or hallucinations In the OLEX was consistent with that seen in the DB epoch (3.8%); there was one severe SAE with delusional jealousy leading to drug discontinuation.

8.5.6. Impulse Control/Compulsive Behavior

The sponsor investigated the occurrence of impulse control disorder and compulsive behavior by administering the modified Minnesota Impulsive Disorders Interview (mMIDI) and conducting an analysis of the HLT, Impulse control disorders (comprised of Preferred Terms: libido increased, hypersexuality, binge eating, gambling, compulsive shopping, gambling disorder, dopamine dysregulation syndrome, compulsions). Analysis by MAED HLT for Impulse Control Disorders did not reveal more than a few instances.

Table 62 Phase 3 DB: MAED analysis of HLT for ICD (source: ADAE).

DB	*OPC 25mg/day (N = 248)*			*OPC 50mg/day (N = 270)*			*Placebo (N = 265)*		
HLT	*Events*	*Count*	*%*	*Events*	*Count*	*%*	*Events*	*Count*	*%*
Impulse control disorders	0	0	0	1	1	0.37	0	0	0

Table 63 Phase 3 OLEX: MAED analysis of HLT for ICD (source: ADAE).

OLEX	*OPC 50mg/day (N = 270)*			*OPC 25mg/day (N = 248)*		
HLT	*Events*	*Count*	*%*	*Events*	*Count*	*%*
Impulse control disorders	0	0	0	2	2	0.81

AE counts that added additional terms to the HLT listing captured this phenomenon more effectively.

Table 64 Phase 3 DB: MAED analysis of ICD using all potentially related PTs found in ADAE.

	Double Blind		OLEX
AESI Category: Search Terms/ Preferred Term	**Placebo N=257**	**All Opicapone N=631**	**OL All OPC N=848**
	n (%)	**n (%)**	**n (%)**
Impulse control disorders: HLT and/or selected preferred terms	0	5 (0.8)	12 (1.4)
Impulse control disorders HLT	0	1 (0.2)	4 (0.5)
Impulse-control disorder	0	0	2 (0.2)
Impulsive behaviour	0	1 (0.2)	2 (0.2)
Additional preferred terms	0	0	0
Gambling disorder	0	1 (0.2)	4 (0.5)
Binge eating	0	1 (0.2)	2 (0.2)
Compulsive shopping	0	0	2 (0.2)
Libido increased	0	0	1 (0.1)
Hypersexuality	0	2 (0.3)	1 (0.1)
Gambling	0	0	1 (0.1)
Compulsions	0	0	0
Dopamine dysregulation syndrome	0	1 (0.2)	0

Surveillance using the mMIDI provided more useful information. It was added by study amendment after the start of the Phase 3 trials, implementing prior FDA advice. As a result, not all participants had baseline measures. On face, buying disorder was the most commonly reported baseline and postbaseline impulse disorder in both the 50 mg and placebo groups of the DB period. Of interest, the mMIDI scores were most different among the treatment groups at baseline and fell across all treatment groups (and differences narrowing) from the baseline measure to the Visit 5 assessment and the end of study assessment. This may suggest that an effect of regression to the mean was occurring for this interview measure.

Table 65 Phase 3 DB: Elements of ICD as revealed by mMIDI structured interviews (source: ISS Report).

Visit Behavior	Placebo N=257	OPC 5 mg N=122	OPC 25 mg N=244	OPC 50 mg N=265	All OPC N=631
	n/m (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)
Baseline (Visit 2)					
Buying disorder	4/78 (5.1)	9/55 (16.4)	7/73 (9.6)	4/77 (5.2)	20/205 (9.8)
Pathological gambling	1/78 (1.3)	2/55 (3.6)	0/73 (0.0)	2/76 (2.6)	4/204 (2.0)
Compulsive sexual behavior	3/76 (3.9)	1/55 (1.8)	1/72 (1.4)	1/77 (1.3)	3/204 (1.5)
Visit 5					
Buying disorder	3/94 (3.2)	8/56 (14.3)	3/81 (3.7)	5/90 (5.6)	16/227 (7.0)
Pathological gambling	1/94 (1.1)	1/56 (1.8)	0/81 (0.0)	1/89 (1.1)	2/226 (0.9)
Compulsive sexual behavior	2/92 (2.2)	0/56 (0.0)	0/79 (0.0)	1/90 (1.1)	1/225 (0.4)
Visit 7/EDV					
Buying disorder	7/136 (5.1)	8/76 (10.5)	3/120 (2.5)	8/118 (6.8)	19/314 (6.1)
Pathological gambling	0/135 (0.0)	1/76 (1.3)	0/120 (0.0)	2/117 (1.7)	3/313 (1.0)
Compulsive sexual behavior	2/134 (1.5)	4/76 (5.3)	1/117 (0.9)	1/116 (0.9)	6/309 (1.9)

A similar effect was noted in the OLEX population where the incidence of buying disorder was highest at entry (6.3%) and fell subsequently (2.9% by end of study). Pathological gambling and compulsive sexual behavior were level at 0.8% and 1.4%, respectively.

8.5.7. Injuries and Falls

Events of injuries and falls were reviewed by the sponsor based upon an analysis of narrow SMQ (Accidents and Injuries).

In the pooled DB cohort, by their analysis, 6.4% of patients in the opicapone 50 mg group and 6.6% of patients in the placebo group reported TEAEs in the injuries and falls AESI. Of these, fall was the most common PT and was reported at a lower incidence in the opicapone 50 mg group (3.0%) than the placebo group (4.7%). One 50 mg/d patient, reported above as a serious event, experienced a fall simultaneous with an SAE of head injury on the same day. Another 50 mg/d patient experienced a fall that resulted in study discontinuation, also reported above. The sponsor's summary of injuries and falls is illustrated in the table below.

Table 66 Phase 3 DB: Narrow SMQ accidents and injuries (source: ISS Report, page 135)

AESI Category: Search Terms/ Preferred Term	Placebo N=257	OPC 5 mg N=122	OPC 25 mg N=244	OPC 50 mg N=265	All OPC N=631
	n (%)	n (%)	n (%)	n (%)	n (%)
Injuries and falls: Accidents and injuries SMQ (Narrow)	17 (6.6)	5 (4.1)	14 (5.7)	17 (6.4)	36 (5.7)
Fall	12 (4.7)	2 (1.6)	11 (4.5)	8 (3.0)	21 (3.3)
Contusion	1 (0.4)	0	1 (0.4)	2 (0.8)	3 (0.5)
Limb injury	2 (0.8)	1 (0.8)	1 (0.4)	1 (0.4)	3 (0.5)
Head injury	1 (0.4)	0	1 (0.4)	1 (0.4)	2 (0.3)
Thermal burn	0	1 (0.8)	1 (0.4)	0	2 (0.3)
Burns first degree	0	0	0	1 (0.4)	1 (0.2)
Chemical burn	0	0	0	1 (0.4)	1 (0.2)
Chest injury	0	0	1 (0.4)	0	1 (0.2)
Face injury	0	0	1 (0.4)	0	1 (0.2)
Hand fracture	0	0	0	1 (0.4)	1 (0.2)
Joint injury	0	0	0	1 (0.4)	1 (0.2)
Laceration	0	0	0	1 (0.4)	1 (0.2)
Lumbar vertebral fracture	0	0	0	1 (0.4)	1 (0.2)
Scratch	0	0	0	1 (0.4)	1 (0.2)
Soft tissue injury	0	0	0	1 (0.4)	1 (0.2)
Wrist fracture	1 (0.4)	1 (0.8)	0	0	1 (0.2)
Femoral neck fracture	1 (0.4)	0	0	0	0
Near drowning	1 (0.4)	0	0	0	0
Radius fracture	2 (0.8)	0	0	0	0

It should be noted that the sponsor's table above represents TEAEs and not simply all AEs reported. Unfortunately, this evaluation of causality was performed by the site investigator and, unless considered an SAE, was unable to be evaluated further. Review of the ADAE dataset for the DB period, for example, PT "Fall," the occurrences for placebo, 25 mg/d and 50 mg/d are 14 (5.4%), 13 (5.4%), and 15 (5.7%), respectively; it is not possible to explain from the information submitted why a greater percentage of falls in the 50mg/d arm are not considered treatment-emergent.

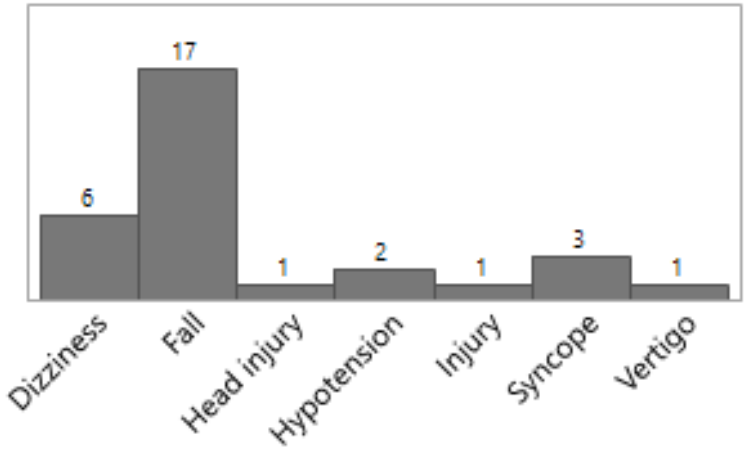
Falls occurred as an AE 42 times in 31 patients. Only two events were considered severe, one in the 50 mg/d group and one in the placebo arm. About two-thirds of falls were considered "mild" and the rest "moderate" in severity. These proportions were the same in all three treatment arms.

While the sample is small for truly meaningful subgroup analysis, it is apparent that advancing age is a risk factor for falls with 60 % of falls occurring in the ≥65 years group. Proportionately, more patients above 65 years of age fell in the placebo arm than active treatment arms (71% vs 53%). Otherwise the distribution of falls for sex and race were proportionate to the study population.

As a result of falls, 7 fractures occurred in 5 patients, five of these being in the wrist or hand, likely injured by extending the arms in a fall. Five of the seven fractures were in people above the age of 65 and 5 of 7 occurred on placebo.

Looking at the contribution of orthostatic hypotension, the patients from suspected of having OH from the ADAE dataset (n=43; see Section 8.5.3 above) were evaluated for injury and falls. Seven patients having 31 AEs were common to both set of DB patients having injuries and probably orthostasis. Of these injuries, 74% were considered mild. One patient (Study 302, (b) (6)) had 3 SAEs and left the study. This was discussed in the relevant sections above. One patient was in the placebo arm, 2 on 25 mg/d and 4 on 50 mg/d opicapone. Three of the seven patients were younger than 65. The following PT were reported for this group (Note the AEs of dizziness and vertigo and that the PT hypotension was not reported to be "orthostatic" or "postural" in these patients.)

Figure 12 Phase 3 DB: AEs in 7 patients who were identified by both the MAED accident injury SMQ and the reviewer's custom SMQ for orthostasis.



8.5.8. Diarrhea

The PT diarrhea and the narrow SMQ: Noninfectious diarrhoea were used to look at AEs in this category. To look for diarrhea potentially attributed to other causes, the following PT were also collated: colitis, colitis microscopic, allergic gastroenteritis, gastrointestinal toxicity

In the DB epochs, approximately equal percentages of active and placebo patients reported diarrhea as an AE: opicapone n=17 (1.6 %); placebo n=5 (1.9%). No other potential etiologies were reported. In the OLEX epochs, 11 patients reported diarrhea (1.4%), with one case reporting the PT colitis, as well. Diarrhea was listed as mild in most cases. One patient in open-label treatment was reported as leaving the study due to diarrhea but review of the narrative suggests that exacerbation of pre-existing hypotension was the more proximate cause for discontinuation.

8.5.9. Hepatotoxicity

Hepatotoxicity was investigated by clinical laboratory surveillance and by a broad SMQ for drug-related hepatic disorders search. The SMQ findings were not helpful; more suggestive cases occurred in the placebo compared to active treatment arms. Analysis focused upon the liver function tests (LFT) themselves. Abnormal LFT were predefined using elevations over the ULN: AST (≥3 × ULN), ALT (≥3 × ULN), and total bilirubin (≥2 × ULN). The sponsor created graphic plots for the evaluation of drug-induced serious hepatotoxicity (eDISH).

Very few patients met abnormal liver function test values (≤2 opicapone-treated subjects for each test) and this made subgroup analysis unmeaningful. Notable for a large abnormal shift was a opicapone 25 mg patient who had a bout of diarrhea followed after 2 days by transient laboratories shifts of ALT (8.8 × ULN), AST (3.4 × ULN), and gamma-glutamyl transferase (GGT) (4.4 × ULN), while bilirubin and ALP were in the normal range at Visit 7. The diagnosis was probable food poisoning and the laboratory values returned to the normal range the following week. The patient continued in the study without reoccurrence.

In the placebo arm, AST ≥3 × ULN with total bilirubin ≥2 × ULN was reported for 1 subject in the placebo group (Patient 330704) who had concurrent acute hepatitis and pancreatitis. In the OLEX population, 4 patients had some modest increase in a hepatic enzyme, none with ALT or AST ≥3 × ULN AND total bilirubin ≥1.5 × ULN or greater in combination.

No opicapone-treated subjects met all 3 criteria for Hy's Law in the DB or OLEX period.

8.5.10. Suicidality

Screening for suicidality using the Columbia -Suicide Severity Rating Scale was instituted after the start of the Phase 3 studies, implementing prior FDA advice by study amendment. For this reason, baseline measures were missing for some patients but there was an attempt to impute pre-study suicidality. Baseline prior suicidality was roughly equivalent across treatment arms. In the DB period 4 patients on 50 mg/d compared to 2 patients on placebo described suicidal ideation. (Identified by the C-SSRS, these were not reported as AEs.) In the OLEX period, 3.8% of participants reported suicidal ideation postbaseline, which is similar to their baseline self-reported lifetime history of suicidal ideation (4.4%). No patients reported suicidal behavior

during the OL period but 4 patients reported TEAEs of suicidal ideation. There was no C-SSRS score greater than 3 for the DB or OLEX epochs.

8.5.11. Cardiovascular (ischemic heart disease)

The sponsor provided an analysis of cardiovascular events potentially related to ischemia using the broad SMQ: Ischaemic heart disease. This SMQ includes the PT for increased creatine phosphokinase, and as discussed in Section 8.4.6 Laboratory Studies, above, this test was likely of poor reliability. Despite this caveat, in the DB epochs, opicapone treated patients had n=23 (3.6%) fulfilling SMQ criteria while 6 patients (2.3%) receiving placebo did so. Removing the increased CPK occurrences left just 1 opicapone-treated and 1 placebo patient fulfilling the SMQ criteria (coronary artery disease and myocardial ischemia, respectively).

In the OLEX population 48 patients (5.7%) fulfilled the SMQ criteria, but again 38 of the events counted were related to increased CPK. Removing those left 13 ischemic cardiovascular events in 11 patients (1.5%), 4 receiving 50 mg/d and 8 taking 25 mg/d. Events in two of these OLEX patients resulted in deaths described above.

Note that this analysis did not include events related to abnormalities of cardiac conduction, structural abnormalities such as valvular disease, or chronic heart failure.

8.5.12. Withdrawal-Emergent Hyperpyrexia and Confusion

There were no reports of withdrawal-emergent hyperpyrexia and confusion reported in the opicapone development program.

8.5.13. Melanoma and Other Cancers

In the course of the Phase 3 studies, nine patients developed cancer in the DB epochs (opicapone, n=5; placebo, n=4). The only melanoma occurred in the placebo arm. In the OLEX studies, 18 patients developed a cancer, the majority of which were skin cancers (melanoma = 3; basal cell = 7; other skin cancers = 5). There is no appreciable difference in the cancer rate in active versus placebo treatment (0.8% vs 1.6%) but these studies were not designed to establish causality or attribution and the incidence is possibly a reflection of the older demographic.

8.6. Safety Analyses by Demographic Subgroups

The analysis of TEAEs by subgroup revealed few differences and none are likely of much clinical importance. The analysis is limited to AEs occurring in ≥3% of patients. AEs occurring at lesser frequency are difficult to interpret sensibly.

Age

The incidence of TEAEs relative to placebo reported in patients <65 years and ≥65 years of age was similar. Occurring somewhat more frequently for those ≥65 years of age, were constipation and dizziness in the opicapone 50 mg arm versus the placebo group. While the incidence of falls was higher overall in the older age group than those <65 years, in both age groups the incidence was lower in the opicapone 50 mg group relative to placebo. No other differences in treatment effect between age groups were notable. ADSL and ADAE

Table 67 Phase 3 DB: AEs in patients <65 and ≥65 (source: ADSL and ADAE datasets)

Preferred Term	Head Count				Percent			
Arm (≥ and < age 65)	50mg <65	50mg ≥65	Placebo <65	Placebo ≥65	50mg <65	50mg ≥65	Placebo <65	Placebo ≥65
N	N=126	N=139	N=145	N=112	N=126	N=139	N=145	N=112
Dyskinesia	29	25	9	7	23	18	6	6
Constipation	5	12	3	2	4	9	2	2
Headache	2	8	7	4	2	6	5	4
Weight decreased	3	7	0	0	2	5	0	0
Urinary tract infection	4	6	0	2	3	4	0	2
Dizziness	2	6	0	3	2	4	0	3
Dry mouth	3	5	0	2	2	4	0	2
Nausea	3	5	5	5	2	4	3	4
Fall	3	5	4	8	2	4	3	7
Insomnia	4	5	1	3	3	4	1	3
Vomiting	1	4	4	1	1	3	3	1
Blood CPK increased	9	4	2	3	7	3	1	3
Tremor	1	4	2	2	1	3	1	2
Hallucination, visual	2	4	1	1	2	3	1	1
Hypotension	1	4	1	0	1	3	1	0
Diarrhoea	3	3	2	3	2	2	1	3
Influenza	0	3	0	1	0	2	0	1
Arthralgia	1	3	1	2	1	2	1	2
Musculoskeletal chest pain	0	3	0	0	0	2	0	0
Pain in extremity	1	3	2	2	1	2	1	2
Parkinson's disease	3	3	6	2	2	2	4	2
Syncope	0	3	1	0	0	2	1	0
Abnormal dreams	0	3	0	2	0	2	0	2
Anxiety	1	3	0	3	1	2	0	3

Sex

The incidence of TEAEs reported in men and women was similar. TEAEs reported at a higher incidence in women treated with opicapone 50 mg compared to placebo included constipation, dry mouth, and urinary tract infection. In men treated with opicapone 50 mg, the incidence of hypertension was higher than in women relative to placebo. No other differences in treatment effect were of note.

Table 68 Phase 3 DB: AEs by sex (source: ADSL and ADAE datasets)

Preferred Term	Head Count				Percent			
Arm (F or M)	50mg (F)	50mg (M)	Placebo (F)	Placebo (M)	50mg (F)	50mg (M)	Placebo (F)	Placebo (M)
N	N=105	N=160	N=115	N=142	N=105	N=160	N=115	N=142
Dyskinesia	23	31	11	5	22	19	10	4
Constipation	10	7	1	4	10	4	1	3
Urinary tract infection	9	1	2	0	9	1	2	0
Headache	7	3	8	3	7	2	7	2
Dry mouth	6	2	0	2	6	1	0	1
Blood CPK increased	5	8	2	3	5	5	2	2
Weight decreased	5	5	0	0	5	3	0	0
Nausea	4	4	6	4	4	3	5	3
Vomiting	4	1	3	2	4	1	3	1
Fall	4	4	6	6	4	3	5	4
Pain in extremity	4	0	3	1	4	0	3	1
Dizziness	4	4	1	2	4	3	1	1
Hallucination, visual	4	2	2	0	4	1	2	0
Leukopenia	3	1	1	0	3	1	1	0
Viral URI	3	2	2	4	3	1	2	3
Crystal urine present	3	1	0	0	3	1	0	0
Musculoskeletal chest pain	3	0	0	0	3	0	0	0
Parkinson's disease	3	3	2	6	3	2	2	4
Somnolence	3	2	2	3	3	1	2	2
Hallucination	3	0	0	1	3	0	0	1
Insomnia	3	6	0	4	3	4	0	3
Abdominal pain upper	2	2	0	0	2	1	0	0
Chronic gastritis	2	0	0	0	2	0	0	0

Race
Two racial groups were represented in the opicapone development program: white and Asian, with the latter representing only 12% of the DB safety population (Asian=104; white=773). The overall incidence of TEAEs reported in white patients was higher than Asian participants across all treatment groups, however, in both races the incidence was similar in the opicapone 50 mg and placebo groups. Difficulty with analysis and interpretation is emphasized by the n of only 33 Asians in the 50 mg cohort and 29 in the 25 mg cohort whereby one additional occurrence of an AE causes it to jump 3% in the AE table.

8.7. Specific Safety Studies/Clinical Trials

Aside from the Thorough QT Study (Study 111), no targeted clinical safety studies were performed.

However, food studies were performed healthy volunteers and demonstrated that the rate and extent of exposure to opicapone were significantly lower in the fed state compared to the fasting state and t_{max} was delayed with food.

8.8. Additional Safety Explorations

The potential for overdose, drug abuse, withdrawal, and rebound were addressed in the application. The sponsor has submitted an 8 factor analysis of the habituation and abuse potential of opicapone consistent with that proposed by FDA guidance. The findings may be summarized as follows:

The structure of opicapone is not related to any known substance with abuse liability. No specific animal behavior studies or human abuse potential studies have been conducted with opicapone. No evidence of psychic or physiological dependence of opicapone has been reported. While an inhibitor of COMT, there is no clinically relevant off target activity. Across clinical studies and populations (healthy subjects and PD patients), there was no apparent relationship between the dose of opicapone and the incidence of TEAEs potentially related to abuse and dependence. The most common of these TEAEs (dizziness, somnolence, hallucination visual, hallucination) each occurred in <5% of OPC-treated subjects in the pooled Phase 3 double blind studies. However, these AEs are commonly reported with levodopa and were attributed to the increases in dopaminergic tone as expected with opicapone inhibition of COMT metabolism. There was 1 incidence of an accidental overdose (Study 302 OL period, Subject 130701 described above) leading to study withdrawal. The subject took 50 mg twice daily for 2 months by mistake; no adverse drug reaction was noted. In addition, single doses of opicapone up to 1200 mg non-micronized (equivalent to 600 mg micronized) have been administered to subjects and were well-tolerated.

Cumulative tabulations of spontaneous adverse drug reactions from EU postmarketing data sources and literature publications reported no cases of drug abuse or intentional overdose

with opicapone to date.

On review, I conclude that abuse liability is not supported by the available data and recommend that opicapone not be scheduled under the Control Substance Act. Section 9.0, Abuse and Dependence may be safely omitted in labeling.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The sponsor has submitted Developmental Safety Update Reports (DSUR) to FDA, the last being #8 covering the year prior to April 30, 2019.

The Development International Birthdate of opicapone is April 30, 2009. The International Birth Date is June 24, 2016 when an EU Marketing Authorization (MA) was granted to Ongentys® (opicapone, 25 mg and 50 mg hard capsules for oral administration) by the European Commission as adjunctive therapy in adults with PD and end-of-dose motor fluctuations. Ongentys® is currently approved in 32 countries but as of this last DSUR it has only been launched in Germany, Italy, Portugal, Spain, and United Kingdom. Using worldwide factory distribution of the medicinal product, (b) (4) capsules sold and delivered to these 5 countries, the sponsor has estimated patient exposure from the time of the MA through April 30, 2019 to be a total of 420,167 patient-months or 35,013 patient-years. There has been no suspension of the MA, imposed restrictions on distribution, dosage modification, or urgent safety restrictions.

The DSUR cumulatively tabulated Serious Adverse Events and assessed them for relatedness to drug and whether they were unexpected. The sponsor's postmarketing safety surveillance investigations found 722 spontaneously-reported suspected adverse drug reactions (ADRs) consisting of 606 non- serious and 116 serious. Events classified as serious and coded more than twice are: hallucination (4), dizziness (3), dyskinesia (4), hyperkinesia (4), somnolence (3), and syncope (3).

Coding for the event "therapy cessation", cumulatively there are 123 cases in which treatment was discontinued. Reported events in these cases with a frequency ≥5 are dyskinesia (15), nausea (14), confusional state (11), hallucination visual (10), hallucination (11), dizziness (13), fall (8), dry mouth (6), anxiety (8), constipation (8), somnolence (7), weight decreased (5), vomiting (7), diarrhoea (11), musculoskeletal stiffness (6), feeling abnormal (6), malaise (6), tremor (6), psychotic disorder (5), inappropriate schedule of product administration (5), on and off phenomenon (5), and headache (5).

The sponsor reviewed publications in the medical literature relevant to the clinical use of opicapone and found no new or relevant safety information.

Postmarketing safety surveillance of opicapone, now in wide general clinical use, has not revealed any new or novel serious or unexpected ADRs.

8.9.2. Expectations on Safety in the Postmarket Setting

Not applicable. See Section 8.9.1, above.

8.9.3. Additional Safety Issues From Other Disciplines

None.

8.10. Integrated Assessment of Safety

Opicapone would be the third COMT inhibitor in its pharmacological class after tolcapone and entacapone. 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 has been observed in the opicapone development program. The most commonly observed adverse events are dyskinesia, dizziness (orthostasis, syncope), constipation, dry mouth, and psychiatric disorders including ICD. These have accompanied the care of PD patients since the introduction of dopamine based pharmacological treatment of PD a half-century ago and represent the bulk of what have been evaluated as Adverse Events of Special Interest in this review.

There have also been other adverse reactions that are associated with specific individual COMT inhibitors. Tolcapone has been associated with severe and occasionally fatal hepatic toxicity, while entacapone has been suspected of causing severe diarrhea and colitis. While the potential for these reactions were identified in their respective development programs, they were better defined after these products achieved wider use. In this regard, opicapone benefits from wide marketed use in the EU and several years of post-marketing surveillance.

In this development program, a possible signal, elevation of creatine phosphokinase (CPK), has been noted. However, my review suggests that it could be related to faulty laboratory evaluation given the equivalent findings between opicapone and placebo treated patients. This CPK elevation has so far not been supported by spontaneous post market reporting for opicapone. Should evidence develop that further supports a possible association, surveillance by clinical laboratory testing of CPK would not be difficult to institute.

Following review of the clinical data submitted by the sponsor, my assessment is that opicapone has the ADRs expected from a member of the class of COMT inhibitors and does not, at this time, appear to have an association with idiosyncratic drug reactions related to its

chemical structure.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee input was sought for this application. Opicapone, a COMT inhibitor, is the third agent in this pharmacological class to be approvable for the treatment of motor fluctuations in PD, after tolcapone and entacapone.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Describing the safe and effective use of opicapone has been the subject of collaborative effort between FDA and the sponsor throughout the review cycle. Information and analyses in support of WARNINGS AND PRECAUTIONS and 6.1 Clinical Trials Experience are described in the Integrated Review of Safety, above.

11. Risk Evaluation and Mitigation Strategies (REMS)

Given the favorable safety profile of this drug, there are no additional risk management strategies required beyond the recommended labeling. The safe and effective use of opicapone in the treatment of motor fluctuations in PD can be adequately described in the drug labeling.

12. Postmarketing Requirements and Commitments

No clinical PMR or PMC is proposed at this time. There are no further efficacy or safety issues that must be explored at this time.

13. Appendices

13.1. Tabular Listing: All Clinical Studies in the Development Program

(Source: Sponsor, eCTD Module 5.2)
Phase 3 Studies:

Type of Study	Study Identifier	Population	Objective(s) of the Study	Study Design and Type of Control	Duration of Treatment	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects Treated/ Completed	Study Status; Type of Report	Non-IND Foreign Clinical Study
Phase 3 Studies									
Safety and Efficacy	BIA-91067-301	Patients with idiopathic Parkinson's disease with "wearing off" phenomenon	Efficacy of 3 different doses of OPC (5 mg, 25 mg, 50 mg) qd, compared with placebo or 200 mg of ENT, when administered with the existing treatment of levodopa/DDCI.	DB Period R, DB, PC, and active control (entacapone), parallel group, multiple dose	14-15 weeks	OPC micronized (5, 25, or 50 mg) qd at bedtime at least 1 h after the last daily dose of levodopa/DDCI, entacapone 200 mg concomitant with each daytime levodopa/DDCI dose (3 to 8 times daily). PBO concomitant with each daytime levodopa/DDCI dose (3 to 8 times daily) and/or at bedtime 1 h after the last daily dose of levodopa/DDCI. PO	OPC: 356/325 ENT: 122/107 PBO: 121/110 Total: 599/542	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
Safety and Efficacy	BIA-91067-301	Patients with idiopathic Parkinson's disease with "wearing off" phenomenon	Safety, tolerability, and maintenance of therapeutic effect of OPC (25 mg qd or 50 mg qd) over 1 year of treatment, administered with existing levodopa/DDCI, in patients who completed the Part I DB Phase of the study.	OL Period	52 weeks	OPC micronized 5, 25, or 50 mg (dose adjusted based on clinical response) qd at bedtime at least 1 h after the last daily dose of levodopa/DDCI. PO	OPC: 495/432	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
Safety and Efficacy	BIA-91067-302	Patients with idiopathic Parkinson's disease with "wearing off" phenomenon	Efficacy of 2 different doses of OPC (25 mg and 50 mg), qd, compared with placebo, when administered with the existing treatment of levodopa/DDCI.	DB Period R, DB, PC, parallel group, multiple dose	14-15 weeks	OPC micronized 25, 50 mg, or PBO qd at bedtime at least 1 h after the last daily dose of levodopa/DDCI. PO	OPC: 275/246 PBO: 136/130 Total: 411/376	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
Safety and Efficacy	BIA-91067-302	Patients with idiopathic Parkinson's disease with "wearing off" phenomenon	Safety, tolerability, and maintenance of therapeutic effect of OPC (25 mg qd or 50 mg qd) over 1 year of treatment, administered with existing levodopa/DDCI, in patients who completed the Part I DB Phase of the study.	OL Period	52 weeks	OPC micronized 25 or 50 mg (dose adjusted based on clinical response) qd at bedtime at least 1 h after the last daily dose of levodopa/DDCI. PO	OPC: 353/286	Completed; Full	Yes 21 CFR 312.120 Compliance Statement

Phase 2 Studies:

Type of Study	Study Identifier	Population	Objective(s) of the Study	Study Design and Type of Control	Duration of Treatment	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects Treated/ Completed	Study Status; Type of Report	Non-IND Foreign Clinical Study

PK/PD	BIA-91067-201	Parkinson's disease patients with predictable signs of end-of-dose deterioration	Effect of OPC on the levodopa PK; Tolerability and safety.	R, DB, PC, 4-period XO, single dose	4 single doses separated by 10 days	OPC nonmicronized 25, 50, 100 mg, or PBO, single dose in the morning on Day 3 of each treatment period concomitant with IR levodopa/carbidopa 100/25 mg or levodopa/benserazide 100/25 mg. PO	OPC: 10/9 PBO: 9/9 Total: 10/9	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK/PD	BIA-91067-202	Parkinson's disease patients with motor fluctuations ("wearing off" phenomenon)	Effect of repeated dosing of OPC on the levodopa PK; Tolerability and safety.	R, DB, PC, parallel group, multiple dose	21-28 days	OPC nonmicronized (5, 15, or 30 mg) or PBO, qd in the morning at least 1 h prior to the dosing of levodopa/carbidopa 100/25 mg or levodopa/benserazide 100/25 mg. PO	OPC: 30/27 PBO: 10/9 Total: 40/36	Completed; Full	Yes 21 CFR 312.120 Compliance Statement

Phase 1 Studies:

Type of Study	Study Identifier	Population	Objective(s) of the Study	Study Design and Type of Control	Duration of Treatment	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects Treated/ Completed	Study Status; Type of Report	Non-IND Foreign Clinical Study
PK/PD	BIA-91067-101	Healthy subjects	Tolerability and safety PK/PD (COMT inhibition).	R, DB, PC, ascending single dose	Single dose	OPC nonmicronized 10, 25, 50, 100, 200, 400, 800, 1200 mg, or PBO in the morning. PO	OPC: 48/48 PBO: 16/16 Total: 64/64	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK/PD	BIA-91067-102	Healthy subjects	Tolerability and safety PK/PD (COMT inhibition).	R, DB, PC, ascending multiple dose	8 days	OPC nonmicronized 5, 10, 20, 30 mg, or PBO qd in the morning for 8 days. PO	OPC: 25/24 PBO: 9/8 Total: 34/32	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
ADME	BIA-91067-103	Healthy subjects	ADME Tolerability and safety.	OL, single group, single arm, single dose, ADME	Single dose	OPC nonmicronized 100 mg with 3.33 MBq or 90 µCi of ^{14}C in the morning. PO	OPC: 4/4	Completed; Full	Yes 21 CFR 312.120 Compliance Statement

BA Food effect	BIA-91067-104	Healthy subjects	Food effect PK; Tolerability and safety.	R, OL, XO, single dose, single arm, BA, food effect	2 single doses separated by at least 7 days	OPC nonmicronized 50 mg (fasted or fed) in the morning. PO	OPC: 12/11	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK Intrinsic Factors	BIA-91067-105	Healthy subjects	Effect of age on OPC PK. Tolerability and safety in healthy young and elderly subjects.	NR, OL, parallel group, single arm, multiple dose, PK between young and elderly subjects	7 days	OPC nonmicronized 30 mg qd in the morning for 7 days. PO	OPC: 24/24	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK Intrinsic Factors	BIA-91067-106	Healthy subjects and subjects with moderate hepatic impairment	Effect of hepatic impairment on OPC PK/PD. Tolerability and safety.	NR, OL, parallel group, single arm, single dose	Single dose	OPC nonmicronized 50 mg in the morning of Day 1. PO	OPC: 16/16	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK/PD	BIA-91067-107	Healthy subjects	Effect of OPC on the levodopa PK. Tolerability and safety.	R, DB, 4-way XO, PC, single dose	4 single doses separated by at least 14 days	OPC nonmicronized 25, 50, 100 mg, or PBO, concomitant with IR 100/25 mg levodopa/benserazide in the morning. PO	OPC: 16/14 PBO: 16/14 Total: 16/14	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK/PD	BIA-91067-108	Healthy subjects	Effect of OPC on the levodopa PK. Tolerability and safety.	R, DB, 4-way XO, PC, single dose	4 single doses separated by at least 14 days	OPC nonmicronized 25, 50, 100 mg, or PBO, concomitant with IR 100/25 mg levodopa/carbidopa in the morning. PO	OPC: 16/14 PBO: 16/14 Total: 16/14	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK/PD	BIA-91067-109	Healthy subjects	Effect of OPC on the levodopa PK. Tolerability and safety.	R, DB, 4-way XO, PC, single dose	4 single doses separated by at least 10 days	OPC nonmicronized 25, 50, 100 mg, or PBO concomitant with CR 100/25 mg levodopa/benserazide in the morning. PO	OPC: 22/20 PBO: 22/20 Total: 22/20	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK/PD	BIA-91067-110	Healthy subjects	Effect of OPC on the levodopa PK. Tolerability and safety.	R, DB, 4-way XO, PC, single dose	4 single doses separated by at least 14 days	OPC nonmicronized 25, 50, 100 mg, or PBO, concomitant with CR 100/25 mg levodopa/carbidopa in the morning. PO	OPC: 12/11 PBO: 12/11 Total: 12/11	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
QT/QTc	BIA-91067-111	Healthy subjects	Effect of OPC on cardiac repolarization. Tolerability and safety.	R, DB PC, OL, active controlled (moxifloxacin), 4-period XO, single dose, cardiac repolarization	4 single doses separated by 7 days	OPC nonmicronized 50 or 800 mg, moxifloxacin 400 mg, or PBO in the morning. PO	OPC: 64/61 Moxifloxacin: 64/61 PBO: 64/61 Total: 64/61	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
DDI	BIA-91067-112	Healthy subjects	Effect of OPC on rasagiline PK. Tolerability and safety.	R, OL, 3-way XO, DDI (rasagiline)	3 single doses separated by at least 14 days	OPC nonmicronized 50 mg concomitant with rasagiline 1 mg or with rasagiline 1 mg administered after 1 h delay, or rasagiline 1 mg alone; single dose in the morning. PO	OPC: 24/24	Completed; Full	Yes 21 CFR 312.120 Compliance Statement

DDI	BIA-91067-113	Healthy subjects	Effect of rasagiline on OPC PK. Tolerability and safety.	R, OL, 3-way XO, DDI (rasagiline)	3 single doses separated by at least 14 days	OPC nonmicronized 50 mg alone, concomitant with rasagiline 1 mg, or with rasagiline 1 mg administered after 1 h delay; in the morning. PO	OPC: 25/24	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK/PD	BIA-91067-114	Healthy subjects	Effect of OPC on the levodopa PK. Tolerability and safety.	R, DB, PC, and active controlled (entacapone), parallel group, multiple dose	7 days	OPC nonmicronized 5, 15, 30 mg, Entacapone 200 mg, or PBO with concomitant single dose of IR 100/25 mg levodopa/carbidopa on last study day. PO	OPC: 49/48 ENT: 16/16 PBO: 16/16 Total: 81/80	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
DDI	BIA-91067-115	Healthy subjects	Effect of OPC on repaglinide PK. Tolerability and safety.	R, OL, 2-way XO, DDI (repaglinide)	2 single doses separated by at least 14 days	OPC nonmicronized 25 mg concomitant with repaglinide 0.5 mg administered 1.25 h after the OPC administration or repaglinide 0.5 mg alone; in the morning. PO	OPC: 27/22	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
DDI	BIA-91067-116	Healthy subjects	Effect of OPC on S/R-warfarin PK. Tolerability and safety.	R, OL, 2-way XO, DDI (warfarin)	2 single doses separated by at least 14 days	OPC nonmicronized 25 mg concomitant with racemic 25 mg warfarin, or 25 mg warfarin alone; in the morning. PO	OPC: 20/20	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK/PD	BIA-91067-117	Healthy subjects	Effect of OPC on the levodopa PK. Tolerability and safety.	R, OL, 4-period XO, single dose	4 single doses separated by at least 3 weeks	OPC nonmicronized 50 mg concomitant with levodopa/carbidopa 100/25 mg or with levodopa/carbidopa 1 h later, 50 mg alone, or levodopa/carbidopa alone; in the morning. PO	OPC: 18/16	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK/PD	BIA-91067-118	Healthy subjects	Effect of OPC on the levodopa PK. Tolerability and safety.	R, DB, PC, multiple dose	28 days	OPC nonmicronized 5, 15, 30 mg, or PBO qd for 28 days, concomitant with a single dose of levodopa/carbidopa 100/25 mg on Day 21 and levodopa/benserazide 100/25 mg on Day 28. PO	OPC: 38/36 PBO: 14/12 Total: 52/48	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
BA/BE	BIA-91067-119	Healthy subjects	BA/BE of 2 OPC formulations (clinical micronized and TBM). Tolerability and safety.	R, OL, 3-part 2-period XO, single dose, BE	2 single doses separated by at least 14 days	OPC micronized 5, 25, or 50 mg (micronized Formulation 1 and 2) in the morning. PO	OPC: 85/83	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
BA/BE	BIA-91067-120	Healthy subjects	BA/BE of 2 OPC formulations (clinical micronized and nonmicronized). Tolerability and safety.	R, OL, 2-way XO, single dose, relative BA	2 single doses separated by at least 14 days	OPC 50 mg (nonmicronized or micronized formulation) in the morning. PO	OPC: 28/28	Completed; Full	Yes 21 CFR 312.120 Compliance Statement

BA/BE	BIA-91067-121	Healthy subjects	Dosage form proportionality of OPC. Tolerability and safety.	R, OL, 2-sequence 2-way XO, single dose, dosage form proportionality	2 single doses separated by at least 10 days	OPC micronized 25 mg (5 × 5 mg or 1 × 25 mg capsules) or OPC 50 mg (2 × 25 mg or 1 × 50 mg capsules); in the morning. PO	OPC: 56/55	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
ADME	BIA-91067-122	Healthy subjects	ADME Tolerability and safety.	OL, single group, single dose, ADME	Single dose	OPC micronized 100 mg with 3.39 MBq of ^{14}C-OPC in the morning. PO	OPC: 6/6	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK/PD	BIA-91067-123	Healthy subjects	Effect of OPC on the levodopa PK. Tolerability and safety.	R, DB, PC, multiple dose	18 days	OPC nonmicronized 5, 15, 50 mg, or PBO qd for 18 days concomitant with IR levodopa/carbidopa 100/25 mg on Day 11 and levodopa/benserazide 100/25 mg on Day 18; in the morning. PO	OPC: 56/54 PBO: 18/18 Total: 74/72	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK/PD	BIA-91067-124	Healthy subjects	Effect of OPC on the levodopa PK. Tolerability and safety.	R, DB, PC, active controlled (entacapone), multiple dose	12 days	OPC micronized 25, 50, or 75 mg qd on Days 1-11 and PBO tid concomitantly with IR levodopa/carbidopa 100/25 mg on Day 12 PBO qd on Days 1-11 and PBO or entacapone 200 mg tid concomitantly IR with levodopa/carbidopa 100/25 mg on Day 12. PO	OPC: 48/47 ENT: 16/16 PBO: 16/16 Total: 80/79	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
DDI	BIA-91067-125	Healthy subjects	Effect of paracetamol on OPC PK.	R, OL, 2-way XO, single dose, DDI (acetaminophen)	2 single doses separated by at least 14 days	3 doses of acetaminophen 1 g separated by 6 h followed by OPC micronized 50 mg 1.5 h after the last dose, or OPC micronized 50 mg alone. PO	OPC: 28/28	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK Intrinsic Factors	BIA-91067-126	Healthy subjects	Effect of ethnicity (Japanese bridging) on OPC PK/PD (COMT inhibition). Tolerability and safety.	R, DB, PC, parallel group, multiple ascending dose, PK/PD, race effect	10 days	OPC micronized 5, 25, 50 mg, or PBO qd for 10 days in the morning. PO	OPC: 76/74 PBO: 29/29 Total: 105/103	Completed; Full	No

DDI	BIA-91067-127	Healthy subjects	Effect of OPC on S/R-warfarin PK. Tolerability and safety.	OL, fixed sequence, single dose, DDI (warfarin)	2 single doses (warfarin) separated by at least 14 days	Period 1: warfarin 25 mg alone; single dose; Period 2: 2 daily loading doses of OPC micronized 475 mg qd, OPC micronized 50 mg qd for 5 days, and OPC micronized 50 mg concomitant with a single dose of warfarin 25 mg on Day 8. PO	OPC: 20/17	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
BA Food effect	BIA-91067-128	Healthy subjects	Food effect; PK; Tolerability and safety.	OL, repeated single dose, food effect	12 days	OPC micronized 50 mg (fasted, fed conditions) qd for 12 days in the evening. PO	OPC: 28/28	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
BA/BE	BIA-91067-129	Healthy subjects	BA/BE of 2 OPC formulations. Tolerability and safety.	R, OL, 2-way XO, single dose, BE	2 single doses separated by at least 14 days	OPC micronized 25, 50 mg qd reference formulation or OPC 25, 50 mg qd test formulation. PO	OPC: 56/52	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
ADME	BIA-91067-130	Healthy subjects	ADME Tolerability and safety.	OL, single dose, ADME	Single dose	Mixed-blended single dose of OPC: nonmicronized 100 mg labeled with 3.39 MBq of ^{14}C PO	OPC: 7/7	Completed; Full	Yes 21 CFR 312.120 Compliance Statement
PK Intrinsic Factors	NBI-OPC-1705	Healthy subjects and subjects with mild hepatic impairment	Effect of hepatic impairment on OPC PK. Tolerability and safety.	OL, single dose, 2 group	Single dose	OPC micronized 50 mg qd in the morning PO	OPC: 16/16	Completed; Full	No
PK/PD	NBI-OPC-1706	Parkinson's disease patients on stable levodopa/carbidopa regimen	Patient PK.	OL, multiple dose, patient PK and PD	14 days	OPC micronized 50 mg qd in the evening PO	OPC: 17/16	Completed; Full	No
DDI	NBI-OPC-1707	Healthy subjects	Effect of quinidine on OPC PK. Tolerability and safety.	OL, 2-period XO, DDI (quinidine)	2 single doses separated by 14 days	OPC micronized 50 mg qd alone or concomitantly with quinidine 600 mg 1 hour after quinidine administration PO	OPC alone or with quinidine: 20/18	Completed; Full	No
DDI	NBI-OPC-1708	Healthy subjects	Effect of OPC on repaglinide PK. Tolerability and safety.	OL, 2-period XO, DDI (repaglinide)	15 days	OPC micronized 50 mg qd with repaglinide 0.5 mg or repaglinide 0.5 mg alone PO	OPC with repaglinide or repaglinide alone: 18/16	Completed; Full	No

13.2. References

None.

13.3. Financial Disclosure

In Study 301, financial disclosure was obtained prospectively on 419 of 427 investigators. Remediation procedures obtained the disclosure information on all but 5 investigators.

In Study 302, financial disclosure was obtained prospectively on 306 of 310 investigators. Remediation procedures obtained the disclosure information on all but 2 investigators.

Covered Clinical Study (Name and/or Number): BIA-91067-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 427 (106 Principal Investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): NOT APPLICABLE Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 8		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): BIA-91067-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 310 (72 Principal Investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): NOT APPLICABLE Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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/

KENNETH J BERGMANN
04/24/2020 09:05:03 AM

GERALD D PODSKALNY
04/24/2020 09:57:13 AM