

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212489Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: April 9, 2020

To: Dave Podskalny, M.D.
Division of Neurology I (DN I)

Stacy Metz, Regulatory Project Manager

Tracy Peters, Associate Director for Labeling, DN I

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for ONGENTYS® (opicapone) capsules, for oral use

NDA: 212489

In response to the DN II consult request dated June 27, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for ONGENTYS® (opicapone) capsules, for oral use.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DN II (Stacy Metz) on March 27, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 20, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

20 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

DHARA SHAH
04/09/2020 11:29:38 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 9, 2020

To: Stacy Metz, PharmD
Senior Health Regulatory Project Manager
Division of Neurology I (DN1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
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Marcia Williams, PhD
Team Leader, Patient Labeling
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From: Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Dhara Shah, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): ONGENTYS (opicapone)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 212489

Applicant: Neurocrine Biosciences, Inc.

1 INTRODUCTION

On April 26, 2019, Neurocrine Biosciences, Inc. submitted for the Agency's review a New Drug Application (NDA) 212489 for their product ONGENTYS (opicapone) capsules, for oral use. The proposed indication is for the adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "OFF" episodes.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology I (DN1) on June 27, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ONGENTYS (opicapone) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft ONGENTYS (opicapone) PPI received on April 26, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 27, 2020.
- Draft ONGENTYS (opicapone) Prescribing Information (PI) received on April 26, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 27, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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04/09/2020 06:07:45 PM



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: April 8, 2020

To: Eric Bastlings, MD, Director (Acting)
Division of Neurology I

Through: Dominic Chiapperino, PhD, Director
Chad Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D. Medical Officer
Jovita Randall-Thompson, PhD, Pharmacologist
Controlled Substance Staff

Subject: **NDA 212489**
Generic Name (Trade Name): opicapone, OPC; BIA 9-1067 (Ongentys)
Dosages: 25 or 50 mg orally once daily at bedtime, with dose escalation schedule
Formulations, route: Hard gelatin capsules: 25, and 50 mg
IND: 104380
Indication(s): Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "OFF" episodes
Applicant: Neurocrine Biosciences, Inc.
PDUFA Goal Date: April 26, 2020

Materials Reviewed:

- NDA 212489, eCTD 0001, April 26, 2019
- Assessment of Abuse Potential, OPC-8 Factor Analysis (eCTD, tab 1.11.4)
- Off-target binding studies including Study Report 11-8004 and 18-Opicapone-001-PH
- Safety pharmacology and toxicity Study Reports 26556, 26555, 26543, B18404, B18393, A73980, B08144, B18382, D38007, D55805, C03508, A73978, A73945, S03328, S03352, S12824, S13825, and S04937
- Meeting minutes, January 16, 2018
- Response to CSS requests in 74-day letter, received September 13, 2019
- Response to CSS IR, received February 6, 2020

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I. SUMMARY

1. Background

This memorandum responds to a consult request dated May 7, 2019 from the Division of Neurology I (DN1) regarding opicapone, trade name Ongentys (NDA 212489, with associated IND 104380). Opicapone is a selective peripheral, and reversible catechol-O-methyltransferase (COMT) inhibitor under development by Neurocrine Biosciences, Inc. (the Applicant). It is a new molecular entity (NME) to be used as adjunctive treatment to levodopa/carbidopa treatment in patients with Parkinson’s disease (PD) experiencing “OFF” episodes, given at a recommended maintenance dose of 25 or 50 mg orally, taken once daily at bedtime. Opicapone has been approved in the European Union since June 2016 under the name Ongentys.

Opicapone’s primary mechanism of action is inhibition of Catechol-O-methyltransferase (COMT). Catechol-O-methyltransferase is one of several enzymes that degrade catecholamines such as dopamine, epinephrine, norepinephrine, and catecholestrogens.

Animal models suggest that opicapone does not cross the blood-brain barrier and is not available in the brain at relevant concentration levels to inhibit central COMT activity. However, the blood-brain-barrier (BBB) is impaired in neurodegenerative disorders such as Parkinson’s disease (Kortekaas et al., 2005; Desai et al., 2007; Bartels et al., 2008; Grey et al., 2015) and BBB P-glycoprotein (P-gp) function

decreases with aging (Bartels et al., 2009), therefore, opicapone will be expected to penetrate the CNS of Parkinson's patients.

Opicapone will be administered with levodopa/carbidopa. When taken with levodopa/carbidopa, opicapone blocks COMT, which is the major peripheral metabolizing enzyme for levodopa. As a result, when COMT is inhibited by opicapone, more levodopa is available to cross the blood brain barrier and to be converted to dopamine. In fact, clinical studies have shown that in PD patients opicapone administered at bedtime increased total levodopa exposure 62-94%, and, peak levodopa concentrations by 44% (Mod 2.7.2).

Opicapone is not a scheduled substance under the Controlled Substances Act (CSA). Based on in vitro ligand binding testing, opicapone does not demonstrate significant binding activity at receptors associated with abuse-related effects, however, its use is associated with central nervous system (CNS)-mediated adverse events. A number of abuse-related adverse events were reported during clinical studies: in healthy volunteers; somnolence, disturbance of attention and, in Parkinson's patients, hallucinations, somnolence, insomnia, confusional state, memory impairment, disturbance of attention, affective disorder, delirium, agitation, restlessness, aggression, impulse control disorder, dopamine dysregulation syndrome, psychotic disorder, feeling abnormal, depression, anxiety, and paranoia. The most common abuse-related AE was hallucination reaching 9.6% in Study # BIA-OPC-401. The majority of abuse-related AEs such as hallucinations, insomnia, depression, confusion, and restlessness, were dose-related, and increased with a dose of 50 mg (study # BIA-OPC-401) which is likely due to the higher exposure to levodopa.

Based on opicapone's potentially abuse-related AEs, CSS recommended that the Applicant evaluate opicapone for abuse potential (Meeting minutes, Jan 18, 2018). In response, the Applicant submitted a receptor binding study and abuse-related and dependence and withdrawal adverse event assessments.

2. Conclusions

1. Opicapone is a new molecular entity (NME) not chemically or pharmacologically similar to any known drug of abuse. The data submitted do not provide a signal of abuse potential and the preliminary data considered during development did not indicate a need for further abuse-related nonclinical or clinical studies. We do not propose to schedule the drug under the Controlled Substances Act.
2. Binding assays demonstrate that opicapone and its metabolite BIA 9-1103 did not bind to targets associated with abuse-related effects.
3. Abuse-related adverse events were more frequent in Parkinson's patients after opicapone administration than placebo including AEs of hallucinations, memory impairment, confusional state, cognitive impairment, agitation, delirium, affective disorder, and disturbance of attention. Some of these AEs were even more frequent than in entacapone-treated group, such as hallucinations [total: OPC 17 (4.8%), vs entacapone 1 (0.8%)]. The total number of hallucinations in study # BIA-OPC-401 in PD patients reached 9.6% which is highly concerning.

4. In the absence of concomitant levodopa administration, COMT inhibitor administration does not increase central dopaminergic activity, thus, abuse of opicapone in healthy individuals is unlikely.
5. This drug may pose abuse and misuse risks mainly to the selected group of Parkinson's patients abusing dopaminergic drugs in a context of dopamine dysregulation syndrome (DDS). This risk can be mitigated with appropriate label warnings. Parkinson's patients in this subpopulation who are prone to, or experiencing DDS might have further worsening of their syndrome, considering that opicapone may serve as a particularly strong levodopa-enhancing drug.
6. The Applicant did not conduct a systematic evaluation of dependence, withdrawal, or rebound in their Phase 2/3 clinical program. However, it is recommended that product labeling advises to taper the drug at the end of treatment, as it is possible that sudden worsening of PD symptoms after drug discontinuation can lead to decreased postural stability and harm to patients from falls.

3. Recommendations

1. Based on the abuse and dependence-related data submitted, opicapone will not require a section 9 Drug Abuse and Dependence in product labeling if NDA 212489 is approved. Opicapone is not being recommended for control under the CSA.
2. Label Recommendations:
 - Drug product labeling should have warnings concerning the potential for PD patients to develop DDS, similar to other dopamine enhancing drugs approved to treat PD. We agree with the Warning section language:

“Use with caution in Parkinson's patients with suspected or diagnosed dopamine dysregulation syndrome.”
 - We recommend advising to taper the drug at the end of therapy, which can be included in section 2 Dosage and Administration.

II. REVIEW AND DISCUSSION

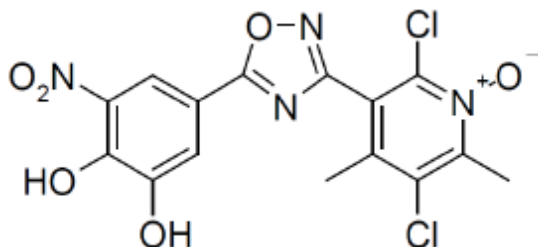
1. Chemistry

1.1 Drug Substance Information

Opicapone's chemical properties:

- Other names: BIA 9-1067
- chemical name

- 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-
- 3-yl)-4,6-dimethylpyridine-1-oxide
- molecular formula is C₁₅H₁₀Cl₂N₄O₆
- molecular weight is 413.17 g/mol
- CAS # 923287-50-7
- structure:



1.2 Drug Product Information

Opicapone is formulated as capsules supplied in two dosage strengths, 25 and 50 mg, for immediate release. In patients with mild hepatic impairment the recommended dose is 50 mg of opicapone orally once daily. In patients with moderate hepatic impairment the recommended dose is 25 mg of opicapone orally once daily. Opicapone should be taken at bedtime and preferably, should not be taken with food.

2. Nonclinical Pharmacology

Opicapone (BIA 9-1067) pharmacokinetic (PK) effects were reported in several animal test species (i.e., mice, rats, dogs, monkeys, rabbits, and minipigs). Behavioral signals of abuse following opicapone administration were evaluated in single- or multiple-dose administration toxicological studies (see below), which were conducted in mice, rats and monkeys.

According to the Applicant, orally administered opicapone was absorbed quickly and there was no relevant accumulation of the drug following repeat-dose administration (Pharmacokinetics Written Summary, pages 17-19).

After oral dosing in rodents, opicapone and select metabolites (including BIA 9-1103, BIA 9-1079, and BIA 9-1106) were widely distributed in plasma and to most tissues (Pharmacokinetics Written Summary, pages 64-65). However, brain levels (**Table 1**, and **2**) were not quantifiable at 10 mg/kg in minimal at 1000 mg/kg/day in rats (OPC-8 Factor Analysis, page 19).

Table 1: Concentrations of radioactivity in organs and tissues at various times following single oral administration of [14C] BIA 9-1067 to male albino rats at a target dose level of 10 mg/kg (Results expressed as ng equiv/g)

Tissue / organ	1 h	4 h	12 h	48 h
LOQ	124	121	124	129
Adrenal cortex	423	444	202	blq
Adrenal medulla	475	453	182	blq
Bone	blq	blq	blq	blq
Bone marrow	232	316	204	blq
Brain	blq	blq	blq	blq
Brown fat	239	267	214	142
Caecum contents	blq	190924	83707	1040
Caecum wall	161	2656	7179	280
Cardiac blood	709	643	244	171
Cardiac muscle	304	363	128	blq
Epididymis	143	139	193	blq
Eye humour	blq	blq	blq	blq
Eye lens	blq	blq	blq	blq
Fur	138	191	blq	blq
Harderian gland	179	233	223	blq
Kidney cortex	3457	4677	2880	1808
Kidney medulla	3280	4174	2549	1692
Large intestine contents	162	25445	188197	1913
Large intestine wall	222	753	1086	237
Liver	4387	7920	4405	2373
Lung	516	613	303	153

LOQ limit of quantification

blq below limit of quantification

Source: Report ZNA15658.003, page 25

Table 2: Summary of opicapone (OPC) and its metabolites brain levels (1000 mg/kg/day) in rats

Study Title: BIA 9-1067 and its Metabolites Quantification in NMRI Mice and Wistar Rat Plasma, Liver and Brain Following p.o. Administration of 1000 mg/kg								
Mean±SEM Plasma Concentration (µg/mL) and Liver and Brain Concentration (µg/g); Mean±SD Plasma and Liver AUC _{0-t} (µg·h/mL / µg·h/g)								
Matrix	Timepoint (h)	OPC	BIA 9-1079	BIA 9-1100	BIA 9-1101	BIA 9-1103	BIA 9-1105	BIA 9-1106
Brain	0	0.04±0.04	0±0	0±0	0±0	0.03±0.01	0±0	0±0
	1	0.24±0.11	0±0	0.01±0.01	0±0	0.27±0.04	0±0	0.03±0.01
	2	0.25±0.01	0±0	0.01±0.01	0±0	0.23±0.06	0±0	0.05±0
	4	0.16±0.06	0±0	0.02±0.01	0±0	0.30±0.09	0±0	0.02±0.01
	8	0.10±0.05	0±0	0.01±0.01	0±0	0.31±0.01	0±0	0±0
	24	0.10±0.06	0±0	0±0	0±0	0.07±0.07	0±0	0±0
	48	0.05±0.05	0±0	0±0	0±0	0±0	0±0	0±0

Source: Report SRAL110222 and Pharmacokinetics Tabulated Summary, page 28

2.1 Receptor Binding and Functional Assays

The Applicant conducted a receptor screening of off-target receptors (approximately 55 receptors, transporters, and ion channels) with opicapone (10 µM concentration), and its main active metabolite BIA 9-1103 (10 µM concentration) (Report 11-8004). There was no disruption of binding (≥50% inhibition of binding) of a radioactively labeled ligand at any abuse-related targets.

Opicapone and metabolites BIA 9-1103, BIA 9-1104, and BIA 9-1079 at concentrations of 10 µM concentration did not bind (≥50% inhibition of binding) to serotonin receptors (5-HT_{4E}, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT₃, 5-HT_{5A}, 5-HT₆, 5-HT₇ and 5-HT_{1D}; Study 18-Opicapone-001-PH).

An assessment for abuse-related adverse event over all phases of development was conducted to further confirm a lack of abuse signal by opicapone.

2.2 Safety Pharmacology/Metabolites

Opicapone is metabolized to a number of circulating metabolites including metabolites BIA 9-1100, BIA 9-1101, BIA 9-1103, BIA 9-1104, BIA 9-1105, BIA 9-1106, and BIA 9-1079. According to the Applicant, following oral administration of opicapone to humans, BIA-1103 is the only major active circulating metabolite representing >10% of the total drug-related exposure in the plasma. BIA 9-1079, BIA 9-1106, BIA 9-1100, and BIA 9-1104 are minor metabolites. BIA 9-1103 was also a circulating metabolite in the species used for toxicological evaluation of opicapone (mice, rats and monkeys), as shown in the Applicant's table (**Table 3**) below.

Table 3: BIA 9-1103 systemic exposure in toxicology species

Species and Route	Dose (mg/kg/day)	Duration of Dosing	Pharmacokinetic Parameter				Study No.
			C _{max} (µg/mL)		AUC _{0-t} (µg•h/mL)		
			Male	Female	Male	Female	
Human (oral)	50 mg/day	14 days	0.506 ^a		10.9 ^{a b}		NBI-OPC-1706
Mouse (oral gavage)	1800	Day 2	0.18 ^c	1.14 ^c	NC	NC	792471
Mouse (oral gavage) ^d	1000	Day 1	0.26	NA	2.81	NA	SRAL110222
Rat (oral gavage)	500	Week 13	8.18	1.95	72.10	16.70	D38007
	1000	Week 13	11.50	3.11	182.00	35.30	
Monkey (oral gavage)	1000	Day 7	1.08 ^a		5.80 ^a		SRAL070509

AUC₀₋₂₄=area under the concentration-time curve from time zero to 24 hours; AUC_{0-t}=area under the concentration time curve from time zero to the time of the last measurable concentration; C_{max}=maximal plasma concentration; NA=not applicable; NC=not calculated.

a Mean value of males and females combined.

b AUC₀₋₂₄

c Plasma concentrations 1 h after the last dose as determined in TK study to support micronucleus test.

d Single oral dose PK study in male mice only.

Notes: Data presented are mean values for male and female animals on the last day when TK sampling occurred. Bolded text indicates NOAEL doses.

Source: Pharmacokinetics Tabulated Summary, page 112

2.3 Findings from Safety Pharmacology and Toxicology Studies

The following sections include a review of opicapone for general behavioral effects when the drug was tested in single and repeated-dose toxicology studies conducted in mice, rats, and monkeys.

Studies evaluating opicapone given orally and included:

- 3 single-dose toxicology studies in mice (CD-1; Study 26556) and rats (Sprague-Dawley; Studies 26555 and 26543)
- 11 repeat-dose toxicology studies in mice (CD-1, Studies BI8404 and BI8393), in rats (Sprague-Dawley and Wister; Studies A73980, B08144, B18382, D38007, and C03508) and in monkeys (Cynomolgus; Study S03328, S03352, S12824 and S13825)

Observations were gathered over multiple drug doses from 100 to 2000 mg/kg/day, given orally (PO) and 1, 5, and 10 mg/kg, intravenously (IV). Behavioral-related observations that were reported included the following:

- Mice (males and females):
 - at doses 100 and 1000 mg/kg/day (PO) – moderate convulsions (females only, Study BI8393)
 - at doses 500 and 1000 mg/kg/day (PO) – decreased activity, hunched posture, and shivering (Study BI8404)

- at dose 1000 mg/kg/day (PO) - slight sedation (in one male, Study BI8393)
- at dose 2000 mg/kg/day (PO) - hunched appearance (Study 26556)
- Rats (males and females):
 - at dose 1 mg/kg (IV) - subdued behavior and hunched appearance (Study 26543)
 - at dose 5 mg/kg (IV) - staggering, unwilling to move unless stimulated and subdued behavior (males only, Study 26543)
 - at dose 10 mg/kg (IV) - convulsions (females only, Study 26543)
 - at doses 100, 500 and 1000 mg/kg/day (PO) - slight emaciation (females only, Study A73980)
 - at doses 500 mg/kg/day (PO) - slight emaciation (in one male, Study B08144)
- Monkeys (males and females):
 - at dose 300 mg/kg/day (PO) - decreased activity followed by death (one male, Study S13825)
 - no relevant clinical signs were observed during recovery periods

3. Clinical Pharmacology

3.1 Pharmacokinetics: Absorption, Distribution, Metabolism, Elimination (ADME)

Absorption

For opicapone (OPC), time to maximum plasma concentration (t_{max}) in healthy subjects ranged between 1.5 and 4.0 hours following single doses of up to 1200 mg nonmicronized OPC and multiple doses up to 50 mg qd nonmicronized OPC. For subjects with PD, opicapone 50 mg administered in the evening resulted in a median t_{max} of 4.0 hours (range: 1.5 to 10 hours). Opicapone exposure increased less than dose-proportionally over a 5 mg to 1200 mg range of nonmicronized OPC.

The $t_{1/2}$ of opicapone is short, ranging between 0.8 and 3.2 hours following single doses of 10 to 1200 mg nonmicronized OPC in healthy subjects. In subjects with PD administered OPC 50 mg in the evening, $t_{1/2}$ values ranged from 1.1 to 2.8 hours (mean: 1.85 hours).

Distribution

Plasma protein binding of BIA 9-1103 was concentration-independent across the concentration range of 0.3 to 30 $\mu\text{g/mL}$. BIA 9-1103 did not affect the plasma binding of 14C-OPC.

Metabolism

BIA 9-1103 (OPC sulphate) is the only main circulating metabolite of OPC, it is not active and does not have clinically relevant off-target activity.

Other metabolic pathways include reduction, methylation, glucuronidation, and glutathione conjugation. BIA 9-1079, BIA 9-1104 and BIA 9-5049 are active metabolites, but only circulate at low exposures. The rate and extent of exposure to OPC were significantly lower in the fed state compared to the fasting state and t_{max} was delayed with food.

Elimination

Following administration of a single dose of ¹⁴C-labeled OPC, a mean of 96% of the administered dose of radioactivity was recovered. The main excretion route was feces, accounting for approximately 70% of the administered radioactivity. The remainder of the radioactivity was excreted in urine (5%) and via expired air (20%). The majority of radioactivity was eliminated within 144 hours postdose.

4. Clinical Studies

4.1 Human abuse potential study

A human abuse potential study was not performed.

4.2 Clinical Development Program Summary

The opicapone clinical development program included 38 studies:

- 34 Phase 1 studies comprised:
 - 31 single or multiple dose studies in healthy volunteers
 - 2 single-dose studies in subjects with mild or moderate hepatic impairment
 - 1 multiple dose (up to 14 days) study in subjects with PD
- 2 Phase 2 studies included:
 - 1 single dose study (BIA-91067-201)
 - 1 multiple dose study (up to 28 days; BIA-91067-202) in subjects with PD
- 2 Phase 3 studies: BIA-91067-301 and BIA-91067-302 were double-blind with open-label extension and active-controlled (Study 301) multicenter studies in subjects diagnosed with idiopathic PD and motor fluctuations who were treated with levodopa plus a DOPA decarboxylase inhibitor (DDCI).
In both Phase 3 studies, subjects were allowed to continue in a 1-year open label (OL) OPC treatment period after completion of the double blind (DB) period.

The Applicant organized safety data into the following pools:

- Phase 1 single-dose studies in healthy subjects and Phase 1 multiple-dose studies in healthy subjects;
- Phase 1/2 studies in PD subjects;
- Phase 3 DB and OL studies in PD subjects.

Drug Exposure:

- In Phase 1 studies in healthy subjects (N=988):
 - single doses were administered at doses up to 1200 mg nonmicronized OPC and up to 50 mg micronized OPC
 - multiple once-daily doses were administered up to 30 mg/day nonmicronized OPC and up to 75 mg/day micronized OPC
- In the Phase 1 and 2 studies in PD patients:
Subjects received micronized OPC 50 mg for 14 days (Study 1706); single doses of nonmicronized OPC 25, 50, and 100 mg (Study 201); or nonmicronized OPC 5, 15, and 30 mg qd for up to 28 days (Study 202) (N=56).

- In Phase 3 studies:
 - PD patients received 5 (Study 301 only), 25, or 50 mg micronized OPC qd for up to 15 weeks during the DB period (N=631);
 - PD patients received 5 (Study 301 only), 25, or 50 mg qd for up to 1 year during the OL period (N=848; 320 subjects previously randomized to placebo or entacapone were newly treated with OPC) during the OL period

4.3 Adverse Event Profile Through all Phases of Development

Abuse Potential Related Adverse Events in Phase 1 Studies

Clinical pharmacology studies in healthy subjects included 34 studies, and the total number of subjects with any exposure to opicapone in these studies was N=988.

The abuse-related AEs in this population were infrequent and included AEs mainly somnolence, and single cases of disturbance of attention and irritability, see Table 4.

Table 4: The table summarizes abuse related adverse events for phase 1 studies. Incidence of treatment-emergent adverse events of drug abuse and dependence in phase 1 single-dose and multiple-dose studies in healthy subjects(OPC-8 Factor Analysis, page 16).

MedDRA System Organ Class Preferred Term	Treatment at Onset of Adverse Event, n (%)							
	Single Dose				Multiple Dose			
	PBO Alone (N=78)	Any OPC Alone (N=475)	PBO + Levo/ DDCI (N=63)	Any OPC + Levo/ DDCI (N=82)	PBO Alone (N=70)	Any OPC Alone (N=295)	PBO + Levo/ DDCI (N=32)	Any OPC + Levo/ DDCI (N=94)
Any TEAE of Drug Abuse and Dependence	0	20 (4.2)	5 (7.9)	22 (26.8)	6 (8.6)	5 (1.7)	5 (15.6)	17 (18.1)
Nervous System Disorders	0	20 (4.2)	5 (7.9)	22 (26.8)	6 (8.6)	4 (1.4)	4 (12.5)	17 (18.1)
Somnolence	0	14 (2.9)	5 (7.9)	20 (24.4)	2 (2.9)	0	3 (9.4)	12 (12.8)
Dizziness	0	6 (1.3)	1 (1.6)	2 (2.4)	4 (5.7)	4 (1.4)	1 (3.1)	4 (4.3)
Disturbance in attention	0	1 (0.2)	0	1 (1.2)	0	0	1 (3.1)	2 (2.1)
Sensory disturbance	0	0	0	0	0	0	0	1 (1.1)
Cardiac Disorders	0	1 (0.2)	0	0	0	0	0	0
Dizziness	0	1 (0.2)	0	0	0	0	0	0
General Disorders and Administrative Site Conditions	0	0	0	0	0	1 (0.3)	0	0
Irritability	0	0	0	0	0	1 (0.3)	0	0
Psychiatric Disorders	0	0	0	0	0	0	1 (3.1)	0
Euphoric mood	0	0	0	0	0	0	1 (3.1)	0

Source: Table 2.1.1, Table 2.1.2, Table 2.2.1, and Table 2.2.2

DDCI=DOPA decarboxylase inhibitor; Levo=levodopa; MedDRA= medical dictionary for regulatory activities; OPC=opicapone; PBO=placebo;

The data summarized in the table show magnification of levodopa effects by opicapone on increased somnolence to 24% from levodopa alone 7.9% in healthy volunteers (HV) in single dose studies; this effect of opicapone decreases at multiple dose studies to only 12.8% vs 9.4% levodopa alone, possibly

due to developing tolerance. There were no other abuse-related adverse events noted except for euphoria (3.1%) in a healthy subject who took placebo/levodopa and DDCI (DDCI=DOPA decarboxylase inhibitor).

Abuse Potential Related Adverse Events in Phase 2 and 3 Studies of Parkinson's patients

In Phase 1/2 there were N=56 PD patients exposed to opicapone and in Phase 3 Studies N=848 Parkinson's patients received the drug. There were a number of neuropsychiatric adverse events including abuse-related AEs (Table 5, and 6). The most frequent abuse-related AEs were hallucinations, somnolence, and confusional state. Hallucinations if added across types constituted # 1 adverse event with a frequency up to 4% for opicapone vs 1.2% for opicapone placebo. Less frequent AEs were agitation, delirium, affective disorder, and memory impairment.

A comparative study with COMT-inhibitors - Opicapone vs Entacapone

Study # BIA-91067-301 Title: 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, randomised, placebo- and active-controlled, parallel-group, multicentre clinical study.

This was an efficacy study with 3 different doses of OPC (5 mg, 25 mg, 50 mg) qd, compared to placebo or 200 mg of entacapone (ENT) which is a COMT inhibitor currently available on the market under brand name Comtan, both COMT inhibitors were administered with the existing treatment of levodopa/DDCI.

Duration

The duration of the study per subject was up to 71 weeks and included:

- up to 2 weeks of Screening,
- 14 to 15 weeks of the DB period,
- 52 weeks of the open-label (OL) period,
- 2 weeks of the safety Follow-up.

Study objectives

- The primary objective was to investigate the efficacy of 3 different doses of opicapone (BIA 9-1067) (5 mg, 25 mg, and 50 mg) qd, compared with placebo or 200 mg of entacapone, when administered with the existing treatment of levodopa (L-DOPA) plus a DDCI, in patients with Parkinson's disease (PD) and end-of-dose motor fluctuations.
- The secondary objectives of the study were to investigate the safety and tolerability of the combined treatment (L-DOPA/DDCI plus opicapone, entacapone, or placebo).

Treatments

A total of 600 subjects were randomized in the DB period: 121 to placebo, 122 to entacapone, 122 to opicapone 5 mg, 119 to opicapone 25 mg, and 116 to opicapone 50 mg.

Table 5: The table summarizes abuse-related adverse events for phase 2/3 (based on Incidence of treatment-emergent adverse events of drug abuse in phase 1/2 and phase 3 studies in Parkinson's disease subjects OPC-8 Factor Analysis Table 2, page 17).

MedDRA System Organ Class Preferred Term	Treatment at Onset of Adverse Event, n (%)				
	Phase 1/2		Phase 3 DB		Phase 3 OL
	PBO + Levo/ DDCI (N=19)	Any OPC + Levo/ DDCI (N=56)	PBO + Levo/ DDCI (N=257)	Any OPC + Levo/ DDCI (N=631)	Any OPC + Levo/ DDCI (N=848)
Any TEAE of Drug Abuse and Dependence	2 (10.5)	7 (12.5)	12 (4.7)	64 (10.1)	71 (8.4)
Nervous System Disorders	2 (10.5)	7 (12.5)	9 (3.5)	44 (7.0)	29 (3.4)
Dizziness	1 (5.3)	5 (8.9)	3 (1.2)	21 (3.3)	16 (1.9)
Somnolence	1 (5.3)	2 (3.6)	5 (1.9)	16 (2.5)	8 (0.9)
Memory impairment	0	0	0	4 (0.6)	4 (0.5)
Disturbance in attention	0	0	0	3 (0.5)	0
Sensory disturbance	0	0	0	1 (0.2)	0
Cognitive disorder	0	0	1 (0.4)	0	2 (0.2)
Mental impairment	0	0	0	0	1 (0.1)
Psychiatric Disorders	0	0	3 (1.2)	27 (4.3)	45 (5.3)
Hallucination, visual	0	0	2 (0.8)	11 (1.7)	13 (1.5)
Hallucination	0	0	1 (0.4)	10 (1.6)	14 (1.7)
Hallucination, auditory	0	0	0	3 (0.5)	3 (0.4)
Aggression	0	0	0	1 (0.2)	1 (0.1)
Agitation	0	0	0	1 (0.2)	3 (0.4)
Confusional state	0	0	0	1 (0.2)	12 (1.4)
Disorientation	0	0	0	1 (0.2)	1 (0.1)
Dopamine dysregulation syndrome	0	0	0	1 (0.2)	0
Hallucinations, mixed	0	0	0	1 (0.2)	0
Affective disorder	0	0	0	0	2 (0.2)
Delirium	0	0	0	0	2 (0.2)
Mood altered	0	0	0	0	1 (0.1)
General Disorders and Administrative Site Conditions	0	0	0	0	1 (0.1)
Irritability	0	0	0	0	1 (0.1)
Injury, poisoning and procedural complications	0	0	0	0	1 (0.1)
Overdose	0	0	0	0	1 (0.1)

Source: Table 2.3.1, Table 2.4.1, and Table 2.4.2

DB=double-blind; DDCI=DOPA decarboxylase inhibitor; Levo=levodopa; MedDRA= medical dictionary for regulatory activities; OL=open-label; OPC=opicapone; PBO=placebo; TEAE=treatment-emergent adverse event

Table 6: The table summarizes abuse-related adverse events for the opicapone-entacapone comparative study, based on Table 14.12.2 Incidence of Treatment-Emergent Adverse Events (TEAEs) - Safety Set, Opicapone Study Report BIA 9-1067, page 986.

Adverse Event PT	Placebo N=121 n (%)	Entacapone 200mg N=122 n (%)	Total OPC 5, 25, 50 mg N=356 All Doses n (%)
Psychiatric Disorders			
Hallucinations	1 (0.8)	1 (0.8)	8 (2.2)
Hallucinations, auditory	-	-	3 (0.8)
Hallucinations, visual	1 (0.8)	-	5 (1.4)
Hallucinations, mixed	-	-	1 (0.3)
Hallucinations-Total	2 (1.7)	1 (0.8)	17 (4.8)
Depression	1 (0.8)	1 (0.8)	4 (1.1)
Depressed mood	-	-	2 (0.6)
Sleep disorder	1 (0.8)	-	5 (1.4)
Dopamine dysregulation synd.	-	-	1 (0.3)
Delusions	-	-	1 (0.3)
Insomnia	1 (0.8)	7 (5.7)	16 (4.5)
Nervous system disorders			
Disturbance in attention	-	-	3 (0.8)
Memory impairments	-	-	2 (0.6)
Somnolence	2 (1.7)	-	7 (2.0)

This comparative study with another frequently used COMT inhibitor entacapone (200 mg) shows that the most frequent abuse-related AEs for opicapone were hallucinations, total 17 (4.8%) vs 1 (0.8%) for entacapone and 2 (1.7%) placebo. Hallucinations were a frequent reason for drug discontinuation: any type of hallucination (1 [0.8%] 5 mg opicapone, 2 [1.7%] 25 mg opicapone and 2 [1.7%] 50 mg opicapone).

Reviewer's comments

This Applicant generally asserts that hallucinations in PD patients on opicapone are adverse events of levodopa therapy and Parkinson's disease, which is true. However, side-by-side comparison with another COMT-inhibitor entacapone in the same patient population on a comparable treatment regimen for Parkinson's disease shows that opicapone has an increased frequency of hallucinations. This might be explained by the relatively high potency of opicapone to increase levodopa levels. In PD patients receiving levodopa every 3 hours (q3h) or every 4 hours (q4h) who were administered 50 mg qd micronized OPC at bedtime had increased total levodopa exposure 62-94% and increased peak levodopa concentrations of 43% to 44% (Mod 2.7.2, p 18). Levels of levodopa after administration of opicapone were much higher ~20-55% than after administration of entacapone (Study # BIA-91067-124).

Another frequent AE in the study was insomnia, however it was higher for entacapone, 7 (5.7%), relative to both opicapone, 16 (4.5%), and placebo, 1 (0.8%), however opicapone rates were higher than placebo

Other adverse events that were more frequent for opicapone than entacapone were depression/depressed mood, somnolence, sleep disorder, disturbance in attention and memory impairments.

Phase 4 Study # BIA-OPC-401: Efficacy and safety of opicapone in clinical practice in Parkinson's Disease patients with wearing-off motor fluctuations.

The study report was submitted in 120 day update. This was a prospective open-label, uncontrolled, single-group, multi-centre trial in PD subjects with wearing-off motor fluctuations.

Study Design

Study Objectives:

- Primary:
To evaluate the change in patient's condition according to the Investigator's Global Assessment of Change after 3 months of treatment with 50 mg opicapone once daily in a heterogeneous patient population reflecting daily clinical practice.
- Secondary:
 - To investigate the safety of opicapone 50 mg once daily in clinical practice.
 - To investigate the efficacy of opicapone 50 mg once daily in clinical practice.
 - To evaluate the influence of a 6-month treatment with opicapone 50 mg once daily on the health economic costs (only for the UK).

Doses

Opicapone 50 mg once daily

Duration

3-month period (in Germany) or a 6-month period (in the UK)

Population

516 Parkinson's patients

Sites

A total of 69 active centres.

Table 7: The table summarizes abuse-related adverse events for opicapone in the phase 4 study, based on Table 15.3.1.2 Incidence of TEAEs, Study Report BIA-OPC-401, page 1223.

Adverse Event PT	Total OPC 50 mg N=356 n (%) Events
Subjects with at least one TEAE	371 (74.9) 1240
Psychiatric Disorders	
Hallucinations	20 (4.0) 24
Hallucinations, auditory	2 (0.4) 2
Hallucinations, visual	11 (2.2) 15
Hallucinations, olfactory	1 (0.2) 2
Hallucinations-Total	34 (9.6)
Insomnia	22 (4.4) 25
Depression	18 (3.6) 18
Depressed mood	8 (1.6) 8
Confusional state	14 (2.8) 16
Restlessness	14 (2.8) 15
Anxiety	13 (2.6) 13
Abnormal dreams	9 (1.8) 10
Agitation	4 (0.8) 4
Disorientation	5 (1.0) 5
Impulse control disorder	2 (0.4) 2
*Hypersexuality	1 (0.2) 1
Paranoia	1 (0.2) 1
Psychotic disorder	1 (0.2) 1
Persecutory delusions	1 (0.2) 1
Nervous system disorders	
Somnolence	10 (2.0) 10
Memory impairment	4 (0.8) 4
Psychomotor hyperactivity	2 (0.4) 2
Disturbance in attention	2 (0.4) 2
Social circumstance	
*Gambling	1 (0.2) 1
Metabolism disorders	
Decreased appetite	5 (1.0)

*-denotes symptoms of impulse control disorder

In this study the relatively high dose of opicapone of 50 mg daily produced hallucinations (34) reached 9.6% and were a top AE reported. Hallucinations and visual hallucinations were also the top AE leading to discontinuation (total 2%).

Additionally, the study shows a clear stimulatory effect of opicapone at 50 mg with AEs of insomnia (4.4%), restlessness (2.4%), anxiety (2.6%), agitation (0.8%), psychomotor hyperactivity (0.2%), and decreased appetite (1%).

Special safety topics

Dopamine dysregulation syndrome (DDS) and Impulse control disorder (ICD)

Dopamine dysregulation disorder is sometimes considered part of ICD spectrum which includes gambling, binge eating, hypersexuality, and compulsive shopping.

Impulse control disorder will be addressed by the division's medical officer, however, from the data provided by the Applicant it seems there was some increase in frequency of ICD, especially with highest with dose 50 mg of opicapone (see **Table 8**). Dopamine dysregulation disorder was noted once. Also, the phase 4 study BIA-OPC-401 already showed clearly stimulatory character of the drug and emergence of impulse control disorder (0.8%), and some of its aspects hypersexuality (0.2%) and gambling (0.2%). These facts together suggest that the drug likely will be abused by Parkinson's patients with dopamine dysregulation syndrome, therefore warning in the label should be included to use caution in patients with Dopamine dysregulation disorder known or suspected.

The Applicant did not use the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP scale) specifically developed to capture different aspects of impulse control disorder which could have provided more granular analysis of DDS and ICD and the tendencies to develop these disorders during the opicapone treatment. The Applicant used only Minnesota Impulsive Disorders Interview - Kleptomania (MIDI), a scale which captures only one of many aspects of ICD.

Table 8: Summary of ICD in phase 3 pooled studies(based on Table 76: Impulse Control Disorders AESI – Phase 3 Pooled DB Period, ISS, page 154)

AESI Category: Search Terms/ Preferred Term	Placebo N=257 n (%)	OPC 5 mg N=122 n (%)	OPC 25 mg N=244 n (%)	OPC 50 mg N=265 n (%)	All OPC N=631 n (%)
Impulse control disorders: HLT or selected preferred terms	0	1 (0.8)	1 (0.4)	3 (1.1)	5 (0.8)
Impulse control disorders HLT	0	0	0	1 (0.4)	1 (0.2)
Impulsive behaviour	0	0	0	1 (0.4)	1 (0.2)
Additional preferred terms					
Hypersexuality	0	1 (0.8)	0	1 (0.4)	2 (0.3)
Binge eating	0	0	1 (0.4)	0	1 (0.2)
Gambling disorder	0	0	0	1 (0.4)	1 (0.2)
Dopamine dysregulation syndrome	0	0	0	1 (0.4)	1 (0.2)
Libido increased	0	0	0	0	0
Gambling	0	0	0	0	0
Compulsive shopping	0	0	0	0	0
Compulsions	0	0	0	0	0

Source: ISS Table 3.1.1.

AESI=adverse event of special interest; DB=double-blind; HLT=high-level term; OPC=opicapone.

Overdose: Accidental and Intentional

During the clinical program of opicapone there was one case of nonintentional overdose:

- 1 incidence of an accidental overdose of 50 mg twice daily for 2 months was reported without any adverse signs or symptoms.
- Single doses of OPC up to 1200 mg nonmicronized (equivalent to 600 mg micronized) have been administered to subjects and apparently was well-tolerated (Study # BIA-91067-101).

No cases of intentional overdose of OPC were reported from postmarketing sources.

There were nonintentional overdoses:

- In one case (BIAL-04422) overdose was reported in which a patient took 100 mg (2 ×50 mg capsules) OPC instead of 50 mg (1 ×50 mg capsule) OPC on one occasion.
- There was a medication error in another patient (BIAL-04755) that involved taking a second dose one time (accidental overdose) that occurred due to product packaging confusion between omeprazole and Ongentys.

Neither case was associated with a serious adverse event.

4.4 Drug Accountability Discrepancies in Clinical Trials

CSS asked the Applicant on July 10, 2019 in 74-day letter to provide drug accountability for the clinical program. The Applicant provided drug accountability data for studies # 301 and 302 on September 13, 2019. Other studies which included outpatient study drug administration included the Phase 1 Study NBI-OPC-1706, where 1 subject (6.3%) of 16 total subjects failed to return ≥10% of study drug; this subject was dispensed 30 capsules for 14-day treatment period, returned 11 capsules, and lost 5 capsules (31.3% of the expected capsules). In the Phase 2 Study BIA-91067-202, which included outpatient study drug administration, all study drug was accounted for.

Table 9: Drug accountability in the clinical studies (based on Table: Number of subjects failing to return OPC capsules, safety population– Study # 301 double-blind treatment period, IR, page 42)

% of OPC Capsules Not Returned as Expected	OPC 5 mg (N=122) n (%)	OPC 25 mg (N=119) n (%)	OPC 50 mg (N=115) n (%)	All OPC (N=356) n (%)
≥10% - <20%	0	1 (0.8)	1 (0.9)	2 (0.6)
≥20% - <30%	0	0	1 (0.9)	1 (0.3)
≥30% - <40%	0	0	0	0
≥40% - <50%	0	1 (0.8)	0	1 (0.3)
≥50%	0	1 (0.8)	0	1 (0.3)

Table 10: Drug accountability in the clinical studies based on Table of Number of Subjects Failing to Return OPC Capsules Safety Population - 301 Open Label Treatment Period, page 43.

% of OPC Capsules Not Returned as Expected	All OPC (N=495) n (%)
>=10% - <20%	14 (2.8)
>=20% - <30%	13 (2.6)
>=30% - <40%	4 (0.8)
>=40% - <50%	0
>=50%	6 (1.2)

Table 11: Drug accountability in the clinical studies(based on Table: Number of subjects failing to return OPC capsules, safety population. – Study # 302 double-blind treatment period, IR , page 44)

% of OPC Capsules Not Returned as Expected	OPC 25 mg (N=125) n (%)	OPC 50 mg (N=150) n (%)	All OPC (N=275) n (%)
>=10% - <20%	0	4 (2.7)	4 (1.5)
>=20% - <30%	0	3 (2.0)	3 (1.1)
>=30% - <40%	0	1 (0.7)	1 (0.4)
>=40% - <50%	1 (0.8)	1 (0.7)	2 (0.7)
>=50%	0	1 (0.7)	1 (0.4)
Missing [1]	0	3 (2.0)	3 (1.1)

Table 12: Drug accountability in the clinical studies (based on Table of Number of Subjects Failing to Return OPC Capsules Safety Population - 302 Open Label Treatment Period, page 45).

% of OPC Capsules Not Returned as Expected	All OPC (N=353) n (%)
>=10% - <20%	12 (3.4)
>=20% - <30%	12 (3.4)
>=30% - <40%	4 (1.1)
>=40% - <50%	3 (0.8)
>=50%	6 (1.7)

Conclusions

There were a few instance of patients who did not return more than 40-50% of dispensed medication, however, the actual numbers of the capsules in these few cases were in ~100 range. It is unclear whether this represents a signal of intentional drug diversion.

4.5 Dependence and Withdrawal in Clinical Studies

The Applicant did not systematically evaluate dependence, withdrawal and rebound in phase 2/3 studies. Questionnaires to assess withdrawal symptoms such as depression, anxiety, sleep disturbance, and suicidality were not administered to the patients during these studies. An assessment for withdrawal symptoms only occurred at the post-study visit, scheduled for 14 ($\pm$ 3) days after drug discontinuation in the Phase 2/3 studies. As the half-life of opicapone is 1.1 to 2.8 hours (mean: 1.85 hours), withdrawal symptoms may begin the day after drug discontinuation. Therefore, this withdrawal assessment likely missed some if not majority of the withdrawal symptoms and did not adequately evaluate dependence and withdrawal.

In the 74-day letter CSS asked the Applicant whether an adequate evaluation of dependence and withdrawal could be conducted in an ongoing or planned placebo-controlled study in PD patients treated with opicapone for at least four weeks. However, the Applicant responded that no ongoing or currently planned placebo-controlled studies of opicapone in patients with Parkinson's disease during which additional withdrawal assessments could be incorporated.

Summary of Available Dependence and Withdrawal Data

For the evaluation of withdrawal and dependence, the Applicant provided results for 4 studies that were conducted in PD subjects exposed to once-daily doses of OPC for at least 2 weeks (2 Phase 3 studies, namely Study BIA-91067-301 and Study BIA-91067-302, Phase 2 Study BIA-91067-202, and Phase 1 Study NBI-OPC-1706).

The following withdrawal-related data were included:

- summaries of withdrawal AEs for studies # BIA-91067-301 and # BIA-91067-302, for double-blind and open-label periods (**Tables 13 and 14**)
- results of Columbia Suicide Severity Rating Scale (C-SSRS), which was administered only to patients who discontinued treatment early as part of the early discontinuation visit (EDV) in Studies 301 and 302.

There were no withdrawal AEs after discontinuation of study drug in PD subjects in one Phase 2 Study (BIA-91067-202) and in one Phase 1 study (NBI-OPC-1706).

Dependence and Withdrawal: Pooled Phase 3 Studies – Double Blind Period

Table 13: The table summarizes withdrawal related adverse events for phase 3 studies during the double-blind period, based on updated Table 3.5.1a Adverse events following treatment discontinuation with a minimum 4 week study drug exposure period - Phase 3 double-blind Parkinson's disease Population Trials - OPC/Placebo administered with levodopa/DDCI, page 4, CSS IR Feb 6 2020.

Adverse Event PT	Placebo + Levodopa/DDCI N=22 n (%) [E]	Total OPC + Levodopa/DDCI 5, 25, 50 mg N=76 All Doses n (%) [E]

Any AE Following Treatment Discontinuation	6 (27.3) [12]	18 (23.7) [29]
Nervous system disorders		
Parkinson's disease	0	2 (2.6) [2]
Dyskinesia	0	1 (1.3) [1]
Hypokinesia	0	1 (1.3) [1]
Syncopy	0	1 (1.3) [1]
Headache	0	1 (1.3) [1]
Dizziness	0	1 (1.3) [1]
Injury		
Fall	0	3 (3.9) [3]
Laceration	0	1 (1.3) [2]
Psychiatric Disorders		
Hallucinations, mixed	0	1 (1.3) [2]
Gastrointestinal disorders		
Nausea	0	1 (1.3) [2]
Musculoskeletal disorders		
Myalgia	0	1 (1.3) [1]

Dependence and Withdrawal: Pooled Phase 3 Studies – Open Label Period

Table 14: The table summarizes withdrawal-related adverse events for phase 3 studies during the open-label period, based on updated Table 3.5.2a Adverse Events Following OPC Discontinuation with a Minimum 4 Week OPC Exposure Period - Phase 3 Open-Label Parkinson’s Disease Population Trials – OPC Administered with Levodopa/DDCI, CSS IR Feb 6 2020, page 8.

Adverse Event PT	Total OPC + Levodopa/DDCI 5, 25, 50 mg N=841 All Doses n (%) [E]
Any AE Following Treatment Discontinuation	173 (20.6) [316]
Cardiac disorders	
Atrial fibrillation	2 (0.2%) [2]
Supraventricular extrasystoles	2 (0.2%) [2]
Cardiogenic shock-death	1 (0.1%) [1]
Cardiovascular insufficiency-death	1 (0.1%) [1]

Myocardial infarction-death	1 (0.1%) [1]
Supraventricular extrasystoles	1 (0.1%) [1]
Sinus tachycardia	1 (0.1%) [1]
Injury	
Fall	4 (0.5%) [4]
Craniocerebral injury-death	1 (0.1%) [1]
Femoral neck fracture	1 (0.1%) [1]
Skull fractured base-death	1 (0.1%) [1]
Contusion	1 (0.1%) [1]
Nervous system disorders	46 (5.5%) [50]
Parkinson's disease	22 (2.6%) [22]
Dyskinesia	6 (0.7%) [6]
Tremor	7 (0.8%) [7]
Cerebral haemorrhage -death	2 (0.2%) [2]
Dystonia	2 (0.2%) [2]
Motor dysfunction	2 (0.2%) [2]
Freezing phenomenon	1 (0.1%) [1]
Haemorrhage intracranial	1 (0.1%) [1]
Hypokinesia	1 (0.1%) [1]
Memory impairment	1 (0.1%) [1]
Movement disorder	1 (0.1%) [1]
Violence-related symptom	1 (0.1%) [1]
Dysarthria	1 (0.1%) [1]
Psychiatric Disorders	15 (1.8) [16]
Sleep disorder	6 (0.7%) [6]
Insomnia	1 (0.1%) [1]
Hallucinations	2 (0.2%) [2]
Hallucination visual	1 (0.1%) [1]
Bradyphrenia	1 (0.1%) [1]
Depression	1 (0.1%) [1]
Depressive symptom	1 (0.1%) [1]
Adjustment disorder with depressed mood	1 (0.1%) [1]
Gastrointestinal disorders	
Constipation	2 (0.2%) [2]
Abdominal pain,	2 (0.2%) [2]
Diarrhea	1 (0.1%) [1]
Nausea	1 (0.1%) [1]
Vascular disorders	17 (2.0) [17]
Orthostatic hypotension	9 (1.1) [9]
Hypertension	3 (0.4%) [3]
Hypertensive crisis	1 (0.1%) [1]
Orthostatic hypertension	1 (0.1%) [1]

Embolism	1 (0.1%) [1]
Respiratory disorders	
Choking	1 (0.1%) [1]
Pulmonary embolism	1 (0.1%) [1]
Respiratory failure	1 (0.1%) [1]

Conclusions

The withdrawal-related AEs were infrequent in double-blind studies; however, open label studies that lasted up to 52 weeks showed many more AEs during opicapone discontinuation.

The analysis of the Phase 3 OL withdrawal data indicated 101 subjects (12.1%) reported TEAEs with onset date <1 week after last dose, 31 subjects (3.7%) with onset date 1 to 2 weeks after last dose, and 27 subjects (3.2%) with onset date >2 weeks after last dose.

The Applicant noted some AEs following discontinuation were potentially associated with withdrawal symptoms (tremor, memory impairment, adjustment disorder with depressed mood, depression, depressive symptoms, and violence-related symptoms).

Suicidality assessment was performed only in patients who discontinued drug early and, therefore, cannot be considered representative for the total treated patient population:

- In the DB population the Applicant evaluated only 20 PD patients (in population of 76) with Columbia Suicide Severity Rating Scale (C-SSRS) at early discontinuation visit, none of patients responded positively.
- In the OL population the Applicant evaluated only 45 PD patients (in population of 835) with Columbia Suicide Severity Rating Scale (C-SSRS) at early discontinuation visit and one (2.2%) patient responded positively with “wishing to be dead.”

After abrupt drug discontinuation a number of symptoms were observed in many organs systems neuropsychiatric AEs included worsening Parkinson’s disease, dyskinesias, tremor, sleep disorders and insomnia, hallucinations, vascular AEs included orthostatic hypotension [9 (1.1%)], gastrointestinal AEs included constipation, abdominal pain, diarrhea and injury such as falls and contusion. The falls which were the most frequent AE during the withdrawal in Pooled Phase 3 Studies – Double Blind Period reached 3.9% for opicapone vs 0% for placebo, these AEs are concerning as they likely represent sudden worsening of Parkinson’s disease and specifically decrease of postural stability. Therefore taper of the drug at the end of treatment will be recommended.

Rebound

Rebound is an aspect of withdrawal and dependence. Rebound is a rapid return of the patient’s original symptoms after the abrupt drug discontinuation at a greater intensity than before the treatment.

Rebound was not evaluated during the clinical studies in Parkinson’s patients.

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/s/

CHAD REISSIG
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Creissig signing on behalf of Dr. Randall-Thompson

DOMINIC CHIAPPERINO
04/08/2020 04:16:35 PM
Signing also for Dr. Alicja Lerner

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: February 26, 2020

TO: Billy Dunn, MD
Director
Division of Neurology Products (DNP)
Office of New Drugs (OND)

FROM: Sripal Reddy Mada, Ph.D.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of Biotrial Rennes, Rennes, France

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study BIA-91067-119 (NDA 212489) conducted at Biotrial Rennes, Rennes, France.

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Official Action Indicated (OAI).

1.1. Recommendation

Objectionable conditions were observed during this inspection, specifically the lack of reserves samples for the test article and reference product. The inspectional findings impact the reliability of the data from the audited study. Thus, the data from study BIA-91067-119 are not reliable to support a regulatory decision.

2. Inspected Study

NDA 212489

Study Number: BIA-91067-119

Study Title: "Relative Bioavailability and Bioequivalence of
Different Formulations of Opicapone in Healthy
Volunteers"

Dates of conduct: 03/30/2014 - 06/25/2014

Clinical site: Biotrial Rennes
7-9, Rue Jean-Louis Bertrand
CS 34246 Rennes, 35042 France

ORA investigator Tawny L. Colling (BIMO Division 2) inspected
Biotrial Rennes, Rennes, France from December 9-13, 2019.

The inspection included a thorough examination of study records
(paper-based), subject records, informed consent process,
protocol compliance, institutional review board approvals,
sponsor and monitor correspondence, test article accountability
and storage, randomization, adverse events, and case report
forms.

3. Inspectional Findings

At the conclusion of the inspection, investigator Tawny L.
Colling observed objectionable conditions and Form FDA 483 was
issued to the clinical site. The Form FDA 483 observation
(**Attachment 1**), the firm's response dated 01/03/2020 (**Attachment
2**), and my evaluation are presented below.

3.1. FDA 483 Observations

3.1.1. Observation 1

**Samples of the test article and reference standard used in a
bioavailability / bioequivalence study were not retained and
available for release to the FDA. Specifically, site received
one shipment of test article and reference standard on 17 MAR
2014. On 04 MAY 2017, the firm received confirmation from the
sponsor to proceed with destruction of the retention sample. The
site subsequently destroyed the sample on 10 JUL 2017. No
retention sample was available for collection during this
inspection.**

Firm's Response: In their response to Form FDA 483, Biotrial
stated that they are aware of FDA's regulatory requirements for
BA/BE studies, including 21 CFR 320.38 and 320.63. However, the
study protocol was written in compliance with EMA regulations
because the sponsor, Bial, is located in Portugal and the study

was conducted at a French clinical site. Biotrial stated that Bial instructed them to follow the EU regulations and guidelines when they contracted with Biotrial to conduct study BIA-91067-119 in 2014. After the EU approval, the sponsor authorized the destruction of the samples on May 4, 2017, without consideration of the licensing agreement on February 15, 2017 with Neurocrine Biosciences (the NDA applicant).

Biotrial stated that only the reference samples from the batches used in study BIA-91067-119 were retained by Bial in their Portugal facilities. The sponsor, Bial, acknowledges that the FDA's BE reserve sample regulation was not followed, and that the decision process to authorize the sample destruction was inadequate. Bial currently understands that personnel within the organization to which the product is licensed must review and approve all destruction requests and authorizations, before any action.

The NDA applicant to FDA, Neurocrine Biosciences became aware of the lack of reserve samples on the second day of the current inspection and acknowledged their obligation to assure proper retention of drug samples for all studies.

OSIS Evaluation: The firm acknowledged that the observation is a regulatory violation because of failure to retain reserve samples of test and reference product per 21 CFR 320.38 and 320.63. The study was conducted during March 30, 2014 to June 25, 2014. On November 24, 2014, the sponsor submitted this study data to the European Union (EU) for its approval for marketing in Europe. The firm planned to retain the reserve samples per the EMA requirement (for 3 years). On June 26, 2016, the sponsor received approval of application to market Ongentys® in Europe. After the EU approval of the product, Bial, the sponsor of the study, and Neurocrine, the NDA applicant to FDA, received a licensing agreement dated February 15, 2017 to market Opicapone in the US. However, the reserves samples were then destroyed on July 10, 2017.

This reviewer is of the opinion that regulations (21 CFR 320.38 and 320.63) for BE reserve samples was violated. The reserve sample issue impacts the data integrity of study BIA-91067-119 because test and reference products that were to be maintained at the study site are no longer available for analysis. Therefore, this reviewer recommends that study BIA-91067-119 is not acceptable for further review.

4. Conclusion

Objectionable conditions were observed during this inspection and Form FDA 483 was issued. The final inspection classification is Official Action Indicated (OAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, the objectionable conditions impacted the reliability of the data from the audited study. I conclude that the data from study BIA-91067-119 (NDA 212489) is not reliable.

Final Classification:

OAI - Biotrial Rennes
Rennes, France
FEI#: 3010211239

cc:

OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Taylor/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/Mada

Draft: SRM 02/21/2020

Edit: YMC 02/24/2020; JAK 02/26/2020

ECMS: <http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f882769bb4>

OSIS File # BE 8601

FACTS: 11938162

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YOUNG M CHOI
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JOHN A KADAVIL
02/26/2020 03:11:38 PM

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: February 3, 2020

TO: Billy Dunn, MD
Director (Acting)
Office of Neuroscience
Office of New Drugs

FROM: Hasan A. Irier, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
DGDSI/OSIS

SUBJECT: Surveillance inspection of [REDACTED] (b) (4)
[REDACTED]

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion of Study BIA 9-1067-119 (NDA 212489, Opicapone) conducted at [REDACTED] (b) (4)
[REDACTED]

I did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

Based on my review of the inspectional findings, I conclude the data from the audited studies are reliable to support a regulatory decision.

2. Inspected Studies

Study BIA 9-1067-119 (NDA 212489)

"Relative Bioavailability and Bioequivalence of Different Formulations of Opicapone in Healthy Volunteers"

Sample Analysis Period: 04/24/2014 - 05/25/2014

3. Scope of Inspection

OSIS scientist, Hasan A. Irier, audited the analytical portion of the above study at [REDACTED] (b) (4)

The inspection included a thorough examination of study records, facilities, laboratory equipment, method validation, and sample analysis, and interviews with the firm's management and staff.

4. Inspectional Findings

At the conclusion of the inspection, I did not observe objectionable conditions. I did not issue Form FDA 483 to [REDACTED] (b) (4). However, I discussed the following items with management during the inspection and at close-out.

4.1. Discussion item

During method validation and study sample analysis, [REDACTED] (b) (4) used the following software: XCalibur (versions 1.4 and 2.0) for instrument control and data acquisition, LCQuan (version 2.5) for peak integration, and Watson Laboratory Information Management System (LIMS; version 7.2) for quantification. However, no audit trails for XCalibur and LCQuan were available for review because the audit trail function of these two software was not turned on.

I discussed the importance of audit trails for reconstruction of the study during regulatory audits with the firm's management [REDACTED] (b) (4) during the inspection and again at the closing of the inspection.

Firm's Response: When I discussed the above issue during the inspection, [REDACTED] (b) (4) management acknowledged that the audit trail was not turned on for XCalibur and LCQuan during the analysis of samples from study BIA 9-1067-119. They explained, however, that the audit trail of the Watson LIMS software (Version 7.2), which was used for the peak quantification and the evaluation of the data, was turned on for the study period. The firm made the audit trail record of the Watson software available to me during the inspection.

OSIS Evaluation: I was able to verify and reconstruct the study sample analysis for study BIA 9-1067-119 based on the audit trail of the Watson LIMS software and the sample processing sheets from the study binders during the inspection. Additionally, I also verified that the audit trail function for XCalibur (version 1.4 and version 2.0), LCQuan (version 2.5) and Watson LIMS (version 7.2) were turned on during the current inspection and available for review. Thus, I conclude that there is no impact on the study data integrity.

5. Conclusion

After review of the inspectional findings, I conclude that data from the audited study are reliable.

Studies using similar methods conducted between January 2017 and the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI - [REDACTED]

(b) (4)

cc: OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Taylor/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/Irier
OND/ON/Dunn/Metz

Draft: HAI 01/24/2020;01/29/2020;02/03/2020

Edit: YMC 01/28/2020; 01/29/2020; 02/03/2020; JAK 01/30/2020;
02/03/2020

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/ANALYTICAL/Swiss [REDACTED] (b) (4)
[REDACTED] First Day of Inspection/Post-
Inspection Folder/EIR & EIR Review

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f882769bde>

OSIS File #: [REDACTED] (b) (4)

FACTS: [REDACTED] (b) (4)

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/s/

HASAN A IRIER
02/04/2020 03:49:48 PM

YOUNG M CHOI
02/04/2020 03:52:51 PM

JOHN A KADAVIL
02/04/2020 06:33:54 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 15, 2020
Requesting Office or Division: Division of Neurology 1 (DN 1)
Application Type and Number: NDA 212489
Product Name and Strength: Ongentys (opicapone) capsule, 25 mg, 50 mg
Applicant/Sponsor Name: Neurocrine Biosciences, Inc.
OSE RCM #: 2019-920-2
DMEPA Safety Evaluator: Chad Morris, PharmD, MPH
DMEPA Team Leader: Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on January 10, 2020 for Ongentys. The Division of Neurology 1 (DN 1) requested that we review the revised container labels for Ongentys (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container labels are acceptable from a medication error perspective. We have no additional recommendations at this time.

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^a Morris, C. Label and Labeling Review MEMO for Ongentys (NDA 212489). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 25. RCM No.: 2019-920-1.

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/s/

JOHN C MORRIS
01/15/2020 01:45:28 PM

BRIANA B RIDER
01/15/2020 01:47:48 PM

Clinical Inspection Summary

Date	9 January 2020
From	Cheryl Grandinetti, PharmD, Clinical Pharmacologist Phillip Kronstein, MD, Acting Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Stacy Metz, RPM Kenneth Bergmann, MD, Clinical Reviewer Gerald Podskalny, MD, Clinical Team Leader Billy Dunn, MD, Division Director, Division of Neurology Products
NDA #	212489
Applicant	Neurocrine Biosciences, Inc.
Drug	Opicapone
NME	Yes
Proposed Indication	As adjunct to levodopa plus a dopa decarboxylase inhibitor in patients with Parkinson's disease experiencing "OFF" episodes
Consultation Request Date	9 July 2019
Summary Goal Date	17 January 2020
Action Goal Date	24 Apr 2020
PDUFA Date	26 Apr 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Rudzinska-Bar, Ferreira, Frost, and Chung were inspected in support of NDA 212489.

Minor data discrepancies related to the off-time for Visit 14, a time-point used in the assessment of the primary efficacy endpoint in the OL portion of the trial, were noted for two subjects (b) (6) during the inspection of Dr. Frost's site. Given these discrepancies are minor and occurred in a small number of subjects from this site, the inspection finding likely does not have a significant impact on the overall efficacy results of the study. However, we recommend that the review division correct these data in the submission.

Overall the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication

II. BACKGROUND

This application was submitted in support of the use of opicapone as an adjunct to levodopa (L-DOPA) plus a dopa decarboxylase inhibitor (DDCI) in patients with Parkinson's disease (PD) experiencing "OFF" episodes. The key studies supporting the application were the following:

- 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."
- BIA-91067-302: "Efficacy and safety of BIA 9-1067 in idiopathic Parkinson's disease in 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."

Protocol BIA-91067-301

This was a Phase III, multicenter, double-blind (DB), randomized, placebo- and active-controlled, parallel group study conducted in adults diagnosed with idiopathic PD. The primary objective of the DB period was to investigate the efficacy of 3 different doses of opicapone (5 mg, 25 mg, and 50 mg) administered once daily, compared with placebo or 200 mg of entacapone, when administered with the existing treatment of L-DOPA plus a DDCI, in PD patients with end-of-dose motor fluctuations. The objective of the open label (OL) period was to investigate the safety, tolerability, and maintenance of therapeutic effect of opicapone (5 mg, 25 mg, or 50 mg once daily) adjusted according to clinical response over 52 weeks of treatment, when administered with the existing treatment of L-DOPA plus a DDCI, in PD's patients with end-of-dose motor fluctuations who completed DB period.

- *Subjects:*
 - DB Period: A total of 600 subjects were randomized: 121 subjects to placebo, 122 to entacapone, 122 to opicapone 5 mg, 119 to opicapone 25 mg, and 116 to opicapone 50 mg; 542 subjects completed the DB period.
 - OL Period: 495 (91.3%) were enrolled; 432 completed the study.
- *Sites:* An estimated 104 sites in approximately 20 countries (Austria, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, France, Germany, Hungary, Italy, Latvia, Lithuania, Montenegro, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Spain and Ukraine).
- *Study Initiation and Completion Dates:*
 - DB Period: 31 Mar 2011 (first subject enrolled) to 30 Nov 2013 (last subject completed).
 - OL period: 17 Dec 2014 (last subject completed)
- *Database lock* for the DB period occurred on 28 April 2014; for the OL period it was 21 April 2015

The study treatment duration was up to 67 weeks and the total study duration per subject was up to 71 weeks. The study consisted of the following periods:

- Screening period of up to 2 weeks
- DB period of 14 to 15 weeks
- OL period of 1 year
- Follow-up period of approximately 2 weeks

During the DB period of the study, eligible subjects were randomly assigned to one of 5 treatment arms (in a 1:1:1:1:1 ratio) using an Interactive Response System (IRS):

- Group 1: opicapone 5 mg po once daily
- Group 2: opicapone 25 mg po once daily
- Group 3: opicapone 50 mg po once daily
- Group 4: entacapone 200 mg po once daily
- Group 5: Placebo po once daily

At the Baseline Visit (Visit 2), the IP was administered with existing treatment of L-DOPA/DDCI. According to subject response, the investigator could adjust the dose from Visit 2 to Visit 4 (first 2 to 3 weeks) of the DB period. The dosage of L-DOPA/DDCI was not changed from Visit 4 through the end of the DB period (final 12 weeks).

At the end of the DB period, subjects had the option to enter a 1-year OL period in which all subjects were treated with opicapone. Subjects entered the OL period on the day after Visit 7 and ended at Visit 14 (52 weeks after Visit 7) and started on 25 mg opicapone for the first week (7 days), until Visit 8. According to subject response and at the investigator's discretion, the dose could be adjusted up to Visit 13, then it should not have been changed through the end of the OL period (from Visit 13 to Visit 14). No new anti-PD drug were to be started during the study and any that were ongoing at the start of the study must have been kept at a stable dose throughout the study.

Protocol BIA-91067-302

This was a Phase III, multicenter, DB, randomized, placebo-controlled, parallel-group study to investigate two different doses of opicapone, given orally for 14 to 15 weeks, in comparison with matching placebo, in subjects with idiopathic PD who were already receiving L-DOPA/DDCI therapy. The primary objective of the DB period was to investigate the efficacy of two different doses of opicapone (25 mg and 50 mg), administered once daily, compared with placebo, when administered with the existing treatment of L-DOPA plus a DDCl, in PD patients with end-of-dose motor fluctuations. The objective of the OL period was to investigate the safety, tolerability, and maintenance of therapeutic effect of opicapone 25 mg or 50 mg once daily adjusted according to clinical response over 1 year of treatment, when administered with the existing treatment of L-DOPA plus a DDCl, in PD patients with end-of-dose motor fluctuations who completed the DB phase of the study.

- *Subjects:*
 - DB Period: A total of 427 subjects were randomized: 121 subjects to placebo, 122 to entacapone, 122 to opicapone 5 mg, 119 to opicapone 25 mg, and 116 to opicapone 50 mg. 376 subjects completed the DB period; 376 completed the DB period
 - OL Period: 367 subjects enrolled in the OL period; 286 completed the OL period.
- *Sites:* A total of 69 sites in 12 countries (Argentina, Australia, Belgium, Chile, Czech Republic, Estonia, India, Israel, South Korea, Russia, South Africa and UK)

- *Study Initiation and Completion Dates:*
 - DB Period: 18 March 2011 (first subject, first visit) to 11 July 2012 (last subject, last visit)
 - OL Period: 01 July 2011 (first subject, first visit) to 25 June 2013 (last subject, last visit)
- *Interim database lock and unblinding* occurred on 15 October 2012 and 16 October 2012, respectively, after all subjects completed the DB period. The *final database lock* (of the DB and OL Periods) occurred on 18 November 2013.

During the DB period of the study, eligible subjects were randomly assigned to one of 3 treatment arms (in a 1:1:1 ratio) using an IRS:

- Group 1: opicapone 25 mg po once daily
- Group 2: opicapone 50 mg po once daily
- Group 3: Placebo po once daily

At the Baseline Visit (Visit 2), the IP was administered with existing treatment of L-DOPA/DDCI. According to subject response, the investigator could adjust the dose from Visit 2 to Visit 4 (first 2 to 3 weeks) of the DB period. The dosage of L-DOPA/DDCI was not changed from Visit 4 through the end of the DB period (final 12 weeks).

At the end of the DB period, subjects had the option to enter a 1-year OL period in which all subjects were treated with opicapone. Subjects entered the OL period on the day after Visit 7 and ended at Visit 14 (52 weeks after Visit 7) and began at a dose of 25 mg opicapone for the first week (7 days), until Visit 8. According to the subject's response and at the investigator's discretion, the dose could have been adjusted up to Visit 13, then it should not have been changed through the end of the OL period (from Visit 13 to Visit 14). No new anti-PD drug were to be started during the study and any that were ongoing at the start of the study must have been kept at a stable dose throughout the study.

Primary Efficacy Endpoint for Protocols BIA-91067-301 and BIA-91067-302

The *primary efficacy endpoint* for the DB and OL portions of the study, respectively, was the change in absolute OFF-time from baseline to the end of the DB period (Visit 7) and to the end of the OL period (Visit 14), as calculated from the average absolute OFF-time reported in subject's paper diaries in the 3-day period preceding each visit.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, low reporting of adverse events, and prior inspectional history. In addition, only foreign data was submitted to support the application, and 4 foreign sites were chosen because this application represents a new molecular entity to treat a serious condition.

III. RESULTS (by site):

1. Monika Rudzinska-Bar, MD
BIA-91067-301
Site #3301
Cracow Academy of Neurology.
Arianska 7/3
Kraków 31-505 Poland

At this site for Protocol BIA-91067-301, for the double-blind (DB) portion of the study, 25 subjects were screened and 20 were enrolled, all of whom completed the study. For the open-label (OL) portion, 19 subjects were enrolled, and 17 subjects completed the study. Records reviewed included, but were not limited to, the study protocol and amendments, Ethics Committee/Minister of Health submissions and approvals, financial disclosure, Form FDA 1572s, informed consent, randomization procedures, source data and records, including paper source diaries for the primary efficacy endpoint, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for the all subjects screened in the DB portion of the study and all subjects enrolled in the open-label portion of the study by this site was conducted.

There was no evidence of under-reporting of adverse events. The paper source diaries for the primary efficacy endpoint were reviewed and verified against the data listings provided by the sponsor for all enrolled subject in the DB portion of the study and all subjects enrolled in the open-label portion of the study. One discrepancy was noted (for Subject (b) (6), randomized to opicapone 5 mg). The subject's source paper diary listed an off-time of 810 minutes for DB Baseline Visit, Day 2, while the sponsor's data listing for this visit had an off-time was 780 minutes.

Reviewer's comment: The difference between the source paper diary and the data listings provided by the sponsor for this visit is small and therefore unlikely to have an impact on the overall efficacy results of the study.

2. Joaquim Ferreira, MD
BIA-91067-301
Site #4201
Centro Hospitalar de Lisboa Norte,
EPE - Hospital de Sta^a Maria - Egas
Moniz Research Centre
Avenida Professor Egas Moniz Lisboa
1649-035 Portugal

At this site for Protocol BIA-91067-301, for the DB portion of the study, 11 subjects were screened and 10 were enrolled, all of whom completed the study. For the OL portion, 10 subjects were enrolled and 8 completed the study. One subject withdrew consent, and a second subject was removed due to non-compliance. Records reviewed included, but were not limited to, the study protocol and amendments, Ethics Committee/Minister of Health submissions and approvals, financial disclosure, Form FDA 1572s, informed consent, randomization procedures, source data and records, including paper source diaries for the primary efficacy endpoint,

electronic case report forms (eCRFs), drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for all subjects screened in the DB portion of the study and all subjects enrolled in the open-label portion of the study by this site was conducted.

There was no evidence of under-reporting of adverse events. The paper diary source diaries for the primary efficacy endpoint were reviewed and verified against the data listings provided by the sponsor for all enrolled subjects in the DB portion of the study and all subjects enrolled in the open-label portion of the study . No discrepancies were noted.

3. Andrew Frost, MD

BIA-91067-302

Site #1904

Vincent Pallotti Hospital

Room 2036, North Wing

Cape Town 7405, SOUTH AFRICA

At this site for Protocol BIA-91067-302, for the DB portion of the study, 15 subjects were screened (which includes 2 subjects who were rescreened), 11 were enrolled, and 10 subjects completed the study. For the OL portion, 10 subjects were enrolled and 9 completed the study. Per the sponsor's data listings, one subject in the DB portion discontinued the study due to an adverse event and one subject in OL portion discontinued due to non-compliance. Records reviewed included, but were not limited to, protocol and amendments, Ethics Committee/ Minister of Health submissions and approvals, financial disclosure, Form FDA 1572s, informed consent, randomization procedures, source data and records, including paper source diaries for the primary efficacy endpoint, electronic case report forms (eCRFs), drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for all subjects screened in the DB portion of the study and all subjects enrolled in the open-label portion of the study by this site was conducted.

The clinical investigator failed to report an incident of vertigo that occurred for Subject (b) (6) during the OL portion of the trial. Dr. Frost stated that the subject had a history of Meniere's disease (which was not properly documented in the subject's medical history and source records), and thus was likely the cause of the vertigo. Otherwise, there was no evidence of under-reporting of adverse events

The paper source diaries for the primary efficacy endpoint were reviewed and verified against the data listings provided by the sponsor for all enrolled subjects in the DB portion of the study and all subjects enrolled in the open-label portion of the study. The following discrepancies were noted:

Subject Number	Study Period/Visit Number/Day/Date	Paper Source Diaries	Data Listings Provided by the Sponsor
(b) (6)	OL/Visit 14/EDV/ Day 1/ 2013-02-23	Total OFF time: 120 minutes Total ON time: 600 minutes	Missing entries
	OL/Visit 14/EDV/Day 2/ 2013-02-24	Total OFF time: 60 minutes Total ON time: 750 minutes	Total OFF time: 45 minutes Total ON time: 780 minutes
	OL/Visit 14/EDV/ Day 1/ 2013-05-11	Total OFF time: 330 minutes Total ON time: 450 minutes	Missing entries
	OL/Visit 14/EDV/ Day 1/ 2013-05-13	Total OFF time: 420 minutes Total ON time: 510 minutes	Total OFF time: 405 minutes Total ON time: 495 minutes

Reviewer's comment: These discrepancies are all related to the off-time for the OL Visit 14 and are used in the assessment of the primary efficacy endpoint in the OL portion of the trial. Given that these discrepancies are minor and occurred in a small number of subjects from this site, the described observation likely does not have a significant effect on overall efficacy results of the study. However, we recommend that the review division correct these data in the submission.

4. Sun-Ju Chung, MD
BIA-91067-302
Site #2002
Asan Medical Center
88 Olympic-ro, 43-gil,
Songpa-gu Seoul, 05505 South Korea

At this site for Protocol BIA-91067-302, for the DB portion of the study, 18 subjects were screened, 18 were enrolled, and 17 subjects completed the study. For the OL portion, 17 subjects were enrolled and 16 completed the study. One subject in the DB portion discontinued due to an adverse event of continued dyskinesia, and one subject did not complete the OL portion due to death from small cell lung cancer. Records reviewed included, but were not limited to, protocol and amendments, Ethics Committee/ Minister of Health submissions and approvals, financial disclosure, Form FDA 1572s, informed consent, randomization procedures, source data and records, including paper source diaries for the primary efficacy endpoint, electronic case report forms (eCRFs), drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters. An audit of the study records for all subjects screened in the DB portion of the study and all subjects enrolled in the open-label portion of the study by this site was conducted.

There was no evidence of under-reporting of adverse events. The paper diary source diaries for the primary efficacy endpoint were reviewed and verified against the data listings provided by the sponsor for all enrolled subjects in the DB portion of the study and all subjects enrolled in the open-label portion of the study. No discrepancies were noted.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
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CONCURRENCE:

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/s/

CHERYL A GRANDINETTI
01/09/2020 04:50:07 PM

PHILLIP D KRONSTEIN
01/09/2020 05:08:13 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: November 25, 2019
Requesting Office or Division: Division of Neurology 1 (DN 1)
Application Type and Number: NDA 212489
Product Name and Strength: Ongentys (opicapone) capsule, 25 mg, 50 mg
Applicant/Sponsor Name: Neurocrine Biosciences, Inc. (Neurocrine)
OSE RCM #: 2019-920-1
DMEPA Safety Evaluator: Chad Morris, PharmD, MPH
DMEPA Team Leader: Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

Neurocrine submitted revised container labels^a received on November 20, 2019 for Ongentys. The Division of Neurology 1 (DN 1) requested that we review the revised container labels Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations we made during a previous label and labeling review.^b

2 CONCLUSION

The revised container labels are unacceptable from a medication error perspective because the manufacturer information on the principal display panel remains too prominent. We provide recommendations to Neurocrine in Section 3.

a

(b) (4)

^b Morris, C. Label and Labeling Review for Ongentys (opicapone) NDA 212489. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 06. RCM No.: 2019-920.

3 RECOMMENDATIONS

We recommend the following be implemented prior to approval of this NDA:

Table 1. Identified Issues and Recommendations for Neurocrine Biosciences, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	The manufacturer information in the gray box on the bottom of the principal display panel (PDP) competes in prominence with important required information. Specifically, the gray box with the manufacturer information consumes one-third of the PDP and "Neurocrine" is more prominent than the established name and dosage form.	The proprietary and established names should be the most prominent information on the PDP, and the manufacturer information should not compete in size and prominence with this important information.	Revise the container label to ensure the proprietary name, established name, and strength are the most prominent information on the PDP. Consider the font type, size, format, and color of the information in the bottom gray box. Also, consider the proportionality of the gray box to the white space that contains the proprietary name, established name, and strength. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.^c

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

^c Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

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/s/

JOHN C MORRIS
11/25/2019 06:13:47 PM

BRIANA B RIDER
11/25/2019 06:33:39 PM

Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 212489
Submission Number	0001
Submission Date	4/26/2019
Date Consult Received	6/26/2019
Clinical Division	DNP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Clinical Overview (SN0001 / SDN001; [link](#));
- Integrated ECG report (SN0001 / SDN001; [link](#));
- TQT study report (SN0001 / SDN001; [link](#));
- Proposed Labeling (SN0001 / SDN001; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (SN0006 / SDN006; [link](#)).

1 SUMMARY

No significant QTc prolongation effect of opicapone was detected in this TQT study.

The QTc effect of opicapone (50 mg and 800 mg) was evaluated in 64 healthy subjects in a randomized, single-dose, double-blind, placebo-controlled and open-label active-controlled, 4-period crossover trial (study BIA-91067-111). The highest evaluated dose, i.e. 800 mg, covered opicapone exposure attained in the worst-case scenario (i.e., Asian subject with mild hepatic impairment) and the therapeutic exposure of the major metabolite at the steady state. The data were analyzed using by-time central tendency as the primary analysis. The largest upper bounds of the 2-sided 90% CI for the time-matched, mean difference between opicapone (50 mg and 800 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in

Figure 1, indicating that assay sensitivity was established. The findings of this analysis are further supported by the concentration-QTc analysis (Section 4.5) and categorical analysis (Section 4.4).

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Opicapone (50 mg and 800 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	N	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Opicapone 50 mg	3	64	1.2	(-0.7, 3.1)
Opicapone 800 mg	3	61	1.1	(-0.8, 3.1)

Treatment	Time (hour)	N	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Moxifloxacin 400 mg*	3	64	11.9	(9.9, 13.8)

* Multicity adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints was 9.2 ms.

The intrinsic/extrinsic factors that substantially increase opicapone exposure are hepatic impairment (up to 1.9-fold with mild impairment) and Asian race (1.4-fold). The recommended dose for patients with moderate hepatic impairment is 25 mg QD. Opicapone is not recommended for patients with severe hepatic impairment.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 PROPOSED LABEL

Below are the proposed edits from the IRT to the label submitted to SN 0001 ([link](#)). Our changes are highlighted ([addition](#), ~~deletion~~) as a suggestion. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)
 (b) (4) times (b) (4)
 -At a dose (b) (4) ONGENTYS did not prolong the (b) (4) [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.

3 SPONSOR’S SUBMISSION

3.1 OVERVIEW

The QT-IRT has not reviewed the QT assessment conducted by the sponsor and we refer the reader to Appendix 5.1 for a detailed review of the sponsor’s QT assessment.

The sponsor conducted a Phase I, TQT study (BIA-91067-111) to evaluate the effect of therapeutic (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 and 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. Subjects 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 as the primary endpoint and QTcF as the secondary endpoint. The primary method is by-time analysis.

The reviewers used QTcF as the primary endpoint because no significant increases or decreases in heart rate were observed.

The sponsor also submitted ECG data from two Phase 3 studies (studies BIA-91067-301 and -302) in the Integrated ECG Report. These two studies were not reviewed because the TQT study alone is adequate to characterize drug effect on the QTc interval and the two Phase 3 studies do not provide additional data to support labeling recommendations.

3.1.1 By-Time Analysis

The by-time analysis of QTcI excluded the 10 ms threshold at the therapeutic and suprathreshold dose levels.

FDA reviewer performed central tendency analysis on TQT study BIA-91067-111. The results of the reviewer's analysis are similar to the sponsor's results. Please see Section 4.3.1 for additional details.

3.1.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm using the by-time central tendency analysis. Both FDA's analysis and the sponsor's analysis confirm that assay sensitivity was established. Please see Section 4.3.1.1 for additional details.

3.1.1.1.1 QT Bias Assessment

Not applicable.

3.1.2 Categorical Analysis

None of the subjects had absolute QTcF >480 ms or an increase from baseline in QTcF >60 ms. The results of the reviewer's analysis are similar to the sponsor's results for QTcF and Δ QTcF. Please see Section 4.4 for additional details.

3.1.3 Safety Analysis

There were no deaths or SAEs. One subject was withdrawn following a moderate anemia which started 6 days after treatment administration of 50 mg BIA 9-1067. There were no cardiac-related TEAEs; however, 1 subject ((b) (6)) presented with orthostatic hypotension at the P2D1H02:00 examination, following the 800 mg BIA 9-1067 administration. The TEAE was moderate in intensity.

One subject ((b) (6)) presented an elevated HR of 121 bpm at P2D1H02:00, after the 400 mg moxifloxacin administration: at that time, the subject also started complaining of moderate nausea and mild asthenia.

3.1.4 Exposure-Response Analysis

The sponsor performed graphical analysis to evaluate the relationship between opicapone and $\Delta\Delta$ QTcI.

The reviewer used ΔQTcF as a response variable for the exposure-response analysis. The reviewer’s results do not suggest positive exposure-response relationship between opicapone exposure and QTc change. Please see Section 4.5 for additional details.

4 REVIEWERS’ ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

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; see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT bias assessment

Not applicable.

4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

The statistical reviewer used repeated measures mixed effects model to analyze the ΔQTcF effect. The model includes treatment, sequence, period, time point, and treatment by time point as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate.

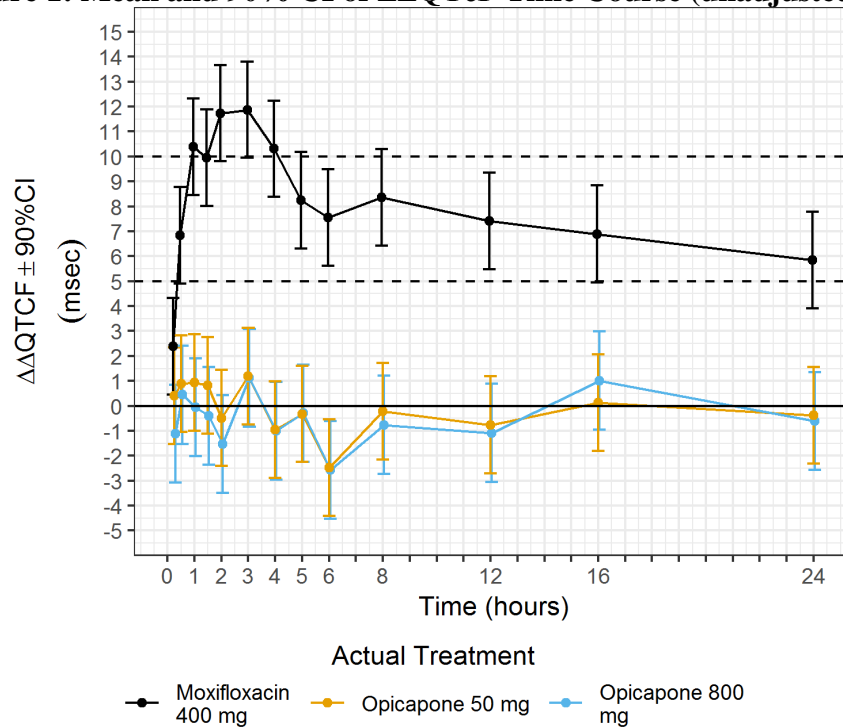
Table 2 lists the analysis results. The largest upper bounds of the 2-sided 90% CI for the mean differences between opicapone 50 mg and placebo, and between opicapone 800 mg and placebo were both 3.1 ms. Figure 1 displays the time profile of $\Delta\Delta\text{QTcF}$ for different treatment groups.

Table 2: Analysis Results of ΔQTcF and $\Delta\Delta\text{QTcF}$

Time (hour)	Opicapone 50 mg (N=64)			Opicapone 800 mg (N=61)		
	ΔQTcF (ms)		$\Delta\Delta\text{QTcF}$ (ms)	ΔQTcF (ms)		$\Delta\Delta\text{QTcF}$ (ms)
	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0	-1.4	-2.6	1.2 (-0.7, 3.1)	-3.2	-2.6	-0.6 (-2.5, 1.4)
0.25	-2.5	-2.9	0.4 (-1.5, 2.3)	-4.0	-2.9	-1.1 (-3.1, 0.8)
0.5	-3.6	-4.5	0.9 (-1.0, 2.8)	-4.0	-4.5	0.4 (-1.5, 2.4)
1	-3.1	-4.0	0.9 (-1.0, 2.9)	-4.1	-4.0	-0.1 (-2.0, 1.9)

Time (hour)	Opicapone 50 mg (N=64)			Opicapone 800 mg (N=61)		
	Δ QTcF (ms)		$\Delta\Delta$ QTcF (ms)	Δ QTcF (ms)		$\Delta\Delta$ QTcF (ms)
	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
1.5	-3.1	-4.0	0.8 (-1.1, 2.8)	-4.4	-4.0	-0.4 (-2.4, 1.5)
2	-2.7	-2.3	-0.5 (-2.4, 1.5)	-3.8	-2.3	-1.5 (-3.5, 0.4)
3	-4.1	-5.3	1.2 (-0.8, 3.1)	-4.2	-5.3	1.1 (-0.8, 3.1)
4	-6.9	-5.9	-1.0 (-2.9, 1.0)	-6.9	-5.9	-1.0 (-3.0, 1.0)
5	-7.3	-7.0	-0.3 (-2.3, 1.6)	-7.3	-7.0	-0.3 (-2.3, 1.7)
6	-7.3	-4.8	-2.5 (-4.4, -0.5)	-7.4	-4.8	-2.6 (-4.5, -0.6)
8	-5.3	-5.1	-0.2 (-2.2, 1.7)	-5.8	-5.1	-0.8 (-2.7, 1.2)
12	-1.0	-0.3	-0.8 (-2.7, 1.2)	-1.4	-0.3	-1.1 (-3.1, 0.9)
16	-4.2	-4.4	0.1 (-1.8, 2.1)	-3.4	-4.4	1.0 (-1.0, 3.0)
24	-2.0	-1.6	-0.4 (-2.3, 1.6)	-2.2	-1.6	-0.6 (-2.6, 1.3)

Figure 1: Mean and 90% CI of $\Delta\Delta$ QTcF Time Course (unadjusted CIs)



4.3.1.1 Assay sensitivity

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 3. The largest unadjusted 90% lower confidence interval was 9.9 ms. By considering Bonferroni multiplicity adjustment, the largest lower confidence interval was 9.2 ms, which indicates that an at least 5 ms QTcF

effect due to moxifloxacin can be detected from the study. The time profile of $\Delta\Delta\text{QTcF}$ for moxifloxacin is displayed in the above Figure 1.

Table 3: Analysis Results of ΔQTcF and $\Delta\Delta\text{QTcF}$ for Moxifloxacin

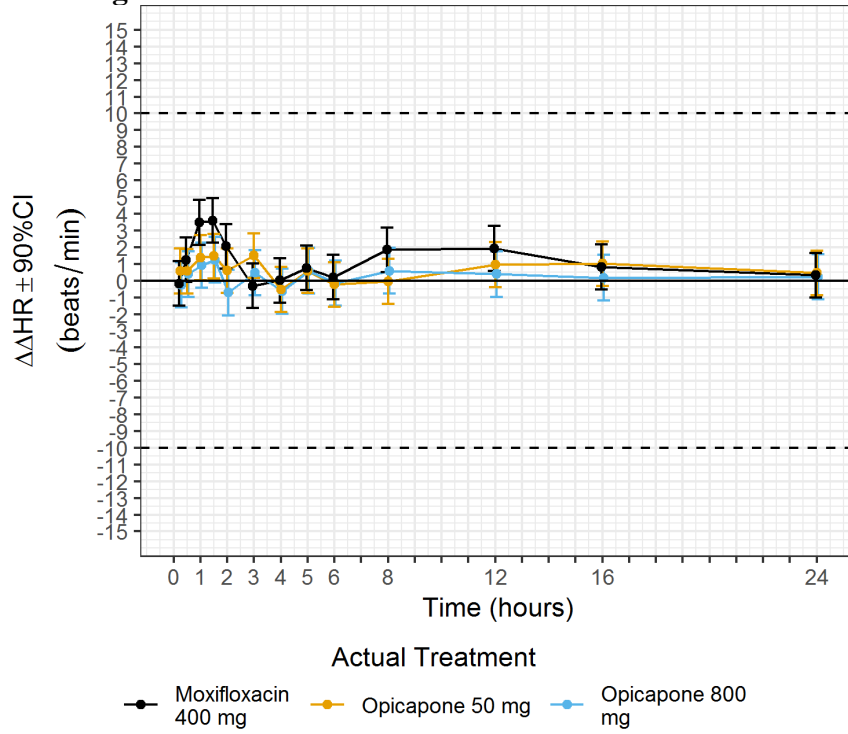
Time (hour)	ΔQTcF (ms) Moxifloxacin 400 mg (N=64)	ΔQTcF (ms) Placebo (N=62)	$\Delta\Delta\text{QTcF}$ (ms) Moxifloxacin 400 mg		
	LSmean	LSmean	LSmean	90% CI	Adjust 90% CI*
0	-1.1	-2.6	1.5	(-0.4, 3.5)	(-1.1, 4.2)
0.25	-0.5	-2.9	2.4	(0.5, 4.3)	(-0.2, 5.0)
0.5	2.4	-4.5	6.9	(4.9, 8.8)	(4.2, 9.5)
1	6.4	-4.0	10.4	(8.5, 12.3)	(7.8, 13.0)
1.5	6.0	-4.0	10.0	(8.0, 11.9)	(7.3, 12.6)
2	9.5	-2.3	11.7	(9.8, 13.7)	(9.1, 14.4)
3	6.5	-5.3	11.9	(9.9, 13.8)	(9.2, 14.5)
4	4.4	-5.9	10.3	(8.4, 12.2)	(7.7, 13.0)
5	1.3	-7.0	8.3	(6.3, 10.2)	(5.6, 10.9)
6	2.7	-4.8	7.6	(5.6, 9.5)	(4.9, 10.2)
8	3.3	-5.1	8.4	(6.4, 10.3)	(5.7, 11.0)
12	7.1	-0.3	7.4	(5.5, 9.4)	(4.8, 10.1)
16	2.5	-4.4	6.9	(5.0, 8.8)	(4.2, 9.5)
24	4.3	-1.6	5.9	(3.9, 7.8)	(3.2, 8.5)

* Bonferroni method was applied to all time points to adjust for multiple endpoint evaluation at 4 time points around moxifloxacin C_{max} .

4.3.2 HR

The same statistical analysis was performed based on HR (Figure 2). The largest upper limits of 90% CI for the HR mean differences between opicapone 50 mg and placebo and opicapone 800 mg and placebo were 2.8 bpm and 2.6 bpm, respectively.

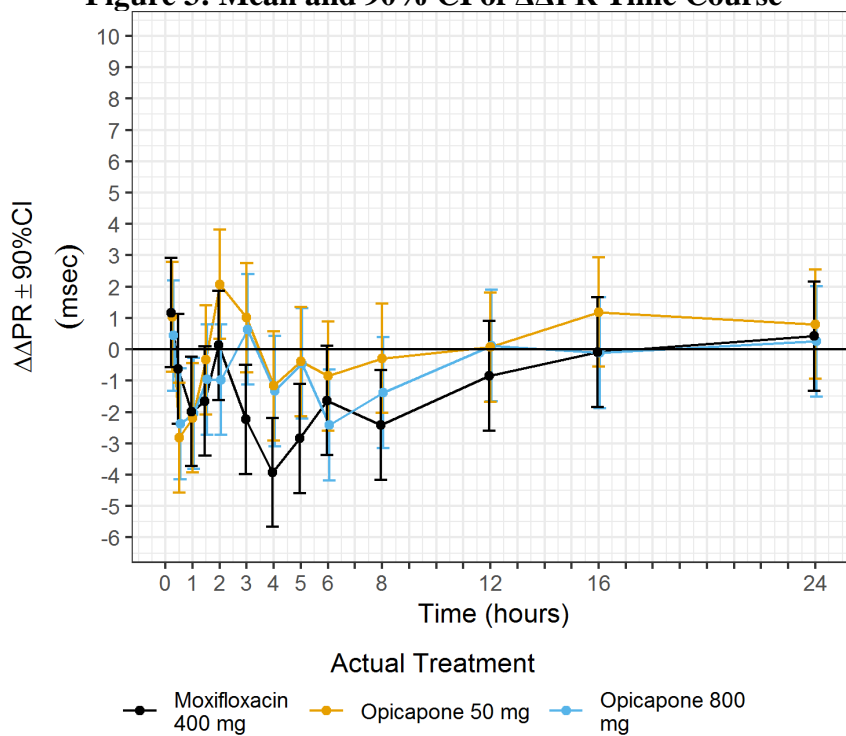
Figure 2: Mean and 90% CI of $\Delta\Delta$ HR Time Course



4.3.3 PR

The same statistical analysis was performed based on PR interval (Figure 3). The largest upper limits of 90% CI for the PR mean differences between opicapone 50 mg and placebo and opicapone 800 mg and placebo were 3.8 ms and 2.7 ms, respectively.

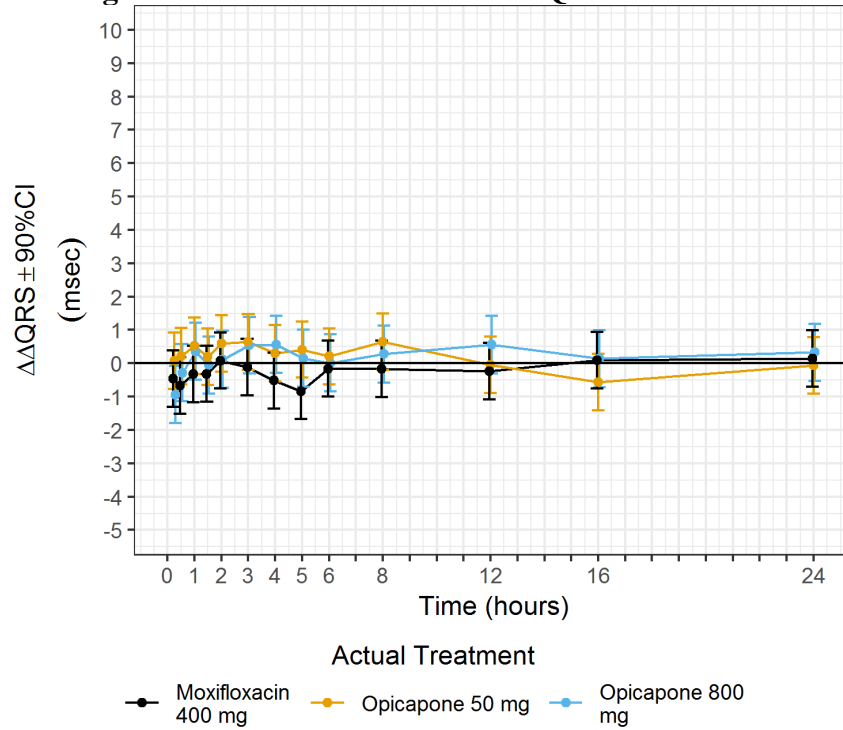
Figure 3: Mean and 90% CI of $\Delta\Delta$ PR Time Course



4.3.4 QRS

The same statistical analysis was performed based on QRS interval (Figure 4). The largest upper limits of 90% CI for the QRS mean differences between opicapone 50 mg and placebo and opicapone 800 mg and placebo were 1.5 ms and 1.4 ms, respectively.

Figure 4: Mean and 90% CI of $\Delta\Delta$ QRS Time Course



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

Table 4 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 4: Categorical Analysis for QTcF

Actual Treatment	Total (N)		Value ≤ 450 msec		450 msec < Value ≤ 480 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Opicapone 50 mg	64	831	64 (100.0%)	831 (100.0%)	0 (0%)	0 (0%)
Opicapone 800 mg	61	792	61 (100.0%)	792 (100.0%)	0 (0%)	0 (0%)
Placebo	62	802	60 (96.8%)	800 (99.8%)	2 (3.2%)	2 (0.2%)

Table 5 lists the categorical analysis results for Δ QTcF. No subject's change from baseline in QTcF was above 60 ms.

Table 5: Categorical Analysis of Δ QTcF

Actual Treatment	Total (N)		Value ≤ 30 msec		30 msec < Value ≤ 60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Opicapone 50 mg	64	831	63 (98.4%)	830 (99.9%)	1 (1.6%)	1 (0.1%)

Actual Treatment	Total (N)		Value <= 30 msec		30 msec < Value <= 60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Opicapone 800 mg	61	792	61 (100.0%)	792 (100.0%)	0 (0%)	0 (0%)
Placebo	62	802	62 (100.0%)	802 (100.0%)	0 (0%)	0 (0%)

4.4.2 PR

The outlier analysis results for PR are presented in Table 6. No subject experienced PR >220 ms with an increase from baseline in PR >25% in placebo and active treatment groups.

Table 6: Categorical Analysis for PR

Actual Treatment	Total (N)		Value <= 220 msec		Value > 220 msec & <= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Opicapone 50 mg	64	831	63 (98.4%)	830 (99.9%)	1 (1.6%)	1 (0.1%)
Opicapone 800 mg	61	792	60 (98.4%)	791 (99.9%)	1 (1.6%)	1 (0.1%)
Placebo	62	802	62 (100.0%)	802 (100.0%)	0 (0%)	0 (0%)

4.4.3 QRS

No subject experienced QRS >120 ms in placebo and the active treatment groups.

4.4.4 HR

The outlier analysis results for HR are presented in Table 7. Two subjects, one in opicapone 50 mg group and one in placebo group, experienced post-dose HR >100 bpm with an increase from baseline >25%.

Table 7: Categorical Analysis for HR

Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Opicapone 50 mg	64	831	63 (98.4%)	830 (99.9%)	1 (1.6%)	1 (0.1%)
Opicapone 800 mg	61	792	61 (100.0%)	792 (100.0%)	0 (0%)	0 (0%)
Placebo	62	802	61 (98.4%)	801 (99.9%)	1 (1.6%)	1 (0.1%)

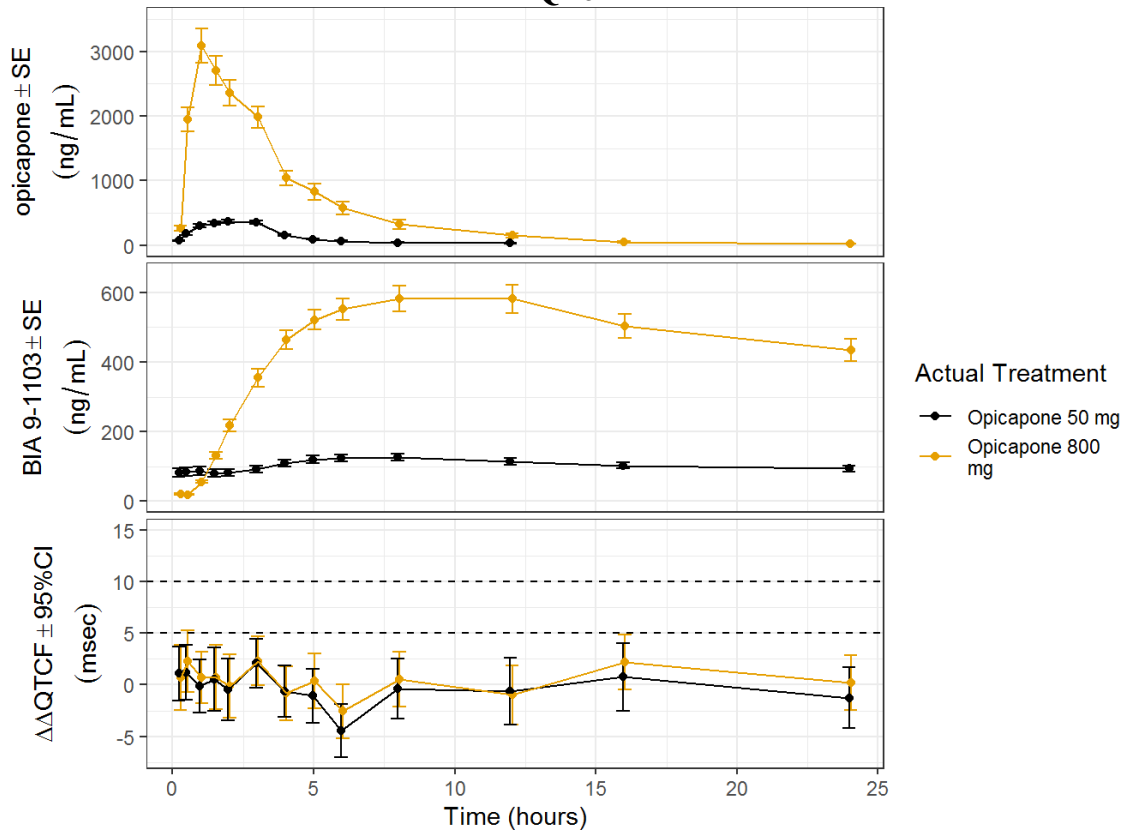
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between drug concentration (opicapone and its major metabolite, BIA 9-1103) and Δ QTcF.

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and Δ QTcF and 3) presence of non-linear relationship. An

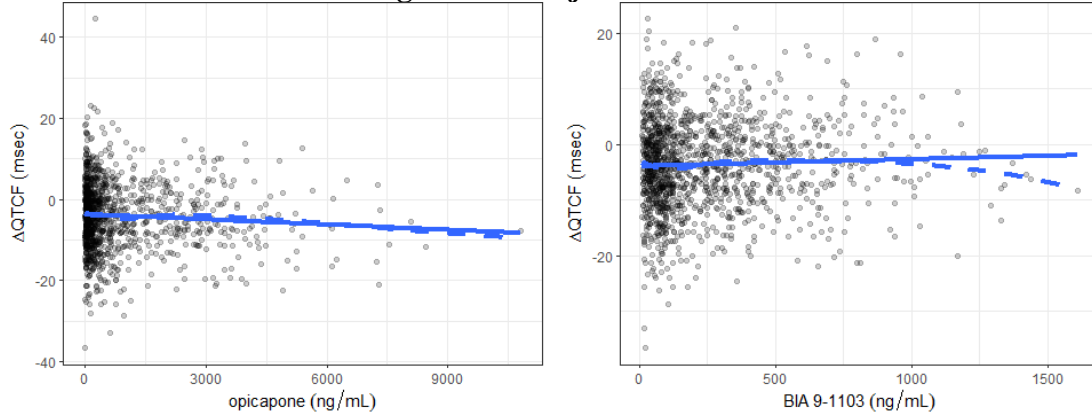
evaluation of the time-course of drug concentration and changes in $\Delta\Delta\text{HR}$ and $\Delta\Delta\text{QTcF}$ is shown in Figure 2 and Figure 5, which shows an absence of significant changes in HR and do not appear to show significant hysteresis. Despite of substantial difference in drug exposure, there is no separation in the time course of $\Delta\Delta\text{QTcF}$ between two dose levels.

Figure 5: Time Course of Parent Drug and Its Major Metabolite Concentration and QTcF



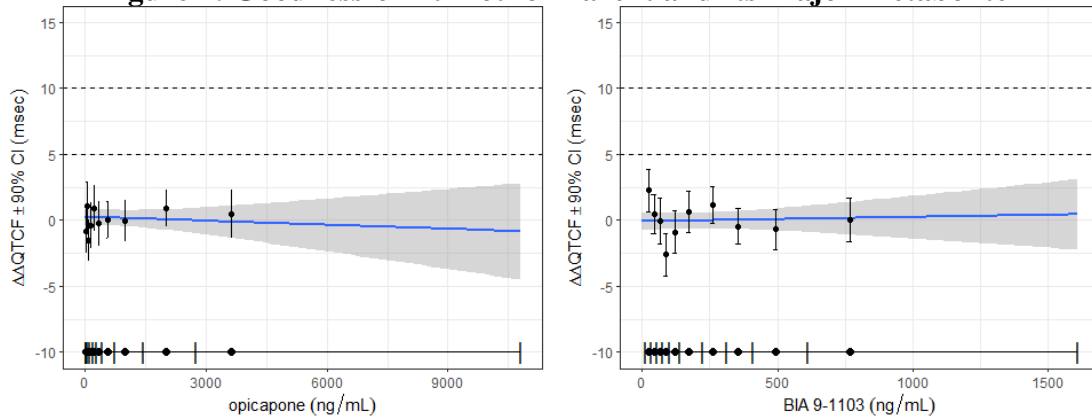
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between drug concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 6: Assessment of Linearity of Concentration-QTc Relationship for Parent Drug and Its Major Metabolite



Finally, the linear mixed effect model ($\Delta QTcF \sim 1 + \text{treatment} + \text{TIME} + \text{adjusted-baseline} + \text{concentration}$, with random effect on the slope and intercept) was applied to the data and the goodness-of-fit plot is shown in Figure 7. The analysis does not suggest a positive exposure-response relationship between $\Delta QTcF$ for parent drug and its major metabolite.

Figure 7: Goodness-of-fit Plot for Parent and Its Major Metabolite



4.5.1 Assay sensitivity

Assay sensitivity was established using by-time central tendency analysis. Please see Section 4.3.1.1 for additional details.

5 APPENDIX

5.1 EVALUATION OF QT ASSESSMENT PLAN

1. Product Information			
Generic Name	opicapone (BIA 9-1067, OPC)	Brand Name	Ongentys
Drug class	Catechol-O-Methyltransferase inhibitor	Combination product	No
Indication	Parkinson's disease		
Therapeutic Dose	50 mg once daily		
Maximum Tolerated Dose	Not known, but maximum dose tested: 1200 mg		
Dosage Form	Capsules	Route of Administration	Oral
2. Safety Pharmacology			
2.1 In vitro			
OPC (0.1, 1, 3, and 10 µg/mL) had no effect on cardiac action potential using dog Purkinje fibers and was considered to have no potential pro-arrhythmic risk up to 10 µg/mL. The IC50 for hERG inhibition is >100 µM. The 10 µM concentration is approximately 9,000-fold higher than the free (unbound) Cmax value at steady state of 4.59 ng/mL (based on 1% fraction unbound) found in human plasma at the 50 mg/day dose level.			
2.2 In vivo			
Single- and repeat-dose administration (oral [po]) of OPC (60, 200, and 600 mg/kg) to conscious dogs in the GLP cardiovascular study (Study 06-094_3) and 28-day toxicity study (Report A73945), respectively, had no effect on arterial blood pressure (BP) and heart rate (HR), and no effects on PR interval, QT interval (QT), or corrected QT (QTc) intervals were noted in electrocardiogram (ECG) assessments. No arrhythmias or other changes in the morphology of the ECG which could be attributed to OPC were observed. The 600 mg/kg dose systemic exposure at 2 hours postdose is approximately 15-fold higher than the Cmax value at steady state of 459 ng/mL found in human plasma at the 50 mg/day dose level. No effects on ECG parameters were noted in Cynomolgus monkeys following once daily administration of OPC at dose levels of 100, 300, or 1000 mg/kg for 52 weeks (ECG recorded during pretest, before and one hour after administration of OPC during weeks 1, 13, 26, and 52).			
3. Clinical cardiac safety			
The OPC clinical development program comprises 38 studies: 34 Phase 1, 2 Phase 2, and 2 Phase 3 studies. Cardiac safety events across the OPC clinical trials were analyzed by performing a standardized MedDRA query of Torsades de pointes/QT prolongation and PT of seizure in the Phase 1, 2, and 3 studies. There were limited numbers of events observed, including in the patient population treated at the maximum proposed therapeutic dose. Refer to the sponsor's highlights of clinical pharmacology and cardiac safety for more details.			

4. QT Studies										
4.1 Primary Studies										
Protocol number / Population	ECG Quality		Arms		Sample size		ECG & PK assessments			
	Assessment	Ok?	Arms	High dose covers?	No subjects	Ok?	Timing	Ok?		
Protocol number: BIA-91067-111 Population: Healthy volunteers	Central read? Yes Blinded? Yes Replicates? Yes	Yes	Highest dose: 800 mg Placebo: Yes Positive control: Yes	Above therapeutic	64	Yes	Baseline: Time-matched Timing: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24.	Yes		
4.2 Secondary Studies										
Protocol number				Reason for excluding						
Protocol number: BIA-91067-301 and BIA-91067-302				The TQT study suggests no effect and is adequate for labeling.						
4.3 Data pooling (N/A)										
5. Analysis plan										
5.1 Study Objective related to QT										
What QTc effect size is the analysis trying to exclude?				10 ms (E14)						
5.2 Dose Justification										
The sponsor conducted a single dose study because of the short half-life (1-2 h) of opicapone relative to the dosing interval (24 h). The suprathreshold dose of 800 mg is adequate to cover both single and steady state exposure of opicapone at proposed therapeutic dose as well as in worst-case scenario (repeat dosing to Asian subjects with moderate hepatic impairment). However, the 800 mg does not cover steady state exposures of its metabolite in the worst-case scenario due to the long half-life of its major metabolite (140 hrs).										
	Therapeutic dose- 50 mg opicapone (N=16)				Worst scenario: 100 mg opicapone (N=6)				QT high dose: 800 mg opicapone (N=61)	
	Parent		Metabolite		Parent		Metabolite		Parent	Metabolite
	Single	Chronic	Single	Chronic	Single	Chronic	Single	Chronic	Single	Single
C _{max} (ng/mL)	464.7	459.2	115.9	505.8	927.2	--	168.2	--	3854.8	635.5
AUC _{0-last} (ng.h/mL)*	1663.8	2021.6	1947.4	10902.7	2343.3	--	2994.8	--	11754	11253
Source: Study NBI-OPC-1706; BIA-91067-101 Table 5 and Table 14.2.1.3; BIA-91067-111 Table 14.2.2; AUC ₀₋₂₄ for metabolite										

5.3 QT correction method	
Is an HR increase or decrease greater than 10 bpm?	No
Primary method for QT correction	QTcI
<i>Reviewer's comments: The sponsor has collected sufficient off-treatment QT/RR pairs to support QTcI. QTcF analysis results are presented as secondary analysis in the sponsor's report.</i>	
5.4 Assay Sensitivity	
Assay sensitivity methods proposed by sponsor	☒ Moxifloxacin ☐ QT bias assessment ☐ Not applicable (objective is large mean effects) ☐ Exposure-margin ☐ Other
5.5 Central Tendency Analysis	
5.5.1 Investigational drug	
Primary analysis	Yes
Did the sponsor use IUT or descriptive statistics?	IUT
For IUT: Does the sponsor use MMRM to analyze longitudinal values that considers the correlation across time-points or use ANCOVA by time-point without considering correlation?	ANCOVA
For IUT: Is the MMRM model specified correctly with regards to covariance structure, covariates, etc?	N/A
<i>Estimate (Standard Error) of the difference between adjusted treatment means using an analysis of covariance (with treatment, period and gender as fixed effects and subject as random effect and with baseline value as covariate) was conducted by the sponsor for BIA 9-1067 minus Placebo. Baseline is defined as the time-matched value at D-1 or D1 H0 of each period. 90% two-sided confidence interval of the estimate were presented for the primary analysis.</i>	
5.5.2 Positive control	
Primary analysis	Yes
Did the sponsor adjust for multiplicity?	Yes
<i>Estimate (Standard Error) of the difference between adjusted treatment means using an analysis of covariance (with treatment, period and gender as fixed effects and subject as random effect and with baseline value as covariate) was conducted by the sponsor for Moxifloxacin minus Placebo. Baseline is defined as the time-matched value at D-1 or D1 H0 of each period. 95% two-sided confidence interval of the estimate were presented for positive control.</i>	
5.6 Concentration-QTc analysis	
5.6.1 Investigational drug	
Primary analysis	No

What is the dependent variable in the sponsor's model?	Double delta
White paper model?	No
Which concentration covariate(s) are included in the model?	Multiple - Univariate
Did the sponsor propose an assessment of delayed effects?	No
Did the sponsor propose an assessment of linearity?	No
Did the sponsor propose model selection criteria?	No
What methods did the sponsor use for predicting the QT effect? (N/A)	☐ Model-based confidence intervals ☐ Bootstrap-derived confidence intervals
<i>The sponsor did not conduct a formal exposure-response analysis.</i>	
4.6.2 Positive control	
Primary analysis	No
Same model as investigational drug	N/A
5.7 Categorical analysis	
QTc?	Yes
Δ QTc?	Yes
PR?	Yes
QRS?	Yes
HR?	Yes
T-wave morphology?	Yes

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 6, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 212489
Product Name and Strength:	Ongentys (opicapone) capsule, 25 mg, 50 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Neurocrine Biosciences, Inc.
FDA Received Date:	April 26, 2019
OSE RCM #:	2019-920
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader (Acting):	Briana Rider, PharmD

1 REASON FOR REVIEW

As part of the approval process for Ongentys (opicapone) capsule, the Division of Neurology Products (DNP) requested that we review the proposed Ongentys Prescribing Information (PI), Patient Prescribing Information (PPI), and sample and trade container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted Prescribing Information (PI), Patient Prescribing Information (PPI), and sample and trade container labels, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology Products (DNP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Recommendations for the labels and labeling			
1.	The storage conditions are presented in an unusual format. That is, 'Do not store at a temperature above 86°F (30°C)'.	May increase the risk for inappropriate storage which could result in degraded drug medication errors.	DMEPA defers to Chemistry, Manufacturing, and Controls (CMC) to recommend the appropriate storage statement for the labels and labeling.

Table 3. Identified Issues and Recommendations for Neurocrine Biosciences, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	The manufacturer information (Neurocrine Biosciences and its associated image) clutters the principal display panel (PDP) and takes readers' attention away from important information such as the proprietary and established names.	The proprietary and established names should be the most prominent information on the PDP, and the manufacturer information should not compete in size and prominence with this important information.	Revise the container label to ensure the proprietary name, established name, and strength are the most prominent information on the PDP. Consider relocating the manufacturer information to the side panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. ^a
2.	The color scheme of the 25 mg strength statement (light blue) and the established name [(opicapone) capsules] appear in the same blue color.	The use of the same blue color font for the established name and one of the product's strengths minimizes the difference between the two strengths, which may lead to wrong strength selection errors.	Revise the font color of the 25 mg strength statement, so the 25 mg strength statement appears in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.
3.	The expiration date (DDMMMYYYY) is not denoted in one of the recommended formats and the portions of the expiration date are not separated by a hyphen or space.	The readability of the expiration date can be improved.	FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to

^a Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

Table 3. Identified Issues and Recommendations for Neurocrine Biosciences, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. ^b
4.	The usual dose statement states [REDACTED] (b) (4)	Not in alignment with 21 CFR 201.55.	To ensure consistency with the Prescribing Information, revise the usual dose statement to read "Recommended Dosage: See prescribing information."

4 CONCLUSION

Our evaluation of the proposed Ongentys Prescribing Information (PI), Patient Prescribing Information (PPI), and sample and trade container labels identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for DNP and Table 3 for Neurocrine Biosciences, Inc. We ask the Division to convey Table 3 in its entirety to Neurocrine Biosciences, Inc. so the recommendations are implemented prior to approval of this NDA.

^b Available from:

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Ongentys that Neurocrine Biosciences, Inc. submitted on April 26, 2019.

Table 4. Relevant Product Information for Ongentys	
Initial Approval Date	N/A
Active Ingredient	Opicapone
Indication	Adjunctive treatment to levodopa/carbidopa (LD/CD) in patients with Parkinson's disease (PD) experiencing "OFF" episodes
Route of Administration	Oral
Dosage Form	Capsule
Strength	25 mg, 50 mg
Dose and Frequency	50 mg once daily (25 mg once daily in patients with moderate hepatic impairment)
How Supplied	Trade 25 mg capsules: Bottles of 30 capsules 50 mg capsules: Bottles of 30 capsules (b) (4) Professional Samples 50 mg: Bottles of 10 capsules
Storage	Do not store at a temperature above 86°F (30°C).
Container Closure	HDPE bottles with foil seal and child-resistant cap

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 8, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Ongentys and opicapone. Our search did not identify any previous reviews relevant to this review.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Ongentys labels and labeling submitted by Neurocrine Biosciences, Inc. on 04/26/2019.

- Trade Container Labels
- Professional Sample Container Label
- Prescribing Information (Image not shown)
- Patient Prescribing Information (Image not shown)

F.2 Label and Labeling Images

Container label(s)

Trade

25 mg capsules

(b) (4)



2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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