IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-04

Opicapone (Parkinson disease) –

Addendum to Commission A16-61[1]

Addendum

Commission: A17-04
Version: 1.0
Status: 22 February 2017

[1] Translation of addendum A17-04 *Opicapon (Parkinsonkrankheit) – Addendum zum Auftrag A16-61* (Version 1.0; Status: 22 February 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Opicapone (Parkinson disease) – Addendum to Commission A16-61

Commissioning agency:
Federal Joint Committee

Commission awarded on:
6 February 2017

Internal Commission No.:
A17-04

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum[2]:

- Ulrike Seay
- Moritz Felsch
- Thomas Kaiser
- Petra Kohlepp

Keywords: opicapone, Parkinson disease, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
AE	adverse event
CGIC	Clinician's Global Impression of Change
DDCI	DOPA decarboxylase inhibitor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
MID	minimally important difference
NMSS	Non-Motor Symptoms Scale
PDQ-39	Parkinson’s Disease Questionnaire
PDSS	Parkinson’s Disease Sleep Scale
PGIC	Patient Global Impression of Change
SAE	serious adverse events
SPC	Summary of Product Characteristics
UPDRS	Unified Parkinson’s Disease Rating Scale

1 Background

On 6 February 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-61 (Opicapone – Benefit assessment according to §35a Social Code Book V [1]).

The pharmaceutical company (hereinafter referred to as "the company") had presented the BIPARK I study in its dossier [2]. The study was not used for the assessment of the added benefit in dossier assessment A16-61 because the randomized double-blind phase of the study with a study duration of only 14 to 15 weeks was not long enough to answer the research question of the benefit assessment of opicapone. This had already been established by the G-BA in a previous assessment in the same therapeutic indication [3].

After the oral hearing on opicapone, the G-BA commissioned IQWiG with the assessment of the BIPARK I study.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment of study BIPARK I

In accordance with the commission, the BIPARK I study [4] is assessed in the following sections. In its dossier [2], the company had used the study to determine the added benefit of opicapone in comparison with entacapone, each as adjunctive therapy to levodopa/DOPA decarboxylase inhibitors (DDCI) in adult patients with Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on levodopa/DDCI combinations.

2.1 Study design and study characteristics

Table 1 and Table 2 describe the BIPARK I study.

Table 1: Characteristics of the study included by the company – RCT, direct comparison: opicapone vs. entacapone

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
BIPARK I	RCT, parallel, double-blind	Adults (30–83 years) with idiopathic Parkinson disease (diagnosed for at least 3 years) ▪ disease severity: stages 1–3 on the modified Hoehn and Yahr scale in ON phases[b] ▪ treatment with L-DOPA/DDCI for at least 1 year ▪ end-of-dose deterioration[c]	L-DOPA/DDCI + ▪ opicapone 5 mg (N = 122)[d] ▪ opicapone 25 mg (N = 119)[d] ▪ opicapone 50 mg (N = 116) ▪ placebo (N = 121)[d] ▪ entacapone 200 mg (N = 122)	▪ Screening: 1-2 weeks ▪ Treatment: 14-15 weeks; then possibility to participate in an open-label extension study BIPARK I-OL (treatment with opicapone alone) for 52 weeks ▪ Observation: 14 days after the last visit	106 study centres in 19 countries: Austria, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, France, Germany[e], Hungary, Italy, Latvia, Lithuania, Montenegro[e], Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Spain, Ukraine ▪ Double-blind phase: 3/2011–11/2013 ▪ Extension phase: 7/2011–12/2014	Primary: change from baseline in absolute OFF time at the end of the double-blind phase Secondary: morbidity, health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Exclusion criterion: dyskinesia disability score > 3 in the UPDRS subscale IV A, item 33.
c: At least 4 weeks before screening; average total daily OFF time while awake of at least 1.5 hours, excluding the morning pre-first dose OFF period, despite optimal anti-Parkinson disease therapy; no severe and/or unpredictable OFF periods.
d: The arm is not relevant for the assessment and is not shown in the next tables. The placebo arm is partly presented in the following result tables as additional information.
e: No participation in the open-label extension study.

AE: adverse event; DDCI: DOPA decarboxylase inhibitor; L-DOPA: levodopa; N: number of randomized patients; RCT: randomized controlled trial; UPDRS: Unified Parkinson's Disease Rating Scale; vs.: versus

Table 2: Characteristics of the intervention – RCT, direct comparison: opicapone vs. entacapone

Study	Intervention	Comparison
BIPARK I	Treatment 14–15 weeks: opicapone 50 mg, orally, once daily (in the evening, at least 1 hour after the last dose of L-DOPA/DDCI) + placebo for entacapone, orally with each dose of L-DOPA/DDCI, 3–8 times daily (daily doses)	Treatment 14–15 weeks: entacapone 200 mg, orally with each dose of L-DOPA/DDCI, 3–8 times daily (daily doses) + placebo for opicapone, orally, once daily (in the evening, at least 1 hour after the last dose of L-DOPA/DDCI)
	Pretreatment and concomitant treatment: ▪ L-DOPA/DDCI: ▫ prior treatment for at least 1 year with clear clinical improvement (based on the investigator's judgment) ▫ prior treatment with 3–8 units daily (including extended-release formulations) ▫ stable dose for at least 4 weeks before screening; during the study treatment, the patients were treated with their individual prior dose ▪ Dose adjustment L-DOPA/DDCI: ▫ In the first 2–3 weeks (V2–V4) of the double-blind phase, the investigator could decrease the dose (keeping the number of daily tables unchanged), and could increase the dose again up to the baseline level. Then the dose was not to be changed until the end of the double-blind phase. ▪ Other anti-PD drugs used at a stable dose for at least 4 weeks before screening were allowed and were to be kept at a stable dose during the study treatment. ▪ No new anti-PD drug was to be started. **Prohibited prior and concomitant treatment:** ▪ Tolcapone, neuroleptics, venlafaxine, MAO inhibitors (except selegiline and rasagiline), antiemetics with dopaminergic action, apomorphine, alpha-methyldopa or reserpine were not allowed within the month before screening.	

DDCI: DOPA decarboxylase inhibitor; L-DOPA: levodopa; MAO inhibitor: monoamine oxidase inhibitor; PD: idiopathic Parkinson disease/idiopathic Parkinson syndrome/Parkinson disease; RCT: randomized controlled trial; V: time point of visit; vs.: versus

The BIPARK I study was a randomized, placebo- and active-controlled double-blind approval study of opicapone. It was a multicentre study conducted in European countries. Patients with idiopathic Parkinson disease and motor fluctuations on a stable regimen of levodopa/DDCI, if applicable together with other Parkinson drugs, were included. Their daily OFF time, excluding the morning pre-first dose OFF period, was at least 1.5 hours. In the study, opicapone was compared with entacapone, each as adjunctive therapy to an ongoing treatment with levodopa/DDCI. 116 patients were enrolled in the opicapone arm and 122 patients in the entacapone arm.

The inclusion criteria for the population included in the BIPARK I study corresponded to the therapeutic indication of opicapone in the present research question.

The patients in the opicapone arm and in the entacapone arm were treated in compliance with the Summaries of Product Characteristics (SPCs) [5,6].

The randomized double-blind phase of the studies was 14 to 15 weeks. In a subsequent, optional, open-label extension phase, patients from the double-blind phase could receive opicapone as adjunctive therapy to levodopa/DDCI for 1 year. The extension phase had no control arm. The extension phase was therefore not relevant for the present benefit assessment.

2.2 Patient characteristics

Table 3 shows the characteristics of the study population in the BIPARK I study.

Table 3: Characteristics of the study population – RCT, direct comparison: opicapone vs. entacapone

Study Characteristics Category	Opicapone	Entacapone
BIPARK I	N[a] = 116	N[a] = 122
Age [years], mean (SD)	64 (9)	64 (9)
Sex [F/M], %	40/60	38/62
Ethnicity, n (%)		
Caucasian	115 (100)	122 (100)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	7.0 (3.8)	7.1 (4.1)
Time since start of motor fluctuations [years], mean (SD)	2.2 (2.3)	2.2 (2.1)
Incidence of dyskinesia[b], n (%)	51 (44.3)	51 (42.5)
Hoehn and Yahr stage[c], mean (SD)	2.4 (0.5)	2.3 (0.6)
Time since start of L-DOPA/DDCI treatment [years], mean (SD)	5.3 (3.8)	5.6 (4.1)
L-DOPA dosage (mg/day), mean (SD)	695 (337.5)	645 (329.7)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	9 (7.8)	15 (12.3)

a: Number of randomized patients; 1 patient in the opicapone arm received no study medication after randomization. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: UPDRS question 32 “presence of dyskinesia: yes/no” at visit 2, any patients > 0.
c: During the ON phases.
DDCI: DOPA decarboxylase inhibitor; F: female; L-DOPA: levodopa; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; UPDRS: Unified Parkinson’s Disease Rating Scale; vs.: versus

The demographic and disease-specific patient characteristics were sufficiently comparable between the 2 study arms.

The mean age of the patients was 64 years; most of them were male and all of them where Caucasian. The mean disease duration in both study arms was about 7 years; about half of the patients had dyskinesia. The mean disease severity was about 2.4 on the Hoehn and Yahr scale and about the same in both study arms. Patients in both study arms had received levodopa/DDCI for somewhat over 5 years on average.

Study discontinuations were more frequent in patients in the entacapone arm (12.3%) than in patients in the opicapone arm (7.8%). In both study arms, the most common reasons reported for study discontinuation were withdrawal of consent and side effects.

2.3 Results

Outcomes included

The following patient-relevant outcomes were considered in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - change in OFF time
  - change in ON time
  - symptoms: Unified Parkinson's Disease Rating Scale (UPDRS)
- Health-related quality of life
  - Parkinson's Disease Questionnaire (PDQ-39)
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - specific AEs

Further outcomes investigated in the BIPARK I study and used by the company

In Module 4 A of its dossier, the company presented results on further outcomes. These were the Parkinson's Disease Sleep Scale (PDSS), the Non-Motor Symptoms Scale (NMSS), the Patient Global Impression of Change (PGIC) and the Clinician's Global Impression of Change (CGIC).

The company presented no references for the PDSS instrument; there was no proof of the validity of this instrument.

The company did present a reference [7] for the NMSS, which was not a validation study, however, but a copy of the survey instrument. In addition, disease-specific symptoms in the NMSS are recorded by the investigator. There was no proof for the validity of the NMSS.

The company presented a number of references for the PGIC and the CGIC in its dossier and with its comment [8] to prove the validity of these instruments in the therapeutic indication of Parkinson disease [9-16]. None of these references show the validity of the PGIC or of the CGIC in the therapeutic indication of Parkinson disease. The company stated for the PGIC that this instrument had been used in studies to investigate a minimally important difference (MID) of the UPDRS scale and that the instrument was therefore relevant in the therapeutic indication of Parkinson disease. The use in studies to determine the MID alone is no sufficient argument for the relevance of the PGIC, however. In addition, the investigations presented by the company (e.g. Hauser 2014 [15]) showed no correlation between the UPDRS and the PGIC. The PGIC is presented as additional information irrespective of this.

The CGIC is used to record the investigator's assessment of the patient's health status irrespective of the patient's own assessment. The CGIC is therefore not considered to be patient-relevant.

Risk of bias

The risk of bias at study level and for all outcomes considered in the assessment was considered as low. This concurs with the company's assessment.

For the outcomes "ON time", "UPDRS" and "PDQ-39", missing values were imputed with the last observation carried forward (LOCF) method. The values have to be missing completely at random to use this method. This point was not discussed by the company. Since the LOCF imputation applied to fewer than 15% of the patients and there were no further causes of bias, this had no influence on the risk of bias.

Results

Table 4 and Table 5 summarize the results of the comparison of opicapone with entacapone in patients with idiopathic Parkinson disease and motor fluctuations. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations. Besides the results from the comparison of the opicapone arm with the entacapone arm, the placebo arm is presented to better classify these results. The common AEs are presented in Appendix A. Common SAEs and discontinuations due to AEs are not presented because only few results occurred.

Table 4: Results (mortality, morbidity and side effects) – RCT, direct comparison: opicapone vs. entacapone

Study **Outcome category** **Outcome**	**Opicapone**		**Entacapone**		***Placebo as supplementary information***		**Opicapone vs. entacapone**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	***N***	***Patients with event n (%)***	**RR [95% CI]; p-value**
BIPARK I							
Mortality							
All-cause mortality	115	0 (0)	122	0 (0)	*121*	*0 (0)*	–
Side effects							
AEs (supplementary information)	115	62 (53.9)	122	69 (56.6)	*121*	*60 (49.6)*	–
SAEs	115	4 (3.5)	122	8 (6.6)	*121*	*6 (5.0)*	0.53 [0.16; 1.71]; 0.293[a]
Discontinuation due to AEs	115	5 (4.3)	122	8 (6.6)	*121*	*8 (6.6)*	0.66 [0.22; 1.97]; 0.533[a]
Dyskinesia (PT)	115	18 (15.7)	122	10 (8.2)	*121*	*5 (4.1)*	1.91 [0.92; 3.96]; 0.080[a]
Psychiatric disorders (SOC)	115	18 (15.7)	122	10 (8.2)	*121*	*12 (9.9)*	1.91 [0.92; 3.96][b]; 0.080[a]

(continued)

Table 4: Results (mortality, morbidity and side effects) – RCT, direct comparison: opicapone vs. entacapone (continued)

Study **Outcome category** **Outcome**	**Opicapone**		**Entacapone**		***Placebo*** ***as supplementary information***		**Opicapone vs. entacapone**
	N	**Patients with event n (%)[c]**	**N**	**Patients with event n (%)[d]**	***N***	***Patients with event n (%)***	**RR [95% CI]; p-value**
Outcome additionally presented							
Health status (PGIC)[e]							
(1) Very much improved	*115*	*2 (1.7)*	*120*	*2 (1.7)*	*120*	*2 (1.7)*	
(2) Much improved	*115*	*33 (28.7)*	*120*	*22 (18.3)*	*120*	*21 (17.5)*	
(3) Minimally improved	*115*	*48 (41.7)*	*120*	*39 (32.5)*	*120*	*38 (31.7)*	
(4) No change	*115*	*22 (19.1)*	*120*	*43 (35.8)*	*120*	*43 (35.8)*	
(5) Minimally worse	*115*	*4 (3.5)*	*120*	*5 (4.2)*	*120*	*7 (5.8)*	
(6) Much worse	*115*	*2 (1.7)*	*120*	*6 (5.0)*	*120*	*7 (5.8)*	
(7) Very much worse	*115*	*2 (1.7)*	*120*	*0 (0)*	*120*	*2 (1.7)*	
PGIC improvement (1) to (2)	*115*	*35 (30.4)[f]*	*120*	*24 (20.0)[f]*	*120*	*23 (19.2)[f]*	*1.52 [0.97; 2.39][b]; 0.071[a]*
PGIC improvement (1) to (3)	*115*	*83 (72.2)*	*120*	*63 (52.5)*	*120*	*61 (50.8)*	*1.38 [1.12; 1.69]; 0.002[a]*

a: Institute's calculation, unconditional exact test (CSZ method according to [17]).
b: Institute's calculation of RR and CI (asymptotic).
c: Additionally, there is 1 (0.9%) patient who was not investigated and 1 (0.9%) patient with missing information.
d: Additionally, there are 2 (1.7%) patients who were not investigated and 1 (0.8%) patient with missing information.
e: Last value recorded within the double-blind phase.
f: Institute's calculation.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; PGIC: Patient Global Impression of Change; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 5: Results (morbidity and health-related quality of life) – RCT, direct comparison: opicapone vs. entacapone

Study **Outcome category** **Outcome**	**Opicapone**			**Entacapone**			***Placebo*** ***as supplementary information***			**Opicapone vs. entacapone**
	N[a]	**Values at start of study mean (SD)**	**Change at end of study mean (SE)[b]**	**N[a]**	**Values at start of study mean (SD)**	**Change at end of study mean (SE)[b]**	***N[a]***	***Values at start of study mean (SD)***	***Change at end of study mean (SE)[b]***	**MD [95% CI][b]; p-value**
BIPARK I										
Morbidity										
OFF time [minutes]	111	372.2 (106.95)	−118.1[c] (13.85)	114	387.6 (130.47)	−99.2[c] (13.44)	*117*	*370.1 (106.72)*	*−57.0[c] (13.31)*	−18.9 [−55.9; 18.1]; 0.316
ON time [minutes][d]	115	591.6 (123.28)	119.0 (14.15)	120	574.7 (128.81)	99.7 (13.60)	*120*	*601.3 (120.53)*	*47.1 (13.56)*	19.3 [−17.6; 56.2]; 0.305
UPDRS[d, e]										
Part I: mentation, behaviour and mood	109	1.8 (1.64)	−0.1 (0.11)	111	1.5 (1.75)	−0.3 (0.11)	*114*	*1.8 (1.80)*	*−0.2 (0.11)*	0.2 [−0.1; 0.5]; 0.204
Part II: ADL in ON status	112	8.6 (5.24)	−1.6 (0.30)	118	8.1 (6.23)	−1.5 (0.29)	*118*	*8.2 (5.06)*	*−1.4 (0.28)*	−0.0 [−0.8; 0.7]; 0.937
Part III: motor exam	112	28.4 (13.74)	−4.5 (0.69)	118	25.8 (13.80)	−4.4 (0.67)	*118*	*27.6 (11.68)*	*−3.7 (0.66)*	−0.1 [−1.9; 1.7]; 0.920
Part IV: dyskinesias	112	1.0 (1.54)	0.0 (0.10)	118	1.0 (1.52)	0.1 (0.10)	*118*	*1.0 (1.49)*	*−0.1 (0.10)*	−0.0 [−0.3; 0.2]; 0.912
Sum score: Part I, II (ON) and III	109	38.8 (18.99)	−6.1 (0.94)	111	35.4 (19.98)	−6.1 (0.93)	*114*	*37.6 (16.56)*	*−5.4 (0.90)*	−0.0 [−2.5; 2.5]; 0.998
Health-related quality of life										
PDQ-39[d, e]										
Sum score	113	32.0 (13.81)	−2.8 (0.95)	117	30.5 (13.97)	−4.0 (0.92)	*120*	*34.1 (15.80)*	*−2.6 (0.89)*	1.2 [−1.3; 3.7]; 0.342

(continued)

Table 5: Results (morbidity and health-related quality of life) – RCT, direct comparison: opicapone vs. entacapone (continued)

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: ANCOVA of the FAS population, adjusted by region and baseline value.
c: MMRM analysis of the FAS population, adjusted by region and baseline value of OFF time.
d: Missing values were imputed using LOCF.
e: Negative changes indicate improvement.

ADL: activities of daily living; ANCOVA: analysis of covariance; CI: confidence interval; FAS: full analysis set; LOCF: last observation carried forward; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; PDQ-39: Parkinson's Disease Questionnaire; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; UPDRS: Unified Parkinson's Disease Rating Scale; vs.: versus

Mortality

All-cause mortality

There was no statistically significant difference between opicapone and entacapone for the outcome “all-cause mortality”.

Morbidity

Change in OFF time and change in ON time

No statistically significant difference between opicapone and entacapone was shown for each of the outcomes “change in OFF time” and “change in ON time”.

Symptoms recorded with the UPDRS

No statistically significant difference between opicapone and entacapone was shown for the outcome “symptoms” recorded with the UPDRS, neither in the individual subscales (Part I [mentation, behaviour and mood]; Part II [activities of daily living; ON]; Part III [motor exam]; Part IV [dyskinesias]), nor in the sum score of Part I to III.

Health-related quality of life

PDQ-39

There was no statistically significant difference between opicapone and entacapone for the outcome “PDQ-39”.

Side effects

Serious adverse events and discontinuation due to adverse events

There was no statistically significant difference between opicapone and entacapone for the outcomes “SAEs” and “discontinuation due to AEs”.

Dyskinesias and psychiatric disorders

Dyskinesias and psychiatric disorders occurred more frequently under opicapone, but the difference was not statistically significant (in each case $p = 0.080$).

Results additionally presented

Outcome “PGIC”

More patients reported improvement under opicapone than under entacapone. This was the case in the 2 categories “minimally improved” and “much improved” of the PGIC, but not in the category “very much improved”.

Different responder analyses are commonly used for the PGIC (e.g. summary of the 2 categories “very much improved” and “much improved” or summary of all 3 categories “very much improved”, “much improved” and “minimally improved” [18]). The responder analysis that summarizes the 2 categories “very much improved” and “much improved” showed no statistically significant result ($p = 0.071$). Adding the category “minimally improved”, the result was statistically significant in favour of opicapone ($p = 0.002$).

Interpretation of the results in comparison with placebo

Considering the results from the placebo arm, it is notable that a difference in favour of the active treatment was only shown for the outcomes "change in OFF time" and "change in ON time". This applied both to opicapone and to entacapone. In all other Parkinson-specific outcomes (particularly in the analyses of the UPDRS and of the PDQ-39 presented above), no notable difference in favour of one of the active therapies was shown. In the placebo arm, the changes in the outcome "PGIC" presented as additional information roughly corresponded to the changes in the entacapone arm. On the one hand, this means that the PGIC results were not consistent with the results of the Parkinson-specific scales (UPDRS and PDQ-39) and, on the other hand, that the PGIC results were not consistent with the change in ON or OFF time because both active treatments (opicapone and entacapone) showed a clear advantage over placebo, but a difference in PGIC versus placebo was only present under opicapone. The cause of the PGIC results ultimately remained unclear.

2.4 Subgroups

The following effect modifiers were considered for the assessment:

- age (< 70 years/≥ 70 years)
- sex
- region (Western Europe/Southern Europe/North-Eastern Europe [Russia + Ukraine]/South-Eastern Europe)
- disease stage (Hoehn and Yahr < 2.5/≥ 2.5)

The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Module 4 A of the dossier contained no subgroup analyses for the UPDRS subscales or for the specific AE outcome "psychiatric disorders". The subgroup analyses showed no statistically significant and relevant effects for the remaining outcomes.

2.5 Summary

In the overall consideration, neither positive nor negative effects were shown for the Parkinson-specific outcomes and for side effects of opicapone in comparison with entacapone, each as adjunctive therapy to levodopa/DDCI in adult patients with Parkinson disease and end-of-dose motor fluctuations. The results of the PGIC (presented as additional information) were not consistent with the results of the Parkinson-specific scales (UPDRS and PDQ-39) and the side effects. The cause of the PGIC results ultimately remained unclear.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Opicapon (Parkinsonkrankheit): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-61 [online]. 22.12.2016 [Accessed: 17.02.2017]. (IQWiG-Berichte; Volume 470). URL: https://www.iqwig.de/download/A16-61_Opicapon_Nutzenbewertung-35a-SGB-V.pdf.

2. Bial-Portela. Opicapon (Ongentys): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4A; Parkinson-Krankheit mit motorischen „End-of-Dose“-Fluktuationen, die mit L-DOPA/DDCI-Kombinationen nicht stabilisiert werden können und die für die tiefe Hirnstimulation oder die Anwendung einer Arzneimittelpumpe noch nicht in Frage kommen; medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 28.09.2016 [Accessed: 09.02.2017]. URL: https://www.g-ba.de/downloads/92-975-1694/2016-09-28_Modul4A_Opicapon.pdf.

3. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL); Anlage XII: Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Safinamid [online]. 05.11.2015 [Accessed: 23.11.2016]. URL: https://www.g-ba.de/downloads/40-268-3425/2015-11-05_AM-RL-XII_Safinamid_2015-05-15-D-168_TrG.pdf.

4. *Portela B, Ca SA. Studienbericht: 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. Studienbericht der Studie BIA-91067-301 DB (BIPARK-I): 2014.

5. Bial. Ongentys 50 mg Hartkapseln: Fachinformation [online]. 07.2016 [Accessed: 14.09.2016]. URL: http://www.fachinfo.de.

6. Neuraxpharm. Entacapon-Neuraxpharm 200 mg Filmtabletten. 02.2013.

7. *International PDN-MG. Non-Motor Symptom assessment scale for Parkinson's Disease [online]. [Accessed: 17.02.2016]. URL: http://www.pdnmg.com/imagelib/pdf/nms-scale08.pdf.

8. Bial-Portela. Stellungnahme zum IQWiG-Bericht Nr. 470: Opicapon (Parkinsonkrankheit); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-61. 2017: [Soon available under:https://www.g-ba.de/informationen/nutzenbewertung/260/tab/beschluesse in the document "Zusammenfassende Dokumentation"].

9. *Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976.

10. *Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 2007; 4(7): 28-37.

11. *Sign. Diagnosis and pharmacological management of Parkinson's disease [online]. [Accessed: 01.02.2016]. URL: http://www.sign.ac.uk.

12. *Parkinson Society C. Canadian Guidelines on Parkinson's Disease. Canadian Journal of Neurological Sciences 2012; 39(4): S4.

13. *Pahwa R, Factor SA, Lyons KE, Ondo WG, Gronseth G, Bronte-Stewart H et al. Practice Parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006; 66(7): 983-995.

14. *Parkinson Study G. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. Arch Neurol 2005; 62(2): 241-248.

15. *Hauser RA, Gordon MF, Mizuno Y, Poewe W, Barone P, Schapira AH et al. Minimal clinically important difference in Parkinson's disease as assessed in pivotal trials of pramipexole extended release. Parkinsons Dis 2014; 2014: 1-8.

16. *Hauser RA, Auinger P, Parkinson Study G. Determination of minimal clinically important change in early and advanced Parkinson's disease. Mov Disord 2011; 26(5): 813-818.

17. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

18. European Medicines Agency. Ongentys: European public assessment report [online]. 28.04.2016 [Accessed: 17.02.2017]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002790/WC500209538.pdf.

Citations marked with * are unedited citations provided by the company.

Appendix A – Results on side effects

Table 6: Common AEs (in the SOC and in the PT ≥ 5% in at least one study arm) – RCT, direct comparison: opicapone vs. entacapone

Study	Patients with event n (%)	
SOC[a] **PT[a]**	**Opicapone** **N = 115**	**Entacapone** **N = 122**
BIPARK I		
Overall rate of adverse events	62 (53.9)	69 (56.6)
Cardiac disorders	6 (5.2)	4 (3.3)
Gastrointestinal disorders[b]	19 (16.5)	20 (16.4)
Constipation	7 (6.1)	5 (4.1)
Nausea	3 (2.6)	8 (6.6)
General disorders and administration site conditions	5 (4.3)	7 (5.7)
Infections and infestations	7 (6.1)	11 (9.0)
Investigations	8 (7.0)	10 (8.2)
Musculoskeletal and connective tissue disorders	6 (5.2)	12 (9.8)
Nervous system disorders	27 (23.5)	23 (18.9)
Dyskinesia	18 (15.7)	10 (8.2)
Psychiatric disorders	18 (15.7)	10 (8.2)
Insomnia	7 (6.1)	7 (5.7)
Renal and urinary disorders[c]	4 (3.5)	8 (6.6)
Vascular disorders	4 (3.5)	9 (7.4)

a: MedDRA version 14.0
b: The PT diarrhoea occurred in 1 (0.9%) patient in the opicapone arm and in 3 (2.5%) patients in the entacapone arm.
c: The PT chromaturia occurred in 0 (0%) patients in the opicapone arm and in 3 (2.5%) patients in the entacapone arm.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus