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Safinamide (Addendum to Commission A15-18)[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CI	confidence interval
COMT inhibitor	catechol-O-methyltransferase inhibitor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
UPDRS	Unified Parkinson's Disease Rating Scale

1 Background

On 22 September 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-18 (Safinamide – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In its comment, the pharmaceutical company (hereinafter referred to as "the company") submitted supplementary information, which went beyond the information provided in the dossier, to prove the added benefit. The G-BA therefore commissioned IQWiG to examine whether the indirect comparison presented by the company in the dossier is suitable for the assessment of the added benefit, taking into account the documents submitted in the commenting procedure and the correction of the information on the BIA-91067-301 study.

In its assessment, IQWiG had evaluated the study pool of the indirect comparison of safinamide with entacapone presented by the company as not sufficiently informed because the BIA-91067-301 study had not been included. Based on the available literature, this was a one-year study on the comparison of entacapone versus placebo ([2], status of the data: 6 January 2015, accessed: 22 June 2015). In the meantime, the sponsor of the BIA-91067-301 study corrected in the framework of the commenting procedure that the observation period of this study for the comparison of entacapone versus placebo had been only 14 to 15 weeks, and corrected its information on results of the study in the trial registry ClinicalTrials.gov ([2,3], status of the data: 1 September 2015). Based on the corrected information, the study pool originally presented by the company in its dossier [4] for the indirect comparison of safinamide versus entacapone is considered to be complete.

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.

1.1 Changes in Version 1.1

The present Version 1.1 from 29 October 2015 replaces Version 1.0 of the Addendum from 15 October 2015. Compared with Version 1.0, Version 1.1 contains the following change: In Section 3.2.1, under the subheading "Concomitant medication", the information on the proportion of patients in the safinamide studies who had received entacapone as part of their basic medication was corrected in the running text. In the subsequent section it was supplemented that the analyses on effect modification by concomitant medication only considered entacapone at the start of the study. The result of the assessment was not affected by this change.

2 Documents subsequently submitted by the company and their relevance for the present addendum

The company subsequently submitted the following documents with its written comments [5].

2.1 Analyses under consideration of the BIA-91067-301 study

The company presented analyses under consideration of the presumed one-year data of the BIA-91067-301 study, and calculated an indirect comparison versus the data at the time point 48 weeks of the safinamide study 018.

In the framework of the commenting procedure, the sponsor of the BIA-91067-301 study corrected that the observation period of this study for the comparison of entacapone versus placebo was not one year, but only 14 to 15 weeks. Hence the study is not relevant according to the inclusion criteria of the research question of the dossier assessment (minimum study duration of 24 weeks) and the study pool [4] originally presented by the company in its dossier for the indirect comparison of safinamide versus entacapone is considered to be complete. The analyses presented by the company under consideration of the BIA-91067-301 study are therefore not relevant for the assessment of the indirect comparison in the present addendum.

2.2 Further analyses subsequently submitted

In the meta-analysis of the safinamide studies originally presented in the dossier, the company considered 2 dose arms (50 mg and 100 mg) from the 016/018 study, each in comparison with the placebo arm of the study. This approach was inadequate because the data of the placebo arm were included twice in the analyses, and therefore led to a wrong increase in precision of the results due the bigger sample size.

In the framework of the commenting procedure, the company presented new analyses based on mixed linear models taking into account that the same placebo group was used in both comparisons. Moreover, the company investigated heterogeneity between the different dosages and between the studies. The methods and the results of these analyses are not sufficiently comprehensible from the documents submitted. For the outcome “nausea”, for example, in contrast to its original analyses, the company calculated a significant p-value for the test of heterogeneity in apparently homogeneous data.

The analyses originally presented in the dossier were therefore primarily used for the present benefit assessment. The problem of double consideration of the placebo group in these analyses, which resulted in confidence intervals (CIs) that were too narrow as described above, was addressed as follows. In case of significant results of an indirect comparison, the Institute conducted its own calculations to check the robustness. This applied to the outcomes “nausea” and “diarrhoea”. The relative risks for the studies 016 and SETTLE were calculated on the basis of the raw rates. The placebo group of the 016 study was divided to the 2 dose

arms of the study, i.e. in each case, the treatment effects for the dose arms 50 mg and 100 mg were calculated on the basis of half the patient and event number of the placebo group [6].

3 Benefit assessment

3.1 Research question

The aim of this report was to assess the added benefit of safinamide in comparison with the appropriate comparator therapy (ACT) in adult patients with idiopathic Parkinson disease as add-on therapy to a stable dose of levodopa (alone or in combination with other Parkinson disease medicinal products) in mid-to late-stage fluctuating patients.

The company followed the specification of the G-BA and, from the options mentioned, chose the catechol-O-methyltransferase (COMT) inhibitor entacapone as comparator therapy.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were to be included in the assessment.

3.2 Study pool

The information retrieval is described in the dossier assessment on safinamide [1].

There were no direct comparative studies of safinamide versus entacapone.

Indirect comparison

The company conducted an adjusted indirect comparison according to Bucher [7] of safinamide versus entacapone with placebo as common comparator. After correction of the published information on the BIA-91067-301 study by the sponsor (see Section 1), there are no indications that the study pool of the company was incomplete.

3.2.1 Studies included

The company included a total of 6 studies in its indirect comparison (see Table 1): 2 studies on the safinamide side (016 and SETTLE, approval studies of the company), and 4 studies on the entacapone side (CSG, NSG, PSG and UK-IESG). Data from studies with a duration of 24 weeks were therefore available for the research question.

Table 1: Study pool – RCT, indirect comparison: safinamide vs. entacapone

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Studies with safinamide			
Study 016	Yes	Yes	No
SETTLE	Yes	Yes	No
Studies with entacapone			
CSG	No	No	Yes
NSG	No	No	Yes
PSG	No	No	Yes
UK-IESG	No	No	Yes

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
RCT: randomized controlled trial; vs.: versus

The study characteristics of the studies included as well as the interventions and the patient characteristics are described in the dossier assessment on safinamide [1].

Similarity of the studies included

Studies included in an indirect comparison have to fulfil the assumption of similarity. This means that they should be comparable with regard to possible effect modifiers [8]. This assumption cannot be investigated with statistical methods, but is checked by thoroughly investigating the studies included. The examination of similarity is described in detail in the dossier assessment on safinamide [1]. Due to the limited information in the publications of the entacapone studies, the similarity between the studies could not be fully assessed for all criteria considered. Overall, based on the available information at patient level (age, sex, disease duration, disease severity, and study discontinuation) and at intervention level, there were no differences of a magnitude that would raise fundamental doubts about the comparability.

There was an important difference between the safinamide and the entacapone studies regarding the time point of the conduct of the studies. The safinamide studies were conducted between 2007 and 2012, whereas the entacapone studies are already notably older. There is no detailed information on the corresponding periods of time for all studies, but the publications are from the years 1996 to 2003.

Concomitant medication

In all 6 studies included, safinamide or entacapone were each used in combination with a stable dose of levodopa. Combination with other Parkinson medicinal products was also allowed, and the majority of the patients in all studies included received further Parkinson medicinal products besides levodopa in their basic medication. The most commonly used

drugs in the entacapone studies were dopamine agonists and selegiline. In both safinamide studies, dopamine agonists were by far the most common concomitant medication in addition to levodopa. Moreover, entacapone was also part of the basic medication in the safinamide studies: 47% of the patients in the SETTLE study, and 38% of the patients in the 016 study received concomitant entacapone. Due to the different time periods in which the studies were conducted it is comprehensible that different substances were available for the basic medication.

For the SETTLE study, analyses on a possible effect modification by basic medication were available for the primary outcome "on" time and for the secondary outcome "off" time. No indications of an effect modification by concomitant medication with entacapone were shown (see Appendix A). The analyses on effect modification by the concomitant medication only considered entacapone at the start of the study, however. In the present assessment, entacapone was considered as part of the concomitant medication in the safinamide studies. For the entacapone studies, in contrast, a possible influence of the concomitant medication on the treatment effect was not clear due to the limited information of the study publications.

Risk of bias at study level

Table 2 shows the risk of bias at study level.

Table 2: Risk of bias at study level – RCT, indirect comparison: intervention vs. comparison

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
Studies with safinamide							
Study 016	Yes	Yes	Yes	Yes	Yes	Yes	Low
SETTLE	Yes	Yes	Yes	Yes	Yes	Yes	Low
Studies with entacapone							
CSG	Yes	Yes	Yes	Yes	Yes	Yes	Low
NSG	Unclear	Unclear	Yes	Yes	Yes	Yes	High[a]
PSG	Yes	Unclear	Yes	Yes	Yes	Yes	High[b]
UK-IESG	Yes	Unclear	Yes	Yes	Yes	Yes	High[b]

a: Missing information on the method of randomization and allocation concealment.
b: Missing information on allocation concealment.
RCT: randomized controlled trial; vs.: versus

Deviating from the company's assessment, the risk of bias of the studies PSG and UK-IESG was rated as high because of the unclear allocation concealment.

3.3 Results on added benefit

3.3.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - change in “on” time
  - change in “off” time
  - symptoms: Unified Parkinson’s Disease Rating Scale (UPDRS) Part I (cognitive function, behaviour and mood)
  - symptoms: UPDRS Part II (activities of daily living)
  - symptoms: UPDRS Part III (motor function)
  - symptoms: UPDRS Part I to III
- Health-related quality of life
- Adverse events
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - dyskinesia
  - gastrointestinal disorders
    - nausea (Preferred Term [PT])
    - diarrhoea (PT)
    - vomiting (PT)
    - abdominal pain (PT)
    - constipation (PT)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4). The company included all documented specific AEs in its analyses. Deviating from this, specific AEs were chosen for the present assessment on the basis of frequency and differences between the intervention and control groups under consideration of the patient relevance. Different PTs from the System Organ Class (SOC) “gastrointestinal disorders” were identified. Since there was no comprehensive operationalization of gastrointestinal events, all PTs from the area of gastrointestinal disorders for which documented events were available were considered in the present assessment.

Table 3 shows for which outcomes data were available in the studies included.

Table 3: Matrix of outcomes – RCT, indirect comparison: safinamide vs. entacapone

Study	Outcomes															
	All-cause mortality	Change in "on" time	Change in "off" time	UPDRS Part I[a]	UPDRS Part II[b]	UPDRS Part III[c]	UPDRS Part I–III	Health-related quality of life	SAEs	Discontinuation due to AEs	Dyskinesia	Nausea	Diarrhoea	Vomiting	Abdominal pain	Constipation
Studies with safinamide																
Study 016	●	●[d]	●	●	●	●	●	○[e]	○[e]	●	○[f]	●	●	○[g]	●	●
SETTLE	●	●[d]	●		●	●		○[e]	○[e]	●	○[f]	●	●	○[g]	●	●
Studies with entacapone																
CSG	●	●	●		●	●				●[h]	○[f]	●[h]	●[h]	○[g]	●[h]	●[h]
NSG		●	●	●	●	●	●			●	○[f]	●	●		●	
PSG				●	●	●	●			●	○[f]	●		○[g]		●
UK-IESG	●	●	●	●	●	●	●				○[f]	●	●		●	●

a: Cognitive function, behaviour and mood.
b: Activities of daily living.
c: Motor function.
d: Change in mean total daily "on" time. In the dossier, the outcome was operationalized differently for the safinamide studies than had been originally planned. "On" time without dyskinesia plus "on" time with mild dyskinesia had been planned. In the indirect comparison, the company analysed "on" time without dyskinesia plus "on" time with minor dyskinesia plus "on" time with troublesome dyskinesia. In an "on" phase, the patient presented the functions according to the phase of disease, irrespective of whether or not dyskinesia occurred.
e: Outcome only available in the safinamide studies; it can therefore not be assessed in the indirect comparison.
f: Different operationalizations in the safinamide and entacapone studies; the outcome can therefore not be assessed in the indirect comparison.
g: Outcome not reported in all entacapone studies, possible publication bias. Data on specific AEs were only used when data were available from at least 3 entacapone studies.
h: Data on outcomes regarding harm were only available for the total population. Since the relevant subpopulation (fluctuating patients) represented > 80% of the total population, the results of the total population were used.

AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event; UPDRS: Unified Parkinson's Disease Rating Scale; vs.: versus

● results available; ○ results available, but not evaluable

Data on dyskinesia not evaluable

Dyskinesia is one of the main complications of Parkinson treatment and is therefore an important outcome for the assessment of Parkinson drugs. Different instruments with different quality of validation are available to assess dyskinesia [9]. In the safinamide studies, the company investigated dyskinesia using the Dyskinesia Rating Scale and the UPDRS Part IV.

In the entacapone studies, however, this outcome was not recorded with specific instruments. The company therefore presented analyses on dyskinesia in its dossier that were based on the documentation of AEs, which were recorded with the PT "dyskinesia". These analyses were not evaluable for the present assessment, however, because the data were based on different operationalizations. In the safinamide studies 016 and SETTLE, the proportions of patients with dyskinesia recorded using the Medical Dictionary for Regulatory Activities (MedDRA) PT "dyskinesia" were considered. In the entacapone studies, the data on dyskinesia were based on deviating operationalizations: In the CSG study, the operationalization not only comprised dyskinesia, but also hyperkinesia. In the NSG study, in contrast, deterioration was recorded, and in the UK-IESG study, the increase of dyskinesia. For the PSG study, the publication contained no further details on the operationalization. In the placebo arm of this study, the proportion of patients with dyskinesia (32.4%) was considerably higher than in all other studies, where this proportion was between 1.2% (Study NSG) and 26.0% (Study CSG) on the entacapone side, and between 5.5% (SETTLE) and 12.6% (Study 016) on the safinamide side. Hence the different operationalizations are also reflected in the results. In addition, there was heterogeneity for the outcome "dyskinesia" even between the 2 safinamide studies. It was therefore not possible to include the present analyses on dyskinesia in the indirect comparison, and no relevant analyses were available for this outcome.

It should also be noted that the occurrence of dyskinesia also depends on the levodopa dose used and of the options to adjust this dose during the course of the study. The extent to which this was possible differed between the studies, however. Correspondingly, the levodopa dose in all entacapone studies at the end of the study was above the baseline value. In the safinamide studies, in contrast, the dose had either decreased (Study 016) or had increased only slightly (SETTLE). This impairs the interpretability of the analyses on dyskinesia. It cannot be conclusively assessed in how far the interpretability of other outcomes was impaired.

Data missing on further outcomes

Since there were no results on SAEs and health-related quality of life from the entacapone studies, no conclusions can be drawn on these 2 outcomes.

3.3.2 Risk of bias

Table 4 shows the risk of bias for the relevant outcomes.

Table 4: Risk of bias at study and outcome level – RCT, indirect comparison: intervention versus comparison

Study	Study level	Outcomes															
		All-cause mortality	Change in "on" time	Change in "off" time	UPDRS Part I[a]	UPDRS Part II[b]	UPDRS Part III[c]	UPDRS Part I–III	Health-related quality of life	SAEs	Discontinuation due to AEs	Dyskinesia (AE)	Nausea	Diarrhoea	Vomiting	Abdominal pain	Constipation
Studies with safinamide																	
Study 016	L	L	L	L	H[d]	H[d]	H[d]	H[d]	-[e]	-[e]	L	-[f]	L	L	-[f]	L	L
SETTLE	L	L	L	L	-[g]	L	L	-[g]	-[e]	-[e]	L	-[f]	L	L	-[f]	L	L
Studies with entacapone																	
CSG	L	L	H[d]	H[d]	-[g]	H[d]	H[d]	-[g]	-[e]	-[e]	L	-[f]	L	L	-[f]	L	L
NSG	H[h]	-[g]	H[d,i]	H[d,i]	H[d,i]	H[d,i]	H[d,i]	H[d,i]	-[e]	-[e]	H[i]	-[f]	H[i]	H[i]	-[g]	H[i]	-[g]
PSG	H[j]	-[g]	-[g]	-[g]	H[d,i]	H[d,i]	H[d,i]	H[d,i]	-[e]	-[e]	H[i]	-[f]	H[i]	-[g]	-[f]	-[g]	H[i]
UK-IESG	H[j]	H[i]	H[d,i]	H[d,i]	H[d,i]	H[d,i]	H[d,i]	H[d,i]	-[e]	-[e]	-[g]	-[f]	H[i]	H[i]	-[g]	H[i]	H[i]

a: Cognitive function, behaviour and mood.
b: Activities of daily living.
c: Motor function.
d: No adequate implementation of ITT principle.
e: No evaluable data available for the entacapone studies. Hence the outcome could not be included in the indirect comparison.
f: Data not evaluable.
g: Outcome not recorded/not reported.
h: Missing information on the method of randomization and allocation concealment.
i: High risk of bias at study level.
j: Missing information on allocation concealment.

AE: adverse event; H: high; ITT: intention to treat; L: low; RCT: randomized controlled trial; SAE: serious adverse event; UPDRS: Unified Parkinson's Disease Rating Scale; vs.: versus

Due to the high risk of bias of the studies PSG and UK-IESG at study level, there is also a high risk of bias for the outcomes considered for these studies. In addition, the company rated the risk of bias as high for the outcomes regarding harm in the CSG study because the analyses also comprised non-fluctuating patients. Deviating from this, the risk of bias of the outcomes regarding harm was rated as low in the CSG study because the proportion of relevant patients in the study population was over 80%.

Possible publication bias in the analysis of specific adverse events

The results on specific AEs come from the entacapone side of the tables of the most common AEs. Hence in contrast to the safinamide side, there was no complete presentation of all AEs. This results in potential bias when results on specific AEs are not reported in the corresponding publication because they do not belong to the most common AEs. For instance, there is no information on the AE "vomiting" in the publications of the studies NSG and UK-IESG. The systematic lack of results in the analyses can therefore lead to systematic bias. The data on specific AEs were therefore considered evaluable only when data were available on the entacapone side for at least 3 of 4 studies. For this reason, the data for the AE "vomiting" were not used.

3.3.3 Results

Table 5 and Table 6 contain the results on the comparison of safinamide with placebo and on the comparison of entacapone with placebo as well as the results on the adjusted indirect comparisons of safinamide with entacapone based on these studies. Where necessary, the data from the company's Module 4 were supplemented by the Institute's calculations (see Section 2.2).

Since this was an indirect comparison according to Bucher and no direct comparative study was available, it was not possible to check consistency. Furthermore, there was a high risk of bias for 3 of the 4 studies on the entacapone side. Hence at most hints of added benefit or harm were derived from the available data.

Table 5: Results (mortality and AEs) – RCT, indirect comparison: safinamide vs. entacapone

Outcome category Outcome Comparison Study	Safinamide or entacapone N	Safinamide or entacapone Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Group difference RR [95% CI]; p-value
Mortality					
All-cause mortality					
Studies with safinamide					
Study 016					
Safinamide 50 mg	223	0 (0)	222	1 (0.5)[a, b]	
Safinamide 100 mg	224	5 (2.2)[a]	222	1 (0.5)[a, b]	
SETTLE	274	1 (0.4)	275	2 (0.7)	
Total					
Studies with entacapone					
CSG	165	0 (0)	87	0 (0)	
NSG	85	ND	86	ND	
PSG	103	ND	102	ND	
UK-IESG	115	0 (0)[c]	57	0 (0)	
Total					
Safinamide vs. entacapone	Due to missing events / data on entacapone side not calculable				
Adverse events					
AEs (supplementary information)					
Studies with safinamide					
Study 016					
Safinamide 50 mg	223	147 (65.9)	222	152 (68.5)	
Safinamide 100 mg	224	147 (65.6)	222	152 (68.5)	
SETTLE	274	186 (67.9)	275	190 (69.1)	
Studies with entacapone					
CSG	197[d]	170 (86.3)	104[d]	77 (74.0)	
NSG	85	ND	86	ND	
PSG	103	100 (97.0)	102	97 (95.0)	
UK-IESG	115	105 (91.3)	57	48 (84.2)	
SAEs	There were no evaluable data.				

(continued)

Table 5: Results (mortality and AEs) – RCT, indirect comparison: safinamide vs. entacapone (continued)

Outcome category Outcome Comparison Study	Safinamide or entacapone N	 Patients with event n (%)	Placebo N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
Discontinuation due to AEs					
Studies with safinamide					
Study 016					
Safinamide 50 mg	223	11 (4.9)	222	11 (5.0)	0.92 [0.46; 1.84]; 0.610
Safinamide 100 mg	224	17 (7.6)	222	11 (5.0)	1.53 [0.73; 3.20]; 0.267[f]
SETTLE	274	15 (5.5)	275	11 (4.0)	1.37 [0.64; 2.93][f]; 0.533
Total					1.31 [0.79; 2.17]; 0.299[f,h]
Studies with entacapone					
CSG	197[d]	41 (20.8)	104[d]	10 (9.6)	2.16 [1.13; 4.14]; ND
NSG	85	6 (7.1)	86	5 (5.8)	1.21 [0.39; 3.83]; ND
PSG	103	5 (4.9)	102	5 (4.9)	0.99 [0.30; 3.32]; ND
UK-IESG	115	ND	57	ND	ND
Total					1.68 [1.01; 2.80]; 0.05
Safinamide vs. entacapone[e]					0.78 [0.38; 1.60][f]; 0.494[f]
Dyskinesia	There were no evaluable data.				
Nausea					
Studies with safinamide					
Study 016					
Safinamide 50 mg	223	7 (3.1)	222	6 (2.7)	1.25 [0.51; 3.02]; 0.592
Safinamide 100 mg	224	8 (3.6)	222	6 (2.7)	1.17 [0.48; 2.84]; 0.724
SETTLE	274	16 (5.8)	275	15 (5.5)	1.10 [0.55; 2.21]; 0.840
Total					1.13 [0.65; 1.96]; 0.671[f,i]
Studies with entacapone					
CSG	197[d]	20 (10.2)	104[d]	5 (4.8)	2.11 [0.82; 5.46]; ND
NSG	85	17 (20.0)	86	7 (8.1)	2.46 [1.07; 5.62]; ND
PSG	103	16 (15.5)	102	5 (4.9)	3.17 [1.21; 8.33]; ND
UK-IESG	115	17 (14.8)	57	5 (8.8)	1.69 [0.65; 4.34]; ND
Total					2.30 [1.45; 3.64]; < 0.001
Safinamide vs. entacapone[e]					0.49 [0.24; 1.01][f]; 0.052[f]

(continued)

Table 5: Results (mortality and AEs) – RCT, indirect comparison: safinamide vs. entacapone (continued)

Outcome category Outcome Comparison Study	Safinamide or entacapone N	 Patients with event n (%)	Placebo N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
Diarrhoea					
Studies with safinamide					
Study 016					
Safinamide 50 mg	223	3 (1.3)	222	4 (1.8)	0.85 [0.27; 2.68]; 0.721
Safinamide 100 mg	224	0 (0.0)	222	4 (1.8)	0.31 [0.07; 1.34]; 0.033
SETTLE	274	7 (2.6)	275	7 (2.5)	0.85 [0.27; 2.67]; 0.993
Total					0.77 [0.32; 1.85]; 0.562[f,k]
Studies with entacapone					
CSG	197[d]	16 (8.1)	104[d]	4 (3.8)	2.11 [0.72; 6.15]; ND
NSG	85	17 (20.0)	86	6 (7.0)	2.87 [1.19; 6.92]; ND
PSG	103	ND	102	ND	ND
UK-IESG	115	13 (11.3)	57	2 (3.5)	3.22 [0.75; 13.80]; ND
Total					2.65 [1.43; 4.90]; 0.002
Safinamide vs. entacapone[e]					0.29 [0.10; 0.85][f]; 0.024[f]
Vomiting	There were no evaluable data.				
Abdominal pain					
Studies with safinamide					
Study 016					
Safinamide 50 mg	223	4 (1.8)	222	1 (0.5)	2.16 [0.57; 8.21]; 0.141
Safinamide 100 mg	224	3 (1.3)	222	1 (0.5)	1.59 [0.37; 6.83]; 0.409
SETTLE	274	0 (0.0)	275	6 (2.2)	0.15 [0.02; 1.20]; 0.014
Total		Heterogeneity:		$Tau^2 = 0.89$; $Chi^2 = 4.73$; df = 2; p = 0.09; $I^2 = 58\%$	
Studies with entacapone					
CSG	197[d]	11 (5.6)	104[d]	5 (4.8)	1.16 [0.41; 3.25]; ND
NSG	85	9 (10.6)	86	5 (5.8)	1.82 [0.64; 5.21]; ND
PSG	103	ND	102	ND	ND
UK-IESG	115	6 (5.2)	57	3 (5.3)	0.99 [0.26; 3.82]
Total					1.33 [0.70; 2.53]; 0.39
Safinamide vs. entacapone[e]					
016[g] vs. entacapone					1.41 [0.44; 4.58]; 0.565[f]
SETTLE vs. entacapone					0.11 [0.01; 0.99]; 0.060[f]

(continued)

Table 5: Results (mortality and AEs) – RCT, indirect comparison: safinamide vs. entacapone (continued)

Outcome category Outcome Comparison Study	Safinamide or entacapone N	Safinamide or entacapone Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Group difference RR [95% CI]; p-value
Constipation					
Studies with safinamide					
Study 016					
Safinamide 50 mg	223	7 (3.1)	222	5 (2.3)	1.28 [0.50; 3.24]; 0.536
Safinamide 100 mg	224	7 (3.1)	222	5 (2.3)	1.23 [0.50; 3.03]; 0.558
SETTLE	274	11 (4.0)	275	11 (4.0)	1.01 [0.43; 2.34]; 0.995
Total					1.16 [0.69; 1.93]; 0.58
Studies with entacapone					
CSG	197[d]	11 (5.6)	104[d]	5 (4.8)	1.16 [0.41; 3.25]; ND
NSG	85	ND	86	ND	ND
PSG	103	14 (13.6)	102	5 (4.9)	2.77 [1.04; 7.42]; ND
UK-IESG	115	14 (12.2)	57	1 (1.8)	6.94 [0.94; 51.47]; ND
Total					2.23 [0.95; 5.25]; 0.07
Safinamide vs. entacapone[e]					0.52 [0.19; 1.41]; 0.201[f]

a: Percentages: Institute's calculation.
b: One additional death occurred following premature study discontinuation.
c: One death occurred one month after completion of the study.
d: Data on safety outcomes were only available for the total population. Since the relevant subpopulation (fluctuating patients) represented > 80% of the total population, the results of the total population were used.
e: Adjusted indirect comparison according to Bucher [7].
f: Institute's calculation.
g: Based on pooled estimate (study arms with the dosages 50 mg and 100 mg): RR 1.88 [0.70; 5.03]; p = 0.21 (heterogeneity: p = 0.76).
h: Based on divided placebo group (study arm 50 mg: 5/111; study arm 100 mg: 6/111).
i: Based on divided placebo group (study arm 50 mg: 3/111; study arm 100 mg: 3/111).
k: Based on divided placebo group (study arm 50 mg: 2/111; study arm 100 mg: 2/111).
AE: adverse event; CI: confidence interval; N: number of analysed patients; n: number of patients with (at least one) event; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 6: Results (continuous outcomes) – RCT, indirect comparison: safinamide vs. entacapone

Outcome category Outcome Study	Safinamide or entacapone			Placebo			Group difference
	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	MD [95% CI]; p-value
Morbidity							
"on" time [hours]							
Studies with safinamide							
Study 016							
Safinamide 50 mg	210	10.39 (2.14)	1.38 (2.41)	211	10.27 (2.26)	0.65 (2.43)	0.73 [0.16; 1.30][b,d]; ND
Safinamide 100 mg	214	10.29 (2.34)	1.34 (2.38)	211	10.27 (2.26)	0.65 (2.43)	0.69 [0.13; 1.25][b]; ND
SETTLE	274	10.21 (2.20)	1.60 (2.34)	275	9.91 (2.19)	0.61 (2.33)	0.99 [0.60; 1.38][b]; ND
Total							0.85 [0.57; 1.13][b,c,e]; < 0.001
Studies with entacapone							
CSG	129	10.0 (2.6)	1.7 (2.6)	74	9.7 (2.8)	0.9 (3.3)	0.80 [-0.08; 1.68][b]; ND
NSG	77	9.3 (2.2)	1.4 (2.2)[d]	86	9.2 (2.5)	0.2 (2.6)[d]	1.20 [0.46; 1.94][b]; ND
PSG	ND	ND	ND	ND	ND	ND	ND
UK-IESG	80	9.5 (2.5)	1.3 (2.45)[e]	44	10.1 (2.8)	0.1 (2.85)[e]	1.20 [0.20; 2.20][b]; ND
Total							1.07 [0.58; 1.57][b]; < 0.001[b]
Safinamide vs. entacapone[f]							-0.22 [-0.79; 0.35][b]; 0.448[b]

(continued)

Table 6: Results (continuous outcomes) – RCT, indirect comparison: safinamide vs. entacapone (continued)

Outcome category Outcome Study	Safinamide or entacapone			Placebo			Group difference
	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	MD [95% CI]; p-value
"off" time [hours]							
Studies with safinamide							
Study 016							
Safinamide 50 mg	210	5.10 (1.93)	-1.38 (2.34)	211	5.31 (2.09)	-0.71 (2.35)	-0.67 [-1.22; -0.12][b]; ND
Safinamide 100 mg	214	5.16 (2.14)	-1.39 (2.31)	211	5.31 (2.09)	-0.71 (2.35)	-0.68 [-1.22; -0.14][b]; ND
SETTLE	274	5.34 (1.97)	-1.65 (2.32)	275	5.38 (2.01)	-0.62 (2.32)	-1.03 [-1.42; -0.64][b]; ND
Total							-0.85 [-1.13;-0.58][b,c]; < 0.001[b, c]
Studies with entacapone							
CSG	129	6.2 (2.7)	-1.6 (2.5)	74	6.7 (3.0)	-0.9 (3.4)	-0.70 [-1.59; 0.19][b]; ND
NSG	77	5.5 (2.2)	-1.3 (2.20)	86	5.3 (2.4)	-0.1 (2.45)[d]	-1.20 [-1.91; -0.49][b] ND
PSG	ND	ND	ND	ND	ND	ND	ND
UK-IESG	80	7.0 (2.6)	-1.1 (2.55)	44	6.9 (2.9)	-0.3 (2.85)[e]	-0.80 [-1.81; -0.47][b] ND
Total							-0.96 [-1.44; -0.47][b]; < 0.001[b]
Safinamide vs. entacapone[f]							0.11 [-0.45; 0.67][b]; 0.699[b]

(continued)

Table 6: Results (continuous outcomes) – RCT, indirect comparison: safinamide vs. entacapone (continued)

Outcome category Outcome Study	Safinamide or entacapone			Placebo			Group difference
	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	SMD [95% CI]; p-value
UPDRS Part I[g]							
Studies with safinamide							
Study 016							
Safinamide 50 mg	170	1.97 (1.51)	-0.17 (1.23)	166	2.01 (1.55)	-0.19 (1.23)	0.02 [-0.20; 0.23]; 0.887
Safinamide 100 mg	167	2.04 (1.58)	-0.26 (1.22)	166	2.01 (1.55)	-0.19 (1.23)	-0.06 [-0.27; 0.16]; 0.520
SETTLE	274	ND	ND	275	ND	ND	ND
Total							-0.02 [-0.17; 0.13]; 0.81
Studies with entacapone							
CSG	ND	ND	ND	ND	ND	ND	ND
NSG	77	1.8 (1.4)	0 (1.40)[d]	75	2.0 (1.5)	0.2 (1.61)[d]	-0.13 [-0.43; 0.17]: ND
PSG	90	1.3 (1.2)	-0.2 (1.13)	92	1.5 (1.7)	0 (1.13)	-0.18 [-0.47; 0.11] ND
UK-IESG	80	1.7 (1.9)	0.30 (2.07)[c]	44	1.4 (1.6)	0.10 (1.65)[c]	0.10 [-0.27; 0.47] ND
Total							-0.09 [-0.27; 0.09]; 0.32
Safinamide vs. entacapone[d]							0.07 [-0.16; 0.30]; 0.551[b]

(continued)

Table 6: Results (continuous outcomes) – RCT, indirect comparison: safinamide vs. entacapone (continued)

Outcome category Outcome Study	Safinamide or entacapone			Placebo			Group difference
	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	SMD [95% CI]; p-value
UPDRS Part II[h]							
Studies with safinamide							
Study 016							
Safinamide 50 mg	203	11.77 (5.66)	-1.89 (4.33)	204	12.26 (5.92)	-1.27 (4.37)	-0.14 [-0.34; 0.05]; 0.094
Safinamide 100 mg	208	12.10 (5.82)	-2.27 (4.29)	204	12.26 (5.92)	-1.27 (4.37)	-0.24 [-0.43; -0.04]; 0.006
SETTLE	274	9.97 (5.54)	-1.22 (3.73)	275	10.43 (6.29)	-0.78 (3.74)	-0.12 [-0.28; 0.05]; 0.149
Total							-0.16 [-0.27; -0.05]; 0.003
Studies with entacapone							
CSG	129	ND	-1.1 (4.72)	74	ND	0.2 (4.72)	-0.27 [-0.56; 0.01] ND
NSG	77	11.2 (5.0)	-1.70 (5.21)[d]	75	11.0 (4.5)	-0.40 (4.66)[d]	-0.26 [-0.58; 0.06]: ND
PSG	90	11.9 (6.2)	-1.1 (3.25)	92	11.7 (6.7)	0 (3.25)	-0.34 [-0.63; -0.04]: ND
UK-IESG	80	12.5 (5.7)	-0.50 (5.65)[e]	44	13.7 (6.9)	-1.10 (7.16)[e]	0.10 [-0.27; 0.46]: ND
Total							-0.22 [-0.39; -0.05]; 0.01
Safinamide vs. entacapone[f]							0.06 [-0.14; 0.26]; 0.557[b]

(continued)

Table 6: Results (continuous outcomes) – RCT, indirect comparison: safinamide vs. entacapone (continued)

Outcome category Outcome Study	Safinamide or entacapone			Placebo			Group difference
	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	SMD [95% CI]; p-value
UPDRS Part III[i]							
Studies with safinamide							
Study 016							
Safinamide 50 mg	203	27.27 (12.67)	-6.63 (9.01)	204	28.74 (12.02)	-4.87 (9.07)	-0.20 [-0.39; 0.00]; 0.022
Safinamide 100 mg	208	28.32 (13.30)	-7.25 (8.91)	204	28.74 (12.02)	-4.87 (9.07)	-0.26 [-0.46; -0.07]; 0.002
SETTLE	274	22.26 (11.66)	-3.52 (7.59)	275	23.05 (12.66)	-1.70 (7.63)	-0.24 [-0.41; -0.07]; 0.003
Total							-0.23 [-0.34; -0.13]; < 0.001
Studies with entacapone							
CSG	129	ND	-3.3 (9.03)	74	ND	-0.1 (9.03)	-0.35 [-0.64; -0.07] ND
NSG	77	25.5 (13.1)	-3.0 (13.46)[d]	75	24.6 (12.3)	4.2 (12.50)[b]	-0.55 [-0.88; -0.23] ND
PSG	90	22.0 (11.7)	-2.4 (6.8)	92	22.6 (12.0)	0 (6.8)	-0.35 [-0.64; -0.06] ND
UK-IESG	80	24.3 (12.2)	-4.5 (11.9)[c]	44	23.6 (12.6)	-4.3 (12.6)[c]	-0.02 [-0.38; 0.35] ND
Total							-0.33 [-0.53; -0.14]; < 0.001
Safinamide vs. entacapone[f]							0.10 [-0.11; 0.31]; 0.351[b]

(continued)

Table 6: Results (continuous outcomes) – RCT, indirect comparison: safinamide vs. entacapone (continued)

Outcome category Outcome Study	Safinamide or entacapone			Placebo			Group difference
	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	SMD [95% CI]; p-value
UPDRS Part I-III							
Studies with safinamide							
Study 016							
Safinamide 50 mg	203	40.91 (17.96)	-9.02 (12.46)	204	43.01 (16.79)	-6.82 (12.55)	-0.18 [-0.37; 0.02]; 0.039
Safinamide 100 mg	208	42.46 (18.41)	-10.24 (12.33)	204	43.01 (16.79)	-6.82 (12.55)	-0.28 [-0.47; -0.08]; 0.001
SETTLE	ND	ND	ND	ND	ND	ND	ND
Total							-0.23 [-0.37; -0.09]; 0.001
Studies with entacapone							
CSG	ND	ND	ND	ND	ND	ND	ND
NSG	77	38.5 (16.8)	-4.4 (17.27)	75	37.4 (15.8)	-1.1 (16.21)	-0.20 [-0.51; 0.12] ND
PSG	90	35.1 (15.9)	-0.5 (8.5)	92	35.6 (17.2)	3.05 (8.5)	-0.42 [-0.71; -0.12] ND
UK-IESG	80	38.4 (17.3)	-4.7 (17.15)[c]	57	38.7 (17.9)	-5.5 (19.04)[c]	0.04 [-0.32; 0.41] ND
Total			Heterogeneity:	$Tau^2 = 0.02$; $Chi^2 = 3.72$; df = 2; p = 0.16; $I^2 = 46\%$			
Safinamide vs. entacapone[f]							
016 vs. NSG							-0.03 [-0.38; 0.32]; 0.867[b]
016 vs. PSG							0.19 [-0.14; 0.52] 0.259[b]
016 vs. UK-IESG							-0.27 [-0.67; 0.13] 0.186[b]

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: Institute's calculation.
c: Calculation based on half the placebo group for dose arms in the 016 study.
d: Calculation in the dossier as difference between the average value during treatment (in weeks 8, 16 and 24) and the baseline value. Missing values at the end of the study were imputed with the LOCF.
e: Calculation in the dossier as difference between the average value after 4 and 6 months and the baseline value. Missing values were not imputed (observed cases analysis).
f: Adjusted indirect comparison according to Bucher [7].
g: Subscale on cognitive function, behaviour and mood; negative changes indicate improvement.
h: Subscale on activities of daily living; negative changes indicate improvement.
i: Subscale on motor function; negative changes indicate improvement.
j: UPDRS total score of Parts I to III; negative changes indicate improvement.

CI: confidence interval; ITT: intention to treat; LOCF: last observation carried forward; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference in the form of Hedges' g; UPDRS: Unified Parkinson's Disease Rating Scale; vs.: versus

Mortality

All-cause mortality

No deaths occurred on the entacapone side in the 2 studies CSG and UK-IESG; the publications of the 2 other studies, NSG and PSG, did not provide any information on deaths. It was therefore not possible to calculate an overall estimator on all-cause mortality for the indirect comparison of safinamide versus entacapone. Hence there was no hint of an added benefit or greater harm of safinamide in comparison with entacapone. An added benefit or greater harm for this outcome is therefore not proven.

This concurs with the company's assessment in Module 4 of the dossier, which stated that the indirect comparison of safinamide versus entacapone could not be conducted for this outcome.

Morbidity

"on" time and "off" time

The indirect comparison showed no statistically significant differences between the treatment groups for the outcomes "on" time and "off" time. Hence there was no hint of an added benefit of safinamide in comparison with entacapone. An added benefit for this outcome is therefore not proven.

This concurs with the assessment of the company in Module 4 of the dossier.

It should also be noted that the change in "on" time based on the patients' diary entries in the safinamide studies was originally recorded under concomitant consideration of dyskinesia and therefore as "on" phases without dyskinesia, with non-troublesome dyskinesia or with troublesome dyskinesia. This kind of differentiating information was not available for the entacapone studies, however, so that any "on" phases, regardless of concomitant dyskinesia, were included in the present analyses.

UPDRS: Part I (cognitive function, behaviour and mood), Part II (activities of daily living), Part III (motor function)

The indirect comparison showed no statistically significant differences between the treatment groups for the 3 parts of the UPDRS. Hence there was no hint of an added benefit of safinamide in comparison with entacapone. An added benefit for these outcomes is therefore not proven.

This concurs with the assessment of the company in Module 4 of the dossier.

UPDRS: Part I to III

On the entacapone side, heterogeneity between the studies was shown for the total score of Parts I to III. The entacapone studies were therefore investigated individually in comparison with safinamide. None of the 3 analyses showed significant differences between the treatment

groups. Hence there was no hint of an added benefit of safinamide in comparison with entacapone. An added benefit for this outcome is therefore not proven.

This concurs with the assessment of the company in Module 4 of the dossier.

Possible negative effects of safinamide in the morbidity outcomes

No significant difference between the treatment groups was shown for any of the morbidity outcomes, and an added benefit is not proven. For the outcome "on" time, there was a statistically non-significant mean difference of -0.22 hours (-13 minutes) with a 95% CI of an "on" time between 47 minutes shorter and 21 minutes longer under safinamide versus entacapone. The longer "on" time was reflected in a correspondingly shorter "off" time. In addition, the data were difficult to interpret because due to the missing information for the entacapone studies it was unclear in how far the increase in "on" time was accompanied by troublesome dyskinesia.

The data on the UPDRS outcomes were also difficult to interpret. The effects of safinamide and entacapone versus placebo were rated as not relevant in the standardized mean difference using Hedges' g. In the indirect comparison of safinamide and entacapone, relatively large CIs in the standardized mean differences were shown for the UPDRS subscores I-III, and the relevance threshold of 0.2 was exceeded. Furthermore, the effect estimates showed a rather unfavourable effect of safinamide versus entacapone.

Overall, a relevant negative effect of safinamide versus entacapone cannot be excluded with certainty, with rather small effects of both substances for the morbidity outcomes recorded using the UPDRS at the same time.

Health-related quality of life

No data evaluable for an indirect comparison were available on health-related quality of life. Hence there was no hint of an added benefit of safinamide in comparison with entacapone. An added benefit for this outcome is therefore not proven.

This concurs with the assessment of the company in Module 4 of the dossier.

Adverse events

Serious adverse events

No data evaluable for an indirect comparison were available on SAEs. Hence there was no hint of an added benefit of safinamide in comparison with entacapone. An added benefit for this outcome is therefore not proven.

This concurs with the assessment of the company in Module 4 of the dossier.

Discontinuation due to AEs

The indirect comparison showed no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". Hence there was no hint of an added benefit of safinamide in comparison with entacapone. An added benefit for this outcome is therefore not proven.

This concurs with the assessment of the company in Module 4 of the dossier.

Nausea

The indirect comparison initially showed a significant advantage of safinamide versus entacapone in the company's calculation for the outcome "nausea". Its upper limit of the CI was close to 1 in the area of an only marginal effect, however (RR: 0.50 CI [0.26; 0.97]). As described in Section 2.2, the calculation methods used by the company in the indirect comparison led to narrower CIs because the placebo arm was considered twice. The Institute therefore conducted its own calculations to check the robustness by dividing the placebo group between the 2 arms of the 016 study. These showed no significant difference between the treatment arms in the indirect comparison. The new calculations submitted by the company in the comment also showed no statistically significant effect. Hence there was no hint of an added benefit of safinamide in comparison with entacapone. An added benefit for this outcome is therefore not proven.

This deviates from the assessment of the company in Module 4 of the dossier, which derived an indication of lesser harm of safinamide in comparison with entacapone on the basis of its calculations. In its comment, however, the company derived no added benefit of safinamide for the outcome "nausea" on the basis of the 24-week data.

Diarrhoea

A significant difference in favour of safinamide was found for the outcome "diarrhoea" both on the basis of the company's analyses and on the Institute's calculations. This results in a hint of lesser harm from safinamide than from entacapone.

This deviates from the assessment of the company in Module 4 of the dossier, which derived an indication of lesser harm.

Vomiting

No evaluable data were available for the outcome "vomiting" because this outcome was only reported in 2 of 4 entacapone studies (see Section 3.3.2). Hence there was no hint of an added benefit of safinamide in comparison with entacapone. An added benefit for this outcome is therefore not proven.

This concurs with the assessment of the company in Module 4 of the dossier, which also derived no added benefit of safinamide in comparison with entacapone for the outcome "vomiting" on the basis of the available data.

Abdominal pain

On the safinamide side, heterogeneity was shown between the studies for the outcome "abdominal pain". The safinamide studies were therefore investigated individually in comparison with entacapone, and there was no clear direction of result. Hence there was no hint of an added benefit of safinamide in comparison with entacapone. An added benefit for this outcome is therefore not proven.

This deviates from the assessment of the company in Module 4 of the dossier, which derived a hint of lesser harm of safinamide in comparison with entacapone on the basis of the indirect comparison of the safinamide study SETTLE versus entacapone.

Constipation

The indirect comparison showed no statistically significant difference between the treatment groups for the outcome "constipation". Hence there was no hint of an added benefit of safinamide in comparison with entacapone. An added benefit for this outcome is therefore not proven.

This concurs with the assessment of the company in Module 4 of the dossier.

3.3.4 Subgroups and effect modifiers

No subgroup analyses were considered for the present benefit assessment of safinamide because of missing information in the entacapone studies. This corresponds to the company's approach in Module 4 of the dossier.

3.4 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [10].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

3.4.1 Assessment of added benefit at outcome level

The data presented in Section 3.3.3 resulted in a hint of a lesser harm. The extent of the respective added benefit at outcome level was estimated from these results (see Table 7).

Table 7: Extent of added benefit at outcome level: safinamide vs. entacapone

Outcome category **Outcome**	**Safinamide vs. entacapone** **Effect estimate [95% CI][a]** **Probability[b];** **p-value**	**Derivation of extent[c]**
Mortality		
All-cause mortality	RR: NC	Added benefit not proven
Morbidity		
"on" time [hours]	MD: -0.22 [-0.79; 0.35]; 0.448	Added benefit not proven
"off" time [hours]	MD: 0.11 [-0.45; 0.67]; 0.699	Added benefit not proven
UPDRS Part I[d]	SMD: 0.07 [-0.16; 0.30]; 0.551	Added benefit not proven
UPDRS Part II[e]	SMD: 0.06 [-0.14; 0.26]; 0.557	Added benefit not proven
UPDRS Part III[f]	SMD: 0.10 [-0.11; 0.31]; 0.351	Added benefit not proven
UPDRS Part I-III	Heterogeneous results[g] No clear direction of result	Added benefit not proven
Health-related quality of life		
	There were no evaluable data	
Adverse events		
Serious adverse events	There were no evaluable data	
Discontinuation due to AEs	RR: 0.78 [0.38; 1.60]; 0.494	Greater/lesser harm not proven
Dyskinesia	There were no evaluable data	
Nausea	RR: 0.49 [0.24; 1.01]; 0.052	Greater/lesser harm not proven
Diarrhoea	RR: 0.29 [0.10; 0.85]; 0.024 probability: "hint"	Outcome category: non-serious/non-severe AEs $0.80 \leq CI_u < 0.90$ lesser harm, extent: "minor"
Vomiting	There were no evaluable data	
Abdominal pain	Heterogeneous results[h] no clear direction of result	Greater/lesser harm not proven
Constipation	RR: 0.52 [0.19; 1.41]; 0.201	Greater/lesser harm not proven

a: Indirect comparison according to Bucher [7].
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: Subscale on cognitive function, behaviour and mood.
e: Subscale on activities of daily living
f: Subscale on motor function.
g: No common effect estimate can be provided due to heterogeneous data.

AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; NC: not calculable; RR: relative risk; SAE; serious adverse event; SMD: standardized mean difference in the form of Hedges' g; UPDRS: Unified Parkinson's Disease Rating Scale; vs.: versus

3.4.2 Overall conclusion on added benefit

Table 8 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 8: Positive and negative effects from the assessment of safinamide in comparison with entacapone

Positive effects	**Negative effects**
Hint of lesser harm – extent: "minor" (non-serious/non-severe adverse events: diarrhoea)	–
With regard to the morbidity outcomes, a relevant negative effect of safinamide versus entacapone cannot be excluded with certainty. Evaluable data on the important outcomes "dyskinesia" and "health-related quality of life" are missing.	

Overall, one positive effect in the outcome category "non-serious/non-severe AEs" initially remains for diarrhoea with a hint of lesser harm (extent: minor). On the other hand, a relevant negative effect of safinamide versus entacapone for the morbidity outcomes cannot be excluded with certainty because of the direction of the effect and the size of the confidence interval. In addition, evaluable results on the outcomes "dyskinesia" and "health-related quality of life" are missing. Ultimately, balancing of benefit and harm is therefore not possible.

Hence in the overall consideration, there is no proof of an added benefit of safinamide in comparison with entacapone.

The result of the assessment of the added benefit of safinamide in comparison with the ACT is summarized in Table 9.

Table 9: Safinamide – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
Treatment of adult patients with idiopathic Parkinson disease as add-on therapy to a stable dose of levodopa (alone or in combination with other Parkinson disease medicinal products) in mid-to late-stage fluctuating patients	Add-on therapy with: ▪ a non-ergot dopamine agonist or ▪ **a COMT inhibitor**[b] or ▪ a MAO-B inhibitor	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: The company chose the COMT inhibitor entacapone as comparator therapy. ACT: appropriate comparator therapy; COMT: catechol-O-methyltransferase inhibitor; G-BA: Federal Joint Committee; MAO-B: monoamine oxidase B		

This deviates from the company's assessment, which derived an indication of a considerable added benefit of safinamide versus the ACT.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

3.5 List of included studies

016

Additional SAS-analyses for studies 016, 018 and SETTLE [unpublished]. 2015.

Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D et al. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. Mov Disord 2014; 29(2): 229-237.

Newron. Efficacy and safety of safinamide (50 and 100mg/Day) versus placebo, in patients with mid-late stage Parkinson's disease: full text view [online]. In: ClinicalTrials.gov. 23 August 2010 [accessed: 18 March 2015]. URL: https://clinicaltrials.gov/show/NCT01187966.

Newron Pharmaceuticals. A phase III, double-blind, placebo-controlled study to determine the efficacy and safety of a low (50 mg/day) and high (100 mg/day) dose of safinamide, as add-on therapy, in patients with idiopathic parkinson's disease with motor fluctuations, treated with a stable dose of levodopa and who may be receiving concomitant treatment with stable doses of a dopamine agonist and/or an anticholinergic [online]. In: EU Clinical Trials Register. [Accessed: 18 March 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-005860-14.

Newron Pharmaceuticals. A phase 3, double-blind, placebo-controlled study to determine the efficacy and safety of a low (50 mg/day) and high (100 mg/day) dose of safinamide, as add-on therapy, in patients with idiopathic Parkinson's disease with motor fluctuations, treated with a stable dose of levodopa and who may be receiving concomitant treatment with stable doses of a dopamine agonist, and/or an anticholinergic: study 016; clinical study report [unpublished]. 2012.

SETTLE

Additional SAS-analyses for studies 016, 018 and SETTLE [unpublished]. 2015.

Newron. Safinamide in idiopathic Parkinson's disease (IPD) with motor fluctuations, as add-on to levodopa (SETTLE): full text view [online]. In: ClinicalTrials.gov. 27 March 2013 [accessed: 18 March 2015]. URL: https://clinicaltrials.gov/show/NCT00627640.

Newron Pharmaceuticals. A phase III, double-blind, placebo-controlled, randomised trial to determine the efficacy and safety of a dose range of 50 to 100 mg/day of safinamide, as add-on therapy, in subjects with idiopathic Parkinson's Disease with motor fluctuations, treated with a stable dose of levodopa and who may be receiving concomitant treatment with stable doses of a dopamine agonist, an anticholinergic and/or amantadine [online]. In: EU Clinical Trials Register. [Accessed: 18 March 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-002964-90.

Newron Pharmaceuticals. A phase III, double-blind, placebo-controlled, randomized trial to determine the efficacy and safety of a dose range of 50 to 100 mg/day of safinamide, as add-on therapy, in subjects with idiopathic Parkinson's disease with motor fluctuations, treated with a stable dose of levodopa and who may be receiving concomitant treatment with stable doses of a dopamine agonist, an anticholinergic and/or amantadine: study SETTLE; clinical study report [unpublished]. 2013.

CSG

Poewe WH, Deuschl G, Gordin A, Kultalahti ER, Leinonen M. Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen study). Acta Neurol Scand 2002; 105(4): 245-255.

NSG

Rinne UK, Larsen JP, Siden A, Worm-Petersen J. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Neurology 1998; 51(5): 1309-1314.

PSG

Parkinson Study Group. Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. Ann Neurol 1997; 42(5): 747-755.

UK-IESG

Brooks DJ, Sagar H. Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomised, placebo controlled, double blind, six month study. J Neurol Neurosurg Psychiatry 2003; 74(8): 1071-1079.

4 References

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Appendix A – Results on the influence of the concomitant medication in the SETTLE study

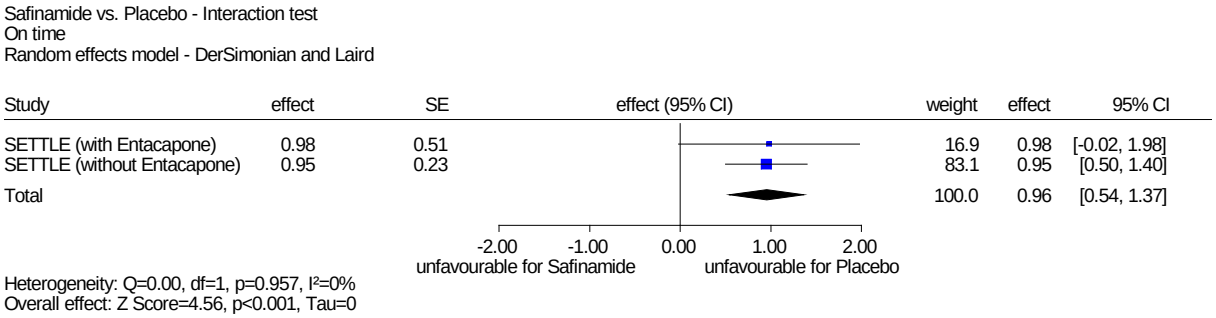

Figure 1: Analysis of a possible effect modification by concomitant treatment (entacapone at the start of the study) for the outcome "on" time in the SETTLE study

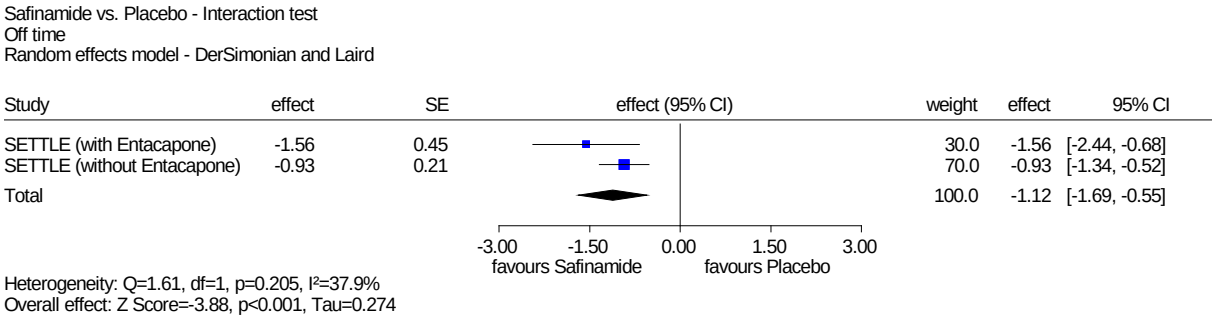

Figure 2: Analysis of a possible effect modification by concomitant treatment (entacapone at the start of the study) for the outcome "off" time in the SETTLE study