IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. 168

Addendum to Commission A13-05 (fidaxomicin)[1]

Addendum

Commission: A13-23
Version: 1.1
Status: 25 June 2013

[1] Translation of the document "Addendum zum Auftrag A13-05 (Fidaxomicin)" (Version 1.1; Status: 25 June 2013). 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:
Addendum to Commission A13-05 (fidaxomicin)

Contracting agency:
Federal Joint Committee

Commission awarded on:
28 May 2013

Internal Commission No.:
A13-23

Address of publisher:
Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum:[2]

- Volker Vervölgyi
- Lars Beckmann
- Thomas Kaiser

Keywords: fidaxomicin, Clostridium difficile, 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 figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AM NutzenV	*Arzneimittel-Nutzenbewertungsverordnung* (Regulation for Early Benefit Assessment of New Pharmaceuticals)
CDI	*Clostridium difficile* infection
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
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
Peto OR	Peto Odds Ratio
RCT	randomized controlled trial
SAE	serious adverse event
vs.	versus

1 Background

On 28 May 2013 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A13-05 (benefit assessment of fidaxomicin [1]).

In the commenting procedure on the assessment of fidaxomicin, on 6 May 2013 the pharmaceutical company (hereinafter abbreviated to "the company") submitted further data to the G-BA going beyond the information in the dossier. These refer to data from Studies 101.1.C.003 and 101.1.C.004 (in each case comparison of fidaxomicin versus vancomycin). Both studies were already included in the company's dossier. The data subsequently provided in particular comprise analyses of the patient-relevant outcomes considered in the Assessment 13-05 for the relevant subpopulations of patients with severe or recurrent course of disease of *Clostridium difficile* infection (CDI) from the relevant Studies 101.1.C.003 and 101.1.C.004.

The GBA's commission for the assessment of the analyses submitted subsequently for Studies 101.1.C.003 und 101.1.C.004 reads as follows:

"In this context the data should be assessed with regard to the question as to whether an added benefit of fidaxomicin versus vancomycin for the subpopulations with severe or recurrent course of disease is proven by means of the data and corresponding analyses subsequently submitted by the company."

In the following Chapter 2, the additional results for Studies 101.1.C.003 and 101.1.C.004 are presented and analysed in compliance with the commission.

The responsibility for the present assessment and the result of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The decision on added benefit is made by the G-BA.

1.1 Changes in Version 1.1

The present Version 1.1 of 25 June 2013 replaces Version 1.0 of the addendum of 12 June 2013. The following changes are contained in Version 1.1 compared with Version 1.0:

- In some places in the addendum the combined patient populations were denoted as "severe or recurrent", even though "severe and/or recurrent" was meant. This was corrected accordingly on pages 7, 11, 12 and 13 and in Figures 3, 6, 9 and 13.
- In Table 4 on page 6, for the outcome "global cure", the footnote "f" had been assigned to the p-value, even though "e" was meant. This has been changed accordingly.

The result of the assessment was not affected by these changes.

2 Assessment

In its comment on IQWiG's dossier assessment, firstly, the company submitted the data that were missing in the dossier [2] on the characteristics of the relevant subpopulations of patients with severe and/or recurrent CDI, and secondly submitted the results on the outcomes relevant to the assessment for these subpopulations.

The characteristics of the relevant subpopulations are presented in Section 2.1. The risk-of-bias assessment for the relevant outcomes and the results on the relevant outcomes are presented in Section 2.2. Tables that remain unchanged compared with Assessment A13-05 are not presented again.

The derivation of the extent and probability of the added benefit of fidaxomicin compared with the appropriate comparator therapy (ACT), on the basis of data presented by the company in the dossier and in the comment, are shown in Section 2.3.

The assessment is based solely on the results of the relevant subpopulation of patients with severe or recurrent CDI. For this purpose, in the following text the results in each case are presented for the subpopulations of patients with severe CDI, patients with recurrent CDI, and the results of the combined population of patients with severe and/or recurrent CDI. If no signs can be inferred from the results that the effects in patients with severe CDI differ from those with recurrent CDI, the assessment is essentially made for the combined population of patients with severe and/or recurrent CDI.

In contrast to Assessment A13-05, the results of the total populations of Studies 101.1.C.003 and 101.1.C.004 are not presented. On the one hand, with the data subsequently provided in the comment, results are available for all outcomes relevant to the assessment for the relevant subpopulation, so that a comprehensive assessment can be conducted on the basis of these results. On the other hand, the data subsequently submitted show that the results of the total population are not applicable to the relevant subpopulation. As can be inferred from the company's comment [3], for the outcome "global cure" the data provided an indication that the effect sizes differed between the subpopulations of patients with severe and/or recurrent CDI and in patients with non-severe and non-recurrent CDI (p-value of the interaction test: 0.18).

2.1 Characteristics of study population

Table 1 shows the information on the characteristics of the relevant subpopulations of patients with severe CDI, patients with recurrent CDI, and the combined population of patients with severe and/or recurrent CDI from Studies 101.1.C.003 and 101.1.C.004.

Table 1: Characteristics of the relevant subpopulations – RCT, direct comparison: fidaxomicin versus vancomycin

Study Group	N[a]	Age [years] mean (SD)	Sex [f/m] %	Severity severe / non-severe[b] %	Recurrence recurrent /non-recurrent [c] %	Treatment setting outpatient / inpatient %	Study discon-tinuations n (%)
101.1.C.003							
Patients with severe CDI							
Fidaxomicin	112	60 (17)	62.5 / 37.5	100 / 0	14.3 / 85.7	36.6 / 63.4	15 (13.2)[d]
Vancomycin	123	62 (17)	64.2 / 35.8	100 / 0	18.7 / 81.3	37.4 / 62.6	14 (11.0)[d]
Patients with recurrent CDI							
Fidaxomicin	48	59 (18)	52.1 / 47.9	33.3 / 66.7	100 / 0	54.2 / 45.8	6 (12.0)[d]
Vancomycin	54	66 (17)	63.0 / 37.0	42.6 / 57.4	100 / 0	44.4 / 55.6	10 (17.8)[d]
Patients with severe and/or recurrent CDI							
Fidaxomicin	144	60 (17)	60.4 / 39.6	77.8 / 22.2	33.3 / 66.7	41.0 / 59.0	18 (12.2)[d]
Vancomycin	154	64 (17)	60.4 / 39.6	80.0 / 20.0	35.1 / 64.9	38.3 / 61.7	23 (14.4)[d]
101.1.C.004							
Patients with severe CDI							
Fidaxomicin	88	65 (17)	59.1 / 40.9	100 / 0	12.5 / 87.5	28.4 / 71.6	23 (25.8)[d]
Vancomycin	90	60 (20)	63.3 / 36.7	100 / 0	12.2 / 87.8	28.9 / 71.1	20 (21.9)[d]
Patients with recurrent CDI							
Fidaxomicin	40	65 (18)	57.5 / 42.5	27.5 / 72.5	100 / 0	25.0 / 75.0	3 (6.9)[d]
Vancomycin	36	64 (21)	50.0 / 50.0	30.6 / 69.4	100 / 0	36.1 / 63.9	7 (18.9)[d]
Patients with severe and/or recurrent CDI							
Fidaxomicin	117	65 (18)	59.0 / 41.0	75.2 / 24.8	34.2 / 65.8	28.2 / 71.8	26 (21.4)[d]
Vancomycin	115	60 (20)	60.9 / 39.1	78.3 / 21.7	31.3 / 68.7	29.6 / 70.4	25 (21.3)[d]

a: Number of patients in the modified intention-to-treat population
b: Classification of severity planned a prior, see Section 2.3.2 of Assessment A13-05 [1]
c: Exactly one previous CDI episode in the last 3 months before study entry
d: Calculated as sum of study discontinuations during treatment or follow-up phase. The percentages are based on the number of randomized patients.
CDI: *Clostridium difficile* infection; f: female; m: male; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation.

On average, patients were aged 59 to 65 years; the proportion of women (approx. 60%) was consistently higher in both studies and both subpopulations than that of men. The sex ratio was only balanced in the vancomycin group in Study 101.1.C.004 and in the fidaxomicin group in Study 101.1.C.004, in each case in the subpopulation of patients with recurrent CDI. With regard to severity and recurrence, in both studies a certain overlapping was notable in both subpopulations of the patients with severe or recurrent CDI. In both studies only about a third of the patients with recurrent CDI at the same time experienced a severe course of

disease. The larger proportion of patients in both studies was treated in hospital. This proportion was overall slightly lower in Study 101.1.C.003 than in Study 101.1.C.004.

2.2 Results of the benefit assessment

Table 2 shows for which patient-relevant outcomes data from the studies included were available for this benefit assessment. The reasons for the selection of outcomes are provided in Assessment A13-05 [1].

Table 2: Matrix of outcomes – RCT, direct comparison: fidaxomicin versus vancomycin

Study	Outcomes					
	All-cause mortality	Global cure	Health-related quality of life	Adverse events	Serious adverse events	Discontinuation due to adverse events
101.1.C.003	yes	yes	–[a]	yes	yes	yes
101.1.C.004	yes	yes	–[a]	yes	yes	yes
a: Outcome not recorded RCT: randomized controlled trial						

Table 3 shows the risk of bias at study level (for reasons see Dossier Assessment A13-05 [1]), as well as the risk of bias of the results for the outcomes relevant to the assessment in the relevant subpopulations.

Table 3: Risk of bias at study and outcome level – RCT, direct comparison: fidaxomicin versus vancomycin

Study	Study level	Outcomes					
		All-cause mortality	Global cure	Health-related quality of life	Adverse events	Serious adverse events	Discontinuation due to adverse events
101.1.C.003							
Patients with severe[a] CDI	low	low	low	–[b]	low	low	low
Patients with recurrent[c] CDI	low	low	low	–[b]	low	low	low
Patients with severe[a] and/or recurrent[c] CDI	low	low	low	–[b]	low	low	low
101.1.C.004							
Patients with severe[a] CDI	low	low	low	–[b]	low	low	low
Patients with recurrent[c] CDI	low	low	low	–[b]	low	low	low
Patients with severe[a] and/or recurrent[c] CDI	low	low	low	–[b]	low	low	low

a: Classification of severity planned a priori; see Section 2.3.2 of Assessment A13-05 [1]
b: Outcome not recorded
c: Exactly one previous CDI episode in the last 3 months before study entry
CDI: *Clostridium difficile* infection; RCT: randomized controlled trial

For all relevant subpopulations the risk of bias was rated as low for the outcomes of all-cause mortality, global cure and outcomes for the group of adverse events.

Table 4 summarizes the results on mortality and morbidity for fidaxomicin versus vancomycin for the relevant subpopulations of patients with severe CDI, patients with recurrent CDI, as well as for the combined population of patients with severe/and recurrent CDI. The data from the company's comment were, where necessary, supplemented by the Institute's calculations. Meta-analyses calculated by the Institute are presented in Appendix A.

Table 4: Results (mortality and morbidity) – RCT, direct comparison: fidaxomicin versus vancomycin

Outcome category Outcome Study	Fidaxomicin		Vancomycin		Fidaxomicin vs. vancomycin	
	N[a]	Patients with events n (%)	N[a]	Patients with events n (%)	RR [95% CI]	P-value
Mortality						
All-cause mortality						
Patients with severe[b] CDI						
101.1.C.003	113	7 (6.2)	127	7 (5.5)	1.12 [0.41; 3.11]	
101.1.C.004	89	9 (10.1)	90	8 (8.9)	1.14 [0.46; 2.82]	
Total					1.13 [0.58; 2.23][c]	0.720[c]
Patients with recurrent[d] CDI						
101.1.C.003	50	2 (4.0)	55	6 (10.9)	0.37 [0.08; 1.73]	
101.1.C.004	43	1 (2.3)	37	3 (8.1)	0.29 [0.03; 2.64]	
Total					0.34 [0.09; 1.21][c]	0.095[c]
Patients with severe[b] and/or recurrent[d] CDI						
101.1.C.003	147	9 (6.1)	158	11 (7.0)	0.88 [0.38; 2.06]	
101.1.C.004	121	10 (8.3)	116	9 (7.8)	1.07 [0.45; 2.53]	
Total					0.97 [0.53; 1.77][c]	0.912[c]
Morbidity						
Global cure						
Patients with severe[b] CDI						
101.1.C.003	112	80 (71.4)	123	80 (65.0)	0.82 [0.56; 1.19][e]	
101.1.C.004	90	64 (71.1)	88	52 (59.1)	0.71 [0.47; 1.06][e]	
Total					0.76 [0.58; 1.01][c,e]	0.058[c,e]
Patients with recurrent[d] CDI						
101.1.C.003	48	33 (68.8)	54	33 (61.1)	0.80 [0.47; 1.37][e]	
101.1.C.004	40	30 (75.0)	36	21 (58.3)	0.60 [0.31; 1.16][e]	
Total					0.72 [0.47; 1.09][c,e]	0.115[c,e]
Patients with severe[b] and/or recurrent[d] CDI						
101.1.C.003	144	103 (71.5)	154	98 (63.6)	0.79 [0.56; 1.09][e]	
101.1.C.004	117	82 (70.1)	115	68 (59.1)	0.73 [0.51; 1.04][e]	
Total					0.76 [0.60; 0.97][c,e]	0.025[c,e]

a: Patients in analysis
b: Classification of severity planned a priori; see Section 2.3.2 of Assessment A13-05 [1]
c: Calculated from meta-analysis with random effects
d: Exactly one previous CDI episode in the last 3 months before study entry
e: Values for patients without events

CDI: *Clostridium difficile* infection; CI: confidence interval; N: number of analysed patients; n: number of patients with events; RCT: randomized controlled trial; RR: relative risk

Mortality

All-cause mortality

No statistically significant difference between treatment groups was shown for any of the relevant subpopulations; this also applied to the combined subpopulation of patients with severe and/or recurrent CDI. With regard to the position of the effect estimates from the meta-analysis, differences between the relevant subpopulations were shown for the outcome "all-cause mortality". Whereas the effect estimate for the subpopulation of patients with severe CDI lay close to the null effect, the corresponding effect estimate for the subpopulation of patients with recurrent CDI clearly showed a numerical difference in the direction of an effect in favour of fidaxomicin. Despite these differences, fundamentally different results between subpopulations are not assumed, as particularly the result for the population of patients with recurrent CDI is based on an imprecise estimate.

An added benefit of fidaxomicin versus the ACT vancomycin in patients with severe and/or recurrent CDI is not proven with regard to all-cause mortality.

Morbidity

Global cure

No statistically significant difference between treatment groups was shown in the meta-analysis of the outcome "global cure" for the subpopulation of patients of severe CDI or for patients with recurrent CDI. The corresponding effect estimates were of a similar magnitude and in each case showed a numerical difference in the direction of an effect in favour of fidaxomicin. In contrast, a statistically significant difference in favour of fidaxomicin was shown for the combined subpopulations of patients with severe and/or recurrent CDI.

For the outcome "global cure" the data provide proof of an added benefit of fidaxomicin versus vancomycin in patients with severe and/or recurrent CDI.

Adverse events

Table 5 show the results on the group of adverse events, in each case for the relevant subpopulations of patients with severe CDI, patients with recurrent CDI, and the combined subpopulation of patients with severe and/or recurrent CDI from the Studies 101.1.C.003 and 101.1.C.004.

Table 5: Results (adverse events) – RCT, direct comparison: fidaxomicin versus vancomycin, total population

Outcome category Outcome Study	Fidaxomicin		Vancomycin		Fidaxomicin vs. vancomycin	
	N[a]	Patients with events n (%)	N[a]	Patients with events n (%)	RR [95% CI]	P-value
Adverse events						
Serious adverse events[b]						
Patients with severe[c] CDI						
101.1.C.003	113	23 (20.4)	127	25 (19.7)	1.03 [0.62; 1.72]	
101.1.C.004	89	24 (27.0)	90	23 (25.6)	1.06 [0.65; 1.72]	
Total					1.04 [0.73; 1.49][d]	0.807[d]
Patients with recurrent[e] CDI						
101.1.C.003	50	15 (30.0)	55	12 (21.8)	1.39 [0.71; 2.65]	
101.1.C.004	43	7 (16.3)	37	8 (21.6)	0.75 [0.30; 1.88]	
Total					1.11 [0.63; 1.95][d]	0.716[d]
Patients with severe[c] and/or recurrent[e] CDI						
101.1.C.003	147	34 (23.1)	158	33 (20.9)	1.11 [0.73; 1.69]	
101.1.C.004	121	30 (24.8)	116	28 (24.1)	1.03 [0.66; 1.61]	
Total					1.07 [0.79; 1.45][d]	0.671[d]
Discontinuation due to adverse events[f]						
Patients with severe[c] CDI						
101.1.C.003	113	9 (8.0)	127	10 (7.9)	1.01 [0.43; 2.40]	
101.1.C.004	89	8 (9.0)	90	10 (11.1)	0.81 [0.33; 1.95]	
Total					0.91 [0.49; 1.68][d]	0.756[d]
Patients with recurrent[e] CDI						
101.1.C.003	50	4 (8.0)	55	4 (7.3)	1.10 [0.29; 4.17]	
101.1.C.004	43	0 (0)	37	2 (5.4)	0.11 [0.01; 1.84][g]	
Total					0.71 [0.15; 3.40][d,h]	0.672[d]
Patients with severec and/or recurrente CDI						
101.1.C.003	147	11 (7.5)	158	14 (8.9)	0.84 [0.40; 1.80]	
101.1.C.004	121	8 (6.6)	116	10 (8.6)	0.77 [0.31; 1.88]	
Total					0.81 [0.46; 1.45][d]	0.478[d]

(continued)

Table 5: Results (adverse events) – RCT, direct comparison: fidaxomicin versus vancomycin, total population (continued)

Outcome category Outcome Study	Fidaxomicin		Vancomycin		Fidaxomicin vs. vancomycin	
	N[a]	Patients with events n (%)	N[a]	Patients with events n (%)	RR [95% CI]	P-value
Adverse events						
Patients with severe[c] CDI						
101.1.C.003	113	71 (62.8)	127	74 (58.3)		
101.1.C.004	89	65 (73.0)	90	69 (76.7)		
Patients with recurrent[e] CDI						
101.1.C.003	50	28 (56.0)	55	30 (54.5)		
101.1.C.004	43	30 (69.8)	37	24 (64.9)		
Patients with severe[c] and/or recurrent[e] CDI						
101.1.C.003	147	90 (61.2)	158	91 (57.6)		
101.1.C.004	121	89 (73.6)	116	85 (73.3)		

a: Patients in analysis
b: Results up to end of follow-up period
c: Classification of severity planned a priori; see Section 2.3.2 of Assessment A13-05 [1]
d: Calculated from meta-analysis with random effects
e: Exactly one previous CDI episode in the last 3 months before study entry
f: Discontinuation due to treatment-related AE up to 7 days after end of treatment
g: Effect estimates and confidence interval for Peto OR due to low proportion (< 1%) of patients with events under fidaxomicin ; Institute's calculation in each case
h: Because of a lack of events under fidaxomicin, calculation of the RR with a consistency correction of 0.5 in both treatment arms

AE: adverse event; CDI: *Clostridium difficile* infection; CI: confidence interval; N: number of analysed patients; n: number of patients with events; RCT: randomized controlled trial; Peto OR: Peto Odds Ratio; RR: relative risk

No statistically significant difference between treatment groups was shown for any of the relevant subpopulations or for any of the outcomes considered (serious adverse events [SAE], treatment discontinuations due to adverse events [AEs]). Due to the low event rates (≤ 1% in at least one cell) in Study 101.1.C.004 in the subpopulation of patients with recurrent CDI, in addition a sensitivity analysis using the Peto Odds Ratio (OR) as an effect measure was performed for the outcome "discontinuation due to AEs". The OR provides a good approximation of the relative risk in the case of low event numbers. Relevant heterogeneity was shown here (p-value in the heterogeneity statistic 0.153) without a clear direction of the effect (see Appendix A).

As already noted in Assessment A13-05, in the evaluation of adverse events the problem arose that those events were also included in the analysis that had already been covered by specifically-recorded outcomes on morbidity (global cure). Because of the statistically significant advantage of fidaxomicin with regard to global cure, this can result in concealment

of potentially greater harm from fidaxomicin. Even with the data subsequently submitted in the company's comment, this aspect still remains unclear. In the comment the company presented no analyses that did not consider such events. The company could have solved this ambiguity by checking whether the corresponding events had also been recorded as AEs in those patients who had been classified as not cured or subsequently experienced a recurrence. An assessment on the basis of the available data is only possible by means of listing the most common AEs and SAEs for the total population of Studies 101.1.C.003 and 101.1.C.004. No noticeable differences between treatment groups were shown here concerning the possible categories (System Organ Classes [acc. to MedDRA]: gastrointestinal disorders, infections and parasitic diseases, general disorders), so that it cannot be assumed that greater harm from fidaxomicin had been concealed.

Overall greater or lesser harm from fidaxomicin than from vancomycin is not proven.

Subgroup analyses

In its comment the company subsequently submitted subgroup analyses for the relevant subpopulations of patients with severe CDI and for those patients with recurrent CDI, but not for the combined subpopulation of patients with severe and/or recurrent CDI. In relation to the outcomes relevant to the assessment, the subgroup analyses submitted subsequently also only covered subgroup analyses for the outcome "mortality". In the subgroup analyses for the subpopulation of patients with severe CDI, it should also be considered that the population used for the subgroup analyses was based on a different definition of classification of severity than the definition used for the analyses of the whole subpopulation. Whereas the criteria specified a prior for severe CDI in the clinical study reports were used for the analyses of the whole subpopulation, the classification for the subgroup analyses was performed on the basis of criteria following the guideline of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [4]. For a more detailed description see Section 2.7.2.2 of Assessment A13-05 [1]. In particular this has an impact on the size of the subpopulations, which – depending on the classification of severity – clearly differ (approx. 37% [definition acc. to clinical study reports] versus approx. 25% [ESCMID criteria]). The subgroup analyses are thus based on a smaller number of patients, and as a result the interaction tests for the subgroups analyses have correspondingly lower power. The company did not provide a reason for this approach. This is incomprehensible, as otherwise the company follows the approach presented in the Dossier Assessment A13-05, both with regard to the selection of outcomes and also with regard to the definition of severity. Overall, for most of the outcomes relevant to the assessment, there are thus still no adequate subgroup analyses available for the relevant subpopulations.

The subgroup characteristics considered for the outcome "mortality" comprise sex, age (< 65 vs. ≥ 65 years), treatment setting (outpatient vs. inpatient), antibiotic pretreatment for *Clostridium difficile* (24 hours before start of study: yes vs. no). *Clostridium difficile* strain (BI strain vs. no BI strain) and systematic antibacterial concomitant therapy (yes vs. no). No

indication ($0.05 \leq p < 0.2$) or proof ($p < 0.05$) of an effect modification by one of these characteristics was shown in patients with severe CDI or in patients with recurrent CDI.

2.3 Extent and probability of added benefit

In the following text the derivation of the extent and probability of added benefit at outcome level is presented for the relevant subpopulations of patients with severe and/or recurrent CDI. The methods used for this purpose are described in Appendix A of Benefit Assessment A11-02 [5].

The derivation of the extent and probability of added benefit for the population of patients with non-severe CDI requiring treatment is shown in Assessment A13-05 [1].

The procedure for derivation of an overall conclusion on added benefit by means of aggregation of conclusions inferred at the outcome level represent a proposal from IQWiG. The G-BA decides on the added benefit.

2.3.1 Assessment of added benefit at outcome level

Patients with recurrent and/or severe course of CDI disease

Table 6 shows the assessment of the extent of added benefit of the data at outcome-level presented in Section 2.2 for the comparison of fidaxomicin with vancomycin in patients with severe and/or recurrent CDI. Either no statistically significant differences between treatment groups were shown for any of the subpopulations (outcomes “all-cause mortality”, “AEs”) or the position of the effect estimates did not differ substantially between the relevant subpopulations (outcome “global cure”). A combination of the subpopulations of patients with severe or recurrent CDI is thus justified. For this reason the determination of the extent of added benefit was only performed on the basis of the results of the combined population of patients with severe and/or recurrent CDI.

Table 6: Fidaxomicin versus vancomycin – Extent of added benefit at outcome level in patients with severe and/or recurrent CDI disease

Outcome	**RR [95% CI] p-value Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0.97 [0.53; 1.77] p = 0.912	lesser benefit/added benefit not proven
Morbidity		
Global cure[c]	0.76 [0.60; 0.97] p = 0.025 Probability: proof	Outcome category : severe/serious symptoms/late complications $0{,}9 \leq CI_u < 1$ Added benefit: extent: minor
Health-related quality of life		
–	No data available	lesser benefit/added benefit not proven
Adverse events		
Overall rate SAE	1.07 [0.79; 1.45] p = 0.671	greater/lesser harm not proven
Discontinuation due to AE	0.81 [0.46; 1.45] p = 0.478	greater/lesser harm not proven

a: Probability provided if statistically significant differences were present.
b: Estimates of effect size performed by outcome category with different limits using the upper limit of the confidence interval (CI_u)
c: Values refer to analyses in which patients without global cure were counted as event
AE: adverse event; CDI: *Clostridium difficile* infection; CI: confidence interval; CI_u: upper limit confidence interval; RR: relative risk; SAE: serious adverse event

As already described in Assessment A13-05, due to its operationalization, the outcome "global cure" was allocated to the outcome category "serious/severe symptoms/late complications" and cannot be equated with curing the disease, the goal stated in the Regulation for Early Benefit Assessment of New Pharmaceuticals (AM-NutzenV, [6]).

2.3.2 Overall conclusion on added benefit

Patients with recurrent and/or severe course of CDI disease

Table 7 summarizes results that are considered in the overall conclusion on extent of added benefit of fidaxomicin for patients with severe and/or recurrent course of CDI disease versus the ACT vancomycin.

Table 7: Positive and negative effects in the assessment of fidaxomicin versus vancomycin; patients with severe and/or recurrent CDI

Positive effects	**Negative effects**
Proof of added benefit; extent: "minor" (serious/severe symptoms/ late complications: global cure)	

For the question of the added benefit of fidaxomicin versus vancomycin in severe and/or recurrent courses of CDI disease, regarding positive effects, the data provide proof of an added benefit of fidaxomicin for the outcome "global cure". The extent is minor. For the outcomes for the group of AEs, greater or lesser harm from fidaxomicin than from the ACT is not proven.

In summary, the data provide proof of a minor added benefit of fidaxomicin versus the ACT in patients with severe and/or recurrent course of CDI.

2.3.3 Extent and probability of added benefit – Summary

The data presented by the company in the dossier [2] and the data subsequently submitted in the comment on the dossier assessment [3] provide the following overview of the extent and probability of added benefit for the various subpopulations for whom fidaxomicin is approved versus the respective ACT (see Table 8).

Table 8: Fidaxomicin: extent and probability of added benefit

Subpopulation	**Appropriate comparator therapy**	**Extent and probability of added benefit**
Patients with non-severe CDI requiring treatment	Metronidazol	Added benefit not proven
Patients with severe and/or recurrent CDI	Vancomycin	Proof of minor added benefit
CDI: *Clostridium difficile* infection		

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Fidaxomicin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A13-05 [online]. 11.04.2013 [accessed 15 April 2013]. (IQWiG Reports; Volume 159). URL: https://www.iqwig.de/download/A13-05_Fidaxomicin_Nutzenbewertung_35a_SGB_V.pdf.

2. Astellas Pharma. Nutzenbewertungsverfahren zum Wirkstoff Fidaxomicin: Dossier [online]. [accessed 5 June 2013]. URL: http://www.g-ba.de/informationen/nutzenbewertung/59/#tab/dossier.

3. Astellas Pharma. Stellungnahme zum IQWiG-Bericht Nr. 159: Fidaxomicin; Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A13-05. [Soon available under: http://www.g-ba.de/informationen/nutzenbewertung/59/#tab/beschluesse in the German-language document "Zusammenfassende Dokumentation"].

4. Bauer MP, Kuijper EJ, Van Dissel JT. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for Clostridium difficile infection (CDI). Clin Microbiol Infect 2009; 15(12): 1067-1079.

5. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to § 35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf

6. Bundesministerium für Gesundheit. Verordnung über die Nutzenbewertung von Arzneimitteln nach § 35a Absatz 1 SGB V für Erstattungsvereinbarungen nach § 130b SGB V (Arzneimittel-Nutzenbewertungsverordnung – AM-NutzenV). Bundesgesetzblatt Teil 1 2010; (68): 2324-2328.

Appendix A – Meta-analyses calculated by IQWiG

All-cause mortality

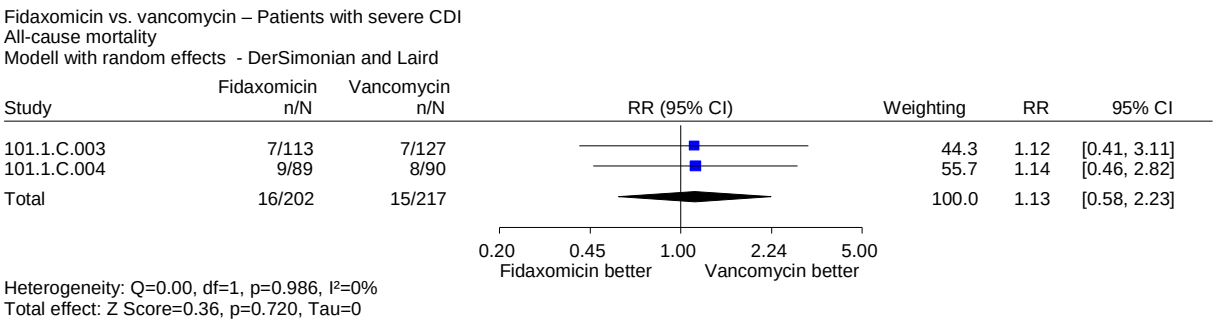

Figure 1: Meta-analysis. All-cause mortality; patients with severe CDI: fidaxomicin versus vancomycin.

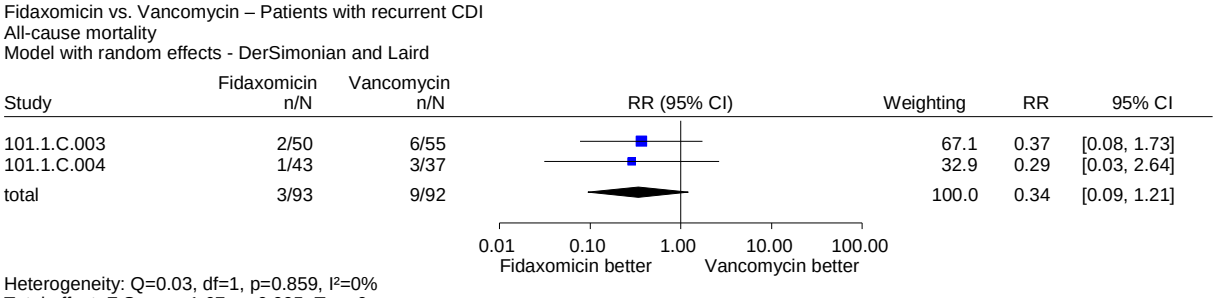

Figure 2: Meta-analysis. All-cause mortality; patients with recurrent CDI: fidaxomicin versus vancomycin.

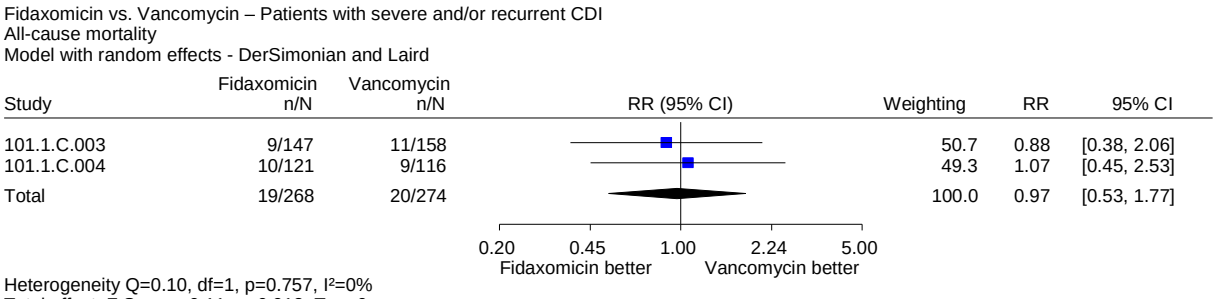

Figure 3: Meta-analysis. All-cause mortality. Patients with severe and/or recurrent CDI: fidaxomicin versus vancomycin.

Global cure

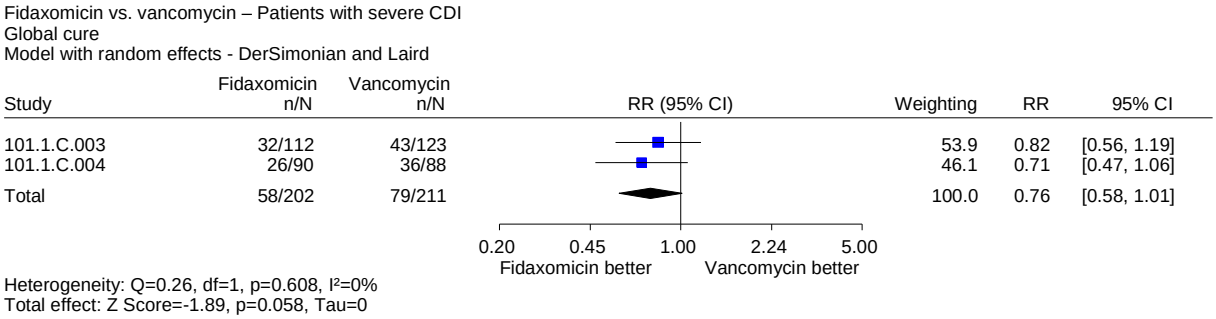

Figure 4: Meta-analysis. Global cure (event: no global cure); patients with severe CDI: fidaxomicin versus vancomycin.

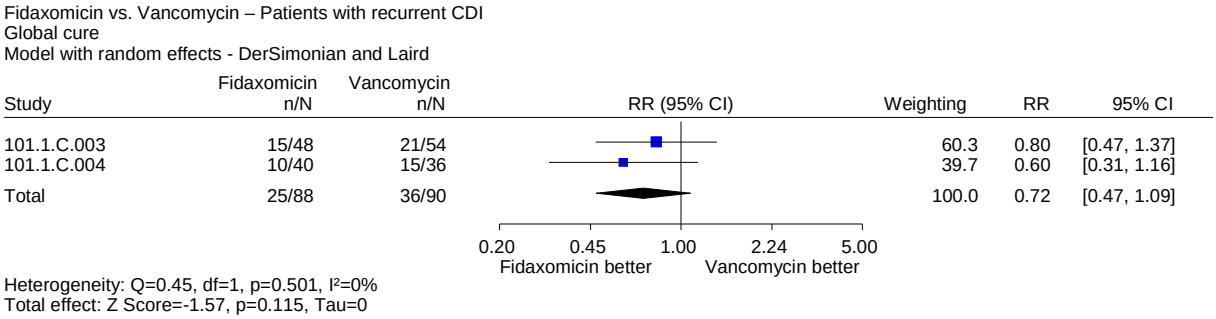

Figure 5: Meta-analysis. Global cure (event: no global cure); patients with recurrent CDI: fidaxomicin versus vancomycin.

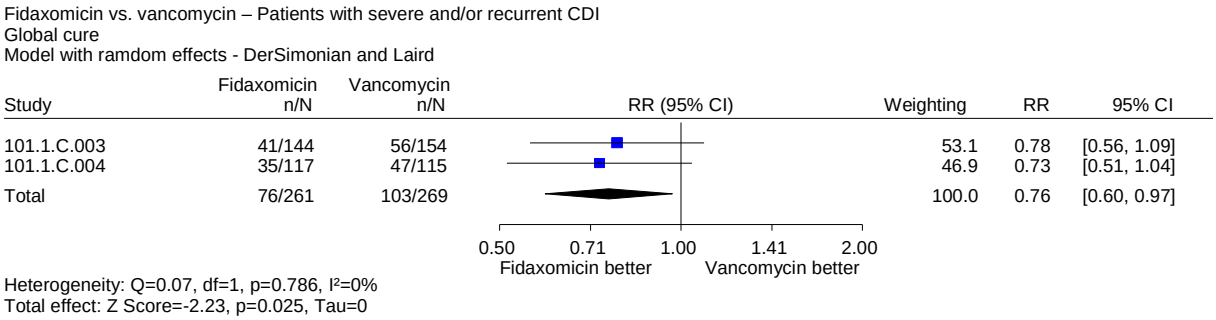

Figure 6: Meta-analysis. Global cure (event: no global cure); patients with severe and/or recurrent CDI: fidaxomicin versus vancomycin.

Serious adverse events

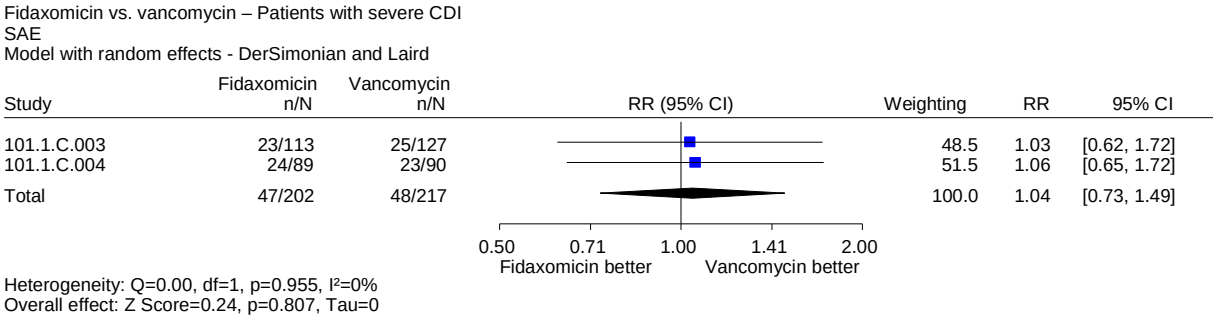

Figure 7: Meta-analysis. SAE; patients with severe CDI: fidaxomicin versus vancomycin.

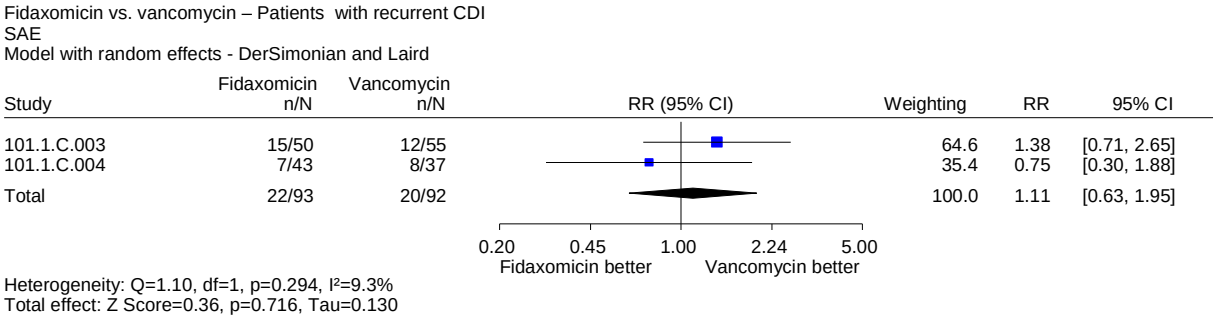

Figure 8: Meta-analysis. SAE; patients with recurrent CDI: fidaxomicin versus vancomycin.

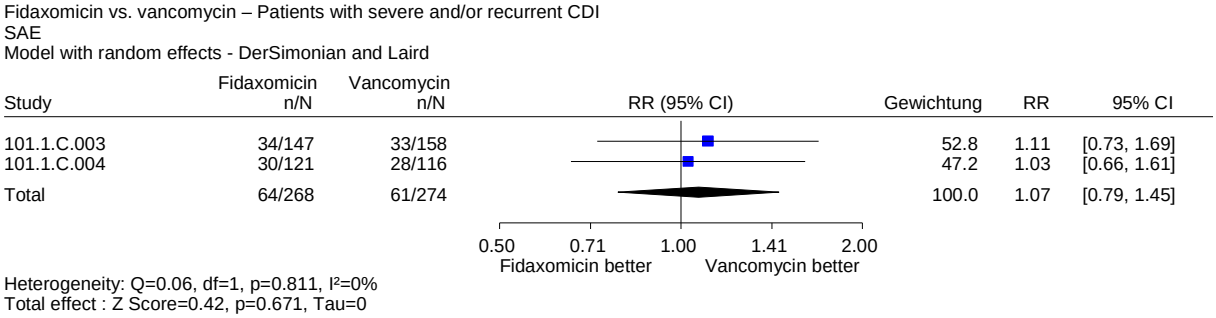

Figure 9: Meta-analysis. SAE; patients with severe and/or recurrent CDI: fidaxomicin versus vancomycin.

Discontinuation due to adverse events

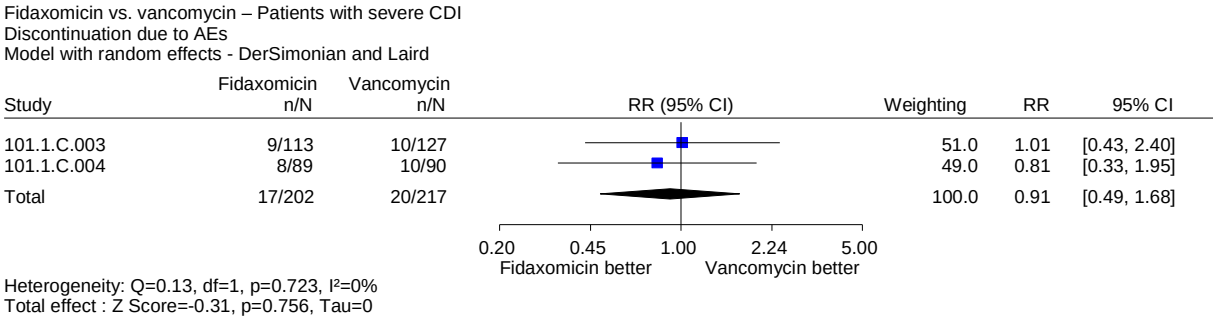

Figure 10: Meta-analysis. Discontinuation due to AEs; patients with severe CDI: fidaxomicin versus vancomycin.

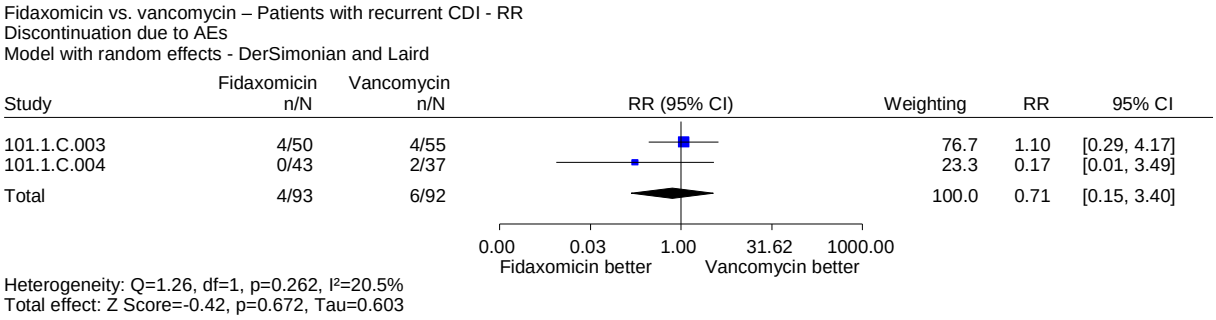

Figure 11: Meta-analysis. Discontinuation due to AEs; patients with recurrent CDI: fidaxomicin versus vancomycin

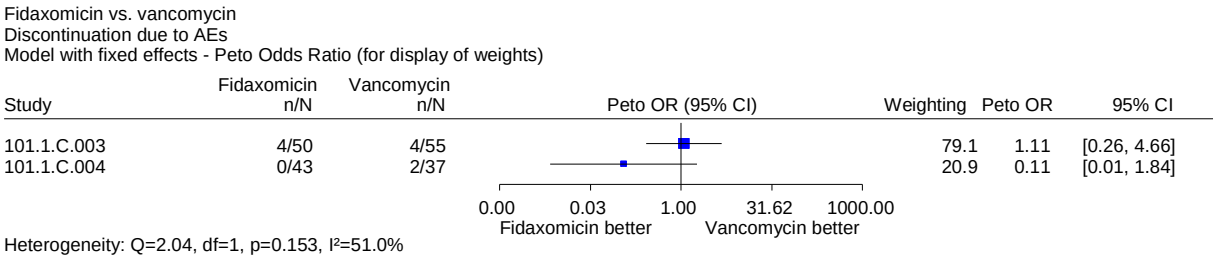

Figure 12: Meta-analysis with Peto OR as effect measure. Discontinuation due to AEs; patients with recurrent CDI: fidaxomicin versus vancomycin.

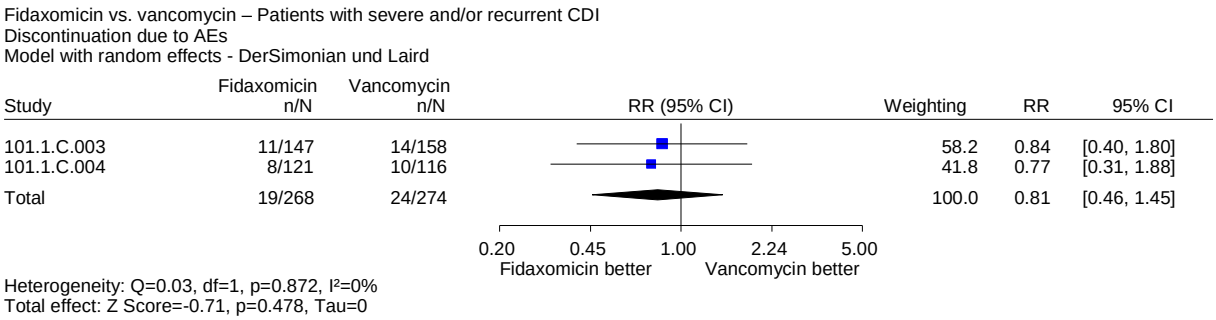

Figure 13: Meta-analysis. Discontinuation due to AEs; patients with severe and/or recurrent CDI: fidaxomicin versus vancomycin.