IQWiG Reports – Commission No. A20-25

Fidaxomicin (*Clostridioides difficile* infection in children and adolescents) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Fidaxomicin (Clostridioides-difficile-Infektion bei Kindern und Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 10 June 2020). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CDAD	*Clostridioides difficile*-associated diarrhoea
CDI	*Clostridioides difficile* infection
CTCAE	Common Terminology Criteria for Adverse Events
EPAR	European Public Assessment Report
ITT	intention to treat
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug fidaxomicin. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 11 March 2020. This commission relates to an extension of the approved therapeutic indication of fidaxomicin to the treatment of children and adolescents up to 18 years of age.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of this report is to assess the added benefit of fidaxomicin in comparison with the appropriate comparator therapy (ACT) in patients from birth to < 18 years of age with *Clostridioides difficile* infection (CDI), also known as *Clostridioides difficile*-associated diarrhoea (CDAD).

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of fidaxomicin

Research question	**Therapeutic indication**	**ACT[a, b]**
1	Patients from birth to < 18 years of age with mild CDI[c] requiring treatment	Metronidazole or **vancomycin**
2	Patients from birth to < 18 years of age with severe and/or recurrent CDI[c]	Vancomycin

a. Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b. In accordance with the G-BA, guidelines on the appropriate use of antibiotics were to be taken into account.
c. The terms CDAD and CDI are synonymous. The term CDI is used throughout this document.

ACT: appropriate comparator therapy; CDAD: *Clostridioides difficile*-associated diarrhoea; CDI: *Clostridioides difficile* infection; G-BA: Federal Joint Committee

For both research questions, the company follows the G-BA's specification; for research question 1, it chooses vancomycin from the presented treatment options.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of added benefit.

Results

Study pool and study characteristics

The study pool for the benefit assessment of fidaxomicin in comparison with the ACT consists of the RCT SUNSHINE. This benefit assessment uses the results of the subpopulation with mild disease course requiring treatment to answer research question 1 and the results of the subpopulation with severe and/or recurrent disease course for research question 2.

The SUNSHINE trial is a randomized, single-blind phase III study comparing fidaxomicin with vancomycin in patients < 18 years of age with confirmed CDI. The markers for CDI diagnosis are not only detection of toxin A, toxin B, or toxigenic *Clostridioides difficile* strains in the stool within 72 hours before randomization, but also patients < 2 years of age exhibiting watery diarrhoea and patients ≥ 2 years of age, at least 3 unformed bowel movements within 24 hours prior to screening.

A total of 148 patients were randomly allocated in a 2:1 ratio to treatment with fidaxomicin (N = 100) or vancomycin (N = 48). Age was used as a stratification factor (< 2 years, ≥ 2 to < 6 years, ≥ 6 to < 12 years, and ≥ 12 to < 18 years). Of these patients, 66 are relevant for assessing research question 1 (patients with mild disease course requiring treatment) and 82 for assessing research question 2 (patients with severe and/or recurrent disease course).

The company allocated patients post hoc to the subpopulation with mild disease course requiring treatment (research question 1) versus severe and/or recurrent disease course (research question 2). The criteria used by the company to define the subpopulations for the two research questions reduce the certainty of results; on this basis, at most hints, e.g. of added benefit, can therefore be derived.

Fidaxomicin was used in accordance with the Summary of Product Characteristics (SPC) or product information. Vancomycin was administered in accordance with the SPC as well, with limitations in terms of the treatment of severe and/or recurrent CDI.

The primary outcome was confirmed clinical response, while patient-relevant secondary outcomes were further morbidity outcomes and adverse event (AE) outcomes. All outcomes were followed up for 30 days after the end of treatment.

Risk of bias

The risk of bias across outcomes is rated as low for the SUNSHINE study. For the results of the outcome of all-cause mortality, the risk of bias at outcome level is rated as low. The results of the remaining outcomes included in the present benefit assessment are rated as potentially highly biased.

Beyond the limitations with regard to the risk of bias of the observed outcomes, the certainty of results of all outcomes is deemed limited due to uncertainty in the allocation to sub-populations.

Overall, at most hints, e.g. of an added benefit, can therefore be derived from the available data.

Results on research question 1: Patients with mild disease course requiring treatment

Mortality

All-cause mortality

For the outcome of overall survival, no statistically significant difference between treatment arms was found for the relevant subpopulation. This results in no hint of added benefit of fidaxomicin in comparison with vancomycin; an added benefit is therefore not proven.

Morbidity

Global cure

For the outcome of global cure, no statistically significant difference between treatment arms was found for the relevant subpopulation. However, an effect modification by sex was found. In boys, there was a statistically significant difference to the disadvantage of fidaxomicin. For girls, no statistically significant difference between treatment arms was found. In boys, this results in a hint of lesser benefit of fidaxomicin in comparison with vancomycin. For girls, there is no hint of added or lesser benefit of fidaxomicin in comparison with vancomycin; an added or lesser benefit is therefore not proven for girls.

Health-related quality of life

The SUNSHINE study did not record any outcomes on health-related quality of life.

AEs

Serious adverse events (SAEs)

For the outcome of SAEs, no statistically significant difference between treatment arms was found for the relevant subpopulation. This results in no hint of greater or lesser harm of fidaxomicin in comparison with vancomycin; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

In the relevant subpopulation, 1 patient in the vancomycin arm discontinued therapy due to the AE of vomiting. No statistically significant difference between treatment arms was found. Consequently, for the outcome of discontinuation due to AEs, there is no hint of greater or lesser harm of fidaxomicin in comparison with vancomycin; greater or lesser harm is therefore not proven.

Results on research question 2: Patients with severe and/or recurrent disease course

Mortality

All-cause mortality

For the outcome of overall survival, no death occurred in the relevant subpopulation. There is no hint of added benefit of fidaxomicin in comparison with vancomycin; an added benefit is therefore not proven.

Morbidity

Global cure

For the outcome of global cure, a statistically significant difference in favour of fidaxomicin was found for the relevant subpopulation. This results in a hint of added benefit of fidaxomicin in comparison with vancomycin.

Health-related quality of life

The SUNSHINE study did not record any outcomes on health-related quality of life.

AEs

SAEs

For the outcome of SAEs, no statistically significant difference between treatment arms was found for the relevant subpopulation. This results in no hint of greater or lesser harm of fidaxomicin in comparison with vancomycin; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

In the relevant subpopulation, 1 patient in the fidaxomicin arm discontinued therapy due to the AE of colitis. No statistically significant difference between treatment arms was found. Consequently, for the outcome of discontinuation due to AEs, there is no hint of greater or lesser harm of fidaxomicin in comparison with vancomycin; greater or lesser harm is therefore not proven.

Nervous system disorders (system organ class [SOC], AEs)

For the outcome of nervous system disorders, a statistically significant difference to the disadvantage of fidaxomicin was found for the relevant subpopulation. This results in a hint of greater harm of fidaxomicin in comparison with vancomycin.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, the probability and extent of added benefit of the drug fidaxomicin in comparison with the ACT are assessed as follows:

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Research question 1: Patients with mild disease course requiring treatment

The aggregate results for boys only show a hint of lesser benefit of minor extent for fidaxomicin in comparison with vancomycin in the outcome category of morbidity.

In summary, for boys from birth to < 18 years of age with mild CDI requiring treatment, there is a hint of lesser benefit of fidaxomicin in comparison with vancomycin. For girls from birth to < 18 years of age with mild CDI requiring treatment, there is no proof of added or lesser benefit of fidaxomicin in comparison with vancomycin.

Research question 2: Patients with severe and/or recurrent disease course

Overall, the analysis shows a positive and a negative effect of fidaxomicin in comparison with vancomycin. On the positive side, a hint of considerable added benefit was found for the outcome of global cure. On the negative side, there is a hint of greater harm of considerable extent for the specific AE of nervous system disorders.

Given that the outcome of global cure was assigned to the outcome category of serious/severe AEs / late complications, yet the observed negative effect is non-serious/non-severe, the positive effect with regard to global cure is assumably not being challenged by the negative effect.

In summary, for patients from birth to < 18 years of age with severe and/or recurrent CDI, there is a hint of considerable added benefit of fidaxomicin in comparison with the ACT of vancomycin.

Table 3 presents a summary of the probability and extent of added benefit of fidaxomicin.

Table 3: Fidaxomicin – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a, b]**	**Probability and extent of added benefit**
1	Patients from birth to < 18 years of age with mild CDI[c] requiring treatment	Metronidazole or **vancomycin**	▪ Boys: Hint of lesser benefit ▪ Girls: Added benefit not proven
2	Patients from birth to < 18 years of age with severe and/or recurrent CDI[c]	Vancomycin	Hint of considerable added benefit

a. Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b. In accordance with the G-BA, guidelines on the appropriate use of antibiotics were to be taken into account.
c. The terms CDAD and CDI are synonymous. The term CDI is used throughout this document.

ACT: appropriate comparator therapy; CDAD: *Clostridioides difficile*-associated diarrhoea;
CDI: *Clostridioides difficile* infection; G-BA: Federal Joint Committee

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

2.2 Research question

The aim of this report is to assess the added benefit of fidaxomicin in comparison with the appropriate comparator therapy (ACT) in patients from birth to < 18 years of age with CDI, also known as CDAD.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of fidaxomicin

Research question	Therapeutic indication	ACT[a, b]
1	Patients from birth to < 18 years of age with mild CDI[c] requiring treatment	Metronidazole or **vancomycin**
2	Patients from birth to < 18 years of age with severe and/or recurrent CDI[c]	Vancomycin

a. Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b. In accordance with the G-BA, guidelines on the appropriate use of antibiotics were to be taken into account.
c. The terms CDAD and CDI are synonymous. The term CDI is used throughout this document.

ACT: appropriate comparator therapy; CDI: *Clostridioides difficile* infection; G-BA: Federal Joint Committee

To simplify presentation and improve readability, the running text of this benefit assessment uses the following designations for the research questions:

- Research question 1: Patients with mild disease course requiring treatment
- Research question 2: Patients with severe and/or recurrent disease course

For both research questions, the company follows the G-BA's specification; for research question 1, it chooses vancomycin from the presented treatment options.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of added benefit.

2.3 Research question 1: Patients with mild disease course requiring treatment

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- Study list on fidaxomicin (status: 03 February 2020)
- Bibliographic literature search on fidaxomicin (most recent search on 03 February 2020)
- Search in trial registries / study results databases on fidaxomicin (most recent search on 03 February 2020)

- Search on the G-BA website on fidaxomicin (most recent search on 03 February 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on fidaxomicin (most recent search on 19 March 2020)

The check did not identify any additional relevant studies.

2.3.1.1 Included studies

The study listed in the table below was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: fidaxomicin vs. vancomycin

Study	Study category			Available sources		
	Approval study for the drug to be assessed (Yes/No)	Sponsored study[a] (Yes/No)	Third-party study (Yes/No)	Clinical study report[b] (Yes/No [reference])	Registry entries[c] (Yes/No [reference])	Publication (Yes/No [reference])
2819-CL-0202 (SUNSHINE[d])	Yes	Yes	No	No	Yes [3-7]	Yes [8]

a. Study sponsored by the company.
b. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.
c. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
d. In the tables below, the study will be referred to using this short name.

RCT: randomized controlled trial

The study pool for the benefit assessment of fidaxomicin consists of the RCT SUNSHINE. This concurs with the company's study pool.

The SUNSHINE study included patients with mild disease course requiring treatment as well as patients with severe and/or recurrent disease course. See Section 2.3.1.2 on the delimitation of the two populations for the research question of the benefit assessment.

In the present benefit assessment, the results of the subpopulation with mild disease course requiring treatment were used for research question 1.

This departs from the company's approach. The company does present the results for both subpopulations. For deriving the added benefit, however, it uses the results of the total population (see Section 2.3.3.2).

Availability of the approved pharmaceutical forms of fidaxomicin

Fidaxomicin is approved in 2 pharmaceutical forms: film-coated tablets and granules for oral suspension. The therapeutic indication of the granules comprises patients from birth [9], while film-coated tablets are approved from a body weight of 12.5 kg [10].

In the SUNSHINE study, both pharmaceutical forms of fidaxomicin were used. Patients were included from birth, thus also presenting with a body weight of less than 12.5 kg. About 68% of patients in the fidaxomicin arm received the granules for oral suspension.

As per the cut-off date of 01 June 2020, the granules had not yet been available on the German market. Hence, going by the therapeutic indication for film-coated tablets, only patients with a body weight of at least 12.5 kg can currently be treated. Yet, in accordance with the G-BA's specification of the therapeutic indication to be assessed (see Section 1.1 of the full dossier assessment), the present benefit assessment is conducted for patients from birth up to age < 18 years.

2.3.1.2 Study characteristics

Table 6 and Table 7 present the study used in the benefit assessment.

Table 6: Characterization of the included study – RCT, direct comparison: fidaxomicin vs. vancomycin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
SUNSHINE	RCT, single-blind[b], parallel	Children and adolescents from birth to < 18 years[c] with confirmed CDI[d]	Fidaxomicin (N = 100) Vancomycin (N = 48) Relevant subpopulations thereof: Research question 1: Patients with mild disease course requiring treatment Fidaxomicin (n = 49) Vancomycin (n = 17) Research question 2: Patients with severe and/or recurrent disease course Fidaxomicin (n = 51) Vancomycin (n = 31)	Screening: 3 days Treatment: 10 days Follow-up observation: 30 days	74 study centres in Belgium, Canada, France, Germany, Hungary, Italy, Poland, Romania, Slovakia, Spain, USA 01/2015–03/2018	Primary: confirmed clinical response Secondary: morbidity, AEs

a. Data on primary outcomes were included irrespective of their relevance for this benefit assessment. Data on secondary outcomes were included only concerning available outcomes relevant for this benefit assessment.
b. The involved investigators were blinded.
c. In the USA, the patient inclusion criterion was ≥ 6 months and < 18 years of age (Protocol Amendment 3, 21 July 2015).
d. Requirement ≥ 72 hours before randomization, either positive detection of toxin A or B in stool or positive detection of toxigenic *Clostridioides difficile* in stool. In addition, patients < 2 years of age had to have watery diarrhoea, and patients ≥ 2 years of age, 3 unformed bowel movements in the 24 hours prior to screening. Patients < 5 years of age had to have tested negative for rotavirus.

AE: adverse event; CDI: *Clostridioides difficile* infection; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characterization of the intervention – RCT, direct comparison: fidaxomicin vs. vancomycin

Study	Intervention	Comparison
SUNSHINE	Fidaxomicin oral for 10 days ▪ patients < 6 years of age or ≥ 6 years with difficulty swallowing[a] in weight-adapted dosage[b] (pharmaceutical form: granules for oral suspension[c]): 32 mg/kg body weight per day ▫ ≤ 3.9 kg: 40 mg twice daily ▫ 4.0–6.9 kg: 80 mg twice daily ▫ 7.0–8.9 kg: 120 mg twice daily ▫ 9.0–12.4 kg: 160 mg twice daily ▫ ≥ 12.5 kg: 200 mg twice daily ▪ Patients ≥ 6 years of age without difficulty swallowing[a] (pharmaceutical form: film-coated tablet[c]): ▫ 200 mg twice daily	vancomycin orally for 10 days ▪ Patients < 6 years of age or ≥ 6 years with difficulty swallowing[a] in weight-adapted dosage[b] (pharmaceutical form: powder for oral suspension[c]): 40 mg/kg body weight per day ▫ ≤ 3.9 kg: 25 mg 4 x daily ▫ 4.0–6.9 kg: 50 mg 4 x daily ▫ 7.0–8.9 kg: 75 mg 4 x daily ▫ 9.0–12.4 kg: 100 mg 4 x daily ▫ ≥ 12.5 kg: 125 mg 4 x daily ▪ Patients ≥ 6 years of age without difficulty swallowing[a] (pharmaceutical form: capsule[c]): ▫ 125 mg 4 x daily
	Permitted pretreatment ▪ ≤ 4 doses, but a maximum of 24 hours of treatment with metronidazole, oral vancomycin, or any other CDI therapy[d] **Permitted concomitant treatment** ▪ Drug-based and non-drug-based therapies, including alternative medicine for chronic and needs-based application[e] ▪ Continuation of therapy with drugs affecting intestinal peristalsis (e.g. loperamide, codeine, morphine, pethidine, fentanyl, methadone, tramadol, other opioids) in the same dose as before randomization ▪ Potent p-glycoprotein inhibitors (e.g. cyclosporine, ketoconazole, erythromycin, clarithromycin, verapamil, dronedarone, amiodarone) permitted, but not recommended **Non-permitted concomitant treatment** ▪ Other CDI therapy[f] (e.g. oral vancomycin, metronidazole, oral bacitracin, fusidic acid, rifaximin, nitazoxanide, linezolid, rifampicin, or foecal transplant)	

a. Inability to swallow tablets or capsules.
b. Dose increases or reductions were not permitted.
c. Changing the pharmaceutical form in the course of treatment was not permitted.
d. To the extent considered necessary by the investigator before receipt of the results of direct or indirect testing for *Clostridioides difficile*.
e. Where possible, patients were not to take any additional drugs without prior consultation of the investigator.
f. Except for therapy due to primary treatment failure or suspected CDI recurrence after initial clinical response; how many patients received this type of concomitant therapy is unclear.

CDI: *Clostridium difficile* infection; RCT: randomized controlled trial

The SUNSHINE trial is a randomized, single-blind phase III study comparing fidaxomicin with vancomycin in patients < 18 years of age with confirmed CDI. The investigators were blinded. However, no blinding was undertaken for patients and their parents or guardians, as well as persons involved in dosing, administration and collection of the study drug, and blood draws for measuring the drug concentration. The markers for CDI diagnosis are not only detection of

toxin A, toxin B, or toxigenic *Clostridioides difficile* strains in the stool within 72 hours before randomization, but also patients < 2 years of age exhibiting watery diarrhoea and patients ≥ 2 years of age, at least 3 unformed bowel movements within 24 hours prior to screening.

Patients with pseudomembranous colitis, fulminant colitis, toxic megacolon, ileus, or prior chronic inflammatory bowel disease (e.g. ulcerative colitis or Crohn's disease) were excluded from the study. Hence, no data are available on these patients, who are also indicated for CDI treatment.

A total of 148 patients were randomly allocated in a 2:1 ratio to treatment with fidaxomicin (N = 100) or vancomycin (N = 48). Age was used as a stratification factor (< 2 years, ≥ 2 to < 6 years, ≥ 6 to < 12 years, and ≥ 12 to < 18 years).

In the SUNSHINE study, fidaxomicin and vancomycin were administered in tablet, capsule, or liquid form. Fidaxomicin was available in the form of film-coated tablets or granules for oral suspension (see Section 2.3.1.1) and vancomycin in the form of hard capsules or as a powder for oral solution.

Patients < 6 years and, if unable to swallow tablets or capsules, patients ≥ 6 years of age were treated with the fidaxomicin suspension or vancomycin solution. The remaining patients received film-coated tablets (fidaxomicin) or hard capsules (vancomycin). Changing the pharmaceutical form in the course of the study was not permitted.

Fidaxomicin was used in accordance with the SPC (film-coated tablets) [10] and Annex I of the product information (granules) [9]. Likewise, vancomycin was administered in accordance with the SPC, with limitations regarding the treatment of severe and/or recurrent CDI [11,12]. According to the SPC, vancomycin hard capsules are to be used only in patients aged 12 years or above. In the SUNSHINE study, the administration of capsules was permitted from the age of 6 years, provided patients were able to swallow them. For this benefit assessement though, this limitation is immaterial given that the ability to swallow solid pharmaceutical forms was assessed before starting study drug administration. Further, while the SPC generally permits vancomycin dose increases in severe or complicated disease courses from the age of 12 years as well as the use of a modified treatment regimen in case of multiple CDI recurrences, these options were not provided. These treatment modifications are, however, optional measures. In addition, the study protocol generally permitted a different CDI therapy to be administered in addition to the study drug in case of primary treatment failure or suspected CDI recurrence after initial response; therefore, undertreatment is unlikely in cases of severe CDI courses. However, no data is available as to how many patients, if any, received additional CDI treatment. Due to their ages, 4 patients were potentially affected by the described limitation (see Table 17).

The primary outcome was confirmed clinical response, while patient-relevant secondary outcomes were further morbidity outcomes and AE outcomes. All outcomes were followed up

for 30 days after the end of treatment. The follow-up observation is deemed sufficiently long for the given therapeutic indication.

SUNSHINE study subpopulations relevant for the assessment

For research questions 1 and 2 of the present benefit assessment, subpopulations of the SUNSHINE study are relevant. Despite having presented its defined subpopulations (see below), the company resorted to the total population to derive the added benefit. The company argued that the subgroup analyses it conducted post hoc on the basis of severity of disease course (patients with mild disease course requiring treatment versus patients with severe and/or recurrent disease course) revealed no effect modification in the total population with regard to the outcomes it considered and that the results of the total population were thus transferable to the subpopulations specified by the G-BA. However, a non-significant interaction test is an insufficient basis for concluding that the subpopulations are similar. Rather, the demonstration of similarity is an equivalence issue; therefore, a statistically non-significant interaction test is, by itself, insufficient to justify the use of results of the total population to draw conclusions on the subpopulation. Furthermore, particularly for the outcome of global cure, deviating effects were found in the subpopulations for research question 1 (patients with mild disease course requiring treatment) and research question 2 (patients with severe and/or recurrent disease course) (see Table 28 of the full dossier assessment). Therefore, the relevant subpopulations were used to assess added benefit in accordance with research questions 1 and 2 of the present benefit assessment.

Operationalization of the relevant subpopulation by the company

According to the study protocol, the SUNSHINE study did not intend to categorize patients by disease severity. Therefore, the company allocated patients post hoc to the subpopulation with mild disease course requiring treatment (research question 1 of the present benefit assessment) or severe and/or recurrent disease course (research question 2 of the present benefit assessment).

Company's approach for defining subpopulations

According to the company, the allocation to severe disease course is based on 3 criteria:

- Fever (> 38.5°C at study start)
- Leukocytosis (≥ 15 000/mm³ leukocytes at study start)
- Elevated serum creatinine (age-dependent)

In this regard, the company points out that the guideline on CDI infections in adults and children [13] does not provide any definition of CDI severity for children.

The company defines a severe CDI course as the presence of at least 1 of the 3 above criteria, following the recommendation of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) for the diagnosis of severe CDI [14]. However, instead of the above

publication's thresholds for pathological serum creatinine values, the company used age-based thresholds in accordance with the recommendation provided by [15]

The company defined recurrent disease courses as those in patients with a history of diarrhoea along with confirmed CDI as per electronic case report form.

The company allocated patients who met at least 1 criterion of severe disease course and/or had a history of diarrhoea to the subpopulation with severe and/or recurrent disease course (research question 2).

Patients who did not meet these criteria were allocated to the subpopulation with mild disease course requiring treatment (research question 1).

Assessment of the company's approach

Currently, no standard exists for categorizing CDI severity in children and adolescents [16]. The literature mentions diverse factors which might correlate with severe CDI in the absence of another explanation for these findings [13,14,17-19].

The European Public Assessment Report (EPAR) applies criteria which differ from those used in company's dossier [20]. They comprise the number of unformed bowel movements per day and the leukocyte count at study start. The disease course was rated as severe in patients who, at study start, had ≥ 10 unformed bowel movements per day and $\geq 15\,000/mm^3$ leukocytes. However, in terms of how many patients have a severe disease course in accordance with this classification, the EPAR cites merely one other paediatric study (OPT-80-206) [20,21]. The initial assessment of fidaxomicin in adults [22] likewise prespecified a severity classification on the basis of these criteria for the studies included. Yet the initial assessment provided results for both severity classifications: a prespecified classification in accordance with EPAR criteria as well as a post hoc classification analogous to the one in the present dossier. Both severity classifications were accepted as equivalent in the initial assessment. However, in that assessment, the results were suitable for confirming that the different classification systems did not lead to any deviations in results for adults.

Most definitions suggested in the literature use various combinations of the criteria relied upon both by the company as well as in the EPAR and in the initial assessment of fidaxomicin. Consequently, neither of the definitions is preferable to any other from a technical standpoint. Nonetheless, the company fails to provide any rationale for deviating from the criteria used in the initial assessment and in the EPAR. In addition, it does not present any sensitivity analyses showing that the results are robust when using different severity classification criteria.

The present benefit assessment uses the results for the subpopulation defined by the company as these are the only ones avaialble. However, different definitions (as described above) might conceivably lead to deviating results. Consequently, the certainty of the available results is limited. On this basis, at most hints, e.g. of an added benefit, can therefore be derived.

Characterization of the study population

Table 8 shows the characteristics of the patients in the relevant subpopulation of the study included.

Table 8: Characterization of the study population – RCT, direct comparison: fidaxomicin vs. vancomycin (research question 1: patients with mild disease course requiring treatment)

Study Characteristics Category	Fidaxomicin N[a] = 49	Vancomycin N[a] = 17
SUNSHINE		
Age [years], mean (SD)	7 (5)	7 (6)
Age groups [years], n (%)		
< 2	13 (26.5)	4 (23.5)
≥ 2–< 6	12 (24.5)	6 (35.3)
≥ 6–< 12	14 (28.6)	2 (11.8)
≥ 12–< 18	10 (20.4)	5 (29.4)
Sex [f/m], %	51/49	53/47
Watery diarrhoea[b], n (%)	13 (100)[c]	4 (100)[c]
Unformed bowel movements[d], mean (SD)	5.4 (4.6)	5.5 (5.6)
Maximum body temperature[e] [°C], median (min; max)	37.0 (35.9; 38.5)	37.1 (36.0; 38.5)
Maximum white blood cell count[e] [10^9/L], median (min; max)	7.26 (0.0; 14.4)	6.30 (0.6; 12.8)
Treatment discontinuation[f], n (%)	ND	ND
Study discontinuation[g], n (%)	ND	ND

a. Number of randomized patients. Values which are based on a different number of patients are marked in the corresponding line, provided the deviation is relevant.
b. Recorded in patients < 2 years of age.
c. IQWiG calculations.
d. Recorded in patients ≥ 2 years of age.
e. Highest value within 3 days before 1st administration of the study drug.
f. No data available on the relevant subpopulation; treatment discontinuation in the total population: 3 vs. 2 patients.
g. No data available on the relevant subpopulation; treatment discontinuation in the total population: 5 vs. 6 patients; among these, 2 and 4 patients, respectively, did not receive any study drug.

CDI: *Clostridioides difficile* infection; f: female; m: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the study population are sufficiently comparable between the two treatment arms. Both treatment arms had a mean patient age of 7 years and an approximately equal sex ratio; there were, however, imbalances in the proportions of patients in age groups ≥ 2 to < 6 years versus ≥ 12 to < 18 years of age and particularly the age group ≥ 6 to < 12. All patients < 2 years of age had watery diarrhoea. The number of unformed bowel movements in patients ≥ 2 years of age was similar at a mean of about 5.5. No data are available on treatment and study discontinuation in the relevant subpopulation.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: fidaxomicin vs. vancomycin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of results	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
SUNSHINE	Yes	Yes	No	Unclear[a]	Yes	Yes	Low
a. Blinding of treatment providers to the study drug was not fully ensured.							
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the SUNSHINE study. This concurs with the company's assessment.

Transferability of the study results to the German healthcare context

The company reports that the available evidence on paediatric patients with the clinical picture is very limited overall. Despite only 5 patients being included in German study centres, the company assumes transferability of the study results to the German healthcare context. The company reasons that, firstly, the SUNSHINE study ensured a similar treatment situation and, secondly, the study drug acts locally in the intestine and is unlikely to be influenced by regional differences.

The company does not present any further information on the transferability of study results to the German healthcare context.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - Global cure
- Health-related quality of life

- AEs
  - SAEs
  - Discontinuation due to AEs
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviated from that of the company, which had used further outcomes in the dossier (Module 4A).

Table 10 shows the outcomes for which the included SUNSHINE study provides data on the relevant subpopulation.

Table 10: Matrix of outcomes – RCT, direct comparison: fidaxomicin vs. vancomycin (research question 1: patients with mild disease course requiring treatment)

Study	Outcomes				
	All-cause mortality	**Global cure**	**Health-related quality of life**	**SAEs**	**Discontinuation due to AEs**
SUNSHINE	Yes	Yes	No[a]	Yes[b]	Yes

a. Outcome not recorded.
b. Includes relevant percentage of events which might be considered either adverse events or disease symptoms.

AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event

According to the study protocol, the SUNSHINE study recorded CDI symptoms as an outcome. In general, symptom outcomes are potentially relevant for the present assessment, but neither further information nor related analyses are available on this topic.

2.3.2.2 Risk of bias

Table 11 presents the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias at study and outcome levels – RCT, direct comparison: Fidaxomicin vs. vancomycin (research question 1: patients with mild disease course requiring treatment)

Study	Study level	Outcomes				
		All-cause mortality	Global cure	Health-related quality of life	SAEs	Discontinuation due to AEs
SUNSHINE	L	L	H[a, b]	–[c]	H[a, d]	H[b]

a. The proportion of patients with incomplete follow-up is unclear.
b. Lack of blinding with subjective recording of outcomes.
c. Outcome not recorded.
d. Includes a relevant percentage of events which might be considered either adverse events or disease symptoms.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event

Concurring with the company's assessment, the outcome-specific risk of bias is deemed low for the results of all-cause mortality. However, the rationale deviates from that of the company, which deems the intention-to-treat (ITT) principle adequately implemented. This runs counter to the fact that the proportion of patients who were incompletely followed up is unclear. Due to the low probability of additional deaths occurring, however, replacing missing values by nonresponders (alive until study end) cannot be deemed adequate.

Furthermore, the results for the outcome of global cure were rated as potentially highly biased due to lack of blinding (of patients and possibly also investigators) with subjective recording of outcomes as well as due to the unclear proportion of replaced values. While data on study discontinuation are lacking for the relevant subpopulations, a relevant difference in study drop-outs between treatment arms (fidaxomicin arm: n = 5 [5.0%]; vancomycin arm: n = 6 [12.5%]) is reported for the total population. It remains unclear which percentage of values was replaced by nonresponse (not cured by study end).

The results for the outcome of SAEs are also associated with a high risk of bias due to the unclear percentage of replaced values. Further, a relevant percentage of events for this outcome might be considered either adverse events or disease symptoms. The results for the outcome of discontinuation due to AEs are associated with a high risk of bias due to lack of blinding with subjective outcome recording.

The company deviates from this assessment by deeming the risk of bias for the results of these outcomes to be low. While reporting that the investigators were blinded, the company added, that according to Module 4 A, Appendix 4-E, there was a possibility of inadvertent unblinding

given the characteristics of the study drug and study population. No further information on inadvertent unblinding is available.

Summary assessment of certainty of results

In summary, the certainty of results for all outcomes is to be rated as limited. This is due to uncertainty in the definition of subpopulations (see Section 2.3.1.2) as well as a high risk of bias of results for the outcomes included (except for overall survival).

Overall, at most hints, e.g. of an added benefit, can therefore be derived from the available data.

2.3.2.3 Results

Table 12 and Table 13 summarize the results on the comparison of fidaxomicin with vancomycin in patients with mild disease course requiring treatment. Where necessary, the data from the company's dossier are complemented by IQWiG calculations. The Kaplan-Meier curves on the supplementary outcome of resolution of diarrhoea are shown in Appendix B of the full dossier assessment and tables on common AEs in Appendix C of the full dossier assessment.

Table 12: Results (mortality, morbidity, adverse events, dichotomous) – RCT, direct comparison: fidaxomicin vs. vancomycin (research question 1: patients with mild disease course requiring treatment)

Study Outcome category	Fidaxomicin		Vancomycin		Fidaxomicin vs. vancomycin
Outcome	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
SUNSHINE					
Mortality					
All-cause mortality	49	3 (6.1)	17	0 (0)	2.52 [0.14; 46.44]; 0.376[b]
Morbidity					
Global cure	49	30 (61.2)	17	10 (58.8)	1.04 [0.66; 1.64][c]; 0.863
AEs					
AEs[d] (supplementary)	48	32 (66.7)	16	12 (75.0)	–
SAEs[d]	48	9 (18.8)	16	4 (25.0)	0.75 [0.27; 2.11]; 0.585
Discontinuation due to AEs[e]	48	0 (0)	16	1 (6.3)	0.12 [0.00; 2.71]; 0.107[b]

a. Unless otherwise indicated, RR, CI, and p-value are based on a logistic regression model stratified by age.
b. IQWiG calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [23]). In light of 0 events occurring in 1 study arm, the correction factor of 0.5 was used in both study arms.
c. IQWiG calculations, reversed direction of effect; company reports the effect for non-occurrence of event.
d. Includes a relevant percentage of events which might be considered either adverse events or disease symptoms.
e. Discontinuation was due to the PT of vomiting.

AE: adverse event; CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 13: Results (morbidity, time to event) – RCT, direct comparison: fidaxomicin vs. vancomycin (research question 1: patients with mild disease course requiring treatment)

Study Outcome category Outcome	Fidaxomicin N	Fidaxomicin Median time to event in hours [95% CI] Patients with event n (%)	Vancomycin N	Vancomycin Median time to event in hours [95% CI] Patients with event n (%)	Fidaxomicin vs. vancomycin HR [95% CI]; p-value[a]
SUNSHINE					
Morbidity					
Resolution of diarrhoea[b] (supplementary outcome)	49	97.0 [39.0; 148.0] 34 (69.4)	17	100.0 [27.0; NR] 11 (64.7)	1.27 [0.63; 2.56][c]; 0.508

a. HR, CI, and p-value: Cox proportional hazards model, stratified by age
b. Duration (recorded in hours, rounded up after ≥ 30 minutes) from the 1st intake of the study drug until the last episode of watery diarrhoea (patients < 2 years of age) or the last unformed bowel movement (patients ≥ 2 to < 18 years of age), each on the day before the first 2 consecutive days without watery diarrhoea or with < 3 unformed bowel movements and sustained to the end of the treatment phase.
c. IQWiG calculations, reversed direction of effect; company reports the effect for non-occurrence of event.

CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial

Due to uncertainty in the definition of subpopulations and high risk of bias at outcome level for all outcomes except overall survival – as discussed in Sections 2.3.1.2 and 2.3.2.2 – the available data can be used to derive at most hints, e.g. of added benefit, for all outcomes.

Mortality

All-cause mortality

In the SUNSHINE study, deaths were recorded under AEs.

For the outcome of overall survival, no statistically significant difference between treatment arms was found for the relevant subpopulation. This results in no hint of added benefit of fidaxomicin in comparison with vancomycin; an added benefit is therefore not proven.

This concurs with the company's approach insofar as it arrives at the same conclusion on the basis of the overall population.

Morbidity

Global cure

Operationalization

The outcome of global cure was defined as clinical response by treatment end or 2 days thereafter, sustained until the end of the study (30 days after treatment end), i.e. without evidence of recurrence of disease. Clinical response was defined depending on age as follows:

- In patients < 2 years of age, as the absence of watery diarrhoea on 2 consecutive days during treatment, sustained until treatment discontinuation or time recorded.
- In patients ≥ 2 years to < 18 years of age, as improvement in the number and consistency of bowel movements, as determined by fewer than 3 unformed bowel movements per day on 2 consecutive treatment days, sustained until treatment discontinuation or time recorded.

In case of recurrence of diarrhoea to an extent greater than that noted at the end of treatment, testing was conducted for the presence of toxigenic *Clostridioides difficile* in stool. Only disease courses of patients with positive test results were defined as recurrent.

The outcome was analysed for all randomized patients.

Result

For the outcome of global cure, no statistically significant difference between treatment arms was found for the relevant subpopulation. The same is true for the supplementary data on time to resolution of diarrhoea. However, an effect modification by sex was found for the outcome of global cure (see Section 2.3.2.4). In boys, there was a statistically significant difference to the disadvantage of fidaxomicin. For girls, no statistically significant difference between treatment arms was found. In boys, this results in a hint of lesser benefit of fidaxomicin in comparison with vancomycin. For girls, there is no hint of added or lesser benefit of fidaxomicin in comparison with vancomycin; an added or lesser benefit is therefore not proven for girls.

This deviates from the company's assessment, which disregards the given effect modification and derives an indication of added benefit for the outcome of global cure on the basis of the total population of the SUNSHINE study (see Table 28 in Appendix A of the full dossier assessment). In its assessment, the company includes time to resolution of diarrhoea as a separate outcome.

Health-related quality of life

The SUNSHINE study did not record any outcomes on health-related quality of life.

AEs

SAEs

For the outcome of SAEs, no statistically significant difference between treatment arms was found for the relevant subpopulation. This results in no hint of greater or lesser harm of fidaxomicin in comparison with vancomycin; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which derives an indication of added benefit from the overall picture of the AE outcomes it considered on the basis of the total population.

Discontinuation due to AEs

In the relevant subpopulation, 1 patient in the vancomycin arm discontinued therapy due to the AE of vomiting. No statistically significant difference between treatment arms was found. Consequently, for the outcome of discontinuation due to AEs, there is no hint of greater or lesser harm of fidaxomicin in comparison with vancomycin; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which derives an indication of added benefit from the overall picture of the AE outcomes it considered on the basis of the total population.

2.3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- Age (< 2 years / ≥ 2 to < 6 years / ≥ 6 to < 12 years / ≥ 12 to < 18 years)
- Sex (female/male)

Interaction tests are performed whenever at least 10 patients per subgroup were included in the analysis. For binary data, there must also be 10 events in at least 1 subgroup.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Table 14 presents the subgroup results of fidaxomicin in comparison with vancomycin.

Table 14: Subgroups (morbidity) – RCT, direct comparison: fidaxomicin vs. vancomycin (research question 1: patients with mild disease course requiring treatment)

Study	Fidaxomicin		Vancomycin		Fidaxomicin vs. vancomycin	
Outcome Characteristic Subgroup	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]	p-value[a]
SUNSHINE						
Morbidity						
Global cure						
Sex						
Male	24	11 (45.8)	8	7 (87.5)	0.52 [0.32; 0.87][b]	0.013
Female	25	19 (76.0)	9	3 (33.3)	2.27 [0.88; 5.88][b]	0.089
Total					Interaction:	0.007

a. RR, CI and p-value as well as p-value of the interaction test from logistic regression model stratified by sex.
b. IQWiG calculations, reversed direction of effect; company reports the effect for non-occurrence of event.

CI: confidence interval; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk

Morbidity

Global cure

For the outcome of global cure, there was an effect modification by the attribute of sex. For boys, a statistically significant difference between treatment arms was found to the disadvantage of fidaxomicin, while no statistically significant difference was found for girls. In boys, this results in a hint of lesser benefit of fidaxomicin in comparison with vancomycin. For girls, there is no hint of added or lesser benefit of fidaxomicin in comparison with vancomycin; an added or lesser benefit is therefore not proven for girls.

This deviates from the company's approach, which reports no relevant effect modifications based on the total population of the SUNSHINE study.

2.3.3 Probability and extent of added benefit

Below, the probability and extent of added benefit for patients from birth to < 18 years with mild CDI requiring treatment are derived at outcome level. The various outcome categories and the effect sizes are taken into account. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on the 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.

2.3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.3.2.3 (see Table 15).

Determination of the outcome category for the considered morbidity outcome

In terms of the morbidity outcome considered in the present benefit assessment, the dossier does not permit an inference as to whether it was serious/severe or non-serious/non-severe. An explanation of the allocation of this outcome is provided below.

Global cure

The outcome of global cure is allocated to the outcome category of non-serious/non-severe symptoms / late complications. This is a consequence of the disease course being rated as mild, albeit requiring treatment, at study start in the subpopulation for research question 1.

This deviates from the company's approach, which allocates global cure to the outcome category of serious/severe symptoms / late complications on the basis of the total population of the SUNSHINE study.

Table 15: Extent of added benefit at outcome level: fidaxomicin vs. vancomycin (research question 1: patients with mild disease course requiring treatment)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Fidaxomicin vs. vancomycin** **Event ratio (%)** **RR [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	6.1% vs. 0% 2.52 [0.14; 46.44]; p = 0.376	Lesser/added benefit not proven
Morbidity		
Global cure Sex		
Male	45.8% vs. 87.5% 0.52 [0.32; 0.87]; p = 0.013 probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_o < 0.90$ Lesser benefit; extent: minor
Female	76.0% vs. 33.3% 2.27 [0.88; 5.88]; p = 0.089	Lesser/added benefit not proven
Health-related quality of life		
–	No outcomes of this category recorded	Lesser/added benefit not proven
AEs		
SAEs[c]	18.8% vs. 25.0% 0.75 [0.27; 2.11]; p = 0.585	Greater/lesser harm not proven
Discontinuation due to AEs[d]	0% vs. 6.3% 0.12 [0.00; 2.71]; p = 0.107	Greater/lesser harm not proven

a. Probability is stated if a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits based on the upper confidence limit (CI_u).
c. Includes relevant percentage of events which might be considered either adverse events or disease symptoms.
d. In the relevant subpopulation, only 1 patient in the vancomycin arm discontinued therapy due to the AE of vomiting.

AE: adverse event; CI: confidence interval; CI_u: upper confidence limit; RR: relative risk; SAE: serious adverse event

2.3.3.2 Overall conclusion on added benefit

Table 16 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of fidaxomicin in comparison with vancomycin (research question 1: Patients with mild disease course requiring treatment)

Positive effects	Negative effects
–	Non-serious/non-severe symptoms / late complications: global cure Sex: male Hint of lesser benefit – extent: minor

The aggregate results for boys only show a hint of lesser benefit of minor extent for fidaxomicin in comparison with vancomycin in the outcome category of morbidity.

In summary, for boys from birth to < 18 years of age with mild CDI requiring treatment, there is a hint of lesser benefit of fidaxomicin in comparison with vancomycin. For girls from birth to < 18 years of age with mild CDI requiring treatment, there is no proof of added or lesser benefit of fidaxomicin in comparison with vancomycin.

The above assessment deviates from that of the company, which derives an indication of considerable added benefit for the entire paediatric patient population regardless of disease severity. Furthermore, the company uses health services data and in vitro data on resistance development to derive added benefit without systematically analysing these data. Irrespective thereof, the company argues that fidaxomicin is an alternative to vancomycin and the development of innovative treatment options is necessary in the present therapeutic indication. However, while irrelevant to the research question of the early benefit assessment, these arguments play a role in the considerations for regulatory approval. After all, relevant differences in resistance can be expected to be reflected by the outcome of global cure as well.

2.4 Research question 2: Patients with severe and/or recurrent disease course

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- Study list on fidaxomicin (status: 03 February 2020)
- Bibliographic literature search on fidaxomicin (most recent search on 03 February 2020)
- Search in trial registries / study results databases on fidaxomicin (most recent search on 03 February 2020)
- Search on the G-BA website on fidaxomicin (most recent search on 03 February 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on fidaxomicin (most recent search on 19 March 2020)

The check did not identify any additional relevant studies.

2.4.1.1 Included studies

The study pool for the benefit assessment of fidaxomicin consists of the RCT SUNSHINE (see Table 5 in Section 2.3.1.1). This concurs with the company's study pool.

In addition to patients with severe and/or recurrent disease course, patients with mild disease course requiring treatment were included in the SUNSHINE study. See Section 2.3.1.2 for the definition of severe or recurrent disease course.

In the present benefit assessment, the results of the subpopulation with severe and/or recurrent disease course were used for research question 2.

This deviates from the company's approach. The company did present the results for both subpopulations. For deriving the added benefit, however, it used the results of the total population (see Section 2.3.3.2).

2.4.1.2 Study characteristics

See Section 2.3.1.2 for a description of the included SUNSHINE trial's study and intervention characteristics.

Subpopulation relevant for the research question

The subpopulation with severe and/or recurrent disease course is relevant for research question 2 of the present benefit assessment. Regarding the definition of this subpopulation, see Section 2.3.1.2.

Characterization of the study population

Table 17 shows the characteristics of the patients in the relevant subpopulation of the study included.

Table 17: Characterization of the study population – RCT, direct comparison: fidaxomicin vs. vancomycin (research question 2: patients with severe and/or recurrent disease course)

Study **Characteristics** **Category**	**Fidaxomicin** **N[a] = 51**	**Vancomycin** **N[a] = 31**
SUNSHINE		
Age [years], mean (SD)	7 (5)	6 (4)
Age groups [years], n (%)		
< 2	7 (13.7)	6 (19.4)
≥ 2–< 6	21 (41.2)	10 (32.3)
≥ 6–< 12	13 (25.5)	11 (35.5)
≥ 12–< 18	10 (19.6)	4 (12.9)
Sex [f/m], %	31/69	39/61
Episode of diarrhoea in prior history[b] , n (%)	35 (68.6)[c]	14 (45.2)[c]
With confirmed CDI	28 (54.9)	13 (41.9)
1 episode	21 (41.2)	8 (25.8)
2 episodes	5 (9.8)	4 (12.9)
≥ 3 episodes	2 (3.9)	1 (3.2)
Without confirmed CDI	6 (11.8)	0 (0)
Unknown CDI confirmation	1 (2.0)	1 (3.2)
Watery diarrhoea[d], n (%)	7 (100)[c]	6 (100)[c]
Unformed bowel movements[e], mean (SD)	7.2 (7.4)	6.3 (5.6)
Maximum body temperature[f] [°C], median (min; max)	37.95 (36.2; 40.7)	38.7 (36.5; 40.6)
Maximum white blood cell count[f] [10^9/L], median (min; max)	6.44 (0.2; 26.2)	6.61 (0.1; 31.7)
Elevated serum creatinine[g], n (%)	ND	ND
Treatment discontinuation[h], n (%)	ND	ND
Study discontinuation[i], n (%)	ND	ND

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. Within 3 months before screening.
c.IQWiG calculations.
d. Recorded in patients < 2 years of age.
e. In patients ≥ 2 years of age; number unknown for 1 patient per treatment arm.
f. Highest value within 3 days before 1st intake of study drug; in 1 person in fidaxomicin arm and 2 persons in the vancomycin arm, body temperature and/or maximum white blood cell count was unknown.
g. Age-adjusted consideration of creatinine thresholds [24].
h. No data available on the relevant subpopulation; treatment discontinuation in the total population: 3 vs. 2 patients.
i. No data available on the relevant subpopulation; treatment discontinuation in the total population: 5 vs. 6 patients; among these, 2 and 4 patients, respectively, did not receive any study drug.

CDI: *Clostridioides difficile* infection; f: female; ITT: intention to treat; max: maximum; min: minimum; m: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the study population are sufficiently comparable between the two study arms. Mean patient age was 7 and 6 years, respectively, and about one-third were female. All patients < 2 years of age had watery diarrhoea. In the age group ≥ 2 years, the mean number of unformed bowel movements was approximately 7 and 6, respectively.

As described in Section 2.3.1.2, the company reported that it allocated patients to the subpopulation with severe disease course if they had met at least 1 of the 3 company-selected criteria for the severity rating (fever, leukocytosis, and elevated serum creatinine). However, for neither the total population nor the relevant subpopulation are any data available on the percentage of patients with elevated serum creatinine. At least half of the patients in the vancomycin arm had fever as defined in Section 2.3.1.2; in the fidaxomicin arm, the median maximum body temperature was slightly below the threshold. Likewise, not all patients had leukocytosis (> 15 000/mm^3 leukocytosis at study start). Even if this precludes an unequivocal allocation as per the company's definition, it is assumed that patients met at least 1 of the criteria employed for allocation to the patient population with severe disease course. In addition, patients with recurrent disease course are allocated to research question 2 of this benefit assessment even if their disease course is not necessarily severe. Hence, the subpopulation formed by the company is assumed to adequately reflect the patient population for research question 2 (patients with severe and/or recurrent disease course).

No data are available on study and treatment discontinuation in the relevant subpopulation.

Risk of bias across outcomes (study level)

For the assessment of the risk of bias across outcomes (risk of bias at study level), see Table 9 in Section 2.3.1.2.

Transferability of the study results to the German healthcare context

On the transferability of the study results to the German healthcare context, see Section 2.3.1.2.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

Patient-relevant outcomes which are included in the assessment are described in Section 2.3.2.1. Table 18 shows the outcomes for which the included SUNSHINE study provides data on the relevant subpopulation.

Table 18: Matrix of outcomes – RCT, direct comparison: fidaxomicin vs. vancomycin (research question 2: patients with severe and/or recurrent disease)

Study	Outcomes					
	All-cause mortality	Global cure	Health-related quality of life	SAEs	Discontinuation due to AEs	Further specific AEs[a]
SUNSHINE	Yes	Yes	No[b]	Yes[c]	Yes	Yes

a. The following event is considered (MedDRA coding): "nervous system disorders (SOC, AEs)".
b. Outcome not recorded.
c. Includes relevant percentage of events which might be considered either adverse events or disease symptoms.

AE: adverse event; RCT: randomized controlled trial; SOC: system organ class; SAE: serious adverse event

According to the study protocol, the SUNSHINE study was to record CDI symptoms. In general, symptom outcomes are potentially relevant for the present assessment, but neither further information nor related analyses are available on this topic.

2.4.2.2 Risk of bias

Table 19 presents the risk of bias for the results of the relevant outcomes.

Table 19: Risk of bias at study and outcome levels – RCT, direct comparison: fidaxomicin vs. vancomycin (research question 2: patients with severe and/or recurrent disease course)

Study	Study level	Outcomes					
		All-cause mortality	Global cure	Health-related quality of life	SAEs	Discontinuation due to AEs	Further specific AEs[a]
SUNSHINE	L	L	H[b, c]	–[d]	H[b, e]	H[c]	H[b, c]

a. The following event is considered (MedDRA coding): "nervous system disorders (SOC, AEs)".
b. Unclear proportion of patients who were incompletely followed up.
c. Lack of blinding with subjective recording of outcomes.
d. Outcome not recorded.
e. Includes relevant percentage of events which might be considered either adverse events or disease symptoms.

CTCAE: Common Terminology Criteria for Adverse Events; H: high; MedDRA: Medical Dictionary for Regulatory Activities; L: low; RCT: randomized controlled trial; SOC: system organ class; SAE: serious adverse event; AE: adverse event

Concurring with the company's assessment, the outcome-specific risk of bias is deemed low for the results of all-cause mortality. However, the rationale deviates from that of the company, which deems the ITT principle adequately implemented. This is contradicted by the fact that the proportion of patients who were incompletely followed up is unclear. Due to the low probability of additional deaths occurring, however, replacing missing values by nonresponders (alive until study end) cannot be deemed adequate.

Furthermore, the results for the outcomes of global cure and nervous system disorders (AEs) were rated as potentially highly biased due to lack of blinding (in patients and possibly investigators as well) with subjective recording of outcomes and the unclear proportion of replaced values. While data on study discontinuation are lacking for the relevant subpopulations, a relevant difference in study drop-outs between treatment arms (fidaxomicin arm: n = 5 [5.0%]; vancomycin arm: n = 6 [12.5%]) is reported for the total population. It remains unclear which percentage of values was replaced by nonresponse (not cured by study end). The results for the outcome of SAEs are also associated with a high risk of bias due to the unclear percentage of replaced values. Further, a relevant percentage of events for this outcome might be considered either adverse events or disease symptoms. The results for the outcome of discontinuation due to AEs are associated with a high risk of bias due to lack of blinding with subjective outcome recording.

In deviation from this, the company excludes the outcome of nervous system disorders from its assessment and rates the risk of bias for the results of the remaining outcomes as low. While it reports that the investigators were blinded, it adds that according to Module 4 A, Appendix 4-E, there was a possibility of inadvertent unblinding given the characteristics of the study drug and study population. No further information on inadvertent unblinding is available.

Summary assessment of certainty of results

In summary, the certainty of results for all outcomes is to be rated as limited. This is due to the uncertainty in the formation of subpopulations (see Section 2.3.1.2) as well as the high risk of bias of results of the outcomes included (except for overall survival).

Overall, at most hints, e.g. of an added benefit, can therefore be derived from the available data.

2.4.2.3 Results

Table 20 and Table 21 summarize the results for the comparison of fidaxomicin with vancomycin in patients with severe and/or recurrent disease course. The Kaplan-Meier curves on the supplementary outcome of resolution of diarrhoea are shown in Appendix B of the full dossier assessment and tables on common AEs in Appendix C of the full dossier assessment.

Table 20: Results (mortality, morbidity, adverse events, dichotomous) – RCT, direct comparison: fidaxomicin vs. vancomycin (research question 2: patients with severe and/or recurrent disease course)

Study Outcome category Outcome	Fidaxomicin N	Fidaxomicin Patients with event n (%)	Vancomycin N	Vancomycin Patients with event n (%)	Fidaxomicin vs. vancomycin RR [95% CI]; p-value[a]
SUNSHINE					
Mortality					
All-cause mortality	51	0 (0)	31	0 (0)	–
Morbidity					
Global cure	51	37 (72.5)	31	12 (38.7)	1.89 [1.16; 3.03][b]; 0.009
AEs					
AEs[c] (supplementary)	50	40 (80.0)	28	21 (75.0)	–
SAEs[c]	50	15 (30.0)	28	8 (28.6)	1.05 [0.51; 2.16]; 0.895
Discontinuation due to AEs[d]	50	1 (2.0)	28	0 (0)	1.71 [0.07; 40.53]; 0.573[e]
Nervous system disorders (SOC, AEs)	50	9 (18.0)	28	0 (0)	OR: 8.19 [1.58; ∞]; 0.014[f]

a. RR, CI, and p-value: logistic regression model, stratified by age.
b. IQWiG calculations, reversed direction of effect; company reports the effect for non-occurrence of event.
c. Includes relevant percentage of events which might be considered either adverse events or disease symptoms.
d. Reason for discontinuation was the PT of colitis.
e. IQWiG calculation of RR, CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [23]). Since in one study arm, 0 events occurred, the correction factor of 0.5 was used in both study arms.
f. IQWiG calculation using SAS 9.4 (procedure "proc logistic", statement "exact", option "exact"), exact conditional logistic regression according to [25]; 1-sided p-value.

AE: adverse event; CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; OR: odds ratio; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 21: Results (morbidity, time to event) – RCT, direct comparison: Fidaxomicin vs. vancomycin (research question 2: patients with severe and/or recurrent disease course)

Study Outcome category Outcome	Fidaxomicin N	Fidaxomicin Median time to event in hours [95% CI] Patients with event n (%)	Vancomycin N	Vancomycin Median time to event in hours [95% CI] Patients with event n (%)	Fidaxomicin vs. vancomycin HR [95% CI]; p-value[a]
SUNSHINE					
Morbidity					
Resolution of diarrhoea[b] (supplementary outcome)	51	42.0 [23.0; 143.0] 40 (78.4)	31	102.0 [45.0; 172.0] 21 (67.7)	1.41 [0.83; 2.44][c]; 0.209

a. HR, CI, and p-value: Cox proportional hazards model, stratified by age.
b. Duration (recorded in hours, rounded up after ≥ 30 minutes) from the 1st intake of the study drug until the last episode of watery diarrhoea (patients < 2 years of age) or the last unformed bowel movement (patients ≥ 2 to < 18 years of age), each on the day before the first 2 consecutive days without watery diarrhoea or with < 3 unformed bowel movements and sustained to the end of the treatment phase.
c. IQWiG calculations, reversed direction of effect; company reports the effect for non-occurrence of event.

CI: confidence interval; HR: hazard ratioA: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial

Due to uncertainty in the definition of subpopulations and high risk of bias at outcome level for all outcomes except overall survival – as discussed in Sections 2.3.1.2 and 2.4.2.2 – the available data can be used to derive at most hints, e.g. of added benefit, for all outcomes.

Mortality

All-cause mortality

In the SUNSHINE study, deaths were recorded under AEs.

For the outcome of overall survival, no death occurred in the relevant subpopulation. There is no hint of added benefit of fidaxomicin in comparison with vancomycin; an added benefit is therefore not proven.

This concurs with the company's approach insofar as it arrives at the same conclusion on the basis of the overall population.

Morbidity

Global cure

Operationalization

See Section 2.3.2.3 regarding the operationalization of global cure.

Result

For the outcome of global cure, a statistically significant difference in favour of fidaxomicin was found for the relevant subpopulation. Conversely, for the supplementary outcome of time to resolution of diarrhoea, no statistically significant difference between treatment arms was found. This results in a hint of added benefit of fidaxomicin in comparison with vancomycin.

This deviates from the company's assessment, which derives an indication of added benefit for the outcome of global cure on the basis of the total population. In its assessment, the company includes time to resolution of diarrhoea as a separate outcome.

Health-related quality of life

The SUNSHINE study did not record any outcomes on health-related quality of life.

AEs

SAEs

For the outcome of SAEs, no statistically significant difference between treatment arms was found for the relevant subpopulation. This results in no hint of greater or lesser harm of fidaxomicin in comparison with vancomycin; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which derives an indication of added benefit from the overall picture of the AE outcomes it considered on the basis of the total population.

Discontinuation due to AEs

In the relevant subpopulation, 1 patient in the fidaxomicin arm discontinued therapy due to the AE of colitis. No statistically significant difference between treatment arms was found. Consequently, for the outcome of discontinuation due to AEs, there is no hint of greater or lesser harm of fidaxomicin in comparison with vancomycin; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which derives an indication of added benefit from the overall picture of the AE outcomes it considered on the basis of the total population.

Specific AEs

Nervous system disorders (SOC, AEs)

For the outcome of nervous system disorders, a statistically significant difference to the disadvantage of fidaxomicin was found for the relevant subpopulation. In this case, the estimate of relative risk (RR) using a continuity correction of 0.5 for all cells of the corresponding fourfold table does not lead to a meaningful 95% confidence interval. In order to still permit conclusions on the extent of the observed effect, the RR was approximated by means of an exact estimate for the odds ratio (see Table 20). This results in a hint of greater harm of fidaxomicin in comparison with vancomycin.

This deviates from the company's assessment, which disregards the outcome of nervous system disorders and, on aggregate view, derives an indication of added benefit from the AE outcomes it considered on the basis of the total population.

2.4.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- Age (< 2 years / ≥ 2 to < 6 years / ≥ 6 to < 12 years / ≥ 12 to < 18 years)
- Sex (female/male)

Interaction tests are performed whenever at least 10 patients per subgroup were included in the analysis. For binary data, there must also be 10 events in at least 1 subgroup.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

According to the above-described methods, no relevant effect modification was identified.

2.4.3 Probability and extent of added benefit

Below, the probability and extent of added benefit for patients from birth to < 18 years of age with severe and/or recurrent CDI requiring treatment are derived at outcome level. The various outcome categories and the effect sizes are taken into account. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on the 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.

2.4.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4.2.3 (see Table 22).

Determination of the outcome category for the considered morbidity outcome

In terms of the morbidity outcome considered in the present benefit assessment, the dossier does not permit an inference as to whether it was serious/severe or non-serious/non-severe. An explanation of the categorization of this outcome is provided below.

Global cure

The outcome of global cure is was assigned to the outcome category of serious/severe symptoms / late complications This results from the severity of the disease course found in the subpopulation for research question 2 at the start of the study, as reflected by severe and/or

recurrent disease course. However, the severity classification is largely based on laboratory values which per se do not provide any information on the severity of symptoms (see Section 2.3.1.2). No further information on the severity of symptoms is available.

This deviates from the approach of the company insofar as the company allocates to the outcome category of serious/severe symptoms / late complications on the basis of the total population of the SUNSHINE study rather than the relevant subpopulation.

Table 22: Extent of added benefit at outcome level: fidaxomicin vs. vancomycin (research question 2: patients with severe and/or recurrent disease course)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Fidaxomicin vs. vancomycin** **Event ratio (%)** **RR [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% –	Lesser/added benefit not proven
Morbidity		
Global cure	72.5% vs. 38.7% 1.89 [1.16; 3.03]; 0.53 [0.33; 0.86][c] p = 0.009 probability: hint	Outcome category: serious/severe symptoms / late complications $0.75 \leq CI_o < 0.90$ Added benefit, extent: considerable
Health-related quality of life		
–	No outcomes of this category recorded	Lesser/added benefit not proven
AEs		
SAEs[d]	30.0% vs. 28.6% 1.05 [0.51; 2.16]; p = 0.895	Greater/lesser harm not proven
Discontinuation due to AEs[e]	2.0% vs. 0% 1.71 [0.07; 40.53]; p = 0.573	Greater/lesser harm not proven
Nervous system disorders (SOC, AEs)	18.0% vs. 0% OR: 8.19 [1.58; ∞]; OR: 0.12 [0; 0.63][f]; p = 0.014 probability: hint	Outcome category: non-serious/non-severe AEs greater harm; extent: considerable

a. Probability given if a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits based on the upper confidence limit (CI_u).
c. Reversed direction of effect to enable use of limits to derive the extent of added benefit.
d. Includes a relevant percentage of events which might be considered either adverse events or disease symptoms.
e. In the relevant subpopulation, only 1 patient in the fidaxomicin arm discontinued therapy due to the AE of colitis.
f. IQWiG calculation, reversed direction of effect to enable use of limits to derive the extent of added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; OR: odds ratio; RR: relative risk; SAE: serious adverse event

2.4.3.2 Overall conclusion on added benefit

Table 23 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 23: Positive and negative effects from the assessment of fidaxomicin in comparison with vancomycin (research question 2: patients with severe and/or recurrent disease course)

Positive effects	**Negative effects**
Serious/severe symptoms / late complications: global cure Hint of added benefit – extent: considerable	Non-serious/non-severe AEs: nervous system disorders (AEs) Hint of greater harm – extent: considerable
AEs: adverse events	

Overall, the analysis shows a positive and a negative effect of fidaxomicin in comparison with vancomycin. On the positive side, a hint of considerable added benefit was found for the outcome of global cure. On the negative side, there is a hint of greater harm of considerable extent for the specific AE of nervous system disorders.

Given that the outcome of global cure was assigned to the outcome category of serious/severe AEs / late complications, yet the observed negative effect is non-serious/non-severe, the positive effect with regard to global cure is assumably not being challenged by the negative effect.

In summary, for patients from birth to < 18 years of age with severe and/or recurrent CDI, there is a hint of considerable added benefit of fidaxomicin in comparison with the ACT of vancomycin.

The above assessment deviates from the one provided by the company, which derives an indication of considerable added benefit for the entire paediatric patient population, regardless of disease severity. Furthermore, the company uses health services data and in vitro data on resistance development to derive added benefit without systematically analysing these data. Irrespective thereof, the company claims that fidaxomicin is an alternative to vancomycin and the development of innovative treatment options is necessary in the present therapeutic indication. These points are, however, irrelevant for an early benefit assessment's research question and instead are of interest for the research question in regulatory approval. After all, relevant differences in resistance can be expected to be reflected by the outcome of global cure as well.

2.5 Probability and extent of added benefit – summary

Table 24 presents a summary of the results of the benefit assessment of fidaxomicin in comparison with the ACT.

Table 24: Fidaxomicin – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a, b]**	**Probability and extent of added benefit**
1	Patients from birth to < 18 years of age with mild CDI[c] requiring treatment	Metronidazole or **vancomycin**	▪ Boys: hint of lesser benefit ▪ Girls: added benefit not proven
2	Patients from birth to < 18 years of age with severe and/or recurrent CDI[c]	Vancomycin	Hint of considerable added benefit

a. Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
b. In accordance with the G-BA, guidelines on the appropriate use of antibiotics were to be taken into account.
c. The terms CDAD and CDI are synonymous. The term CDI is used throughout this document.

ACT: appropriate comparator therapy; CDAD: *Clostridioides difficile*-associated diarrhoea; CDI: *Clostridioides difficile* infection; G-BA: Federal Joint Committee

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

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Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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