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Ivacaftor/tezacaftor/elexacaftor and ivacaftor (cystic fibrosis, 6 to 11 years, F508del mutation, MF mutation, heterozygous) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ivacaftor/Tezacaftor/Elexacaftor und Ivacaftor (zystische Fibrose, 6 bis 11 Jahre, F508del-Mutation, MF-Mutation, heterozygot) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 May 2022). 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Table of contents

List of tables[2]

Page

[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
BMI	body mass index
BSC	best supportive care
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LCI	Lung Clearance Index
MF	minimal function
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference

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) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination of ivacaftor/tezacaftor/elexacaftor plus ivacaftor as well as the benefit of the drug combination of ivacaftor plus ivacaftor/tezacaftor/elexacaftor. 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 8 February 2022.

Research question

The aim of this report is to assess the added benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (hereinafter referred to as ivacaftor/tezacaftor/elexacaftor + ivacaftor) in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in cystic fibrosis (CF) patients 6 to 11 years of age who are heterozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and have a minimal function (MF) mutation on the 2nd allele.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of ivacaftor/tezacaftor/elexacaftor + ivacaftor

Therapeutic indication	**ACT**[a]
CF patients 6 to 11 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [within the meaning of the German Guideline on Remedies] under exhaustion of all possible dietary interventions).

ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; MF: minimal function

The company designated BSC as the ACT, thus following the G-BA's specification.

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) with a minimum duration of 24 weeks were used for the derivation of added benefit.

Study pool and study design

The benefit assessment uses the VX19-445-116 study for the direct comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC with placebo + BSC.

The study enrolled CF patients aged 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele of this gene. At screening, patients had to have a forced expiratory volume in 1 second (FEV_1) of ≥ 70% of predicted normal for age, sex, and height as well as a Lung Clearance Index ($LCI_{2.5}$) ≥ 7.5. The study excluded patients with acute upper or lower airway infection, pulmonary exacerbations, or lung infection with organisms associated with faster deterioration of pulmonary status. In addition, the baseline CF medication was to have been continued unchanged for 28 days before treatment start.

The study randomized a total of 121 patients in a 1:1 ratio either to treatment with ivacaftor/tezacaftor/elexacaftor+ ivacaftor + BSC or to placebo + BSC.

Patients were treated with ivacaftor/tezacaftor/elexacaftor+ ivacaftor in accordance with the Summary of Product Characteristics (SPC) or received a placebo. In both study arms, patients additionally received accompanying baseline therapy.

Primary outcome of the study was the change in $LCI_{2.5}$; patient-relevant secondary outcomes were all-cause morbidity as well as outcomes on morbidity, health-related quality of life, and adverse events (AEs).

Implementation of the appropriate comparator therapy

The G-BA specified BSC as the ACT for ivacaftor/tezacaftor/elexacaftor + ivacaftor in the treatment of CF patients aged 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation.

In the VX19-445-116 study, patients' existing symptomatic therapy was to be continued simultaneously with treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor or placebo. The study protocol required that no changes be made to the concomitant medication from 28 days before study start until the end of the study. For inclusion, the study additionally required participants to be willing to forego any changes to the CF-related concomitant treatment for the entire duration of the study.

The data on prior and concomitant treatment show that, at study start, patients received antibiotics, inhaled medication (including saline solution), digestive enzymes, vitamins, and physical therapy for symptomatic treatment of CF. Detailed information on the number of accompanying therapies administered over the course of the study suggests that during the study, adjustments were made to antibiotic therapy. Detailed information on other therapies, in contrast, does not show whether adjustments were made over the course of the study because at baseline, the majority of included patients already received inhaled medication, mucolytics, or physical therapy. The available information does not show any increases in the number of administered therapies over the course of the study for any of the further therapies except antibiotics. Additionally, the available data do not show in how many patients, if any, the concomitant treatment was adjusted, e.g. by increasing the dose or frequency of drug or non-

drug treatment. Furthermore, it is unclear how many, if any, patients discontinued the concomitant treatment over the course of the study.

In summary, it remains unclear whether the concomitant treatment used in the VX19-445-116 study represents a full ACT implementation of BSC. This conclusion has been informed by the fact that no details are available on treatment adjustments in the form of dose or frequency increases of symptomatic treatment over the course of the study. This circumstance did not, however, lead to exclusion of the study. Rather, it was assumed that the study results are suitable for drawing conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT. However, the uncertainties described were taken into account in the assessment of the certainty of conclusions of the results.

Risk of bias and assessment of the certainty of conclusions

For the VX194-45-16 study, the risk of bias on the study level and the risk of bias for all outcomes included in the present benefit assessment are deemed low.

For the present research question, the certainty of study results is reduced due to the above-described ambiguities concerning the implementation of the ACT. Based on the VX19-445-16 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

Results

Mortality

Overall survival

No deaths occurred in the course of the study. There is no hint of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC for the outcome of all-cause mortality; an added benefit is therefore not proven.

Morbidity

Pulmonary exacerbations

For the outcome of pulmonary exacerbations (reported as AEs, surveyed via the PT "infective pulmonary exacerbation of cystic fibrosis"), there is a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. For pulmonary exacerbations, this results in a hint of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC.

Serious pulmonary exacerbations

For the outcome of serious pulmonary exacerbations (reported as serious adverse events [SAEs], surveyed using the PT “infective pulmonary exacerbation in cystic fibrosis”), no statistically significant difference between treatment groups was found. This results in no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

Symptoms measured using the Cystic Fibrosis Questionnaire-Revised (CFQ-R)

Respiratory symptoms and digestive symptoms domains

For each of the respiratory symptoms and digestive symptoms domains, there is a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with placebo + BSC regarding the mean change over the course of the study from baseline to the respective measurement time. The standardized mean difference (SMD) in the form of Hedges' g was used to assess the relevance of the result. The 95% confidence interval (CI) was not fully outside the irrelevance range [-0.2; 0.2] for either of them. It was therefore impossible to infer the effect to be relevant. For the CFQ-R respiratory symptoms and digestive symptoms domains, this results in no hint of added benefit of ivacaftor/tezacaftor/elexacaftor+ ivacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

Physical functioning, emotional functioning, body image, eating disturbances, and treatment burden domains

In the physical functioning, emotional functioning, body image, eating disturbances, and treatment burden domains, no statistically significant difference between treatment groups was found regarding the mean changes over the course of the study from baseline to the respective measurement time. This results in no hint of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC for the CFQ-R domains of physical functioning, emotional functioning, body image, eating disturbances, and treatment burden; therefore, there is no hint of an added benefit.

Social functioning domain

In the social functioning domain, there is a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with placebo + BSC regarding mean changes over the course of the study from baseline to the respective measurement time. The 95% CI was not fully outside the irrelevance range [-0.2; 0.2]. The effect can therefore not be inferred to be relevant. For the CFQ-R social functioning domain, this results in no hint of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

There was no statistically significant difference between the treatment groups for either of the outcomes of SAEs and discontinuation due to AEs. This results in no hint of greater or lesser harm from ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC for either of them; greater or lesser harm is therefore not proven.

Abdominal pain (PT, AEs)

For the outcome of abdominal pain (PT, AEs), there is a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. This results in a hint of lesser harm from ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC.

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

On the basis of the results presented, the probability and extent of added benefit of the drug combination of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT are assessed as follows:

All things considered, exclusively favourable effects of ivacaftor/tezacaftor/elexacaftor + ivacaftor were found in comparison with BSC. There is a hint of considerable added benefit for the outcome of pulmonary exacerbations, while a hint of lesser harm of the same extent is found for the outcome of abdominal pain.

In summary, this results in a hint of considerable added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT of BSC for CF patients 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation.

Table 3 summarizes the probability and extent of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor.

Table 3: Ivacaftor/tezacaftor/elexacaftor + ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with cystic fibrosis from 6 to 11 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele	BSC[b]	Hint of considerable added benefit

a: Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [within the meaning of the German Guideline on Remedies] under exhaustion of all possible dietary interventions).

ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; MF: minimal function

[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].

The result of the assessment equally applies to ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor.

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 ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (hereinafter referred to as ivacaftor/tezacaftor/elexacaftor + ivacaftor) in comparison with BSC as the ACT in CF patients 6 to 11 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of ivacaftor/tezacaftor/elexacaftor + ivacaftor

Therapeutic indication	**ACT[a]**
CF patients 6 to 11 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [within the meaning of the German Guideline on Remedies] under exhaustion of all possible dietary interventions).

ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; MF: minimal function

The company designated BSC as the ACT, thus following the G-BA's specification. The company additionally reports that all CF patients were to receive individualized treatment for the alleviation of symptoms and improvement of quality of life, in addition to treatment with CFTR modulators. This is appropriate.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 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 lists on ivacaftor/tezacaftor/elexacaftor + ivacaftor (status: 15 November 2021)
- bibliographic literature search on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 15 November 2021)
- search in trial registries / study results databases on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 15 November 2021)
- search on the G-BA website for ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 15 November 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 24 February 2022); see Appendix A of the full dossier assessment for the search strategies.

The check did not identify any additional relevant study.

Additional evidence presented by the company

The company presented the VX18-445-106 study [3] and the VX19-445-107 study [4] as additional evidence under "Other Investigations". The VX18-445-106 study is a single-arm study presented by the company to the European Medicines Agency (EMA) for approval purposes. The VX18-445-106 study included CF patients aged 6 to 11 years who are either homozygous for the F508del mutation in the CFTR gene or heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele of this gene. In the associated ongoing VX19-445-107 extension study, VX18-445-106 participants had the option of being treated for another 96 weeks. All patients received ivacaftor/tezacaftor/elexacaftor + ivacaftor. Since neither study allows a comparison with the ACT, they were disregarded in the present benefit assessment.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
VX19-445-116	No	Yes	No	Yes [5,6]	Yes [7,8]	No

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.

BSC: best supportive care; CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The VX19-445-116 study was used for the benefit assessment. The study pool for RCTs concurs with that of the company.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
VX19-445-116	RCT, double-blind, parallel	CF patients aged 6 to 11 years with ▪ heterozygous F508del mutation and ▪ MF mutation on the 2nd allele of the CFTR gene and ▪ FEV_1 (in % of predicted normal) ≥ 70% at screening and ▪ $LCI_{2.5}$ ≥ 7.5 at screening	Ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC (N = 60) Placebo + BSC (N = 61)	Screening: up to 28 days Treatment duration: 24 weeks[b] Follow-up: 28 days[b]	34 centres in Australia, Canada, Denmark, France, Germany, Israel, Netherlands, Spain, Switzerland, United Kingdom 6/2020–5/2021	Primary: $LCI_{2.5}$ (absolute change) Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
b. Following completion of the 24-week treatment, patients had the option to participate in the open-label extension study VX20-445-119. Patients participating in the extension study did not require follow-up observation in the VX19-45-116 study.

AE: adverse event; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; FEV_1: forced expiratory volume in 1 second; LCI: Lung Clearance Index; MF: minimal function; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC

Study	Intervention	Comparison
VX19-445-116	Ivacaftor/tezacaftor/elexacaftor[a], in the mornings, orally ▫ 75 mg/50 mg/100 mg (< 30 kg body weight at screening) ▫ 150 mg/100 mg/200 mg (≥ 30 kg body weight at screening) + ivacaftor, in the evenings, orally ▫ 75 mg (< 30 kg body weight at screening) ▫ 150 mg (≥ 30 kg body weight at screening) + BSC[b]	Placebo[a], in the mornings and evenings, orally + BSC[b]
	Dose adjustments were not allowed[a]	
	Allowed prior and concomitant treatment ▪ CF medication unchanged for 28 days before the start of the study until the end of the study ▪ Prednisone or prednisolone ≤ 10 mg long-term or ≤ 60 mg for 5 days **Disallowed prior and concomitant treatment** ▪ Moderate and strong CYP3A inductors or inhibitors (except ciprofloxacin) from 2 weeks prior to study start until study end ▪ CFTR modulators except the study medication from 4 weeks prior to study start until study end	

a. If the study medication was discontinued for > 72 hours, resumption of the study medication was allowed only in clinically stable patients following a thorough examination.
b. In the study, basic CF medication was administered in addition to ivacaftor/tezacaftor/elexacaftor+ ivacaftor or placebo.

ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; CYP: cytochrome P450; RCT: randomized controlled trial

Study design

The VX19-445-116 study is a randomized, double-blind study comparing ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC with placebo + BSC.

The study enrolled CF patients aged 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele of this gene. The CF diagnosis had to be confirmed by the investigator, with the criteria used to establish the diagnosis being unclear. At screening, patients additionally had to have a forced expiratory volume in 1 second (FEV_1) ≥ 70% of predicted normal for age, sex, and height as well as an $LCI_{2.5}$ ≥ 7.5. The study excluded patients with acute upper or lower airway infection, pulmonary exacerbations, or lung infection with organisms associated with faster deterioration of pulmonary status. In addition, the basic CF medication was to have been continued unchanged for 28 days before treatment start.

The study randomized a total of 121 patients at a 1:1 ratio either to treatment with ivacaftor/tezacaftor/elexacaftor+ ivacaftor + BSC (N = 60) or to placebo + BSC (N = 61).

Patients were treated with ivacaftor/tezacaftor/elexacaftor + ivacaftor in accordance with the Summaries of Product Characteristics (SPCs) [9,10] or received a placebo. In both study arms,

patients additionally received accompanying basic therapy (see section on the implementation of the ACT).

The study's primary outcome was a change in $LCI_{2.5}$; patient-relevant secondary outcomes were all-cause morbidity as well as outcomes on morbidity, health-related quality of life, and AEs.

Following the 24-week treatment phase, patients had the option of participating in a single-arm extension study.

Patient characteristics

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

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC

Study Characteristic Category	IVA/TEZ/ELX + IVA + BSC N = 60	Placebo + BSC N = 61
VX19-445-116		
Age [years], mean (SD)	9.1 (1.8)	9.2 (1.7)
Sex [f/m], %	58/42	57/43
Ancestry, n (%)		
White	45 (75)	42 (69)
Not surveyed in accordance with local regulations	11 (18)	18 (30)
Other[a]	4 (7)[b]	1 (2)[b]
Region, n (%)		
Europe	43 (72[b])	49 (80[b])
Others (Canada, Israel, and Australia)	17 (28[b])	12 (20[b])
Body weight [kg], mean (SD)	29.1 (7.6)	29.8 (8.6)
Body weight [kg] at screening, n (%)		
< 30 kg	39 (65)	38 (62)
≥ 30 kg	21 (35)	23 (38)
BMI [kg/m²], mean (SD)	16.3 (1.8)	16.1 (2.3)
Sweat chloride concentration [mmol/L], mean (SD)	102.8 (10.0)	102.6 (8.6)
$LCI_{2.5}$ at screening, mean (SD)	10.3 (2.2)	9.8 (2.0)
FEV_1 (in % of predicted normal at baseline), n (%)		
< 70	4 (7)	10 (16)
≥ 70 to ≤ 90	20 (33)	23 (38)
> 90	36 (60)	28 (46)
Treatment discontinuation, n (%)	1 (2[b])	0 (0)
Study discontinuation, n (%)	1 (2[b])	0 (0)

a. Comprises Black or African American, Asian, Native American or Alaska Native, others and multiple origins.
b. IQWiG calculation.

BMI: body mass index; BSC: best supportive care; ELX: elexacaftor; FEV_1: forced expiratory volume in 1 second; IVA: ivacaftor; f: female; LCI: Lung Clearance Index; m: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; TEZ: tezacaftor

The patients' demographic and clinical characteristics were largely balanced between the 2 study arms. The patients' mean age was 9 years. The mean height and body weight or body mass index (BMI) were within the normal range.

According to the VX19-445-116 study's inclusion criteria, patients were to exhibit an FEV_1 of ≥ 70 (in % of predicted normal) at screening. Nevertheless, some patients had an FEV_1 of < 70%.

Implementation of the appropriate comparator therapy

The G-BA specified BSC as the ACT for ivacaftor/tezacaftor/elexacaftor + ivacaftor in the treatment of CF patients aged 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation. BSC is the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics against pulmonary infections, mucolytic agents, pancreatic enzymes in case of pancreatic insufficiency, physical therapy [within the meaning of the German Guideline on Remedies] under exhaustion of all possible dietary interventions).

In the VX19-445-116 study, patients' existing symptomatic therapy was to be continued simultaneously with treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor or placebo. The study protocol required that no changes be made to the concomitant medication from 28 days before study start until the end of the study. For inclusion, the study additionally required participants to be willing to forego any changes to the CF-related concomitant treatment for the entire duration of the study.

The information available on prior and concomitant treatment used in the study shows that the majority of study participants received concomitant treatment of CF symptoms both at study start and during the study.

Table 9 shows the prior and concomitant treatment of VX19-445-116 participants.

Table 9: Medication before the 1st dose of study treatment and concomitant medication – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC

Study	IVA/TEZ/ELX + IVA + BSC		Placebo + BSC	
	Treatment before the 1st dose of study medication n (%)	Concomitant medication[a] n (%)	Treatment before the 1st dose of study medication n (%)	Concomitant medication[a] n (%)
VX19-445-116	**N = 60**		**N = 61**	
Drug treatment				
Antibiotics	22 (36.7)[b]	32 (53.3)[b]	19 (31.1)[b]	47 (77.0)[b]
Intravenous antibiotics	0 (0)	1 (1.7)[b]	0 (0)	10 (16.4)[b]
Inhaled medication	57 (95.0)[b]	57 (95.0)[b]	59 (96.7)[b]	59 (96.7)[b]
Mucolytics	54 (90.0)[b]	55 (91.7)[b]	58 (95.1)[b]	58 (95.1)[b]
Bronchodilators	41 (68.3)[b]	42 (70.0)[b]	47 (77.1)[b]	48 (78.7)[b]
Inhaled saline solution	46 (76.7)[c]	ND	46 (75.4)[c]	ND
Digestive agents, including enzymes	57 (95.0)[c]	57 (95.0)	61 (100)[c]	61 (100)
Pancreatin	52 (86.7)[c]	52 (86.7)	53 (86.9)[c]	53 (86.9)
Pancrelipase	4 (6.7)[c]	4 (6.7)	7 (11.5)[c]	7 (11.5)
Vitamins	58 (96.7)[c]	59 (98.3)	61 (100)[c]	61 (100)
Non-drug treatment				
Physiotherapy	44 (73.3)[b]	44 (73.3)[b]	49 (80.3)[b]	50 (82.0)[b]

a. Sum of the patients who received the treatment at study start and those who started the treatment during the study. It is unclear how many patients, if any, discontinued the concomitant treatment over the course of the study.
b. IQWiG calculation.
c. Number of patients on a therapy within 56 days before the 1st dose of the study drug.

BSC: best supportive care; ELX: elexacaftor; IVA: ivacaftor; N: number of analysed patients; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; TEZ: tezacaftor

The data on prior and concomitant treatment show that, at study start, patients received antibiotics, inhaled medication (including saline solution), digestive enzymes, vitamins, and physical therapy for symptomatic treatment of CF.

The company furthermore provides detailed information on the number of concomitant therapies over the course of the study for the different concomitant medications (see Table 23 in Appendix C of the full dossier assessment). For antibiotic treatment, this information suggests that adjustments were made over the course of the study. Out of the patients who had no antibiotic therapy at baseline, 26% in the intervention arm and 67% in the comparator arm received at least 1 antibiotic over the course of the study. Regarding the use of bronchodilators, the detailed information does not show many patients starting new treatment during the study. The information on other therapies does not show whether any adjustments were made over the course of the study since the majority of included patients already received inhaled medication, mucolytics, or physical therapy at baseline. The available information does not show any

increases in the number of administered therapies over the course of the study for any of the other therapies except antibiotics. Additionally, the available data do not show in how many patients, if any, the concomitant treatment was adjusted, e.g. by increasing the dose or frequency of drug or non-drug treatment. Furthermore, it is unclear how many, if any, patients discontinued the concomitant treatment over the course of the study.

In summary, it remains unclear whether the concomitant treatment used in the VX19-445-116 study represents a full ACT implementation of BSC. This conclusion has been informed by the fact that no details are available on treatment adjustments in the form of dose or frequency increases of symptomatic treatment over the course of the study. This circumstance did not, however, lead to exclusion of the study. Rather, it was assumed that the study results are suitable for drawing conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT. However, the described uncertainties were taken into account in the assessment of the certainty of conclusions of results (see Section 2.4.2).

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of other aspects	Risk of bias at study level
			Patients	Treatment providers			
VX19-445-116	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial							

The risk of bias across outcomes for the VX19-445-116 study is rated as low.

Transferability of the study results to the German health care context

The company stated that the majority of included patients was white and the study was conducted primarily in specialized European or North American centres. According to the company, care in Germany is likewise provided primarily in specialized practices and hospital outpatient clinics. Further, the study medication was administered alongside participants' drug and non-drug baseline therapy, which, according to the company, corresponds to the approach to care taken for these patients in Germany. The company also reports that in addition to participants being predominantly white, other characteristics of the study population support transferability. Overall, the company therefore presumes very good transferability of results to the German health care context.

The company did not provide any further information on the transferability of study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - pulmonary exacerbations
  - serious pulmonary exacerbations
  - symptoms measured with the symptom domains of the CFQ-R
- Health-related quality of life
  - measured with the CFQ-R instrument's domains on health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - further specific AEs, if any

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

Table 11 shows the outcomes for which data were available in the included study.

Table 11: Matrix of outcomes – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC

Study	Outcomes							
	All-cause mortality	Pulmonary exacerbations[a]	Serious pulmonary exacerbations[b]	Symptoms (CFQ-R)	Health-related quality of life (CFQ-R)	SAEs[c]	Discontinuation due to AEs[c]	Abdominal pain (PT, AEs)
VX19-445-116	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Recorded as "infective pulmonary exacerbation of cystic fibrosis" (PT, AE); the operationalization of PT as "AE" is comparable to the operationalization "pulmonary exacerbation" as used in previous benefit assessments, which is why it is used as an alternative morbidity outcome in the present benefit assessment.
b. Recorded as "infective pulmonary exacerbation of cystic fibrosis" (PT, SAE); the operationalization of the PT as "serious event" is comparable to the operationalization "hospitalization due to pulmonary exacerbations" used in previous benefit assessments, which is why it is used as an alternative morbidity outcome in the present benefit assessment.
c. Without the PT "infective pulmonary exacerbation of cystic fibrosis".

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event

The following outcomes are presented as supplementary information in Appendix B of the full dossier assessment:

- Lung function using $LCI_{2.5}$:

LCI is a lung function parameter serving as a measure for ventilation inhomogeneity [11]. $LCI_{2.5}$ indicates the number of turnovers needed to reduce the concentration of a marker gas to 2.5% of its initial concentration. The company explains that a pathologically elevated $LCI_{2.5}$ is diagnostically and prognostically relevant since it very reliably predicts structural lung damage and can indicate both later deterioration of lung function and the frequency of exacerbations. Therefore, the company deems $LCI_{2.5}$ to be directly patient relevant.

Relevant for the benefit assessment are patient-noticeable symptoms associated with a change in $LCI_{2.5}$ which were directly recorded in the studies. In addition, the company did not present any sources showing that $LCI_{2.5}$ can be viewed as a valid surrogate outcome for a patient-relevant outcome. $LCI_{2.5}$ was therefore excluded from the present benefit assessment.

- Lung function using FEV_1:

The outcome "FEV_1" (in % of predicted normal) is a lung function parameter. Relevant for benefit assessments are patient-noticeable symptoms associated with a change in FEV_1 or the associated reduction in health-related quality of life which were directly recorded in the studies.

Like in prior dossiers on the assessment of CFTR modulators, the company used FEV_1 as a surrogate for CF-related mortality (see, e.g. [12]). However, the sources cited by the company did not demonstrate the validity of FEV_1 as a surrogate. In its current dossier on ivacaftor/tezacaftor/elexacaftor + ivacaftor, the company does not discuss any new aspects. For a detailed rationale for the outcome of FEV_1 not qualifying as a valid surrogate outcome for mortality, see, e.g. dossier assessment A19-70 on the drug ivacaftor in combination with tezacaftor/ivacaftor [13].

- BMI and z-score of the BMI:

Body weight or BMI is highly relevant in the present therapeutic indication because developmental disorders and nutrient malabsorption are typical signs of CF. In its assessment, the company used BMI as a measure for patients' developmental status or as a parameter for the extent of a developmental disorder.

In the present situation, the relevance of BMI as a measure of malnutrition is not directly evident, since patients' mean BMI in the included study VX19-445-116 was within the normal range both at baseline and after 24 weeks of treatment.

Outcome of severe AEs (grade 3 or 4)

All AEs which occurred in the study were assigned severity grades by the investigator. The study protocol does, however, contain discrepant information as to the criteria on which this classification was to be based. For instance, the study protocol cites a document with notes from the U.S. Food and Drug Administration (FDA) on the severity grading of AEs for vaccine studies [14]. Later, however, the company mentions that, in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), events of severity levels 4 and 5 are viewed as life-threatening and that the CTCAE reference range may not be applicable to children. In the dossier's Module 4 A, in turn, the company reports that severity was assessed by the investigator.

While developed for recording AE severity in oncological indications, the CTCAE severity grading is a suitable operationalization of severe AEs in the present therapeutic indication. However, the AE severity grading for vaccine studies according to the FDA document [14] is unsuitable for the present therapeutic indication. Since it remains unclear whether occurred AEs were assessed by the investigator in accordance with a classification for vaccine studies or the CTCAE, the outcome of severe AEs (grade 3 or 4) was disregarded in the benefit assessment. Irrespective of the basis on which the assessment was made, 2 patients in each study arm had severe AEs (grade 3 or 4) over the course of the study.

2.4.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC

Study	Study level	Outcomes							
		All-cause mortality	Pulmonary exacerbations[a]	Serious pulmonary exacerbations[b]	Symptoms (CFQ-R)	Health-related quality of life (CFQ-R)	SAEs[c]	Discontinuation due to AEs[c]	Abdominal pain (PT, AEs)
VX19-445-116	L	L	L	L	L	L	L	L	L

a. Recorded as "infective pulmonary exacerbation of cystic fibrosis" (PT, AE); the operationalization of PT as "AE" is comparable to the operationalization "pulmonary exacerbation" as used in previous benefit assessments, which is why it is used as an alternative morbidity outcome in the present benefit assessment.
b. Recorded as "infective pulmonary exacerbation of cystic fibrosis" (PT, SAE); the operationalization of the PT as a serious event is comparable to the operationalization "hospitalization due to pulmonary exacerbations" used in previous benefit assessments, which is why it is used as an alternative morbidity outcome in the present benefit assessment.
c. Without the PT "infective pulmonary exacerbation of cystic fibrosis".

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; L: low; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event

The risk of bias for the results on all outcomes included in the present benefit assessment is rated as low.

Summary assessment of the certainty of conclusions

For the present benefit assessment, it remains unclear whether the concomitant treatment used in the VX19-445-116 study represents a full ACT implementation of BSC. This conclusion has been informed by the fact that no details are available on treatment adjustments in the form of dose or frequency increases of symptomatic treatment over the course of the study (for a discussion, see Section 2.3.2, Implementation of the appropriate comparator therapy). The certainty of conclusions of the study results for the present research question is therefore reduced. Based on the VX19-445-116 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

2.4.3 Results

Table 13 and Table 14 summarize the results on the comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC in CF patients aged 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele. Where necessary, IQWiG calculations are provided to supplement the data.

Tables on common AEs, common SAEs, and discontinuation due to AEs, including the PT "infective pulmonary exacerbation of cystic fibrosis" are presented in Appendix D of the full dossier assessment.

Table 13: Results (mortality, morbidity, and side effects, dichotomous) – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC

Study Outcome category Outcome	IVA/TEZ/ELX + IVA + BSC		Placebo + BSC		IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
VX19-445-116 (Week 24)					
Mortality					
All-cause mortality	60	0 (0.0)	61	0 (0.0)	–
Morbidity					
Pulmonary exacerbations[b]	60	1 (1.7)	61	16 (26.2)	0.06 [0.01; 0.46]; < 0.001
Serious pulmonary exacerbations[c]	60	0 (0.0)	61	3 (4.9)	0.15 [0.01; 2.75]; 0.094[d]
Side effects					
AEs (supplementary information)[e]	60	48 (80.0)	61	54 (88.5)	–
SAEs[e]	60	4 (6.7)	61	6 (9.8)	0.68 [0.20, 2.28]; 0.569
Discontinuation due to AEs[e]	60	1 (1.7)	61	0 (0.0)	–[f]; 0.367
Abdominal pain (PT, AEs)	60	5 (8.3)	61	17 (27.9)	0.30 [0.12; 0.76]; 0.006

a. RR, CI (asymptotic) and p-value (IQWiG calculation; unconditional exact test, CSZ method according to [15]).
b. Surveyed as "infective pulmonary exacerbation of cystic fibrosis" (PT) using AEs.
c. Surveyed as "infective pulmonary exacerbations of cystic fibrosis" (PT) using SAEs.
d. IQWiG calculation: The correction factor 0.5 was used for the calculation of effect and CI in both study arms.
e. Without the PT "infective pulmonary exacerbation of cystic fibrosis".
f. Effect estimate and 95% CI not meaningfully interpretable.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z-score; ELX: elexacaftor; IVA: ivacaftor; 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; TEZ: tezacaftor

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC (multipage table)

Study Outcome category Outcome	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Mean change by Week 24 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change by Week 24 mean (SE)[b]	MD [95% CI]; p-value[c]
VX19-445-116 (Week 24)							
Morbidity							
Symptoms (CFQ-R, symptom domains, children [6 to 11 years])[d]							
Respiratory symptoms	60	85.69 (11.69)	5.94 (1.61)	61	82.65 (14.13)	0.47 (1.59)	5.47 [0.98; 9.96]; 0.017 Hedges' g: 0.44 [0.08; 0.80]
Digestive symptoms	60	78.33 (22.82)	6.85 (2.65)	61	74.86 (26.29)	-1.81 (2.62)	8.66 [1.24; 16.07]; 0.023 Hedges' g: 0.42 [0.06; 0.78]
Weight	Domain not provided in questionnaire for children (6 to 11 years)						
Symptoms (CFQ-R, symptoms domains, parent/caregiver version [children 6 to 11 years]; presented as supplementary information)[d]							
Respiratory symptoms	*60*	*85.44 (13.75)*	*9.87 (1.58)*	*61*	*83.61 (15.33)*	*1.14 (1.56)*	*8.73 [4.31; 13.15]; < 0.001* *Hedges' g: 0.71 [0.34; 1.08]*
Digestive symptoms	*60*	*76.30 (20.91)*	*7.06 (1.92)*	*61*	*70.86 (20.40)*	*3.30 (1.91)*	*3.76 [-1.63; 9.15]; 0.170*
Weight	*60*	*63.89 (36.97)*	*18.02 (3.83)*	*61*	*65.03 (36.22)*	*1.31 (3.79)*	*16.71 [6.00; 27.43]; 0.003* *Hedges' g: 0.56 [0.20; 0.93]*
Health-related quality of life							
Health-related quality of life (CFQ-R, health-related quality of life domains, children [6 to 11 years])[d]							
Physical functioning	60	86.17 (13.58)	4.33 (1.57)	61	80.51 (22.69)	0.44 (1.55)	3.89 [-0.50; 8.28]; 0.082
Emotional functioning	60	78.06 (11.43)	4.36 (1.50)	61	76.74 (13.94)	1.83 (1.49)	2.53 [-1.68; 6.73]; 0.236
Social functioning	60	65.74 (15.60)	3.23 (1.68)	61	67.62 (17.57)	-1.88 (1.66)	5.12 [0.43; 9.81]; 0.033 Hedges' g 0.39 [0.03; 0.75]
Vitality	Domain not provided in questionnaire for children (6 to 11 years)						
School functioning	Domain not provided in questionnaire for children (6 to 11 years)						
Body image	60	84.63 (20.87)	8.39 (2.19)	61	84.34 (20.32)	4.45 (2.16)	3.94 [-2.18; 10.06]; 0.205

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC (multipage table)

Study **Outcome category** **Outcome**	**IVA/TEZ/ELX + IVA + BSC**			**Placebo + BSC**			**IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC**
	N[a]	**Values at baseline mean (SD)**	**Mean change by Week 24 mean (SE)[b]**	**N[a]**	**Values at baseline mean (SD)**	**Mean change by Week 24 mean (SE)[b]**	**MD [95% CI]; p-value[c]**
Eating disturbances	60	81.67 (23.13)	7.76 (2.16)	61	79.60 (23.15)	2.70 (2.14)	5.06 [-0.97; 11.10]; 0.099
Treatment burden	60	72.22 (18.69)	3.11 (2.03)	61	74.13 (20.26)	3.21 (2.01)	-0.09 [-5.77; 5.58]; 0.974
Health perceptions	Domain not provided in questionnaire for children (6 to 11 years)						
Health-related quality of life							
Health-related quality of life (CFQ-R, domains on health-related quality of life, parent/caregiver version [children 6 to 11 years]; presented as supplementary information[d]							
Physical functioning	*60*	*90.49 (10.88)*	*2.06 (1.30)*	*61*	*85.31 (16.45)*	*-1.14 (1.28)*	*3.21 [-0.42; 6.83]; 0.083*
Emotional functioning	*60*	*85.22 (10.57)*	*1.53 (1.33)*	*61*	*82.84 (16.12)*	*-0.23 (1.31)*	*1.76 [-1.94; 5.47]; 0.348*
Social functioning	*Domain not provided in questionnaire for parents/caregivers*						
Vitality	*60*	*74.11 (13.05)*	*3.56 (1.51)*	*61*	*70.82 (16.29)*	*0.43 (1.50)*	*3.13 [-1.10; 7.36]; 0.146*
School functioning[e]	*60*	*80.83 (17.58)*	*2.09 (1.83)*	*61*	*78.96 (18.42)*	*0.78 (1.81)*	*1.31 [-3.80; 6.43]; 0.612*
Body image	*60*	*78.70 (19.55)*	*7.77 (1.92)*	*61*	*81.24 (22.18)*	*2.15 (1.90)*	*5.62 [0.27; 10.98]; 0.040* *Hedges' g: 0.38 [0.02; 0.74]*
Eating disturbances	*58*	*79.31 (23.63)*	*5.81 (2.53)*	*61*	*76.23 (27.63)*	*1.89 (2.46)*	*3.92 [-3.11; 10.94]; 0.272*
Treatment burden	*60*	*59.26 (20.93)*	*6.61 (2.19)*	*61*	*60.11 (20.12)*	*2.41 (2.16)*	*4.20 [-1.92; 10.31]; 0.177*
Health perceptions	*60*	*77.96 (15.65)*	*5.28 (1.96)*	*61*	*70.31 (19.32)*	*3.05 (1.94)*	*2.23 [-3.25; 7.71]; 0.421*

a. Number of patients included in the analysis for calculating the effect estimation; baseline values may be based on different patient numbers.
b. Mean change by Week 24 from MMRM.
c. MMRM; adjusted for $LCI_{2.5}$ and baseline body weight; additionally study time point, treatment x study time point as fixed effects in the model. The effect represents the difference between treatment groups in mean changes over the course of the study (to Week 24) from baseline to the respective time point.
d. Higher (increasing) values indicate better symptoms / health-related quality of life; favourable effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).
e. Referred to as "role functioning" in the company's Module 4 A.

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC (multipage table)

Study Outcome category Outcome	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Mean change by Week 24 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change by Week 24 mean (SE)[b]	MD [95% CI]; p-value[c]
BSC: best supportive care; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; ELX: ivacaftor; IVA: ivacaftor; LCI: Lung Clearance Index; MD: mean difference, MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; TEZ: tezacaftor							

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.4.2).

Mortality

All-cause mortality

No deaths occurred in the course of the study. There is no hint of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC for the outcome of all-cause mortality; an added benefit is therefore not proven.

Morbidity

Pulmonary exacerbations

Operationalization

In contrast to the studies sponsored by the company in the context of prior benefit assessments, the VX19-445-116 study did not operationalize or survey the outcomes of pulmonary exacerbations and hospitalization due to pulmonary exacerbations (for the operationalization as symptoms outcomes, see A20-83 [16]). Instead, for the VX19-445-116 study, analyses are available only for events documented using the surveying of AEs and SAEs in the PT "infective pulmonary exacerbation of cystic fibrosis". The events surveyed via SAEs were deemed, with sufficient certainty, to be the same events which were recorded via the previously common operationalization of hospitalizations due to pulmonary exacerbations. Regarding the events surveyed via AEs, despite the uncertainty regarding the events surveyed, analysis results are assumed not to differ to a relevant extent from the previously common analyses on the basis of the definition as a symptoms outcome; in view of the available evidence, this assumption rests on effect size.

For the present benefit assessment, the company additionally presents analyses only on the percentage of patients with at least 1 event. Hence, no analyses based on the number of events per patient year (event rates) which take into account not only the occurrence but also the

frequency of pulmonary exacerbations are available for the present benefit assessment. Given the available data, however, the results of the analyses presented by the company on the percentage of patients with at least 1 event are assumed not to differ, to a relevant extent, from analyses on the basis of event rates (number of events / patient years).

Overall, for the present benefit assessment, the company's analyses of relative risk regarding AEs and SAEs of the PT "infective pulmonary exacerbation of cystic fibrosis" were used for the outcomes of pulmonary exacerbations and serious pulmonary exacerbations.

Results

Pulmonary exacerbations

For the outcome of pulmonary exacerbations (reported as AEs, surveyed via the PT "infective pulmonary exacerbation of cystic fibrosis"), there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. For pulmonary exacerbations, this results in a hint of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC.

Serious pulmonary exacerbations

For the outcome of serious pulmonary exacerbations (reported as SAEs, surveyed using the PT "infective pulmonary exacerbation in cystic fibrosis"), no statistically significant difference between treatment groups was found. This results in no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

Symptoms measured using the CFQ-R

Operationalization

For children aged 6 to 11 years, the VX19-445-116 study surveyed symptoms outcomes directly in the children using the respiratory symptoms and digestive symptoms domains of the disease-specific patient-reported instrument CFQ-R. For this age group, the study also used a parent/caregiver version of the CFQ-R, which surveys not only the domains of respiratory symptoms and digestive symptoms, but also the weight domain. The questionnaire's patient version was used for assessing added benefit. In this benefit assessment, the parent/caregiver version is presented as supplementary information.

In addition to continuous analyses on the basis of mean differences, the company submitted post hoc analyses of the CFQ-R on 15% of the scale range in accordance with IQWiG General Methods [1] (responder analyses for improvement by ≥ 15 points), and for the CFQ-R domains, it included both analyses in its derivation of added benefit. Regarding the responder analyses, the company reports that change over 24 weeks is defined as the arithmetic mean of all changes in CFQ-R within the respective domain from baseline to Week 24. The company did not submit any other information on the calculation of responder analyses. On the basis of the available information, it remains unclear whether the patients registered as responders in the responder

analyses exceeded the response threshold for improvement at a single time point or at multiple time points over the course of the study. Therefore, the continuous analyses were used for the present benefit assessment. The results of the responder analyses are consistent with the those of the continuous analyses.

Results

Respiratory symptoms and digestive symptoms domains

For each of the respiratory symptoms and digestive symptoms domains, there is a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with placebo + BSC regarding the mean change over the course of the study from baseline to the respective measurement time. The SMD in the form of Hedges' g was used to assess the relevance of the result. The 95% CI was not fully outside the irrelevance range [-0.2; 0.2] for either of them. It was therefore impossible to infer the effect to be relevant. For each of the CFQ-R domains of respiratory symptoms and digestive symptoms, this results in no hint of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

For the respiratory symptoms domain, the results of the CFQ-R parent/caregiver version show a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with placebo + BSC. The 95% CI of the SMD in the form of Hedges' g was completely outside the irrelevance threshold [-0.2; 0.2]. No statistically significant difference between treatment groups was shown for the digestive symptoms domain in the parent/caregiver version.

Health-related quality of life

Operationalization

For children aged 6 to 11 years, the VX19-445-116 study surveyed health-related quality of life outcomes directly in the children using the physical functioning, emotional functioning, social functioning, body image, eating disturbances, and treatment burden domains of the disease-specific patient-reported instrument CFQ-R. In addition, the study used a parent/caregiver version of the CFQ-R for this age group, with this version surveying all above-mentioned domains except social functioning and adding the domains of vitality, school functioning, and health perceptions. The questionnaire's patient version was used for assessing added benefit. In the present benefit assessment, the parent/caregiver version is presented as supplementary information.

In addition to continuous analyses on the basis of mean differences, the company submitted post hoc analyses of the CFQ-R on 15% of the scale range in accordance with IQWiG General Methods [1] (responder analyses for improvement by ≥ 15 points), and for the CFQ-R domains, it included both analyses in its derivation of added benefit. The present benefit assessment uses the continuous analyses (for a discussion, see the above section on symptoms measured using

the CFQ-R). The results of the responder analyses are consistent with the those of the continuous analyses.

Results

Physical functioning, emotional functioning, body image, eating disturbances, and treatment burden domains

In the physical functioning, emotional functioning, body image, eating disturbances, and treatment burden domains, no statistically significant difference between treatment groups was found regarding the mean changes over the course of the study from baseline to the respective measurement time. This results in no hint of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC for the CFQ-R domains of physical functioning, emotional functioning, body image, eating disturbances, and treatment burden; therefore, there is no hint of an added benefit.

These results are consistent with the results of the parent/caregiver version. For the body image domain, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. However, the 95% CI of the SMD in the form of Hedges' g was not completely outside the irrelevance threshold [-0.2; 0.2].

Social functioning domain

In the social functioning domain, there is a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with placebo + BSC regarding the mean changes over the course of the study from baseline to the respective measurement time. The 95% CI was not fully outside the irrelevance range [-0.2; 0.2]. The effect can therefore not be inferred to be relevant. For the CFQ-R social functioning domain, this results in no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

This domain is not included in the questionnaire's parent/caregiver version.

Side effects

SAEs

No statistically significant difference between treatment groups was shown for the outcome of SAEs. This results in no hint of greater or lesser harm from ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There was no statistically significant difference between treatment groups for the outcome of discontinuation due to AEs. This results in no hint of greater or lesser harm from ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Abdominal pain (PT, AEs)

For the outcome of abdominal pain (PT, AEs), there is a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. This results in a hint of lesser harm from ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with BSC.

2.4.4 Subgroups and other effect modifiers

The present assessment accounts for the following potential effect modifier:

- sex (female/male)

The VX19-445-116 study protocol did not provide for any subgroup analyses a priori. In the dossier, the company presented subgroup analyses for all outcomes of the present benefit assessment.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there have to be at least 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 1 subgroup.

Using the methods described above, the available subgroup results do not reveal any effect modifications.

2.5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

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

2.5.1 Assessment of the 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 (see Table 15).

Table 15: Extent of added benefit at outcome level: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. BSC (multipage table)

Outcome category **Outcome** **Domain**	**IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC** **Proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% –	Lesser/added benefit not proven
Morbidity		
Pulmonary exacerbations	1.7% vs. 26.2% RR: 0.06 [0.01; 0.46] p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms / late complications CI_u < 0.80 Added benefit; extent: considerable
Serious pulmonary exacerbations	0% vs. 4.9% RR: 0.15 [0.01; 2.75]; p = 0.094	Lesser/added benefit not proven
Symptoms (CFQ-R, symptom domains)		
Respiratory symptoms	Mean change: 5.94 vs. 0.47 MD: 5.47 [0.98; 9.96]; p = 0.017 Hedges' g: 0.44 [0.08; 0.80][c]	Lesser/added benefit not proven
Digestive symptoms	Mean change: 6.85 vs. -1.81 MD: 8.66 [1.24; 16.07]; p = 0.023 Hedges' g: 0.42 [0.06; 0.78][e]	Lesser/added benefit not proven
Health-related quality of life (CFQ-R, domains on health-related quality of life)		
Physical functioning	Mean change: 4.33 vs. 0.44 MD: 3.89 [-0.50; 8.28]; p = 0.082	Lesser/added benefit not proven
Emotional functioning	Mean change: 4.36 vs. 1.83 MD: 2.53 [-1.68; 6.73]; p = 0.236	Lesser/added benefit not proven
Social functioning	Mean change: 3.23 vs. -1.88 MD: 5.12 [0.43; 9.81]; p = 0.033 Hedges' g: 0.39 [0.03; 0.75][c]	Lesser/added benefit not proven
Body image	Mean change: 8.39 vs. 4.45 MD: 3.94 [-2.18; 10.06]; p = 0.205	Lesser/added benefit not proven
Eating disturbances	Mean change: 7.76 vs. 2.70 MD: 5.06 [-0.97; 11.10]; p = 0.099	Lesser/added benefit not proven
Treatment burden	Mean change: 3.11 vs. 3.21 MD: -0.09 [-5.77; 5.58]; p = 0.974	Lesser/added benefit not proven

Table 15: Extent of added benefit at outcome level: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. BSC (multipage table)

Outcome category **Outcome** **Domain**	**IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC** **Proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	6.7% vs. 9.8% RR: 0.68 [0.20; 2.28] p = 0.569	Greater/lesser harm not proven
Discontinuation due to AEs	1.7% vs. 0% RR: –; p = 0.367	Greater/lesser harm not proven
Abdominal pain (PT, AEs)	8.3% vs. 27.9% RR: 0.30 [0.12; 0.76] p = 0.006 probability: hint	Outcome category: non-serious/non-severe side effects[d] $CI_u < 0.80$ Lesser harm, extent: considerable

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. If the CI of Hedges' g is fully outside the irrelevance range [-0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be inferred.
d. It is questionable whether the effect is actually to be allocated to the outcome category of side effects or whether it rather reflects the symptoms of the disease.

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; CI_u: upper limit of confidence interval; ELX: elexacaftor; IVA: ivacaftor; MD: mean difference; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; TEZ: tezacaftor

2.5.2 Overall conclusion on added benefit

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

Table 16: Favourable and unfavourable effects from the assessment of ivacaftor/tezacaftor/elexacaftor + ivacaftor compared with BSC

Favourable effects	**Unfavourable effects**
Non-serious/non-severe symptoms / late complications ▪ Pulmonary exacerbations: hint of an added benefit – extent: considerable	–
Non-serious/non-severe side effects[a]: ▪ Abdominal pain (AEs): hint of lesser harm – extent: considerable	–

a. It is questionable whether the effect is in fact attributable to the outcome category of AEs or rather reflects the symptoms of the disease.

AE: adverse events; BSC: best supportive care

All things considered, exclusively favourable effects of ivacaftor/tezacaftor/elexacaftor + ivacaftor were found in comparison with BSC. There is a hint of considerable added benefit for the outcome of pulmonary exacerbations, while a hint of lesser harm of the same extent is found for the outcome of abdominal pain.

In summary, this results in a hint of considerable added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT of BSC for CF patients 6 to 11 years who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation.

Table 17 summarizes the result of the assessment of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT.

Table 17: Ivacaftor/tezacaftor/elexacaftor + ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients 6 to 11 years of age who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele	BSC[b]	Hint of considerable added benefit

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [within the meaning of the German Guideline on Remedies] under exhaustion of all possible dietary interventions).

ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; MF: minimal function

The result of the assessment equally applies to ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor.

The assessment described above deviates from that made by the company, which derived an indication of major added benefit based on the results of the study VX19-445-116.

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

References for English extract

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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