IQWiG Reports – Commission No. A20-83

Ivacaftor (combination with ivacaftor/ tezacaftor/elexacaftor; cystic fibrosis, 12 years and older, 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 (Kombination mit Ivacaftor/Tezacaftor/ Elexacaftor; zystische Fibrose, ab 12 Jahre, F508del-Mutation, MF-Mutation, heterozygot) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 November 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
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
FEV1	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)
MF	minimal function
RCT	randomized controlled trial
SAE	serious adverse event
SMD	standardized mean difference
SGB	Sozialgesetzbuch (Social Code Book)

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 ivacaftor in combination with 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 1 September 2020.

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 the present report is to assess the added benefit of ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor (hereinafter referred to as ivacaftor + ivacaftor/tezacaftor/elexacaftor) in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in patients with cystic fibrosis (CF) aged 12 years and older 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.

For the present benefit assessment, the G-BA's specification of the ACT has resulted in the research question presented in Table 2.

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

Therapeutic indication	**ACT[a]**
CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC is defined as the treatment which ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

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 named BSC as ACT and thus followed 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 the added benefit.

Study pool and study design

The benefit assessment included the double-blind RCT VX17-445-102, which compared ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC.

The study included CF patients 12 years and older 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 also had to have a forced expiratory volume in 1 second (FEV1) of ≥ 40% and ≤ 90% of predicted normal for age, sex, and body height.

The study included a total of 405 patients, who were randomized either to treatment with ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC (N = 201) or a corresponding placebo + BSC (N = 204). Stratification factors were age (< 18 years / ≥ 18 years), sex (male/female), and FEV1 in percent of predicted normal (< 70% / ≥ 70%).

Patients were treated with ivacaftor + ivacaftor/tezacaftor/elexacaftor as per the summary of product characteristics (SPC) or received a placebo. In both study arms, patients additionally received accompanying baseline therapy.

The primary outcome of the study was FEV1 (in % of predicted normal). Patient-relevant secondary outcomes were all-cause mortality, symptoms, health-related quality of life, and adverse events (AEs).

Implementation of the ACT

The G-BA specified BSC as the ACT for ivacaftor in the treatment of CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation.

In the VX17-445-102 study, patients were to continue their ongoing symptomatic treatment while being treated with ivacaftor/tezacaftor/elexacaftor or placebo. As per its protocol, the VX17-445-102 study required that the concomitant medication remain stable from 4 weeks before study start.

The available information shows that at the time of study inclusion, patients received antibiotics, inhaled medication, as well as physical therapy as symptomatic treatment of CF. While the available data suggest that some patients started concomitant treatment after the 1st intake of the study drug, it remains unclear whether more patients would have needed an adjustment over the 24-week course of the study. However, it cannot be inferred from the data whether the concomitant treatment was adjusted, e.g. by increasing the dose or frequency of drug and nondrug treatment over the course of the study, and if so, in how many patients this was the case. 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 VX17-445-102 study represents a complete implementation of the ACT of BSC. This conclusion is based on

the fact that no information is 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 the exclusion of the study. Rather, the results of the study were deemed suitable for drawing conclusions on any added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with the ACT. Said missing details did, in turn, affect the assessment of the certainty of results.

Risk of bias and assessment of reliability

The risk of bias across outcomes is rated as low for the VX17-445-102 study.

Except for the outcome of serious adverse events (SAEs), the risk of bias regarding the results is assessed as low for all included outcomes. For the outcome of SAEs, the risk of bias of results is rated as high.

For the present research question, the certainty of the study results is reduced due to the above missing details concerning the implementation of the ACT, and for the outcome of SAEs, it is additionally reduced due to the risk of bias already being high for other reasons. On the basis of the VX17-445-102 study, at most hints, e.g. of an added benefit, can be derived for all presented outcomes.

Results

Mortality

All-cause mortality

There were no deaths over the course of the study. For the outcome of all-cause mortality, there is no hint of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

Morbidity

Pulmonary exacerbations

For pulmonary exacerbations, there is a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC. This results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC for pulmonary exacerbations.

Hospitalization due to pulmonary exacerbations

For hospitalization due to pulmonary exacerbations, there is a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC. For hospitalization due to pulmonary exacerbations, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC.

Symptoms measured using the CFQ-R

Symptom outcomes were surveyed using the respiratory symptoms, digestive symptoms, and weight domains of the disease-specific, patient-reported instrument Cystic Fibrosis Questionnaire – Revised (CFQ-R).

Respiratory symptoms domain

In the respiratory symptoms domain, there is a statistically significant difference in the mean change over the course of the study from baseline to the respective measurement time to the advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with placebo + BSC. The standardized mean difference (SMD) in the form of Hedges' g was used to assess the relevance of the result. The 95% confidence interval (95% CI) is fully outside the irrelevance range [−0.2; 0.2]. This is interpreted as a relevant effect. An effect modification by the attribute of age was found. However, since the results in both subgroups do not differ in extent or direction of effect from the results of the entire study population (see Section 2.4.4), the attribute was disregarded in the further analysis of the respiratory symptoms domain. For the respiratory symptoms domain of the CFQ-R, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC for patients aged < 18 years as well as for patients aged ≥ 18 years.

Digestive symptoms domain

For the digestive symptoms domain, no statistically significant difference between treatment groups was found for the mean change over the course of the study from baseline to the respective measurement time. For the digestive symptoms domain of CFQ-R, this results in no hint of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

Weight domain

In the weight domain, there is a statistically significant difference in the mean change over the course of the study from baseline to the respective measurement time to the advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with placebo + BSC. The 95% CI is fully outside the irrelevance range [−0.2; 0.2]. This is interpreted as a relevant effect. An effect modification was found by the attribute of age. For the CFQ-R weight domain in patients ≥ 18 years of age, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC in comparison with BSC. In contrast, no added benefit was found for patients < 18 years of age.

Health-related quality of life

Health-related quality of life was surveyed using the CFQ-R domains of physical functioning, emotional functioning, vitality, social functioning, role functioning, body image, eating disorders, treatment burden, and health perceptions.

Physical functioning, social functioning, and treatment burden domains

In the physical functioning, social functioning, and treatment burden domains, there is a statistically significant difference in the mean change over the course of the study from baseline to the respective measurement time to the advantage of ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC in comparison with placebo + BSC. The 95% CI for SMD is fully outside the irrelevance range [−0.2; 0.2]. This is interpreted as a relevant effect in each case. For all 3 domains, an effect modification by the attribute of age was found, however. For each of the CFQ-R domains of physical functioning, social functioning, and treatment burden, there is a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC for patients aged ≥ 18 years. For patients aged < 18 years, in contrast, none of them resulted in any added benefit.

Emotional functioning and body image domains

In the emotional functioning and body image domains, there are statistically significant differences in the mean change over the course of the study from baseline to the respective measurement time to the advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with placebo + BSC. However, the 95% CI for SMD is not fully outside the irrelevance range [−0.2; 0.2]. The effect can therefore not be inferred to be relevant for any of them. For each of the CFQ-R domains of emotional functioning and body image, there is no hint of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC; an added benefit is therefore not proven for any of them.

Domains of vitality, role functioning, eating disorders, and health perception

For the vitality, role functioning, eating disorders, and health perception domains, statistically significant differences were found in the mean change over the course of the study from baseline to the respective measurement time to the advantage of ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC in comparison with placebo + BSC. The 95% CI for SMD is fully outside the irrelevance range [−0.2; 0.2]. This is interpreted as a relevant effect in each case. For each of the CFQ-R domains of vitality, role functioning, eating disorders, and health perceptions, there is therefore a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC.

AEs

SAEs and discontinuation due to AEs

For each of the outcomes of SAEs and discontinuation due to AEs, no statistically significant differences between treatment groups were found. Consequently, for the outcomes of SAEs and discontinuation due to AEs, there is no hint of greater or lesser harm of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

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

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

All things considered, exclusively favourable effects of ivacaftor + ivacaftor/tezacaftor/ elexacaftor were found in comparison with BSC. For hospitalization due to pulmonary exacerbations, there is a hint of major added benefit. In addition, there is a hint of considerable added benefit regarding pulmonary exacerbations. Several domains concerning symptoms and health-related quality of life each show a hint of non-quantifiable added benefit albeit this hint is limited to the subgroup of patients aged ≥ 18 years in some cases.

In summary, this results in a hint of major added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor versus the ACT of BSC for CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation.

Table 3 shows a summary of the probability and extent of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor.

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation	BSC[b]	Hint of major added benefit

a. Presented is the ACT specified by the G-BA.
b. BSC is defined as the treatment which ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

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

[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].

2.2 Research question

The aim of the present report is to assess the added benefit of ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor (hereinafter referred to as ivacaftor + ivacaftor/tezacaftor/elexacaftor) in comparison with BSC as the ACT in CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele.

For the present benefit assessment, the G-BA's specification of the ACT results in the research question presented in Table 4.

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

Therapeutic indication	**ACT**[a]
CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC is defined as the treatment which ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

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. RCTs with a minimum duration of 24 weeks were used for the derivation of the 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 cited by the company in the dossier:

- study list on ivacaftor + ivacaftor/tezacaftor/elexacaftor (as of 9 July 2020)
- bibliographic literature search on ivacaftor + ivacaftor/tezacaftor/elexacaftor (most recent search on 9 July 2020)
- search in trial registries / study results databases on ivacaftor + ivacaftor/tezacaftor/elexacaftor (most recent search on 9 July 2020)
- search on the G-BA website for ivacaftor + ivacaftor/tezacaftor/elexacaftor (most recent search on 9 July 2020)

To check the completeness of the study pool:

- search in trial registries on ivacaftor + ivacaftor/tezacaftor/elexacaftor (most recent search on 8 September 2020)

The check did not identify any additional relevant studies.

Additional evidence presented by the company

The company presented the VX17-445-105 study [3] as additional evidence under Further Investigations. It did not carry out an information retrieval on this topic. The VX17-445-105 study is a 1-arm extension study which included patients with homozygous F508del mutation (from the VX17-445-103 study [4]) as well as patients with heterozygous F508del mutation (from the VX17-445-102 study [5]) in the CFTR gene. All patients in the study received ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC. Since the VX17-445-105 study allows no comparison to the ACT, it was disregarded in the present benefit assessment.

2.3.1 Included studies

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

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

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 (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication (yes/no [reference])
VX17-445-102	Yes	Yes	No	No[c]	Yes [5-8]	Yes [9]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. 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.

BSC: best supportive care; RCT: randomized controlled trial

2.3.2 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: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
VX17-445-102	RCT, double-blind, parallel-group	CF patients aged ≥ 12 years with ▪ heterozygous F508del mutation and ▪ MF mutation on the 2nd allele of the CFTR gene and ▪ FEV1 (in % of predicted normal) of ≥ 40% and ≤ 90%	Ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC (N = 201) Placebo + BSC (N = 204)	Screening: 4 weeks Treatment: 24 weeks[b] Follow-up observation: 4 weeks (± 7 days)[c]	115 centres in Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Greece, Italy, Netherlands, Sweden, United Kingdom, United States 6/2018–4/2019	Primary: FEV1 (in % of predicted normal) Secondary: symptoms, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. At the Week-24 visit, patients who fulfilled the inclusion criteria had the opportunity to enrol in an open-label extension study (VX17-445-105).
c. Participation in the follow-up observation was not required for study participants who were included in the VX17-445-105 extension study within 28 days of the last dose of the study medication after completing the 24-week treatment.

AE: adverse event; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; FEV1: forced expiratory volume in 1 second; MF: minimal function; N: number of randomized patients; RCT: randomized controlled trial

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

Study	Intervention	Comparison
VX17-445-102	Ivacaftor + ivacaftor/tezacaftor/elexacaftor[a] + BSC[b]	Placebo[a] + BSC[b]
	▪ In the morning: ivacaftor/tezacaftor/elexacaftor 150 mg/100 mg/200 mg or placebo orally, in tablet form, within 30 minutes after starting a fat-containing meal ▪ In the evening: ivacaftor 150 mg orally, in tablet form, within 30 minutes after starting a fat-containing meal	
	Permitted prior and concomitant treatment ▪ Stable medication for CF treatment 28 days before study start until study end ▪ Prednisone or prednisolone ≤ 10 mg long-term or ≤ 60 mg for 5 days **Non-permitted prior and concomitant treatment** ▪ Moderate and strong CYP3A inducers and inhibitors (except ciprofloxacin) as well as sensitive OATP1B1 substrates (e.g. HMG-CoA reductase inhibitors) within 2 weeks before study start until study end ▪ CFTR modulators except the study medication within 4 weeks before study start until study end ▪ Solid-organ or haematological transplantations before study start	

a. Dose adjustments were not allowed; in case of interruption of the study medication for > 72 hours, continuation of the study medication was allowed only if approved by the clinical monitor.
b. In the study, basic medication for CF was given in addition to ivacaftor/tezacaftor/elexacaftor or placebo.

BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; CYP: cytochrome P450; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; OATP: organo-anion transporter; RCT: randomized controlled trial

Study design

The VX17-445-102 study is a randomized, double-blind study comparing ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC.

The study included CF patients 12 years and older 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, but it is unclear which criteria were used for diagnosis. At screening, patients had to also have a forced expiratory volume in 1 second (FEV1) of ≥ 40% and ≤ 90% of predicted normal for age, sex, and body height. The study excluded patients with acute upper or lower airway infection or infection of the lung with organisms associated with faster deterioration of the pulmonary status.

The study included a total of 405 patients, who were randomized at a 1:1 ratio either to treatment with ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC (N = 201) or to a corresponding placebo + BSC (N = 204). Stratification factors were age (< 18 years / ≥ 18 years), sex (male/female), and FEV1 in percent of predicted normal (< 70% / ≥ 70%).

Patients were treated with ivacaftor + ivacaftor/tezacaftor/elexacaftor as per the SPC [10] or received a placebo. In both study arms, patients additionally received accompanying basic therapy (see section on the implementation of the ACT).

The primary outcome of the study was FEV1 (in % of predicted normal). Patient-relevant secondary outcomes were all-cause mortality, symptoms, health-related quality of life, and AEs. All outcomes were surveyed up to a maximum of 4 weeks (± 7 days) after treatment end.

Following the 24-week treatment phase, patients who had completed the study visits in the treatment phase had the opportunity to participate in the 1-arm extension study VX17-445-105.

Table 8 shows the patient characteristics of the included study.

Table 8: Characterization of the study population – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC (multi-page table)

Study Characteristic Category	**IVA + IVA/TEZA/ELEXA + BSC N[a] = 200**	**Placebo + BSC N[a] = 203**
VX17-445-102		
Age [years], mean (SD)	26 (10)	27 (11)
Age group, n (%)		
< 18 years	56 (28)	60 (30)
≥ 18 years	144 (72)	143 (70)
Sex [f/m], %	48/52	48/52
Ancestry[b], n (%)		
White	186 (93.0)	184 (90.6)
Black / African American	4 (2.0)	2 (1.0)
Asian	0 (0)	1 (0.5)
Other	2 (1.0)	2 (1.0)
Not surveyed	9 (4.5)	16 (7.9)
Region, n (%)		
North America	118 (59.0)	120 (59.1)
Europe or Australia	82 (41.0)	83 (40.9)
FEV1 (in % of predicted normal), n (%)		
< 40%	18 (9.0)	16 (7.9)
≥ 40% to < 70%	114 (57.0)	120 (59.1)
≥ 70% to ≤ 90%	66 (33.0)	62 (30.5)
> 90%	2 (1.0)	5 (2.5)
BMI [kg/m²], mean [SD]	21.5 (3.1)	21.3 (3.1)
BMI z-score[c], mean [SD]	−0.37 (0.8)	−0.40 (1.0)
Sweat chloride concentration [mmol/L], mean (SD)	102.3 (11.9)	102.9 (9.8)
Treatment before study inclusion[d], n (%)		
Inhaled antibiotics	118 (59.0)	132 (65.0)
Inhaled bronchodilators	187 (93.5)	191 (94.1)
Inhaled hypertonic saline solution	147 (73.5)	127 (62.6)
Inhaled corticosteroids	120 (60.0)	119 (58.6)
Pseudomonas aeruginosa infection[e], n (%)	150 (75.0)	142 (70.0)

Table 8: Characterization of the study population – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC (multi-page table)

Study Characteristic Category	IVA + IVA/TEZA/ELEXA + BSC Na = 200	Placebo + BSC Na = 203
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	3 (1.5)[f]	0 (0)

a. Number of patients who received at least 1 dose of the study medication. Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. In Module 4 A, the company indicated that multiple responses were allowed.
c. BMI adjusted for age and sex; only for patients who were aged < 20 years at screening (ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC: n = 71; placebo + BSC: n = 74)
d. Medication taken within 56 days before screening was documented.
e. In the 2 years prior to screening.
f. IQWiG calculations.

BMI: body mass index; BSC: best supportive care; ELEXA: elexacaftor; f: female; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; ND: no data; m: male; n: number of patients in the category; N: number of patients who received at least 1 dose of the study drug; RCT: randomized controlled study; SD: standard deviation; TEZA: tezacaftor

Both study arms were very similar in terms of patients' demographic and clinical characteristics. Most patients were white, and their average age was about 26 years. The study arms contained equal numbers of male and female patients. Patients from Europe or Australia made up about 41% of included patients. The mean sweat chloride concentration was 102 mmol/L.

The study's inclusion criteria required patients to have an FEV1 (in % of predicted normal) of ≥ 40% and ≤ 90% at screening. Departing from these criteria, the study included some patients with an FEV1 of < 40% or > 90% at study start. However, only about 10% of patients in each study arm were outside the predefined range.

Implementation of the ACT

The G-BA specified BSC as the ACT for ivacaftor in the treatment of CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation. BSC is the therapy that 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], while exhausting all possible dietetic measures).

In the VX17-445-102 study, patients were to continue their ongoing symptomatic treatment while being treated with ivacaftor/tezacaftor/elexacaftor or placebo. The study protocol required that the concomitant medication remain stable from 4 weeks before study start. For

inclusion, the study additionally required that participants be willing to maintain a stable CF-related concomitant treatment over the entire study period.

In Module 4 A, the company analysed prior and concomitant treatment, broken down merely by drug class rather than by drugs. However, the data show that the majority of patients in the study received concomitant symptomatic treatment of CF both before the first administration of the study drug and during the study.

Table 9 shows the prior and concomitant treatment of patients in the VX17-445-102 study.

Table 9: Treatment before the first administration of the study drug and concomitant treatment – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC

Study	IVA + IVA/TEZA/ELEXA + BSC		Placebo + BSC	
	Treatment before the first administration of the study drug[a] n (%)	Concomitant treatment[b], n (%)	Treatment before the first administration of the study drug[a] n (%)	Concomitant treatment[b], n (%)
VX17-445-102	**N = 202**		**N = 201**	
Drug treatment				
Antibiotics	149 (73.8)	187 (92.6)	156 (77.6)	197 (98.0)
Intravenous antibiotics	1 (0.5)	23 (11.4)	0 (0)	68 (33.8)
Inhaled medication	199 (98.5)	199 (98.5)	196 (97.5)	197 (98.0)[c]
Mucolytics	187 (92.6)	187 (92.6)	183 (91.0)	184 (91.5)[c]
Bronchodilators	189 (93.6)	191 (94.6)[c]	189 (94.0)	191 (95.0)[c]
Inhaled saline solution[d]	147 (73.5)[e]	ND	127 (62.6)[f]	ND
Non-medicinal treatment				
Physical therapy	149 (73.8)	151 (74.8)[c]	148 (73.6)	150 (74.6)[c]

a. Ongoing therapy at start of treatment.
b. Sum of patients who received the treatment at study start and started a new regimen during the study. It is unclear how many patients, if any, discontinued the concomitant treatment over the course of the study.
c. IQWiG calculations.
d. As per study protocol, the inhalation of saline solution was generally permitted.
e. Baseline; based on N = 200 patients.
f. Baseline; based on N = 203 patients.

BSC: best supportive care; ELEXA: elexacaftor; IVA: ivacaftor; N: number of analysed patients of the safety population; RCT: randomized controlled trial; TEZA: tezacaftor

The available information shows that at the time of study inclusion, patients received antibiotics, inhaled medication, as well as physical therapy as symptomatic treatment of CF. The data do not show which drugs were administered. Module 4 A does not discuss treatment with inhaled saline solution, a standard CF therapy, during the study. As per study protocol, however, the use of inhaled saline solution was generally allowed. While the available data

suggest that some patients started concomitant treatment after the 1st dose of the study drug (see Table 9), it remains unclear whether more patients would have needed an adjustment over the 24-week course of the study. Additionally, it cannot be inferred from the data whether the concomitant treatment was adjusted, e.g. by increasing the dose or frequency in drug and nondrug treatment over the course of the study, and if so, for how many patients this was the case. 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 VX17-445-102 study represents a complete implementation of the ACT of BSC. This conclusion is based on the fact that no information is 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 the exclusion of the study. Rather, the results of the study were deemed suitable for drawing conclusions on any added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with the ACT. Said missing details did, in turn, affect the assessment of the certainty 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 + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of results	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
VX17-445-102	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the VX17-445-102 study. This concurs with the company's assessment.

Transferability of the study results to the German healthcare context

The company stated that the majority of patients was of Caucasian origin and the study was conducted exclusively in European, North American, and Australian centres. The company therefore concluded that the study results are transferable to the German healthcare context.

The company did not present any further information on the transferability of study results to the German healthcare 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
  - Hospitalization due to pulmonary exacerbations
  - Symptoms measured with the symptom domains of the CFQ-R
- Health-related quality of life
  - Measured using the health-related quality of life domains of the CFQ-R instrument
- AEs
  - SAEs
  - Discontinuation due to AEs
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviates from that 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 study included.

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

Study	Outcomes						
	All-cause mortality	Pulmonary exacerbations	Hospitalization due to pulmonary exacerbations	Symptoms (CFQ-R)	Health-related quality of life (CFQ-R)	SAEs[a]	Discontinuation due to AEs[a]
VX17-445-102	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Without the PT “infectious pulmonary exacerbation of CT”.

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 FEV1

The outcome of FEV1 (in % of predicted normal) is a lung function parameter. Relevant for the benefit assessment are symptoms which are perceived by patients and associated with a change in FEV1 or the associated reduction in health-related quality of life; the studies directly surveyed these outcomes.

Like in prior dossiers assessing ivacaftor, the company considered FEV1 a surrogate for CF-associated mortality [11-15]. However, the sources cited by the company did not demonstrate the validity of FEV1 as a surrogate. In its current dossier on ivacaftor + ivacaftor/tezacaftor/ elexacaftor, the company does not discuss any new aspects. For a detailed rationale for the outcome of FEV1 not qualifying as a valid surrogate outcome for mortality, see dossier assessment A19-70 on the drug ivacaftor in combination with tezacaftor/ivacaftor, Section 2.7.5.3.2 [16]).

- Body mass index (BMI)

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

In the present situation, the importance of the BMI as a measure of malnutrition is not directly evident since the mean BMI of patients in the included study VX17-445-102 was in the normal range both at baseline and after 24 weeks of treatment.

2.4.2 Risk of bias

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

Table 12: Risk of bias at study and outcome levels – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC

Study	Study level	Outcomes						
		All-cause mortality	Pulmonary exacerbations	Hospitalization due to pulmonary exacerbations	Symptoms (CFQ-R)	Health-related quality of life (CFQ-R)	SAEs[a]	Discontinuation due to AEs[a]
VX17-445-102	L	L	L	L	L	L	H[b]	L

a. Without the PT "infectious pulmonary exacerbation of CT".
b. The analyses of SAEs do not include the PT "infectious pulmonary exacerbations of CF", but it is unclear whether they include further events which could be potentially attributed to the underlying disorder. The company did not comment on this topic in Module 4 A.

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

Concurring with the company's assessment, the risk of bias for the results of the outcomes of all-cause mortality, pulmonary exacerbations, hospitalization due to pulmonary exacerbations, symptoms (measured with the CFQ-R), health-related quality of life (measured with the CFQ-R), and discontinuation due to AEs is deemed low. Departing from the company's assessment, the risk of bias of results is rated as high for the outcome of SAEs.

Summary assessment of the certainty of results

For the present benefit assessment, it remains unclear whether the concomitant treatment used in the VX17-445-102 study represents a full implementation of the ACT of BSC. This conclusion is based on the fact that no information is available on treatment adjustments in the form of dose or frequency increases of symptomatic treatment over the course of the study. The certainty of results of the study results for the present research question is therefore reduced. On the basis of the VX17-445-102 study, at most hints, e.g. of an added benefit, can be derived for all presented outcomes.

2.4.3 Results

Table 13 to Table 15 summarize the results on the comparison of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC in CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and exhibit an MF mutation. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier.

Tables on common AEs, common SAEs, and discontinuation due to AEs are presented in Appendix A of the full dossier assessment.

Table 13: Results (mortality, AEs) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC

Study Outcome category Outcome	IVA + IVA/TEZA/ELEXA + BSC		Placebo + BSC		IVA + IVA/TEZA/ELEXA + BSC vs. placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
VX17-445-102					
Mortality					
All-cause mortality	202	0 (0)	201	0 (0)	–
AEs					
AEs[a] (supplementary information)	202	187 (92.6)	201	187 (93.0)	–
SAEs[a]	202	20 (9.9)	201	16 (8.0)	1.24 [0.66; 2.33]; 0.533[b]
Discontinuation due to AEs[a]	202	2 (1.0)	201	0 (0)	4.98 [0.24; 102.99][c]; 0.212[b]

a. Without the PT "infectious pulmonary exacerbation of CT".
b. IQWiG calculation: p-value (unconditional exact test, CSZ method according to [17]).
c. IQWiG calculation: RR, CI (asymptotic) with correction factor 0.5 in both study arms

AE: adverse event; BSC: best supportive care; CI: confidence interval; ELEXA: elexacaftor; IVA: ivacaftor; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TEZA: tezacaftor

Table 14: Results (morbidity, dichotomous) – RCT, direct comparison: ivacaftor + ivacaftor/ tezacaftor/elexacaftor + BSC vs. placebo + BSC

Study Outcome category Outcome	IVA + IVA/TEZA/ELEXA + BSC		Placebo + BSC		IVA + IVA/TEZA/ELEXA + BSC vs. placebo + BSC
	N	Number of events nE (nE/patient years)[a]	N	Number of events nE (nE/patient years)[a]	Rate ratio [95% CI]; p-value[b]
VX17-445-102					
Morbidity					
Pulmonary exacerbations	200	41 (0.40[c])	203	113 (1.07[c])	0.37 [0.25; 0.55]; < 0.001
Hospitalization due to pulmonary exacerbations	200	8[c] (0.08)	203	28[c] (0.26[c])	0.29 [0.14; 0.61]; ND

a. The event rate (nE/patient years) is calculated from the total number of events divided by the total number of years (sum of the observation period of all patients included in the analysis).
b. Negative binomial model.
c. IQWiG calculations.

BSC: best supportive care; CI: confidence interval; ELEXA: elexacaftor; IVA: ivacaftor; N: number of analysed patients; ND: no data; nE: number of events; RCT: randomized controlled trial; TEZA: tezacaftor

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC (multi-page table)

Study Outcome category Outcome	IVA + IVA/TEZA/ELEXA + BSC			Placebo + BSC			IVA + IVA/TEZA/ELEXA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	MD [95% CI]; p-value[c]
VX17-445-102							
Morbidity							
Symptoms (CFQ-R, symptom domains, children [12 to 13 years] and adolescents or adults – pooled)[d]							
Respiratory symptoms	200	68.28 (16.91)	16.99 (18.39)	203	69.98 (17.76)	−2.46 (16.40)	20.23 [17.50; 22.96]; < 0.001 Hedges' g: 1.45 [1.23; 1.67]
Digestive symptoms	200	83.06 (18.10)	0.73 (16.99)	203	83.36 (16.89)	−0.06 (15.89)	2.51 [−0.10; 5.13]; 0.059
Weight[e]	185	74.41 (30.99)	14.94 (28.95)	179	74.12 (31.71)	0.75 (30.26)	13.11 [8.35; 17.88]; < 0.001 Hedges' g: 0.56 [0.35; 0.77]
Health-related quality of life							
Health-related quality of life (CFQ-R, health-related quality of life domains, children [12 to 13 years], and adolescents or adults – pooled)[d]							
Physical functioning	200	76.54 (21.67)	8.85 (17.83)	203	76.44 (21.57)	−4.27 (15.47)	12.45 [9.92; 14.99]; < 0.001 Hedges' g: 0.96 [0.75; 1.17]
Emotional functioning	200	82.05 (15.99)	2.60 (12.63)	203	80.20 (16.71)	−1.20 (12.58)	3.37 [1.50; 5.25]; < 0.001 Hedges' g: 0.35 [0.16; 0.55]
Vitality[e]	185	62.79 (17.07)	6.66 (17.66)	179	63.78 (18.26)	−5.07 (15.38)	13.12 [10.45; 15.79]; < 0.001 Hedges' g: 1.00 [0.78; 1.22]
Social functioning	200	70.55 (17.01)	5.95 (14.83)	203	68.84 (17.88)	−1.44 (11.85)	5.86 [3.71; 8.02]; < 0.001 Hedges' g: 0.53 [0.33; 0.73]
Role functioning[e]	185	81.67 (17.48)	4.55 (15.40)	179	83.30 (15.23)	−2.45 (14.02)	6.84 [4.58; 9.10]; < 0.001 Hedges' g: 0.62 [0.41; 0.83]

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC (multi-page table)

Study Outcome category Outcome	IVA + IVA/TEZA/ELEXA + BSC			Placebo + BSC			IVA + IVA/TEZA/ELEXA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	MD [95% CI]; p-value[c]
Body image	200	78.78 (22.14)	4.43 (17.44)	203	77.18 (23.46)	0.38 (16.60)	3.84 [1.18; 6.49]; 0.005 Hedges' g: 0.28 [0.09; 0.48]
Eating disorders	200	90.00 (17.93)	2.19 (16.21)	203	89.11 (17.55)	−2.03 (14.92)	4.88 [2.62; 7.15]; < 0.001 Hedges' g: 0.42 [0.22; 0.62]
Treatment burden	200	59.17 (19.23)	5.67 (16.21)	203	61.41 (20.15)	−1.37 (13.40)	6.83 [4.50; 9.16]; < 0.001 Hedges' g: 0.57 [0.37; 0.77]
Health perceptions[e]	185	63.48 (20.49)	12.44 (18.17)	179	64.25 (20.13)	−4.53 (16.13)	17.05 [14.07; 20.02]; < 0.001 Hedges' g: 1.17 [0.95; 1.39]

a. Number of patients included in the analysis for the calculation of the effect estimation; the values over the course of the study and at study end may be based on different patient numbers.
b. Refers to the change from baseline to the last time point of measurement.
c. MMRM: treatment, study time point, treatment x study time point as fixed effects; adjusted by age, sex, and FEV1; the effect presents the difference between treatment groups in terms of the mean changes over the course of the study from baseline to the respective measurement time.
d. Higher values indicate better symptoms / health-related quality of life; a positive difference between groups means an advantage for ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC.
e. Domain for adolescents or adults; not intended for children [12 to 13 years].

BSC: best supportive care; CI: confidence interval; ELEXA: elexacaftor; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; MD: mean difference; MMRM: mixed effect model repeated measurement; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; TEZA: tezacaftor

Due to missing details concerning the implementation of the ACT and regarding the outcome of SAEs, and given that the risk of bias for all outcomes was already high for other reasons, it was impossible to derive more than a hint, e.g. of added benefit, on the basis of the available data.

Mortality

All-cause mortality

There were no deaths over the course of the study. For the outcome of all-cause mortality, there is no hint of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Pulmonary exacerbations

Operationalization

In the study, pulmonary exacerbations were defined as new, or changed, antibiotic therapy (intravenous, inhaled, or oral) being required for any 4 or more of the following signs or symptoms:

- Change in sputum
- New or increased haemoptysis
- Increased cough
- Increased dyspnoea
- Malaise, fatigue, or lethargy
- Temperature > 38°C
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination findings of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

This definition of pulmonary exacerbations is deemed adequate.

The company classified pulmonary exacerbations in 3 operationalizations:

- Pulmonary exacerbations
- Hospitalization due to pulmonary exacerbations
- Pulmonary exacerbations requiring intravenous antibiotic treatment

For the present dossier assessment, pulmonary exacerbations and hospitalization due to pulmonary exacerbations were each analysed using the event quantity and event rate (number

of events/patient years) in order to consider not only the occurrence, but also the frequency of pulmonary exacerbations over the entire course of the study. In this process, hospitalization due to pulmonary exacerbations represents the occurrence of serious exacerbations.

Results

Pulmonary exacerbations

For pulmonary exacerbations, there is a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC. This results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC for pulmonary exacerbations.

This deviates from the assessment by the company, which derived an indication of added benefit from the analysis of patients with events as well as from event-time analyses.

Hospitalization due to pulmonary exacerbations

For hospitalization due to pulmonary exacerbations, there is a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC. For hospitalization due to pulmonary exacerbations, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC.

This deviates from the assessment by the company, which derived an indication of added benefit from the analysis of patients with events as well as from event-time analyses.

Symptoms measured using the CFQ-R

Operationalization

To assess the outcomes of symptoms and health-related quality of life, the study used the instrument CFQ-R. This instrument comprises multiple versions: a patient version for various age groups (6 to 11 years, 12 to 13 years, and ≥ 14 years) and a parent/guardian version.

In adolescents and adults (≥ 14 years of age), the instrument consists of 3 domains on symptoms, while for children from 12 to 13 years of age, the domain of weight is excluded from the questionnaire. In addition, the CFQ-R for adolescents and adults contains 9 domains on health-related quality of life. For children from 12 to 13 years of age, the domains of vitality, role functioning, and health perceptions are not included.

In the present dossier assessment, the analyses based on a mixed-effects model repeated measures (MMRM) are examined for all domains of the CFQ-R. These analyses allow a consistent evaluation of all domains of the CFQ-R and hence a meaningful interpretation of the validated instrument, taking into account improvements as well as deteriorations in symptoms or health-related quality of life, given a potentially progressive course of disease. A responder analysis is available only for 1 of the 12 domains of the CFQ-R.

Results

Respiratory symptoms domain

In the respiratory symptoms domain, there is a statistically significant difference in the mean change over the course of the study from baseline to the respective measurement time to the advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with placebo + BSC. The SMD in the form of Hedges' g was used to assess the relevance of the result. The 95% confidence interval (95% CI) is fully outside the irrelevance range [−0.2; 0.2]. This is interpreted as a relevant effect. There is an effect modification by the attribute of age. However, since the results in both subgroups do not differ in extent or direction of effect from the results of the entire study population (see Section 2.4.4), the attribute was disregarded in the further analysis of the respiratory symptoms domain. For the respiratory symptoms domain of the CFQ-R, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC.

This deviates from the assessment by the company, which derived an indication of added benefit from the mean value difference as well as from the responder analysis.

Digestive symptoms domain

For the digestive symptoms domain, no statistically significant difference between treatment groups was found for the mean change over the course of the study from baseline to the respective measurement time. For the digestive symptoms domain of CFQ-R, this results in no hint of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

This deviates from the assessment by the company, which derived an indication of added benefit on the basis of all non-respiratory domains combined.

Weight domain

In the weight domain, there is a statistically significant difference in the mean change over the course of the study from baseline to the respective measurement time to the advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with placebo + BSC. The 95% CI is fully outside the irrelevance range [−0.2; 0.2]. This is interpreted as a relevant effect. An effect modification by the attribute of age was found, however. For the CFQ-R weight domain in patients ≥ 18 years of age, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC. For patients < 18 years of age, in turn, no added benefit was found (see Section 2.4.4).

This deviates from the assessment by the company, which looked at the effect modification for the weight domain, but overall, derived an indication of added benefit on the basis of all non-respiratory domains combined.

Health-related quality of life

Health-related quality of life was surveyed using the CFQ-R domains of physical functioning, emotional functioning, vitality, social functioning, role functioning, body image, eating disorders, treatment burden, and health perceptions.

Results

Physical functioning, social functioning, and treatment burden domains

In the physical functioning, social functioning, and treatment burden domains, there is a statistically significant difference in the mean change over the course of the study from baseline to the respective measurement time to the advantage of ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC in comparison with placebo + BSC. The 95% CI for SMD is fully outside the irrelevance range [−0.2; 0.2]. This is interpreted as a relevant effect in each case. For all 3 domains, an effect modification by the attribute of age was found, however. For each of the CFQ-R domains of physical functioning, social functioning, and treatment burden, there is a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC for patients aged ≥ 18 years. For patients aged < 18 years, on the other hand, no added benefit was found (see Section 2.4.4).

This deviates from the assessment by the company, which disregarded the effect modification for the social functioning domain. Despite factoring in effect modifications for both the physical functioning domain and the treatment burden domain, the company ended up deriving an indication of added benefits based on all non-respiratory domains combined.

Emotional functioning and body image domains

In the emotional functioning and body image domains, there are statistically significant differences in the mean change over the course of the study from baseline to the respective measurement time to the advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with placebo + BSC. However, the 95% CI for SMD is not fully outside the irrelevance range [−0.2; 0.2]. The effect can therefore not be inferred to be relevant for any of them. For each of the CFQ-R domains emotional functioning and body image, this results in no hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC; this results in no proof of added benefit for any of them.

This deviates from the assessment by the company, which derived an indication of added benefit on the basis of all non-respiratory domains combined.

Domains of vitality, role functioning, eating disorders, and health perception

For the vitality, role functioning, eating disorders, and health perception domains, statistically significant differences were found in the mean change over the course of the study from baseline to the respective measurement time to the advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with placebo + BSC. The 95% CI for SMD is fully outside the irrelevance range [−0.2; 0.2]. This is interpreted as a relevant effect in

each case. For each of the CFQ-R domains of vitality, role functioning, eating disorders, and health perceptions, there is therefore a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC.

This deviates from the assessment by the company, which derived an indication of added benefit on the basis of all non-respiratory domains combined.

AEs

SAEs and discontinuation due to AEs

For each of the outcomes of SAEs and discontinuation due to AEs, no statistically significant differences between treatment groups were found. Consequently, for the outcomes of SAEs and discontinuation due to AEs, there is no hint of greater or lesser harm of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

2.4.4 Subgroups and other effect modifiers

For the present assessment, the following subgroups were used:

- Age (< 18 / ≥ 18 years)
- Sex (female/male)

Interaction tests were performed if 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 16 presents the subgroup results on the comparison of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC.

Table 16: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC (multi-page table)

Study Outcome Characteristic Subgroup	IVA + IVA/TEZA/ELEXA + BSC			Placebo + BSC			IVA + IVA/TEZA/ELEXA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	MD [95% CI]; p-value[c]
VX17-445-102							
Morbidity							
Symptoms (CFQ-R, symptoms domain, adolescents or adults)[d]							
Respiratory symptoms							
Age							
< 18 years	56	74.11 (17.47)	15.69 (16.34)	60	78.94 (15.24)	−0.83 (14.79)	15.63 [10.75; 20.51]; < 0.001 Hedges' g: 1.12 [0.73; 1.51]
≥ 18 years	144	66.01 (16.19)	17.47 (19.14)	143	66.22 (17.44)	−3.15 (17.04)	22.08 [18.80; 25.37]; < 0.001 Hedges' g: 1.54 [1.28; 1.81]
Total						Interaction:	p-value = 0.031
Weight[e]							
Age							
< 18 years	41	79.67 (27.77)	6.67 (22.90)	36	70.37 (30.63)	9.26 (30.46)	−0.12 [−9.49; 9.25]; 0.980
≥ 18 years	144	72.92 (31.77)	17.25 (30.09)	143	75.06 (32.01)	−1.41 (29.94)	16.81 [11.33; 22.29]; < 0.001 Hedges' g: 0.71 [0.47; 0.94]
Total						Interaction:	p-value = 0.004
Health-related quality of life							
Health-related quality of life (CFQ-R, domains on health-related quality of life, children [12 to 13 years] and adolescents or adults – pooled)[d]							
Physical functioning							
Age							
< 18 years	56	81.32 (21.80)	6.24 (12.47)	60	83.91 (16.22)	1.18 (11.72)	4.01 [0.48; 7.54]; 0.026 Hedges' g: 0.40 [0.03; 0.77]
≥ 18 years	144	74.68 (21.41)	9.85 (19.45)	143	73.31 (22.79)	−6.56 (16.30)	15.89 [12.71; 19.07]; < 0.001 Hedges' g: 1.15 [0.90; 1.40]
Total						Interaction:	p-value < 0.001
Social functioning							
Age							
< 18 years	56	75.08 (14.20)	2.11 (12.27)	60	71.59 (19.66)	2.48 (13.26)	0.00 [−4.07; 4.07]; > 0.999
≥ 18 years	144	68.79 (17.71)	7.42 (15.49)	143	67.69 (17.02)	−3.08 (10.84)	8.24 [5.74; 10.74]; < 0.001 Hedges' g: 0.76 [0.52; 1.00]
Total						Interaction:	p-value < 0.001

Table 16: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC vs. placebo + BSC (multi-page table)

Study Outcome	IVA + IVA/TEZA/ELEXA + BSC			Placebo + BSC			IVA + IVA/TEZA/ELEXA + BSC vs. placebo + BSC
Characteristic Subgroup	N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	MD [95% CI]; p-value[c]
Treatment burden							
Age							
< 18 years	56	66.47 (16.61)	1.21 (15.96)	60	72.78 (19.67)	−1.11 (16.07)	2.75 [−1.89; 7.39]; 0.242
≥ 18 years	144	56.33 (19.47)	7.38 (16.04)	143	56.64 (18.43)	−1.48 (12.17)	8.50 [5.82; 11.17]; < 0.001 Hedges' g: 0.73 [0.49; 0.97]
Total						Interaction:	p-value = 0.042

a. Number of patients included in the analysis for the calculation of the effect estimation; the values over the course of the study and at study end may be based on different patient numbers.
b. Refers to the change from baseline to the last time point of measurement.
c. MMRM: treatment, study time point, treatment x study time point as fixed effects; adjusted by age, sex, and FEV1; the effect presents the difference between treatment groups in terms of the mean changes over the course of the study from baseline to the respective measurement time.
d. Higher values indicate improved symptoms / health-related quality of life; a positive difference between groups means an advantage for ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC.
e. Domain for adolescents or adults; not intended for children [12 to 13 years].

BSC: best supportive care; CI: confidence interval; ELEXA: elexacaftor; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; MD: mean difference; MMRM: mixed effect model repeated measurement; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; TEZA: tezacaftor

Morbidity

Symptoms measured using the CFQ-R

Respiratory symptoms domain

An effect modification by the attribute of age was found for the respiratory symptoms domain. For both subgroups, the mean changes over the course of the study from baseline to the respective measurement time show statistically significant differences to the advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with placebo + BSC. The 95% CI for SMD is fully outside the irrelevance range [−0.2; 0.2]. This is interpreted as a relevant effect in each case. In both subgroups, the above as well as the extent agree with the results for the entire study population. For the CFQ-R respiratory symptoms domain, the attribute of age is therefore disregarded below.

This concurs with the company's assessment.

Weight domain

For the weight domain, an effect modification by the attribute of age was found. For patients aged ≥ 18 years, the mean changes over the course of the study from baseline to the respective

measurement time show a statistically significant difference to the advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with placebo + BSC. The 95% CI is fully outside the irrelevance range [−0.2; 0.2]. This is interpreted as a relevant effect. For the CFQ-R domain of weight in patients aged ≥ 18 years, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC. In contrast, for patients aged < 18 years, no statistically significant difference was found between the treatment groups; hence, there is no proof of added benefit for ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus BSC for these patients.

This deviates from the assessment by the company, which, despite factoring in effect modifications for the weight domain, ended up deriving an indication of added benefit based on all non-respiratory domains combined.

Health-related quality of life measured using the CFQ-R

Physical functioning domain

An effect modification by the attribute of age was found for the physical functioning domain. For both subgroups, the mean changes over the course of the study from baseline to the respective measurement time show statistically significant differences to the advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with placebo + BSC. For patients aged ≥ 18 years, the 95% CI for SMD is fully outside the irrelevance range [−0.2; 0.2]. This is interpreted as a relevant effect. For the CFQ-R domain of physical functioning, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC for patients aged ≥ 18 years. In contrast, for patients aged < 18 years, the 95% CI for SMD is not fully outside the irrelevance range [−0.2; 0.2]. The effect cannot be inferred to be relevant; an added benefit is therefore not proven for these patients.

This deviates from the assessment by the company, company, which, despite factoring in effect modifications for the physical functioning domain, ended up deriving an indication of added benefit based on all non-respiratory domains combined.

Social functioning and treatment burden domains

An effect modification by the attribute of age was found for the social functioning and treatment burden domains. For patients aged ≥ 18 years, the mean changes over the course of the study from baseline to the respective measurement time each show a statistically significant difference to the advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with placebo + BSC. The 95% CI for SMD is fully outside the irrelevance range for each of them [−0.2; 0.2]. This is interpreted as a relevant effect in each case. For each of the social functioning and treatment burden domains of the CFQ-R, this results in a hint of added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC in comparison with BSC for patients aged ≥ 18 years. In contrast, for patients aged < 18 years, none of the comaprisons of ivacaftor + ivacaftor/tezacaftor/elexacaftor + BSC versus placebo + BSC yielded a statistically significant difference; hence, there is no proof of added benefit for these patients.

This deviates from the assessment by the company, which disregarded the effect modification for the social functioning domain. Despite factoring in effect modifications for the treatment burden domain, the company ended up deriving an indication of added benefit on the basis of all nonrespiratory domains combined.

2.5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are presented below. The various outcome categories and the effect sizes have been 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 any added benefit by aggregating the conclusions reached at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated on the basis of the results presented in Section 2.4 (see Table 17).

Determination of the outcome category for outcomes on symptoms and adverse events

Not for all outcomes examined in the present benefit assessment does the dossier permit inferences as to whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

The definition for the outcome of pulmonary exacerbations (see Section 2.4.3) includes events which are not severe or serious per se. Hospitalizations due to pulmonary exacerbations, which reflect serious exacerbations, account for the minority of pulmonary exacerbation events. It is for this reason that, in this assessment report, the outcome of pulmonary exacerbations has been listed under the outcome category of non-serious/non-severe symptoms / late complications.

The company did not report whether the data on the CFQ-R symptoms domain were severe or serious events. This assessment report lists these CFQ-R domains under the outcome category of non-serious/non-severe symptoms / late complications. The allocation is of no consequence in the determination of the extent of added benefit since, for different reasons, the added benefit derived from these domains is non-quantifiable.

Table 17: Extent of added benefit at outcome level: ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC vs. placebo + BSC (multi-page table)

Outcome category **Outcome** **Domain** **Effect modifier** **Subgroup**	**Ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC vs. placebo + BSC** **event rate or mean change or event rate (%)** **effect estimate [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser/added benefit not proven
Morbidity		
Pulmonary exacerbations	Rate: 0.40 vs. 1.07 Rate ratio: 0.37 [0.25; 0.55]; p < 0.001 Probability: hint	Outcome category: non-serious/ non-severe symptoms / late complications CI_u < 0.80 Added benefit, extent: considerable
Hospitalization due to pulmonary exacerbations	Rate: 0.08 vs. 0.26 Rate ratio: 0.29 [0.14; 0.61]; ND Probability: hint	Outcome category: serious/severe symptoms / late complications CI_u < 0.75, risk ≥ 5%[c] Added benefit, extent: major
Symptoms (CFQ-R, symptom domains)		
Respiratory symptoms	Mean change: 16.99 vs. −2.46 MD: 20.23 [17.50; 22.96]; p < 0.001 Hedges' g: 1.45 [1.23; 1.67][d] Probability: hint	Outcome category: non-serious/ non-severe symptoms / late complications Added benefit, extent: non-quantifiable
Digestive symptoms	Mean change: 0.73 vs. −0.06 MD: 2.51 [−0.10; 5.13]; p = 0.059	Lesser/added benefit not proven
Weight Age < 18 years	Mean change: 6.67 vs. 9.26 MD: −0.12 [−9.49; 9.25]; p = 0.980	Lesser/added benefit not proven
≥ 18 years	Mean change: 17.25 vs. −1.41 MD: 16.81 [11.33; 22.29]; p < 0.001 Hedges' g: 0.71 [0.47; 0.94][d] Probability: hint	Outcome category: non-serious/ non-severe symptoms / late complications Added benefit, extent: non-quantifiable

Table 17: Extent of added benefit at outcome level: ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC vs. placebo + BSC (multi-page table)

Outcome category **Outcome** **Domain** **Effect modifier** **Subgroup**	**Ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC vs. placebo + BSC** **event rate or mean change or event rate (%)** **effect estimate [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
Physical functioning Age < 18 years	Mean change: 6.24 vs. 1.18 MD: 4.01 [0.48; 7.54]; p = 0.026 Hedges' g: 0.40 [0.03; 0.77][d]	Lesser/added benefit not proven
≥ 18 years	Mean change: 9.85 vs. −6.56 MD: 15.89 [12.71; 19.07]; p < 0.001 Hedges' g: 1.15 [0.90; 1.40][d] Probability: hint	Outcome category: health-related quality of life Added benefit, extent: non-quantifiable
Emotional functioning	Mean change: 2.60 vs. −1.20 MD: 3.37 [1.50; 5.25]; p < 0.001 Hedges' g: 0.35 [0.16; 0.55][d]	Lesser/added benefit not proven
Vitality	Mean change: 6.66 vs. −5.07 MD: 13.12 [10.45; 15.79]; p < 0.001 Hedges' g: 1.00 [0.78; 1.22][d] Probability: hint	Outcome category: health-related quality of life Added benefit, extent: non-quantifiable
Social functioning Age < 18 years	Mean change: 2.11 vs. 2.48 MD: 0.00 [−4.07; 4.07]; p > 0.999	Lesser/added benefit not proven
≥ 18 years	Mean change: 7.42 vs. −3.08 MD: 8.24 [5.74; 10.74]; p < 0.001 Hedges' g: 0.76 [0.52; 1.00][d] Probability: hint	Outcome category: health-related quality of life Added benefit, extent: non-quantifiable
Role functioning	Mean change: 4.55 vs. −2.45 MD: 6.84 [4.58; 9.10]; p < 0.001 Hedges' g: 0.62 [0.41; 0.83][d] Probability: hint	Outcome category: health-related quality of life Added benefit, extent: non-quantifiable

Table 17: Extent of added benefit at outcome level: ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC vs. placebo + BSC (multi-page table)

Outcome category **Outcome** **Domain** **Effect modifier** **Subgroup**	**Ivacaftor + ivacaftor/tezacaftor/ elexacaftor + BSC vs. placebo + BSC** **event rate or mean change or event rate (%)** **effect estimate [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Body image	Mean change: 4.43 vs. 0.38 MD: 3.84 [1.18; 6.49]; p = 0.005 Hedges' g: 0.28 [0.09; 0.48][d]	Lesser/added benefit not proven
Eating disorders	Mean change: 2.19 vs. −2.03 MD: 4.88 [2.62; 7.15]; p < 0.001 Hedges' g: 0.42 [0.22; 0.62][d] Probability: hint	Outcome category: health-related quality of life Added benefit, extent: non-quantifiable
Treatment burden Age < 18 years	Mean change: 1.21 vs. −1.11 MD: 2.75 [−1.89; 7.39]; p = 0.242	Lesser/added benefit not proven
≥ 18 years	Mean change: 7.38 vs. −1.48 MD: 8.50 [5.82; 11.17]; p < 0.001 Hedges' g: 0.73 [0.49; 0.97][d] Probability: hint	Outcome category: health-related quality of life Added benefit, extent: non-quantifiable
Health perceptions	Mean change: 12.44 vs. −4.53 MD: 17.05 [14.07; 20.02]; p < 0.001 Hedges' g: 1.17 [0.95; 1.39][d] Probability: hint	Outcome category: health-related quality of life Added benefit, extent: non-quantifiable
AEs		
SAEs	9.9% vs. 8.0% RR: 1.24 [0.66; 2.33]; p = 0.533	Greater/lesser harm not proven
Discontinuation due to AEs	1.0% vs. 0% RR: 4.98 [0.24; 102.99]; p = 0.212	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. Hospitalization due to pulmonary exacerbations in 7 patients in the intervention arm (3.5%) and 27 patients in the comparator arm (13.3%).
d. 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 concluded.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of CI; MD: mean difference; ND: no data; RR: relative risk; SAE: serious adverse event

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

Table 18: Favourable and unfavourable effects from the assessment of ivacaftor + ivacaftor/ tezacaftor/elexacaftor in comparison with BSC

Favourable effects	**Unfavourable effects**
Serious/severe symptoms / late complications ▪ Hospitalization due to pulmonary exacerbations: hint of added benefit – extent: major	–
Non-serious/non-severe symptoms / late complications ▪ Pulmonary exacerbations: hint of added benefit – extent: considerable ▪ Symptoms ▫ Respiratory symptoms domain: hint of added benefit – extent: non-quantifiable ▫ Weight[a] - Age ≥ 18 years: hint of added benefit – extent: non-quantifiable	–
Health-related quality of life ▪ Domains of physical functioning, social functioning, treatment burden ▫ Age ≥ 18 years: hint of added benefit – extent: non-quantifiable ▪ Domains of vitality[a], role functioning[a], eating disorders, and health perceptions[a]: hint of added benefit – extent: non-quantifiable	–
a. Domain surveyed only for adolescents or adults since it is not intended for children [12 to 13 years]. BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire – Revised	

All things considered, exclusively favourable effects of ivacaftor + ivacaftor/tezacaftor/ elexacaftor were found in comparison with BSC. For hospitalization due to pulmonary exacerbations, there is a hint of major added benefit. In addition, there is a hint of considerable added benefit regarding pulmonary exacerbations. Several domains concerning symptoms and health-related quality of life each show a hint of non-quantifiable added benefit, albeit this hint is limited to the subgroup of patients aged ≥ 18 years in some cases.

In summary, this results in a hint of major added benefit of ivacaftor + ivacaftor/tezacaftor/ elexacaftor versus the ACT of BSC for CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation.

The result of the assessment of the added benefit of ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor in comparison with the ACT is summarized in Table 19.

Table 19: ivacaftor + ivacaftor/tezacaftor/elexacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation	BSC[b]	Hint of major added benefit

a. Presented is the ACT specified by the G-BA.
b. BSC is defined as the treatment which ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

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 above assessment deviates from that by the company, which derived an indication of major added benefit.

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.

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