IQWiG Reports – Commission No. A19-68

Ivacaftor (cystic fibrosis, 18 years and older, with R117H mutation) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Ivacaftor (zystische Fibrose, ab 18 Jahre mit R117H-Mutation) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 November 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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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
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)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SPC	Summary of Product Characteristics
SOC	System Organ Class

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. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 28 August 2019.

Research question

The aim of the present report is the assessment of the added benefit of ivacaftor in comparison with the appropriate comparator therapy (ACT) best supportive care (BSC) in the treatment of patients with cystic fibrosis (CF) aged 18 years and older who have an R117H mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Table 2: Research question of the benefit assessment of ivacaftor

Subindication	**ACT[a]**
Patients with cystic fibrosis aged 18 years and older who have an R117H mutation in the CFTR gene	BSC
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

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

The RCT VX11-770-110, which compared ivacaftor + BSC with placebo + BSC, was included in the benefit assessment. The study included patients aged ≥ 6 years with CF and an R117H mutation in at least one allele in the CFTR gene. A total of 70 patients were randomly allocated to both study arms in a 1:1 ratio. The subpopulation of patients ≥ 18 years (50 patients) is relevant for the present benefit assessment.

Treatment with ivacaftor or placebo was in addition to basic therapy. Patients in the ivacaftor arm received 1 tablet of 150 mg ivacaftor every 12 hours in compliance with the Summary of Product Characteristics (SPC).

Primary outcome of the study was the forced expiratory volume in 1 second (FEV1, in % of predicted normal). Patient-relevant secondary outcomes were all-cause mortality, symptoms, health-related quality of life, and adverse events (AEs). All outcomes were recorded until at most 4 weeks after the end of treatment.

Implementation of the appropriate comparator therapy

The G-BA specified BSC as ACT for ivacaftor in adult patients with CF who have an R117H mutation in the CFTR gene.

The study protocol recommended that patients who were on stable CF medication in the 4 weeks before baseline should remain on this medication until the end of the study. There were important restrictions for certain concomitant therapies for inhaled hypertonic saline solution. This was not permitted within 4 weeks before the first intake of the study medication until shortly before the end of the study or had to be discontinued before the start of the study to allow inclusion in the study. Shortly before the end of the study, a protocol change allowed the use of inhaled hypertonic saline solution (study start: 3 July 2012; protocol change: 11 June 2013; end of study: 25 October 2013). From the time point of the protocol change, however, only 4 patients (8.0%) of the relevant subpopulation (≥ 18 years) were included who could still have benefited from this extension of the concomitant medication. According to the information provided in the study protocol, there were no further restrictions. With the exception of hypertonic saline solution, concomitant medication for the symptomatic therapy of CF, e.g. inhalation with dornase alfa, use of bronchodilators, antibiotics and vitamin preparations, and use of physiotherapy were therefore not excluded for patients.

In Module 4 A, the company did not provide information on the medications the patients in the relevant subpopulation (71.4% of the patients in the total population) actually received in the 4 weeks before baseline as well as during the course of the study. Information was only available for the total study population. It was shown for this population that the patients received the regularly used drugs for the symptomatic therapy of CF as concomitant medication. The proportion of patients under the respective concomitant medication remained largely unchanged in the total population before and after the first intake of the study medication. Only individual patients started concomitant medication after the first intake of the study medication. A clear increase in concomitant medication after the first intake of the study medication was shown, for example, for antibiotics (including ciprofloxacin and tobramycin) and analgesics (ibuprofen and paracetamol). However, there was no information on whether and how many patients had their concomitant treatment adjusted, for example in the sense of an increase in dose or frequency in the course of the study.

In summary, the concomitant treatment used in the VX11-770-110 study did not constitute a complete implementation of the ACT BSC. This assessment is based particularly on the exclusion of inhaled saline solution, a standard therapy in CF, until shortly before the end of the study. However, the uncertainties mentioned regarding the implementation of the ACT did not lead to the exclusion of the study. Instead, it was assumed that conclusions on the added benefit of ivacaftor in comparison with the ACT can be drawn on the basis of the results of the study. The uncertainties described were considered in the assessment of the certainty of conclusions of the results.

Risk of bias and assessment of the certainty of conclusions

The risk of bias at study level was rated as low for the VX11-770-110 study. The risk of bias for the results of the following outcomes was rated as low: all-cause mortality, pulmonary exacerbations, hospitalization due to pulmonary exacerbations, symptoms measured using the Cystic Fibrosis Questionnaire-Revised (CFQ-R), health related quality of life measured using the CFQ-R, discontinuation due to AEs, and oropharyngeal pain (Preferred Term, PT). The events of pulmonary exacerbation of CF were included in the recording of serious AEs (SAEs). However, SAEs without events attributable to the underlying disease are relevant for the benefit assessment. The risk of bias for SAEs was therefore rated as high.

As described above, it is not assumed for the present benefit assessment that the concomitant treatment used in the VX11-770-110 study was a complete implementation of the ACT in the sense of BSC. The certainty of conclusions of the study results for the present research question is therefore reduced. Based on the VX11-770-110 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

Results

Mortality

All-cause mortality

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

Morbidity

Pulmonary exacerbations

No statistically significant difference was shown between the treatment groups for the outcome “pulmonary exacerbations”. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

Hospitalization due to pulmonary exacerbations

No statistically significant difference was shown between the treatment groups for the outcome “hospitalization due to pulmonary exacerbations”. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

Symptoms measured using the CFQ-R

Symptom outcomes were recorded with the domains “respiratory symptoms”, “digestive symptoms” and “weight” of the disease-specific patient-reported instrument CFQ-R.

- Domain “respiratory symptoms”

A statistically significant difference in favour of ivacaftor + BSC versus BSC was shown for the change from baseline in the domain “respiratory symptoms”. The standardized mean

difference (SMD) in the form of Hedges' g was considered to assess the relevance of the result. The 95% confidence interval (CI) was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. For the CFQ-R domain "respiratory symptoms", this resulted in a hint of an added benefit of ivacaftor + BSC in comparison with BSC.

- Domains "digestive symptoms" and "weight"

In the domains "digestive symptoms" and "weight", no statistically significant differences were shown between the treatment groups. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for each of these 2 domains; an added benefit is therefore not proven.

Health-related quality of life

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

- Domains "role functioning", "body image" and "treatment burden"

In the domains of role functioning, body image and treatment burden, no statistically significant differences were shown between the treatment groups. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for these domains; an added benefit is therefore not proven.

- Domains "physical functioning" and "eating problems"

Statistically significant differences in favour of ivacaftor + BSC versus BSC were shown in each of the domains of physical functioning and eating problems. However, the respective 95% CI of the SMD in the form of Hedges' g was not completely outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for the CFQ-R domains of physical functioning and eating problems; an added benefit is therefore not proven.

- Domains "emotional functioning", "vitality" and "social functioning"

Statistically significant differences in favour of ivacaftor + BSC versus BSC were shown in each of the domains of emotional functioning, vitality and social functioning. For the domains of emotional functioning and vitality, the 95% CI of the SMD in the form of Hedges' g was fully above the irrelevance threshold of 0.2. For the domain of social functioning, the 95% CI of the SMD in the form of Hedges' g was not completely outside the irrelevance range of −0.2 to 0.2, however. However, there were effect modifications by the characteristic of *Pseudomonas aeruginosa* infection status (domain "emotional functioning") or by the characteristic of sex (domains "vitality" and "social functioning") for all 3 domains.

For the domain "emotional functioning", there was a hint of an added benefit of ivacaftor + BSC in comparison with BSC for patients with positive *Pseudomonas aeruginosa* infection status. For patients with negative infection status, in contrast, no added benefit was shown.

There was a hint of an added benefit of ivacaftor + BSC in comparison with BSC for women for the domains of vitality and social functioning. For men, in contrast, no added benefit was shown.

- Domain "health perceptions"

No statistically significant difference between the treatment groups was shown in the domain "health perceptions". However, there was an effect modification by the characteristic "sex". There was a hint of an added benefit of ivacaftor + BSC in comparison with BSC for women. For men, in contrast, no added benefit was shown.

Side effects

Serious adverse events

The events of pulmonary exacerbation were included in the recording of SAEs. However, SAEs without events attributable to the underlying disease are relevant for the benefit assessment. Without recording of these events, there was one patient with SAEs in the ivacaftor arm and no patient with SAEs in the comparator arm. Statistically significant differences between the treatment groups were shown neither with nor without recording of the exacerbation events.

Overall, there was no hint of greater or lesser harm from ivacaftor + BSC in comparison with BSC for the outcome "SAEs"; greater or lesser harm is therefore not proven.

Discontinuation due to adverse events

No discontinuations due to AEs occurred in the course of the study. This resulted in no hint of greater or lesser harm from ivacaftor + BSC in comparison with BSC for the outcome "discontinuation due to AEs"; greater or lesser harm is therefore not proven.

Specific adverse events

- Oropharyngeal pain (PT, AE)

A statistically significant difference to the disadvantage of ivacaftor + BSC was shown for the outcome "oropharyngeal pain". This resulted in a hint of greater harm from ivacaftor + BSC in comparison with BSC for this outcome.

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

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

On the side of positive effects, hints of a non-quantifiable added benefit were shown for the outcome category of morbidity (CFQ-R domain of respiratory symptoms) and in the category of health-related quality of life for women (domains of vitality, social functioning, health perceptions) and for patients with positive *Pseudomonas aeruginosa* infection status (domain of emotional functioning). In contrast, there was a hint of greater harm of non-quantifiable extent based on one specific AE (oropharyngeal pain) on the side of negative effects.

The positive effects outweighed the negative effects. In summary, there is a hint of a non-quantifiable added benefit of ivacaftor versus the ACT BSC for adult patients with CF who have an R117H mutation in the CFTR gene.

Table 3 shows a summary of probability and extent of the added benefit of ivacaftor.

Table 3: Ivacaftor – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Patients with cystic fibrosis aged 18 years and older who have an R117H mutation in the CFTR gene	BSC	Hint of a non-quantifiable added benefit
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The approach for deriving an overall conclusion on the 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 the assessment of the added benefit of ivacaftor in comparison with the ACT BSC in the treatment of patients with CF aged 18 years and older who have an R117H mutation in the CFTR gene.

Table 4: Research question of the benefit assessment of ivacaftor

Subindication	**ACT[a]**
Patients with cystic fibrosis aged 18 years and older who have an R117H mutation in the CFTR gene	BSC
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

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. 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 of the company in the dossier:

- study lists on ivacaftor (status: 4 June 2019)
- bibliographical literature search on ivacaftor (status: 4 June 2019)
- search in trial registries for studies on ivacaftor (status: 4 June 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ivacaftor (last search on 5 September 2019)

The check identified no additional relevant study.

2.3.1 Studies included

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

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
VX11-770-110	Yes	Yes	No
a: Study sponsored by the company. BSC: best supportive care; RCT: randomized controlled trial; vs.: versus			

Concurring with the company, the subpopulation of adult patients of the VX11-770-110 study was considered for the benefit assessment.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: 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]
VX11-770-110	RCT, double-blind, parallel	Patients aged ≥ 6 years with cystic fibrosis and an R117H mutation in at least one allele in the CFTR gene and FEV1 40–90% or 40–105% at screening[b]	Ivacaftor (N = 34) placebo (N = 36[c]) Relevant subpopulation thereof (≥ 18 years): ivacaftor (n = 24) placebo (n = 26)	Screening and run-in[d] up to 35 days Treatment duration: 24 weeks[e] Follow-up[f]: up to 4 weeks after the last dose of the study medication	27 centres in United Kingdom and USA 7/2012–10/2013	Primary: FEV1 (in % of predicted normal) Secondary: all-cause mortality, symptoms, health-related quality of life, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: FEV1 (in % of predicted normal): 40 to 105% in patients aged 6 to 11 years; 40 to 90% in patients aged 12 years and older.
c: One patient in the comparator arm did not receive any study medication and was not considered in the analyses.
d: Stabilization of concomitant treatment during the 2 weeks before the first intake of study medication.
e: The study was ended by the company before the end of treatment of all patients, as the predefined minimum number of study participants had been reached. As a result, 4 patients in the adult subpopulation relevant for the present benefit assessment (2 patients in the ivacaftor arm and 2 in the comparator arm) did not undergo the entire treatment phase.
f: After the follow-up, there was the possibility of participating in the open-label extension study VX12-770-112 (treatment with ivacaftor or observation without ivacaftor treatment); see Section 2.7.7 of the full dossier assessment for details.

AE: adverse event; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; FEV1: forced expiratory volume in 1 second; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

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

Study	Intervention	Comparison
VX11-770-110	Ivacaftor 150 mg, orally, as tablet, every 12 hours with a fat-containing meal[a] + BSC[b]	Placebo, orally, every 12 hours with a fat-containing meal[a] + BSC[b]
	Prior and concomitant treatment <u>Not allowed</u> ▪ any CYP3A inducers or inhibitors, including certain herbal products (e.g. St. John's Wort) and grapefruit, within 2 weeks before first intake of the study medication and during the treatment phase ▪ inhaled hypertonic saline solution within 4 weeks before first intake of the study medication until end of study[c] ▪ solid organ or haematological transplantation before start of study	
a: Dose adjustments were not allowed. Interruptions of medication were allowed after consultation with the clinical monitor. b: In addition to ivacaftor or placebo, the basic medication was to be continued at stable dosing from 4 weeks before baseline until the end of observation. c: Patients who had received inhaled hypertonic saline solution before baseline had to undergo a 4-week washout period to be included in the study. The protocol change from 11 June 2013 allowed stable concomitant medication with inhaled hypertonic saline solution during the study period if this had already been used at baseline. From the time point of the protocol change, however, only 4 patients (8.0%) of the relevant subpopulation (≥ 18 years) were included who could still have benefited from this medication. BSC: best supportive care; CYP: cytochrome P450; RCT: randomized controlled trial; vs.: versus		

The VX11-770-110 study was a randomized, double-blind study, in which ivacaftor + BSC was compared with placebo + BSC. The study included patients aged ≥ 6 years with CF and an R117H mutation in at least one allele in the CFTR gene. The following criteria had to be met as inclusion criterion for the definition of CF: chronic sinopulmonary disease and either sweat chloride value of ≥ 60 mmol/L or 2 CF-causing mutations.

A total of 70 patients were randomly allocated to both study arms in a 1:1 ratio. Stratification was by age (6 to 11, 12 to 17, ≥ 18 years) and the FEV1 as proportion of predicted normal in per cent (< 70%, ≥ 70% to ≤ 90%, > 90%).

Treatment with ivacaftor or placebo was in addition to basic therapy (see text passage on the implementation of the ACT below).

Patients in the ivacaftor arm received 1 tablet of ivacaftor 150 mg every 12 hours, which is in compliance with the recommendations of the SPC [3].

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 recorded until at most 4 weeks after the end of treatment.

After the follow-up, there was the possibility of participating in the unblinded extension study VX12-770-112, where patients received ivacaftor. However, patients who did not consent to participation in the ivacaftor arm of the study also had the possibility to participate in the study in an observation arm (without ivacaftor administration).

Table 8 shows the characteristics of the patients in the subpopulation relevant for the present benefit assessment (≥ 18 years) of the study included.

Table 8: Characteristics of the study population (≥ 18 years) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study Characteristics Category	**Ivacaftor + BSC**	**Placebo + BSC**
VX11-770-110	N[a] = 24	N[a] = 26
Age [years], mean (SD)	38 (12)	41 (13)
Sex [F/M], %	54/46	62/38
BMI [kg/m^2], mean (SD)	26.9 (5.2)	24.9 (5.7)
Ethnicity, white n (%)	24 (100.0)	26 (100.0)
Region n (%)		
North America	16 (66.7)	21 (80.8)
Europe	8 (33.3)	5 (19.2)
Genotype, n (%)		
R117H/F508del	19 (79.2)	19 (73.1)
R117H/R117H	1 (4.2)	0 (0)
R117H/other mutation	4 (16.7)[b]	6 (23.1)[b]
R117H/unknown	0 (0)	1 (3.8)
Poly-T status on the R117H allele		
5T	17 (70.8)	21 (80.8)
7T	6 (25.0)	4 (15.4)
Unknown	1 (4.2)	1 (3.8)
FEV1 (in % of predicted normal), n (%)		
< 70%	13 (54.2)	15 (57.5)
≥ 70% to ≤ 90%	10 (41.7)	11 (42.3)
> 90%	1 (4.2)	0 (0)
Sweat chloride concentration [nmol/L], mean (SD)[c]	69.3 (24.1)	73.0 (17.3)
Pseudomonas aeruginosa infection, n (%)	14 (58.3)	18 (69.2)
Pancreatic insufficiency (faecal elastase-1 < 200 µg/g)	2 (8.3)	5 (19.2)
Treatment discontinuation[e], n (%)	ND[d]	ND[d]
Study discontinuation[e], n (%)	0 (0)	0 (0)

a: Number of randomized patients of the subpopulation relevant for the present benefit assessment (≥ 18 years). Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Institute's calculation.
c: According to the inclusion criteria, patients with a sweat chloride concentration < 60 nmol/L could also be included if – in addition to chronic sinopulmonary disease – 2 CF-causing mutations were present.
d: Information on the number of patients in the adult subpopulation relevant for the present benefit assessment was not available; information on the total population of the VX11-770-110 study: treatment discontinuation: 2 (5.9%) in the ivacaftor and 0 (0%) in the intervention arm.
e: The study was ended by the company before the end of treatment of all patients, as the predefined minimum number of study participants had been reached. As a result, 4 patients in the relevant adult subpopulation (2 patients in the ivacaftor arm and 2 in the comparator arm) did not undergo the entire treatment phase.
BMI: body mass index; BSC: best supportive care; F: female; FEV1: forced expiratory volume in 1 second; M: male; n: number of patients in the category; N: number of included patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The demographic characteristics were largely balanced between the 2 study arms. The proportions of women and of patients from North America were higher in the comparator arm than in the ivacaftor + BSC arm. Regarding clinical characteristics, there were larger proportions of patients with *Pseudomonas aeruginosa* infection and with pancreatic insufficiency, measured with faecal elastase-1, in the comparator arm. In addition, the proportion of the poly-T variant 5T on the R117H allele, which is associated with a more severe disease compared with the 7T variant [3], was higher in the comparator arm.

Implementation of the appropriate comparator therapy

The G-BA specified BSC as ACT for ivacaftor in adult patients with CF who have an R117H mutation in the CFTR gene. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

The company stated in the dossier that all patients included in the VX11-770-110 study received individual medications to alleviate symptoms in accordance with a physician's decision and the personal needs of the patients and that the placebo study arm therefore reflected the clinical care practice of BSC.

The study protocol recommended that patients who were on stable CF medication in the 4 weeks before baseline should remain on this medication until the end of the study. There were important restrictions for certain concomitant therapies for inhaled hypertonic saline solution. This was not permitted within 4 weeks before the first intake of the study medication until shortly before the end of the study or had to be discontinued before the start of the study to allow inclusion in the study. Shortly before the end of the study, a protocol change allowed the use of inhaled hypertonic saline solution (study start: 3 July 2012; protocol change: 11 June 2013; end of study: 25 October 2013). From the time point of the protocol change, however, only 4 patients (8.0%) of the relevant subpopulation (≥ 18 years) were included who could still have benefited from this extension of the concomitant medication. According to the study documents, it can be assumed that the patients already enrolled before the protocol change did not have the possibility to inhale with hypertonic saline solution. According to the information provided in the study protocol, there were no further restrictions. With the exception of hypertonic saline solution, concomitant medication for the symptomatic therapy of CF, e.g. inhalation with dornase alfa, use of bronchodilators, antibiotics and vitamin preparations, and use of physiotherapy were therefore not excluded for patients.

In Module 4 A, the company did not provide information on the medications the patients in the relevant subpopulation (71.4% of the patients in the total population) actually received in the 4 weeks before baseline as well as during the course of the study. The study documents provide such information only for the entire study population of the study.

It was shown for the total population of the VX11-770-110 study that the patients received the regularly used drugs for the symptomatic therapy of CF as concomitant medication (see

Table 22 in Appendix A of the full dossier assessment). In the total population, these comprised dornase alfa, antibiotics, bronchodilators, corticosteroids, analgesics, vitamin preparations and physiotherapy, among others. A small proportion of patients additionally received sodium chloride as concomitant treatment; however, as described above, a maximum of 4 patients in the relevant subpopulation may have received inhaled saline solution. Mannitol (approved for CF since 2012) was not used.

In the total population of the VX11-770-110 study, the proportion of patients under the respective concomitant medication remained largely unchanged before and after the first intake of the study medication. Only individual patients started concomitant medication after the first intake of the study medication (see Table 22, Appendix A of the full dossier assessment). A clear increase in concomitant medication after the first intake of the study medication was shown, for example, for antibiotics (including ciprofloxacin and tobramycin) and analgesics (ibuprofen and paracetamol). However, there was no information on whether and how many patients had their concomitant treatment adjusted, for example in the sense of an increase in dose or frequency in the course of the study.

In summary, the concomitant treatment used in the VX11-770-110 study did not constitute a complete implementation of the ACT BSC. This assessment is based particularly on the exclusion of inhaled saline solution, a standard therapy in CF [4], until shortly before the end of the study. In addition, there is no information at all regarding concomitant medication in the relevant subpopulation and no information on treatment adjustments in the sense of an increase in dose or frequency of the symptomatic therapy during the study. These uncertainties did not result in exclusion of the study, however. Instead, it was assumed that conclusions on the added benefit of ivacaftor in comparison with the ACT can be drawn on the basis of the results of the study. However, the uncertainties described were considered in the assessment of the certainty of conclusions of the results (see Section 2.4.2).

Risk of bias across outcomes (study level)

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

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
VX11-770-110	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the VX11-770-110 study. This concurs with the company's assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

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

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 D) (see Section 2.7.4.3.2 of the full dossier assessment).

Table 10 shows for which outcomes in the included VX11-770-110 study data are available.

Table 10: Matrix of outcomes – RCT, direct comparison: ivacaftor + 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	Oropharyngeal pain (PT, AE)
VX11-770-110	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Pulmonary exacerbation events were included in the recording of AEs; see Section 2.7.4.3.2 of the full dossier assessment for information on how the result of the outcome "SAEs" was handled.

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; MedDRA: Medical Dictionary for Regulatory Activities; PT: MedDRA Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.4.2 Risk of bias

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

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ivacaftor + 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	Discontinuation due to AEs	Oropharyngeal pain (PT, AE)
VX11-770-110	L	L	L	L	L	L	H[a]	L	L

a: Pulmonary exacerbation events were included in the recording of AEs; see Section 2.7.4.3.2 of the full dossier assessment for information on how the outcome "SAEs" was handled.

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: MedDRA Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Concurring with the company's assessment, the risk of bias was rated as low for the results of the following outcomes: all-cause mortality, pulmonary exacerbations, hospitalization due to pulmonary exacerbations, symptoms (measured using the CFQ-R), health-related quality of life (measured using the CFQ-R), and discontinuation due to AEs. The risk of bias for the results of the outcome "oropharyngeal pain" (PT) was also rated as low. The company assessed the risk of bias of all results of the AE outcomes according to System Organ Class (SOC) and PT as low.

The events of pulmonary exacerbation of CF were included in the recording of SAEs. However, SAEs without events attributable to the underlying disease are relevant for the benefit assessment (see Section 2.7.4.3 of the full dossier assessment). The risk of bias of the results for the outcome "SAEs" was therefore rated as high. The company assumed a low risk of bias of the results for this outcome.

Overall assessment of the certainty of conclusions

It is not assumed for the present benefit assessment that the concomitant treatment used in the VX11-770-110 study was a complete implementation of the ACT in the sense of BSC. This assessment is based particularly on the exclusion of inhaled saline solution, a standard therapy in CF, until shortly before the end of the study. In addition, there is no information at all regarding prior and concomitant medication for the relevant subpopulation (≥ 18 years) of the VX11-770-110 study and no information on treatment adjustments in the sense of an increase in dose or frequency of the symptomatic therapy during the study. The certainty of conclusions of the study results for the present research question is therefore reduced. Based on the VX11-770-110 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

2.4.3 Results

Table 12 to Table 14 summarize the results on the comparison of ivacaftor + BSC with placebo + BSC in adult patients with CF who have an R117H mutation in the CFTR gene. Where necessary, the data from the company's dossier are supplemented with the Institute's calculations.

Table 12: Results (mortality and side effects, dichotomous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study Outcome category Outcome	Ivacaftor + BSC N	Ivacaftor + BSC Patients with event n (%)	Placebo + BSC N	Placebo + BSC Patients with event n (%)	Ivacaftor + BSC vs. placebo + BSC RR [95% CI]; p-value
VX11-770-110					
Mortality					
All-cause mortality	24	0 (0)	26	0 (0)	–
Side effects					
AEs (supplementary information)	24	23 (95.8)	26	26 (100)	–
SAEs[a]	24	2 (8.3)	26	6 (23.1)	0.36 [0.08; 1.62]; 0.160
Discontinuation due to AEs	24	0 (0)	26	0 (0)	–
Specific AEs					
Oropharyngeal pain (PT, AE)	24	4 (16.7)	26	0 (0)	–; 0.033[b]

a: Including events of the underlying disease (PT "infective pulmonary exacerbation of cystic fibrosis"); without recording of these events, there is also no statistically significant difference between the treatment arms (one patient with the SAE "cellulitis" (PT) remains in the ivacaftor arm versus 0 patients with SAEs in the comparator arm).
b: Institute's calculation: unconditional exact test (CSZ method according to [5]); discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods; effect estimation and CI not presented because not informative.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 13: Results (morbidity, dichotomous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study Outcome category Outcome	Ivacaftor + BSC N	Ivacaftor + BSC Number of events n_E (n_E/patient years)[a]	Placebo + BSC N	Placebo + BSC Number of events n_E (n_E/patient years)[a]	Ivacaftor + BSC vs. placebo + BSC Rate ratio [95% CI]; p-value[b]
VX11-770-110					
Morbidity					
Pulmonary exacerbations	24	13 (1.23[c])	26	17 (1.51[c])	0.74 [0.35; 1.56]; 0.434
Hospitalization due to pulmonary exacerbations	24	2 (0.19[c])	26	7 (0.62[c])	0.33 [0.07; 1.61]; 0.171

a: The event rate (n_E/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: treatment as fixed effect, adjusted for continuous baseline value of FEV1 (in % of predicted normal) and log(study time) as offset.
c: Institute's calculation.

BSC: best supportive care; CI: confidence interval; FEV1: forced expiratory volume in 1 second; n_E: number of events; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

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

Study Outcome category Outcome	Ivacaftor + BSC			Placebo + BSC			Ivacaftor + 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]
VX11-770-110							
Morbidity							
Symptoms (CFQ-R, symptom domains)[d]							
Respiratory symptoms	24	68.43 (19.12)	14.66 (20.37)	26	59.19 (23.20)	−0.72 (21.27)	12.10 [4.52; 19.68]; 0.002 Hedges' g: 0.91 [0.32; 1.50]
Digestive symptoms	24	90.28 (15.48)	−2.12 (13.89)	26	83.76 (20.90)	−4.83 (11.02)	0.95 [−4.13; 6.03]; p = 0.708
Weight	24	93.06 (19.61)	0.00 (21.08)	26	88.46 (22.98)	−4.35 (23.15)	2.10 [−4.99; 9.20]; 0.554
Health-related quality of life							
CFQ-R (health-related quality of life domains)[d]							
Physical functioning	24	71.01 (27.84)	10.52 (24.67)	26	60.90 (32.96)	−3.62 (25.42)	10.42 [2.10; 18.75]; p = 0.015 Hedges' g: 0.71 [0.13; 1.29]
Emotional functioning	24	90.00 (11.96)	2.54 (9.30)	26	79.23 (21.44)	−2.61 (11.32)	6.04 [1.88; 10.20]; 0.005 Hedges' g: 0.83 [0.25; 1.42]
Vitality	24	63.89 (18.17)	11.11 (21.14)	26	53.21 (22.37)	−4.35 (19.60)	12.59 [3.76; 21.41]; 0.006 Hedges' g: 0.82 [0.23; 1.40]
Social functioning	24	73.15 (16.44)	5.82 (18.30)	26	66.24 (21.77)	0.48 (10.45)	6.61 [0.45; 12.76]; 0.036 Hedges' g: 0.61 [0.04; 1.18]
Role functioning	24	90.97 (11.50)	3.57 (12.79)	26	78.85 (20.44)	−6.52 (19.62)	2.76 [−4.16; 9.68]; 0.425
Body image	24	89.81 (15.69)	3.17 (12.24)	26	86.32 (16.12)	−3.38 (13.16)	3.39 [−0.99; 7.77]; 0.126
Eating problems	24	92.13 (15.18)	2.65 (15.68)	26	92.74 (11.31)	−6.76 (19.17)	5.04 [0.69; 9.39]; 0.024 Hedges' g: 0.66 [0.08; 1.23]
Treatment burden	24	75.00 (20.79)	1.06 (7.78)	26	61.11 (21.60)	5.80 (12.02)	−3.28 [−9.74; 3.18]; 0.312
Health perceptions	24	74.07 (16.60)	8.99 (18.80)	26	59.40 (25.52)	−1.45 (16.17)	6.22 [−2.47; 14.90]; p = 0.157

(continued)

Table 14: Results (morbidity and health-related quality of life, continuous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

a: Number of patients considered in the analysis for the calculation of the effect; the values at baseline may be based on other patient numbers.
b: Refers to the change from baseline to the last time point of measurement.
c: MMRM: treatment, study time point, treatment × study time point as fixed effects, patient as random effect, adjusted for continuous baseline values of age, FEV1 (in % of predicted normal) and respective CFQ-R domain score; effect presents the difference between the treatment groups of the changes averaged over the course of the study between the respective time points of measurement and the start of the study.
d: Higher values indicate better symptoms/health-related quality of life; a positive group difference indicates an advantage of ivacaftor + BSC.
BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; FEV1: forced expiratory volume in 1 second; MD: mean difference, MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

As described in Section 2.4.2, the certainty of conclusions of the results is reduced. Based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

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

The assessment concurs with that of the company.

Morbidity

Pulmonary exacerbations

No statistically significant difference was shown between the treatment groups for the outcome “pulmonary exacerbations”. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

The assessment concurs with that of the company.

Hospitalization due to pulmonary exacerbations

No statistically significant difference was shown between the treatment groups for the outcome “hospitalization due to pulmonary exacerbations”. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

The assessment concurs with that of the company.

Symptoms measured using the CFQ-R

Symptom outcomes were recorded with the domains "respiratory symptoms", "digestive symptoms" and "weight" of the disease-specific patient-reported instrument CFQ-R.

Domain "respiratory symptoms"

A statistically significant difference in favour of ivacaftor + BSC versus BSC was shown for the change from baseline in the domain "respiratory symptoms". The SMD in the form of Hedges' g was considered to assess the relevance of the result. The 95% CI was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. For the CFQ-R domain "respiratory symptoms", this resulted in a hint of an added benefit of ivacaftor + BSC in comparison with BSC.

This deviates from the assessment of the company, which derived no added benefit on the basis of responder analyses and an indication of an added benefit on the basis of the mean differences. Deviating from the present assessment, the company allocated the domain "respiratory symptoms" to health-related quality of life.

Domains "digestive symptoms" and "weight"

In the domains "digestive symptoms" and "weight", no statistically significant differences were shown between the treatment groups. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for each of these 2 domains; an added benefit is therefore not proven.

The assessment concurs with that of the company. Deviating from the present assessment, the company allocated the domains "digestive symptoms" and "weight" to health-related quality of life.

Health-related quality of life

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

Domains "role functioning", "body image" and "treatment burden"

In the domains of role functioning, body image and treatment burden, no statistically significant differences were shown between the treatment groups. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for these domains; an added benefit is therefore not proven.

The assessment concurs with that of the company.

Domains "physical functioning" and "eating problems"

Statistically significant differences in favour of ivacaftor + BSC versus BSC were shown in each of the domains of physical functioning and eating problems. However, the respective

95% CI of the SMD in the form of Hedges' g was not completely outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for the CFQ-R domains of physical functioning and eating problems; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of an added benefit for each of these 2 domains.

Domains "emotional functioning", "vitality" and "social functioning"

Statistically significant differences in favour of ivacaftor + BSC versus BSC were shown in each of the domains of emotional functioning, vitality and social functioning. For the domains of emotional functioning and vitality, the 95% CI of the SMD in the form of Hedges' g was fully above the irrelevance threshold of 0.2. For the domain of social functioning, the 95% CI of the SMD in the form of Hedges' g was not completely outside the irrelevance range of −0.2 to 0.2, however. However, there were effect modifications by the characteristic of *Pseudomonas aeruginosa* infection status (domain "emotional functioning") or by the characteristic of sex (domains "vitality" and "social functioning") for all 3 domains.

For the domain "emotional functioning", there was a hint of an added benefit of ivacaftor + BSC in comparison with BSC for patients with positive *Pseudomonas aeruginosa* infection status. For patients with negative infection status, in contrast, no added benefit was shown (see Section 2.4.4).

There was a hint of an added benefit of ivacaftor + BSC in comparison with BSC for women for the domains of vitality and social functioning. For men, in contrast, no added benefit was shown (see Section 2.4.4).

This deviates from the assessment of the company insofar as the company derived an indication of an added benefit for the 3 domains for the total population of adult patients.

Domain "health perceptions"

No statistically significant difference between the treatment groups was shown in the domain "health perceptions". However, there was an effect modification by the characteristic "sex". There was a hint of an added benefit of ivacaftor + BSC in comparison with BSC for women. For men, in contrast, no added benefit was shown (see Section 2.4.4).

This deviates from the assessment of the company, which derived no added benefit for this domain.

Side effects

Serious adverse events

The events of pulmonary exacerbation of CF were also included in the recording of SAEs. However, SAEs without events attributable to the underlying disease are relevant for the benefit

assessment. Without recording of these events, there was one patient with SAEs in the ivacaftor arm and no patient with SAEs in the comparator arm. Statistically significant differences between the treatment groups were shown neither with nor without recording of the exacerbation events.

Overall, there was no hint of greater or lesser harm from ivacaftor + BSC in comparison with BSC for the outcome "SAEs"; greater or lesser harm is therefore not proven.

This concurs with the company's approach insofar as it derived no added benefit for the outcome "SAEs". The company did not address the influence the inclusion of exacerbation events had on the result, however.

Discontinuation due to adverse events

No discontinuations due to AEs occurred in the course of the study. This resulted in no hint of greater or lesser harm from ivacaftor + BSC in comparison with BSC for the outcome "discontinuation due to AEs"; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Specific adverse events

Oropharyngeal pain (PT, AE)

A statistically significant difference to the disadvantage of ivacaftor + BSC was shown for the outcome "oropharyngeal pain". This resulted in a hint of greater harm from ivacaftor + BSC in comparison with BSC for this outcome.

This assessment deviates from that of the company. The company did not derive greater or lesser harm in its consideration of AEs according to SOC and PT.

2.4.4 Subgroups and other effect modifiers

The following subgroups were used for the present assessment:

- sex (female, male)
- region (North America, Europe)
- FEV1 (in % of predicted normal) at baseline (< 70%, ≥ 70%)
- *Pseudomonas aeruginosa* infection status at baseline
- poly-T status on the R117H allele (5T, 7T)

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

Only results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup

results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 15 summarizes the subgroup results on the comparison of ivacaftor + BSC with placebo + BSC in adult patients with CF who have an R117H mutation in the CFTR gene.

Table 15: Subgroups (health-related quality of life, continuous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study **Outcome category**	**Ivacaftor + BSC**			**Placebo + BSC**			**Ivacaftor + 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]**
VX11-770-110							
Health-related quality of life (CFQ-R)[d]							
Emotional functioning							
Pseudomonas aeruginosa infection status							
Positive	14	87.62 (12.77)	4.44 (9.57)	18	76.30 (21.72)	−2.22 (13.25)	8.11 [2.48; 13.73]; 0.006 Hedges' g: 1.04 [0.28; 1.80]
Negative	10	93.33 (10.42)	0.00 (8.82)	8	85.83 (20.61)	−3.33 (7.13)	1.92 [−4.82; 8.66]; 0.550
Total						Interaction:	p-value = 0.043
Vitality							
Sex							
Men	11	65.91 (16.01)	8.33 (10.39)	10	51.67 (19.56)	3.70 (18.69)	1.70 [−13.61; 17.01]; 0.818
Women	13	62.18 (20.30)	13.64 (27.96)	16	54.17 (24.53)	−9.52 (19.02)	19.85 [7.48; 32.21]; 0.003 Hedges' g: 1.25 [0.43; 2.07]
Total						Interaction:	p-value = 0.036
Social functioning							
Sex							
Men	11	73.23 (16.07)	2.22 (14.63)	10	62.78 (22.69)	5.56 (9.21)	−2.43 [−12.39; 7.53]; 0.610
Women	13	73.08 (17.40)	9.09 (21.27)	16	68.40 (21.63)	−2.78 (10.16)	12.96 [3.66; 22.27]; p = 0.008 Hedges' g: 1.08 [0.28; 1.88]
Total						Interaction:	p-value = 0.022

(continued)

Table 15: Subgroups (health-related quality of life, continuous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

Study Outcome category	Ivacaftor + BSC			Placebo + BSC			Ivacaftor + 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]
VX11-770-110							
Health-related quality of life (CFQ-R)[d]							
Health perceptions							
Sex							
Men	11	73.74 (18.77)	5.56 (15.93)	10	57.78 (19.46)	7.41 (17.57)	−2.76 [−20.44; 14.91]; 0.745
Women	13	74.36 (15.31)	12.12 (21.35)	16	60.42 (29.25)	−7.14 (12.79)	14.22 [3.81; 24.63]; 0.009 Hedges' g: 1.05 [0.26; 1.85]
Total						Interaction:	p-value = 0.038

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b: Refers to the change from baseline to the last time point of measurement.
c: MMRM: treatment, study time point, treatment × study time point as fixed effects, patient as random effect, adjusted for continuous baseline values of age, FEV1 (in % of predicted normal) and respective CFQ-R domain score; effect presents the difference between the treatment groups of the changes averaged over the course of the study between the respective time points of measurement and the start of the study.
d: Higher values indicate better health-related quality of life; a positive group difference indicates an advantage of ivacaftor + BSC.
BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; FEV1: forced expiratory volume in 1 second; MD: mean difference, MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Domain "emotional functioning"

There was an effect modification by the characteristic of *Pseudomonas aeruginosa* infection status at baseline for the CFQ-R domain "emotional functioning". A statistically significant difference between the treatment groups in favour of ivacaftor + BSC was shown for patients with positive infection status. The 95% CI of the SMD in the form of Hedges' g was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect.

There was a hint of an added benefit of ivacaftor + BSC in comparison with BSC for patients with positive *Pseudomonas aeruginosa* infection status at baseline.

In contrast, no statistically significant difference between the treatment groups was shown for patients with negative infection status for the domain "emotional functioning"; an added benefit for these patients is therefore not proven.

Domains "vitality", "social functioning" and "health perceptions"

There were effect modifications by the characteristic of sex for each of the CFQ-R domains of vitality, social functioning and health perceptions. A statistically significant difference between the treatment groups in favour of ivacaftor + BSC versus BSC was shown for women. The 95% CI of the SMD in the form of Hedges' g was completely above the irrelevance threshold of 0.2 in each case. The effects were therefore interpreted to be relevant effects.

There was a hint of an added benefit of ivacaftor + BSC in comparison with BSC for the domains of vitality, social functioning and health perceptions for women.

In contrast, no statistically significant differences between the treatment groups were shown for men for the domains of vitality, social functioning and health perceptions; an added benefit for these patients is therefore not proven.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.5.1 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 16).

Determination of the outcome category for outcomes on symptoms and side effects

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The allocation of these outcomes is described below.

The company did not provide any information as to whether the information on the CFQ-R domain "respiratory symptoms" referred to serious/severe or non-serious/non-severe events. The CFQ-R domain "respiratory symptoms" was allocated to the outcome category "non-serious/non-severe symptoms/late complications" in the present assessment. The allocation had no consequence for the determination of the extent of added benefit, as a non-quantifiable added benefit can be derived from this domain for other reasons.

The specific AE "oropharyngeal pain" was an outcome of the category of non-severe/non-serious side effects, as all events included in the outcome were non-severe/non-serious.

Table 16: Extent of added benefit at outcome level: RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Outcome category **Outcome**	**Ivacaftor + BSC vs. placebo + BSC** **Number of events/patient years or mean change or proportion of events (%)** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	No deaths	Lesser benefit/added benefit not proven
Morbidity		
Pulmonary exacerbations	n_E (n_E/patient years): 13 (1.23) vs. 17 (1.51) rate ratio: 0.74 [0.35; 1.56]; p = 0.434;	Lesser benefit/added benefit not proven
Hospitalization due to pulmonary exacerbations	n_E (n_E/patient years): 2 (0.19) vs. 7 (0.62) rate ratio: 0.33 [0.07; 1.61]; p = 0.171	Lesser benefit/added benefit not proven
Symptoms (CFQ-R, symptom domains)		
Respiratory symptoms	Mean change: 14.66 vs. −0.72 MD: 12.10 [4.52; 19.68]; p = 0.002 Hedges' g: 0.91 [0.32; 1.50][c] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Digestive symptoms	Mean change: −2.12 vs. −4.83 MD: 0.95 [−4.13; 6.03]; p = 0.708	Lesser benefit/added benefit not proven
Weight	Mean change: 0.00 vs. −4.35 MD: 2.10 [−4.99; 9.20]; p = 0.554	Lesser benefit/added benefit not proven
Health-related quality of life (CFQ-R)		
Physical functioning	Mean change: 10.52 vs. −3.62 MD: 10.42 [2.10; 18.75]; p = 0.015 Hedges' g: 0.71 [0.13; 1.29][c]	Lesser benefit/added benefit not proven
Emotional functioning		
Pseudomonas aeruginosa infection status		
Positive	Mean change: 4.44 vs. −2.22 MD: 8.11 [2.48; 13.73]; p = 0.006 Hedges' g: 1.04 [0.28; 1.80][c] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
Negative	Mean change: 0.00 vs. −3.33 MD: 1.92 [−4.82; 8.66]; p = 0.550	Lesser benefit/added benefit not proven

(continued)

Table 16: Extent of added benefit at outcome level: RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

Outcome category **Outcome**	**Ivacaftor + BSC vs. placebo + BSC** **Number of events/patient years or mean change or proportion of events (%)** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Health-related quality of life (CFQ-R)		
Vitality		
Sex		
Men	Mean change: 8.33 vs. 3.70 MD: 1.70 [−13.61; 17.01]; p = 0.818	Lesser benefit/added benefit not proven
Women	Mean change: 13.64 vs. −9.52 MD: 19.85 [7.48; 32.21]; p = 0.003 Hedges' g: 1.25 [0.43; 2.07][c] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
Social functioning		
Sex		
Men	Mean change: 2.22 vs. 5.56 MD: −2.43 [−12.39; 7.53]; p = 0.610	Lesser benefit/added benefit not proven
Women	Mean change: 9.09 vs. −2.78 MD: 12.96 [3.66; 22.27]; p = 0.008 Hedges' g: 1.08 [0.28; 1.88][c] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
Role functioning	Mean change: 3.57 vs. −6.52 MD: 2.76 [−4.16; 9.68]; p = 0.425	Lesser benefit/added benefit not proven
Body image	Mean change: 3.17 vs. −3.38 MD: 3.39 [−0.99; 7.77]; p = 0.126	Lesser benefit/added benefit not proven
Eating problems	Mean change: 2.65 vs. −6.76 MD: 5.04 [0.69; 9.39]; p = 0.024 Hedges' g: 0.66 [0.08; 1.23]	Lesser benefit/added benefit not proven
Treatment burden	Mean change: 1.06 vs. 5.80 MD: −3.28 − 9.74; 3.18]; p = 0.312	Lesser benefit/added benefit not proven
Health perceptions		
Sex		
Men	Mean change: 5.56 vs. 7.41 MD: −2.76 [−20.44; 14.91]; p = 0.745	Lesser benefit/added benefit not proven
Women	Mean change: 12.12 vs. −7.14 MD: 14.22 [3.81; 24.63]; p = 0.009 Hedges' g: 1.05 [0.26; 1.85][c] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"

(continued)

Table 16: Extent of added benefit at outcome level: RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

Outcome category **Outcome**	**Ivacaftor + BSC vs. placebo + BSC** **Number of events/patient years or mean change or proportion of events (%)** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	8.3% vs. 23.1% RR: 0.36 [0.08; 1.62]; p = 0.160	Greater/lesser harm not proven
Discontinuation due to AEs	No events	Greater/lesser harm not proven
Oropharyngeal pain (PT, AE)	16.7% vs. 0.0% –; p = 0.033[d] probability: "hint"	Outcome category: non-serious/non-severe side effects Greater harm, extent: "non-quantifiable"

a: Probability provided if there is a statistically significant and relevant effect.
b: Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
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 derived.
d: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods; effect estimation and CI not presented because not informative.

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; MD: mean difference; n_E: number of events; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of ivacaftor in comparison with the ACT BSC

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications ▫ CFQ-R (domain "respiratory symptoms"): hint of an added benefit – extent: "non-quantifiable"	–
Health-related quality of life ▪ Sex: women ▫ CFQ-R (domains "vitality", "social functioning", "health perceptions"): hint of an added benefit – extent: "non-quantifiable" ▪ *Pseudomonas aeruginosa* infection status: positive ▫ CFQ-R (domain "emotional functioning"): hint of an added benefit – extent: "non-quantifiable"	–
	Non-serious/non-severe side effects ▫ specific AEs: oropharyngeal pain – hint of greater harm – extent: "non-quantifiable"

ACT: appropriate comparator therapy; AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised

On the side of positive effects, hints of a non-quantifiable added benefit were shown for the outcome category of morbidity (CFQ-R domain of respiratory symptoms) and in the category of health-related quality of life for women (domains of vitality, social functioning, health perceptions) and for patients with positive *Pseudomonas aeruginosa* infection status (domain of emotional functioning). In contrast, there was a hint of greater harm of non-quantifiable extent based on one specific AE (oropharyngeal pain) on the side of negative effects.

The positive effects outweighed the negative effects. In summary, there is a hint of a non-quantifiable added benefit of ivacaftor versus the ACT BSC for adult patients with CF who have an R117H mutation in the CFTR gene.

The result of the assessment of the added benefit of ivacaftor in comparison with the ACT is summarized in Table 18.

Table 18: Ivacaftor – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Patients with cystic fibrosis aged 18 years and older who have an R117H mutation in the CFTR gene	BSC	Hint of a non-quantifiable added benefit
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit of ivacaftor.

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

2.6 List of included studies

Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. Lancet Respir Med 2015; 3(7): 524-533.

Vertex Pharmaceuticals. Study of ivacaftor in subjects with cystic fibrosis (CF) who have the R117H-CF transmembrane conductance regulator (CFTR) mutation (KONDUCT): study details [online]. In: ClinicalTrials.gov. 12.02.2015 [Accessed: 18.09.2019]. URL: https://ClinicalTrials.gov/show/NCT01614457.

Vertex Pharmaceuticals. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor in subjects with cystic fibrosis who have the R117H-CFTR mutation [online]. In: EU Clinical Trials Register. [Accessed: 18.09.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-000387-19.

Vertex Pharmaceuticals. Study of ivacaftor in subjects with cystic fibrosis (CF) who have the R117H-CF transmembrane conductance regulator (CFTR) mutation (KONDUCT): study results [online]. In: ClinicalTrials.gov. 12.02.2015 [Accessed: 18.09.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01614457?show_locs=Y.

Vertex Pharmaceuticals. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor in subjects with cystic fibrosis who have the R117H-CFTR mutation: clinical trial results [online]. In: EU Clinical Trials Register. 28.06.2016 [Accessed: 18.09.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-000387-19/results.

Vertex Pharmaceuticals. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor in subjects with cystic fibrosis who have the R117H-CFTR mutation: study VX11-770-110; clinical study protocol [unpublished]. 2013.

Vertex Pharmaceuticals. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor in subjects with cystic fibrosis who have the R117H-CFTR mutation: study VX11-770-110; statistical analysis plan [unpublished]. 2013.

Vertex Pharmaceuticals. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor in subjects with cystic fibrosis who have the R117H-CFTR mutation: study VX11-770-110; clincal study report [unpublished]. 2014.

Vertex Pharmaceuticals. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor in subjects with cystic fibrosis who have the R117H-CFTR mutation: study VX11-770-110; Zusatzanalysen [unpublished]. 2014.

Vertex Pharmaceuticals. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ivacaftor in subjects with cystic fibrosis who have the R117H-CFTR mutation: study VX11-770-110; Zusatzanalysen [unpublished]. 2019.

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.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58.

3. Vertex Pharmaceuticals. Kalydeco 150 mg Filmtabletten: Fachinformation. 04.2019.

4. Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F et al. ECFS best practice guidelines: the 2018 revision. J Cyst Fibros 2018; 17(2): 153-178.

5. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-68-ivacaftor-cystic-fibrosis-18-years-and-older-with-r117h-mutation-benefit-assessment-according-to-35a-social-code-book-v.12571.html.