IQWiG Reports – Commission No. A20-52

Ivacaftor (cystic fibrosis, 6 months to < 18 years, 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, 6 Monate bis < 18 Jahre, mit R117H-Mutation) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 September 2020). 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
BMI	body mass index
BSC	best supportive care
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	cystic fibrosis transmembrane conductance regulator
EMA	European Medicines Agency
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)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug 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 25 June 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 the assessment of the added benefit of ivacaftor in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in patients with cystic fibrosis (CF) aged 6 months to < 18 years who have an R117H mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

The research questions presented in Table 2 resulted from the G-BA's specification.

Table 2: Research questions of the benefit assessment of ivacaftor

Research question	Subindication	ACT[a]
Patients with cystic fibrosis who have an R117H mutation in the CFTR gene		
1	Patients aged 6 months to < 6 years	BSC
2	Patients aged 6 to < 18 years	BSC
a. Presentation of the respective 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. This concurs with the company's inclusion criteria.

Transfer of the results of the VX11-770-110 study from adults to patients < 18 years of age is not possible

The company stated that it only used the RCT VX11-770-110 for the derivation of the added benefit. It derived the added benefit of ivacaftor under consideration of the results of the adult patients, without differentiating according to the research questions of the present assessment.

It assumed that the results can be transferred from the subpopulation of adults (≥ 18 years) to patients aged 6 months to < 18 years.

The company's approach of transferring study results from adults to the population of patients aged 6 months to < 6 years (research question 1), which is relevant for the present assessment, is understandable due to the lack of directly comparative data. However, the concrete implementation of the company is not suitable for this purpose, neither for the transfer to patients aged 6 months to < 6 years (research question 1) nor to patients aged 6 to < 18 years (research question 2). An added benefit of ivacaftor in comparison with the ACT cannot be transferred from the data of the subpopulation of adults in the VX11-770-110 study to either of the 2 populations. This is justified below.

CF is a progressive disease. Hence, the greater the age difference between the population to be assessed and the population from which the transfer is to be made, the more questionable the transferability of results appears.

When comparing the results from the RCT VX11-770-110 for adults and patients aged 6 to < 18 years, there are differences in the clinical characteristics of the populations, as is to be expected in progressive disease. For example, just over half of the adults had a forced expiratory volume in 1 second (FEV1) of < 70%, while this did not apply to any of the 6 to < 18 year olds. Furthermore, markedly more adults (about 64%) had *Pseudomonas aeruginosa* infection than those aged 6 to < 18 years (about 11%). Besides, in the results on outcomes in the domain "respiratory symptoms" of the Cystic Fibrosis Questionnaire-Revised (CFQ-R), there were results that were not in the same direction. Whereas a statistically significant and clinically relevant difference between the treatment groups in favour of ivacaftor + BSC was shown in adults, there was no statistically significant group difference for patients aged 6 to < 18 years (moreover, with opposing effect estimate). The outcome "FEV1" presented as supplementary information showed opposing effects in both populations. In addition, a qualitative consideration of the results on health-related quality of life between adults and patients aged 6 to < 18 years did not show results in the same direction for individual domains.

Overall, on the basis of the data presented and due to the progressive course of CF and the large age difference between the subpopulations of the RCT VX11-770-110, it can be assumed that the patients aged 6 to < 18 years were at a less advanced stage of the disease than the adults, whose average age was about 40 years. For this reason, it is not meaningful to transfer results of the adults to patients aged 6 to < 18 years. It is also not meaningful to transfer the results of the adults to even younger children, i.e. children aged 6 months to < 6 years. The data described above speak against the transferability of the effects from the adults in the VX11-770-110 study to children aged 6 months to < 6 years and to patients aged 6 to < 18 years.

The company did not present any additional data from studies with the ACT BSC for children aged 6 months to < 6 years, so that the treatment effects of ivacaftor versus BSC cannot be

estimated. It did not address the question in the dossier why it had not conducted an information retrieval on the ACT.

Research question 1: patients with cystic fibrosis aged 6 months to < 6 years who have an R117H mutation in the CFTR gene

The company did not present any relevant data for the assessment of the added benefit of ivacaftor in comparison with the ACT BSC in patients with CF aged 6 months to < 6 years who have an R117H mutation in the CFTR gene. Hence, there was no hint of an added benefit of ivacaftor in comparison with BSC for this age group; an added benefit is therefore not proven.

Research question 2: patients with cystic fibrosis aged 6 years to < 18 years who have an R117H mutation in the CFTR gene

Study pool and study characteristics

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 randomized. The subpopulation of patients aged 6 to < 18 years was considered for research question 2.

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 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. 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.

It was recommended in the VX11-770-110 study 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. Concomitant medication for the symptomatic therapy of CF, e.g. inhalation with dornase alfa, use of bronchodilators, antibiotics, vitamin preparations, and physiotherapy was, in principle, possible for the patients. The VX11-770-110 had major restrictions regarding concomitant treatment with inhaled hypertonic saline solution, however. 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). Hence, it can be assumed that the patients already enrolled before the

protocol change did not have the possibility to inhale with hypertonic saline solution. It is unclear how many patients in the relevant subpopulation (6 years to < 18 years) were included from the time point of the protocol change who could still have benefited from this expanded concomitant medication.

In Module 4 G, the company presented information on the medications actually administered to the patients of the relevant subpopulation aged 6 to < 18 years in the 4 weeks before the start of the study and during the course of the study, according to type of therapy for the groups of antibiotics, inhaled medication and physiotherapy. However, data broken down by drugs and data on pancreatic enzymes and vitamin preparations are only available for the entire study population. The available data show that in the relevant subpopulation of patients aged 6 to < 18 years, treatment with inhaled medication and physiotherapy was particularly common at the start of the study. It cannot be inferred from the available data whether and how many patients had their concomitant treatment adjusted in the course of the study, for example in the sense of an increase in dose or frequency.

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. The uncertainties mentioned 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. The uncertainties described were considered in the assessment of the certainty of conclusions of the results, however.

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. Concurring with the company's assessment, the risk of bias for the results of all outcomes included was rated as low.

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 VX11-70-110 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

There were no pulmonary exacerbations, and thus also no hospitalizations due to pulmonary exacerbations in the course of the study. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for these 2 outcomes; an added benefit is therefore not proven.

Symptoms measured using the CFQ-R, domains "respiratory symptoms" and "digestive symptoms"

No statistically significant difference between the treatment groups was shown for the CFQ-R symptom domains "respiratory symptoms" and "digestive symptoms". In each case, this resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

Domains "physical functioning", "emotional functioning", "social functioning", "body image", "eating problems" and "treatment burden" – recorded with the CFQ-R

No statistically significant difference between the treatment groups was shown for the following CFQ-R domains on health-related quality: physical functioning, emotional functioning, social functioning, body image, eating problems and treatment burden. In each case, this resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

Side effects

SAEs

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

Discontinuation due to AEs

There was 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.

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:

Overall, neither positive nor negative effects were found. Hence, there was no hint of an added benefit of ivacaftor in comparison with the ACT BSC for patients with CF aged 6 months to < 18 years who have an R117H mutation in the CFTR gene; an added benefit is therefore not proven.

Probability and extent of added benefit – summary

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

Table 3: Ivacaftor – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
Patients with cystic fibrosis who have an R117H mutation in the CFTR gene			
1	Patients aged 6 months to < 6 years	BSC	Added benefit not proven
2	Patients aged 6 to < 18 years	BSC	Added benefit not proven[b]

a. Presentation of the respective ACT specified by the G-BA.
b. The VX11-770-110 study included only 2 patients of the age group of 12–17 years. It remains unclear whether the observed results can be transferred to patients in this age group.

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 BSC as ACT in patients with CF aged 6 months to < 18 years who have an R117H mutation in the CFTR gene. Ivacaftor is to be used in the form of granules in patients from 6 months of age with a body weight between 5 kg and < 25 kg. Patients from 6 years of age with a body weight of ≥ 25 kg are to receive the drug in the form of tablets [3,4].

The research questions presented in Table 4 resulted from the G-BA's specification.

Table 4: Research questions of the benefit assessment of ivacaftor

Research question	Subindication	ACT[a]
Patients with cystic fibrosis who have an R117H mutation in the CFTR gene		
1	Patients aged 6 months to < 6 years	BSC
2	Patients aged 6 to < 18 years	BSC
a. Presentation of the respective 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. However, the company did not differentiate according to the research questions presented (see also Section 2.3.1). The present assessment was conducted according to the research questions separated by age groups formulated by the G-BA.

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

The study pool of the assessment was compiled on the basis of the following information jointly for both research questions of the benefit assessment:

Sources of the company in the dossier:

- study list on ivacaftor (status: 5 May 2020)
- bibliographical literature search on ivacaftor (last search on 5 May 2020)
- search in trial registries/trial results databases for studies on ivacaftor (last search on 8 June 2020)
- search on the G-BA website for ivacaftor (last search on 5 May 2020)

To check the completeness of the study pool:

- search in trial registries for studies on ivacaftor (last search on 16 July 2020)

Besides the RCT VX11-770-110 also included by the company for the benefit assessment, no additional relevant study was identified by the check.

Besides the RCT VX11-770-110, the company also presented further investigations as supplementary information. For these further investigations, the company conducted no information retrieval for the intervention or for the ACT. It justified the submission of these further investigations with the fact that they had been used by the European Medicines Agency (EMA) for the approval. These were data from the 2 studies VX12-770-112 and VX15-770-122, for which the company provided descriptive presentations without aiming for a comparison with the ACT. The company stated that it did not use these studies for the derivation of the added benefit. Its study pool for the derivation of the added benefit of ivacaftor consisted exclusively of the RCT VX11-770-110 mentioned above.

The VX12-770-112 study [5,6] is an open-label non-randomized extension study with 2 arms, which the company had already presented as supplementary information in its dossier on ivacaftor in adults with the same gene mutation A19-68 [7,8]. The intervention arm of the study included patients who had previously received ivacaftor as intervention in the RCT VX11-770-110 or 2 further intervention studies. There was also an observation arm (without intervention) in which patients could be enrolled who had previously received ivacaftor for at least 4 weeks and who had decided against entering the ivacaftor arm in the extension study. This study did not include a comparison with the ACT. From this extension study, the company presented the data of the patients < 18 years of age who had previously been included in the VX11-770-110 study.

The VX15-770-122 study [5] is a registry-based observational study with the company being the responsible sponsor for the underlying registry. According to the company, the study collected available data from everyday health care of relevant patients from the United States Cystic Fibrosis Foundation (CFF) Registry [9]. The study consisted of a total of 2 cohorts of patients with R117H mutation aged 2 years to < 18 years. One cohort included patients in whom treatment with ivacaftor had been initiated between 2015 and 2016, and for whom data were collected 36 months before and after the start of therapy. Recording of the data before the start of therapy was conducted retrospectively. After enrolment, the patients were observed prospectively. A historical cohort included patients recorded in the CFF Patient Registry who had not received treatment with ivacaftor between 2009 and 2011. In its dossier, the company provided a descriptive presentation of the data for 36 months before and after the start of therapy with ivacaftor as supplementary information, without aiming for a comparison with the ACT.

As described above, the study pool of the company for the benefit assessment of ivacaftor in the present therapeutic indication overall consisted of the RCT VX11-770-110. The data of the 2 studies VX12-770-112 and VX15-770-122 presented as supplementary information by the company in the dossier were not used for the present assessment, as no conclusions on the added

benefit of ivacaftor in comparison with the ACT can be derived due to the missing comparison. Furthermore, the completeness of the study pool for the further investigations is not guaranteed due to the lack of information retrieval for the intervention and the ACT.

2.3.1 Evidence provided by the company

For the benefit assessment of ivacaftor, no relevant study is available for research question 1 (patients aged 6 months to < 6 years). For research question 2 (patients aged 6 to < 18 years), the RCT VX11-770-110, which included children from the age of 6, was used. The data of the subpopulation of patients aged 6 to < 18 years are relevant for research question 2 (see Section 2.5).

Transfer of the results of the VX11-770-110 study from adults to patients < 18 years of age is not possible

The company stated that it only used the RCT VX11-770-110 for the derivation of the added benefit. It derived the added benefit of ivacaftor under consideration of the results of the adult patients, without differentiating according to the research questions of the present assessment. It assumed that the results can be transferred from the subpopulation of adults (≥ 18 years) to patients aged 6 months to < 18 years. It justified this with a sufficient comparability of mechanism of action of the intervention, of manifestation of the disease and of efficacy and safety of ivacaftor for adults (≥ 18 years) and for patients aged 6 months to < 18 years.

The company's approach of transferring study results from adults to the population of patients aged 6 months to < 6 years (research question 1), which is relevant for the present assessment, is understandable due to the lack of directly comparative data. However, the concrete implementation of the company is not suitable for this purpose, neither for the transfer to patients aged 6 months to < 6 years (research question 1) nor to patients aged 6 to < 18 years (research question 2). An added benefit of ivacaftor in comparison with the ACT cannot be transferred from the data of the subpopulation of adults in the VX11-770-110 study to either of the 2 populations. This is justified below.

CF is a progressive disease. Hence, the greater the age difference between the population to be assessed and the population from which the transfer is to be made, the more questionable the transferability of results appears.

When comparing the results from the RCT VX11-770-110 for adults and patients aged 6 to < 18 years, there are differences in the clinical characteristics of the populations, as is to be expected in progressive disease (see Table 8 and Table 26 of the full dossier assessment). For example, just over half of the adults had an FEV1 of < 70%, while this did not apply to any of the patients aged 6 to < 18 year years. Furthermore, markedly more adults (about 64%) had *Pseudomonas aeruginosa* infection than those aged 6 to < 18 years (about 11%). The results for the outcomes for the 2 age groups also differed markedly (see the results for patients aged 6 to < 18 years in Table 15, and for adults in Table 29 of the full dossier assessment). In particular, there were results that were not in the same direction in the domain "respiratory

symptoms" of the CFQ-R. Whereas a statistically significant and clinically relevant difference between the treatment groups in favour of ivacaftor + BSC was shown in adults, there was no statistically significant group difference for patients aged 6 to < 18 years. Moreover, the effect estimate was opposing to the result in adults. Another lung function parameter, the outcome "FEV1", presented as additional information, also showed opposing effects. In addition, a qualitative consideration of the results on health-related quality of life between adults and patients aged 6 to < 18 years did not show results in the same direction for the outcomes "physical functioning" and "body image".

Overall, on the basis of the data presented and due to the progressive course of CF and the large age difference between the subpopulations of the RCT VX11-770-110, it can be assumed that the patients aged 6 to < 18 years (relevant subpopulation for research question 2) were at a less advanced stage of the disease than the adults, whose average age was about 40 years. For this reason, it is not meaningful to transfer results of the adults to patients aged 6 to < 18 years. It is also not meaningful to transfer the results of the adults to even younger children, i.e. children aged 6 months to < 6 years. The data described above speak against the transferability of the effects from the adults in the VX11-770-110 study to children aged 6 months to < 6 years (research question 1 of the present assessment) and to patients aged 6 to < 18 years (research question 2 of the present assessment).

The company did not present any additional data from studies with the ACT BSC for children aged 6 months to < 6 years, so that the treatment effects of ivacaftor versus BSC cannot be estimated. It did not address the question in the dossier why it had not conducted an information retrieval on the intervention or on the ACT.

2.4 Research question 1: patients with cystic fibrosis aged 6 months to < 6 years who have an R117H mutation in the CFTR gene

2.4.1 Study pool

As already described in Section 2.3, the company did not present any suitable data for the benefit assessment of ivacaftor in comparison with the ACT in children with CF aged 6 months to < 6 years who have an R117H mutation in the CFTR gene.

2.4.2 Results on added benefit

The company did not present any relevant data for the assessment of the added benefit of ivacaftor in comparison with the ACT BSC in patients with CF aged 6 months to < 6 years who have an R117H mutation in the CFTR gene. Hence, there was no hint of an added benefit of ivacaftor in comparison with BSC for this age group; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

Since the company did not present any data for the assessment of the added benefit of ivacaftor in comparison with BSC in patients with CF aged 6 months to < 6 years who have an R117H

mutation in the CFTR gene, an added benefit of ivacaftor in comparison with the ACT BSC is not proven for this age group.

2.5 Research question 2: patients with cystic fibrosis aged 6 years to < 18 years who have an R117H mutation in the CFTR gene

2.5.1 Study pool

The study listed in the following table was included for research question 2.

Table 5: Study pool (population aged 6 to < 18 years) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
VX11-770-110	Yes	Yes	No	No[d]	Yes [10-12]	Yes [5,7]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website.
d. 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; CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial; vs.: versus

The subpopulation of patients aged 6 to < 18 years of the VX11-770-110 study was considered for research question 2. This study is already known from the assessment of ivacaftor in adults with the same gene mutation. At that time, the subpopulation of adults from this study was used for the assessment.

In its current dossier, the company presented the subpopulation of patients aged 6 to < 18 years of the VX11-770-110 study.

2.5.2 Study characteristics

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

Table 6: Characteristics of the study included (population aged 6 to < 18 years) – 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 40–105% or 40–90% at screening[b]	Ivacaftor (N = 34) placebo (N = 36[c]) Relevant subpopulation thereof (< 18 years): ivacaftor (n = 10) placebo (n = 10[c])	Screening and run-in[d]: up to 35 days Treatment: 24 weeks[e] Follow-up[f]: at most until 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. Continuation of the concomitant treatment on a stable dose from 4 weeks before the first intake of study medication.
e. The study was ended before the end of treatment of all patients; the company justified this with the fact that the predefined minimum number of study participants had been reached. As a result, 3 patients in the subpopulation relevant for the present benefit assessment (2 patients in the ivacaftor arm and one 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 2.3 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 (population aged 6 to < 18 years) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study	Intervention	Comparison
VX11-770-110	Ivacaftor 150 mg, as oral 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 Not allowed ▪ 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. It is unclear how many patients of the relevant subpopulation (6 years to < 18 years) were included from the time point of the protocol change.

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 150 mg ivacaftor every 12 hours (total daily dose: 300 mg). For patients with a body weight of ≥ 25 kg, this is in compliance with the specifications of the SPC for film-coated tablets [3]. Patients with a body weight of 15 kg or more could also be included in the VX11-770-110 study. According to the approval, patients with a body weight between 5 kg and 24 kg should be treated with ivacaftor in the form of granules [4]. The company did not present any information on the number of patients in the relevant subpopulation of the RCT VX11-770-110 who had a body weight of < 25 kg. Based

on the available information, it is not assumed that this had a consequence for the assessment, however.

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 relevant subpopulation of patients aged 6 to < 18 years in the study included.

Table 8: Characteristics of the study population (population aged 6 to < 18 years) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (multipage table)

Study **Characteristic** **Category**	**Ivacaftor + BSC** **N[a] = 10**	**Placebo + BSC** **N[a] = 9**
VX11-770-110		
Age [years], mean (SD)	9 (2)	10 (3)
Age groups [years], n (%)		
6 to 11	9 (90[b])	8 (89[b])
12 to 17	1 (10[b])	1 (11[b])
Sex [F/M], %	60/40	44/56
Body weight [kg]		
Mean (SD)	37.8 (20.0)	37.1 (12.6)
Median [min; max]	ND	ND
Height [cm]		
Mean (SD)	137.6 (17.6)	142.9 (12.8)
Median [min; max]	ND	ND
BMI z-score		
Mean (SD)	0.4 (1.0)	0.0 (0.9)
Median [min; max]	ND	ND
Faecal elastase [µg/g]		
< 200	0 (0)	0 (0)
≥ 200	10 (100)	8 (88.9)
Not specified	0 (0)	1 (11.1)
LCI, mean (SD)	ND	ND
Family origin, white n (%)	10 (100)	9 (100)
Region, n (%)		
Europe	2 (20.0)	0 (0)
North America	8 (80.0)	9 (100)
Genotype, n (%)		
R117H/F508del	9 (90.0)	6 (66.7)
R117H/R117H	0 (0)	1 (11.1)
R117H/W1282X	0 (0)	1 (11.1)
R117H/2184insA	0 (0)	1 (11.1)
R117H/S489X	1 (10.0)	0 (0)
Poly-T status on the R117H allele, n (%)		
5T	4 (40.0)	6 (66.6)
7T	6 (60.0)	3 (33.3)
FEV1 (in % of predicted normal), n (%)		
< 70%	0 (0)	0 (0)
≥ 70% to ≤ 90%	4 (40.0)	3 (33.3)
> 90%	6 (60.0)	6 (66.7)

Table 8: Characteristics of the study population (population aged 6 to < 18 years) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (multipage table)

Study **Characteristic** **Category**	**Ivacaftor + BSC** **N[a] = 10**	**Placebo + BSC** **N[a] = 9**
Sweat chloride concentration [mmol/L], mean (SD)[c]	61.9 (22.2)[d]	74.7 (26.8)
Pseudomonas aeruginosa infection, n (%)	1 (10.0)	1 (11.1)
Treatment discontinuation[e], n (%)	1 (10.0)	0 (0)
Study discontinuation[e], n (%)	1 (10.0)	0 (0)

a. Number of randomized patients of the subpopulation relevant for the present benefit assessment (6 years to < 18 years). Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculations.
c. According to the inclusion criteria, patients with a sweat chloride concentration < 60 mmol/L could also be included if – in addition to chronic sinopulmonary disease – 2 CF-causing mutations were present.
d. For one patient in the ivacaftor + BSC arm, data on sweat chloride concentration are missing.
e. The study was ended before the end of treatment of all patients; the company justified this with the fact that the predefined minimum number of study participants had been reached. As a result, 3 patients of the relevant subpopulation (2 patients in the ivacaftor arm and 1 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; LCI: lung clearance index; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Patient characteristics were largely balanced between the 2 study arms. Almost all the patients were aged between 6 and 11 years. The majority of patients had normal lung function at baseline (FEV1: > 90%), measured using the FEV1 in % of predicted normal. The mean body mass index (BMI) z-score at baseline did also not show any relevant deviation from age- and sex-specific normal weight.

Implementation of the appropriate comparator therapy

The G-BA specified BSC as ACT for ivacaftor in patients with CF aged 6 to < 18 years 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 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 treatments used therefore reflected the clinical care practice of BSC.

It was recommended in the VX11-770-110 study 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. Concomitant medication for the symptomatic therapy of CF, e.g. inhalation with dornase

alfa, use of bronchodilators, antibiotics, vitamin preparations, and physiotherapy was, in principle, possible for the patients. The VX11-770-110 had major restrictions regarding concomitant treatment with inhaled hypertonic saline solution, however. 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). Hence, it can be assumed that the patients already enrolled before the protocol change did not have the possibility to inhale with hypertonic saline solution. It is unclear how many patients in the relevant subpopulation (population aged 6 to < 18 years) were included from the time point of the protocol change who could still have benefited from this expanded concomitant medication.

In Module 4 G, the company presented information on the medications actually administered to the patients of the relevant subpopulation aged 6 to < 18 years in the 4 weeks before the start of the study and during the course of the study, according to type of therapy for the groups of antibiotics, inhaled medication and physiotherapy. However, data broken down by drugs and data on pancreatic enzymes and vitamin preparations are only available for the entire study population (see dossier assessment A19-68).

Table 9 shows the types of therapies of the relevant subpopulation aged 6 to < 18 years that were administered as pretreatments or concomitant treatments in the included study.

Table 9: Ongoing treatment at baseline and concomitant treatment (population aged 6 to < 18 years) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study Type of therapy	Ivacaftor + BSC			Placebo + BSC		
	Ongoing treatment at baseline n (%)	Concomitant treatment n (%)		Ongoing treatment at baseline n (%)	Concomitant treatment n (%)	
		Initiated[a]	Total[b]		Initiated[a]	Total[b]
VX11-770-110	N = 10	N = 10	N = 10	N = 9	N = 9	N = 9
Drug treatment						
Antibiotics (total)	3 (30.0)	4 (40.0)	7 (70.0)	4 (44.4)	3 (33.3)	7 (77.8)
Antibiotics (IV)	0 (0)	1 (10.0)	1 (10.0)	0 (0)	0 (0)	0 (0)
Inhaled medication[c] (total)	9 (90.0)	0 (0)	9 (90.0)[d]	7 (77.8)	1 (11.1)	8 (88.9)[d]
Inhaled mucolytics	5 (50.0)	0 (0)	5 (50.0)[d]	6 (66.7)	0 (0)	6 (66.7)[d]
Broncho-dilators	9 (90.0)	0 (0)	9 (90.0)[d]	7 (77.8)	1 (11.1)	8 (88.9)[d]
Non-drug treatment						
Physiotherapy	6 (60.0)	0 (0)	6 (60.0)[d]	8 (88.9)	0 (0)	8 (88.9)[d]

a. Patients who were not receiving such therapy at baseline.
b. Patients, regardless of the time of the start of the medication.
c. Unclear proportion of patients using inhaled saline solution among the patients on inhaled medication.
d. Institute's calculation.

BSC: best supportive care; IV: intravenous; n: number of patients with administration of the respective medication; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

The available data show that in the relevant subpopulation, treatment with inhaled medication and physiotherapy was particularly common at the start of the study. It cannot be inferred from the available data whether and how many patients had their concomitant treatment adjusted in the course of the study, for example in the sense of an increase in dose or frequency.

The data for the total population of the VX11-770-110 study show that the patients overall received the regularly used drugs for the symptomatic therapy of CF as concomitant medication (see Table 22 in Appendix A of dossier assessment A19-68). In the total population, these comprised dornase alfa, antibiotics, bronchodilators, corticosteroids, analgesics, vitamin preparations and physiotherapy, among others. However, it is questionable to what extent this statement about concomitant medication of the total population is transferable to the relevant subpopulation of patients aged 6 to < 18 years.

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 [13], until shortly before the end

of the study. In addition, there is no information regarding concomitant medication by drugs for 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 2.5.3.2).

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 + 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 across outcomes was rated as low for the VX11-770-110 study. This concurs with the company's assessment.

2.5.3 Results on added benefit

2.5.3.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - pulmonary exacerbations
  - hospitalization due to pulmonary exacerbations
  - symptoms measured using the symptom domains of the CFQ-R instrument
- Health-related quality of life
  - measured using the health-related quality of life domains of the CFQ-R instrument

- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to AEs
  - if applicable, further specific AEs

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

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

Table 11: Matrix of outcomes (population aged 6 to < 18 years) – 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	Discontinuation due to AEs
VX11-770-110	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

In addition to the patient-relevant outcomes, the following outcomes are additionally presented in Appendix B of the full dossier assessment:

- Lung function using FEV1

The outcome “FEV1” (in % of predicted normal) is a lung function parameter. Relevant for benefit assessment are patient-noticeable symptoms associated with a change in FEV1 or the associated reduction in health-related quality of life, which were directly recorded in the studies.

Like in Module 4 D on the assessment of ivacaftor in adults with the same gene mutation, the company used FEV1 both as patient-relevant outcome and as a surrogate for CF-associated mortality [8]. However, the sources cited by the company did not demonstrate the validity of FEV1 as a surrogate. In its current dossier, the company did not provide any new aspects. For a detailed rationale on the outcome of FEV1 not qualifying as a valid surrogate outcome for

mortality, see dossier assessment A19-68 on the drug ivacaftor in adults with R117H mutation, Section 2.7.4.3.2.

- Age- and sex-dependent BMI z-score

Body weight or BMI z-score is highly relevant in the present therapeutic indication since developmental disorders and nutrient malabsorption are typical signs of CF. In its assessment, the company used the BMI z-score 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 z-score as a measure of malnutrition is not directly evident since the mean BMI z-score of the relevant subpopulation in the VX11-770-110 study was in the normal range both at the start of therapy and after 24 weeks of treatment. It is also unclear whether the BMI z-score is a suitable construct for representing a developmental disorder.

2.5.3.2 Risk of bias

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

Table 12: Risk of bias across outcomes and outcome-specific risk of bias (population aged 6 to < 18 years) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study	Outcomes							
	Study level	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
VX11-770-110	L	L	L	L	L	L	L	L

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

Concurring with the company's assessment, the risk of bias for the results of all outcomes included was rated as low.

Overall assessment of the certainty of conclusions

It is not assumed for the present benefit assessment that the concomitant treatment used in the comparator arm of the VX11-770-110 study was a complete implementation of the ACT in the sense of BSC (see Section 2.5.1). 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. Furthermore, the information on pre- and concomitant medication for the relevant subpopulation (6 years to < 18 years) is not comprehensive. 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.

2.5.3.3 Results

Table 13 to Table 15 summarize the results on the comparison of ivacaftor + BSC with placebo + BSC in patients with CF aged 6 to < 18 years who have an R117H mutation in the CFTR gene. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Table 13: Results (mortality and side effects, dichotomous) (population aged 6 to < 18 years) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study Outcome category	Ivacaftor + BSC		Placebo + BSC		Ivacaftor + BSC vs. placebo + BSC
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
VX11-770-110					
Mortality					
All-cause mortality	10	0 (0)	9	0 (0)	–
Side effects[a]					
AEs (supplementary information)	10	8 (80.0)	9	9 (100.0)	–
SAEs	10	1 (10.0)[b]	9	0 (0)	2.73 [0.12; 59.57]; 0.523[c]
Discontinuation due to AEs	10	0 (0)	9	0 (0)	–

a. Recording of AEs in RCT VX11-770-110 in principle with events of the underlying disease; for the present dossier assessment, the company presented analyses without the event of the underlying disease "infective pulmonary exacerbation of cystic fibrosis" (PT).
b. It cannot be excluded that the event in the ivacaftor + BSC arm (PT "constipation") is an event of the underlying disease (see Table 24 of the full dossier assessment).
c. Institute's calculation of effect and CI (asymptotic) (in case of 0 events in one study arm with correction factor 0.5 in both study arms); p-value by means of unconditional exact test [CSZ method according to [14]).

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; vs.: versus

Table 14: Results (morbidity, dichotomous) (population aged 6 to < 18 years) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study Outcome category Outcome	Ivacaftor + BSC		Placebo + BSC		Ivacaftor + BSC vs. placebo + BSC
	N	Number of events n_E (n_E/patient years)	N	Number of events n_E (n_E/patient years)	Rate ratio [95% CI]; p-value
VX11-770-110					
Morbidity					
Pulmonary exacerbations	10	0 (0)[a]	9	0 (0)[a]	–
Hospitalization due to pulmonary exacerbations	10	0 (0)[a]	9	0 (0)[a]	–

a. Derived on the basis of the number of patients with events; the company described in its dossier that it did not present any analyses of the number of pulmonary exacerbations because no events had occurred.

BSC: best supportive care; CI: confidence interval; n_E: number of events; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 15: Results (morbidity and health-related quality of life, continuous) (population aged 6 to < 18 years)– 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, e]							
Respiratory symptoms	9	93.52 (6.94)	−1.39 (8.19)	8	89.93 (7.99)	3.57 (9.45)	−4.87 [−14.76; 5.01]; 0.303
Digestive symptoms	8	77.78 (33.33)	16.67 (27.89)	8	87.50 (17.25)	4.76 (12.60)	0.49 [−6.88; 7.86]; 0.885
Health-related quality of life							
CFQ-R (health-related quality of life domains)[d, e]							
Physical functioning	9	88.89 (11.78)	−6.48 (32.09)	8	83.51 (12.78)	2.98 (13.14)	−11.73 [−29.63; 6.16]; 0.180
Emotional functioning	9	81.94 (6.91)	6.25 (9.77)	8	79.17 (16.06)	3.21 (9.83)	3.15 [−4.09; 10.40]; 0.365
Social functioning	9	64.29 (17.66)	10.32 (13.27)	8	64.48 (22.46)	4.08 (17.59)	7.13 [−3.24; 17.50]; 0.162
Body image	9	91.36 (10.80)	−3.70 (15.18)	8	90.28 (12.51)	6.35 (12.60)	−11.06 [−23.55; 1.43]; 0.078
Eating problems	9	87.65 (23.20)	−5.56 (9.30)	8	75.00 (23.57)	12.70 (21.69)	13.74 [−4.46; 31.94]; 0.127
Treatment burden	9	71.61 (24.29)	11.11 (12.17)	8	58.33 (20.36)	14.29 (17.82)	−2.41 [−19.81; 15.00]; 0.768

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, and treatment × study time point as fixed effects, patient as random effect, adjusted for continuous baseline values of age, FEV1 (in % of predicted normal) and the 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.
e. The domains "weight" (symptoms), as well as "role functioning", "vitality" and "subjective health perceptions" (health-related quality of life) are exclusively included in the questionnaires for patients aged ≥ 14 years; in the relevant subpopulation (aged 6 years to < 18 years), data were available only for one patient; the results for these domains were therefore not presented by the company.

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 shown in Section 2.5.3.2, the certainty of conclusions of the results was reduced. On the basis of the available data, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Deviating from the company's approach, the added benefit was derived on the basis of the results of the subpopulation relevant to the present research question. This differs from company insofar as it assessed the added benefit in the present therapeutic indication taking into account the results of the adult subpopulation. It therefore did not comment on the added benefit of ivacaftor at outcome level in the relevant subpopulation for research question 2. Thus, the company's assessment of the added benefit for individual outcomes is not given in the following.

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

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
- fever > 38°C
- anorexia or weight loss
- sinus pain or tenderness
- change in sinus discharge
- change in physical examination 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 number of events and the 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 marks the occurrence of serious exacerbations.

Results

There were no pulmonary exacerbations, and thus also no hospitalizations due to pulmonary exacerbations in the course of the study. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for either of these 2 outcomes; an added benefit is therefore not proven.

Symptoms measured using the CFQ-R domains

Operationalization

The disease-specific patient-reported CFQ-R instrument used in study VX11-770-110 for the recording of symptoms comprises several versions: a patient version for different age groups (6 to 11 years, 12 to 13 years, and ≥ 14 years) and a parent/caregiver version (for a description of the questionnaires, see [15], for example). In the subpopulation relevant to the present research question, almost all patients were between 6 and 11 years of age (one patient in each of the study arms was between 12 and 17 years of age). For these patients, the corresponding version for the age group of 6 to 11-year-olds was used and completed by the investigator or a representative together with the children during an interview. Patients aged 12 to < 18 years completed the questionnaire corresponding to their age group on their own.

Since in the age group from 12 to < 18 years, data were available for only one patient, the company analysed only the domains included in the questionnaire versions for patients aged 6 to 11 years. The domain "weight" was therefore not included in the analysis of symptoms. Regarding symptoms, information on the CFQ-R domains "respiratory symptoms" and "gastrointestinal symptoms" is therefore available for the present benefit assessment.

Results

Domains "respiratory symptoms" and "digestive symptoms"

No statistically significant difference between the treatment groups was shown for the CFQ-R symptom domains "respiratory symptoms" and "digestive symptoms". In each case, this

resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life

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

Like symptoms, health-related quality of life was recorded using the described versions of CFQ-R. In analogy to the approach used for symptoms, the company analysed exclusively domains from the version for 6 to 11-year-olds also for health-related quality of life. These are the CFQ-R domains of physical functioning, emotional functioning, social functioning, body image, eating problems and treatment burden.

Results

Domains "physical functioning", "emotional functioning", "social functioning", "body image", "eating problems" and "treatment burden"

No statistically significant difference between the treatment groups was shown for the following CFQ-R domains on health-related quality: physical functioning, emotional functioning, social functioning, body image, eating problems and treatment burden. In each case, this resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

Side effects

SAEs

In the recording of AEs in the RCT VX11-770-110, events of the underlying disease of CF were also recorded. In its current dossier, the company addressed the criticism from dossier assessment A19-68 and provided analyses of the AEs in which the event of the underlying disease "infective pulmonary exacerbation of cystic fibrosis" (Preferred Term [PT]) is not included. This is appropriate. The only SAE "PT constipation" (in the ivacaftor + BSC arm; see Table 24 of the full dossier assessment) that occurred in the study can be both an AE and an event of the underlying disease.

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in 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 AEs

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.

2.5.3.4 Subgroups and other effect modifiers

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup. These requirements

are not met because of the small number of patients in the relevant subpopulation (ivacaftor: N = 10; placebo: N = 9). Analogous to the approach of the company, no subgroup analyses are presented.

2.5.4 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. 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.

2.5.4.1 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).

Table 16: Extent of added benefit at outcome level (population aged 6 to < 18 years) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (multipage table)

Outcome category **Outcome**	**Ivacaftor + BSC vs. placebo + BSC** **Mean change or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Pulmonary exacerbations	0% vs. 0%	Lesser benefit/added benefit not proven
Hospitalization due to pulmonary exacerbations	0% vs. 0%	Lesser benefit/added benefit not proven
Symptoms (CFQ-R, symptom domains)		
Respiratory symptoms	Mean change: −1.39 vs. 3.57 MD: −4.87 [−14.76; 5.01] p = 0.303	Lesser benefit/added benefit not proven
Digestive symptoms	Mean change: 16.67 vs. 4.76 MD: 0.49 [−6.88; 7.86] p = 0.885	Lesser benefit/added benefit not proven
Health-related quality of life		
Physical functioning	Mean change: −6.48 vs. 2.98 MD: −11.73 [−29.63; 6.16] p = 0.180	Lesser benefit/added benefit not proven
Emotional functioning	Mean change: 6.25 vs. 3.21 MD: 3.15 [−4.09; 10.40] p = 0.365	Lesser benefit/added benefit not proven
Social functioning	Mean change: 10.32 vs. 4.08 MD: 7.13 [−3.24; 17.50] p = 0.162	Lesser benefit/added benefit not proven
Body image	Mean change: −3.70 vs. 6.35 MD: −11.06 [−23.55; 1.43] p = 0.078	Lesser benefit/added benefit not proven
Eating problems	Mean change: −5.56 vs. 12.70 MD: 13.74 [−4.46; 31.94] p = 0.127	Lesser benefit/added benefit not proven
Treatment burden	Mean change: 11.11 vs. 14.29 MD: −2.41 [−19.81; 15.00] p = 0.768	Lesser benefit/added benefit not proven

Table 16: Extent of added benefit at outcome level (population aged 6 to < 18 years) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (multipage table)

Outcome category **Outcome**	**Ivacaftor + BSC vs. placebo + BSC** **Mean change or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	10.0% vs. 0% RR: 2.73 [0.12; 59.57] p = 0.523	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 0%	Greater/lesser harm not proven

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).

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; CI_u: upper limit of confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.4.2 Overall conclusion on added benefit

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

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

Positive effects	**Negative effects**
–	–
ACT: appropriate comparator therapy; BSC: best supportive care	

In the overall consideration, there were neither positive nor negative effects of ivacaftor in patients with CF aged 6 to < 18 years who have an R117H mutation in the CFTR gene. Hence, there was no hint of an added benefit of ivacaftor in comparison with BSC for this age group; an added benefit is therefore not proven.

2.6 Probability and extent of added benefit – summary

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

Research question	Subindication	ACT[a]	Probability and extent of added benefit
Patients with cystic fibrosis who have an R117H mutation in the CFTR gene			
1	Patients aged 6 months to < 6 years	BSC	Added benefit not proven
2	Patients aged 6 to < 18 years	BSC	Added benefit not proven[b]

a. Presentation of the respective ACT specified by the G-BA.
b. The VX11-770-110 study included only 2 patients of the age group of 12–17 years. It remains unclear whether the observed results can be transferred to patients in this age group.

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, taking into account the study results for the adult subpopulation, derived a non-quantifiable added benefit without addressing its probability.

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

References for English extract

Please see full dossier assessment for full reference list.

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

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