IQWiG Reports – Commission No. A19-65

Ivacaftor (cystic fibrosis, 6 years and older, with G551D 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 6 Jahre, mit G551D-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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Ivacaftor (cystic fibrosis, 6 years and older, with G551D mutation) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

28 August 2019

Internal Commission No.:

A19-65

Address of publisher:

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

No advisor on medical and scientific questions was available for the present dossier assessment.

IQWiG employees involved in the dossier assessment:

- Kirsten Janke
- Christiane Balg
- Katharina Biester
- Marco Knelangen
- Petra Kohlepp
- Annette Pusch-Klein
- Min Ripoll
- Cornelia Rüdig
- Anke Schulz

Keywords: Ivacaftor, Cystic Fibrosis, Child, Adolescent, Adult, Benefit Assessment, NCT00909532, NCT00909727

Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
EQ-5D	European Quality of Life-5 Dimensions visual analogue scale
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
VAS	visual analogue scale

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 best supportive care (BSC) as appropriate comparator therapy (ACT) in the treatment of cystic fibrosis (CF) in patients aged 6 years and older and weighing 25 kg or more who have the G551D gating 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 6 years and older and weighing 25 kg or more who have the G551D gating mutation in the CFTR gene	BSC[b]
a: Presentation of the ACT specified by the G-BA. b: 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. 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. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

Study pool

The RCTs VX08-770-102 and VX08-770-103, each comparing ivacaftor with placebo, were included in the benefit assessment. The design of the studies was comparable except for a few aspects. CF patients aged 12 years and older (study VX08-770-102) and between 6 and 11 years of age (study VX08-770-103) and with the G551D gating mutation in at least one allele of the CFTR gene were enrolled. Only patients with a forced expiratory volume in 1 second (FEV1) of 40% to 90% of predicted normal for age, sex, and height at screening were included in the VX08-770-102 study. For the VX08-770-103 study, the FEV1 at study entry was allowed to be 40% to 105% of predicted normal for age, sex, and height.

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). Treatment in the study was originally planned for 24 weeks. The randomized and blinded treatment phase was extended from 24 to 48 weeks following an amendment to the study protocol. The data at 48 weeks were considered for the present benefit assessment.

In the VX08-770-102 study, a total of 167 patients were randomly allocated in a ratio of 1:1 to the 2 study arms. All patients included in the study weighed 25 kg or more; hence ivacaftor was used in compliance with the approval for the total study population.

In the VX08-770-103 study, a total of 52 children were randomly allocated in a ratio of 1:1 to the 2 study arms. However, not all children included in the study weighed 25 kg or more; hence, ivacaftor was used in compliance with the approval only for part of the study population. The relevant subpopulation of children with a body weight in compliance with the approval was about 73% of the total study population. Deviating from the company, the relevant subpopulation of the VX08-770-103 study was used for the present benefit assessment.

Primary outcome of both studies was the absolute change in FEV1 (in % of predicted normal) after 24 weeks. Patient-relevant secondary outcomes were all-cause mortality, symptoms, health status (only recorded in the VX08-770-102 study), health-related quality of life, and adverse events (AEs).

Meta-analytic summary of study results not meaningful with regard to content

The comparison of the data on the total populations of the studies VX08-770-102 and VX08-770-103 showed differences in demographic and clinical characteristics (age, anthropometric measures, FEV1) of the included populations, which resulted as a consequence of the different inclusion/exclusion criteria mainly regarding the age of the study populations. Since the company did not provide any data for the characterization of the relevant subpopulation for study VX08-770-103, but only data for the total study population, the comparability of the populations relevant for the benefit assessment from the 2 studies cannot be conclusively assessed.

Overall, based on the data presented, it can be assumed that, due to the progressive course of CF and the large age difference between the study populations, the children in the relevant subpopulation in the VX08-770-103 study were in a less advanced stage of disease than the patients in the VX08-770-102 study. Against this background, a meta-analytic summary of the data does not appear to be meaningful with regard to content. In addition, the results for both age groups in the studies VX08-770-102 and VX08-770-103 differed from each other.

Implementation of the appropriate comparator therapy

The G-BA specified BSC as ACT for ivacaftor in the treatment of patients aged 6 years and older with a G551D mutation in the CFTR gene.

According to the study protocol, it was recommended for both studies that patients remain on stable CF medication from 6 weeks before the first study medication in the part of the study relevant for the benefit assessment until the end of the study. There was an important restriction of the concomitant therapy regarding inhaled hypertonic saline solution, which was not allowed within 4 weeks before the first intake of the study medication until the end of the study. According to the study protocols, there were no restrictions regarding other concomitant therapies in both studies.

It can be inferred from the company's dossier that all patients in both studies received concomitant medication for the symptomatic treatment of CF both before the start of the study and during the study. For the VX08-770-103 study, only information on the total study population was available.

It was evident for the total population of both studies that a large number of drugs were given for the symptomatic therapy of CF. In addition, the data on concomitant treatment before and after the first intake of the study medication show that medications were initiated and discontinued individually for some drug groups, including a large number of different antibiotics and analgesics. It cannot be inferred from the available data for both studies 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 studies VX08-770-102 and VX08-770-103 did not constitute a complete implementation of the ACT BSC. This assessment is based in particular on the fact that the study design excluded treatment with inhaled saline solution, a standard therapy for CF. 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 studies. 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 across outcomes and the risk of bias for the outcome "all-cause mortality" were rated as low for both studies. The risk of bias for the following outcomes was rated as high for both studies: pulmonary exacerbations, hospitalizations due to pulmonary exacerbations, symptoms (recorded with the Cystic Fibrosis Questionnaire Revised [CFQ-R]) and health-related quality of life (recorded with the CFQ-R). For the VX08-770-102 study, the risk of bias was additionally rated as high for the following outcomes: health status (using the European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]), discontinuation due to AEs, rash and dizziness. For the VX08-770-103 study, the risk of bias was rated as low for the outcome "discontinuation due to AEs". In the recording of serious AEs (SAEs), both studies included, among others, pulmonary exacerbation events in the recording of the Preferred Term (PT) "cystic fibrosis lung". However, SAEs without events attributable to the underlying disease are relevant for the benefit assessment. The data on SAEs are therefore not usable.

The certainty of conclusions of the study results for the present research question is reduced both for conclusions on patients aged 12 years and older based on the VX08-770-102 study and for children between 6 and 11 years of age based on the VX08-770-103 study. The reason for this is that the concomitant treatment of the studies did not completely represent the ACT BSC. Only one study is available for each of both age groups. Under consideration of the fact that the ACT BSC was not completely implemented in the studies, at most hints, e.g. of an added benefit, can be derived for the age groups for all outcomes presented.

Results

Mortality

All-cause mortality

No deaths occurred during the studies VX08-770-102 and VX08-770-103. 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

For the outcome "pulmonary exacerbations", the VX08-770-102 study showed a statistically significant difference in favour of ivacaftor + BSC versus BSC on the basis of the event rates (number of events/patient years). This resulted in a hint of an added benefit of ivacaftor + BSC in comparison with BSC for patients aged 12 years and older.

There were no effect estimations on the basis of the event rates (number of events/patient years) for the VX08-770-103 study. Based on analyses of patients with at least one event, there was no statistically significant difference 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 for children between 6 and 11 years of age; an added benefit is therefore not proven.

Hospitalizations due to pulmonary exacerbations

For the outcome "hospitalizations due to pulmonary exacerbations", the VX08-770-102 study showed no statistically significant difference between the treatment groups on the basis of the event rates (number of events/patient years). This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for patients aged 12 years and older for this outcome; an added benefit is therefore not proven.

There were no effect estimations on the basis of the event rates (number of events/patient years) for the VX08-770-103 study. Based on analyses of patients with at least one event, there was no statistically significant difference between the treatment groups for the outcome "hospitalizations due to pulmonary exacerbations". This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for this outcome for children between 6 and 11 years of age; an added benefit is therefore not proven.

Symptoms measured using the CFQ-R

The VX08-770-102 study measured symptom outcomes for adolescents aged 14 years and older and adults using the domains "respiratory symptoms", "digestive symptoms" and "weight" of the disease-specific patient-reported instrument CFQ-R. For children between 12 and 13 years of age in the VX08-770-102 study and for children between 6 and 11 years of age in the VX08-770-103 study, the domains "respiratory symptoms" and "digestive symptoms" were also recorded directly from the children with a CFQ-R patient version. The domain "weight" is not included in the questionnaire versions for children between 6 and 11 years and children between 12 and 13 years of age.

Patients aged 12 years and older

- Domain "respiratory symptoms"

For the benefit assessment, joint analyses of children aged 12 and 13 years and adolescents aged 14 years and older and adults were used for the VX08-770-102 study. For this study, 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 for patients aged 12 years and older.

- Domains "digestive symptoms" and "weight"

In the domains "digestive symptoms" and "weight", no statistically significant differences were shown between the treatment groups for the VX08-770-102 study. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for these 2 domains for the age groups investigated in each case; an added benefit is therefore not proven.

Children between 6 and 11 years of age

- Domains "respiratory symptoms" and "digestive symptoms"

For the VX08-770-103 study, no statistically significant differences were shown between the treatment groups in each of the domains "respiratory symptoms" and "digestive symptoms". This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for these 2 domains for children between 6 and 11 years of age; an added benefit is therefore not proven.

Health status measured using the EQ-5D VAS

In the VX08-770-102 study, no statistically significant difference was shown between the treatment groups for the outcome "health status". This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

The outcome “health status” was not recorded in the VX08-770-103 study.

Health-related quality of life

Study VX08-770-102 recorded health-related quality of life for adolescents aged 14 years and older and adults using the following domains of the disease-specific patient-reported CFQ-R: physical functioning, emotional functioning, vitality, social functioning, role functioning, body image, eating problems, treatment burden, and health perceptions. For children between 12 and 13 years of age in the VX08-770-102 study and for children between 6 and 11 years of age in the VX08-770-103 study, the domains “physical functioning, “emotional functioning”, “social functioning”, “body image”, “eating problems” and “treatment burden” were also recorded directly from the children with a CFQ-R patient version. The domains “vitality”, “role functioning” and “health perceptions” are not included in the questionnaire versions for children between 6 and 11 years and children between 12 and 13 years of age.

Patients aged 12 years and older

- Domains “emotional functioning”, “role functioning” and “body image”

For the benefit assessment, joint analyses of children aged 12 and 13 years and adolescents aged 14 years and older and adults were used for the VX08-770-102 study. For this study, no statistically significant differences were shown between the treatment groups in each of the domains “emotional functioning”, “role functioning” and “body image”. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for these domains for the age groups investigated in each case; an added benefit is therefore not proven.

- Domains “social functioning”, “eating problems” and “treatment burden”

For the VX08-770-102 study, statistically significant differences in favour of ivacaftor were shown in each of the domains “social functioning”, “eating problems” and “treatment burden”. However, the respective 95% CI of the SMD in the form of Hedges’ g for the domains was not completely outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. For patients aged 12 years and older, this resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for each of the CFQ-R domains “social functioning”, “eating problems” and “treatment burden”; an added benefit is therefore not proven.

- Domains “physical functioning” and “vitality”

For the domains “physical functioning” and “vitality”, statistically significant differences in favour of ivacaftor + BSC were shown in the total population of the VX08-770-102 study. However, the respective 95% CI of the SMD in the form of Hedges’ g for both domains was not completely outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. However, there were effect modifications by the characteristic “FEV1 at baseline” in each case. For the domains, there was a hint of an added benefit of ivacaftor + BSC in comparison with BSC for patients with baseline FEV1 of < 70% of predicted normal for the

age groups investigated in each case (physical functioning: patients aged 12 years and older; vitality: patients aged 14 years and older). In contrast, no added benefit was shown for patients with baseline FEV1 of ≥ 70% of predicted normal.

- Domain "health perceptions"

The VX08-770-102 study showed a statistically significant difference in favour of ivacaftor + BSC versus BSC for the domain "health perceptions". 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. For the CFQ-R domain "health perceptions", this resulted in a hint of an added benefit of ivacaftor + BSC in comparison with BSC for adolescents and adults aged 14 years and older.

Children between 6 and 11 years of age

For the VX08-770-103 study, no statistically significant differences were shown between the treatment groups in each of the domains "physical functioning", "emotional functioning", "social functioning", "body image", "eating problems" and "treatment burden". This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for children between 6 and 11 years of age; an added benefit is therefore not proven.

Serious adverse events

In the recording of SAEs, the studies VX08-770-102 and VX08-770-103 included, among others, pulmonary exacerbations in the recording of the PT "cystic fibrosis lung". The results on the outcome were therefore not usable.

Discontinuation due to adverse events

In the studies VX08-770-102 and VX08-770-103, no statistically significant differences between the treatment groups were shown for the outcome "discontinuation due to AEs". 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

Rash

The VX08-770-102 study showed a statistically significant difference to the disadvantage of ivacaftor + BSC versus BSC for the outcome "rash". The extent of the effect was no more than marginal, however. This resulted in no hint of greater or lesser harm from ivacaftor + BSC in comparison with BSC for this outcome; greater or lesser harm is therefore not proven.

For the VX08-770-103 study, the company did not present any data for the relevant subpopulation. Therefore, the outcome cannot be assessed for this study.

Dizziness

The VX08-770-102 study showed a statistically significant difference to the disadvantage of ivacaftor + BSC versus BSC for the outcome "dizziness". This resulted in a hint of greater harm from ivacaftor + BSC in comparison with BSC for this outcome.

For the VX08-770-103 study, the company did not present any data for the relevant subpopulation. Therefore, the outcome cannot be assessed for this study.

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:

Patients aged 12 years and older

Based on the VX08-770-102 study, several positive effects with the probability "hint" of an added benefit were shown for patients aged 12 years and older. This concerns morbidity in the outcome "pulmonary exacerbations", symptom outcomes (recorded using the CFQ-R domain "respiratory symptoms") but also health-related quality of life in some CFQ-R domains (physical functioning, vitality and health perceptions). The extent of these effects was only quantifiable for the outcome "pulmonary exacerbations" and was rated as "considerable". In contrast, there was a hint of greater harm of minor extent based on one specific AE (dizziness) on the side of negative effects.

The positive effects outweighed the negative effects. Besides the improvements in the outcomes "pulmonary exacerbations" and "symptoms", there were some positive effects in health-related quality of life. However, uncertainty remained about the negative effects, as no usable data were available for the outcome "SAEs".

In summary, there is therefore a hint of a minor added benefit of ivacaftor + BSC versus the ACT BSC for patients with CF aged 12 years and older and weighing 25 kg or more who have the G551D gating mutation in the CFTR gene.

Children between 6 and 11 years of age

For children between 6 and 11 years of age and weighing 25 kg or more, neither positive nor negative effects of ivacaftor + BSC in comparison with BSC resulted from the VX08-770-103

[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].

study. There is therefore no hint of an added benefit of ivacaftor + BSC versus the ACT BSC for children with CF between 6 and 11 years of age and weighing 25 kg or more who have the G551D gating mutation in the CFTR gene. An added benefit is therefore not proven.

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**
Children with cystic fibrosis between 6 and 11 years of age and weighing 25 kg or more who have the G551D gating mutation in the CFTR gene	BSC[b]	Added benefit not proven
Patients with cystic fibrosis aged 12 years and older and weighing 25 kg or more who have the G551D gating mutation in the CFTR gene	BSC[b]	Hint of minor added benefit
a: Presentation of the respective ACT specified by the G-BA. b: 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. 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.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2012. In this assessment, the G-BA had determined a considerable added benefit of ivacaftor for patients aged 12 years and older and a minor added benefit for children between 6 and 11 years of age. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

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 the treatment of CF in patients aged 6 years and older and weighing 25 kg or more who have the G551D gating mutation in the CFTR gene.

Table 4: Research question of the benefit assessment of ivacaftor

Subindication	**ACT[a]**
Patients with cystic fibrosis aged 6 years and older and weighing 25 kg or more who have the G551D gating mutation in the CFTR gene	BSC[b]
a: Presentation of the ACT specified by the G-BA. b: 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. 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 studies listed in the following table were 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)
VX08-770-102	Yes	Yes	No
VX08-770-103	Yes	Yes	No
a: Study sponsored by the company. BSC: best supportive care; RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the studies 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]
VX08-770-102 (≥ 12 years)	RCT, double-blind, parallel	Patients aged ≥ 12 years with cystic fibrosis and the G551D mutation in at least one allele of the CFTR gene and FEV1 40–90% of predicted normal at screening	Ivacaftor (N = 84) placebo (N = 83)	Screening: 21 days Run-in phase: 14 days Randomized, blinded phase: ▪ treatment: 24 weeks ▪ extension: 24 weeks Follow-up: 4 weeks ± 7 days[b]	65 centres in North America, Europe and Australia 6/2009–1/2011	Primary: change in FEV1 (in % of predicted normal) over 24 weeks Secondary: all-cause mortality, symptoms, health status, health-related quality of life, AEs
VX08-770-103 (6–11 years)	RCT, double-blind, parallel, 2-phase study (Part A and B)	Children aged 6–11 years with cystic fibrosis and the G551D mutation in at least one allele of the CFTR gene, weighing ≥ 15 kg, and FEV1 40–105% of predicted normal at screening	Part A[c, d] ivacaftor single dose, 100 mg (N = 12[e]) Part B[c] ivacaftor (N = 26) placebo (N = 26) Thereof relevant subpopulation weighing ≥ 25 kg: ivacaftor (n = 20) placebo (n = 18)	Part A: Screening: 27 days Treatment: single dose and pharmacokinetics recordings within 2 days Observation: 8 days ± 2 days Part B: Screening: 21 days Run-in phase: 14 days Randomized, blinded phase: ▪ treatment: 24 weeks ▪ extension: 24 weeks Follow-up: 4 weeks ± 7 days[b]	24 centres in North America, Europe and Australia Part A: 8/2009–11/2009 Part B: 3/2010–4/2011	Primary: change in FEV1 (in % of predicted normal) over 24 weeks 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: No follow-up was required for study participants enrolled in the open-label extension study VX08-770-105 after completion of 48 weeks of treatment. All study participants who were not enrolled in the extension study and treated for longer than 4 weeks had to undergo long-term follow-up within 2 years of the last study medication.
c: Study participants from Part A were given the opportunity to participate in Part B of the study following the follow-up observation in Part A. If patients participated, Part B could be started with the 14-day run-in phase. 7 participants from Part A participated in Part B.
d: Part A of the study is not relevant for the assessment and is not shown in the next tables.
e: 3 of the included participants did not receive any study medication.

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/included patients; RCT: randomized controlled trial; vs.: versus

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

Study	Intervention	Comparison
VX08-770-102 (≥ 12 years)	Ivacaftor 150 mg[a] orally, as a tablet, every 12 hours, within 30 minutes after starting a fat-containing meal	Placebo[a] orally, as a tablet, every 12 hours, within 30 minutes after starting a fat-containing meal
	+ BSC[b]	+ BSC[b]
	Prior and concomitant treatment not allowed: ▪ any CYP3A4 inducers or inhibitors, including certain herbal products (e.g. St. John's Wort) and grapefruit/grapefruit juice, 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 ▪ solid organ or haematological transplantation before start of study	
VX08-770-103 (6–11 years)	Ivacaftor 150 mg[a] orally, as a tablet, every 12 hours, within 30 minutes after starting a fat-containing meal	Placebo[a] orally, as a tablet, every 12 hours, within 30 minutes after starting a fat-containing meal
	+ BSC[b]	+ BSC[b]
	Prior and concomitant treatment not allowed: ▪ any CYP3A4 inducers or inhibitors, including certain herbal products (e.g. St. John's Wort) and grapefruit/grapefruit juice, 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 ▪ solid organ or haematological transplantation before start of study	

a: Dose adjustments of ivacaftor were not allowed. Interruptions of medication were allowed in case of side effects after consultation with the clinical monitor.
b: In both study arms, basic medication was administered in addition to ivacaftor or placebo. It was recommended to maintain stable basic medication from 6 weeks before the start of the study until the end of the observation period.
BSC: best supportive care; CYP: cytochrome P450; RCT: randomized controlled trial; vs.: versus

Description of the study design

Study VX08-770-102

The VX08-770-102 study was a randomized, double-blind study, in which ivacaftor was compared with placebo.

CF patients aged 12 years and older with the G551D gating mutation in at least one allele of the CFTR gene were included in the study. According to the inclusion criteria of the study, diagnosis of CF was defined by the presence of either chronic sinopulmonary disease or gastrointestinal or nutritional anomalies. In addition, the patients had to either have a sweat chloride value of ≥ 60 mmol/L or carry 2 CF-causing mutations. Besides, only patients with an FEV1 of 40% to 90% of predicted normal for age, sex, and height at screening were included.

Patients infected at the time point of screening with microorganisms associated with a particularly rapid deterioration of respiratory function, such as *B. cenocepacia*, *B. dolosa* und *M. abscessus*, were excluded.

A total of 167 patients were randomly allocated in a ratio of 1:1 to the 2 study arms. Stratification was by age (< 18 years, ≥ 18 years) and FEV1 at screening (< 70%, ≥ 70% of predicted normal).

Treatment with ivacaftor or placebo was in addition to basic therapy (see text passage on the implementation of the ACT below). Treatment in the study was originally planned for 24 weeks. The randomized and blinded treatment phase was extended from 24 to 48 weeks following an amendment to the study protocol. The data at 48 weeks were considered for the present benefit assessment.

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]. All patients included in the study weighed 25 kg or more; hence ivacaftor was used in compliance with the approval for the total study population.

Primary outcome of the study was the absolute change in FEV1 (in % of predicted normal) after 24 weeks. Patient-relevant secondary outcomes were all-cause mortality, symptoms, health status, health-related quality of life, and AEs. All outcomes were recorded for 4 weeks after the last study medication, except for pulmonary exacerbations, which were recorded until the last administration of the study medication. In addition, there was long-term follow-up for 2 years after the last study medication for the recording of SAEs.

Study VX08-770-103

The VX08-770-103 study was conducted in 2 parts (Part A and B). The non-randomized Part A of the study assessed the pharmacokinetics after intake of a single dose of ivacaftor. This part of the study is not relevant for the present benefit assessment. The randomized, double-blind Part B of the study compared ivacaftor with placebo. Study participants from Part A were given the opportunity to also participate in Part B of the study. In this case, the run-in phase of Part B was started after the follow-up in Part A according to study planning, so that a washout phase of at least 3 weeks was completed after the single dose. 7 of the 12 children included in Part A participated in Part B of the study.

The inclusion criteria of the VX08-770-103 study largely concur with those of the VX08-770-102 study. Deviations are described below.

Children with CF between 6 and 11 years of age were included in both parts of the study. At the time point of study inclusion the children had to weigh 15 kg or more, and the FEV1 had to be 40% to 105% of predicted normal for age, sex, and height.

In Part B of the study, which is the relevant part for the present benefit assessment, a total of 52 children were randomly allocated in a ratio of 1:1 to the 2 study arms. Stratification was by FEV1 (in % of predicted normal) at the start of the 14-day run-in phase of Part B (< 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). Treatment in Part B of the study was originally planned for 24 weeks. The randomized and blinded treatment phase was extended from 24 to 48 weeks following an amendment to the study protocol.

Primary outcome of the study was the absolute change in FEV1 (in % of predicted normal) after 24 weeks. Patient-relevant secondary outcomes were all-cause mortality, symptoms, health-related quality of life, and AEs. All outcomes were recorded until 4 weeks after the last study medication, except for pulmonary exacerbations, which were recorded until the last administration of the study medication. In addition, there was long-term follow-up for 2 years after the last study medication for the recording of SAEs.

Subpopulation of the VX08-770-103 study relevant for the benefit assessment

Children 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]. However, not all children included in the study weighed 25 kg or more; hence, ivacaftor was used in compliance with the approval only for part of the study population. The relevant subpopulation of children with a body weight in compliance with the approval was about 73% of the total study population (20 of 26 patients in the ivacaftor arm, 18 of 26 in the placebo arm). Although the company described this in Module 4 A, it used the total population of the study for its assessment. Deviating from the company, the relevant subpopulation of the VX08-770-103 study was used for the present benefit assessment (see also Section 2.7.2 of the full dossier assessment).

Patient characteristics

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

Table 8: Characteristics of the study populations – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study	VX08-770-102 (≥ 12 years)		VX08-770-103 (6–11 years)	
Characteristics	Ivacaftor + BSC	Placebo + BSC	Ivacaftor + BSC	Placebo + BSC
Category	N[a] = 83	N[a] = 78	N[b] = 26	N[b] = 26
Age [years], mean (SD)	26 (10)	25 (9)	9 (2)	9 (2)
Age group, n (%)				
6–8 years	–	–	12 (46.2)	13 (50.0)
9–11 years	–	–	11 (42.3)	12 (46.2)
> 11 years	–	–	3 (11.5)	1 (3.8)
< 18 years	19 (22.9)	17 (21.8)	–	–
≥ 18 years	64 (77.1)	61 (78.2)	–	–
Sex [F/M], %	53/47	51/49	65/35	38/62
Family origin, n (%)				
White	81 (97.6)	77 (98.7)	22 (84.6)	23 (88.5)
Other	0 (0)	0 (0)	2 (7.7)	1 (3.8)
Question not allowed according to current guidelines	2 (2.4)	1 (1.3)	2 (7.7)	2 (7.7)
Region, n (%)				
North America	50 (60.2)	50 (64.1)	12 (46.2)	15 (57.7)
Europe	23 (27.7)	19 (24.4)	6 (23.1)	5 (19.2)
Australia	10 (12.0)	9 (11.5)	8 (30.8)	6 (23.1)
FEV1 (in % of predicted normal) at baseline, n (%)				
< 70%	49 (59.0)	45 (57.7)	4 (15.4)	8 (30.8)
≥ 70%	34 (41.0)	33 (42.3)	–	–
≥ 70% to ≤ 90%	–	–	12 (46.2)	6 (23.1)
> 90%	–	–	10 (38.5)	12 (46.2)
Height [cm]				
Mean (SD)	168 (10)	167 (10)	135 (14)	133 (12)
median (min; max)	168 (143; 185)	168 (142; 190)	133 (115; 169)	131 (111; 156)
Body weight [kg]				
Mean (SD)	61.7 (14.3)	61.2 (13.9)	31.8 (9.9)	30.0 (7.2)
Median (min; max)	58.8 (30.2; 107.2)	58.7 (31.9; 109.9)	28.2 (18.8; 62.6)	29.7 (17.8; 46.3)
Weight categories, n (%)				
< 25 kg	0 (0)	0 (0)	6 (23.1[c])	8 (30.8[c])
≥ 25 kg	83 (100[c])	78 (100[c])	20 (76.9[c])	18 (69.2[c])
BMI [kg/m²], mean (SD)	21.7 (3.7)	21.9 (3.5)	17.1 (2.6)	16.8 (1.7)
Treatment discontinuation[d], n (%)	6 (7.2)	10 (12.8)	0 (0)	4 (15.4)
Study discontinuation[d, e], n (%)	7 (8.3)[c]	15 (18.1)[c]	0 (0)	4 (15.4)

(continued)

Table 8: Characteristics of the study populations – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

a: Randomized patients: 84 (ivacaftor + BSC) vs. 83 (placebo + BSC)
b: Study participants from Part B; no information on the relevant subpopulation of the 18 vs. 20 patients with ≥ 25 kg body weight.
c: Institute's calculation.
d: After 48 weeks.
e: Proportion of patients from randomized patients.
BMI: body mass index; BSC: best supportive care; F: female; FEV1: forced expiratory volume in 1 second; M: male; max: maximum; min.: minimum; n: number of patients in the category; N: number of patients who had received at least one dose of the study medication; in the VX08-770-103 study equivalent to the randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

For study VX08-770-102, the demographic and clinical characteristics were balanced between both study arms. However, there was a difference in the proportion of patients who discontinued the study: about 10% more patients discontinued the study in the placebo arm than in the ivacaftor arm.

For the VX08-770-103 study, the company did not present any data on the characteristics of the relevant subpopulation, but only data for the total study population. Hence, it cannot be conclusively assessed whether there were relevant differences in the subpopulation between the study arms. Differences in sex ratios were shown for the total population of the study with more girls in the ivacaftor arm than in the placebo arm. Besides, fewer children with a baseline FEV1 of < 70% of predicted normal were included in the ivacaftor arm. Similar to the VX08-770-102 study, there was a difference in the total population regarding the proportion of patients who discontinued the study, with about 15% more children who discontinued the study in the placebo arm than in the ivacaftor arm. Whether the observed differences for the relevant subpopulation were lower, comparable or higher, cannot be assessed because the company did not provide any data for the relevant subpopulation.

Meta-analytic summary of study results not meaningful with regard to content

The comparison of the data on the total populations of the studies VX08-770-102 and VX08-770-103 showed differences in demographic and clinical characteristics of the included populations, which resulted as a consequence of the different inclusion/exclusion criteria mainly regarding the age of the study populations. Since the company did not present any data on the relevant subpopulation for the VX08-770-103 study, the comparability of the populations relevant for the benefit assessment cannot be conclusively assessed.

The VX08-770-102 study included patients with a mean age of approximately 25 years, with more than 75% of patients older than 18 years (maximum 53 years). In contrast, the VX08-770-103 study included children with a mean age of 9 years. Differences between both study populations were shown not only in age and the associated different anthropometric measures, but also in FEV1 at baseline. As to be expected in a progressive disease, a higher proportion of about 60% had an FEV1 of < 70% of predicted normal in the VX08-770-102

study in older patients. In the VX08-770-103 study, only about 15% and 30% of the children in the total study population had an FEV1 of < 70% of predicted normal. It remains unclear whether these children were also included in the relevant subpopulation of the study.

Overall, based on the data presented, it can be assumed that, due to the progressive course of CF and the large age difference between the study populations, the children in the relevant subpopulation in the VX08-770-103 study were in a less advanced stage of disease than the patients in the VX08-770-102 study. Against this background, a meta-analytic summary of the data does not appear to be meaningful with regard to content. In addition, the results for both age groups in the studies VX08-770-102 and VX08-770-103 differed from each other (see Section 2.4.3 for details). This concurs with the approach of the company, which also did not present a meta-analytic summary of the data.

Implementation of the appropriate comparator therapy

The G-BA specified BSC as ACT for ivacaftor in the treatment of patients aged 6 years and older with a G551D 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.

In the studies VX08-770-102 and VX08-770-103, patients were to continue their ongoing symptomatic treatments at the same time as their treatments with ivacaftor or placebo. The company stated in the dossier that all included patients 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.

According to the study protocol, it was recommended for study VX08-770-102 and the relevant Part B of study VX08-770-103 that patients remain on stable CF medication from 6 weeks prior to the first study medication until the end of the study. There was an important restriction of the concomitant therapy regarding inhaled hypertonic saline solution, which was not allowed within 4 weeks before the first intake of the study medication until the end of the study. According to the study protocols, there were no restrictions for other concomitant treatments such as inhalation with dornase alfa and the use of bronchodilators, antibiotics, vitamin preparations and physiotherapeutic measures in both studies.

In Module 4 A, the company did not provide any information on the pretreatment of the patients included in the studies and only little information on the concomitant medication in the included studies. It can be inferred from the company's dossier, however, that all patients in both studies received concomitant medication for the symptomatic treatment of CF both before the start of the study and during the study. For the VX08-770-103 study, only information on the total study population was available, and no information on the relevant subpopulation.

Table 9 shows the prior and concomitant treatments of the patients in the studies included.

Table 9: Treatment before the first administration of the study medication and concomitant treatment (≥ 10% and ≥ 15% in at least one study arm) for patients aged 12 years and older (study VX08-770-102) and children between 6 and 11 years of age (study VX08-770-103), direct comparison: ivacaftor + BSC vs. placebo + BSC

Study **PT**	**VX08-770-102[a] (≥ 12 years)**				**VX08-770-103[b] (6–11 years)**			
	Ivacaftor + BSC		**Placebo + BSC**		**Ivacaftor + BSC**		**Placebo + BSC**	
	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)
	N = 83	N = 83	N = 78	N = 78	N = 26	N = 26	N = 26	N = 26
Drug treatment[e]								
Pancrelipase	73 (88.0)	74 (89.2)	72 (92.3)	74 (94.9)	25 (96.2)	25 (96.2)	25 (96.2)	25 (96.2)
Dornase alfa	54 (65.1)	57 (68.7)	57 (73.1)	57 (73.1)	18 (69.2)	18 (69.2)	22 (84.6)	22 (84.6)
Azithromycin	51 (61.4)	57 (68.7)	50 (64.1)	55 (70.5)	12 (46.2)	15 (57.7)	12 (46.2)	14 (53.8)
Adeks (dietary supplement)	42 (50.6)	45 (54.2)	45 (57.7)	46 (59.0)	10 (38.5)	11 (42.3)	14 (53.8)	14 (53.8)
Salbutamol	35 (42.2)	38 (45.8)	42 (53.8)	43 (55.1)	11 (42.3)	12 (46.2)	11 (42.3)	12 (46.2)
Tobramycin	28 (33.7)	41 (49.4)	35 (44.9)	54 (69.2)	5 (19.2)	13 (50.0)	5 (19.2)	13 (50.0)
Seretide (salmeterol/ fluticasone propionate)	23 (27.7)	24 (28.9)	32 (41.0)	36 (46.2)	3 (11.5)	5 (19.2)	5 (19.2)	7 (26.9)
Omeprazole	23 (27.7)	27 (32.5)	17 (21.8)	20 (25.6)	–	5 (19.2)	–	5 (19.2)
Salbutamol sulfate	18 (21.7)	19 (22.9)	14 (17.9)	17 (21.8)	4 (15.4)	6 (23.1)	5 (19.2)	5 (19.2)
Tocopherol	20 (24.1)	20 (24.1)	11 (14.1)	12 (15.4)		–		–
Sodium chloride[f]	17 (20.5)	27 (32.5)	9 (11.5)	16 (20.5)	5 (19.2)	8 (30.8)	7 (26.9)	9 (34.6)
Vitamin D[g]	15 (18.1)	20 (24.1)	11 (14.1)	12 (15.4)	–	–	–	–
Multivitamin preparation	15 (18.1)	16 (19.3)	10 (12.8)	12 (15.4)	–	–	–	–
Ibuprofen	14 (16.9)	25 (30.1)	9 (11.5)	22 (28.2)	–	8 (30.8)	–	5 (19.2)

(continued)

Table 9: Treatment before the first administration of the study medication and concomitant treatment (≥ 10% and ≥ 15% in at least one study arm) for patients aged 12 years and older (study VX08-770-102) and children between 6 and 11 years of age (study VX08-770-103), direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

Study **PT**	**VX08-770-102[a] (≥ 12 years)**				**VX08-770-103[b] (6–11 years)**			
	Ivacaftor + BSC		**Placebo + BSC**		**Ivacaftor + BSC**		**Placebo + BSC**	
	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)
	N = 83	N = 83	N = 78	N = 78	N = 26	N = 26	N = 26	N = 26
Fluticasone propionate	10 (12.0)	13 (15.7)	11 (14.1)	14 (17.9)	2 (7.7)	2 (7.7)	5 (19.2)	5 (19.2)
Hypertonic solution[f]	8 (9.6)	–	12 (15.4)	–	0 (0)	–	4 (15.4)	–
Paracetamol	10 (12.0)	30 (36.1)	10 (12.8)	22 (28.2)	–	14 (53.8)	–	7 (26.9)
Macrogol	7 (8.4)	8 (9.6)	12 (15.4)	13 (16.7)	4 (15.4)	5 (19.2)	2 (7.7)	4 (15.4)
Montelukast sodium	5 (6.0)	6 (7.2)	13 (16.7)	13 (16.7)	2 (7.7)	2 (7.7)	4 (15.4)	4 (15.4)
Vitamin K[g]	10 (12.0)	12 (14.5)	8 (10.3)	11 (14.1)	–		–	
Ciprofloxacin	10 (12.0)	31 (37.3)	6 (7.7)	43 (55.1)	–	6 (23.1)	–	8 (30.8)
Lansoprazole	7 (8.4)	8 (9.6)	9 (11.5)	9 (11.5)	5 (19.2)	5 (19.2)	4 (15.4)	5 (19.2)
Mometasone furoate	6 (7.2)	7 (8.4)	10 (12.8)	9 (11.5)	2 (7.7)	4 (15.4)	5 (19.2)	6 (23.1)
Ursodeoxycholic acid	7 (8.4)	8 (9.6)	9 (11.5)	10 (12.8)	3 (11.5)	3 (11.5)	4 (15.4)	4 (15.4)
Monovalent influenza vaccine	7 (8.4)	8 (9.6)	8 (10.3)	9 (11.5)	–	–	–	–
Acetylcysteine	9 (10.8)	9 (10.8)	5 (6.4)	5 (6.4)	–	–	–	–
Ascorbic acid	10 (12.0)	10 (12.0)	4 (5.1)	6 (7.7)	–	–	–	–
Budesonide	9 (10.8)	9 (10.8)	5 (6.4)	7 (9.0)	–	–	–	–
Colistin	9 (10.8)	10 (12.0)	5 (6.4)	9 (11.5)	3 (11.5)	3 (11.5)	6 (23.1)	5 (19.2)
Esomeprazole magnesium	5 (6.0)	5 (6.0)	9 (11.5)	9 (11.5)	–	–	–	–

(continued)

Table 9: Treatment before the first administration of the study medication and concomitant treatment (≥ 10% and ≥ 15% in at least one study arm) for patients aged 12 years and older (study VX08-770-102) and children between 6 and 11 years of age (study VX08-770-103), direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

Study **PT**	**VX08-770-102[a] (≥ 12 years)**				**VX08-770-103[b] (6–11 years)**			
	Ivacaftor + BSC		**Placebo + BSC**		**Ivacaftor + BSC**		**Placebo + BSC**	
	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)
	N = 83	N = 83	N = 78	N = 78	N = 26	N = 26	N = 26	N = 26
Budesonide/formoterol fumarate	4 (4.8)	6 (7.2)	9 (11.5)	11 (14.1)	–	–	–	–
Calcium carbonate	1 (1.2)	2 (2.4)	8 (10.3)	9 (11.5)	–	–	–	–
Minocycline	0 (0)	0 (0)	8 (10.3)	14 (17.9)	–	–	–	–
Influenza vaccine	–	19 (22.9)	–	20 (25.6)	–	3 (11.5)	–	6 (23.1)
Bactrim (trimethoprim/ sulfamethoxazole)	–	17 (20.5)	–	18 (23.1)	–	2 (7.7)	–	9 (34.6)
Levofloxacin	–	13 (15.7)	–	14 (17.9)	–	–	–	–
Ceftazidime	–	8 (9.6)	–	17 (21.8)	–	–	–	–
Meropenem	–	7 (8.4)	–	16 (20.5)	–	–	–	–
Aztreonam	–	8 (9.6)	–	13 (16.7)	–	–	–	–
Colecalciferol	–	13 (15.7)	–	8 (10.3)	4 (15.4)	4 (15.4)	3 (11.5)	4 (15.4)
Co-trimoxazole	–	7 (8.4)	–	13 (16.7)	–	6 (23.1)	–	5 (19.2)
Prednisone	–	6 (7.2)	–	14 (17.9)	–	–	–	–
Doxycycline	–	11 (13.3)	–	8 (10.3)	–	–	–	–
Augmentin (amoxicillin/ clavulanic acid)	–	8 (9.6)	–	8 (10.3)	–	5 (19.2)	–	6 (23.1)

(continued)

Table 9: Treatment before the first administration of the study medication and concomitant treatment (≥ 10% and ≥ 15% in at least one study arm) for patients aged 12 years and older (study VX08-770-102) and children between 6 and 11 years of age (study VX08-770-103), direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

Study **PT**	**VX08-770-102[a] (≥ 12 years)**				**VX08-770-103[b] (6–11 years)**			
	Ivacaftor + BSC		**Placebo + BSC**		**Ivacaftor + BSC**		**Placebo + BSC**	
	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)	Treatment before first administration of study medication[c] n (%)	Concomitant treatment[d] n (%)
	N = 83	N = 83	N = 78	N = 78	N = 26	N = 26	N = 26	N = 26
Cetirizine hydrochloride	–	7 (8.4)	–	8 (10.3)	–	4 (15.4)	–	6 (23.1)
Diphenhydramine hydrochloride	–	6 (7.2)	–	8 (10.3)	–	–	–	–
Heparin	–	3 (3.6)	–	9 (11.5)	–	–	–	–
Amoxicillin with potassium clavulanate	–	–	–	–	–	6 (23.1)	–	5 (19.2)
Fats/carbohydrates/ proteins/minerals/vitamins	–	–	–	–	2 (7.7)	2 (7.7)	6 (23.1)	6 (23.1)
Timentin (ticarcillin/ clavulanic acid)	–	–	–	–		3 (11.5)	–	5 (19.2)
Flucloxacillin	–	–	–	–		4 (15.4)	–	2 (7.7)
Ranitidine hydrochloride	–	–	–	–	4 (15.4)	4 (15.4)	1 (3.8)	1 (3.8)
Ondansetron	–	–	–	–	–	0 (0)	–	4 (15.4)
Non-drug treatment[h]								
Physiotherapy of the chest	40 (48.2)	43 (51.8)	51 (65.4)	52 (66.7)	19 (73.1)	19 (73.1)	18 (69.2)	18 (69.2)
Physiotherapy	–	10 (12.0)	–	8 (10.3)	4 (15.4)	4 (15.4)	3 (11.5)	3 (11.5)
Kinesiotherapy	11 (13.3)	13 (15.7)	7 (9.0)	7 (9.0)	–	–	–	–

(continued)

Table 9: Treatment before the first administration of the study medication and concomitant treatment (≥ 10% and ≥ 15% in at least one study arm) for patients aged 12 years and older (study VX08-770-102) and children between 6 and 11 years of age (study VX08-770-103), direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

– not presented, as not ≥ 10% or ≥ 15% in at least one study arm
a: Presentation of ≥ 10% in at least one study arm.
b: Data of the relevant subpopulation are not available; information refers to the total population (presentation of ≥ 15% in at least one study arm).
c: Within 30 days before the screening visit until the first dose of the study medication.
d: After the first dose of the study medication.
e: PT, coded according to WHO-DD, December 2007.
f: Inhalation of hypertonic saline solution was not allowed during the study and within 4 weeks before the first study medication.
g: Not otherwise specified.
h: PT, coded according to MedDRA, Version 12.

BSC: best supportive care; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with administration of at least one medication or non-drug treatment within a PT; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; vs.: versus; WHO-DD: World Health Organization Drug Dictionary

The available data show that a large number of symptomatic therapies for CF were used in both studies, including pancreatic enzymes, dornase alfa, bronchodilators, antibiotics, analgesics, vitamin preparations and physiotherapeutic measures. Mannitol, which has been approved for CF since 2012, was not used as concomitant treatment. In addition, there was a small proportion of patients pretreated with hypertonic solution. Since this treatment was not listed as concomitant treatment, it was presumably the inhaled hypertonic saline solution that was not allowed in both studies from 4 weeks before the first study medication, according to inclusion criteria.

The data on concomitant treatment before and after the first intake of the study medication show for the total population of both studies that medications were initiated and discontinued individually for some drug groups, including a large number of different antibiotics (e.g. azithromycin, tobramycin, ciprofloxacin, Bactrim and co-trimoxazole) and analgesics (ibuprofen and paracetamol).

In addition, for some of the drugs, there were differences of more than 10% of the treated patients between the study arms in the intake of the medication both before the first intake of the study medication and after the first intake of the study medication. For the VX08-770-102 study, this applied to the antibiotics tobramycin and minocycline, Seretide (salmeterol/fluticasone propionate), and to non-drug physiotherapy of the chest. For the total population of the VX08-770-103 study, such differences were found for dornase alfa, the antihistamine ranitidine hydrochloride, some dietary supplements and the glucocorticoid fluticasone propionate. It cannot be inferred from the available data for both studies 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. Overall, no conclusive assessment of the data is possible for the VX08-770-103 study, as there is no information on prior and concomitant treatment for the relevant subpopulation.

In summary, the concomitant treatment used in the studies VX08-770-102 and VX08-770-103 did not constitute a complete implementation of the ACT BSC. This assessment is based in particular on the fact that the study design excluded treatment with inhaled saline solution, a standard therapy for CF [4]. In addition, there is no information at all for the VX08-770-103 study 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 studies. 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 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			
VX08-770-102 (≥ 12 years)	Yes	Yes	Yes	Yes	Yes	Yes	Low
VX08-770-103 (6–11 years)	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 both studies. 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
  - hospitalizations due to pulmonary exacerbations
  - symptoms measured with the symptom domains of the CFQ-R instrument
  - health status (EQ-5D VAS)
- 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 deviates from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.4.3 of the full dossier assessment).

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

Table 11: 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 status (EQ-5D VAS)	Health-related quality of life (CFQ-R)	SAEs[a]	Discontinuation due to AEs	Rash (PT, AE)	Dizziness (PT, AE)
VX08-770-102 (≥ 12 years)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
VX08-770-103 (6–11 years)	Yes	Yes	Yes	Yes	No[b]	Yes	Yes	Yes	No[c]	No[c]

a: Using the PT "cystic fibrosis lung", 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.
b: Outcome not recorded.
c: No data available for the relevant subpopulation.
AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire Revised; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: MedDRA Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

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

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

Study	Study level	Outcomes									
		All-cause mortality	Pulmonary exacerbations	Hospitalization due to pulmonary exacerbations	Symptoms (CFQ-R)	Health status (EQ-5D VAS)	Health-related quality of life (CFQ-R)	SAEs	Discontinuation due to AEs	Rash[a] (PT, AE)	Dizziness[a] (PT, AE)
VX08-770-102 (≥ 12 years)	L	L	H[b]	H[b]	H[c]	H[d]	H[c]	–[e]	H[f]	H[b]	H[b]
VX08-770-103 (6–11 years)	L	L	H[b]	H[b]	H[c]	–[g]	H[c]	–[e]	L	–[h]	–[h]

a: Coded according to MedDRA Version 12.
b: Incomplete observations (for potentially informative reasons).
c: Large difference between the treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis.
d: Unclear proportion of patients who were not considered in the analysis; proportion > 10% plausible.
e: No usable data available.
f: Events included that can be both side effects and symptoms of the disease.
g: Outcome not recorded.
h: No data available (for the relevant subpopulation).
AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire Revised; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: MedDRA Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Concurring with the company's assessment, the risk of bias for the outcome "all-cause mortality" was rated as low for both studies.

The risk of bias for the following outcomes was rated as high for both studies: pulmonary exacerbations, hospitalizations due to pulmonary exacerbations, symptoms (recorded with the CFQ-R) and health-related quality of life (recorded with the CFQ-R). The company assumed a low risk of bias for these outcomes for both studies.

The risk of bias for the outcome "health status" (using the EQ-5D VAS) was also rated as high for the VX08-770-102 study. The company assumed a low risk of bias for the outcome.

In the recording of SAEs, both studies included, among others, pulmonary exacerbation events in the recording of the PT "cystic fibrosis lung". 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 data on SAEs are therefore not usable. The company assumed a low risk of bias for the outcome "SAEs".

For the outcome "discontinuation due to AEs", the risk of bias was rated as high for the VX08-770-102 study, as it included a large proportion of events that can be both side effects and symptoms of the disease. The company assumed a low risk of bias for the outcome. Concurring with the company's assessment, the risk of bias was rated as low for the outcome "discontinuation due to AEs" for the VX08-770-103 study. The available data show that no events that can be both side effects and symptoms of the disease occurred in the study.

The risk of bias for the VX08-770-102 study was rated as high for the outcomes "rash" and "dizziness". The company assumed a low risk of bias for these outcomes.

Detailed reasons for the assessment of the risk of bias can be found in Section 2.7.4.2 of the full dossier assessment.

Overall assessment of the certainty of conclusions

It is not assumed for the present benefit assessment that the concomitant treatment used in the studies VX08-770-102 and VX08-770-103 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, which was not allowed during the studies. In addition, there is no information on treatment adjustments in the sense of an increase in dose or frequency of the symptomatic therapy during both studies, and no information at all on prior and concomitant medication for the relevant subpopulation of the VX08-770-103 study. Hence, the certainty of conclusions of the study results for the present research question is reduced both for conclusions on patients aged 12 years and older based on the VX08-770-102 study and for children between 6 and 11 years of age based on the VX08-770-103 study. Only one study is available for each of both age groups. Under consideration of the fact that the ACT BSC was not completely implemented in the studies, at most hints, e.g. of an added benefit, can be derived for the age groups for all outcomes presented.

2.4.3 Results

Table 13 to Table 15 summarize the results of the comparison of ivacaftor + BSC with BSC in patients with CF aged 6 years and older and weighing 25 kg or more who have the G551D gating 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) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Outcome category Outcome Study	Ivacaftor + BSC		Placebo + BSC		Ivacaftor + BSC vs. placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p-value
Mortality					
All-cause mortality					
VX08-770-102 (≥ 12 years)	84	0 (0)	83	0 (0)	–
VX08-770-103 (6–11 years)	20	0 (0)	18	0 (0)	–
Side effects					
AEs (supplementary information)					
VX08-770-102 (≥ 12 years)	83	82 (98.8)	78	78 (100.0)	–
VX08-770-103 (6–11 years)	20	20 (100.0)	18	17 (94.4)	–
SAEs[a]					
VX08-770-102 (≥ 12 years)				Not usable[b]	
VX08-770-103 (6–11 years)				Not usable[c]	
Discontinuation due to AEs					
VX08-770-102 (≥ 12 years)	83	1 (1.2)	78	4 (5.1)	0.23 [0.03; 2.06]; 0.153[d]
VX08-770-103 (6–11 years)	20	0 (0)	18	1 (5.6)	0.30 [0.01; 6.97]; 0.353[e, f]
Rash (PT, AE)					
VX08-770-102 (≥ 12 years)	83	12 (14.5)	78	4 (5.1)	2.82 [0.95; 8.37]; 0.049[e, g]
VX08-770-103 (6–11 years)	ND	ND	ND	ND	ND
Dizziness (PT, AE)					
VX08-770-102 (≥ 12 years)	83	10 (12.0)	78	1 (1.3)	9.40 [1.23; 71.72]; 0.007[e]
VX08-770-103 (6–11 years)	ND	ND	ND	ND	ND

a: Events of the underlying disease were included in the recording of AEs, including, for example, pulmonary exacerbation events using the PT "cystic fibrosis lung"; see Section 2.7.4.3.2 of the full dossier assessment for information on how the outcome "SAEs" was handled.
b: Data are not usable, as they contain a large proportion of patients with events of the PT "cystic fibrosis lung" and events that can be both side effects and symptoms of the disease.
c: Data are not usable, as there are no data on the type of the included events for the relevant subpopulation. The total population includes a relevant proportion of patients with events of the PT "cystic fibrosis lung" and with events that can be both side effects and symptoms of the disease.
d: Mantel and Haenszel, unstratified.
e: Institute's calculation of RR and CI. Institute's calculation of p-value, unconditional exact test (CSZ method according to [5]).
f: Institute's calculation with continuity correction.
g: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
AE: adverse event; BSC: best supportive care; CF: cystic fibrosis; CI: confidence interval; CSZ: convexity, symmetry, z score; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of patients with at least one dose of the study medication, considered as treated, not as randomized; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

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

Outcome category Outcome Study	N	Ivacaftor + BSC Number of events n_E (n_E/patient years)[a]	N	Placebo + BSC Number of events n_E (n_E/patient years)[a]	Ivacaftor + BSC vs. placebo + BSC Rate ratio [95% CI]; p-value
Morbidity					
Pulmonary exacerbations					
VX08-770-102 (≥ 12 years)	83	47 (0.63[b])	78	99 (1.48[b])	0.43 [0.27; 0.68]; < 0.001[c]
VX08-770-103 (6–11 years)	20	4 (0.22[b])	18	3 (0.21[b])	ND
Hospitalizations due to pulmonary exacerbations					
VX08-770-102 (≥ 12 years)	83	21 (0.28[b])	78	31 (0.46[b])	0.64 [0.32; 1.26]; 0.195[c]
VX08-770-103 (6–11 years)	20	2 (0.11[b])	18	1 (0.07[b])	ND
	N	Ivacaftor + BSC Patients with event n (%)	N	Placebo + BSC Patients with event n (%)	Ivacaftor + BSC vs. placebo + BSC RR [95% CI]; p-value
Pulmonary exacerbations					
VX08-770-103 (6–11 years)	20	4 (20.0)	18	3 (16.7)	1.20 [0.31; 4.65]; 0.847[d]
Hospitalizations due to pulmonary exacerbations					
VX08-770-103 (6–11 years)	20	2 (10.0)	18	1 (5.6)	1.80 [0.18; 18.21]; 0.712[d]

a: Event rate (n_E/patient years) is calculated from the total number of events divided by the total number of years (sum of the time in the study of all patients included in the analysis).
b: Institute's calculation.
c: Negative binomial model.
d: Institute's calculation of RR and CI. Institute's calculation of p-value, unconditional exact test (CSZ method according to [5]).

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 patients with at least one dose of the study medication; ND: no data; n_E: number of events; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

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

Outcome category Outcome Study	Ivacaftor + BSC N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	Placebo + BSC N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	Ivacaftor + BSC vs. placebo + BSC MD [95% CI]; p-value[c]
Morbidity							
Symptoms (CFQ-R, symptom domains)[d]							
Respiratory symptoms							
VX08-770-102 (children [12 to 13 years] and adolescents or adults – pooled)							
	80	70.21 (16.40)	6.39 (16.81)	71	68.97 (19.17)	−3.93 (14.21)	8.60 [5.32; 11.87]; < 0.001 Hedges' g: 0.84 [0.50; 1.17]
VX08-770-103 (children [6 to 11 years])							
	20	80.00 (17.61)	6.25 (19.10)	17	82.87 (14.98)	2.97 (16.54)	5.42 [−2.98; 13.82]; 0.198
Digestive symptoms							
VX08-770-102 (children [12 to 13 years] and adolescents or adults – pooled)							
	80	85.15 (12.98)	0.60 (14.10)	70	85.81 (18.38)	−1.79 (14.25)	0.48 [−2.29; 3.25]; 0.732
VX08-770-103 (children [6 to 11 years])							
	20	76.67 (26.72)	10.00 (24.42)	16	72.24 (20.61)	11.90 (28.05)	5.55 [−4.83; 15.93]; 0.284
Weight							
VX08-770-102 (adolescents or adults; not intended for children [12 to 13 years])							
	76	78.95 (30.72)	8.33 (25.48)	64	78.79 (31.84)	−4.02 (30.00)	5.28 [−0.08; 10.63]; 0.053
VX08-770-103 (children [6 to 11 years])							
			Domain not provided in questionnaire for children from 6 to 11 years				
Additional information for study VX08-770-103 (CFQ-R – parent/caregiver version [children from 6 to 11 years], symptom domains)[d]							
Respiratory symptoms	20	81.38 (15.75)	5.28 (17.14)	17	81.48 (16.50)	0.39 (14.36)	3.83 [−2.17; 9.83]; 0.203
Digestive symptoms	20	79.46 (14.98)	4.44 (14.13)	16	77.79 (17.04)	2.38 (10.82)	1.23 [−3.29; 5.74]; 0.584
Weight	20	81.68 (25.30)	14.99 (31.48)	16	66.67 (28.02)	7.14 (23.29)	13.14 [2.13; 24.14]; 0.021 Hedges' g: 0.86 [0.17; 1.56]

(continued)

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

Outcome category Outcome Study	Ivacaftor + BSC N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	Placebo + BSC N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	Ivacaftor + BSC vs. placebo + BSC MD [95% CI]; p-value[c]
Health status							
EQ-5D VAS[d]							
VX08-770-102	76	77.70 (15.07)	3.06 (16.09)	65	78.83 (13.95)	−0.78 (10.34)	3.96 [−0.23; 8.14]; 0.064[e]
VX08-770-103	Outcome not recorded						
Health-related quality of life							
CFQ-R (health-related quality of life domains)[d]							
Physical functioning							
VX08-770-102 (children [12 to 13 years] and adolescents or adults – pooled)							
	80	76.10 (24.13)	5.96 (15.42)	70	80.61 (22.14)	−4.63 (17.22)	4.44 [1.33; 7.55]; 0.006 Hedges' g: 0.42 [0.10; 0.75]
VX08-770-103 (children [6 to 11 years])							
	20	86.21 (17.65)	2.79 (11.22)	16	87.96 (15.74)	3.58 (12.06)	−1.11 [−7.25; 5.02]; 0.714
Emotional functioning							
VX08-770-102 (children [12 to 13 years] and adolescents or adults – pooled)							
	80	86.02 (13.95)	1.59 (12.56)	70	83.95 (15.86)	−1.40 (11.08)	2.12 [−0.38; 4.63]; 0.096
VX08-770-103 (children [6 to 11 years])							
	20	77.09 (16.52)	7.50 (10.96)	16	81.24 (13.87)	5.96 (15.66)	1.31 [−2.21; 4.83]; 0.455
Vitality							
VX08-770-102 (adolescents or adults; not intended for children [12 to 13 years])							
	76	64.25 (16.26)	2.08 (17.73)	64	65.53 (18.88)	−3.88 (15.71)	5.45 [1.97; 8.94]; 0.002 Hedges' g: 0.50 [0.17; 0.84]
VX08-770-103 (children [6 to 11 years])							
	Domain not provided in questionnaire for children from 6 to 11 years						

(continued)

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

Outcome category Outcome Study	Ivacaftor + BSC N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	Placebo + BSC N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	Ivacaftor + BSC vs. placebo + BSC MD [95% CI]; p-value[c]
Social functioning							
VX08-770-102 (children [12 to 13 years] and adolescents or adults – pooled)							
	80	72.11 (16.43)	4.79 (13.69)	70	72.47 (17.96)	−1.50 (12.14)	4.25 [1.52; 6.98]; 0.003 Hedges' g: 0.48 [0.16; 0.81]
VX08-770-103 (children [6 to 11 years])							
	20	68.82 (18.24)	5.48 (12.20)	16	72.67 (20.96)	0.79 (19.15)	3.10 [−2.12; 8.32]; 0.235
Role functioning							
VX08-770-102 (adolescents or adults; not intended for children [12 to 13 years])							
	76	86.30 (13.52)	1.38 (14.93)	64	85.99 (15.76)	−3.45 (17.31)	−0.58 [−3.10; 1.94]; 0.651
VX08-770-103 (children [6 to 11 years])							
	Domain not provided in questionnaire for children from 6 to 11 years						
Body image							
VX08-770-102 (children [12 to 13 years] and adolescents or adults – pooled)							
	80	80.98 (20.17)	3.00 (14.51)	70	80.88 (21.03)	−2.51 (17.23)	2.70 [−0.38; 5.77]; 0.086
VX08-770-103 (children [6 to 11 years])							
	20	88.34 (19.58)	6.66 (12.16)	16	92.60 (12.04)	0.79 (8.10)	2.71 [−2.00; 7.43]; 0.250
Eating problems							
VX08-770-102 (children [12 to 13 years] and adolescents or adults – pooled)							
	80	91.81 (14.11)	3.45 (15.15)	70	91.98 (15.62)	−2.33 (15.21)	3.34 [1.23; 5.44]; 0.002 Hedges' g: 0.50 [0.17; 0.83]
VX08-770-103 (children [6 to 11 years])							
	20	82.23 (22.34)	13.33 (23.80)	16	85.81 (20.09)	6.34 (17.80)	1.91 [−4.67; 8.48]; 0.559

(continued)

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

Outcome category Outcome Study	Ivacaftor + BSC N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	Placebo + BSC N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SD)	Ivacaftor + BSC vs. placebo + BSC MD [95% CI]; p-value[c]
Treatment burden							
VX08-770-102 (children [12 to 13 years] and adolescents or adults – pooled)							
	80	64.46 (19.73)	6.15 (17.06)	70	65.76 (17.67)	−0.72 (14.05)	3.31 [0.12; 6.50]; 0.042 Hedges' g: 0.32 [−0.01; 0.64]
VX08-770-103 (children [6 to 11 years])							
	20	73.35 (23.75)	0.56 (19.55)	16	68.52 (27.03)	5.56 (21.68)	−0.96 [−8.97; 7.05]; 0.809
Health perceptions							
VX08-770-102 (adolescents or adults; not intended for children [12 to 13 years])							
	76	72.09 (18.91)	5.40 (18.36)	64	72.07 (18.93)	−5.74 (16.15)	7.57 [4.41; 10.73]; < 0.001 Hedges' g: 0.75 [0.41; 1.10]
VX08-770-103 (children [6 to 11 years])							
			Domain not provided in questionnaire for children from 6 to 11 years				
Additional information for study VX08-770-103 (CFQ-R – parent/caregiver version [children from 6 to 11 years], health-related quality of life domains)[d]							
Physical functioning	20	83.53 (20.80)	4.39 (1.00)	16	93.01 (15.03)	−0.79 (11.16)	−0.087 [−5.62; 5.45]; 0.975
Emotional functioning	20	86.67 (14.18)	0.01 (11.45)	16	84.46 (14.81)	0.49 (8.86)	−1.51 [−6.26; 3.23]; 0.519
Vitality	20	72.00 (16.69)	5.67 (13.56)	16	77.40 (18.60)	6.68 (15.91)	1.70 [−5.29; 8.68]; 0.624
Body image	20	85.01 (24.52)	10.00 (22.19)	16	87.66 (18.23)	0 (18.47)	3.14 [−3.26; 9.54]; 0.324
Eating problems	20	85.00 (22.23)	8.34 (26.21)	16	76.84 (25.66)	5.96 (16.79)	−1.81 [−10.67; 7.05]; 0.680
Treatment burden	20	64.46 (17.53)	−0.56 (17.45)	16	59.88 (26.45)	−2.38 (26.90)	2.40 [−7.17; 11.98]; 0.613
Health perceptions	20	77.80 (16.91)	6.11 (12.72)	16	80.26 (21.41)	−0.79 (19.21)	−0.13 [−7.67; 7.41]; 0.973
School functioning	20	76.12 (21.42)	6.11 (17.45)	16	78.41 (18.85)	−3.17 (24.79)	2.66 [−6.65; 11.97]; 0.565

(continued)

Table 15: 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 MMRM for the calculation of the effect estimation; the values at baseline may be based on more patients, the values at the end of study may be based on fewer patients.
b: Refers to the change from baseline to the last time point of measurement.
c: MMRM; 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. Model: dependent variable absolute change from baseline; study time point and treatment as fixed effects; adjusted for continuous baseline values of age, FEV1 (in % of predicted normal), and – for CFQ-R domains – CFQ-R domain score.
d: Higher values indicate better health-related quality of life or symptoms; a positive group difference corresponds to an advantage of ivacaftor.
e: MMRM; effect presents the difference between the treatment groups of the changes from the start of the study until week 48. Model: dependent variable absolute change from baseline; treatment×study time point, study time point and treatment as fixed effects; adjusted for continuous baseline values of age, EQ-5D VAS score and FEV1 (in % of predicted normal).
BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire Revised; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; 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; VAS: visual analogue scale; vs.: versus

Based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes due to the high risk of bias and the limited implementation of the ACT (as shown in Sections 2.3.2 and 2.4.2). For the VX08-770-103 study, the company derived the added benefit at outcome level on the basis of the total population of the study. For the present benefit assessment, however, the subpopulation of patients weighing 25 kg or more was considered relevant and was used for the benefit assessment (see Section 2.3.2). In the following result description, deviations from the company are therefore not described for the individual outcomes of the VX08-770-103 study.

Mortality

All-cause mortality

No deaths occurred during the studies VX08-770-102 and VX08-770-103. 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 company also described that no deaths during the studies were reported.

Morbidity

Pulmonary exacerbations

For the outcome “pulmonary exacerbations”, the VX08-770-102 study showed a statistically significant difference in favour of ivacaftor + BSC versus BSC on the basis of the event rates (number of events/patient years). This resulted in a hint of an added benefit of ivacaftor + BSC in comparison with BSC for patients aged 12 years and older.

This deviates from the assessment of the company, which derived an indication of an added benefit on the basis of the event rates for the VX08-770-102 study.

There were no effect estimations on the basis of the event rates (number of events/patient years) for the VX08-770-103 study. Based on analyses of patients with at least one event, there was no statistically significant difference 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 for children between 6 and 11 years of age; an added benefit is therefore not proven.

Hospitalizations due to pulmonary exacerbations

For the outcome "hospitalizations due to pulmonary exacerbations", the VX08-770-102 study showed no statistically significant difference between the treatment groups on the basis of the event rates (number of events/patient years). This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for patients aged 12 years and older for this outcome; an added benefit is therefore not proven.

This deviates from the company's approach insofar as the company used several types of analysis for the derivation of the added benefit (see Section 2.7.4.3.2 of the full dossier assessment). On the basis of the event rates, it reached the same conclusion on the added benefit.

There were no effect estimations on the basis of the event rates (number of events/patient years) for the VX08-770-103 study. Based on analyses of patients with at least one event, there was no statistically significant difference between the treatment groups for the outcome "hospitalizations due to pulmonary exacerbations". This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for this outcome for children between 6 and 11 years of age; an added benefit is therefore not proven.

Symptoms measured using the CFQ-R

The VX08-770-102 study measured symptom outcomes for adolescents aged 14 years and older and adults using the domains "respiratory symptoms", "digestive symptoms" and "weight" of the disease-specific patient-reported instrument CFQ-R. For children between 12 and 13 years of age in the VX08-770-102 study and for children between 6 and 11 years of age in the VX08-770-103 study, the domains "respiratory symptoms" and "digestive symptoms" were also recorded directly from the children with a CFQ-R patient version. The domain "weight" is not included in the questionnaire versions for children between 6 and 11 years and children between 12 and 13 years of age. A parent/caregiver version of the CFQ-R was additionally used in the studies for these age groups. This questionnaire asks parents and caregivers about symptoms in the domains "respiratory symptoms", "digestive symptoms" and "weight". The patient version of the questionnaire was primarily used for the assessment of the added benefit. The parent/caregiver version is presented as additional information for the VX08-770-103 study in the present benefit assessment.

Due to the small number of children aged 12 and 13 years in study VX08-770-102, no supplementary presentation of the parent/caregiver version is provided for this study (ivacaftor + BSC: 4 of 83 children versus placebo + BSC: 6 of 78 children in the joint analysis). For the benefit assessment, joint analyses of children aged 12 and 13 years and adolescents aged 14 years and older and adults were used for this study (see Section 2.7.4.3.2 of the full dossier assessment). This deviates from the approach of the company, which used the parent/caregiver version in addition to the joint analyses for the derivation of the added benefit.

Patients aged 12 years and older

- Domain "respiratory symptoms"

For the VX08-770-102 study, the joint analyses of the CFQ-R patient versions of patients aged 12 years and older showed a statistically significant difference in favour of ivacaftor + BSC versus BSC 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 for patients aged 12 years and older.

The assessment regarding the domain "respiratory symptoms" deviates from that of the company, which derived an indication of an added benefit both on the basis of responder analyses and on the basis of mean differences. Besides, the company also used the parent/caregiver version of the CFQ-R for children aged 12 and 13 years for the derivation of the added benefit.

- Domains "digestive symptoms" and "weight"

In the domains "digestive symptoms" and "weight", no statistically significant differences were shown between the treatment groups for the VX08-770-102 study. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for these 2 domains for the age groups investigated in each case; an added benefit is therefore not proven.

The assessment of the added benefit for the domains "digestive symptoms" and "weight" concurs with that of the company.

Children between 6 and 11 years of age

- Domains "respiratory symptoms" and "digestive symptoms"

For the VX08-770-103 study, no statistically significant differences were shown between the treatment groups in each of the domains "respiratory symptoms" and "digestive symptoms". This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for these 2 domains for children between 6 and 11 years of age; an added benefit is therefore not proven. This result is consistent with the results of the CFQ-R (parent/caregiver version).

- Domain “weight”

For the domain “weight”, there are no data for children between 6 and 11 years of age; an added benefit is therefore not proven.

Deviating from the present assessment, the company allocated the domains “respiratory symptoms”, “digestive symptoms” and “weight” to health-related quality of life for both studies.

Health status measured using the EQ-5D VAS

In the VX08-770-102 study, no statistically significant difference was shown between the treatment groups for the outcome “health status”. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC; an added benefit is therefore not proven.

This concurs with the company’s assessment.

The outcome “health status” was not recorded in the VX08-770-103 study.

Health-related quality of life

Study VX08-770-102 recorded health-related quality of life for adolescents aged 14 years and older and adults using the following domains of the disease-specific patient-reported CFQ-R: physical functioning, emotional functioning, vitality, social functioning, role functioning, body image, eating problems, treatment burden, and health perceptions. For children between 12 and 13 years of age in the VX08-770-102 study and for children between 6 and 11 years of age in the VX08-770-103 study, the domains “physical functioning, “emotional functioning”, “social functioning”, “body image”, “eating problems” and “treatment burden” were also recorded directly from the children with a CFQ-R patient version. The domains “vitality”, “role functioning” and “health perceptions” are not included in the questionnaire versions for children between 6 and 11 years and children between 12 and 13 years of age. A parent/caregiver version of the CFQ-R was additionally used in the studies for these age groups. This questionnaire asks parents and caregivers about health-related quality of life using the domains of physical functioning, vitality, emotional functioning, school functioning, body image, eating problems, treatment burden, and health perceptions. The patient version of the questionnaire was primarily used for the assessment of the added benefit. The parent/caregiver version is presented as additional information for the VX08-770-103 study in the present benefit assessment.

Due to the small number of children aged 12 and 13 years in study VX08-770-102, no supplementary presentation is provided for this study (see above). For the benefit assessment, joint analyses of children aged 12 and 13 years and adolescents aged 14 years and older and adults were used for this study (see Section 2.7.4.3.2 of the full dossier assessment). This deviates from the approach of the company, which used the parent/caregiver version in addition to the joint analyses for the derivation of the added benefit.

Patients aged 12 years and older

- Domains “emotional functioning”, “role functioning” and “body image”

For the VX08-770-102 study, no statistically significant differences were shown between the treatment groups in each of the domains “emotional functioning”, “role functioning” and “body image”. This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for these domains for the age groups investigated in each case; an added benefit is therefore not proven.

- Domains “social functioning”, “eating problems” and “treatment burden”

For the VX08-770-102 study, statistically significant differences in favour of ivacaftor were shown in each of the domains “social functioning”, “eating problems” and “treatment burden”. However, the respective 95% CI of the SMD in the form of Hedges’ g for the domains was not completely outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. For patients aged 12 years and older, this resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for each of the CFQ-R domains “social functioning”, “eating problems” and “treatment burden”; an added benefit is therefore not proven.

- Domains “physical functioning” and “vitality”

For the domains “physical functioning” and “vitality”, statistically significant differences in favour of ivacaftor + BSC were shown in the total population of the VX08-770-102 study. However, the respective 95% CI of the SMD in the form of Hedges’ g for both domains was not completely outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. However, there were effect modifications by the characteristic “FEV1 at baseline” in each case. For the domains, there was a hint of an added benefit of ivacaftor + BSC in comparison with BSC for patients with baseline FEV1 of < 70% of predicted normal for the age groups investigated in each case (physical functioning: patients aged 12 years and older; vitality: patients aged 14 years and older). In contrast, no added benefit was shown for patients with baseline FEV1 of ≥ 70% of predicted normal (see Section 2.4.4).

- Domain “health perceptions”

The VX08-770-102 study showed a statistically significant difference in favour of ivacaftor + BSC versus BSC for the domain “health perceptions”. 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. For the CFQ-R domain “health perceptions”, this resulted in a hint of an added benefit of ivacaftor + BSC in comparison with BSC for adolescents and adults aged 14 years and older.

For patients aged 12 years and older, the assessments of the added benefit for the health-related quality of life domains of the CFQ-R deviate from those of the company. It derived indications of an added benefit for domains with statistically significant group differences regardless of the

relevance of the effect and possible effect modifiers. The company also used the parent/caregiver version of the CFQ-R for children aged 12 and 13 years for the derivation of the added benefit.

Children between 6 and 11 years of age

For the VX08-770-103 study, no statistically significant differences were shown between the treatment groups in each of the domains "physical functioning", "emotional functioning", "social functioning", "body image", "eating problems" and "treatment burden". This resulted in no hint of an added benefit of ivacaftor + BSC in comparison with BSC for children between 6 and 11 years of age; an added benefit is therefore not proven. This result is consistent with the results of the CFQ-R (parent/caregiver version).

Side effects

Serious adverse events

In the recording of SAEs, the studies VX08-770-102 and VX08-770-103 included, among others, pulmonary exacerbations in the recording of the PT "cystic fibrosis lung" (see Section 2.7.4.3.2 of the full dossier assessment). The results on the outcome were therefore not usable.

This deviates from the approach of the company, which derived an indication of lesser harm from ivacaftor + BSC on the basis of the data on the outcome "SAEs" from the VX08-770-102 study, and which found no indication of greater or lesser harm on the basis of the data on the total population for the VX08-770-103 study.

Discontinuation due to adverse events

In the studies VX08-770-102 and VX08-770-103, no statistically significant differences between the treatment groups were shown for the outcome "discontinuation due to AEs". 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

Rash

The VX08-770-102 study showed a statistically significant difference to the disadvantage of ivacaftor + BSC versus BSC for the outcome "rash". The extent of the effect was no more than marginal, however. This resulted in no hint of greater or lesser harm from ivacaftor + BSC in comparison with BSC for this outcome; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which derived an indication of greater harm for the VX08-770-102 study.

For the VX08-770-103 study, the company did not present any data for the relevant subpopulation. Therefore, the outcome cannot be assessed for this study.

Dizziness

The VX08-770-102 study showed a statistically significant difference to the disadvantage of ivacaftor + BSC versus BSC for the outcome "dizziness". This resulted in a hint of greater harm from ivacaftor + BSC in comparison with BSC for this outcome.

This deviates from the assessment of the company, which derived an indication of greater harm for the VX08-770-102 study.

For the VX08-770-103 study, the company did not present any data for the relevant subpopulation. Therefore, the outcome cannot be assessed for this study.

2.4.4 Subgroups and other effect modifiers

The following subgroups were used for the present assessment:

- age (< 18 years, ≥ 18 years)
- sex (female, male)
- region (North America, Europe, Australia)
- FEV1 (in % of predicted normal) at baseline (< 70%, ≥ 70%)
- *Pseudomonas aeruginosa* infection status at baseline

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.

Table 16 summarizes the subgroup results from study VX08-770-102 on the comparison of ivacaftor with BSC in patients with CF aged 12 years and older with a G551D mutation in the CFTR gene.

For the VX08-770-103 study on the comparison of ivacaftor with BSC in children with CF between 6 and 11 years of age with a G551D mutation in the CFTR gene, the company did not present any subgroup analyses for the relevant subpopulation, but only for the total population of the study. These analyses were not used for the benefit assessment.

Table 16: Subgroups (health-related quality of life, continuous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study Outcome	Ivacaftor + BSC			Placebo + BSC			Ivacaftor + BSC vs. placebo + BSC
Characteristic Subgroup	N[a]	Values at baseline mean (SD)	Change at end of study mean (SD)	N[a]	Values at baseline mean (SD)	Change at end of study mean (SD)	MD[b] [95% CI]; p-value
VX08-770-102 (≥ 12 years)							
Health-related quality of life (CFQ-R)[c]							
Physical functioning (children [12 to 13 years] and adolescents or adults – pooled)							
Geographical region							
North America	50	77.62 (24.29)	3.95 (14.20)	49	81.30 (22.95)	−6.43 (18.36)	3.90 [−0.03; 7.84]; 0.052
Europe	20	72.02 (24.15)	7.95 (17.51)	12	73.27 (24.17)	3.61 (14.60)	0.44 [−6.27; 7.15]; 0.893
Australia	10	76.67 (24.85)	12.51 (16.67)	9	87.34 (10.34)	−7.74 (9.75)	11.13 [−3.92; 26.17]; 0.134
Total						Interaction:	p-value = 0.027[d]
FEV1 (in % of predicted normal) at baseline							
< 70%	47	70.26 (24.42)	4.76 (14.78)	39	73.02 (24.79)	−5.15 (16.98)	8.35 [3.95; 12.75]; < 0.001 Hedges' g: 0.75 [0.31; 1.19]
≥ 70%	33	84.43 (21.43)	7.94 (16.50)	31	90.09 (13.51)	−3.96 (17.83)	−2.07 [−5.46; 1.32]; 0.227
Total						Interaction:	p-value = 0.009[d]
Vitality (adolescents or adults; not intended for children [12 to 13 years])							
FEV1 (in % of predicted normal) at baseline							
< 70%	46	64.31 (16.17)	−0.74 (19.20)	36	63.28 (19.19)	−6.31 (15.32)	9.06 [3.92; 14.19]; < 0.001 Hedges' g: 0.77 [0.31; 1.22]
≥ 70%	30	64.17 (16.69)	6.79 (14.06)	28	68.39 (18.42)	−0.66 (15.94)	0.85 [−3.60; 5.30]; 0.702
Total						Interaction:	p-value = 0.017[d]

(continued)

Table 16: Subgroups (health-related quality of life, continuous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

Study Outcome	Ivacaftor + BSC			Placebo + BSC			Ivacaftor + BSC vs. placebo + BSC
Characteristic Subgroup	N[a]	Values at baseline mean (SD)	Change at end of study mean (SD)	N[a]	Values at baseline mean (SD)	Change at end of study mean (SD)	MD[b] [95% CI]; p-value
Health perceptions (adolescents or adults; not intended for children [12 to 13 years])							
Geographical region							
North America	47	75.20 (17.83)	5.07 (16.83)	46	71.64 (20.05)	−5.69 (17.05)	5.86 [1.91; 9.80]; 0.004 Hedges' g: 0.58 [0.16; 1.00]
Europe	19	68.42 (21.70)	−1.96 (13.73)	11	71.31 (18.64)	−7.06 (15.91)	4.82 [−1.42; 11.07]; 0.124
North America and Europe							5.56 [2.23; 8.90]; 0.001[e] Hedges' g: 0.59 [0.23; 0.95][f]
Australia	10	64.46 (16.42)	20.98 (25.12)	7	76.21 (11.87)	−3.70 (11.46)	22.83 [7.61; 38.05]; 0.007 Hedges' g: 1.83 [0.63; 3.03]
Total							p-value = 0.001[d]

a: Number of patients considered in the MMRM for the calculation of the effect estimation; the values at baseline may be based on more patients, the values at the end of study may be based on fewer patients.
b: MMRM. The following is averaged in the effect formation across all time points of measurement after baseline: the differences of the changes from baseline to the respective time point of measurement between the arms. Model: dependent variable absolute change from baseline; time point of measurement and treatment as fixed effects; adjusted for continuous baseline values of age and CFQ-R domain score. Additionally adjusted for the continuous baseline value of FEV1 (in % of predicted normal) in the subgroup characteristic of geographical region.
c: Higher values indicate better symptoms/health-related quality of life; a positive group difference corresponds to an advantage of ivacaftor.
d: p-value on the interaction test of the company according to the original division of the subgroups.
e: Institute's calculation of the meta-analysis.
f: Institute's calculation.

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

For the VX08-770-102 study, there was an effect modification by the characteristic "geographical region" for the CFQ-R domain "physical functioning". Pairwise comparisons of the different regions showed no effect modifications for Europe versus North America

(interaction p-value: 0.383) or North America versus Australia (interaction p-value: 0.363). The derivation of the added benefit for this domain was therefore based on the total population.

There was an additional effect modification by the characteristic "baseline FEV1 (in % of predicted normal)" for the domain "physical functioning". There was an additional effect modification by this characteristic also for the domain "vitality". For patients with a baseline FEV1 (in % of predicted normal) of < 70%, there was a statistically significant difference in favour of ivacaftor + BSC between the treatment groups. In each case, the 95% CI was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. For each of the domains "physical functioning" and "vitality", this resulted in a hint of an added benefit of ivacaftor + BSC in comparison with BSC for patients with a baseline FEV1 (in % of predicted normal) of < 70%.

In contrast, there were no statistically significant differences between the treatment groups for the domains "physical functioning" and "vitality" in patients with a baseline FEV1 (in % of predicted normal) of ≥ 70%; an added benefit for these patients is therefore not proven.

There was an effect modification by the characteristic "geographical region" for the domain "health perceptions". Pairwise comparisons of the different regions showed no effect modification for Europe versus North America (interaction p-value: 0.783), which is why the regions were considered jointly. The pairwise comparison of North America versus Australia showed an effect modification (interaction p-value: 0.034), which is why Australia was considered separately from the other 2 regions. A statistically significant difference between the treatment groups in favour of ivacaftor + BSC versus BSC was shown both for North America/Europe and for Australia. In each case, the 95% CI was completely above the irrelevance threshold of 0.2. This corresponds to the results of the total population of the VX08-770-102 study. The added benefit was therefore derived on the basis of the total population.

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 17).

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 classification of these outcomes is justified below.

Based on the definition for the outcome "pulmonary exacerbations" (see Section 2.7.4.3.2 of the full dossier assessment), severe or serious events were not recorded per se. Hospitalizations due to pulmonary exacerbations overall did not constitute the majority of the events of pulmonary exacerbations. For this reason, the outcome "pulmonary exacerbations" was allocated to the outcome category "non-serious/non-severe symptoms/late complications" in the present assessment.

The company did not provide any information as to whether the information on the CFQ-R domain "respiratory symptoms" referred to severe or serious 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 AEs "rash" and "dizziness" were outcomes of the categories "non-severe/non-serious side effects", as all of the events included in the outcomes were non-severe/non-serious.

Table 17: Extent of added benefit at outcome level: ivacaftor + BSC vs. placebo + BSC

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ivacaftor + BSC vs. placebo + BSC** **Event rate or mean change or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality		
VX08-770-102 (≥ 12 years)	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
VX08-770-103 (6–11 years)	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Pulmonary exacerbations		
VX08-770-102 (≥ 12 years)	Rate: 0.63 vs. 1.48 rate ratio: 0.43 [0.27; 0.68]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit, extent: "considerable"
VX08-770-103 (6–11 years)	20.0% vs. 16.7% RR: 1.20 [0.31; 4.65]; p = 0.847	Lesser benefit/added benefit not proven
Hospitalizations due to pulmonary exacerbations		
VX08-770-102 (≥ 12 years)	Rate: 0.28 vs. 0.46 rate ratio: 0.64 [0.32; 1.26]; p = 0.195	Lesser benefit/added benefit not proven
VX08-770-103 (6–11 years)	10.0% vs. 5.6% RR: 1.80 [0.18; 18.21]; p = 0.712	Lesser benefit/added benefit not proven
Symptoms (CFQ-R, symptom domains)		
Respiratory symptoms		
VX08-770-102 (≥ 12 years)	Mean change: 6.39 vs. -3.93 MD: 8.60 [5.32; 11.87]; p < 0.001 Hedges' g: 0.84 [0.50; 1.17][c] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
VX08-770-103 (6–11 years)	Mean change: 6.25 vs. 2.97 MD: 5.42 [−2.98; 13.82]; p = 0.198	Lesser benefit/added benefit not proven
Digestive symptoms		
VX08-770-102 (≥ 12 years)	Mean change: 0.60 vs. −1.79 MD: 0.48 [−2.29; 3.25]; p = 0.732	Lesser benefit/added benefit not proven
VX08-770-103 (6–11 years)	Mean change: 10.00 vs. 11.90 MD: 5.55 [−4.83; 15.93]; p = 0.284	Lesser benefit/added benefit not proven
Weight		
VX08-770-102 (≥ 14 years[d])	Mean change: 8.33 vs. −4.02 MD: 5.28 [−0.08; 10.63]; p = 0.053	Lesser benefit/added benefit not proven
VX08-770-103 (6–11 years)	Domain not provided in questionnaire for children from 6 to 11 years	–

(continued)

Table 17: Extent of added benefit at outcome level: ivacaftor + BSC vs. placebo + BSC (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ivacaftor + BSC vs. placebo + BSC** **Event rate or mean change or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Health status		
EQ-5D VAS		
VX08-770-102 (≥ 12 years)	Mean change: 3.06 vs. −0.78 MD: 3.96 [−0.23; 8.14]; p = 0.064	Lesser benefit/added benefit not proven
VX08-770-103 (6–11 years)	Outcome not recorded	–
Health-related quality of life (CFQ-R)		
Physical functioning		
VX08-770-102 (≥ 12 years) FEV1 (in % of predicted normal) at baseline		
< 70%	Mean change: 4.76 vs. −5.15 MD: 8.35 [3.95; 12.75]; p < 0.001 Hedges' g: 0.75 [0.31; 1.19][c] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
≥ 70%	Mean change: 7.94 vs. −3.96 MD: −2.07 [−5.46; 1.32]; p = 0.227	Lesser benefit/added benefit not proven
VX08-770-103 (6–11 years)	Mean change: 2.79 vs. 3.58 MD: −1.11 [−7.25; 5.02]; p = 0.714	Lesser benefit/added benefit not proven
Emotional functioning		
VX08-770-102 (≥ 12 years)	Mean change: 1.59 vs. −1.40 MD: 2.12 [−0.38; 4.63]; p = 0.096	Lesser benefit/added benefit not proven
VX08-770-103 (6–11 years)	Mean change: 7.50 vs. 5.96 MD: 1.31 [−2.21; 4.83]; p = 0.455	Lesser benefit/added benefit not proven
Vitality		
VX08-770-102 (≥ 14 years[d]) FEV1 (in % of predicted normal) at baseline		
< 70%	Mean change: −0.74 vs. −6.31 MD: 9.06 [3.92; 14.19]; p < 0.001 Hedges' g: 0.77 [0.31; 1.22][c] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
≥ 70%	Mean change: 6.79 vs. −0.66 MD: 0.85 [−3.60; 5.30]; p = 0.702	Lesser benefit/added benefit not proven
VX08-770-103 (6–11 years)	Domain not provided in questionnaire for children from 6 to 11 years	–

(continued)

Table 17: Extent of added benefit at outcome level: ivacaftor + BSC vs. placebo + BSC (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ivacaftor + BSC vs. placebo + BSC** **Event rate or mean change or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Social functioning		
VX08-770-102 (≥ 12 years)	Mean change: 4.79 vs. −1.50 MD: 4.25 [1.52; 6.98]; p = 0.003 Hedges' g: 0.48 [0.16; 0.81][c]	Lesser benefit/added benefit not proven
VX08-770-103 (6–11 years)	Mean change: 5.48 vs. 0.79 MD: 3.10 [−2.12; 8.32]; p = 0.235	Lesser benefit/added benefit not proven
Role functioning		
VX08-770-102 (≥ 14 years[d])	Mean change: 1.38 vs. −3.45 MD: −0.58 [−3.10; 1.94]; p = 0.651	Lesser benefit/added benefit not proven
VX08-770-103 (6–11 years)	Domain not provided in questionnaire for children from 6 to 11 years	–
Body image		
VX08-770-102 (≥ 12 years)	Mean change: 3.00 vs. −2.51 MD: 2.70 [−0.38; 5.77]; p = 0.086	Lesser benefit/added benefit not proven
VX08-770-103 (6–11 years)	Mean change: 6.66 vs. 0.79 MD: 2.71 [−2.00; 7.43]; p = 0.250	Lesser benefit/added benefit not proven
Eating problems		
VX08-770-102 (≥ 12 years)	Mean change: 3.45 vs. −2.33 MD: 3.34 [1.23; 5.44]; p = 0.002 Hedges' g: 0.50 [0.17; 0.83][c]	Lesser benefit/added benefit not proven
VX08-770-103 (6–11 years)	Mean change: 13.33 vs. 6.34 MD: 1.91 [−4.67; 8.48]; p = 0.559	Lesser benefit/added benefit not proven
Treatment burden		
VX08-770-102 (≥ 12 years)	Mean change: 6.15 vs. −0.72 MD: 3.31 [0.12; 6.50]; p = 0.042 Hedges' g: 0.32 [−0.01; 0.64][c]	Lesser benefit/added benefit not proven
VX08-770-103 (6–11 years)	Mean change: 0.56 vs. 5.56 MD: −0.96 [−8.97; 7.05]; p = 0.809	Lesser benefit/added benefit not proven
Health perceptions		
VX08-770-102 (≥ 14 years[d])	Mean change: 5.40 vs. −5.74 MD: 7.57 [4.41; 10.73]; p < 0.001 Hedges' g: 0.75 [0.41; 1.10][c] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
VX08-770-103 (6–11 years)	Domain not provided in questionnaire for children from 6 to 11 years	–

(continued)

Table 17: Extent of added benefit at outcome level: ivacaftor + BSC vs. placebo + BSC (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ivacaftor + BSC vs. placebo + BSC** **Event rate or mean change or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
Serious adverse events		
VX08-770-102 (≥ 12 years)	No usable data	Greater/lesser harm not proven
VX08-770-103 (6–11 years)	No usable data	Greater/lesser harm not proven
Discontinuation due to AEs		
VX08-770-102 (≥ 12 years)	1.2% vs. 5.1% RR: 0.23 [0.03; 2.06]; p = 0.153	Greater/lesser harm not proven
VX08-770-103 (6–11 years)	0% vs. 5.6% RR: 0.30 [0.01; 6.97]; p = 0.353	Greater/lesser harm not proven
Rash (PT, AE)		
VX08-770-102 (≥ 12 years)	14.5% vs. 5.1% RR: 2.82 [0.95; 8.37] RR[e]: 0.35 [0.12; 1.05] p = 0.049	Outcome category: Non-serious/non-severe side effects $0.90 \leq CI_u$ lesser benefit/added benefit not proven[f]
VX08-770-103 (6–11 years)	No data for the relevant subpopulation	Greater/lesser harm not proven
Dizziness (PT, AE)		
VX08-770-102 (≥ 12 years)	12.0% vs. 1.3% RR: 9.40 [1.23; 71.72] RR[e]: 0.11 [0.01; 0.81] p = 0.007 Probability: "hint"	Outcome category: Non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ Greater harm, extent: "minor"
VX08-770-103 (6–11 years)	No data for the relevant subpopulation	Greater/lesser harm not proven

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the 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: Domain is not provided in questionnaire for children between 12 and 13 years of age.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire Revised; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FEV1: forced expiratory volume in 1 second; MD: mean difference; n_E: number of events; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of ivacaftor + BSC compared with BSC

Positive effects	Negative effects
VX08-770-102 (≥ 12 years)	
Non-serious/non-severe symptoms/late complications ▪ Pulmonary exacerbations: hint of an added benefit – extent: "considerable" ▪ Symptoms (CFQ-R) domain "respiratory symptoms": hint of an added benefit – extent: "non-quantifiable"	–
Health-related quality of life (CFQ-R) ▪ Domain "physical functioning" ▫ FEV1 (in % of predicted normal) at baseline (< 70%): hint of an added benefit – extent: "non-quantifiable" ▪ Domain "vitality" ▫ FEV1 (in % of predicted normal) at baseline (< 70%, ≥ 14 years): hint of an added benefit – extent: "non-quantifiable" ▪ Domain "health perceptions" (≥ 14 years): hint of an added benefit – extent: "non-quantifiable"	–
–	Non-serious/non-severe side effects ▪ Dizziness (PT, AE): hint of greater harm – extent: "minor"
No usable data on SAEs available	
VX08-770-103 (6–11 years)	
–	–
AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire Revised; FEV1: forced expiratory volume in 1 second; PT: Preferred Term; SAE: serious adverse event	

Patients aged 12 years and older

Based on the VX08-770-102 study, several positive effects with the probability "hint" of an added benefit were shown for patients aged 12 years and older. This concerns morbidity in the outcome "pulmonary exacerbations", symptom outcomes (recorded using the CFQ-R domain "respiratory symptoms") but also health-related quality of life in some CFQ-R domains (physical functioning, vitality and health perceptions). The extent of these effects was only quantifiable for the outcome "pulmonary exacerbations" and was rated as "considerable". In contrast, there was a hint of greater harm of minor extent based on one specific AE (dizziness) on the side of negative effects.

The positive effects outweighed the negative effects. Besides the improvements in the outcomes "pulmonary exacerbations" and "symptoms", there were some positive effects in health-related quality of life. However, uncertainty remained about the negative effects, as no usable data were available for the outcome "SAEs". In summary, there is therefore a hint of a minor added benefit of ivacaftor + BSC versus the ACT BSC for patients with CF aged 12 years and older and weighing 25 kg or more who have the G551D gating mutation in the CFTR gene.

Children between 6 and 11 years of age

For the VX08-770-103 study, there were neither positive nor negative effects of ivacaftor + BSC in comparison with BSC. There is therefore no hint of an added benefit of ivacaftor + BSC versus the ACT BSC for children with CF between 6 and 11 years of age and weighing 25 kg or more who have the G551D gating mutation in the CFTR gene. An added benefit is therefore not proven.

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

Table 19: Ivacaftor – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Children with cystic fibrosis between 6 and 11 years of age and weighing 25 kg or more who have the G551D gating mutation in the CFTR gene	BSC[b]	Added benefit not proven
Patients with cystic fibrosis aged 12 years and older and weighing 25 kg or more who have the G551D gating mutation in the CFTR gene	BSC[b]	Hint of minor added benefit

a: Presentation of the respective ACT specified by the G-BA.
b: 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.
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 major added benefit for both age groups jointly.

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

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2012. In this assessment, the G-BA had determined a considerable added benefit of ivacaftor for patients aged 12 years and older and a minor added benefit for children between 6 and 11 years of age. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

2.6 List of included studies

Study VX08-770-102

Borowitz D, Lubarsky B, Wilschanski M, Munck A, Gelfond D, Bodewes F et al. Nutritional status improved in cystic fibrosis patients with the G551D mutation after treatment with ivacaftor. Dig Dis Sci 2016; 61(1): 198-207.

Flume PA, Wainwright CE, Elizabeth Tullis D, Rodriguez S, Niknian M, Higgins M et al. Recovery of lung function following a pulmonary exacerbation in patients with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor. J Cyst Fibros 2018; 17(1): 83-88.

Konstan MW, Plant BJ, Elborn JS, Rodriguez S, Munck A, Ahrens R et al. Efficacy response in CF patients treated with ivacaftor: post-hoc analysis. Pediatr Pulmonol 2015; 50(5): 447-455.

Quittner A, Suthoff E, Rendas-Baum R, Bayliss MS, Sermet-Gaudelus I, Castiglione B et al. Effect of ivacaftor treatment in patients with cystic fibrosis and the G551D-CFTR mutation: patient-reported outcomes in the STRIVE randomized, controlled trial. Health Qual Life Outcomes 2015; 13: 93.

Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011; 365(18): 1663-1672.

Solem CT, Vera-Llonch M, Liu S, Botteman M, Castiglione B. Impact of pulmonary exacerbations and lung function on generic health-related quality of life in patients with cystic fibrosis. Health Qual Life Outcomes 2016; 14: 63.

Vertex Pharmaceuticals. Study of ivacaftor in cystic fibrosis subjects aged 12 years and older with the G551D mutation (STRIVE): study results [online]. In: ClinicalTrials.gov. 18.01.2013 [Accessed: 18.09.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00909532.

Vertex Pharmaceuticals. A phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of VX 770 in subjects with cystic fibrosis and the G551D 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/2008-007416-15/results.

Vertex Pharmaceuticals. Study of ivacaftor in cystic fibrosis subjects aged 12 years and older with the G551D mutation (STRIVE): study details [online]. In: ClinicalTrials.gov. 18.01.2013 [Accessed: 18.09.2019]. URL: https://ClinicalTrials.gov/show/NCT00909532.

Vertex Pharmaceuticals. A phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of VX 770 in subjects with cystic fibrosis and the G551D mutation [online]. In: EU Clinical Trials Register. [Accessed: 18.09.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-007416-15.

Vertex Pharmaceuticals. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of VX-770 in subjects with cystic fibrosis and the G551D mutation: study VX08-770-102; clinical study report [unpublished]. 2011.

Vertex Pharmaceuticals. A phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of VX-770 in subjects with cystic fibrosis and the G551D mutation: study VX08-770-102; Zusatzanalysen [unpublished]. 2019.

Study VX08-770-103

Borowitz D, Lubarsky B, Wilschanski M, Munck A, Gelfond D, Bodewes F et al. Nutritional status improved in cystic fibrosis patients with the G551D mutation after treatment with ivacaftor. Dig Dis Sci 2016; 61(1): 198-207.

Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. Am J Respir Crit Care Med 2013; 187(11): 1219-1225.

Konstan MW, Plant BJ, Elborn JS, Rodriguez S, Munck A, Ahrens R et al. Efficacy response in CF patients treated with ivacaftor: post-hoc analysis. Pediatr Pulmonol 2015; 50(5): 447-455.

Stalvey MS, Pace J, Niknian M, Higgins MN, Tarn V, Davis J et al. Growth in prepubertal children with cystic fibrosis treated with ivacaftor. Pediatrics 2017; 139(2): e20162522.

Vertex Pharmaceuticals. Study of ivacaftor in cystic fibrosis subjects aged 6 to 11 years with the G551D mutation (ENVISION): study results [online]. In: ClinicalTrials.gov. 21.08.2012 [Accessed: 18.09.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00909727.

Vertex Pharmaceuticals. A phase 3, 2-part, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the pharmacokinetics, efficacy and safety of VX-770 in subjects aged 6 to 11 years with cystic fibrosis and the G551D mutation: clinical trial results [online]. In: EU Clinical Trials Register. 13.07.2016 [Accessed: 18.09.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-007479-26/results.

Vertex Pharmaceuticals. Study of ivacaftor in cystic fibrosis subjects aged 6 to 11 years with the G551D mutation (ENVISION): study details [online]. In: ClinicalTrials.gov. 21.08.2012 [Accessed: 18.09.2019]. URL: https://ClinicalTrials.gov/show/NCT00909727.

Vertex Pharmaceuticals. A phase 3, 2 part, randomized, double-blind, placebo controlled, parallel group study to evaluate the pharmacokinetics, efficacy and safety of VX 770 in subjects aged 6 to 11 years with cystic fibrosis and the G551D mutation [online]. In: EU Clinical Trials Register. [Accessed: 18.09.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-007479-26.

Vertex Pharmaceuticals. A phase 3, 2-part, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the pharmacokinetics, efficacy, and safety of VX-770 in subjects aged 6 to 11 years with cystic fibrosis and the G551D mutation: study VX08-770-103; clinical study report [unpublished]. 2012.

Vertex Pharmaceuticals. A phase 3, 2-part, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the pharmacokinetics, efficacy, and safety of VX-770 in subjects aged 6 to 11 years with cystic fibrosis and the G551D mutation: study VX08-770-103; 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. Fachinformation: Kalydeco 150 mg Filmtabletten. 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/a19-65-ivacaftor-cystic-fibrosis-6-years-and-older-with-g551d-mutation-benefit-assessment-according-to-35a-social-code-book-v.12568.html.