IQWiG Reports – Commission No. A19-66

Ivacaftor (cystic fibrosis, 6 years and older, non-G551D gating 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, non-G551D Gating-Mutation) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 November 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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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
EMA	European Medicines Agency
FEV1	forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model repeated measures
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ivacaftor. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 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 patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more. The patients must have one of the following 8 gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

Table 2: Research questions of the benefit assessment of ivacaftor

Subindication	**ACT**[a]
Patients with CF aged 6 years and older and weighing at least 25 kg who have one of the following 8 gating (class III) mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R[b]	BSC
a: Presentation of the ACT specified by the G-BA. b: These 8 mutations belong to the group of non-G551D gating mutations. ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; 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.

Evidence provided by the company

The company presented the study VX12-770-111 for the assessment of the added benefit. This was a 2-part study. Part 1 had a randomized, double-blind, phase 3 crossover design, in which 8-week treatment with ivacaftor was compared with placebo. The patients received symptomatic concomitant medication during the study. However, this concomitant medication did not constitute a complete implementation of the ACT BSC (see below). Part 2 of the study consisted of an open-label treatment phase without comparator therapy. The company used only results of the 8-week randomized Part 1 for the derivation of the added benefit. Due to the treatment phase of only 8 weeks, the study included by the company is unsuitable for a benefit

assessment in the therapeutic indication of CF. CF is a chronic disease requiring lifelong treatment. No conclusions can be drawn on the basis of short-term studies as to whether short-term effects persist in the longer term. It is also not possible to record any effects that only become apparent in the longer term, such as for pulmonary exacerbations and their consequences or for adverse events (AEs).

The company justified the 8-week inclusion criterion it used with long-term results from studies in which patients with the G551D mutation were included. The transferal of results from patients with G551D mutation to those with non-G551D cannot be derived from the available results.

Overall, studies of at least 24 weeks are necessary to compare benefit and harm for the benefit assessment in the therapeutic indication of CF. Hence, the VX12-770-111 study was too short to be included in the present benefit assessment. However, due to the rarity of the mutations to be investigated and the fact that children are affected in the present therapeutic indication, the VX12-770-111 study and the corresponding short-term results are presented as supplementary information in the present dossier assessment. A conclusion on the added benefit is not derived from it.

Special features of the crossover study design

A crossover design only produces informative results if certain conditions are met:

1) Carry-over effects are negligible
2) The statistical analyses must make adequate provisions for period effects

Assuming that the 2 conditions described above are sufficiently fulfilled for the VX12-770-111 study, the short-term results of this study are presented as supplementary information in the present dossier assessment. Further information on the period effect and specific consequences of possible carry-over effects are described and considered in the assessment of the risk of bias of the short-term results below.

A crossover design is usually not adequate for irreversible outcomes. This concerns the outcomes “all-cause mortality” and “discontinuation due to AEs” (if the discontinuation did not allow participation in the following treatment periods). However, no deaths or discontinuations due to AEs occurred in the VX12-770-111 study.

Implementation of the appropriate comparator therapy

Regarding their ongoing symptomatic treatment at baseline, the study protocol of the VX12-770-111 study recommended that patients remain on stable CF medication from 4 weeks before baseline until end of study. Besides, inhaled hypertonic saline solution as concomitant medication was not allowed within 4 weeks before the first intake of the study medication until end of study.

The available information suggests that the patients were given a variety of drugs for symptomatic treatment of CF, including dornase alfa, as well as pancreatin and antibiotics, at the time point of study entry and during the treatment periods. Inhaled hypertonic saline solution was prohibited. It cannot be inferred from the data whether and how many patients had their concomitant treatment adjusted, for example in the sense of an increase in dose or frequency.

Hence, the concomitant treatment used in the VX12-770-111 study did not constitute a complete implementation of the ACT BSC. This assessment is based particularly on the exclusion of inhaled saline solution, a standard therapy in CF, and the concomitant medication that was to be maintained stable.

Short-term results of the study included by the company

Overall, the results from the VX12-770-111 study had a high risk of bias. The results on serious adverse events (SAEs) are not usable, as events attributable to the underlying disease were also recorded for the recording of side effects.

Morbidity

Pulmonary exacerbations

There was no statistically significant difference between the treatment groups both for patients aged 12 years and older (including adults) and for children from 6 to 11 years of age.

Hospitalization due to pulmonary exacerbations

There was 1 event under treatment with ivacaftor + BSC in patients aged 12 years and older, and 4 events under treatment with BSC in 8 weeks. The company did not present an effect measure or calculation on the statistical significance of the group difference. There was no statistically significant difference between the treatment groups for patients from 6 to 11 years of age.

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

In all age groups, symptom outcomes were recorded with the domains “respiratory symptoms” and “digestive symptoms” of the disease-specific patient-reported instrument CFQ-R. In compliance with the questionnaire, the domain “weight” was only recorded for patients aged 14 years and older.

- Domain “respiratory symptoms”

For patients aged 12 years and older, a statistically significant difference in favour of ivacaftor + BSC versus placebo + 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. Hence, there was a relevant effect.

There was no statistically significant difference between the treatment groups for children from 6 to 11 years of age.

- Domain "digestive symptoms"

There was no statistically significant difference between the treatment groups for children from 6 to 11 years of age and for patients aged 12 years and older (including adults) in the domain "digestive symptoms".

There was an effect modification by *Pseudomonas aeruginosa* infection at baseline, however. There was an advantage of ivacaftor + BSC versus placebo + BSC for patients without *Pseudomonas aeruginosa* infection at baseline.

- Domain "weight"

There was no statistically significant difference between the treatment groups for patients aged 14 years and older (including adults) in the domain "weight".

Health-related quality of life

In all age groups, health-related quality of life was recorded using the domains of physical functioning, emotional functioning, social functioning, body image, eating problems and treatment burden of the CFQ-R. In compliance with the questionnaire, the domains "vitality", "role functioning" and "health perceptions" were only recorded for patients aged 14 years and older.

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

A statistically significant difference between the treatment groups was neither shown for patients aged 12 years and older (including adults) nor for children from 6 to 11 years of age in any of the domains of physical functioning, emotional functioning, social functioning, body image, eating problems or treatment burden.

Domains "vitality" and "health perceptions"

Statistically significant effects in favour of ivacaftor + BSC versus placebo + BSC were shown for patients aged 14 years and older (including adults) in the domains of vitality and health perceptions. In both cases, the 95% CI of the SMD in the form of Hedges' g was above the irrelevance threshold of 0.2. Hence, there was a relevant effect in these 2 domains.

Domain "role functioning"

There was no statistically significant difference between the treatment groups in the domain "role functioning" for adolescents aged 14 years and older (including adults).

Side effects

Serious adverse events and discontinuation due to adverse events

The results on SAEs are not usable.

There was no discontinuation due to AEs. This resulted in no statistically significant difference between the treatment groups.

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:

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

Table 3: Ivacaftor – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Patients with CF aged 6 years and older and weighing at least 25 kg who have one of the following 8 gating (class III) mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R[b]	BSC	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. b: These 8 mutations belong to the group of non-G551D gating mutations. ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

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 2015. In this assessment, the G-BA had determined a minor added benefit of ivacaftor. 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.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of the present report is the assessment of the added benefit of ivacaftor in comparison with BSC as ACT in patients with CF aged 6 years and older and weighing 25 kg or more. The patients must have one of the following 8 gating (class III) mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

Table 4: Research questions of the benefit assessment of ivacaftor

Subindication	**ACT**[a]
Patients with CF aged 6 years and older and weighing at least 25 kg who have one of the following 8 gating (class III) mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R[b]	BSC
a: Presentation of the ACT specified by the G-BA. b: These 8 mutations belong to the group of non-G551D gating mutations. ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; 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 deviates from the company's inclusion criteria, which specified a minimum duration of 8 weeks.

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)

No relevant study was identified from the check.

Evidence provided by the company

In its dossier, the company used the VX12-770-111 study [3-8] for the assessment of the added benefit in the present research question. The VX12-770-111 study was a 2-part study. Part 1 had a randomized, double-blind, phase 3 crossover design, in which 8-week treatment with ivacaftor was compared with placebo. The patients received concomitant medication during the

study (see Section 2.3.2). This was followed by an open-label treatment phase without comparator therapy in Part 2 of the study. The company used only results of the 8-week randomized Part 1 for the derivation of the added benefit.

Due to the treatment phase of only 8 weeks, the VX12-770-111 study (Part 1) included by the company is unsuitable for a benefit assessment in the therapeutic indication of CF. CF is a chronic disease requiring lifelong treatment. The European Medicines Agency (EMA) guideline recommends a minimum study duration of 6 months for the investigation of a clinical outcome [9]. IQWiG's *General Methods* also consider long-term studies to be necessary for the benefit assessment in chronic diseases [1]. Short-term studies are inadequate for the benefit assessment in the therapeutic indication of CF, as ivacaftor is a long-term treatment. No conclusions can be drawn on the basis of short-term studies as to whether short-term effects persist in the longer term. It is also not possible to record any effects that only become apparent in the longer term, such as for pulmonary exacerbations and their consequences or AEs. Pulmonary exacerbations are a common cause of lung damage or death in patients with CF [10-13]. In Module 4 B, the company justified the 8-week inclusion criterion it used with long-term results from studies in which patients with the G551D mutation were included. The company's rationale was not followed. This was mainly due to the fact that it cannot be assumed that the mutations relevant for the present therapeutic indication (non-G551D gating mutations) and the G551D mutation are sufficiently similar. Therefore, the transferal of results from patients with G551D mutation to those with non-G551D cannot be derived from the available results (see Section 2.7.2 of the full dossier assessment for a detailed description).

Overall, studies of at least 24 weeks are necessary to compare benefit and harm for the benefit assessment in the therapeutic indication of CF. Hence, the VX12-770-111 study was too short to be included in the present benefit assessment. However, due to the rarity of the mutations to be investigated and the fact that children are affected in the present therapeutic indication, the VX12-770-111 study and the corresponding short-term results are presented as supplementary information in the present dossier assessment. A conclusion on the added benefit is not derived from it.

In its dossier (Module 4 B, Section 4.2.2) the company presented results from the single-arm Part 2 of the VX12-770-111 study (after 24 weeks) and from the non-comparative VX12-770-112 study as supplementary information. These results are not relevant for the present benefit assessment, as, in both cases, there are no data for an assessment of ivacaftor in comparison with the ACT. These results are not presented below as supplementary information.

2.3.1 Study included by the company

The study included by the company is shown in the following table.

Table 5: Study pool of the company – 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)
VX12-770-111	Yes	Yes	No

a: Study sponsored by the company.
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus

2.3.2 Study characteristics of the study included by the company

Table 6 and Table 7 describe the VX12-770-111 study included by the company.

Table 6: Characteristics of the study included by the company – 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]
VX12-770-111	RCT, double-blind, crossover design with subsequent open-label treatment phase	Patients with CF ▪ ≥ 6 years and ▪ one of the following non-G551D gating mutations in the CFTR gene: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P or G1349D ▪ and FEV1 (in % of predicted normal) at baseline of ≥ 40%	Part 1 (N = 39): Treatment sequence 1: ivacaftor – washout period – placebo (N = 20) Treatment sequence 2: placebo – washout period – ivacaftor (N = 19) Part 2 (N = 36)[b]: ivacaftor	Screening: 3 weeks Run-in: 2 weeks Part 1: Treatment period 1: 8 weeks Washout period: 4 weeks[c] Treatment period 2: 8 weeks Part 2: Open-label treatment phase: 16 weeks Follow-up[d]: 4 weeks	12 centres in Belgium, France, USA 7/2012–10/2013	Primary: FEV1 (in % of predicted normal) Secondary: symptoms, health-related quality of life, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes from the information provided by the company in Module 4 B of the dossier.
b: Part 2 is not relevant for the assessment of the results of ivacaftor in comparison with BSC, as no data on the ACT are available.
c: In case of stable treatment with inhaled cyclic antibiotics, the washout period could be extended up to 8 weeks, so that treatment period 2 (visit at week 12) took place at the end of an "off" cycle, but not later than 14 days after the last dose of antibiotics.
d: After completion of the study, patients could receive ivacaftor for 2 years in the treatment arm or participate in the observation arm (without ivacaftor) in the framework of the open-label VX12-770-112 study. From the VX12-770-111 study, 35 patients were included in the ivacaftor arm, and 2 patients in the observation arm of the VX12-770-112 study.

ACT: appropriate comparator therapy; AE: adverse event; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; FEV1: forced expiratory volume in 1 second; N: number of randomized (included) patients; RCT: randomized controlled trial; vs.: versus

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

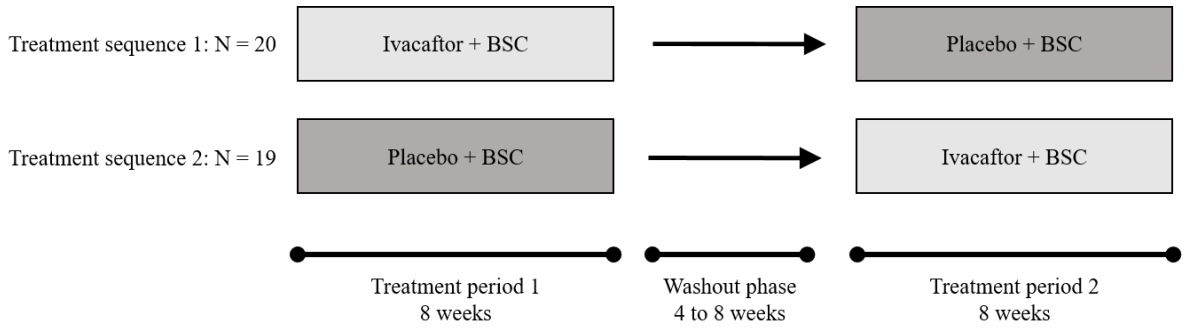
Study	Intervention	Comparison
VX12-770-111 (Part 1)	Ivacaftor 150 mg, orally, as tablet, every 12 hours with a high-fat, high-calorie meal[a] + BSC[b]	Placebo, orally, every 12 hours with a high-fat, high-calorie meal[a] + BSC[b]
	Prior and concomitant treatment Not allowed ▪ any CYP3A inducers or inhibitors, including certain herbal products (e.g. St. John's Wort) and grapefruit, within 2 weeks before first intake of the study medication and during treatment with the study medication ▪ inhaled hypertonic saline solution within 4 weeks before first intake of the study medication until end of study[c] ▪ solid organ or haematological transplantation before start of study	

a: Dose adjustments were not allowed. Interruptions of medication were allowed after consultation with the clinical monitor.
b: In addition to ivacaftor or placebo, the basic medication was to be continued at stable dosing from 4 weeks before baseline until the end of observation.
c: Patients who ended treatment with an inhaled hypertonic saline solution before baseline had to undergo a 4-week washout period before inclusion in the study.
BSC: best supportive care; CYP: cytochrome P450; RCT: randomized controlled trial; vs.: versus

The VX12-770-111 study was a 2-part study. Part 1 had a randomized, controlled, double-blind crossover design, in which 8-week treatment with ivacaftor was compared with placebo. The patients received concomitant medication during the study (see paragraph *Implementation of the appropriate comparator therapy* on page 15). This was followed by an open-label treatment phase without comparator therapy in Part 2 of the study. The company used only results of the 8-week randomized Part 1 for the derivation of the added benefit. The study included 39 patients with CF aged 6 years and older with one of 9 mutations in the CFTR gene.

According to the inclusion criteria of the study, diagnosis of CF was defined by the presence of chronic sinopulmonary disease. In addition, the patients had to either have a sweat chloride value of ≥ 60 mmol/L or carry 2 CF-causing mutations. Patients with a forced expiratory volume in 1 second (FEV1) in % of predicted normal of < 40% were excluded from the study.

In accordance with the crossover design, the patients were randomized in a 1:1 ratio to 2 treatment sequences:



N: Number of randomized patients. Stable concomitant medication in the sense of treatment with BSC was given in the washout period and in the treatment periods.

Figure 1: Treatment sequences of the VX12-770-111 study

20 study participants were allocated to treatment sequence 1, and 19 study participants to treatment sequence 2. Allocation was stratified by age (6 to 11 years, 12 to 17 years, and ≥ 18 years) and FEV1 severity grade (< 70%, ≥ 70% to ≤ 90%, and > 90%). In the treatment periods, 150 mg ivacaftor or placebo was taken twice daily over a period of 8 weeks. Treatment with ivacaftor in the study was in compliance with the Summary of Product Characteristics (SPC) [14]. Administration of ivacaftor or placebo was discontinued in the washout period. Afterwards a crossover took place: Patients previously treated with ivacaftor received placebo in the second treatment period and vice versa. During the entire study phase (Part 1 of the study), including the washout period, the patients received continuous symptomatic concomitant treatment (see paragraph: *Implementation of the appropriate comparator therapy*, page 15).

Primary outcome of the study was FEV1 (in % of predicted normal). Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and AEs.

The randomized, double-blind Part 1 of the study was followed by Part 2 of the study, in which all participants from Part 1 received unblinded treatment with ivacaftor 150 mg for 16 weeks. Part 2 is not considered for the assessment of the short-term results of ivacaftor + BSC in comparison with BSC, as no data on the ACT are available. The company used only Part 1 of the study for its benefit assessment.

Special features of the crossover study design

A crossover design allows intra-individual comparison of an experimental intervention with a control therapy, since all participants receive both therapies (see Figure 1). In a rare disease such as CF, a crossover design is a possibility to achieve a power even with smaller sample sizes, which in a parallel group design could only be achieved with greater sample sizes. However, a crossover design only produces informative results if certain conditions are met [15]:

1) Carry-over effects are negligible

   Carry-over effects occur when the therapies in treatment period 1 influence the effects in treatment period 2, so that there is an interaction between period and therapy. Washout periods between the treatment periods are used to prevent carry-over effects.

2) The statistical analyses must make adequate provisions for period effects

   Period effects are effects that lead to different effects being observed in treatment period 1 than in treatment period 2 due to external circumstances. This applies equally to both therapies. In addition to a rapid progression of the disease, a strong influence of the season on the observed outcomes could also lead to period effects, for example. Period effects would be unavoidable in a rapidly progressive disease.

The company did not provide sufficient information on the extent to which both conditions are fulfilled.

Curves on the course of FEV1 (in % of predicted normal) from the VX12-770-111 study presented by the company showed a deterioration in FEV1 value in treatment period 1 from about 79% to 75% under treatment with placebo + BSC (see Figure 2 in Appendix B of the full dossier assessment). This could suggest that the CF was not sufficiently stable in the patients in the study. Such a deterioration was not shown for the domain “respiratory symptoms” in the CFQ-R questionnaire (see Figure 3 in Appendix B of the full dossier assessment). Curves on the courses of other outcomes are not available.

Overall, it remains unclear whether the course of the disease was sufficiently stable during the study duration. Therefore, the short-term results from the VX12-770-111 study are presented in the present dossier assessment as supplementary information under the assumption that the 2 conditions described above can be considered sufficiently fulfilled for the VX12-770-111 study. Specific consequences of possible carry-over and period effects are considered in the assessment of the risk of bias of the short-term results below.

A crossover design is usually not adequate for irreversible outcomes [16]. This concerns the outcomes “all-cause mortality” and “discontinuation due to AEs” (if the discontinuation did not allow participation in the following treatment periods). However, no deaths or discontinuations due to AEs occurred in the VX12-770-111 study (Part 1).

Patient characteristics

Table 8 and Table 9 show the characteristics of the patients in the VX12-770-111 study separately for the randomized treatment sequences.

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

Study **Characteristics** **Category**	**Treatment sequence 1** **ivacaftor + BSC** **→ placebo + BSC**	**Treatment sequence 2** **placebo + BSC** **→ ivacaftor + BSC**
VX12-770-111	N[a] = 20	N[a] = 19
Age [years], mean (SD)	23.8 (13.3)	21.7 (12.9)
Age group [years], n (%)		
6 to 11 years	3 (15.0)	5 (26.3)
12 to 17 years	6 (30.0)	5 (26.3)
≥ 18 years	11 (55.0)	9 (47.4)
Sex [F/M], %	35/65	53/47
Family origin, n (%)		
White	15 (75.0)	14 (73.7)
Black or African American	1 (5.0)	1 (5.3)
Not recorded	4 (20.0)	4 (21.1)
Region, n (%)		
North America	11 (55.0)	11 (57.9)
Europe	9 (45.0)	8 (42.1)
FEV1 (in % of predicted normal), n (%)		
< 70%	7 (35.0)	6 (31.6)
≥ 70% to ≤ 90%	6 (30.0)	6 (31.6)
> 90%	7 (35.0)	7 (36.8)
BMI [kg/m²], mean (SD)	22.3 (4.1)	22.0 (5.9)
BMI z score, mean (SD)[b]	0.5 (1.16)	0.23 (1.09)
Height[c] [cm]		
Mean (SD)	161.3 (19.6)	153.8 (20.9)
median (min; max)	168.0 (106.0; 177.0)	158.0 (114.0; 181.0)
Body weight [kg][c, d]		
Mean (SD)	59.8 (18.7)	55.0 (25.8)
Median (min; max)	62.0 (20.0; 88.0)	54.0 (22.0; 126.0)
Sweat chloride concentration [nmol/L], mean (SD)	94.6 (22.7)	100.7 (12.8)
Pseudomonas aeruginosa infection at baseline, n (%)	10 (50.0[d])	10 (52.6[e])
Treatment discontinuation, n (%)	0 (0)	0 (0)
Study discontinuation[f], n (%)	2 (10.0)	1 (5.3)

(continued)

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

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: BMI adjusted for age and sex; only for patients aged < 20 years at screening (treatment sequence 1: n = 9; treatment sequence 1: n = 10).
c: No separate information available for age.
d: 2 patients weighed less than 25 kg and were therefore not comprised by the therapeutic indication of ivacaftor [14].
e: Institute's calculation.
f: Reasons for discontinuation were: other reasons (n = 2) ("washout period extended due to administration of antibiotics" and decision by the sponsor) and "lost to follow-up" (n = 1). Discontinuation of all 3 patients took place in the second treatment period.

BMI: body mass index; BSC: best supportive care; F: female; FEV1: forced expiratory volume in 1 second; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 9: Mutations – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study **Characteristics** **Category**	**Treatment sequence 1** **ivacaftor + BSC** **→ placebo + BSC**	**Treatment sequence 2** **placebo + BSC** **→ ivacaftor + BSC**
VX12-770-111	N[a] = 20	N[a] = 19
Gating mutation on the first allele		
S1251N, n (%)	4 (20.0)	4 (21.1)
G178R, n (%)	3 (15.0)	3 (15.8)
S549N, n (%)	3 (15.0)	3 (15.8)
G1244E, n (%)	1 (5.0)	4 (21.1)
S549R, n (%)	2 (10.0)	2 (10.5)
G970R[b], n (%)	3 (15.0)	1 (5.3)
G551S, n (%)	1 (5.0)	1 (5.3)
S1255P, n (%)	2 (10.0)	0 (0)
G1349D, n (%)	1 (5.0)	1 (5.3)
Mutation on the second allele		
F508del, n (%)	10 (50.0)[c]	14 (73.7)[c]
Other, n (%)	10 (50.0)[c]	5 (26.3)[c]

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: This mutation is not comprised by the therapeutic indication of ivacaftor [14].
c: Institute's calculation.

BSC: best supportive care; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

The demographic characteristics were largely balanced between the 2 study arms. Due to the crossover design, data of the patients in both treatment sequences were included both in the analysis on ivacaftor + BSC and in the analysis on placebo + BSC. It can therefore be assumed

that minor imbalances in the distribution of the characteristics between the treatment sequences did not influence the observed effects.

Patients aged 6 years and older were included in the VX12-770-111 study: 8 children in the age group from 6 to 11 years (20.5%), 11 children and adolescents in the age group from 12 to 17 years (28.2%). About half of the study participants were adults (aged 18 years and older).

With 8 study participants, the S1251N mutation was the most common mutation; the mutations G551S, S1255P and G1349D, with 2 participants each, were the least common mutations. 24 of the 39 patients (61.5%) had the F508del mutation on the second allele. One of the 9 missense mutations defined in the protocol had to be present in at least 1 allele (i.e. heterozygous) in the participants. Of these 9 mutations, one mutation (G970R) is not comprised by the approved therapeutic indication of ivacaftor [14]. The VX12-770-111 study included 4 patients with the G970R mutation. In addition, the study included 2 patients who weighed less than 25 kg and were therefore also not comprised by the approved therapeutic indication of ivacaftor [14]. Since the 4 patients with the G970R mutation weighed more than 25 kg, the study population included a total of 6 (15.4%) patients who were not comprised by the therapeutic indication.

Implementation of the appropriate comparator therapy

The G-BA specified BSC as ACT for ivacaftor in patients with CF aged 6 years and older and weighing at least 25 kg who have one of the gating mutations G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R 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 VX12-770-111 study, patients were to continue their ongoing symptomatic treatment at baseline at the same time as treatment with ivacaftor or placebo. However, the study protocol recommended that patients remain on stable CF medication from 4 weeks before baseline until end of study. Besides, inhaled hypertonic saline solution as concomitant medication was not allowed within 4 weeks before the first intake of the study medication until end of study.

The medication taken within 28 days before the first intake of the study medication was recorded as pretreatment. The medication taken after the first intake of the study medication was recorded as concomitant treatment. Concomitant treatment was recorded during the total study duration of 40 weeks. Medication that was taken both within the 28 days before the first intake of the study medication and during the treatment periods of the randomized study phase is shown in both tables (information on prior and concomitant treatment: Table 10 and Table 11). Presentation in Table 10 is separately for the patients within one treatment sequence and in Table 11 separately for the treatment groups.

Table 10: Treatment before first administration of study medication (≥ 15% in at least one study arm) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study Characteristics Category	**Treatment sequence 1 ivacaftor + BSC → placebo + BSC**	**Treatment sequence 2 placebo + BSC → ivacaftor + BSC**
VX12-770-111	N[a] = 20	N[a] = 19
Drug treatment[b], n (%)		
Dornase alfa	18 (90.0)	14 (73.7)
Azithromycin	13 (65.0)	6 (31.6)
Pancreatin	10 (50.0)	14 (73.7)
Salbutamol	9 (45.0)	9 (47.4)
Vitamins with zinc	9 (45.0)	3 (15.8)
Seretide	8 (40.0)	4 (21.1)
Macrogol	7 (35.0)	2 (10.5)
Fluticasone propionate	6 (30.0)	3 (15.8)
Sodium chloride[c]	5 (25.0)	7 (36.8)
Colistimethate sodium	5 (25.0)	2 (10.5)
Tobramycin	5 (25.0)	2 (10.5)
Colecalciferol	4 (20.0)	7 (36.8)
Vitamin D	4 (20.0)	2 (10.5)
Salbutamol sulfate	4 (20.0)	1 (5.3)
Fluticasone furoate	4 (20.0)	1 (5.3)
Tocopheryl acetate	3 (15.0)	6 (31.6)
Levosalbutamol hydrochloride	3 (15.0)	5 (26.3)
Multivitamins with minerals/90003801	3 (15.0)	3 (15.8)
Omeprazole	3 (15.0)	3 (15.8)
Cetirizine	3 (15.0)	1 (5.3)
Paracetamol	3 (15.0)	1 (5.3)
Montelukast	2 (10.0)	3 (15.8)
Budesonide with formoterol fumarate	1 (5.0)	3 (15.8)
Ibuprofen	1 (5.0)	5 (26.3)
Retinol	0 (0)	3 (15.8)
Non-drug treatment		
Physiotherapy (chest)	13 (65.0)	11 (57.9)
Breathing therapy	0 (0)	4 (21.1)
Kinesiotherapy	3 (15.0)	0 (0)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: PT, coded according to WHO-DD, March 2012.
c: Inhaled saline solution was prohibited during the study and 4 weeks before baseline.
BSC: best supportive care; n: number of patients in the category; N: number of randomized patients; PT: Preferred Term; RCT: randomized controlled trial; vs.: versus; WHO-DD: World Health Organization Drug Dictionary

Table 11: Concomitant treatment (≥ 15% in at least one study arm) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study Characteristics Category	Ivacaftor + BSC	Placebo + BSC
VX12-770-111	N[a] = 38	N[a] = 37
Drug treatment[b], n (%)		
Dornase alfa	30 (78.9)	30 (81.1)
Pancreatin	24 (63.2)	24 (64.9)
Azithromycin	20 (52.6)	19 (51.4)
Salbutamol	17 (44.7)	16 (43.2)
Seretide	12 (31.6)	13 (35.1)
Vitamins with zinc	12 (31.6)	12 (32.4)
Paracetamol	12 (31.6)	8 (21.6)
Colecalciferol	11 (28.9)	11 (29.7)
Bactrim	11 (28.9)	11 (29.7)
Ibuprofen	11 (28.9)	9 (24.3)
Macrogol	10 (26.3)	9 (24.3)
Sodium chloride[c]	9 (23.7)	10 (27.0)
Tocopheryl acetate	9 (23.7)	9 (24.3)
Tobramycin	8 (21.1)	9 (24.3)
Fluticasone propionate	8 (21.1)	8 (21.6)
Levosalbutamol hydrochloride	7 (18.4)	8 (21.6)
Omeprazole	7 (18.4)	7 (18.9)
Amoxicillin/clavulanic acid	7 (18.4)	6 (16.2)
Colistimethate sodium	6 (15.8)	9 (24.3)
Vitamin D	6 (15.8)	7 (18.9)
Multivitamins with minerals/90003801	6 (15.8)	6 (16.2)
Multivitamins	5 (13.2)	6 (16.2)
Levofloxacin	1 (2.6)	6 (16.2)
Influenza vaccine	5 (13.2)	6 (16.2)
Non-drug treatment, n (%)		
Physiotherapy (chest)	24 (63.2)	23 (62.2)

a: Number of analysed patients. Patients from both treatment sequences are included in the analysis with the values from the respective treatment periods.
b: PT, coded according to WHO-DD, March 2012.
c: Inhaled saline solution was prohibited during the study and 4 weeks before baseline.
BSC: best supportive care; n: number of patients in the category; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; vs.: versus; WHO-DD: World Health Organization Drug Dictionary

The available information suggests that the patients were given a variety of drugs for symptomatic treatment of CF, including dornase alfa, as well as pancreatin and antibiotics, at the time point of study entry and during the treatment periods. Inhaled hypertonic saline

solution was prohibited. It cannot be inferred from the data whether and how many patients had their concomitant treatment adjusted, for example in the sense of an increase in dose or frequency.

In summary, the concomitant treatment used in the VX12-770-111 study did not constitute a complete implementation of the ACT BSC. This assessment is based particularly on the exclusion of inhaled saline solution, a standard therapy in CF [17], and the concomitant medication that was to be maintained stable.

Risk of bias across outcomes (study level) for the study used by the company

Table 12 shows the risk of bias across outcomes (risk of bias at study level) for the short-term results of the study included by the company.

Table 12: 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			
VX12-770-111	Yes	Yes	Yes	Yes	Yes	No[a]	Low

a: Insufficient information on carry-over and period effects.
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low. This concurs with the company's assessment.

There were the following additional aspects for the study in the crossover design:

The company considered the 4- to 8-week washout period to be long enough to exclude carry-over effects. The company did not show for all patient-relevant outcomes that the baseline values in the relevant outcomes before the start of the first treatment period and before the start of the second treatment period were comparable. The available data on the FEV1 show that the values in treatment sequence 1 (ivacaftor + BSC → placebo + BSC) were lower at the start of treatment period 1 than at the start of treatment period 2. A notable decrease in values was seen during the washout period, however (see Figure 2 in Appendix B of the full dossier assessment).

Regarding the outcomes of FEV1 and the CFQ-R domain "respiratory symptoms", the company additionally referred to statistical tests conducted in the framework of mixed-effects model repeated measures (MMRM) analyses for the assessment of carry-over effects. These produced no statistically significant effects for the factors "treatment sequence" and "treatment period". For the primary outcome "FEV1" (in % of predicted normal), the company also calculated

effect estimations for the first treatment period, which the company considered to be of a similar magnitude as the analyses that included both treatment periods. However, the necessary [15,16] corresponding data were missing for each treatment period and each treatment sequence for the patient-relevant symptom outcomes (symptoms measured with the CFQ-R and pulmonary exacerbations) and health-related quality of life (measured with the CFQ-R).

Overall, an uncertainty remains as to whether the washout period in the VX12-770-111 study was long enough to exclude carry-over effects. Period-specific effect estimations for these outcomes are also necessary for an assessment of period effects [15,16]. The effects of the missing data on carry-over and period effects are considered in the assessment of the outcome-specific risk of bias.

2.4 Short-term results of the study included by the company

2.4.1 Patient-relevant outcomes in the VX12-770-111 study

The following patient-relevant outcomes are presented as supplementary information for the VX12-770-111 study included by the company (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

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

No meaningful investigation of the outcome “mortality” is possible in the crossover design. It is therefore not taken into account in the following tables. No deaths occurred in the VX12-770-111 study. Regarding the outcome “discontinuation due to AEs”, it is assumed in the present dossier assessment that the discontinuation principally allowed participation in subsequent treatment periods.

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

Table 13 shows for which outcomes data from the VX12-770-111 study are available.

Table 13: Matrix of outcomes – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study	Outcomes					
	Pulmonary exacerbations	Hospitalization due to pulmonary exacerbations	Symptoms (CFQ-R)	Health-related quality of life (CFQ-R)	SAEs	Discontinuation due to AEs
VX12-770-111	Yes	Yes	Yes	Yes	–[a]	Yes

a: No usable data available (see Section 2.4.2 and Section 2.7.4.3.2 of the full dossier assessment).
AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The VX12-770-111 study comprised patients aged 6 years and older. CF is a progressive disease. Therefore, the greater the age difference between patients, the more questionable a consideration across age groups appears. If separate analyses according to age groups are available for the outcomes considered, these are presented. If no separate analyses according to age groups are available, the short-term results on the basis of the total study population are presented.

2.4.2 Risk of bias

Table 14 describes the risk of bias for the short-term results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study	Study level	Outcomes					
		Pulmonary exacerbations	Hospitalization due to pulmonary exacerbations	Symptoms (CFQ-R)	Health-related quality of life (CFQ-R)	SAEs	Discontinuation due to AEs
VX12-770-111	L	H[a, b]	H[a, b]	H[b]	H[b]	-[c]	L

a: No adequate method of analysis.
b: Insufficient data for the assessment of carry-over and period effects.
c: No usable data available (see Section 2.7.4.3.2 of the full dossier assessment).
AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

To analyse the number of pulmonary exacerbations, the company used the effect measure rate ratio based on a negative binomial model with treatment and treatment sequence as fixed effects, adjusted for baseline values of FEV1 and age and log(study time) as offset. The treatment period was not taken into account in the available analyses. The company justified this by wanting to ensure the convergence of the models. However, an adequate analysis of a crossover study requires consideration of the treatment period [15,16]. Due to the deficiencies in the methods for the analysis of the data and insufficient data for the assessment of carry-over and period effects, the risk of bias of the results for the outcomes on pulmonary exacerbations was rated as high.

The risk of bias of the results for the outcomes on symptoms (CFQ-R) and health-related quality of life (CFQ-R) is assessed as follows:

The company used MMRM for the analysis of continuous variables (CFQ-R on symptoms and health-related quality of life). These models included treatment, treatment sequence, treatment period, time point of study (within the treatment period), treatment x time point of study (within the treatment period) as fixed effects. The patient was included as random effect. In addition, an adjustment was performed according to continuous baseline values of age, FEV1 and respective CFQ-R domain score. According to the company, the results in the CFQ-R referred to the overall effect across all documentation time points within one treatment period. The methodological approach of the company for the analysis of the data is adequate. Due to insufficient data for the assessment of carry-over and period effects (see Section 2.3.2), the risk of bias was in summary rated as high for the outcomes on symptoms (CFQ-R) and health-related quality of life (CFQ-R).

The company used the effect measure relative risk (RR), calculated with the Mantel-Haenszel method, for the description of the results in dichotomous outcomes. This approach was inadequate, since the crossover design of the study was not taken into account and relevant factors such as treatment period and dependence of the measurements within one person were not included in the available analyses [15,16]. Thus, no usable data are available for the outcome “SAEs” also for this reason (for the further reason, see Section 2.7.4.3.2 of the full dossier assessment). This deviates from the assessment of the company, which assessed the risk of bias as low for the results of all outcomes it included.

The risk of bias for the results on the outcome “discontinuation due to AEs” was rated as low. There were no events in both treatment groups. Hence, no effect estimation is required for this outcome.

2.4.3 Results

Table 15, Table 16 and Table 17 present the short-term results over a period of 8 weeks on the comparison of ivacaftor + BSC versus BSC in patients with CF aged 6 years and older and weighing 25 kg or more who have one of the gating mutations G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R in the CFTR gene as supplementary information.

Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Table 15: Short-term results (treatment duration of 8 weeks) (side effects, dichotomous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study Outcome category	Ivacaftor + BSC		Placebo + BSC		Ivacaftor + BSC vs. placebo + BSC
Outcome	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value
VX12-770-111					
Side effects					
AEs (supplementary information)	38	28 (73.7)	37	31 (83.8)	–
SAEs				Not usable[c]	
Discontinuation due to AEs	38	0 (0)	37	0 (0)	–[b]

a: Number of analysed patients. Due to the crossover design, patients from both treatment sequences are included in the analysis with the values from the respective treatment periods.
b: No meaningful calculation possible.
c: 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.
AE: adverse event; BSC: best supportive care; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 16: Short-term results (treatment duration of 8 weeks) (morbidity, dichotomous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study **Outcome category** **Outcome**	**Ivacaftor + BSC**		**Placebo + BSC**		**Ivacaftor + BSC vs. placebo + BSC**
	N[a]	**Number of events n_E (n_E/patient years)[b]**	**N[a]**	**Number of events n_E (n_E/patient years)[b]**	**Rate ratio [95% CI]; p-value[c]**
VX12-770-111					
Morbidity					
Pulmonary exacerbations					
Children, adolescents and adults [12 years and older]					
	30	8 (1.20[d])	29	8 (1.25[d])	0.84 [0.30; 2.36]; 0.740
Children [6 to 11 years]					
	8	2 (1.30[d])	8	2 (1.22[d])	ND[e]
Hospitalization due to pulmonary exacerbations					
Children, adolescents and adults [12 years and older]					
	30	1 (0.15[d])	29	4 (0.62[d])	ND[e]
Children [6 to 11 years]					
	8	1 (0.65[d])	8	1 (0.61[d])	ND[e]

a: Number of analysed patients. Due to the crossover design, patients from both treatment sequences are included in the analysis with the values from the respective treatment periods.
b: Event rate (n_E/patient years) is calculated from the total number of events divided by the total number of years (sum of the observation period of all patients included in the analysis).
c: Negative binomial model: treatment and treatment sequence as fixed effects, adjusted for baseline values of FEV1 and age and log(study time) as offset; calculation was conducted if there were at least 5 patients with event in each group.
d: Institute's calculation.
e: Not calculated by the company due to the small numbers of events.

BSC: best supportive care; CI: confidence interval; FEV1: forced expiratory volume in 1 second; n: number of patients with (at least one) event; N: number of analysed patients; n_E: total number of events; ND: no data; RCT: randomized controlled trial; versus

Table 17: Short-term results (treatment duration of 8 weeks) (morbidity, continuous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC

Study Outcome category Outcome	Ivacaftor + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	Placebo + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	Ivacaftor + BSC vs. placebo + BSC MD [95% CI]; p-value[c]
VX12-770-111							
Morbidity							
Symptoms (CFQ-R, symptom domains [d])							
Respiratory symptoms							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	70.56 (18.28)	9.10 (16.45)	29	73.56 (20.93)	−2.11 (18.57)	9.88 [4.16; 15.60]; 0.001 Hedges' g: 0.88 [0.34; 1.42]
Children [6 to 11 years]							
	8	70.83 (14.77)	23.96 (13.68)	8	78.13 (20.38)	−3.13 (28.50)	11.29 [−4.25; 26.84]; 0.135
Digestive symptoms							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	80.59 (17.18)	3.45 (15.74)	29	82.38 (16.13)	2.30 (8.60)	3.68 [−0.47; 7.84]; 0.081
Children [6 to 11 years]							
	8	70.83 (33.03)	8.33 (49.60)	8	83.33 (25.20)	4.17 (33.03)	−2.08 [−21.82; 17.67]; 0.811
Weight[e]							
Adolescents or adults, not intended for children [12 to 13 years and 6 to 11 years]							
	27	81.48 (33.76)	14.81 (28.24)	27	91.36 (17.52)	−1.23 (21.64)	4.52 [−2.68; 11.71]; 0.212
CFQ-R – parent/caregiver version, children from 6 to 11 years, symptom domains[d]							
Respiratory symptoms	*8*	*75.14 (15.41)*	*20.00 (14.14)*	*8*	*79.86 (14.83)*	*1.25 (14.91)*	*11.26 [−2.17; 24.69]; 0.084*
Digestive symptoms	*8*	*76.39 (15.07)*	*−1.39 (16.20)*	*8*	*79.17 (16.20)*	*0.00 (14.55)*	*2.13 [−1.30; 5.57]; 0.183*
Weight	*8*	*75.00 (38.83)*	*0.00 (0.00)*	*8*	*70.83 (37.53)*	*−4.17 (41.55)*	*1.51 [−12.79; 15.82]; 0.818*

(continued)

Table 17: Short-term results (treatment duration of 8 weeks) (morbidity, continuous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

Study Outcome category Outcome	Ivacaftor + BSC			Placebo + BSC			Ivacaftor + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	MD [95% CI]; p-value[c]
VX12-770-111							
Morbidity							
FEV1 (in % of predicted normal, absolute change)[d]	*38*	*76.37 (20.33)*	*8.13 (9.95)*	*37*	*79.34 (20.84)*	*−5.87 (7.24)*	*13.76 [9.94; 17.57]; < 0.001*
FEV1 (in % of predicted normal, relative change)[d]	*38*	*76.37 (20.33)*	*11.44 (13.10)*	*37*	*79.34 (20.84)*	*−6.60 (8.89)*	*17.73 [12.80; 22.67]; < 0.001*
BMI [kg/m²] (absolute change)	*38*	*22.24 (5.19)*	*0.75 (0.58)*	*37*	*22.53 (5.00)*	*0.04 (0.70)*	*0.69 [0.45; 0.92]; < 0.001*
BMI (age-dependent z score, absolute change)[f]	*18*	*0.32 (1.1)*	*0.27 (0.24)*	*17*	*0.49 (1.08)*	*0.0 (0.33)*	*0.23 [0.07; 0.39] p = 0.006*
Health-related quality of life							
CFQ-R, symptom domains, children [12 to 13 years] and adolescents or adults – pooled[d]							
Physical functioning							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	75.93 (21.05)	3.83 (10.98)	29	72.37 (23.30)	4.50 (11.13)	0.57 [−3.33; 4.48]; 0.769
Children [6 to 11 years]							
	8	72.92 (29.91)	−1.39 (14.77)	8	75.00 (27.38)	−6.94 (17.25)	3.70 [−8.86; 16.27]; 0.525
Emotional functioning							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	75.86 (19.21)	4.91 (10.59)	29	76.84 (22.42)	1.75 (13.03)	0.42 [−4.48; 5.31]; 0.863
Children [6 to 11 years]							
	8	80.21 (14.56)	8.33 (13.73)	8	78.13 (13.86)	1.56 (13.90)	1.97 [−4.52; 8.47]; 0.501

(continued)

Table 17: Short-term results (treatment duration of 8 weeks) (morbidity, continuous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

Study Outcome category Outcome	Ivacaftor + BSC			Placebo + BSC			Ivacaftor + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	MD [95% CI]; p-value[c]
VX12-770-111							
Health-related quality of life							
CFQ-R, symptom domains, children [12 to 13 years] and adolescents or adults – pooled[d]							
Vitality[e]							
Adolescents or adults, not intended for children [12 to 13 years and 6 to 11 years]							
	27	60.80 (18.61)	7.10 (18.16)	27	62.96 (19.66)	0.00 (14.06)	7.09 [2.40; 11.78]; 0.004 Hedges' g: 0.79 [0.24; 1.35][g]
Social functioning							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	69.92 (18.22)	4.16 (12.79)	29	67.16 (19.33)	−1.75 (9.144)	1.05 [−2.78; 4.87] 0.580
Children [6 to 11 years]							
	8	60.71 (23.15)	1.19 (16.84)	8	66.07 (19.62)	−10.71 (17.77)	4.87 [−9.56; 19.31]; 0.447
Role functioning[e]							
Adolescents or adults, not intended for children [12 to 13 years and 6 to 11 years]							
	27	79.01 (16.57)	5.86 (13.83)	27	81.79 (16.51)	0.93 (12.94)	2.99 [−1.48; 7.46]; 0.183
Body image							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	77.41 (23.79)	4.60 (16.40)	29	81.99 (18.88)	−1.92 (11.14)	4.00 [−1.44; 9.43]; 0.145
Children [6 to 11 years]							
	8	72.22 (28.48)	8.33 (12.94)	8	77.78 (24.49)	5.56 (18.78)	0.63 [−14.03; 15.28]; 0.924
Eating problems							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	92.22 (14.92)	3.83 (10.40)	29	92.34 (13.31)	1.53 (13.52)	2.39 [−1.13; 5.92]; 0.178
Children [6 to 11 years]							
	8	76.39 (20.09)	−1.39 (27.50)	8	70.83 (27.18)	4.17 (15.64)	−13.22 [−35.85; 9.41]; 0.204

(continued)

Table 17: Short-term results (treatment duration of 8 weeks) (morbidity, continuous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

Study Outcome category Outcome	Ivacaftor + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	Placebo + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	Ivacaftor + BSC vs. placebo + BSC MD [95% CI]; p-value[c]
VX12-770-111							
Health-related quality of life							
CFQ-R, symptom domains, children [12 to 13 years] and adolescents or adults – pooled[d]							
Treatment burden							
Children [12 to 13 years] and adolescents or adults – pooled							
	30	60.37 (24.18)	1.53 (14.46)	29	57.09 (24.44)	1.53 (13.84)	1.94 [−4.36; 8.24]; 0.535
Children [6 to 11 years]							
	8	76.39 (17.25)	0.00 (17.82)	8	63.89 (26.39)	1.39 (34.85)	0.85 [−24.62; 26.32]; 0.938
Health perceptions[e]							
Adolescents or adults							
	27	60.08 (21.23)	12.76 (14.02)	27	60.91 (19.58)	0.41 (11.73)	8.23 [2.82; 13.64]; 0.004 Hedges' g: 0.85 [0.29; 1.41]
CFQ-R – parent/caregiver version, children [6 to 11 years], health-related quality of life domains[d]							
Physical functioning	*8*	*77.78 (18.89)*	*8.80 (12.03)*	*8*	*86.57 (12.03)*	*−11.57 (16.38)*	*14.81 [2.24; 27.38]; 0.026* *Hedges' g: 1.09 [0.02; 2.16][f]*
Emotional functioning	*8*	*83.33 (9.43)*	*1.67 (9.92)*	*8*	*90.83 (7.07)*	*−4.17 (7.92)*	*2.17 [−8.26; 12.61]; 0.650*
Vitality	*8*	*69.17 (4.96)*	*3.33 (7.13)*	*8*	*72.50 (13.54)*	*−0.83 (19.33)*	*1.28 [−9.31; 11.87]; 0.779*
Body image	*8*	*77.78 (31.98)*	*−2.78 (9.85)*	*8*	*75.00 (29.55)*	*5.56 (14.55)*	*−5.56 [−13.84; 2.72]; 0.163*
Eating problems	*8*	*81.25 (22.60)*	*−6.25 (12.40)*	*8*	*83.33 (19.92)*	*−12.50 (34.21)*	*−4.99 [−24.14; 14.17]; 0.530*
Treatment burden	*8*	*70.83 (13.20)*	*9.72 (24.80)*	*8*	*77.78 (11.88)*	*0.00 (11.88)*	*−1.10 [−10.97; 8.77]; 0.801*
Health perceptions	*8*	*77.78 (17.82)*	*2.78 (7.86)*	*8*	*83.33 (11.88)*	*0.00 (13.28)*	*1.94 [−8.98; 12.87]; 0.670*
School functioning	*8*	*69.44 (16.53)*	*11.11 (22.22)*	*8*	*75.00 (15.43)*	*−1.39 (16.20)*	*3.06 [−12.74; 18.86]; 0.669*

(continued)

Table 17: Short-term results (treatment duration of 8 weeks) (morbidity, continuous) – RCT, direct comparison: ivacaftor + BSC vs. placebo + BSC (continued)

Results presented in italics: no interpretation of advantages and disadvantages of treatment
a: Number of patients considered in the analysis for the calculation of the effect estimation. Baseline values (if applicable, at other time points) may be based on other patient numbers. Due to the crossover design, patients from both treatment sequences are included in the analysis with the values from the respective treatment periods.
b: Refers to the change from baseline to the last time point of measurement.
c: MMRM: treatment, treatment sequence, treatment period and time point of study as fixed effects, patient as random effect, adjusted for baseline values for age, FEV1 and respective CFQ-R score; effect refers to the difference across all documentation time points after baseline.
d: Higher values indicate better quality of life or symptoms; a positive group difference corresponds to an advantage of ivacaftor.
e: The domain is not included in the questionnaire for children between 6 and 11 years and children between 12 and 13 years of age.
f: Only for patients < 20 years of age.
g: Institute's calculation.
BMI: body mass index; 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

The short-term results of the study included by the company are described below. All outcomes have a high risk of bias.

Morbidity

Pulmonary exacerbations

There was no statistically significant difference between the treatment groups both for patients aged 12 years and older (including adults) and for children from 6 to 11 years of age.

Hospitalizations due to pulmonary exacerbations

There was 1 event under treatment with ivacaftor + BSC in patients aged 12 years and older, and 4 events under treatment with BSC in 8 weeks. The company did not present an effect measure or calculation on the statistical significance of the group difference. There was no statistically significant difference between the treatment groups for patients from 6 to 11 years of age.

Symptoms measured using the CFQ-R

In all age groups, symptom outcomes were recorded with the domains "respiratory symptoms" and "digestive symptoms" of the disease-specific patient-reported instrument CFQ-R. In compliance with the questionnaire, the domain "weight" was only recorded for patients aged 14 years and older.

Domain "respiratory symptoms"

For patients aged 12 years and older, a statistically significant difference in favour of ivacaftor + BSC versus placebo + BSC was shown for the change from baseline in the domain "respiratory

symptoms". The SMD in the form of Hedges' g was considered to assess the relevance of the result. The 95% CI was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect.

There was no statistically significant difference between the treatment groups for children from 6 to 11 years of age. This result is consistent with the results of the CFQ-R (parent/caregiver version).

Domain "digestive symptoms"

There was no statistically significant difference between the treatment groups for patients aged 12 years and older (including adults) in the domain "digestive symptoms". There was an effect modification by *Pseudomonas aeruginosa* infection at baseline, however. There was an advantage of ivacaftor + BSC versus placebo + BSC for patients without *Pseudomonas aeruginosa* infection at baseline (see Section 2.4.4).

There was no statistically significant difference between the treatment groups for children from 6 to 11 years of age. This result is consistent with the results of the CFQ-R (parent/caregiver version).

Domain "weight"

There was no statistically significant difference between the treatment groups in the domain "weights" for adolescents aged 14 years and older (including adults).

Health-related quality of life

In all age groups, health-related quality of life was recorded using the domains of physical functioning, emotional functioning, social functioning, body image, eating problems and treatment burden of the CFQ-R. There are pooled analyses for patients aged 12 years and older (including adults) and separate analyses for children from 6 to 11 years of age. In compliance with the questionnaire, the domains "vitality", "role functioning" and "health perceptions" were only recorded for patients aged 14 years and older.

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

Over a period of 8 weeks, a statistically significant difference between the treatment groups was neither shown for patients aged 12 years and older (including adults) nor for children from 6 to 11 years of age in any of the domains of physical functioning, emotional functioning, social functioning, body image, eating problems or treatment burden.

Domains "vitality" and "health perceptions"

Statistically significant effects in favour of ivacaftor + BSC versus placebo + BSC were shown for patients aged 14 years and older (including adults) in the domains of vitality and health perceptions. In both cases, the CI of Hedges' g was above the irrelevance threshold of 0.2. Hence, there was a relevant effect in these 2 domains.

Domain "role functioning"

There was no statistically significant difference between the treatment groups in the domain "role functioning" for adolescents aged 14 years and older (including adults).

Side effects

Serious adverse events and discontinuation due to adverse events

The results on SAEs are not usable to draw a conclusion on this outcome (see Section 2.7.4.3.2 of the full dossier assessment).

No discontinuations due to AEs occurred during the 8-week treatment periods. This resulted in no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs".

2.4.4 Subgroups and other effect modifiers on the basis of the study included by the company

The following subgroup characteristics are considered for the presentation of the results of the VX12-770-111 study:

- sex (female, male)
- region (North America, Europe)
- FEV1 (in % of predicted normal) at baseline, (< 70%, ≥ 70% to ≤ 90%, > 90%)
- *Pseudomonas aeruginosa* infection at baseline (yes, no)

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. This largely concurs with the company's approach.

Only results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The subgroup results are presented in Table 18.

Table 18: Subgroups, treatment duration of 8 weeks (morbidity, 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[b] (SD)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	MD [95% CI]; p-value[c]
VX12-770-111							
Symptoms: CFQ-R domain "digestive symptoms", children [12 to 13 years] and adolescents or adults – pooled							
Pseudomonas aeruginosa infection at baseline							
Yes	17	84.31 (16.69)	−1.31 (10.31)	18	82.72 (17.56)	3.09 (8.35)	−2.81 [−7.01; 1.40]; 0.180
No	13	80.34 (18.23)	10.19 (19.80)	11	81.82 (14.29)	1.01 (9.24)	11.21 [3.83; 18.60]; 0.005 Hedges' g: 1.09 [0.204; 1.97]
Total						Interaction:	p-value < 0.001

a: Number of patients considered in the analysis for the calculation of the effect estimation. Baseline values (if applicable, at other time points) may be based on other patient numbers. Due to the crossover design, patients from both treatment sequences are included in the analysis with the values from the respective treatment periods.
b: Refers to the change from baseline to the last time point of measurement.
c: MMRM analogous to the analysis in the total population.
BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Morbidity

CFQ-R domain "digestive symptoms"

For children, adolescents and adults (12 years and older), there was an effect modification by *Pseudomonas aeruginosa* infection at baseline (yes, no) in the CFQ-R domain "digestive symptoms".

There was no statistically significant effect between the treatment groups for patients with *Pseudomonas aeruginosa* infection at baseline. There was a statistically significant effect to the advantage of ivacaftor + BSC versus placebo + BSC for patients without *Pseudomonas aeruginosa* infection at baseline. The 95% CI of the SMD in the form of Hedges' g was completely above the irrelevance threshold of 0.2. Hence, there is a relevant effect.

2.4.5 Summary

Studies with a minimum duration of 24 weeks are necessary for the benefit assessment in the therapeutic indication of CF. The company only presented comparative data over a period of 8 weeks. These only show short-term effects, however, which are unsuitable for the derivation

of an added benefit in the present therapeutic indication. However, due to the rarity of the mutations to be investigated and the fact that children are affected, the study is presented as supplementary information in the present dossier assessment and the short-term effects are described.

Overall, the following advantages or disadvantages of ivacaftor + BSC in comparison with placebo + BSC result from the short-term results of the VX12-770-111 study (8-week period):

- Morbidity – symptoms: advantage of ivacaftor + BSC in comparison with placebo + BSC in the domain "respiratory symptoms", recorded with the CFQ-R for patients aged 12 years and older
- Morbidity – symptoms: advantage of ivacaftor + BSC in comparison with placebo + BSC in the domain "digestive symptoms", recorded with the CFQ-R for patients aged 12 years and older without *Pseudomonas aeruginosa* infection at baseline
- Health-related quality of life: advantage of ivacaftor + BSC in comparison with placebo + BSC in the domains "vitality" and "health perceptions", recorded with the CFQ-R for patients aged 14 years and older

Each of these results has a high risk of bias.

2.5 Probability and extent of added benefit

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

Table 19: Ivacaftor – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Patients with CF aged 6 years and older and weighing at least 25 kg who have one of the following 8 gating (class III) mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R[b]	BSC	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. b: These 8 mutations belong to the group of non-G551D gating mutations. ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit on the basis of the short-term effects in the VX12-770-111 study.

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 2015. In this assessment, the G-BA had determined a minor added benefit of ivacaftor. 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

Not applicable as the company did not present any relevant data for the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

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

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