IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Lumacaftor/ivacaftor (cystic fibrosis) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Lumacaftor/Ivacaftor (zystische Fibrose) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 April 2018). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
CSR	clinical study report
CYP	cytochrome P450
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LCI	lung clearance index (measurement for assessment of ventilation inhomogeneity of the lung using the gas washout test) A subscript number after the abbreviation indicates the target concentration of the tracer gas.
ppFEV1	percent predicted forced expiratory volume in 1 second
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination lumacaftor/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 1 February 2018.

Research question

The aim of the present report was the assessment of the added benefit of lumacaftor/ivacaftor in comparison with the appropriate comparator therapy (ACT) in the treatment of cystic fibrosis (CF) in patients between 6 and 11 years of age who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Table 2 shows the therapeutic indication to be assessed and the corresponding ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of lumacaftor/ivacaftor

Therapeutic indication	**ACT[a]**
CF patients between 6 and 11 years of age who are homozygous for the F508del mutation in the CFTR gene	Best symptomatic treatment (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [in the sense of the "Heilmittel-Richtlinie" (Remedies Directive)]), under exhaustion of all possible dietary measures
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company cited best symptomatic treatment as ACT, without mentioning therapeutic measures specified under best symptomatic treatment by the G-BA, however.

The present benefit assessment was conducted in comparison with the G-BA's ACT. The implementation of the best symptomatic treatment (in accordance with the G-BA's specification) in the studies was checked.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Results

The randomized, double-blind, placebo-controlled study VX14-809-109 was included in the benefit assessment. This study investigated children with CF who were between 6 and (including) 11 years of age and homozygous for the F508del mutation in the CFTR gene.

In the study, a total of 206 children were randomly allocated in a 1:1 ratio, either to the lumacaftor/ivacaftor arm (104 children) or to the placebo arm (102 children). Randomization was stratified by body weight (< 25 kg versus ≥ 25 kg) and percent predicted forced expiratory volume in 1 second (ppFEV1) (< 90% versus ≥ 90%). Treatment with lumacaftor/ivacaftor or placebo was in addition to basic therapy. The dosage of lumacaftor/ivacaftor in the study was without relevant deviations from the Summary of Product Characteristics (SPC).

Primary outcome of the study was the lung clearance index ($LCI_{2.5}$). Patient-relevant secondary outcomes were overall survival, symptoms, health-related quality of life, and adverse events (AEs). All outcomes, except the outcomes on pulmonary exacerbations, were recorded for a maximum of 4 weeks after the study medication. Observation of pulmonary exacerbations was conducted at most until week 24.

Implementation of the appropriate comparator therapy

The G-BA defined best symptomatic treatment as ACT for lumacaftor/ivacaftor for the treatment of CF patients between 6 and 11 years of age who are homozygous for the F508del mutation in the CFTR gene. The G-BA further specified that this therapy is understood to include, in particular, antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy (in the sense of the “Heilmittel-Richtlinie” [Remedies Directive]), under exhaustion of all possible dietary measures.

In the VX14-809-109 study, the children were randomly assigned to treatment with lumacaftor/ivacaftor or placebo, each in addition to basic therapy. In accordance with the study requirements on the use of concomitant medication, it was recommended in the study to maintain a stable level of the basic medication that the children had been receiving already 4 weeks before randomization.

The available information overall indicated that the children were receiving comprehensive symptomatic drug treatment at the time point of study inclusion (including dornase alfa, sodium chloride, pancreatin and salbutamol, as well as antibiotics, dietary supplements/vitamin products and corticosteroids). In the course of the study, some adjustments were made to the drug treatment, particularly regarding antibiotic treatment. However, more detailed information on the intensified therapy, e.g. increased dosage or frequency of administration, was missing. Based on the study documents presented, it can also not be checked whether the patients received physiotherapy, which also forms part of the concept of symptomatic therapy. Information on dietary measures was also not available in the company’s dossier.

In summary, it was uncertain whether the concomitant treatment used in the VX14-809-109 study constituted an adequate best symptomatic treatment in the sense of the ACT. These uncertainties described did not result in exclusion of the study, however. Instead, it was assumed that conclusions on the added benefit of lumacaftor/ivacaftor in comparison with the ACT can be drawn on the basis of the study results. Nonetheless, these uncertainties were considered in the assessment of the certainty of conclusions of the results.

Risk of bias and overall assessment of the certainty of conclusions

The risk of bias at study level was rated as low. The risk of bias was rated as low for the following outcomes: all-cause mortality, pulmonary exacerbations, hospitalizations due to pulmonary exacerbations, symptoms (presented as additional information using the Cystic Fibrosis Questionnaire Revised [CFQ-R] parent/caregiver version), health-related quality of life (presented as additional information using the CFQ-R parent/caregiver version), and discontinuation due to AEs. The risk of bias was rated as high for the outcomes "symptoms (CFQ-R patient version)" and "health-related quality of life (CFQ-R patient version)". The risk of bias for the outcome "serious AEs (SAEs)" was not assessed as the SAEs recorded in the study also included pulmonary exacerbation events. The exact number of SAEs without these events was unknown.

The overall certainty of conclusions of the study results for the present research question was reduced. As shown above, it remained unclear for the present benefit assessment whether some measures of the ACT specified by the G-BA were implemented in the study. Based on the VX14-809-109 study, at most hints, e.g. of an added benefit, can therefore be derived for all outcomes presented.

Results

Mortality

No child died during the study. There was no hint of an added benefit of lumacaftor/ivacaftor in comparison with best symptomatic treatment for all-cause mortality; an added benefit is therefore not proven.

Morbidity

- Pulmonary exacerbations and hospitalizations due to pulmonary exacerbations

There was no statistically significant difference between the treatment groups for the outcomes "pulmonary exacerbations" and "hospitalizations due to pulmonary exacerbations". This resulted in no hint of an added benefit of lumacaftor/ivacaftor in comparison with best symptomatic treatment for these outcomes; an added benefit is therefore not proven.

- Symptoms measured using the CFQ-R

Symptom outcomes were recorded directly in the children using the individual CFQ-R (patient version) domains of respiratory system and gastrointestinal symptoms. The CFQ-R (parent/caregiver version) was additionally used in the study. This questionnaire asks parents

and caregivers about symptoms in the domains of respiratory system, gastrointestinal symptoms and weight problems. 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 in the present benefit assessment.

The CFQ-R (patient version) domain of respiratory system showed no statistically significant difference between the treatment groups in the difference averaged over the course of the study versus the start of the study. A statistically significant difference in favour of lumacaftor/ivacaftor was shown in the CFQ-R (patient version) domain of gastrointestinal symptoms. However, the confidence interval (CI) for Hedges' g was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is clinically relevant.

Overall, there was no hint of an added benefit of lumacaftor/ivacaftor in comparison with best symptomatic treatment for the CFQ-R (patient version) symptom domains of respiratory system and gastrointestinal symptoms; an added benefit is therefore not proven.

This result was consistent with the results of the CFQ-R (parent/caregiver version).

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

Health-related quality of life was measured directly in the children using the individual domains of physical wellbeing, emotional state, body image, eating disturbances, treatment constraints, and social limitations of the disease-specific instrument CFQ-R (patient version). The CFQ-R (parent/caregiver version) was additionally used in the study. This questionnaire asks parents and caregivers about health-related quality of life using the domains of physical wellbeing, vitality, emotional state, school performance, body image, eating disturbances, treatment constraints, and subjective health perception. 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 in the present benefit assessment.

Individual CFQ-R (patient version) domains showed no statistically significant difference between the treatment groups in the difference averaged over the course of the study versus the start of the study. Overall, there was no hint of an added benefit of lumacaftor/ivacaftor in comparison with best symptomatic treatment for health-related quality of life measured using the CFQ-R (patient version); an added benefit is therefore not proven.

This result was consistent with the results of the CFQ-R (parent/caregiver version).

Side effects

- Serious adverse events

The SAEs recorded in the study included a relevant number of pulmonary exacerbation events. The Institute conducted calculations to check the influence the inclusion of exacerbation events had on the result for the outcome "SAEs (without exacerbation events)". Based on the information provided in the clinical study report (CSR), there were 5 to 7 patients with at least

1 SAE in the lumacaftor/ivacaftor arm, and 6 to 9 patients with at least 1 SAE in the comparator arm. There was no statistically significant difference between the proportions of patients with at least 1 SAE for different scenarios based on these numbers.

Overall, this resulted in no hint of greater or lesser harm of lumacaftor/ivacaftor in comparison with best symptomatic treatment for the outcome "SAEs"; greater or lesser harm is therefore not proven.

- Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm of lumacaftor/ivacaftor in comparison with best symptomatic treatment for this outcome; greater or lesser harm is therefore not proven.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug lumacaftor/ivacaftor compared with the ACT is assessed as follows:

Overall, there were neither positive nor negative effects of lumacaftor/ivacaftor in comparison with best symptomatic treatment.

In summary, there is no hint of an added benefit of lumacaftor/ivacaftor in comparison with best symptomatic treatment for children with CF between 6 and 11 years of age who are homozygous for the F508del mutation in the CFTR gene. An added benefit is therefore not proven.

Table 3 presents a summary of the probability and extent of the added benefit of lumacaftor/ivacaftor.

[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].

Table 3: Lumacaftor/ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients between 6 and 11 years of age who are homozygous for the F508del mutation in the CFTR gene	Best symptomatic treatment (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [in the sense of the "Heilmittel-Richtlinie" (Remedies Directive)]), under exhaustion of all possible dietary measures	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; 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.

2.2 Research question

The aim of the present report was the assessment of the added benefit of lumacaftor/ivacaftor in comparison with the ACT in the treatment of CF in patients between 6 and 11 years of age who are homozygous for the F508del mutation in the CFTR gene.

Table 4 shows the therapeutic indication to be assessed and the corresponding ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of lumacaftor/ivacaftor

Therapeutic indication	**ACT[a]**
CF patients between 6 and 11 years of age who are homozygous for the F508del mutation in the CFTR gene	Best symptomatic treatment (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [in the sense of the "Heilmittel-Richtlinie" (Remedies Directive)]), under exhaustion of all possible dietary measures
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company cited best symptomatic treatment as ACT, but, throughout the entire dossier, used the term "best supportive care (BSC)" instead. The company did not mention therapeutic measures further specified by the G-BA as components of best symptomatic treatment.

The present benefit assessment was conducted in comparison with the G-BA's ACT. The implementation of the best symptomatic treatment (in accordance with the G-BA's specification) in the studies was checked.

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 list on lumacaftor/ivacaftor (status: 20 November 2017)
- bibliographical literature search on lumacaftor/ivacaftor (last search on 20 November 2017)
- search in trial registries for studies on lumacaftor/ivacaftor (last search on 22 November 2017)

To check the completeness of the study pool:

- search in trial registries for studies on lumacaftor/ivacaftor (last search on 7 February 2018)

The check identified no additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: lumacaftor/ivacaftor + BST vs. placebo + BST

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
VX14-809-109	Yes	Yes	No
a: Study sponsored by the company. BST: best symptomatic treatment; RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: lumacaftor/ivacaftor + BST vs. placebo + BST

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
VX14-809-109	RCT, double-blind, parallel	Children with CF who are between 6 and (including) 11 years of age and homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor + BST (N = 104) placebo + BST (N = 102)	Screening: 4 weeks (+ 1 week for extended preliminary examinations) Treatment: 24 weeks Follow-up: outcome-specific, up to 4 weeks after the last dose of the study medication	54 centres in North America, Europe and Australia 7/2015–9/2016	Primary: $LCI_{2.5}$ 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 exclusively include information on the relevant available outcomes for this benefit assessment.

AE: adverse event; BST: best symptomatic treatment; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; $LCI_{2.5}$: lung clearance index (number of breaths needed to lower the concentration of the tracer gas to 2.5% of its initial concentration); N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

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

Study	Intervention	Comparison	Prior and concomitant medication
VX14-809-109	Lumacaftor/ivacaftor	Placebo	**Pretreatment**
	200 mg/250 mg every 12 hours, orally, within 30 minutes after a fat-containing meal		not allowed (14 days before the first dose of the study medication): ▪ strong CYP3A inducers/inhibitors
	+ BST[b]	+ BST[b]	**Concomitant treatment**
	Interruption of medication was allowed if side effects occurred. Dose adjustments were not allowed.		not allowed: ▪ strong CYP3A inducers[a]

a: CYP3A inhibitors, CYP2C and CYP2B6 substrates during the treatment were allowed if special caution was taken.
b: In both study arms, basic medication was administered in addition to lumacaftor/ivacaftor or placebo. It was recommended to maintain stable basic medication from 4 weeks before the start of the study until the end of the observation period.
BST: best symptomatic treatment; CYP: cytochrome P450; RCT: randomized controlled trial; vs.: versus

The VX14-809-109 study was a randomized, double-blind, placebo-controlled study. The study included children with CF who were between 6 and (including) 11 years of age and homozygous for the F508del mutation in the CFTR gene. Genotyping was conducted in the screening phase.

In the study, a total of 206 children were randomly allocated in a 1:1 ratio, either to the lumacaftor/ivacaftor arm (104 children) or to the placebo arm (102 children). Randomization was stratified by body weight (< 25 kg versus ≥ 25 kg) and ppFEV1 (< 90% versus ≥ 90%). Treatment with lumacaftor/ivacaftor or placebo was in addition to basic therapy (see text passage on the implementation of the ACT below).

Patients in the lumacaftor/ivacaftor arm received 2 tablets lumacaftor 100 mg/ivacaftor 125 mg every 12 hours, which is in compliance with the recommendations of the SPC [3]. The SPC recommends to reduce the dose of lumacaftor/ivacaftor to one tablet daily for the first week of treatment in patients taking strong cytochrome P450 (CYP)3A inhibitors to allow for the induction effect of lumacaftor. Such dose adjustment was not mandated in the study. It was not assumed, however, that this had a relevant influence on the study results.

Primary outcome of the study was the $LCI_{2.5}$. Patient-relevant secondary outcomes were all-cause mortality, symptoms, health-related quality of life, and AEs. All outcomes, except the outcomes on pulmonary exacerbations, were recorded for a maximum of 4 weeks after the study medication. Observation of pulmonary exacerbations was conducted at most until week 24.

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

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

Study Characteristics Category	Lumacaftor/ivacaftor + BST	Placebo + BST
VX14-809-109	N[a] = 103	N[a] = 101
Age [years], mean (SD)	9 (2)	9 (2)
Sex [F/M], %	61/39	57/43
BMI [kg/m^2], mean (SD)	16.38 (1.7)	16.55 (2.0)
Origin, n (%)		
White	100 (97.1)	96 (95.0)
Other	3 (2.9)	5 (5.0)
ppFEV1 at baseline, n (%)		
< 70 %	10 (9.7)	1 (1.0)
≥ 70 % to < 90 %	42 (40.8)	47 (46.5)
≥ 90 % to ≤ 105 %	38 (36.9)	44 (43.6)
> 105 %	12 (11.7)	9 (8.9)
Treatment before study inclusion[b], n (%)		
Inhaled antibiotics	20 (19.4)	30 (29.7)
Inhaled bronchodilators	85 (82.5)	82 (81.2)
Inhaled hypertonic saline	67 (65.0)	54 (53.5)
Inhaled corticosteroids	38 (36.9)	47 (46.5)
Dornase alfa	88 (85.4)	88 (87.1)
Pseudomonas aeruginosa infection within 2 years before start of the study, n %	44 (42.7)	43 (42.6)
Treatment discontinuation, n (%)	6 (5.8)	5 (5.0)
Study discontinuation, n (%)	5 (4.9)	3 (3.0)

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: The treatment could be continued during the study.
BMI: body mass index; BST: best symptomatic treatment; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ppFEV1: percent predicted forced expiratory volume in 1 second; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics between the arms of the VX14-809-109 study were largely balanced. The mean age of the children was 9 years and most of them were of Caucasian origin. More girls (about 60%) than boys were included in both arms. About 42% of the children had had Pseudomonas aeruginosa infection within 2 years before the start of the study. Existing individual differences regarding inhaled symptomatic pretreatment did not indicate that one of the arms included children with more severe disease. The overall proportion of children who discontinued treatment or the study was low. After the end of the study, more than 96% of the children were switched to the single-arm follow-up study VX15-809-110.

Implementation of the appropriate comparator therapy

The G-BA defined best symptomatic treatment as ACT for lumacaftor/ivacaftor for the treatment of CF patients between 6 and 11 years of age who are homozygous for the F508del mutation in the CFTR gene. The G-BA further specified that this therapy is understood to include, in particular, antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy (in the sense of the "Heilmittel-Richtlinie" [Remedies Directive]), under exhaustion of all possible dietary measures.

In the VX14-809-109 study, the children were randomly assigned to treatment with lumacaftor/ivacaftor or placebo, each in addition to basic therapy. The company stated in the dossier that all components of basic therapy could be individually supplemented and optimized during the entire study period if this was deemed necessary by the investigators at the specialized CF centres. It was checked for the present benefit assessment whether the basic therapy administered in the study concurred with the G-BA's specifications for the ACT. The result of this check is explained in the following paragraph:

In accordance with the study requirements on the use of concomitant medication, it was recommended in the VX14-809-109 study to maintain a stable level of the basic medication that the children had been receiving already 4 weeks before randomization. An additional inclusion criterion was the readiness to maintain a stable CF medication over the entire study duration. The study documented the use of medications before the first dose of the study medication and during the study, as well as switching selected inhaled basic therapeutics in the course of the study (see Table 9 and Table 10).

Table 9: Medication before first administration of study treatment and concomitant medication (≥ 15 % in at least one study arm), direct comparison: lumacaftor/ivacaftor + BST vs. placebo + BST

Study	**Lumacaftor/ivacaftor + BST**		**Placebo + BST**	
	Medication before first administration of study treatment n (%)	Concomitant medication[a] n (%)	Medication before first administration of study treatment n (%)	Concomitant medication[a] n (%)
VX14-809-109	N = 103	N = 103	N = 101	N = 101
Dornase alfa	88 (85.4)	88 (85.4)	88 (87.1)	89 (88.1)
Sodium chloride	75 (72.8)	75 (72.8)	68 (67.3)	70 (69.3)
Pancreatin	72 (69.9)	71 (68.9)	78 (77.2)	78 (77.2)
Salbutamol	68 (66.0)	71 (68.9)	66 (65.3)	67 (66.3)
Azithromycin	29 (28.2)	35 (34.0)	32 (31.7)	36 (35.6)
Cholecalciferol	25 (24.3)	28 (27.2)	26 (25.7)	27 (26.7)
Omeprazole	25 (24.3)	26 (25.2)	28 (27.7)	29 (28.7)
Pancrelipase	25 (24.3)	26 (25.2)	21 (20.8)	22 (21.8)
Aquadeks (dietary supplement)	24 (23.3)	24 (23.3)	32 (31.7)	31 (30.7)
Fluticasone propionate	23 (22.3)	26 (25.2)	29 (28.7)	31 (30.7)
Macrogol	21 (20.4)	22 (21.4)	28 (27.7)	29 (28.7)
Vitamin D[b]	21 (20.4)	23 (22.3)	18 (17.8)	19 (18.8)
Vitamins[b]	20 (19.4)	21 (20.4)	7 (6.9)	7 (6.9)
Vitamins[b] with zinc	20 (19.4)	21 (20.4)	19 (18.8)	19 (18.8)
Sulfamethoxazole/ trimethoprim	7 (6.8)	28 (27.2)	6 (5.9)	27 (26.7)
Tobramycin	14 (13.6)	25 (24.3)	20 (19.8)	35 (34.7)
Paracetamol	3 (2.9)	21 (20.4)	13 (12.9)	34 (33.7)
Ibuprofen	8 (7.8)	18 (17.5)	7 (6.9)	26 (25.7)
Mometasone furoate	14 (13.6)	16 (15.5)	9 (8.9)	11 (10.9)
Amoxicillin/clavulanic acid	2 (1.9)	19 (18.4)	3 (3.0)	20 (19.8)

a: Continuation or initiation of the medication at or after initial dose of the study medication until 28 days after the last dose of the study medication.
b: Not otherwise specified.
BST: best symptomatic treatment; n: number of patients with administration of the respective medication; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 10: Switching of basic therapy in the course of the study, direct comparison: lumacaftor/ivacaftor + BST vs. placebo + BST

Study **Type of basic therapy** **Treatment before study inclusion**[a] **Treatment in the course of the study**[b]	**Lumacaftor/ivacaftor + BST** **n (%)**	**Placebo + BST** **n (%)**
VX14-809-109	N[c] = 103	N[c] = 101
Inhaled antibiotics		
Yes, thereof	20 (19.4)	30 (29.7)
Long-term[d]	19 (95.0)	28 (93.3)
Discontinued	1 (5.0)	0
Intermittent[e]	0	2 (6.7)
No, thereof	83 (80.6)	71 (70.3)
Long-term[d]	4 (4.8)	5 (7.0)
Intermittent[e]	5 (6.0)	8 (11.3)
Inhaled bronchodilators		
Yes, thereof	85 (82.5)	82 (81.2)
Long-term[d]	84 (98.8)	81 (98.8)
Discontinued	0	1 (1.2)
Intermittent[e]	1 (1.2)	0
No, thereof	18 (17.5)	19 (18.8)
Long-term[d]	1 (5.6)	0
Intermittent[e]	1 (5.6)	2 (10.5)
Inhaled hypertonic saline		
Yes, thereof	67 (65.0)	54 (53.5)
Long-term[d]	65 (97.0)	53 (98.1)
Discontinued	1 (1.5)	0
Intermittent[e]	1 (1.5)	1 (1.9)
No, thereof	36 (35.0)	47 (46.5)
Long-term[d]	2 (5.6)	1 (2.1)
Intermittent[e]	0	2 (4.3)
Inhaled corticosteroids		
Yes, thereof	38 (36.9)	47 (46.5)
Long-term[d]	38 (100.0)	47 (100.0)
Discontinued	0	0
Intermittent[e]	0	0
No, thereof	65 (63.1)	54 (53.5)
Long-term[d]	4 (6.2)	1 (1.9)
Intermittent[e]	1 (1.5)	1 (1.9)

(continued)

Table 10: Switching of basic therapy in the course of the study, direct comparison: lumacaftor/ivacaftor + BST vs. placebo + BST (continued)

Study **Type of basic therapy** **Treatment before study inclusion[a]** **Treatment in the course of the study[b]**	**Lumacaftor/ivacaftor + BST** **n (%)**	**Placebo + BST** **n (%)**
VX14-809-109	N[c] = 103	N[c] = 101
Dornase alfa		
Yes, thereof	88 (85.4)	88 (87.1)
Long-term[d]	88 (100.0)	88 (100.0)
Discontinued	0	0
Intermittent[e]	0	0
No, thereof	15 (14.6)	13 (12.9)
Long-term[d]	0	0
Intermittent[e]	0	1 (7.7)

a: Percentages refer to the number of randomized patients.
b: Percentages refer to the number of patients in the category "treatment before study inclusion (yes/no)".
c: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
d: Used in ≥ 25 % of the treatment days.
e: Used in < 25 % of the treatment days.
BST: best symptomatic treatment; n: number of patients in the category (treatment in the course of the study); N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The information provided on the concomitant drug treatment before and after the first dose of the study medication (see Table 9) shows that the most commonly used drugs were given for symptomatic CF treatment. Symptomatic treatment included, among others, dornase alfa, sodium chloride, pancreatin and salbutamol, as well as antibiotics, dietary supplements/vitamin products, and corticosteroids. It was visible that the majority of the children under the respective symptom-oriented treatment were mostly stable during the treatment period versus the time before the start of the intervention, or that individual children started these treatments in the course of the study. Only in the case of antibiotics (e.g. tobramycin or sulfamethoxazole/ trimethoprim) as well as paracetamol and ibuprofen, there was a more pronounced increase in the proportion of children receiving these treatments during the course of the study in comparison with the start of the study. It cannot be inferred overall from this presentation whether and in how many children the respective treatment was intensified, e.g. in the sense of increased dosing or increased frequency of administration.

Most children who were receiving inhaled basic therapy before study inclusion (see Table 10) used this treatment on a long-term basis also during the course of the study. In individual children, administration of the drugs was discontinued or intermittent. It cannot be assessed also on the basis of this presentation whether and in how many children treatment was intensified during the study, e.g. in the sense of an increased frequency of administration. It was visible, however, that inhaled treatments were initiated in some children.

This information overall indicates that the children were receiving comprehensive symptomatic drug treatment at the time point of study inclusion and that some adjustments to the drug treatment were made in the study, particularly regarding antibiotic treatment. However, more detailed information on the intensified therapy was missing. Intensified therapy can comprise increased dosing or increased frequency of administration, for example. In addition, the implementation of some measures that are components of the ACT cannot be assessed. Based on the study documents presented, it cannot be checked whether the patients received physiotherapy, which also forms part of the concept of symptomatic therapy. Information on dietary measures was also not available in the company's dossier.

In summary, it was uncertain whether the concomitant treatment used in the VX14-809-109 study constituted an adequate best symptomatic treatment in the sense of the ACT. These uncertainties did not result in exclusion of the study, however. Instead, it was assumed that conclusions on the added benefit of lumacaftor/ivacaftor in comparison with the ACT can be drawn on the basis of the study results. Nonetheless, the described uncertainties were considered in the assessment of the certainty of conclusions of the results (see Section 2.4.2).

Risk of bias across outcomes

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: lumacaftor/ivacaftor + BST vs. placebo + BST

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			
VX14-809-109	Yes	Yes	Yes	Yes	Yes	Yes	Low
BST: best symptomatic treatment; RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the VX14-809-109 study was rated as low. 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 2.7.2.4.3 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 (patient version) instrument (the corresponding domains of the parent/caregiver version are presented as additional information)
- Health-related quality of life
  - measured with the health-related quality of life domains of the CFQ-R (patient version) instrument (the corresponding domains of the parent/caregiver version are presented as additional information)
- Side effects
  - SAEs
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which, among other aspects, used further outcomes in the dossier (Module 4A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: lumacaftor/ivacaftor + BST vs. placebo + BST

Study	Outcomes								
	All-cause mortality	Pulmonary exacerbations	Hospitalizations due to pulmonary exacerbations	Symptoms (CFQ-R patient version)	Additional information: symptoms (CFQ-R parent/caregiver version)	Health-related quality of life (CFQ-R patient version)	Additional information: health-related quality of life (CFQ-R parent/caregiver version)	SAEs	Discontinuation due to AEs
VX14-809-109	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[a]	Yes

a: The SAEs recorded in the study included pulmonary exacerbation events; see Section 2.7.2.4.3 of the full dossier assessment for information on how this outcome was handled.

AE: adverse event; BST: best symptomatic treatment; CFQ-R: Cystic Fibrosis Questionnaire Revised; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.4.2 Risk of bias

Table 13 describes the risk of bias for the relevant outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: lumacaftor/ivacaftor + BST vs. placebo + BST

Study		Outcomes								
	Study level	All-cause mortality	Pulmonary exacerbations	Hospitalizations due to pulmonary exacerbations	Symptoms (CFQ-R patient version)	Additional information: symptoms (CFQ-R parent/caregiver version)	Health-related quality of life (CFQ-R patient version)	Additional information: health-related quality of life (CFQ-R parent/caregiver version)	SAEs	Discontinuation due to AEs
VX14-809-109	L	L	L	L	H[a]	L	H[a]	L	-[b]	L

a: Large proportion of patients (about 25% in both treatment arms) who were not considered in the analysis.

b: The SAEs recorded in the study included pulmonary exacerbation events; see Section 2.7.2.4.3 of the full dossier assessment for information on how this outcome was handled.

AE: adverse event; BST: best symptomatic treatment; CFQ-R: Cystic Fibrosis Questionnaire Revised; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Concurring with the company's assessment, the risk of bias was rated as low for the following outcomes: all-cause mortality, pulmonary exacerbations, hospitalizations due to pulmonary exacerbations, symptoms (presented as additional information using the CFQ-R parent/caregiver version), health-related quality of life (presented as additional information using the CFQ-R parent/caregiver version), and discontinuation due to AEs.

In contrast to the company's assessment, the risk of bias was rated as high for the outcomes "symptoms (CFQ-R patient version)" and "health-related quality of life (CFQ-R patient version)". For the outcomes "symptoms (CFQ-R patient version)" and "health-related quality of life (CFQ-R patient version)", the risk of bias resulted from the high proportion of patients who were not considered in the analysis.

The SAEs recorded in the study included a relevant number of pulmonary exacerbation events (see Section 2.7.2.4.3 of the full dossier assessment). The exact number of SAEs without exacerbations is unknown. The risk of bias for the outcome "SAEs" was therefore not assessed. The company assumed a low risk of bias for the outcome "SAEs".

Detailed reasons for the assessment of the risk of bias can be found in Section 2.7.2.4.2 of the full dossier assessment.

Overall assessment of the certainty of conclusions

As explained in Section 2.3.2, it remained unclear for the present benefit assessment whether some measures of the ACT specified by the G-BA were implemented in the study. It cannot be assessed whether the children received physiotherapy and whether all possible dietary measures were exhausted. Detailed information on the intensification of symptomatic therapy was also missing. Hence, the certainty of conclusions of the study results for the present research question was reduced. Based on the VX14-809-109 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

2.4.3 Results

Table 14 and Table 15 summarize the results on the comparison of lumacaftor/ivacaftor with BST in children with CF. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Table 14: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: lumacaftor/ivacaftor + BST vs. placebo + BST

Study Outcome category Outcome	Lumacaftor/ivacaftor + BST		Placebo + BST		Lumacaftor/ivacaftor + BST vs. placebo + BST
	N	Patients with event n (%) or events n_E/patient years	N	Patients with event n (%) or events n_E/patient years	RR [95 % CI] or rate ratio [95 % CI]; p-value
VX14-809-109					
Mortality					
All-cause mortality	103	0 (0)	101	0 (0)	–
Morbidity					
Pulmonary exacerbations	103	24/50.0	101	18/49.8	1.33 [0.70; 2.53]; 0.386[a]
Hospitalizations due to pulmonary exacerbations	103	8/50.0	101	6/49.8	1.33 [0.44; 3.99]; 0.608[a]
Side effects					
AEs (additional information)	103	98 (95.1)	101	98 (97.0)	–
SAEs[b]	103	ND	101	ND	–
Discontinuation due to AEs	103	3 (2.9)	101	2 (2.0)	1.45 [0.25; 8.40][c]; 0.671

a: Rate ratio, CI und p-value from negative binomial model, adjusted for weight (< 25 kg vs. ≥ 25 kg) and ppFEV1 % (< 90 vs. ≥ 90), log(study time) as offset.
b: The SAEs recorded in the study included exacerbation events (see Section 2.7.2.4.3 of the full dossier assessment). Calculations of the SAEs without exacerbation events conducted by the Institute resulted in 5 to 7 patients with at least 1 SAE in the intervention arm, and 6 to 9 patients with at least 1 SAE in the comparator arm. These calculations produced no statistically significant differences.
c: RR, CI and p-value from generalized linear model stratified by weight (< 25 kg vs. ≥ 25 kg) and ppFEV1 (< 90 vs. ≥ 90).
AE: adverse event; BST: best symptomatic treatment; CI: confidence interval; n: number of patients with (at least one) event; n_E: number of events; N: number of analysed patients; ND: no data; ppFEV1: percent predicted forced expiratory volume in 1 second; 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: lumacaftor/ivacaftor + BST vs. placebo + BST

Study Outcome category Outcome	Lumacaftor/ivacaftor + BST			Placebo + BST			Lumacaftor/ivacaftor + BST vs. placebo + BST
	N[a]	Values at start of study mean (SD)	Change at end of study mean (SD)	N[a]	Values at start of study mean (SD)	Change at end of study mean (SD)	MD[b] [95% CI]; p-value
VX14-809-109							
Morbidity							
Symptoms (CFQ-R patient version, symptom domains)							
Respiratory system	76	78.68 (13.95)	5.04 (10.08)	78	77.14 (15.46)	3.42 (12.42)	2.50 [−0.14; 5.14]; 0.063
Gastrointestinal symptoms	76	71.00 (26.13)	9.18 (20.55)	77	68.40 (25.87)	5.30 (21.76)	5.32 [1.04; 9.60]; 0.015 Hedges' g: 0.36 [0.04; 0.68]
Additional information: symptoms (CFQ-R parent/caregiver version, symptom domains)							
Respiratory system	102	82.07 (14.89)	1.18 (11.12)	99	82.19 (15.27)	−0.33 (13.50)	1.29 [−1.17; 3.75]; 0.302
Gastrointestinal symptoms	102	73.89 (19.54)	2.38 (14.04)	99	74.78 (15.14)	2.06 (12.72)	0.01 [−2.92; 2.95]; 0.992
Weight problems	102	60.84 (40.27)	7.41 (29.35)	99	60.33 (35.67)	4.38 (22.13)	3.53 [−2.02; 9.08]; 0.211
Health-related quality of life							
CFQ-R patient version, health-related quality of life domains							
Physical wellbeing	76	83.72 (15.83)	1.67 (12.73)	78	81.70 (19.14)	2.15 (14.73)	0.33 [−3.46; 4.11]; 0.865
Emotional state	76	76.08 (12.42)	5.84 (9.31)	78	74.20 (14.28)	5.19 (9.74)	1.75 [−0.54; 4.04]; 0.133
Body image	76	87.52 (20.63)	4.02 (11.17)	78	87.32 (17.15)	4.97 (12.12)	−0.81 [−3.59; 1.97]; 0.565
Eating disturbances	76	78.79 (21.19)	4.13 (16.04)	78	78.06 (22.22)	3.63 (14.18)	0.70 [−3.28; 4.69]; 0.727
Treatment constraints	76	74.89 (19.53)	4.32 (15.45)	78	75.36 (16.48)	0.98 (15.08)	3.08 [−1.17; 7.33]; 0.154
Social limitations	76	70.25 (14.04)	1.96 (10.97)	78	69.59 (15.96)	0.97 (10.71)	1.49 [−1.56; 4.53]; 0.336

(continued)

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

Study Outcome category Outcome	Lumacaftor/ivacaftor + BST			Placebo + BST			Lumacaftor/ivacaftor + BST vs. placebo + BST
	N[a]	Values at start of study mean (SD)	Change at end of study mean (SD)	N[a]	Values at start of study mean (SD)	Change at end of study mean (SD)	MD[b] [95% CI]; p-value
VX14-809-109							
Health-related quality of life							
Additional information: CFQ-R parent/caregiver version, health-related quality of life domains							
Physical wellbeing	102	89.90 (13.97)	−0.19 (10.65)	98	88.88 (12.53)	−1.15 (10.25)	1.36 [−1.20; 3.92]; 0.296
Vitality	102	74.21 (13.37)	0.86 (10.67)	98	74.27 (12.50)	−0.01 (10.60)	0.90 [−1.60; 3.39]; 0.480
Emotional state	102	85.57 (13.82)	1.72 (9.23)	98	85.93 (11.94)	0.51 (9.55)	1.10 [−1.00; 3.19]; 0.304
School performance	102	76.70 (24.23)	2.16 (14.21)	98	78.00 (22.56)	1.44 (16.58)	0.56 [−2.89; 4.02]; 0.748
Body image	102	77.13 (24.04)	4.94 (15.41)	98	77.28 (22.91)	3.79 (16.35)	1.18 [−2.54; 4.90]; 0.532
Eating disturbances	102	71.84 (28.30)	2.17 (17.81)	98	73.67 (25.97)	0.85 (16.76)	0.93 [−3.28; 5.14]; 0.663
Treatment constraints	102	57.17 (21.47)	4.38 (13.68)	98	54.44 (20.32)	4.21 (13.27)	0.87 [−2.68; 4.43]; 0.628
Subjective health perception	102	80.47 (17.63)	−1.61 (11.29)	98	74.89 (16.68)	0.50 (13.63)	−0.18 [−3.32; 2.96]; 0.910

a: Number of patients considered in the analysis for the calculation of the effect; the values at the start of the study may be based on other patient numbers.
b: MMRM, adjusted for body weight (< 25 kg vs. ≥ 25 kg) and ppFEV1 (< 90 vs. ≥ 90) at the time point of screening and baseline CFQ-R score.
BST: best symptomatic treatment; CFQ-R: Cystic Fibrosis Questionnaire Revised; CI: confidence interval; MD: mean difference, MMRM: mixed-effects model repeated measures; N: number of analysed patients; ppFEV1: percent predicted forced expiratory volume in 1 second; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

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

Mortality

All-cause mortality

No child died during the study. There was no hint of an added benefit of lumacaftor/ivacaftor in comparison with best symptomatic treatment for all-cause mortality; an added benefit is therefore not proven.

The company also described that no deaths during the study were reported.

Morbidity

Pulmonary exacerbations

No statistically significant difference was shown between the treatment groups for the outcome "pulmonary exacerbations". This resulted in no hint of an added benefit of lumacaftor/ivacaftor in comparison with best symptomatic treatment for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

Hospitalizations due to pulmonary exacerbations

No statistically significant difference was shown between the treatment groups for the outcome "hospitalizations due to pulmonary exacerbations". This resulted in no hint of an added benefit of lumacaftor/ivacaftor in comparison with best symptomatic treatment for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

Symptoms measured using the CFQ-R

Symptom outcomes were recorded directly in the children using the individual domains of respiratory system and gastrointestinal symptoms of the disease-specific instrument CFQ-R (patient version). The parent/caregiver version of the CFQ-R was additionally used in the study. This questionnaire asks parents and caregivers about symptoms in the domains of respiratory system, gastrointestinal symptoms and weight problems. 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 in the present benefit assessment (see Section 2.7.2.4.3 of the full dossier assessment).

The CFQ-R (patient version) domain of respiratory system showed no statistically significant difference between the treatment groups in the difference averaged over the course of the study versus the start of the study. A statistically significant difference in favour of lumacaftor/ivacaftor was shown in the CFQ-R (patient version) domain of gastrointestinal symptoms. However, the CI for Hedges' g was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect is clinically relevant.

Overall, there was no hint of an added benefit of lumacaftor/ivacaftor in comparison with best symptomatic treatment for the CFQ-R (patient version) symptom domains of respiratory system and gastrointestinal symptoms; an added benefit is therefore not proven.

This result was consistent with the results of the CFQ-R (parent/caregiver version) The individual CFQ-R (parent/caregiver version) symptom domains showed no statistically significant difference between the treatment groups in the difference averaged over the course of the study versus the start of the study.

The assessment partly deviates from that of the company. The company derived an indication of a minor added benefit for the domains of gastrointestinal symptoms of the CFQ-R (patient version) instrument, which it classified as belonging to health-related quality of life. Based on a subgroup analysis, it additionally derived an indication of a minor added benefit for the CFQ-R (parent/caregiver version) domain of respiratory system for the characteristic "sex" for boys.

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

Health-related quality of life was measured directly in the children using the individual domains of physical wellbeing, emotional state, body image, eating disturbances, treatment constraints, and social limitations of the disease-specific instrument CFQ-R (patient version). The parent/caregiver version of the CFQ-R was additionally used in the study. This questionnaire asks parents and caregivers about health-related quality of life using the domains of physical wellbeing, vitality, emotional state, school performance, body image, eating disturbances, treatment constraints, and subjective health perception. 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 in the present benefit assessment (see Section 2.7.2.4.3 of the full dossier assessment).

Individual CFQ-R (patient version) domains showed no statistically significant difference between the treatment groups in the difference averaged over the course of the study versus the start of the study. Overall, there was no hint of an added benefit of lumacaftor/ivacaftor in comparison with best symptomatic treatment for health-related quality of life measured using the CFQ-R (patient version); an added benefit is therefore not proven.

This result was consistent with the results of the CFQ-R (parent/caregiver version) The individual CFQ-R (parent/caregiver version) domains showed no statistically significant difference between the treatment groups in the difference averaged over the course of the study versus the start of the study.

This largely concurred with the assessment of the company, which derived no added benefit for the individual domains of health-related quality of life of the CFQ-R (patient version). For the subgroup of children treated with corticosteroids before/at study inclusion, however, it derived an indication of an added benefit for each of the CFQ-R (parent/caregiver version) domains of emotional state and treatment constraints.

Side effects

Serious adverse events

The SAEs recorded in the study included a relevant number of pulmonary exacerbation events (see Section 2.7.2.4.3 of the full dossier assessment). The Institute conducted calculations to check the influence of the included exacerbation events on the result for the outcome "SAEs (without exacerbation events)". Based on the information provided in the CSR (see Table 24 in Appendix A of the full dossier assessment), there were 5 to 7 patients with at least 1 SAE in the

lumacaftor/ivacaftor arm, and 6 to 9 patients with at least 1 SAE in the comparator arm. There was no statistically significant difference between the proportions of patients with at least 1 SAE for different scenarios based on these numbers.

Overall, this resulted in no hint of greater or lesser harm of lumacaftor/ivacaftor in comparison with best symptomatic treatment for the outcome "SAEs"; greater or lesser harm is therefore not proven.

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

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm of lumacaftor/ivacaftor in comparison with best symptomatic treatment for this outcome; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

2.4.4 Subgroups and other effect modifiers

The following subgroups were used for the present assessment:

- sex (female, male)
- region (North America, Europe, Australia)
- Pseudomonas aeruginosa infection status at baseline (positive, negative)

Only the 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 clinically relevant effect in at least one subgroup.

In accordance with the methods described above, no relevant effect modification was identified for the present research question.

2.5 Probability and extent of added benefit

The derivation of probability and extent of the added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on 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 added benefit at outcome level

The extent of the respective added benefit at outcome level (Table 16) was estimated from the results presented in Section 2.4.

Table 16: Extent of added benefit at outcome level: lumacaftor/ivacaftor + BST vs. placebo + BST

Outcome category **Outcome**	**Lumacaftor/ivacaftor + BST vs. placebo + BST** **Number of events/patient years or mean change or proportion of events (%)** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0 % vs. 0 %	Lesser benefit/added benefit not proven
Morbidity		
Pulmonary exacerbations	24/50.0 vs. 18/49.8 rate ratio: 1.33 [0.70; 2.53]; p = 0.386	Lesser benefit/added benefit not proven
Hospitalizations due to pulmonary exacerbations	8/50.0 vs. 6/49.8 rate ratio: 1.33 [0.44; 3.99]; p = 0.608	Lesser benefit/added benefit not proven
Symptoms (CFQ-R patient version, symptom domain)		
Respiratory system	Mean change: 5.04 vs. 3.42 MD: 2.50 [−0.14; 5.14]; p = 0.063	Lesser benefit/added benefit not proven
Gastrointestinal symptoms	Mean change: 9.18 vs. 5.30 MD: 5.32 [1.04; 9.60]; p = 0.015 Hedges' g[c]: 0.36 [0.04; 0.68]	Lesser benefit/added benefit not proven
Health-related quality of life		
CFQ-R patient version, health-related quality of life domain		
Physical wellbeing	Mean change: 1.67 vs. 2.15 MD: 0.33 [−3.46; 4.11]; p = 0.865	Lesser benefit/added benefit not proven
Emotional state	Mean change: 5.84 vs. 5.19 MD: 1.75 [−0.54; 4.04]; p = 0.133	Lesser benefit/added benefit not proven
Body image	Mean change: 4.02 vs. 4.97 MD: −0.81 [−3.59; 1.97]; p = 0.565	Lesser benefit/added benefit not proven
Eating disturbances	Mean change: 4.13 vs. 3.63 MD: 0.70 [−3.28; 4.69]; p = 0.727	Lesser benefit/added benefit not proven
Treatment constraints	Mean change: 4.32 vs. 0.98 MD: 3.08 [−1.17; 7.33]; p = 0.154	Lesser benefit/added benefit not proven
Social limitations	Mean change: 1.96 vs. 0.97 MD: 1.49 [−1.56; 4.53]; p = 0.336	Lesser benefit/added benefit not proven
Side effects		
SAEs	–d	Greater/lesser harm not proven
Discontinuation due to adverse events	2.9 % vs. 2.0 % RR: 1.45 [0.25; 8.40]; p = 0.671	Greater/lesser harm not proven

(continued)

Table 16: Extent of added benefit at outcome level: lumacaftor/ivacaftor + BST vs. placebo + BST (continued)

a: Probability provided if a statistically significant and relevant effect is present
b: Estimations of effect size are made depending on the outcome category with different limits based on the 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 clinically relevant effect. In other cases, the presence of a clinically relevant effect cannot be derived.
d: The SAEs recorded in the study included exacerbation events. Calculations of the SAEs without exacerbation events conducted by the Institute produced no statistically significant differences.
AE: adverse event; BST: best symptomatic treatment; CFQ-R: Cystic Fibrosis Questionnaire Revised; CI: confidence interval; CI_u: upper limit of confidence interval; MD: mean difference; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

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

Table 17: Positive and negative effects from the assessment of lumacaftor/ivacaftor + BST in comparison with placebo + BST

Positive effects	**Negative effects**
–	–
BST: best symptomatic treatment	

Overall, there were neither positive nor negative effects of lumacaftor/ivacaftor in comparison with best symptomatic treatment.

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

Table 18: Lumacaftor/ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients between 6 and 11 years of age who are homozygous for the F508del mutation in the CFTR gene	Best symptomatic treatment (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [in the sense of the "Heilmittel-Richtlinie" (Remedies Directive)]), under exhaustion of all possible dietary measures	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

In summary, there is no hint of an added benefit of lumacaftor/ivacaftor in comparison with best symptomatic treatment for children with CF between 6 and 11 years of age who are

homozygous for the F508del mutation in the CFTR gene. An added benefit is therefore not proven.

The assessment described above does not concur with that of the company, which derived an indication of non-quantifiable added benefit of lumacaftor/ivacaftor.

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

2.6 List of included studies

Ratjen F, Hug C, Marigowda G, Tian S, Huang X, Stanojevic S et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. Lancet Respir Med 2017; 5(7): 557-567.

Vertex Pharmaceuticals Incorporated. A study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects with CF, homozygous for the F508del-CFTR mutation: study details [online]. In: ClinicalTrials.gov. 23.10.2017 [Accessed: 04.03.2018]. URL: https://ClinicalTrials.gov/show/NCT02514473.

Vertex Pharmaceuticals Incorporated. A phase 3, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 6 through 11 years with cystic fibrosis, homozygous for the F508del-CFTR mutation [online]. In: EU Clinical Trials Register. [Accessed: 04.03.2018]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-000543-16.

Vertex Pharmaceuticals Incorporated. A phase 3, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 6 through 11 years with cystic fibrosis, homozygous for the F508del-CFTR mutation: study VX14-809-109; clinical study protocol version 2.0 [unpublished]. 2015.

Vertex Pharmaceuticals Incorporated. A phase 3, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 6 through 11 years with cystic fibrosis, homozygous for the F508del-CFTR mutation: study VX14-809-109; statistical analysis plan version 2.0 [unpublished]. 2016.

Vertex Pharmaceuticals Incorporated. A phase 3, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 6 through 11 years with cystic fibrosis, homozygous for the F508del-CFTR mutation: study VX14-809-109; clinical study report [unpublished]. 2017.

Vertex Pharmaceuticals Incorporated. A phase 3, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 6 through 11 years with cystic fibrosis, homozygous for the F508del-CFTR mutation: study VX14-809-109; Zusatzanalysen [unpublished]. 2017.

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.

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3. Vertex. Orkambi Filmtabletten: Fachinformation [online]. 01.2018 [Accessed: 21.03.2018]. URL: https://www.fachinfo.de.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-08-lumacaftor-ivacaftor-cystic-fibrosis-benefit-assessment-according-to-35a-social-code-book-v.8883.html.