IQWiG Reports – Commission No. A21-122

Lumacaftor/ivacaftor (cystic fibrosis, 2 to 5 years, F508del mutation, homozygous) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Lumacaftor/Ivacaftor (zystische Fibrose, 2 bis 5 Jahre, F508del-Mutation, homozygot) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 23 December 2021). Please note: This document was translated by an external translator and 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent for participating in the written exchange about how they experienced the disease and its treatment, and about treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
BSC	best supportive care
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
LCI	lung clearance index
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MRI	magnetic resonance imaging
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

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 lumacaftor/ivacaftor. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 29 September 2021.

The present assessment is a reassessment after expiry of the decision. The G-BA imposed a time limit on its decision regarding the previous assessment because during the assessment period, the randomized controlled trial (RCT) VX16-809-121 was ongoing, and no results were available yet. The imposed time limit required submission of the final results of the VX16-809-121 study.

Research question

The aim of the present report was to assess the added benefit of lumacaftor/ivacaftor in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) for the treatment of cystic fibrosis (CF) in patients aged 2 to 5 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

The research question presented in Table 2 resulted from the ACT specified by the G-BA.

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

Therapeutic indication	**ACT**[a]
Patients aged 2 to 5 years with CF who are homozygous for the F508del mutation in the CFTR gene	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (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).

ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee

The company designated BSC as the ACT, thus following 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 added benefit.

Study pool and study design

In the benefit assessment, the VX16-809-121 study is used for the direct comparison of lumacaftor/ivacaftor + BSC with placebo + BSC.

Additional evidence presented by the company

In addition to the RCT VX16-809-121, the company's dossier also presented results from a non-randomized comparative study and from other investigations. In addition, the company included a survival time model in its arguments on deriving added benefit. Further, the company argues that the added benefit of lumacaftor/ivacaftor can be extrapolated from CF patients ages 6 to 12 years to the age group to be assessed, 2 to 5 years. All in all, the company did not derive added benefit on the basis of the results of the VX16-809-121 RCT, but from an overall analysis of the presented results and arguments.

The documents presented by the company alongside the RCT VX16-809-121 are irrelevant for the present benefit assessment. In departure from the company's approach, the added benefit of lumacaftor/ivacaftor versus the ACT was derived only on the basis of the results of the RCT VX16-809-121.

VX16-809-121 study

The VX16-809-121 study is a randomized, double-blind, 2-part study, with the 1st part comparing lumacaftor/ivacaftor + BSC with placebo + BSC. Following the 48-week double-blind treatment phase, the 2nd part involved all patients being treated with lumacaftor/ivacaftor for another 48 weeks.

The study included CF patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene. It excluded patients with an acute infection of the upper or lower respiratory tract or pulmonary exacerbations. In addition, the baseline medication for CF was to have been continued unchanged for 28 days before treatment start.

The study randomized a total of 51 patients at a 2:1 ratio either to treatment with lumacaftor/ivacaftor + BSC or to placebo + BSC. The study was conducted only in Germany.

Patients were treated with lumacaftor/ivacaftor in accordance with the Summary of Product Characteristics (SPC) or received a placebo. In both study arms, patients additionally received accompanying baseline therapy.

The primary outcome of the study was a change in the Global Chest Score, measured using magnetic resonance imaging (MRI) of the respiratory tract. Patient-relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity and adverse events (AEs).

Implementation of the ACT

The G-BA specified BSC as the ACT for lumacaftor/ivacaftor in CF patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene.

In the VX16-809-121 study, the existing symptomatic therapy of patients was to be continued during the lumacaftor/ivacaftor or placebo treatment. The study protocol required that no changes be made to the concomitant medication from 28 days before study start until the end of the study. For inclusion, the study additionally required participants to be willing to maintain a stable CF-related concomitant treatment for the entire duration of the study.

The data on prior and concomitant treatment show that, at the time of study inclusion, patients received inhaled medication (including saline solution), digestive enzymes, vitamins, and physical therapy for symptomatic treatment of CF. While the available data suggest that some patients started concomitant treatment after the 1st dose of the study drug, it remains unclear whether more patients would have needed an adjustment over the 48-week course of the study. Additionally, the data do not show in how many patients, if any, the concomitant treatment was adjusted, e.g. by increasing the dose or frequency of drug or non-drug treatment. Furthermore, it is unclear how many, if any, patients discontinued the concomitant treatment over the course of the study.

In summary, it remains unclear whether the concomitant treatment used in the VX16-809-121 study represents a full implementation of the ACT of BSC. This conclusion has been informed by the fact that no information is available on treatment adjustments in the form of dose or frequency increases of symptomatic treatment over the course of the study. This circumstance did not, however, lead to exclusion of the study. 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. The uncertainties described were, however, taken into account when assessing the certainty of conclusions of the results.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes was rated as low for the VX16-809-121 study.

Except for the outcome of SAEs, the risk of bias regarding the results is assessed as low for all included outcomes. The risk of bias for the results was rated as high for the outcome of SAEs.

For the present research question, the certainty of the study results is reduced due to the above-described missing details concerning the implementation of the ACT; for the outcome of SAEs, it is additionally reduced due to the already higher risk of bias for other reasons. Based on the VX16-809-121 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

Results

Mortality

Overall survival

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

Morbidity

Pulmonary exacerbations

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

Hospitalization due to pulmonary exacerbations

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

Health-related quality of life

Health-related quality of life outcomes were not recorded in the VX16-809-121 study.

Side effects

SAEs

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

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, no events occurred in the course of the study. This resulted in no hint of greater or lesser harm from lumacaftor/ivacaftor + BSC in comparison with BSC; 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 in comparison with the ACT is assessed as follows:

The VX16-809-121 study showed neither effects in favour nor effects to the disadvantage of lumacaftor/ivacaftor + BSC.

[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].

In summary, there is no hint of an added benefit of lumacaftor/ivacaftor + BSC in comparison with the ACT of BSC for CF patients between 2 and 5 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.

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene	BSC[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (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).

ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee

The approach for the derivation of 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 to assess the added benefit of lumacaftor/ivacaftor in comparison with BSC as the ACT for the treatment of CF in patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene.

The research question presented in Table 4 resulted from the ACT specified by the G-BA.

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

Therapeutic indication	**ACT[a]**
CF patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (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).

ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee

The company designated BSC as the ACT, thus following 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 added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- Study lists on lumacaftor/ivacaftor (status: 12 July 2021)
- Bibliographical literature search on lumacaftor/ivacaftor (last search on 5 July 2021)
- Search in trial registries / trial results databases for studies on lumacaftor/ivacaftor (last search on 5 July 2021)
- Search on the G-BA website for lumacaftor/ivacaftor (last search on 5 July 2021)

To check the completeness of the study pool:

- Search in trial registries for lumacaftor/ivacaftor (last search on 8 October 2021); see Appendix A of the full dossier assessment for search strategies.

Concurring with the company, the check for completeness of the study pool found no relevant study other than the RCT VX16-809-121 for the direct comparison of lumacaftor/ivacaftor + BSC versus placebo + BSC.

Additional evidence presented by the company

In addition to the RCT VX16-809-121, the company's dossier presented results from a non-randomized comparative study (cohort study VX14-809-108 [3]) and from further investigations (1-arm study VX16-809-116 [4] [subsequent study to VX15-809-115 [5]]). However, the company did not carry out a comprehensive information retrieval in this regard. In addition, the company included a model on survival time [6] in its arguments for deriving added benefit. In the company's opinion, this model shows longer survival for patients starting lumacaftor/ivacaftor treatment at age 2 years. Further, the company argues that the added benefit of lumacaftor/ivacaftor can be extrapolated from CF patients ages 6 to 12 years to the age group to be assessed, 2 to 5 years. All in all, the company did not derive added benefit on the basis of the results of the VX16-809-121 RCT, but from an overall analysis of the presented results and arguments.

In departure from the company's approach, the added benefit of lumacaftor/ivacaftor versus the ACT was derived only on the basis of the results of the RCT VX16-809-121. The documents presented by the company in addition to RCT VX16-809-121 are irrelevant for the present benefit assessment. This is justified below.

No conclusions can be drawn from the non-randomized cohort study VX14-809-108 regarding the comparison between lumacaftor/ivacaftor versus the ACT in the present therapeutic indication because the comparator cohort included only patients with a different mutation type (F508del heterozygous mutation instead of F508del homozygous mutation in the intervention cohort). In its study list on non-randomized comparative studies, the company additionally lists the non-randomized cohort study VX14-809-128 [7]. According to the study protocol [8], the comparator cohort of this study -- unlike VX14-809-108 -- comprises patients with homozygous F508del mutation. The company reports that this study is still ongoing and that no results are currently available.

The VX16-809-116 study is the subsequent study to the 1-arm VX15-809-115 study, which has already been described in the previous benefit assessment (dossier assessment A19-13 [9]). The company's reasoning regarding the extrapolation of added benefit from older patient groups to the age group relevant for the present benefit assessment has already been discussed in dossier assessment A19-13.

The survival time model to which the company refers is likewise unsuitable for the present benefit assessment. For this model, patient profiles were simulated based on patient characteristics from various studies on lumacaftor/ivacaftor and registries, and they were each allocated to treatment with and without lumacaftor/ivacaftor as an add-on to standard therapy. The probability of dying was estimated cyclically on the basis of a regression model by Liou et al. from 2001 [10], and the patients' profiles were adjusted. In the process, numerous assumptions regarding treatment effects were made based on prognostic factors found in patient profiles for survival. These assumptions are based, for the most part, on data from studies with short treatment durations. It remains unclear whether these assumptions can be extrapolated to long-term treatment effects for the entire modelling period (lifetime of all simulated patients). In addition, it remains unclear whether the regression coefficients selected according to Liou et al. are appropriate for the current healthcare context. All things considered, the model is subject to substantial uncertainties and is therefore unsuitable for the present benefit assessment.

2.3.1 Studies included

The study presented in the table below was included in the benefit assessment.

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
VX16-809-121	No	Yes	No	Yes [11]	Yes [12,13]	No

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
BSC: best supportive care; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The VX16-809-121 study was used for the benefit assessment. The study pool of RCTs concurs with that of the company.

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 + 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]
VX16-809-121	Part 1: RCT, double-blind, parallel-group Part 2: 1-arm, open-label	Children aged 2-5 years with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene	Part 1: Lumacaftor/ivacaftor + BSC (N = 35) Placebo + BSC (N = 16) Part 2: Lumacaftor/ivacaftor + BSC (N = 49)	Part 1: Screening: 28 days Double-blind treatment phase: 48 weeks Part 2: Open-label treatment phase: 48 weeks Follow-up: 2 weeks	5 centres in Germany Part 1: 8/2018–10/2020 Part 2: ongoing	Primary: MRI Global Chest Score Secondary: all-cause mortality, morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.

AE: adverse event; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; N: number of randomized patients; RCT: randomized controlled trial

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

Study	Intervention	Comparison
VX16-809-121	Lumacaftor/ivacaftor every 12 hours, orally; granules or tablets[a] ▪ Body weight at baseline < 14 kg[b]: ▫ 100 mg lumacaftor ▫ 125 mg ivacaftor ▪ Body weight at baseline ≥ 14 kg: ▫ 150 mg lumacaftor ▫ 188 mg ivacaftor ▪ + BSC[c]	Placebo every 12hours, orally, granules + BSC[c]
	No dose reduction allowed	
	Pretreatment ▪ Baseline CF medication stable for at least 28 days before treatment start **Concomitant treatment** ▪ If possible, continuation of stable CF treatment; modifications possible where necessary **Non-permitted concomitant treatment** ▪ Strong CYP3A inhibitors or inducers within 14 days before treatment start ▪ CYP3A inducers until study end	

a. Patients who turned 6 years old in or after Week 48 received lumacaftor/ivacaftor in tablet form in Part 2 of the study.
b. In patients who weighed ≥ 14 kg at two consecutive visits during the study, the dose was increased to 150 mg lumacaftor and 188 mg ivacaftor.
c. In the study, baseline medication for the CF treatment was administered in addition to lumacaftor/ivacaftor or placebo.

BSC: best supportive care; CF: cystic fibrosis; CYP: cytochrome P450; RCT: randomized controlled trial

Study design

The VX16-809-121 study is a randomized, double-blind 2-part study, with Part 1 comparing lumacaftor/ivacaftor + BSC with placebo + BSC. In Part 2, which followed the 48-week double-blind treatment phase, all patients were treated with lumacaftor/ivacaftor for another 48 weeks.

The study included CF patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene. According to the study's inclusion criteria, the CF diagnosis was defined as a sweat chloride concentration ≥ 60 mmol/L and clinical manifestation. The study excluded patients with an acute infection of the upper or lower respiratory tract or pulmonary exacerbations. In addition, the baseline CF medication was to have been continued unchanged for 28 days before treatment start.

The study randomized a total of 51 patients at a 2:1 ratio either to treatment with lumacaftor/ivacaftor + BSC (N = 35) or to placebo + BSC (N = 16). The study was conducted only in Germany.

Patients were treated with lumacaftor/ivacaftor in accordance with the SPC [14] or received a placebo. In both study arms, patients additionally received accompanying baseline therapy (see section on the implementation of the ACT).

The primary outcome of the study was a change in the Global Chest Score, measured using MRI of the respiratory tract. Patient-relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity and AEs.

Patient characteristics

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

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

Study **Characteristic** **Category**	**Lumacaftor/ivacaftor + BSC** **N[a] = 35**	**Placebo + BSC** **N[a] = 16**
VX16-809-121		
Age [years], mean (SD)	4.2 (1.0)	4.2 (1.0)
Sex [f/m], %	31/69	44/56
Ancestry, n (%)		
White	35 (100)	16 (100)
Other	0 (0)	0 (0)
Body weight [kg], mean (SD)	17.1 (2.6)	17.3 (4.0)
Height [cm], mean (SD)	105.2 (7.9)	104.1 (9.4)
BMI [kg/m^2], mean (SD)	15.4 (1.3)	15.8 (1.5)
$LCI_{2.5}$, mean (SD)	8.9 (2.0)	9.0 (2.4)
Foecal elastase-1 [µg/g], median [min; max]	7.5 [7.5; 423.0]	7.5 [7.5; 27.0]
Sweat chloride concentration [mmol/L], mean (SD)	104.0 (16.7)	100.6 (7.9)
Treatment discontinuation, n (%)	2 (5.7)	0 (0)
Study discontinuation, n (%)	2 (5.7)	0 (0)

a. Number of randomized patients. Data in this table that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

BMI: body mass index; BSC: best supportive care; f: female; LCI: lung clearance index; m: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients were largely balanced between the two study arms. The mean age of the patients was 4 years. Mean height and body weight or body mass index (BMI) was within the normal range. Differences in sex ratios were found, with more boys in the lumacaftor/ivacaftor arm than in the placebo arm. In addition, a difference in the mean concentration of foecal elastase-1 was found, but it was mostly due to outliers. For this characteristic, the median is therefore presented.

Implementation of the ACT

The G-BA specified BSC as the ACT for lumacaftor/ivacaftor in CF patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene. BSC is the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (particularly antibiotics against pulmonary infections, mucolytic agents, pancreatic enzymes in case of pancreatic insufficiency, physical therapy [within the meaning of the German Guideline on Remedies], while exhausting all possible dietetic measures).

In the VX16-809-121 study, the existing symptomatic therapy of patients was to be continued during the lumacaftor/ivacaftor or placebo treatment. The study protocol required that no changes were made to the concomitant medication from 28 days before study start until the end of the study. For inclusion, the study additionally required participants to be willing to maintain a stable CF-related concomitant treatment for the entire duration of the study.

The information available on the prior and concomitant treatment used in the study shows that the majority of study participants received concomitant treatment of CF symptoms both before the first dose of the study medication and during the study.

Table 9 shows the prior and concomitant treatment of patients in the VX16-809-121 study.

Table 9: Medication before the 1st dose of study treatment and concomitant medication – RCT, direct comparison: lumacaftor/ivacaftor + BSC vs. placebo + BSC

Study	Lumacaftor/ivacaftor + BSC		Placebo + BSC	
	Treatment before the 1st dose of study medication[a] n (%)	Concomitant medication[b] n (%)	Treatment before the 1st dose of study medication[a] n (%)	Concomitant medication[b] n (%)
VX16-809-121	**N = 35**		**N = 16**	
Drug treatment				
Antibiotics	8 (22.9)	27 (77.1)	0 (0)	15 (93.8)
Intravenous antibiotics	0 (0)	4 (11.4)	0 (0)	1 (6.3)
Inhaled medication	34 (97.1)	35 (100)[c]	16 (100)	16 (100)[c]
Mucolytics	34 (97.1)	35 (100)[c]	16 (100)	16 (100)[c]
Bronchodilators	28 (80)	34 (97.1)[c]	13 (81.3)	15 (93.8)[c]
Inhaled saline solution	35 (100)[d]	34 (97.1)[e]	16 (100)[d]	16 (100)[e]
Digestive agents, including enzymes	34 (97.1)[d]	34 (97.1)[e]	16 (100)[d]	16 (100)[e]
Pancreatin	29 (82.9)[d]	29 (82.9)[e]	14 (87.5)[d]	14 (87.5)[e]
Pancrelipase	5 (14.3)[d]	5 (14.3)[e]	2 (12.5)[d]	2 (12.5)[e]
Vitamins	35 (100)[d]	35 (100)[e]	16 (100)[d]	16 (100)[e]
Non-drug treatment				
Physiotherapy	26 (74.3)	25 (71.4)[c]	14 (87.5)	14 (87.5)[c]

a. Ongoing therapy at the start of treatment with the study medication.
b. Sum of the patients who received the treatment at study start and those who started the treatment during the study. It is unclear how many patients, if any, discontinued the concomitant treatment over the course of the study.
c. IQWiG calculation.
d. Number of patients on a therapy within 28 days before the 1st dose of the study drug.
e. Number of patients who started or continued the therapy while being treated with the study medication.

BSC: best supportive care; IQWiG: Institute for Quality and Efficiency in Health Care; N: number of randomized patients; RCT: randomized controlled trial

The data on prior and concomitant treatment show that at the time of study inclusion, patients received inhaled medication (including saline solution), digestive enzymes, vitamins, and physical therapy for symptomatic CF treatment. While the available data suggest that some patients started concomitant treatment after the 1st dose of the study drug (see Table 9), it remains unclear whether more patients would have needed an adjustment over the 48-week course of the study. Additionally, the data do not show in how many patients, if any, the concomitant treatment was adjusted, e.g. by increasing the dose or frequency of drug or non-drug treatment. Furthermore, it is unclear how many, if any, patients discontinued the concomitant treatment over the course of the study.

In summary, it remains unclear whether the concomitant treatment used in the VX16-809-121 study represents a full implementation of the ACT of BSC. This conclusion has been informed by the fact that no information is available on treatment adjustments in the form of dose or

frequency increases of symptomatic treatment over the course of the study. This circumstance did not, however, lead to exclusion of the study. Rather, 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. However, the uncertainties described were taken into account when assessing the certainty of conclusions of the results (see Section 2.4.2).

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: lumacaftor/ivacaftor + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Non-selective reporting	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
VX16-809-121	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the VX16-809-121 study.

Transferability of the study results to the German health care context

The company reports that the study was conducted only in German centres and that all included patients were of Caucasian ancestry. It concludes that the transferability of results to the German healthcare context is ensured.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - All-cause mortality
- Morbidity
  - Pulmonary exacerbations
  - Hospitalization due to pulmonary exacerbations

- Health-related quality of life
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Further specific AEs, if any

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

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

Table 11: Matrix of outcomes – RCT, direct comparison: lumacaftor/ivacaftor + BSC vs. placebo + BSC

Study	Outcomes						
	All-cause mortality	Pulmonary exacerbations	Hospitalization due to pulmonary exacerbations	Health-related quality of life	SAEs[a]	Discontinuation due to AEs[a]	Specific AEs
VX16-809-121	Yes	Yes	Yes	No[b]	Yes	Yes	No[c]

a. Without the PT "infectious pulmonary exacerbation of CF".
b. Outcome not recorded.
c. No specific AEs were identified.

AE: adverse event; BSC: best supportive care; CF: cystic fibrosis; RCT: randomized controlled trial; SAE: serious adverse event

The following outcomes are presented as supplementary information in Appendix B of the full dossier assessment:

- Lung function via Lung Clearance Index ($LCI_{2.5}$):

LCI is a lung function parameter that is used as a measure for ventilation inhomogeneity [15]. $LCI_{2.5}$ indicates the number of turnovers needed to reduce the concentration of a marker gas to 2.5% of its initial concentration. The company explains that a pathologically elevated $LCI_{2.5}$ is diagnostically and prognostically relevant since it very reliably predicts structural lung damage and can indicate both later deterioration of lung function and the frequency of exacerbations. Therefore, the company deems the $LCI_{2.5}$ to be directly patient relevant.

Relevant for the benefit assessment are patient-noticeable symptoms associated with a change in $LCI_{2.5}$, which were directly recorded in the studies. In addition, the company did not present any sources showing that $LCI_{2.5}$ can be viewed as a valid surrogate outcome for a patient-relevant outcome. The $LCI_{2.5}$ was therefore excluded from the present benefit assessment.

- BMI and z-score of BMI

Body weight or BMI is highly relevant in the present indication since developmental issues and nutrient malabsorption are typical signs of CF. In its assessment, the company used BMI as a measure for developmental status or as a parameter for the extent of a developmental disorder in patients.

In the present situation, the relevance of BMI as a measure of malnutrition is not directly evident since the mean BMI of patients in the included study VX16-809-121 was within the normal range both at baseline and after 48 weeks of treatment.

MRI scores: Global Chest Score, Morphological Chest Score, Perfusion Chest Score

The company states that the MRI scores of Global Chest Score, Morphological Chest Score, and Perfusion Chest Score are instruments for assessing structural and functional lung changes in patients with CF. For the various scores, MRI scans of the lung are assessed for a variety of parameters (e.g. anomalies, bronchiectases). Each parameter is allocated a value based on the percentage of affected lung tissue. A total score is then calculated from the sum of the parameters. The company deems the MRI scores to be patient-relevant outcomes.

The MRI scores are calculated exclusively from ratings based on imaging. Relevant for the benefit assessment are patient-noticeable symptoms associated with the change, which were directly recorded in the studies. The outcome is therefore not deemed patient relevant and is excluded from the benefit assessment.

Outcome of severe AEs (grade 3 or 4)

All AEs which occurred in the study were assigned grades by the investigator. According to the study protocol, this was to be done, where possible, using the Common Terminology Criteria for Adverse Events (CTCAE); however, it must be noted that the CTCAE reference ranges might not be suitable for extrapolation to children. In Module 4 A, the company reports that severity was assessed by the investigator.

Since it ultimately remains unclear whether the AEs that occurred were assessed by the investigator or in accordance with the CTCAE, the outcome of severe AEs was excluded from the benefit assessment. Regardless of the basis on which severity was assessed, only 1 severe AE occurred in the course of the study (preferred term [PT] alanine aminotransferase increased).

2.4.2 Risk of bias

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

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

Study	Study level	Outcomes						
		All-cause mortality	Pulmonary exacerbations	Hospitalization due to pulmonary exacerbations	Health-related quality of life	SAEs[a]	Discontinuation due to AEs[a]	Further specific AEs
VX16-809-121	L	L	L	L	–[b]	H[c]	L	–

a. Without the PT "infectious pulmonary exacerbation of CF".
b. Outcome not recorded.
c. The analyses of SAEs do not include the PT "infectious pulmonary exacerbations of CF", but they include further events which could be either side effects or symptoms of the underlying disorder.

AE: adverse event; BSC: best supportive care; CF: cystic fibrosis; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event

The risk of bias for the results of the outcomes of all-cause mortality, pulmonary exacerbations, hospitalization due to pulmonary exacerbations, and discontinuation due to AEs is deemed low. The risk of bias for the results was rated as high for the outcome of SAEs.

Overall assessment of the certainty of conclusions

For the present benefit assessment, it remains unclear whether the concomitant treatment used in the VX16-809-121 study represents a full implementation of the ACT of BSC because no information is available on treatment adjustments in the form of dose or frequency increases of symptomatic treatment over the course of the study. The certainty of conclusions of the study results for the present research question is therefore reduced. Based on the VX16-809-121 study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

2.4.3 Results

Table 13 and Table 14 summarize the results on the comparison of lumacaftor/ivacaftor + BSC versus placebo + BSC in CF patients aged 2 to 5 years who have an F508del mutation in the CFTR gene. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier.

Tables on common AEs and common SAEs are presented in Appendix C of the full dossier assessment.

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

Study Outcome category Outcome	Lumacaftor/ivacaftor + BSC N	Lumacaftor/ivacaftor + BSC Number of events nE (nE/patient-years)[a]	Placebo + BSC N	Placebo + BSC Number of events nE (nE/patient-years)[a]	Lumacaftor/ivacaftor + BSC vs. placebo + BSC Rate ratio [95% CI]; p-value
VX16-809-121					
Morbidity					
Pulmonary exacerbations	35	26 (0.75)	16	19 (1.17)	ND
Hospitalization due to pulmonary exacerbations	35	5 (0.14)	16	1 (0.06)	ND
	Lumacaftor/ivacaftor + BSC		**Placebo + BSC**		**Lumacaftor/ivacaftor + BSC vs. placebo + BSC**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[b]**
Pulmonary exacerbations	35	15 (42.9)	16	10 (62.5)	0.69 [0.40; 1.18]; 0.170
Hospitalization due to pulmonary exacerbations	35	5 (14.3)	16	1 (6.3)	2.29 [0.29; 18.00]; 0.432

a. The company calculates the event rate (nE/patient years) from the total number of events divided by the total number of years (sum of the follow-up period of all patients included in the analysis in days, divided by 336).
b. Generalized linear model using the binomial distribution and a log-link function.

BSC: best supportive care; CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; nE: number of events; RCT: randomized controlled trial; RR: relative risk

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

Study Outcome category Outcome	Lumacaftor/ivacaftor + BSC		Placebo + BSC		Lumacaftor/ivacaftor + BSC vs. placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
VX16-809-121					
Mortality					
All-cause mortality	35	0 (0)	16	0 (0)	–
Side effects					
AEs[a] (supplementary information)	35	34 (97.1)	16	16 (100)	–
SAEs[a]	35	4 (11.4)	16	1 (6.3)	1.83 [0.22; 15.08]; 0.733[b]
Discontinuation due to AEs[a]	35	0 (0)	16	0 (0)	–

a. Without the PT "infectious pulmonary exacerbation of CF".
b. p-value: IQWiG calculation (unconditional exact test, CSZ method according to [16]).

AE: adverse event; BSC: best supportive care; CI: confidence interval; CF: cystic fibrosis; CSZ: convexity, symmetry, z-score; IQWiG: Institute for Quality and Efficiency in Health Care; n: number of patients with (at least 1) event; N: number of analysed patients; nE: number of events; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.4.2).

Mortality

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

Morbidity

Pulmonary exacerbations

Operationalization

In the VX16-809-121 study, pulmonary exacerbation was defined as the need for new or changed antibiotic therapy (intravenous, inhaled, or oral) and the occurrence of ≥ 1 criterion from List A or ≥ 2 criteria from List B within 3 days prior to the start of antibiotic treatment.

List A

- Lung function (forced expiratory volume in 1 second [FEV_1]) reduced by ≥ 10% from the highest value in the previous 6 months
- Oxygen saturation < 90% (in closed rooms) or ≥ 5% decrease from baseline
- New lobar infiltrates or atelectasis on the chest X-ray

- Haemoptysis

List B

- Increasing strains from respiration or respiratory frequency (≥ 3 days)
- New or worsening adventitious sounds in lung examination (≥ 3 days)
- Weight loss by ≥ 5% from the highest weight measured or decrease by a full percentile by age in the prior 6 months
- Worsening cough (≥ 3 days)
- Worsened dyspnoea on exertion (≥ 3 days)
- Increasing chest tightness or change in sputum (≥ 3 days)

Given the available data, this definition of pulmonary exacerbations is used for the benefit assessment.

The company classified pulmonary exacerbations in 3 operationalizations:

- Pulmonary exacerbations
- Hospitalization due to pulmonary exacerbations
- Pulmonary exacerbations requiring intravenous antibiotic treatment

Pulmonary exacerbations and hospitalization due to pulmonary exacerbations are used for the present benefit assessment, with hospitalization due to pulmonary exacerbations reflecting the occurrence of severe exacerbations.

While results on the number of events per patient-year (event rates) are available for both outcomes, the company's dossier does not present any analyses of incidence density based on adequate statistical models. For the present benefit assessment, no analyses are therefore available which take into account not only the occurrence, but also the frequency of pulmonary exacerbations over the entire course of the study. The company's dossier presents analyses of the percentage of patients with an event using relative risk. Given the available data, the results of the analyses presented by the company on the percentage of patients with an event are assumed not to differ to a relevant extent from analyses on the basis of event rates. The analyses presented by the company on relative risk are therefore included in the present benefit assessment.

Results

Pulmonary exacerbations

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

Hospitalization due to pulmonary exacerbations

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

Health-related quality of life

Health-related quality of life outcomes were not recorded in the VX16-809-121 study.

Side effects

SAEs

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

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, no events occurred in the course of the study. This resulted in no hint of greater or lesser harm from lumacaftor/ivacaftor + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

2.4.4 Subgroups and other effect modifiers

The VX16-809-121 study plan did not include any subgroup analyses.

For the present benefit assessment, the company's dossier presents post hoc subgroup analyses on the characteristic of baseline $LCI_{2.5}$ because the company views this characteristic to reflect the patients' severity of disease. As a threshold, the company uses the median baseline $LCI_{2.5}$ (8.02). However, it remains unclear whether the severity of disease can be adequately measured via $LCI_{2.5}$ with a threshold chosen on the basis of the study results. The subgroup analyses presented by the company for this characteristic were therefore excluded from the present benefit assessment.

The company did not present any analyses on further subgroup characteristics.

2.5 Probability and extent of added benefit

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

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

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 15).

Table 15: Extent of added benefit at outcome level: lumacaftor/ivacaftor + BSC vs. BSC

Outcome category **Outcome**	**Lumacaftor/ivacaftor + BSC vs. placebo + BSC** **Event ratio (%)** **RR [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	42.9% vs. 62.5% 0.69 [0.40; 1.18]; p = 0.170	Lesser benefit/added benefit not proven
Hospitalization due to pulmonary exacerbations	14.3% vs. 6.3% 2.29 [0.29; 18.00]; p = 0.432	Lesser benefit/added benefit not proven
Health-related quality of life		
Outcome not recorded		
Side effects		
SAEs	11.4% vs. 6.3% 1.83 [0.22; 15.08]; p = 0.733	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 0% –	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of confidence interval; RR: relative risk; SAE: serious adverse event

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 16: Favourable and unfavourable effects from the assessment of lumacaftor/ivacaftor in comparison with BSC

Favourable effects	**Unfavourable effects**
–	–
Outcomes from the category of health-related quality of life were not recorded.	
BSC: best supportive care	

The VX16-809-121 study showed neither effects in favour nor effects to the disadvantage of lumacaftor/ivacaftor + BSC.

In summary, there is no hint of an added benefit of lumacaftor/ivacaftor + BSC in comparison with the ACT of BSC for CF patients between 2 and 5 years of age who are homozygous for the F508del mutation in the CFTR gene. An added benefit is therefore not proven.

Table 17 summarizes the result of the assessment of added benefit of lumacaftor/ivacaftor in comparison with the ACT.

Table 17: Lumacaftor/ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene	BSC[b]	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (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). ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The above assessment departs from the view of the company, which derived, overall, a hint of considerable added benefit on the basis of the VX16-809-121 study results (particularly regarding the outcomes of BMI z-score and sweat chloride concentration) as well as in consideration of additional documents (see Section 2.3).

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

References for English extract

Please see full dossier assessment for full reference list.

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

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