IQWiG Reports – Commission No. A19-70

Ivacaftor (combination with tezacaftor/ivacaftor; cystic fibrosis, 12 years and older, with F508del mutation, homozygous) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Ivacaftor (Kombination mit Tezacaftor/Ivacaftor; zystische Fibrose, ab 12 Jahre, F508del-Mutation, homozygot) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 November 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
CYP3A	cytochrome P450
FEV1	forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ivacaftor in combination with tezacaftor/ivacaftor. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 28 August 2019.

Research question

The aim of the present report is the assessment of the added benefit of ivacaftor in combination with tezacaftor/ivacaftor in comparison with the appropriate comparator therapy (ACT) lumacaftor/ivacaftor in patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Table 2: Research question of the benefit assessment of ivacaftor + tezacaftor/ivacaftor

Therapeutic indication	**ACT[a]**
CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor
a: Presentation of the respective 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 designated lumacaftor/ivacaftor as ACT. This concurred with the G-BA's specification. The company also stated that the ACT lumacaftor/ivacaftor, like ivacaftor + tezacaftor/ivacaftor, the drug to be assessed, was used in addition to an individual best symptomatic treatment and was included in the presentation of the added benefit.

The present benefit assessment was conducted in comparison with lumacaftor/ivacaftor, the ACT specified by the G-BA. An additional symptomatic treatment for the patient population is comprehensible.

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

Results

Study pool and study characteristics

No RCTs of direct comparison were identified for the assessment of the added benefit of ivacaftor + tezacaftor/ivacaftor in comparison with the ACT lumacaftor/ivacaftor. In the present benefit assessment, the added benefit was derived on the basis of an adjusted indirect comparison. For this purpose, one study for ivacaftor + tezacaftor/ivacaftor and 2 studies for lumacaftor/ivacaftor were included. The 2 latter studies were included in the indirect comparison as a meta-analytical summary. The comparison was conducted using placebo as the common comparator. Treatment in the 3 studies was conducted against the background of concomitant symptomatic treatment in all arms.

VX14-661-106 (study with ivacaftor + tezacaftor/ivacaftor)

The VX14-661-106 study was a randomized, double-blind, parallel-group study, in which patients were treated with ivacaftor + tezacaftor/ivacaftor or received matching placebo, each against the background of concomitant symptomatic treatment.

The study included patients aged 12 years and older who were homozygous for the F508del mutation in the CFTR gene and who had confirmed diagnosis of CF defined as a sweat chloride value of ≥ 60 mmol/L. In addition, the patients had to have a forced expiratory volume in 1 second (FEV1) of ≥ 40% and ≤ 90% of predicted normal for age, sex, and height at screening.

The study included a total of 510 patients, who were randomized in a 1:1 ratio either to treatment with ivacaftor + tezacaftor/ivacaftor (N = 251) or to matching placebo (N = 259). Stratification factors were age (< 18 years/≥ 18 years), sex (male/female) and FEV1 in percent of predicted normal (< 70%/≥ 70%).

Treatment with ivacaftor in combination with tezacaftor/ivacaftor was largely in compliance with the recommendations of the Summary of Product Characteristics (SPC).

Primary outcome of the study was the absolute change in FEV1 in percent of predicted normal. Patient-relevant secondary outcomes were all-cause mortality, symptoms, health-related quality of life, and adverse events (AEs).

VX12-809-103 and VX12-809-104 (studies with lumacaftor/ivacaftor)

The studies VX12-809-103 and VX12-809-104 were randomized, double-blind, parallel-group studies, in which patients were treated with lumacaftor/ivacaftor or received matching placebo, each against the background of concomitant symptomatic treatment.

Except for the definition of the confirmed diagnosis of CF, the inclusion and exclusion criteria of the studies are largely comparable with those described above for the VX14-661-106 study. CF in the studies VX12-809-103 and VX12-809-104 was defined as a sweat chloride value of ≥ 60 mmol/L or 2 CF-causing mutations and chronic sinopulmonary disease or gastrointestinal/ nutrition-related abnormalities.

Study VX12-809-103 included 559 patients, and study VX12-809-104 included 563 patients, who were in each case randomly allocated in a ratio of 1:1:1 to the following study arms:

- lumacaftor (600 mg, once daily) and ivacaftor (250 mg, every 12 hours)
- lumacaftor (400 mg, every 12 hours) and ivacaftor (250 mg, every 12 hours)
- placebo

Patients in both studies, VX12-809-103 and VX12-809-104, received additional concomitant treatment. The 3 treatment arms included 185 versus 187 versus 187 patients in the VX12-809-103 study, and 187 versus 189 versus 187 patients in the VX12-809-104 study. The stratification factors in both studies were identical to those in the VX14-661-106 study: age (< 18 years/≥ 18 years), sex (male/female) and FEV1 in percent of predicted normal (< 70%/≥ 70%).

Lumacaftor in combination with ivacaftor is only approved at a dosage of 400 mg every 12 hours. The study arms of both studies in which lumacaftor was administered at a dosage of 600 mg once daily are therefore not relevant for the present benefit assessment and will not be considered further in the following.

Treatment with lumacaftor (400 mg)/ivacaftor (250 mg) every 12 hours in both studies largely concurred with the recommendations of the SPC.

Primary outcome of both studies was the absolute change in FEV1 in percent of predicted normal. Patient-relevant secondary outcomes were all-cause mortality, symptoms, health-related quality of life, and AEs.

Concomitant symptomatic treatment in the studies VX14-661-106, VX12-809-103 and VX12-809-104

Administration of symptomatic treatment in addition to the study medication (ivacaftor + tezacaftor/ivacaftor or lumacaftor/ivacaftor) was allowed in the studies VX14-661-106, VX12-809-103 and VX12-809-104. However, according to the information provided in the study protocols, patients in all 3 studies had to be willing to continue the CF medication they had been receiving from 4 weeks before the start of the study at a stable dosage for 24 weeks until the end of the study.

For all 3 studies (VX14-661-106, VX12-809-103 and VX12-809-104), it can be inferred from the study documents that patients received the regularly used medication for symptomatic treatment of CF. The proportion of patients under the respective concomitant medication remained largely unchanged before and after the first intake of the study medication. However, the information provided shows that individual adjustments to the concomitant treatment were made in all 3 studies. A clear increase in concomitant medication after the first intake of the study medication in all arms of the 3 studies was shown, for example, for antibiotics (including ciprofloxacin) and analgesics (ibuprofen and paracetamol). However, there was no information

on whether and how many patients had their concomitant treatment adjusted, for example in the sense of an increase in dose or frequency in the course of the study.

Similarity of the studies for the indirect comparison

The available data on the study, intervention and patient characteristics of the 3 studies of the indirect comparison show that the studies were sufficiently similar regarding design and included patient populations.

The demographic and clinical characteristics of the patients were both balanced both between the treatment arms of the individual studies and largely comparable between the 3 studies. With regard to inhaled symptomatic pretreatment, there were individual differences in the proportions, but these do not indicate that the patients differed in the severity grade of the disease between the studies. Regarding concomitant medication, there were no noticeable deviations between the studies and the drugs were administered in largely similar proportions. The suitability of the studies VX14-661-106, VX12-809-103 and VX12-809-104 for an adjusted indirect comparison was thus not called into question.

Risk of bias

The risk of bias across outcomes was rated as low for all 3 studies.

The risk of bias for the results of the following outcomes was rated as low for all 3 studies: all-cause mortality, pulmonary exacerbations, hospitalization due to pulmonary exacerbations, symptoms (recorded with the Cystic Fibrosis Questionnaire-Revised [CFQ-R]) and health-related quality of life (recorded with the CFQ-R).

Events that can be both side effects and symptoms of the underlying disease were included in the recording of AEs. As a result, the results of the outcome “serious adverse events (SAEs)” were not usable, and the results of the outcome “discontinuation due to AEs” had a high risk of bias. The risk of bias of the results of the AE outcome “rash” was rated as low in all 3 studies of the indirect comparison.

Mortality

All-cause mortality

No deaths occurred during all 3 studies of the indirect comparison. There was no hint of an added benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for all-cause mortality; an added benefit is therefore not proven.

Morbidity

Pulmonary exacerbations

For the outcome “pulmonary exacerbations”, the adjusted indirect comparison based on the event rate (n_E/patient years: total number of events divided by total number of years) showed no statistically significant difference between ivacaftor + tezacaftor/ivacaftor and lumacaftor/

ivacaftor. This resulted in no hint of an added benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for this outcome.

Hospitalization due to pulmonary exacerbations

For the outcome "hospitalization due to pulmonary exacerbations", the adjusted indirect comparison based on the event rate (n_E/patient years: total number of events divided by total number of years) showed a statistically significant difference to the disadvantage of ivacaftor + tezacaftor/ivacaftor versus lumacaftor/ivacaftor. This resulted in a hint of lesser benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for this outcome.

Symptoms measured using the CFQ-R

Symptom outcomes were recorded with the domains "respiratory symptoms", "digestive symptoms" and "weight" of the disease-specific patient-reported instrument CFQ-R.

Domain "respiratory symptoms"

In the domain "respiratory symptoms", the adjusted indirect comparison showed a statistically significant difference in favour of ivacaftor + tezacaftor/ivacaftor versus lumacaftor/ivacaftor regarding the changes between the respective time point of measurement and baseline, averaged over the course of the study. The standardized mean difference (SMD) in the form of Hedges' g was considered to assess the relevance of the result. The 95% confidence interval (CI) was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect was relevant. There was no hint of an added benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for the CFQ-R domain "respiratory symptoms"; an added benefit is therefore not proven.

Domains "digestive symptoms" and "weight"

The company presented solely SMDs with a 95% CI in the form of Hedges' g for the domains of digestive symptoms and weight. The adjusted indirect comparison showed no statistically significant differences between ivacaftor + tezacaftor/ivacaftor and lumacaftor/ivacaftor regarding the changes between the respective time point of measurement and baseline, averaged over the course of the study. This resulted in no hint of an added benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for either of both domains; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded using the domains of physical functioning, emotional functioning, vitality, social functioning, role functioning, body image, eating problems, treatment burden and health perceptions of the CFQ-R.

Domains of physical functioning, emotional functioning, vitality, social functioning, role functioning, body image, eating problems and health perceptions

The company presented solely SMDs with a 95% CI in the form of Hedges' g for the domains of physical functioning, emotional functioning, vitality, social functioning, role functioning, body image, eating problems and health perceptions. The adjusted indirect comparison showed no statistically significant differences between ivacaftor + tezacaftor/ivacaftor and lumacaftor/ivacaftor regarding the changes between the respective time point of measurement and baseline, averaged over the course of the study. This resulted in no hint of an added benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for each of these domains; an added benefit is therefore not proven.

Domain "treatment burden"

The company presented solely SMDs with a 95% CI in the form of Hedges' g for the domain "treatment burden". The adjusted indirect comparison showed a statistically significant difference in favour of ivacaftor + tezacaftor/ivacaftor versus lumacaftor/ivacaftor regarding the changes between the respective time point of measurement and baseline, averaged over the course of the study. The 95% CI was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect was relevant. There was no hint of an added benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for the CFQ-R domain "treatment burden"; an added benefit is therefore not proven.

Side effects

Serious adverse events

In the studies VX12-809-103, VX12-809-104 and VX14-661-106, events of pulmonary exacerbation of CF were also included in the recording of SAEs. As a result, the results on this outcome are not usable.

Overall, there was no hint of greater or lesser harm from ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for the outcome "SAEs"; greater or lesser harm is therefore not proven.

Discontinuation due to adverse events

For the outcome "discontinuation due to AEs", there is only one study, which additionally has a high risk of bias of the results, on the intervention side of the indirect comparison. As a result, an effect estimation for the indirect comparison has no sufficient certainty of results.

Overall, there was no hint of greater or lesser harm from ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for the outcome "discontinuation due to AEs"; greater or lesser harm is therefore not proven.

Specific adverse events

Rash

The adjusted indirect comparison showed a statistically significant difference in favour of ivacaftor + tezacaftor/ivacaftor versus lumacaftor/ivacaftor for the outcome "rash". This resulted in a hint of lesser harm from ivacaftor + tezacaftor/ivacaftor versus lumacaftor/ ivacaftor for this outcome.

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 ivacaftor + tezacaftor/ivacaftor compared with the ACT is assessed as follows:

Overall, there is one positive effect of ivacaftor + tezacaftor/ivacaftor in the outcome category of non-serious/non-severe side effects with the extent "considerable", and one negative effect of tezacaftor/ivacaftor in the outcome category of serious/severe symptoms/late complications, each in comparison with the ACT lumacaftor/ivacaftor.

The lack of usability of the outcome "SAEs" was taken into account when balancing the results. Overall, this resulted in a hint of lesser benefit of ivacaftor in combination with ivacaftor + tezacaftor/ivacaftor versus the ACT lumacaftor/ivacaftor for patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

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

Table 3: Ivacaftor + tezacaftor/ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor	Hint of lesser benefit
a: Presentation of the respective 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.

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of ivacaftor in combination with tezacaftor/ivacaftor in comparison with the ACT lumacaftor/ivacaftor in patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

Table 4: Research question of the benefit assessment of ivacaftor + tezacaftor/ivacaftor

Therapeutic indication	**ACT[a]**
CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor
a: Presentation of the respective 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 designated lumacaftor/ivacaftor as ACT. This concurred with the G-BA's specification. The company also stated that the ACT lumacaftor/ivacaftor, like ivacaftor + tezacaftor/ivacaftor, the drug to be assessed, was used in addition to an individual best symptomatic treatment and was included in the presentation of the added benefit.

The present benefit assessment was conducted in comparison with lumacaftor/ivacaftor, the ACT specified by the G-BA. An additional symptomatic treatment for the patient population is comprehensible.

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on ivacaftor + tezacaftor/ivacaftor and lumacaftor/ivacaftor (status: 6 June 2019)
- bibliographical literature search on ivacaftor + tezacaftor/ivacaftor (last search on 6 June 2019)
- search in trial registries for studies on ivacaftor + tezacaftor/ivacaftor (last search on 6 June 2019)
- bibliographical literature search on the ACT (last search on 6 June 2019)
- search in trial registries for studies on the ACT (last search on 6 June 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ivacaftor + tezacaftor/ivacaftor (last search on 4 September 2019)
- search in trial registries for studies on lumacaftor/ivacaftor (last search on 4 September 2019)

Concurring with the company, no relevant RCT on the direct comparison of ivacaftor + tezacaftor/ivacaftor versus the ACT was identified from the check (see Section 2.7.3 of the full dossier assessment).

The company identified 3 studies for an adjusted indirect comparison based on RCTs. For the indirect comparison presented by the company (see Section 2.3.1), no additional relevant studies were identified from the check of the completeness of the study pool (see Section 2.7.3 of the full dossier assessment).

2.3.1 Studies included

In the present benefit assessment, the added benefit was derived on the basis of an adjusted indirect comparison. For this purpose, one study for ivacaftor + tezacaftor/ivacaftor and 2 studies for lumacaftor/ivacaftor were included. The 2 latter studies were included in the indirect comparison as a meta-analytical summary. The comparison was conducted using placebo as the common comparator. Treatment in the 3 studies was conducted against the background of concomitant symptomatic treatment in all arms.

The studies included in the benefit assessment are listed in Table 5. The study pool concurs with that of the company. A schematic presentation of the adjusted indirect comparison is shown in Figure 1.

Table 5: Study pool – RCT, indirect comparison: ivacaftor + tezacaftor/ivacaftor vs. lumacaftor/ivacaftor

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Study with ivacaftor + tezacaftor/ivacaftor[b] vs. placebo[b]			
VX14-661-106	Yes	Yes	No
Studies with lumacaftor/ivacaftor[b] vs. placebo[b]			
VX12-809-103	No	Yes	No
VX12-809-104	No	Yes	No

a: Study sponsored by the company.
b: Treatment was against the background of concomitant symptomatic treatment.
RCT: randomized controlled trial; vs.: versus

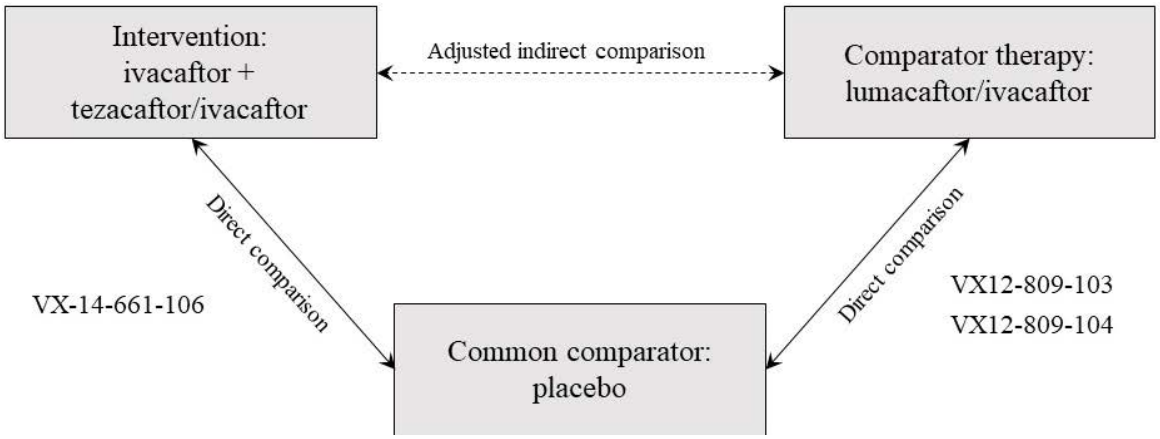

Figure 1: Study pool for the indirect comparison between ivacaftor + tezacaftor/ivacaftor and the ACT lumacaftor/ivacaftor. Treatment in all arms of the 3 studies was against the background of concomitant symptomatic treatment.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the included studies – RCT, indirect comparison: ivacaftor + tezacaftor/ivacaftor vs. lumacaftor/ivacaftor

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study with ivacaftor + tezacaftor/ivacaftor[b] vs. placebo[b]						
VX14-661-106	RCT, double-blind, parallel	Patients with CF ≥ 12 years with F508del mutation in both alleles of the CFTR gene (homozygous) und FEV1[c] ≥ 40% and ≤ 90% at screening	Ivacaftor + tezacaftor/ivacaftor[b] (N = 251) placebo[b] (N = 259)	Screening: 4 weeks Treatment: 24 weeks[d] Follow-up observation of AEs (safety follow-up): 4 weeks (± 7 days)[e]	91 centres in Canada, Denmark, England, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland, USA 1/2015–1/2017	Primary: change in FEV1[c] Secondary: all-cause mortality, symptoms, health-related quality of life, AEs
Studies with lumacaftor/ivacaftor[b] vs. placebo[b]						
VX12-809-103	RCT, double-blind, parallel	Patients with CF ≥ 12 years with F508del mutation in both alleles of the CFTR gene (homozygous) und FEV1[c] ≥ 40% and ≤ 90% at screening	Lumacaftor/ivacaftor[b] 400 mg/250 mg (N = 187) lumacaftor/ivacaftor[b, f] 600 mg/250 mg (N = 185) placebo[b] (N = 187)	Screening: 4 weeks Treatment: 24 weeks[g] Follow-up observation of AEs (safety follow-up): 4 weeks (± 7 days)[h]	96 centres in Australia, Canada, Czech Republic, France, Germany, Great Britain, Ireland, Italy, Netherlands, Sweden, USA 5/2013–4/2014	Primary: change in FEV1[c] Secondary: all-cause mortality, symptoms, health-related quality of life, AEs
VX12-809-104	RCT, double-blind, parallel	Patients with CF ≥ 12 years with F508del mutation in both alleles of the CFTR gene (homozygous) und FEV1[c] ≥ 40% and ≤ 90% at screening	Lumacaftor/ivacaftor[b] 400 mg/250 mg (N = 189) lumacaftor/ivacaftor[b, f] 600 mg/250 mg (N = 187) placebo[b] (N = 187)	Screening: 4 weeks Treatment: 24 weeks[g] Follow-up observation of AEs (safety follow-up): 4 weeks (± 7 days)[h]	91 centres in Australia, Austria, Belgium, Canada, Denmark, France, Germany, Great Britain, Spain, USA	Primary: change in FEV1[c] Secondary: all-cause mortality, symptoms, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the included studies – RCT, indirect comparison: ivacaftor + tezacaftor/ivacaftor vs. lumacaftor/ivacaftor (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: Treatment was against the background of concomitant symptomatic treatment.
c: In % of predicted normal.
d: At the visit at week 24, the patients had the possibility to be enrolled in the ivacaftor + tezacaftor/ivacaftor arm of an open-label extension study (VX14-661-110) if they fulfilled the inclusion criteria. Patients < 18 years of age who had received at least 4 weeks of study medication in the VX14-661-106 study and who did not meet the inclusion criteria for enrolment in the ivacaftor + tezacaftor/ivacaftor arm of the extension study, or who decided against enrolment, could participate in the study in an observation arm without administration of study medication if they met the criteria for inclusion in the observation arm.
e: Participation in the follow-up observation of AEs (safety follow-up) was not required for study participants who were included in the extension study VX14-661-110 within 28 days of the last dose of the study medication after completion of the 24-week treatment.
f: The treatment arm is not relevant for the assessment and is not shown in the next tables.
g: At the visit at week 24, patients who had completed the visits in the treatment phase had the possibility to be switched either to the treatment arm or to the observation arm of an open-label extension study (VX12-809-105) even if they had discontinued the study medication during the treatment phase.
h: Participation in the follow-up observation of AEs (safety follow-up) was not required for study participants who were included in the treatment arm of the extension study VX12-809-105 after completion of the 24-week treatment and for patients who had discontinued study treatment before week 16.

AE: adverse event; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; FEV1: forced expiratory volume in 1 second; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, indirect comparison: ivacaftor + tezacaftor/ivacaftor vs. lumacaftor/ivacaftor

Study	Ivacaftor + tezacaftor/ivacaftor or lumacaftor/ivacaftor	Placebo
Ivacaftor + tezacaftor/ivacaftor vs. placebo		
VX14-661-106	Tezacaftor/ivacaftor 100 mg/150 mg orally, as tablets, in the morning + ivacaftor 150 mg orally, as tablets, in the evening each within 30 minutes after starting a fat-containing meal[a, b]	Placebo orally, in the morning and evening, within 30 minutes after starting a fat-containing meal[a, b]
	Pretreatment and concomitant treatment: not allowed: ▪ moderate and strong CYP3A inducers and inhibitors, including certain fruit and fruit juices, certain herbal drugs (e.g. St. John's Wort) within 14 days before the first dose of the study medication until the end of follow-up, except ciprofloxacin ▪ solid organ or haematological transplantation before start of study	
Lumacaftor/ivacaftor vs. placebo		
VX12-809-103	Lumacaftor/ivacaftor 400 mg/250 mg, orally, as tablets, in the morning and evening, within 30 minutes after starting a fat-containing meal[a, b]	Placebo orally, in the morning and evening, within 30 minutes after starting a fat-containing meal[a, b]
	Pretreatment and concomitant treatment: not allowed: ▪ moderate and strong CYP3A inducers and strong inhibitors, including certain fruit and fruit juices, certain herbal drugs (e.g. St. John's Wort) within 14 days before the first dose of the study medication until the end of treatment ▪ solid organ or haematological transplantation before start of study	
VX12-809-104	Lumacaftor/ivacaftor 400 mg/250 mg, orally, as tablets, in the morning and evening, within 30 minutes after starting a fat-containing meal[a, b]	Placebo orally, in the morning and evening, within 30 minutes after starting a fat-containing meal[a, b]
	Pretreatment and concomitant treatment: ▪ see information on VX12-809-103	

a: Dose adjustments were not allowed; in case of interruption of the study medication for > 72 hours, continuation of the study medication was only allowed if approved by the clinical monitor.
b: Treatment was against the background of symptomatic basic medication. This medication was to be continued at stable dosing from 4 weeks before baseline until the end of follow-up.
CYP3A: cytochrome P450; RCT: randomized controlled trial; vs.: versus

Study design

VX14-661-106 (study with ivacaftor + tezacaftor/ivacaftor)

The VX14-661-106 study was a randomized, double-blind, parallel-group study, in which patients were treated with ivacaftor + tezacaftor/ivacaftor or received matching placebo, each against the background of concomitant symptomatic treatment (see section on prior and concomitant medication further below).

The study included patients aged 12 years and older who were homozygous for the F508del mutation in the CFTR gene and who had confirmed diagnosis of CF defined as a sweat chloride value of ≥ 60 mmol/L. In addition, the patients had to have a FEV1 of ≥ 40% and ≤ 90% of predicted normal for age, sex, and height at screening.

The study included a total of 510 patients, who were randomized in a 1:1 ratio either to treatment with ivacaftor + tezacaftor/ivacaftor (N = 251) or to matching placebo (N = 259). Stratification factors were age (< 18 years/≥ 18 years), sex (male/female) and FEV1 in percent of predicted normal (< 70%/≥ 70%).

Treatment with ivacaftor in combination with ivacaftor + tezacaftor/ivacaftor (see Table 7) was largely in compliance with the recommendations of the SPC [3]. According to the recommendations in the SPC, the dose should be adjusted when co-administered with strong or moderate cytochrome P450 (CYP3A) inhibitors. This was not mandated in the study. It is not assumed, however, that this had a relevant influence on the study results.

Primary outcome of the study was the absolute change in FEV1 in percent of predicted normal. Patient-relevant secondary outcomes were all-cause mortality, symptoms, health-related quality of life, and AEs.

After the 24-week treatment phase, there was the possibility of participating in the open-label extension study VX14-661-110, where patients received ivacaftor + tezacaftor/ivacaftor. Patients < 18 years of age who had received at least 4 weeks of study medication in the VX14-661-106 study and who did not meet the inclusion criteria for enrolment in the treatment arm of the extension study, or who decided against enrolment in the treatment arm, could participate in the study in an observation arm without administration of study medication if they met the criteria for inclusion in the observation arm.

VX12-809-103 and VX12-809-104 (studies with lumacaftor/ivacaftor)

The studies VX12-809-103 and VX12-809-104 were randomized, double-blind, parallel-group studies, in which patients were treated with lumacaftor/ivacaftor or received matching placebo, each against the background of concomitant symptomatic treatment (see section on prior and concomitant medication further below).

Except for the definition of the confirmed diagnosis of CF, the inclusion and exclusion criteria of the studies are largely comparable with those described above for the VX14-661-106 study. CF in the studies VX12-809-103 and VX12-809-104 was defined as a sweat chloride value of ≥ 60 mmol/L or 2 CF-causing mutations and chronic sinopulmonary disease or gastrointestinal/ nutrition-related abnormalities.

Study VX12-809-103 included 559 patients, and study VX12-809-104 included 563 patients, who were in each case randomly allocated in a ratio of 1:1:1 to the following study arms:

- lumacaftor (600 mg, once daily) and ivacaftor (250 mg, every 12 hours)

- lumacaftor (400 mg, every 12 hours) and ivacaftor (250 mg, every 12 hours)
- placebo

Patients in both studies, VX12-809-103 and VX12-809-104, received additional concomitant treatment (see section on prior and concomitant medication further below). The 3 treatment arms included 185 versus 187 versus 187 patients in the VX12-809-103 study, and 187 versus 189 versus 187 patients in the VX12-809-104 study. The stratification factors in both studies were identical to those in the VX14-661-106 study: age (< 18 years/≥ 18 years), sex (male/female) and FEV1 in percent of predicted normal (< 70%/≥ 70%).

Lumacaftor in combination with ivacaftor is only approved at a dosage of 400 mg every 12 hours [4]. The study arms of both studies in which lumacaftor was administered at a dosage of 600 mg once daily are therefore not relevant for the present benefit assessment and will not be considered further in the following.

Treatment with lumacaftor (400 mg)/ivacaftor (250 mg) every 12 hours in both studies largely concurred with the recommendations of the SPC [4]. According to the recommendations in the SPC, the dose should be temporarily adjusted in patients already receiving lumacaftor/ivacaftor when initiating treatment with strong CYP3A inhibitors. This was not mandated in the study. It is not assumed, however, that this had a relevant influence on the study results.

Primary outcome of both studies was the absolute change in FEV1 in percent of predicted normal. Patient-relevant secondary outcomes were all-cause mortality, symptoms, health-related quality of life, and AEs.

Following the 24-week treatment phase, patients in both studies who had completed the study visits in the treatment phase had the possibility to participate either in the treatment arm or in the observation arm of the open-label extension study VX12-809-105. In this study, patients received either lumacaftor/ivacaftor in the treatment arm or no active study medication in the observation arm.

Study population

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

Table 8: Characteristics of the study populations – RCT, indirect comparison: ivacaftor + tezacaftor/ivacaftor vs. lumacaftor/ivacaftor

Study	**VX14-661-106**		**VX12-809-103**		**VX12-809-104**	
Characteristics	**IVA + TEZA/IVA[a]**	**Placebo[a]**	**LUMA/IVA[a]**	**Placebo[a]**	**LUMA/IVA[a]**	**Placebo[a]**
Category	**N[b] = 248**	**N[b] = 256**	**N[b] = 182**	**N[b] = 184**	**N[b] = 187**	**N[b] = 187**
Age [years], mean (SD)	27 (11)	26 (10)	26 (10)	25 (11)	25 (9)	26 (10)
Age group, n (%)						
< 18 years	58 (23.4)	58 (22.7)	52 (28.6)	53 (28.8)	46 (24.6)	43 (23.0)
≥ 18 years	190 (76.6)	198 (77.3)	130 (71.4)	131 (71.2)	141 (75.4)	144 (77.0)
Sex [F/M], %	49/51	49/51	46/54	46/54	52/48	52/48
Family origin, n (%)						
Caucasian	245 (98.8)	254 (99.2)	176 (96.7)	183 (99.5)	185 (98.9)	186 (99.5)
Other[c]	3 (1.2)	2 (0.8)	6 (3.3)	1 (0.5)	2 (1.1)	1 (0.5)
Region, n (%)						
North America	59 (23.8)	68 (26.6)	91 (50.0)	99 (53.8)	111 (59.4)	122 (65.2)
Europe	189 (76.2)	188 (73.4)	75 (41.2)	72 (39.1)	59 (31.6)	49 (26.2)
Australia	0 (0)	0 (0)	16 (8.8)	13 (7.1)	17 (9.1)	16 (8.6)
FEV1[d] at baseline, n (%)						
< 40%	23 (9.3)	24 (9.4)	12 (6.6)	11 (6.0)	17 (9.1)	17 (9.1)
≥ 40% to < 70%	157 (63.3)	152 (59.4)	116 (63.7)	122 (66.3)	117 (62.6)	116 (62.0)
≥ 70% to ≤ 90%	65 (26.2)	73 (28.5)	51 (28.0)	48 (26.1)	49 (26.2)	49 (26.2)
> 90%	2 (0.8)	7 (2.7)	1 (0.5)	0 (0)	2 (1.1)	3 (1.6)
Missing value	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BMI [kg/m²], mean [SD]	21.0 (3.0)	21.1 (2.9)	21.7 (3.2)	21.0 (3.0)	21.3 (2.9)	21.0 (2.9)
BMI z score, mean [SD][e]	−0.58 (0.95)	−0.37 (0.83)	−0.36 (0.81)	−0.59 (0.98)	−0.33 (0.90)	−0.50 (0.89)
Sweat chloride concentration [mmol/L], mean (SD)	101.3 (10.9)	100.5 (10.2)	ND	ND	ND	ND

(continued)

Table 8: Characteristics of the study populations – RCT, indirect comparison: ivacaftor + tezacaftor/ivacaftor vs. lumacaftor/ivacaftor (continued)

Study	VX14-661-106		VX12-809-103		VX12-809-104	
Characteristics	IVA + TEZA/IVA[a]	Placebo[a]	LUMA/IVA[a]	Placebo[a]	LUMA/IVA[a]	Placebo[a]
Category	N[a] = 248	N[a] = 256	N[a] = 182	N[a] = 184	N[a] = 187	N[a] = 187
Treatment before study inclusion[f], n (%)						
Dornase alfa	166 (66.9)	185 (72.3)	123 (67.6)	135 (73.4)	150 (80.2)	146 (78.1)
Inhaled antibiotics	136 (54.8)	160 (62.5)	113 (62.1)	122 (66.3)	112 (59.9)	136 (72.7)
Inhaled bronchodilators	221 (89.1)	234 (91.4)	171 (94.0)	172 (93.5)	169 (90.4)	170 (90.9)
Inhaled hypertonic saline solution	126 (50.8)	133 (52.0)	112 (61.5)	100 (54.3)	115 (61.5)	120 (64.2)
Inhaled corticosteroids	139 (56.0)	162 (63.3)	109 (59.9)	113 (61.4)	103 (55.1)	107 (57.2)
Pseudomonas aeruginosa infection, n (%)	185 (74.6)	182 (71.1)	151 (83.0)	134 (72.8)	135 (72.2)	142 (75.9)
Treatment discontinuation, n (%)	ND	ND	10 (5.5)	4 (2.2)	15 (8.0)	5 (2.7)
Study discontinuation, n (%)	15 (6.0[g])	17 (6.6[g])	6 (3.3)	2 (1.1)	7 (3.7)	2 (1.1)

a: Treatment was against the background of concomitant symptomatic treatment.
b: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c: Institute's calculation; includes black/African American, Asian, native Americans or Alaskans and others or those not recorded according to local guidelines.
d: In % of predicted normal.
e: BMI adjusted for age and sex; only for patients aged < 20 years at screening (study VX14-661-106: ivacaftor + tezacaftor/ivacaftor: n = 80 and placebo: n = 76; study VX12-809-103: ivacaftor + tezacaftor/ivacaftor: n = 62 and placebo: n = 72; study VX12-809-104: ivacaftor + tezacaftor/ivacaftor: n = 61 and placebo: n = 57).
f: Medication started until 28 days before the first study medication and continued during treatment with the study medication.
g: Institute's calculation.
BMI: body mass index; F: female; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; LUMA: lumacaftor; M: male; n: number of patients in the category; N: number of randomized or included patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; TEZA: tezacaftor; vs.: versus

The demographic and clinical characteristics of the patients were both balanced both between the treatment arms of the individual studies and largely comparable between the 3 studies.

Most patients in all 3 studies were of Caucasian family origin; their mean age was between 25 and 27 years. The proportions of men and women were balanced in all study arms. Most patients in the VX14-661-106 study were from Europe (about 75%), whereas the proportions of patients from Europe were lower (26 to 41%) in the studies VX12-809-103 and VX12-809-104. With the exception of the VX12-809-103 study, where the proportion of patients with *Pseudomonas aeruginosa* infection at baseline was higher in the lumacaftor/ivacaftor arm than in the placebo arm, the proportions of patients with *Pseudomonas aeruginosa* infection at baseline were balanced within and between the studies. With regard to inhaled symptomatic pretreatment, there were individual differences in the proportions, but these do not indicate that the patients differed in the severity grade of the disease between the studies.

Concomitant symptomatic treatment in the studies VX14-661-106, VX12-809-103 and VX12-809-104

Table 9 shows the symptomatic medication before the first administration of the study treatment and the concomitant symptomatic treatment used during the studies.

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

	VX14-661-106				VX12-809-103				VX12-809-104			
	IVA + TEZA/IVA[a]		Placebo[a]		LUMA/IVA[a]		Placebo[a]		LUMA/IVA[a]		Placebo[a]	
	N[b] = 248	N[b] = 248	N[b] = 256	N[b] = 256	N[b] = 182	N[b] = 182	N[b] = 248	N[b] = 248	N[b] = 256	N[b] = 256	N[b] = 182	N[b] = 182
	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)
Pancreatin	190 (76.6)	191 (77.0)	190 (74.2)	190 (74.2)	123 (67.6)	122 (67.0)	118 (64.1)	120 (65.2)	147 (78.6)	148 (79.1)	133 (71.1)	134 (71.7)
Dornase alfa	166 (66.9)	169 (68.1)	185 (72.3)	191 (74.6)	123 (67.6)	124 (68.1)	135 (73.4)	137 (74.5)	150 (80.2)	149 (79.7)	146 (78.1)	148 (79.1)
Salbutamol	140 (56.5)	144 (58.1)	145 (56.6)	149 (58.2)	129 (70.9)	129 (70.9)	127 (69.0)	132 (71.7)	115 (61.5)	123 (65.8)	124 (66.3)	134 (71.7)
Azithromycin	135 (54.4)	140 (56.5)	141 (55.1)	146 (57.0)	95 (52.2)	97 (53.3)	109 (59.2)	112 (60.9)	120 (64.2)	119 (63.6)	124 (66.3)	130 (69.5)
Sodium chloride	132 (53.2)	138 (55.6)	137 (53.5)	139 (54.3)	119 (65.4)	125 (68.7)	115 (62.5)	122 (66.3)	119 (63.6)	122 (65.2)	135 (72.2)	143 (76.5)
Ursodeoxycholic acid	82 (33.1)	82 (33.1)	71 (27.7)	73 (28.5)	46 (25.3)	46 (25.3)	41 (22.3)	41 (22.3)	39 (20.9)	39 (20.9)	33 (17.6)	34 (18.2)
Omeprazole	75 (30.2)	79 (31.9)	65 (25.4)	68 (26.6)	46 (25.3)	50 (27.5)	44 (23.9)	46 (25.0)	50 (26.7)	54 (28.9)	43 (23.0)	47 (25.1)
Colecalciferol	72 (29.0)	75 (30.2)	82 (32.0)	87 (34.0)	44 (24.2)	50 (27.5)	41 (22.3)	46 (25.0)	60 (32.1)	62 (33.2)	38 (20.3)	39 (20.9)
Tobramycin	69 (27.8)	95 (38.3)	77 (30.1)	115 (44.9)	67 (36.8)	85 (46.7)	84 (45.7)	114 (62.0)	69 (36.9)	91 (48.7)	70 (37.4)	111 (59.4)
Colistimethate sodium	61 (24.6)	76 (30.6)	50 (19.5)	68 (26.6)	35 (19.2)	43 (23.6)	29 (15.8)	39 (21.2)	17 (9.1)	21 (11.2)	33 (17.6)	34 (18.2)
Salmeterol/ fluticasone propionate	50 (20.2)	53 (21.4)	58 (22.7)	62 (24.2)	58 (31.9)	60 (33.0)	61 (33.2)	65 (35.3)	56 (29.9)	56 (29.9)	59 (31.6)	65 (34.8)
Aquadeks (dietary supplement)	49 (19.8)	47 (19.0)	36 (14.1)	35 (13.7)	36 (19.8)	38 (20.9)	50 (27.2)	50 (27.2)	45 (24.1)	47 (25.1)	49 (26.2)	50 (26.7)
Tocopherol	49 (19.8)	48 (19.4)	65 (25.4)	67 (26.2)	34 (18.7)	35 (19.2)	33 (17.9)	33 (17.9)	27 (14.4)	28 (15.0)	24 (12.8)	26 (13.9)

(continued)

Table 9: Medication before first administration of study treatment and concomitant medication (≥ 15% in at least one study arm) – RCT, indirect comparison: ivacaftor + tezacaftor/ivacaftor vs. lumacaftor/ivacaftor (continued)

	VX14-661-106				VX12-809-103				VX12-809-104			
	IVA + TEZA/IVA[a]		Placebo[a]		LUMA/IVA[a]		Placebo[a]		LUMA/IVA[a]		Placebo[a]	
	N[b] = 248	N[b] = 248	N[b] = 256	N[b] = 256	N[b] = 182	N[b] = 182	N[b] = 248	N[b] = 248	N[b] = 256	N[b] = 256	N[b] = 182	N[b] = 182
	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)
Vitamins[e] with zinc	47 (19.0)	54 (21.8)	45 (17.6)	49 (19.1)	37 (20.3)	41 (22.5)	41 (22.3)	42 (22.8)	40 (21.4)	41 (21.9)	46 (24.6)	46 (24.6)
Budesonide/ formoterol fumarate	41 (16.5)	43 (17.3)	46 (18.0)	47 (18.4)	17 (9.2)	14 (7.7)	10 (5.5)	17 (9.2)	29 (15.5)	35 (18.7)	22 (11.8)	27 (14.4)
Pancrelipase	41 (16.5)	42 (16.9)	57 (22.3)	57 (22.3)	52 (28.6)	52 (28.6)	62 (33.7)	64 (34.8)	34 (18.2)	35 (18.7)	44 (23.5)	46 (24.6)
Vitamins[e]	40 (16.1)	42 (16.9)	39 (15.2)	39 (15.2)	35 (19.2)	35 (19.2)	25 (13.6)	26 (14.1)	30 (16.0)	30 (16.0)	32 (17.1)	33 (17.6)
Tocopheryl acetate	39 (15.7)	38 (15.3)	33 (12.9)	33 (12.9)	16 (8.8)	16 (8.8)	20 (10.9)	20 (10.9)	14 (7.5)	14 (7.5)	7 (3.7)	7 (3.7)
Aztreonam lysine	38 (15.3)	48 (19.4)	57 (22.3)	62 (24.2)	35 (19.2)	45 (24.7)	34 (18.5)	45 (24.5)	45 (24.1)	52 (27.8)	59 (31.6)	71 (38.0)
Acetylcysteine	36 (14.5)	40 (16.1)	35 (13.7)	37 (14.5)	17 (9.3)	17 (9.3)	15 (8.2)	15 (8.2)	13 (7.0)	15 (8.0)	18 (9.6)	21 (11.2)
Vitamin D[e]	31 (12.5)	31 (12.5)	41 (16.0)	41 (16.0)	42 (23.1)	44 (24.2)	49 (26.6)	50 (27.2)	34 (18.2)	37 (19.8)	51 (27.3)	56 (29.9)
Ciprofloxacin	5 (2.0)	78 (31.5)	10 (3.9)	93 (36.3)	3 (1.6)	54 (29.7)	6 (3.3)	58 (31.5)	18 (9.6)	59 (31.6)	14 (7.5)	83 (44.4)
Ibuprofen	25 (10.1)	62 (25.0)	25 (9.8)	55 (21.5)	20 (11.0)	37 (20.3)	18 (9.8)	33 (17.9)	32 (17.1)	59 (31.6)	23 (12.3)	55 (29.4)
Paracetamol	17 (6.9)	46 (18.5)	16 (6.3)	60 (23.4)	7 (3.8)	44 (24.2)	6 (3.3)	42 (22.8)	18 (9.6)	47 (25.1)	14 (7.5)	49 (26.2)
Bactrim	18 (7.3)	44 (17.7)	20 (7.8)	58 (22.7)	7 (3.8)	23 (12.6)	12 (6.5)	46 (25.0)	21 (11.2)	40 (21.4)	19 (10.2)	59 (31.6)
Influenza vaccination	3 (1.2)	27 (10.9)	2 (0.8)	27 (10.5)	4 (2.2)	35 (19.2)	7 (3.8)	54 (29.3)	0 (0)	50 (26.7)	1 (0.5)	47 (25.1)

(continued)

Table 9: Medication before first administration of study treatment and concomitant medication (≥ 15% in at least one study arm) – RCT, indirect comparison: ivacaftor + tezacaftor/ivacaftor vs. lumacaftor/ivacaftor (continued)

	VX14-661-106				VX12-809-103				VX12-809-104			
	IVA + TEZA/IVA[a]		Placebo[a]		LUMA/IVA[a]		Placebo[a]		LUMA/IVA[a]		Placebo[a]	
	N[b] = 248	N[b] = 248	N[b] = 256	N[b] = 256	N[b] = 182	N[b] = 182	N[b] = 184	N[b] = 184	N[b] = 187	N[b] = 187	N[b] = 187	N[b] = 187
	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)	Medication before start of study[c], n (%)	Concomitant medication[d] n (%)
Fluticasone propionate	33 (13.3)	36 (14.5)	17 (6.6)	20 (7.8)	38 (20.9)	38 (20.9)	24 (13.0)	30 (16.3)	28 (15.0)	34 (18.2)	37 (19.8)	42 (22.5)
Montelukast sodium	15 (6.0)	17 (6.9)	22 (8.6)	23 (9.0)	19 (10.4)	19 (10.4)	20 (10.9)	21 (11.4)	25 (13.4)	27 (14.4)	30 (16.0)	30 (16.0)
Salbutamol sulfate	21 (8.5)	21 (8.5)	29 (11.3)	29 (11.3)	14 (7.7)	8 (4.4)	19 (10.3)	14 (7.6)	28 (15.0)	26 (13.9)	27 (14.4)	31 (16.6)
Non-drug treatment												
Physiotherapy	120 (47.8)[f]	122 (48.6)[f]	124 (48.1)[f]	129 (50.0)[f]	ND	ND	ND	ND	ND	ND	ND	ND

a: Treatment was against the background of concomitant symptomatic treatment.
b: Number of patients in the FAS population.
c: Medication before first administration of study treatment.
d: 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.
e: Not otherwise specified.
f: Information refers to all patients who have received at least one dose of the study medication (safety population) (ivacaftor + tezacaftor/ivacaftor N = 251; placebo N = 258).

FAS: full analysis set; IVA: ivacaftor; LUMA: lumacaftor; n: number of patients in the category; N: Number of randomized patients; ND: no data; RCT: randomized controlled trial; TEZA: tezacaftor; vs.: versus

Administration of symptomatic treatment in addition to the study medication (ivacaftor + tezacaftor/ivacaftor or lumacaftor/ivacaftor) was allowed in the studies VX14-661-106, VX12-809-103 and VX12-809-104. However, according to the information provided in the study protocols, patients in all 3 studies had to be willing to continue the CF medication they had been receiving from 4 weeks before the start of the study at a stable dosage according to plan for 24 weeks, and if necessary at a stable dosage until the end of follow-up observation of AEs (safety follow-up) until the end of the study.

Unchanged continuation of pretreatment without the possibility of treatment optimization does not meet the criteria of an individualized concomitant treatment. However, the company described in the dossier that in all 3 studies adjustments of the concomitant medication had been made during the course of the studies and thus the individual medical needs in terms of symptomatic therapy had been met.

For all 3 studies (VX14-661-106, VX12-809-103 and VX12-809-104), it can be inferred from the study documents that patients received the regularly used medication for symptomatic treatment of CF (see Table 9). These included, among others, dornase alfa, bronchodilators, antibiotics, analgesics and vitamin preparations. Treatment with inhaled saline solution was not explicitly excluded in all studies.

The proportion of patients under the respective concomitant medication remained largely unchanged before and after the first intake of the study medication (see Table 9). A clear increase in concomitant medication after the first intake of the study medication in all arms of the 3 studies was shown, for example, for antibiotics (including ciprofloxacin) and analgesics (ibuprofen and paracetamol). However, there was generally no information on whether and how many patients had their concomitant treatment adjusted, for example in the sense of an increase in dose or frequency in the course of the study. In contrast to the VX14-661-106 study, no information is available for the studies VX12-809-103 and VX12-809-104 as to whether physiotherapeutic measures could be taken during the studies (see Table 9).

In summary, the information provided shows that individual adjustments to the concomitant treatment were made in all 3 studies. Nevertheless, there was no information on increases in dose or frequency of the respective therapies during the studies or on physiotherapy in the studies VX12-809-103 and VX12-809-104.

2.3.3 Similarity of the studies for the indirect comparison

The available data on the study, intervention and patient characteristics and on the concomitant medication of the 3 studies of the indirect comparison show that the studies were sufficiently similar regarding design, included patient populations and concomitant medication.

2.3.4 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, indirect comparison: tezacaftor/ivacaftor vs. lumacaftor/ivacaftor

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			
VX14-661-106	Yes	Yes	Yes	Yes	Yes	Yes	Low
VX12-809-103	Yes	Yes	Yes	Yes	Yes	Yes	Low
VX12-809-104	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for all 3 studies. This concurs with the company's assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.5.3.2 of the full dossier assessment):

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

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.5.3 of the full dossier assessment).

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

Table 11: Matrix of outcomes – RCT, indirect comparison: tezacaftor/ivacaftor vs. lumacaftor/ivacaftor

Study	Outcomes							
	All-cause mortality	Pulmonary exacerbations	Hospitalization due to pulmonary exacerbations	Symptoms (CFQ-R)	Health-related quality of life (CFQ-R)	SAEs[b]	Discontinuation due to AEs[b]	Rash (PT, AE)
VX14-661-106[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
VX12-809-103[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
VX12-809-104[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: An analysis in the indirect comparison is not possible for outcomes that were recorded either only in the study on the intervention (VX14-661-106) or in the 2 studies on the comparator therapy (VX12-809-103 and VX12-809-104) (see Section 2.7.5.3.2 of the full dossier assessment). These outcomes are therefore not listed in the table and are not considered further.
b: Pulmonary exacerbation events were included in the recording of AEs; see Section 2.7.5.2 of the full dossier assessment for information on how the results of the outcomes "SAEs" and "discontinuation due to AEs" were handled.
AE: adverse event; CFQ-R: Cystic Fibrosis Questionnaire-Revised; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.4.2 Risk of bias

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

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: tezacaftor/ivacaftor vs. lumacaftor/ivacaftor

Study	Study level	Outcomes							
		All-cause mortality	Pulmonary exacerbations	Hospitalization due to pulmonary exacerbations	Symptoms (CFQ-R)	Health-related quality of life (CFQ-R)	SAEs	Discontinuation due to AEs	Rash (PT, AE)
VX14-661-106	L	L	L	L	L	L	–[a]	H[a]	L
VX12-809-103	L	L	L	L	L	L	–[a]	H[a]	L
VX12-809-104	L	L	L	L	L	L	–[a]	H[a]	L

a: Pulmonary exacerbation events were included in the recording of AEs (see Section 2.7.5.2 of the full dossier assessment); as a result, the results for the outcome "SAEs" are not usable, and the outcome "discontinuation due to AEs" has a high risk of bias.

AE: adverse event; CFQ-R: Cystic Fibrosis Questionnaire-Revised; H: high; L: low; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Concurring with the company's assessment, the risk of bias for the results of the following outcomes was rated as low for all 3 studies: all-cause mortality, pulmonary exacerbations, hospitalization due to pulmonary exacerbations, symptoms (recorded with the CFQ-R) and health-related quality of life (recorded with the CFQ-R).

In all 3 studies, events of pulmonary exacerbations of CF were included in the recording of SAEs to a large extent. However, SAEs without events attributable to the underlying disease are relevant for the benefit assessment (see Section 2.7.5.2 of the full dossier assessment). Due to the possibly large proportion of patients in whom only these pulmonary exacerbations were recorded as event for the outcome "SAEs" (see Table 23, Table 26 and Table 29 of the full dossier assessment), it is not possible to assess the effect estimation for the results not containing this Preferred Term (PT). Thus, the results are not usable and the risk of bias for the results of this outcome is not assessed. The company assumed a low risk of bias for the results of the outcome "SAEs".

Results of the outcome "discontinuation due to AEs" contain events that form part of the symptoms of the underlying disease or that can be both side effects and symptoms of the underlying disease (see Section 2.7.5.2 and Table 24, Table 27 and Table 30 of the full dossier assessment). Due to the overall small number of events that led to the discontinuation of the study medication, the events that form part of the symptoms of the underlying disease (e.g. PT infective pulmonary exacerbation of cystic fibrosis) may lead to a marked shift in the effect

estimation. The risk of bias for the results of the outcome “discontinuation due to AEs” was therefore rated as high. The company assumed a low risk of bias for the results of this outcome.

The risk of bias of the results of the AE outcome “rash” was rated as low in all 3 studies of the indirect comparison. The company did not use the outcome “rash” for the derivation of the added benefit and therefore did also not assess the risk of bias.

2.4.3 Results

Table 13 to Table 15 summarize the results on the comparison of ivacaftor + tezacaftor/ ivacaftor with lumacaftor/ivacaftor in patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier. Results on patient-relevant outcomes that were recorded on both sides of the indirect comparison are presented. Tables on common AEs are presented in Appendix A of the full dossier assessment.

Table 13: Results (mortality, side effects, dichotomous) – RCT, indirect comparison using common comparators: ivacaftor + tezacaftor/ivacaftor vs. lumacaftor/ivacaftor

Outcome category Outcome Comparison Study	IVA + TEZA/IVA[a] or LUMA/IVA[a]		Placebo[a]		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality					
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]					
VX14-661-106	251	0 (0)	258	0 (0)	–
Lumacaftor/ivacaftor[a] vs. placebo[a]					
VX12-809-103	182	0 (0)	184	0 (0)	–
VX12-809-104	187	0 (0)	186	0 (0)	–
Side effects					
AEs (supplementary information)					
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]					
VX14-661-106	251	227 (90.4)	258	245 (95.0)	–
Lumacaftor/ivacaftor[a] vs. placebo[a]					
VX12-809-103	182	174 (95.6)	184	174 (94.6)	–
VX12-809-104	187	177 (94.7)	186	181 (97.3)	–
SAEs					
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]					
VX14-661-106	251	31 (12.4)	258	47 (18.2)	–[b]
Lumacaftor/ivacaftor[a] vs. placebo[a]					
VX12-809-103	182	33 (18.1)	184	49 (26.6)	–[b]
VX12-809-104	187	31 (16.6)	186	57 (30.6)	–[b]
Discontinuation due to AEs[b]					
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]					
VX14-661-106	251	7 (2.8)	258	8 (3.1)	0.90 [0.33; 2.44]; 0.835
Lumacaftor/ivacaftor[a] vs. placebo[a]					
VX12-809-103	182	6 (3.3)	184	4 (2.2)	1.52 [0.44; 5.28]; 0.513
VX12-809-104	187	11 (5.9)	186	2 (1.1)	5.47 [1.23; 24.34]; 0.026
Total[c]					2.57 [0.99; 6.70]; 0.053
Indirect comparison using common comparators[d]:					
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]					–[e]

(continued)

Table 13: Results (mortality, side effects, dichotomous) – RCT, indirect comparison using common comparators: ivacaftor + tezacaftor/ivacaftor vs. lumacaftor/ivacaftor (continued)

Outcome category **Outcome** **Comparison** **Study**	**IVA + TEZA/IVA[a] or LUMA/IVA[a]** **N**	**Patients with event n (%)**	**Placebo[a]** **N**	**Patients with event n (%)**	**Group difference** **RR [95% CI]; p-value**
Side effects					
Rash (PT, AE)					
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]					
VX14-661-106	251	4 (1.6)	258	13 (5.0)	0.32 [0.10; 0.96]; 0.032[f]
Lumacaftor/ivacaftor[a] vs. placebo[a]					
VX12-809-103	182	7 (3.8)	184	2 (1.1)	3.54 [0.75; 16.81]; 0.097[f]
VX12-809-104	187	18 (9.6)	186	5 (2.7)	3.58 [1.36; 9.44]; 0.005[f]
Total[g]					3.57 [1.57; 8.13]; 0.002
Indirect comparison using common comparators[h]:					
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]					0.09 [0.02; 0.35]; < 0.001

a: Treatment was against the background of concomitant symptomatic treatment.
b: Events of the underlying disease were included in the recording of AEs (see Section 2.7.5.3.2 of the full dossier assessment); as a result, the results of the outcome "SAEs" are not usable, and the outcome "discontinuation due to AEs" has a high risk of bias.
c: Fixed-effect model.
d: Indirect comparison according to Bucher [5].
e: No presentation of effect estimates, as there is only one study with outcome-specific high risk of bias on the intervention side, and thus no hint of greater or lesser harm is derived (Section 2.7.5.2 of the full dossier assessment).
f: Institute's calculation, unconditional exact test (CSZ method according to [6]).
g: Institute's calculation, meta-analysis, fixed-effect model, Mantel-Haenszel method.
h: Institute's calculation, indirect comparison according to Bucher [5].

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; IVA: ivacaftor; LUMA: lumacaftor; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TEZA: tezacaftor; vs.: versus

Table 14: Results (morbidity, dichotomous) – RCT, indirect comparison using common comparators: ivacaftor + tezacaftor/ivacaftor vs. lumacaftor/ivacaftor

Outcome category **Outcome** **Comparison** **Study**	**IVA + TEZA/IVA[a] or LUMA/IVA[a]**		**Placebo[a]**		**Group difference**
	N	**Number of events (n_E/patient years)[b]**	**N**	**Number of events (n_E/patient years)[b]**	**Rate ratio [95% CI]; p-value[c]**
Morbidity					
Pulmonary exacerbations[d]					
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]					
VX14-661-106	248	78 (0.69[e])	256	122 (1.05[e])	0.65 [0.48; 0.88]; 0.005
Lumacaftor/ivacaftor[a] vs. placebo[a]					
VX12-809-103	182	73 (0.89[e])	184	112 (1.31[e])	0.66 [0.48; 0.92]; 0.014
VX12-809-104	187	79 (0.93[e])	187	139 (1.62[e])	0.57 [0.42; 0.77]; < 0.001
Total					0.61 [0.49; 0.76]; < 0.001[f]
Indirect comparison using common comparators:					
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]					1.06 [0.73; 1.55]; 0.760[g]
Hospitalization due to pulmonary exacerbations					
Tezacaftor/ivacaftor[a] vs. placebo[a]					
VX14-661-106	248	26 (0.23[e])	256	33 (0.28[e])	0.78 [0.44; 1.36]; 0.380
Lumacaftor/ivacaftor[a] vs. placebo[a]					
VX12-809-103	182	17 (0.21[e])	184	46 (0.54[e])	0.38 [0.22; 0.66]; < 0.001
VX12-809-104	187	23 (0.27[e])	187	59 (0.69[e])	0.39 [0.24; 0.64]; < 0.001
Total					0.38 [0.27; 0.56]; < 0.001[f]
Indirect comparison using common comparators:					
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]					2.02 [1.03; 3.95]; 0.040[g]

a: Treatment was against the background of concomitant symptomatic treatment.
b: The event rate (n_E/patient years) is calculated from the total number of events divided by the total number of years (sum of the observation period of all patients included in the analysis).
c: Negative binomial model with treatment, sex, age group at baseline (< 18 years vs. ≥ 18 years) and FEV1 at baseline as covariates.
d: Defined as new or changed antibiotic therapy due to ≥ 4 sinopulmonary signs/symptoms.
e: Institute's calculation.
f: Institute's calculation; meta-analysis with fixed effect; inverse variance method.
g: Institute's calculation; indirect comparison according to Bucher [5].
CI: confidence interval; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; LUMA: lumacaftor; n_E: number of events; N: number of analysed patients; RCT: randomized controlled trial; TEZA: tezacaftor; vs.: versus

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison using common comparators: tezacaftor/ivacaftor vs. lumacaftor/ivacaftor

Outcome category Outcome Domain Comparison Study	IVA + TEZA/IVA[a] or LUMA/IVA[a]			Placebo[a]			Group difference
	N[b]	Values at baseline mean (SD)	Change at end of study mean[c] (SD)	N[b]	Values at baseline mean (SD)	Change at end of study mean[c] (SD)	MD [95% CI]; p-value[d]
Morbidity							
Symptoms (CFQ-R, symptom domains, children [12 to 13 years] and adolescents or adults – pooled)[e]							
Respiratory symptoms							
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]							
VX14-661-106	246	70.06 (16.81)	4.11 (15.88)	256	69.92 (16.64)	−1.36 (16.60)	5.11 [3.20; 7.02]; < 0.001[f]
Lumacaftor/ivacaftor[a] vs. placebo[a]							
VX12-809-103	172	69.29 (17.42)	1.60 (16.92)	184	70.54 (16.03)	−0.50 (15.89)	1.51 [−1.58; 4.61]; 0.355[g]
VX12-809-104	179	67.36 (18.54)	3.51 (18.76)	185	67.05 (18.39)	0.71 (17.06)	2.85 [−0.38; 6.08]; 0.098[g]
Total							2.15 [−0.08; 4.38]; 0.058
Indirect comparison using common comparators[h]:							
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]							2.96 [0.03; 5.89] 0.048[i] Hedges' g: 0.29 [0.06; 0.52][j]
Digestive symptoms							
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]							
VX14-661-106	246	82.03 (16.22)	−0.52 (18.30)	256	80.47 (19.07)	0.82 (16.48)	−0.10 [−1.93; 1.72]; 0.911[f]
Lumacaftor/ivacaftor[a] vs. placebo[a]							
VX12-809-103	171	81.97 (16.07)	−0.23 (16.58)	184	83.95 (16.62)	−0.18 (16.23)	−1.05 [−4.20; 2.09]; 0.511[g]
VX12-809-104	179	82.83 (19.28)	−1.18 (15.04)	185	82.25 (19.22)	0.60 (18.41)	−1.65 [−4.72; 1.43]; 0.293[g]
Total[k]							Hedges' g: −0.09 [−0.23; 0.06]; 0.252
Indirect comparison using common comparators[l]:							
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: 0.08 [−0.15; 0.30]; 0.514[i]

(continued)

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison using common comparators: tezacaftor/ivacaftor vs. lumacaftor/ivacaftor (continued)

Outcome category Outcome Domain Comparison Study	IVA + TEZA/IVA[a] or LUMA/IVA[a] N[b]	Values at baseline mean (SD)	Change at end of study mean[c] (SD)	Placebo[a] N[b]	Values at baseline mean (SD)	Change at end of study mean[c] (SD)	Group difference MD [95% CI]; p-value[d]
Morbidity							
Weight							
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]							
VX14-661-106	223	74.52 (32.47)	2.34 (27.59)	231	76.01 (30.77)	−1.22 (24.34)	0.51 [−2.89; 3.90]; 0.770[f]
Lumacaftor/ivacaftor[a] vs. placebo[a]							
VX12-809-103	158	77.85 (33.49)	0.21 (28.02)	165	73.94 (33.56)	1.62 (27.74)	−0.50 [−5.69; 4.69]; 0.850[g]
VX12-809-104	166	73.88 (34.21)	3.62 (28.43)	166	74.80 (32.33)	−1.60 (27.65)	4.86 [−0.47; 10.19]; 0.074[g]
Total[k]							Hedges' g: 0.08 [−0.07; 0.23]; 0.292
Indirect comparison using common comparators[l]:							
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: −0.06 [−0.30; 0.18]; 0.623[i]
Health-related quality of life							
CFQ-R (health-related quality of life domains, children [12 to 13 years] and adolescents or adults – pooled)[e]							
Physical functioning							
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]							
VX14-661-106	246	77.56 (20.94)	2.01 (16.50)	256	78.23 (21.71)	−1.08 (14.78)	3.85 [1.88; 5.82]; < 0.001[f]
Lumacaftor/ivacaftor[a] vs. placebo[a]							
VX12-809-103	171	79.03 (19.33)	−0.97 (17.83)	184	80.70 (19.23)	−2.21 (15.67)	0.80 [−2.59; 4.18]; 0.644[g]
VX12-809-104	180	78.90 (19.75)	0.54 (19.14)	184	78.77 (21.01)	−3.89 (18.32)	4.28 [0.63; 7.93]; 0.022[g]
Total[k]							Hedges' g 0.14 [−0.01; 0.29]; 0.064
Indirect comparison using common comparators[l]:							
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: 0.17 [−0.06; 0.40]; 0.146[i]

(continued)

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison using common comparators: tezacaftor/ivacaftor vs. lumacaftor/ivacaftor (continued)

Outcome category Outcome Domain Comparison Study	IVA + TEZA/IVA[a] or LUMA/IVA[a]			Placebo[a]			Group difference
	N[b]	Values at baseline mean (SD)	Change at end of study mean[c] (SD)	N[b]	Values at baseline mean (SD)	Change at end of study mean[c] (SD)	MD [95% CI]; p-value
Health-related quality of life							
Emotional functioning							
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]							
VX14-661-106	246	82.61 (15.73)	−0.02 (12.01)	256	81.90 (16.18)	−0.37 (13.61)	0.59 [−1.02; 2.21]; 0.471[f]
Lumacaftor/ivacaftor[a] vs. placebo[a]							
VX12-809-103	171	81.32 (16.09)	1.46 (13.41)	184	81.33 (15.02)	0.59 (11.89)	0.79 [−1.59; 3.17]; 0.514[g]
VX12-809-104	180	90.25 (10.41)	1.97 (12.97)	184	83.91 (16.17)	−1.16 (11.30)	3.21 [0.88; 5.54]; 0.007[g]
Total[k]							Hedges' g: 0.17 [0.02; 0.32]; 0.024
Indirect comparison using common comparators[k]:							
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: −0.11 [−0.34; 0.12]; 0.343[i]
Vitality							
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]							
VX14-661-106	223	64.58 (18.59)	−0.61 (18.38)	231	62.25 (17.92)	−1.22 (15.85)	2.30 [0.10; 4.49]; 0.040[f]
Lumacaftor/ivacaftor[a] vs. placebo[a]							
VX12-809-103	157	64.78 (17.55)	−1.17 (16.81)	166	64.56 (16.48)	−2.39 (15.69)	1.04 [−2.37; 4.45]; 0.550[g]
VX12-809-104	167	63.62 (18.05)	0.70 (18.75)	165	62.70 (17.09)	−1.88 (16.85)	2.86 [−0.68; 6.39]; 0.113[g]
Total[k]							Hedges' g: 0.11 [−0.04; 0.26]; 0.155
Indirect comparison using common comparators[l]:							
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: 0.05 [−0.19; 0.29]; 0.694[i]

(continued)

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison using common comparators: tezacaftor/ivacaftor vs. lumacaftor/ivacaftor (continued)

Outcome category Outcome Domain Comparison Study	IVA + TEZA/IVA[a] or LUMA/IVA[a]			Placebo[a]			Group difference
	N[b]	Values at baseline mean (SD)	Change at end of study mean[c] (SD)	N[b]	Values at baseline mean (SD)	Change at end of study mean[c] (SD)	MD [95% CI]; p-value[d]
Health-related quality of life							
Social functioning							
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]							
VX14-661-106	246	72.06 (16.85)	0.82 (12.24)	256	73.93 (16.32)	−1.06 (12.21)	1.52 [0.03; 3.01]; 0.045[f]
Lumacaftor/ivacaftor[a] vs. placebo[a]							
VX12-809-103	173	74.02 (16.54)	−1.74 (12.72)	184	73.29 (17.17)	−1.44 (13.45)	−0.30 [−2.86; 2.27]; 0.821[g]
VX12-809-104	180	74.46 (16.42)	−1.40 (14.50)	185	73.27 (16.71)	−2.68 (13.64)	1.40 [−1.28; 4.08]; 0.306[g]
Total[k]							Hedges' g: 0.04 [−0.10; 0.18]; 0.587
Indirect comparison using common comparators[l]:							
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]							0.12 [−0.10; 0.35]; 0.288[i]
Role functioning							
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]							
VX14-661-106	223	83.93 (17.02)	1.73 (14.04)	230	84.02 (16.79)	0.31 (14.15)	1.53 [−0.31; 3.37]; 0.103[f]
Lumacaftor/ivacaftor[a] vs. placebo[a]							
VX12-809-103	157	82.72 (16.35)	0.69 (13.28)	166	84.74 (17.50)	−1.81 (14.06)	2.16 [−0.72; 5.04]; 0.140[g]
VX12-809-104	166	83.86 (15.70)	0.72 (17.63)	166	84.03 (17.76)	−2.55 (15.96)	3.08 [−0.29; 6.44]; 0.073[g]
Total[k]							Hedges' g: 0.17 [0.01; 0.32]; 0.034
Indirect comparison using common comparators[l]:							
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: −0.04 [−0.28; 0.20]; 0.756[i]

(continued)

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison using common comparators: tezacaftor/ivacaftor vs. lumacaftor/ivacaftor (continued)

Outcome category Outcome Domain Comparison Study	IVA + TEZA/IVA[a] or LUMA/IVA[a]			Placebo[a]			Group difference
	N[b]	Values at baseline mean (SD)	Change at end of study mean[c] (SD)	N[b]	Values at baseline mean (SD)	Change at end of study mean[c] (SD)	MD [95% CI]; p-value[d]
Health-related quality of life							
Body image							
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]							
VX14-661-106	246	76.30 (22.09)	0.05 (14.80)	256	77.47 (23.15)	1.68 (14.70)	−0.51 [−2.31; 1.29]; 0.577[f]
Lumacaftor/ivacaftor[a] vs. placebo[a]							
VX12-809-103	173	77.91 (21.89)	2.05 (16.97)	184	76.94 (22.66)	2.90 (16.89)	−0.56 [−3.75; 2.64]; 0.732[g]
VX12-809-104	180	78.29 (21.07)	1.51 (15.39)	185	77.13 (22.47)	−0.30 (18.83)	2.10 [−1.18; 5.38]; 0.209[g]
Total[k]							Hedges' g: 0.05 [−0.09; 0.19]; 0.498
Indirect comparison using common comparators[l]:							
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: −0.10 [−0.32; 0.13]; 0.406[i]
Eating problems							
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]							
VX14-661-106	246	89.74 (17.34)	−0.63 (13.64)	256	91.15 (17.06)	−0.84 (12.73)	1.05 [−0.59; 2.70]; 0.209[f]
Lumacaftor/ivacaftor[a] vs. placebo[a]							
VX12-809-103	172	90.89 (15.70)	0.36 (15.66)	183	92.58 (15.20)	−1.03 (12.02)	0.90 [−1.67; 3.47]; 0.492[g]
VX12-809-104	180	93.02 (13.89)	−1.67 (14.11)	185	91.27 (16.40)	−2.94 (16.34)	1.69 [−1.28; 4.65]; 0.263[g]
Total[k]							Hedges' g: 0.09 [−0.06; 0.24]; 0.225
Indirect comparison using common comparators[l]:							
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: 0.01 [−0.22; 0.24]; 0.911[i]

(continued)

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison using common comparators: tezacaftor/ivacaftor vs. lumacaftor/ivacaftor (continued)

Outcome category Outcome Domain Comparison Study	IVA + TEZA/IVA[a] or LUMA/IVA[a] N[b]	Values at baseline mean (SD)	Change at end of study mean[c] (SD)	Placebo[a] N[b]	Values at baseline mean (SD)	Change at end of study mean[c] (SD)	Group difference MD [95% CI]; p-value[d]
Health-related quality of life							
Treatment burden							
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]							
VX14-661-106	246	60.53 (19.69)	2.88 (13.77)	256	62.11 (20.02)	−0.68 (13.03)	3.37 [1.65; 5.10]; < 0.001[f]
Lumacaftor/ivacaftor[a] vs. placebo[a]							
VX12-809-103	173	57.73 (19.90)	3.43 (13.53)	184	57.86 (18.02)	2.29 (14.03)	1.12 [−1.58; 3.81]; 0.416[g]
VX12-809-104	180	57.87 (21.25)	2.56 (18.28)	185	57.11 (20.15)	3.09 (17.84)	−0.19 [−3.48; 3.10]; 0.909[g]
Total[k]							Hedges' g: 0.03 [−0.11; 0.18]; 0.649
Indirect comparison using common comparators[l]:							
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: 0.28 [0.05; 0.51]; 0.018[i]
Health perceptions							
Ivacaftor + tezacaftor/ivacaftor[a] vs. placebo[a]							
VX14-661-106	223	64.35 (21.36)	1.82 (15.66)	231	64.90 (20.33)	−2.60 (17.35)	3.20 [1.15; 5.24]; 0.002[f]
Lumacaftor/ivacaftor[a] vs. placebo[a]							
VX12-809-103	159	64.59 (20.79)	1.12 (18.62)	166	69.36 (19.70)	−2.68 (15.52)	2.32 [−1.19; 5.83]; 0.195[g]
VX12-809-104	167	66.00 (20.49)	0.67 (16.95)	166	65.49 (20.79)	−1.67 (15.78)	2.40 [−0.84; 5.63]; 0.146[g]
Total[k]							Hedges' g: 0.14 [−0.02; 0.29]; 0.081
Indirect comparison using common comparators[l]:							
Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: 0.10 [−0.14; 0.34]; 0.404[i]

(continued)

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison using common comparators: tezacaftor/ivacaftor vs. lumacaftor/ivacaftor (continued)

a: Treatment was against the background of concomitant symptomatic treatment.
b: Number of patients considered in the MMRM for the calculation of the effect estimation; the values at baseline may be based on more patients, the values at the end of study may be based on fewer patients.
c: Refers to the change from baseline to the last time point of measurement.
d: Results on the MD are only presented if these were provided by the company.
e: Higher values indicate better health-related quality of life or symptoms.
f: MMRM: effect presents the difference between the treatment groups of the changes averaged over the course of the study between the respective time point of measurement and the start of the study. Model: sex, age at screening, CFQ-R score at baseline, treatment, time point of study, treatment × time point of study, CFQ-R score at baseline × time point of study as fixed effects.
g: MMRM: effect presents the difference between the treatment groups of the changes averaged over the course of the study between the respective time point of measurement and the start of the study. Model: treatment, time point of study, treatment × time point of study as fixed effects, patients as random effect, adjusted for age, sex, screening FEV1 (in % of predicted normal) and CFQ-R at baseline.
h: Indirect comparison according to Bucher [5].
i: Institute's calculation of p-value under the assumption of asymptotic normal distribution.
j: Institute's calculation; indirect comparison according to Bucher [5].
k: Meta-analysis with fixed effect using the Hedges' g effect measure; no information on MD.
l: Indirect comparison according to Bucher [5] using the Hedges' g effect measure; no information on MD.
BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; LUMA: lumacaftor; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; TEZA: tezacaftor; vs.: versus

Only one study is available on the intervention side of the indirect comparison. Hence, the homogeneity for ivacaftor + tezacaftor/ivacaftor versus placebo is not checked. Since there is no study of direct comparison for the comparison of ivacaftor + tezacaftor/ivacaftor with lumacaftor/ivacaftor, the consistency of the results cannot be checked. The adjusted indirect comparisons therefore have a maximum low certainty of results. Hence, at most hints, e.g. of an added benefit, can be derived based on the data available from the adjusted indirect comparison. There was a high risk of bias in all 3 studies of the indirect comparison for the outcome "discontinuation due to AEs" (see Section 2.4.2). Since there is only one study, which additionally has an outcome-specific high risk of bias, for this outcome on the intervention side of the indirect comparison, the certainty of results of an effect estimation for the indirect comparison for this outcome is not sufficient, and no hint of greater or lesser harm is derived.

These assessments deviate from the approach of the company, which derived indications on the basis of the results from the adjusted indirect comparison. In addition, there are no usable data for SAEs (see Section 2.7.5.2 of the full dossier assessment). This is taken into account in the overall consideration (see Section 2.5.2).

Mortality

All-cause mortality

No deaths occurred during all 3 studies of the indirect comparison. There was no hint of an added benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for all-cause mortality; an added benefit is therefore not proven.

The assessment concurs with that of the company.

Morbidity

Pulmonary exacerbations

For the outcome "pulmonary exacerbations", the adjusted indirect comparison based on the event rate (n_E/patient years: total number of events divided by total number of years) showed no statistically significant difference between ivacaftor + tezacaftor/ivacaftor and lumacaftor/ivacaftor. This resulted in no hint of an added benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for this outcome.

This deviates from the assessment of the company, which derived an indication of lesser benefit for the subgroup of patients < 18 years of age for this outcome on the basis of the frequency of occurrence of any pulmonary exacerbation and the time to occurrence of the first pulmonary exacerbation.

Hospitalization due to pulmonary exacerbations

For the outcome "hospitalization due to pulmonary exacerbations", the adjusted indirect comparison based on the event rate (n_E/patient years: total number of events divided by total number of years) showed a statistically significant difference to the disadvantage of ivacaftor + tezacaftor/ivacaftor versus lumacaftor/ivacaftor. This resulted in a hint of lesser benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for this outcome.

This deviates from the assessment of the company, which derived an indication of lesser benefit of ivacaftor + tezacaftor/ivacaftor versus lumacaftor/ivacaftor for this outcome on the basis of the number of patients with hospitalization due to pulmonary exacerbation and the time to occurrence of the first hospitalization due to pulmonary exacerbation.

Symptoms measured using the CFQ-R

Symptom outcomes were recorded with the domains "respiratory symptoms", "digestive symptoms" and "weight" of the disease-specific patient-reported instrument CFQ-R.

Domain "respiratory symptoms"

In the domain "respiratory symptoms", the adjusted indirect comparison showed a statistically significant difference in favour of ivacaftor + tezacaftor/ivacaftor versus lumacaftor/ivacaftor regarding the changes between the respective time point of measurement and baseline, averaged over the course of the study. The SMD in the form of Hedges' g was considered to assess the

relevance of the result. The 95% CI was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect was relevant. There was no hint of an added benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for the CFQ-R domain "respiratory symptoms"; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of a minor added benefit for this outcome on the basis of the responder analyses and the mean differences. Deviating from the present assessment, the company allocated the domain "respiratory symptoms" to health-related quality of life.

Domains "digestive symptoms" and "weight"

The company presented solely SMDs with a 95% CI in the form of Hedges' g for the domains of digestive symptoms and weight. The adjusted indirect comparison showed no statistically significant differences between ivacaftor + tezacaftor/ivacaftor and lumacaftor/ivacaftor regarding the changes between the respective time point of measurement and baseline, averaged over the course of the study. This resulted in no hint of an added benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for either of both domains; an added benefit is therefore not proven.

The assessment concurs with that of the company, which described an added benefit as not proven for the CFQ-R domains of digestive symptoms and weight.

Health-related quality of life

Health-related quality of life was recorded using the domains of physical functioning, emotional functioning, vitality, social functioning, role functioning, body image, eating problems, treatment burden and health perceptions of the CFQ-R.

Domains of physical functioning, emotional functioning, vitality, social functioning, role functioning, body image, eating problems and health perceptions

The company presented solely SMDs with a 95% CI in the form of Hedges' g for the domains of physical functioning, emotional functioning, vitality, social functioning, role functioning, body image, eating problems and health perceptions The adjusted indirect comparison showed no statistically significant differences between ivacaftor + tezacaftor/ivacaftor and lumacaftor/ivacaftor regarding the changes between the respective time point of measurement and baseline, averaged over the course of the study. This resulted in no hint of an added benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for each of these domains; an added benefit is therefore not proven.

The assessment concurs with that of the company, which described an added benefit as not proven for the CFQ-R domains of physical functioning, emotional functioning, vitality, social functioning, role functioning, body image, eating problems and health perceptions.

Domain "treatment burden"

The company presented solely SMDs with a 95% CI in the form of Hedges' g for the domain "treatment burden". The adjusted indirect comparison showed a statistically significant difference in favour of ivacaftor + tezacaftor/ivacaftor versus lumacaftor/ivacaftor regarding the changes between the respective time point of measurement and baseline, averaged over the course of the study. The 95% CI was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect was relevant. There was no hint of an added benefit of ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for the CFQ-R domain "treatment burden"; an added benefit is therefore not proven.

This concurs with the assessment of the company, which described an added benefit as not proven for the domain "treatment burden".

Side effects

Serious adverse events

In the studies VX12-809-103, VX12-809-104 and VX14-661-106, events of pulmonary exacerbation of CF were also included in the recording of SAEs (see Section 2.7.5.2 of the full dossier assessment). As a result, the results on this outcome are not usable.

Overall, there was no hint of greater or lesser harm from ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for the outcome "SAEs"; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company insofar as the company described an added benefit as not proven for the indirect comparison on the basis of the data on the outcome "SAEs".

Discontinuation due to AEs

For the outcome "discontinuation due to AEs", there is only one study, which additionally has a high risk of bias of the results, on the intervention side of the indirect comparison. As a result, an effect estimation for the indirect comparison has no sufficient certainty of results (see Section 2.7.5.2 of the full dossier assessment).

Overall, there was no hint of greater or lesser harm from ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor for the outcome "discontinuation due to AEs"; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company insofar as the company described an added benefit as not proven for the indirect comparison on the basis of the data on the outcome "discontinuation due to AEs".

Specific adverse events

Rash

The adjusted indirect comparison showed a statistically significant difference in favour of ivacaftor + tezacaftor/ivacaftor versus lumacaftor/ivacaftor for the outcome "rash". This resulted in a hint of lesser harm from ivacaftor + tezacaftor/ivacaftor versus lumacaftor/ ivacaftor for this outcome.

The company did not consider the outcome "rash" in its assessment.

2.4.4 Subgroups and other effect modifiers

The methods used by the company for the investigations of potential effect modifiers were inadequate and resulted in a choice of results that cannot be interpreted in a meaningful way (see Section 2.7.5.3.4 of the full dossier assessment).

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.5.1 Assessment of the added benefit at outcome level

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

Determination of the outcome category for the outcome "rash"

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

The specific AE "rash" was allocated to the outcome category of non-serious/non-severe side effects, as it almost exclusively occurred as non-severe/non-serious AE.

The company did not consider this outcome in the derivation of the added benefit and therefore did not allocate it to an outcome category.

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

Outcome category **Outcome**	**Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]** **Event rate or mean change or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Pulmonary exacerbations	Rate: 0.69 vs. 0.89–0.93 rate ratio: 1.06 [0.73; 1.55]; p = 0.760	Lesser benefit/added benefit not proven
Hospitalization due to pulmonary exacerbations	Rate: 0.23 vs. 0.21–0.27 rate ratio: 2.02 [1.03; 3.95]; rate ratio: 0.49 [0.25; 0.97][d]; p = 0.040 probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit, extent: "minor"
Symptoms (CFQ-R, symptom domains)		
Respiratory symptoms	Mean change: 4.11 vs. 1.60–3.51 MD: 2.96 [0.03; 5.89]; p = 0.048 Hedges' g: 0.29 [0.06; 0.52][e]	Lesser benefit/added benefit not proven
Digestive symptoms	Mean change: −0.52 vs. −1.18–(−0.23) Hedges' g: 0.08 [−0.15; 0.30]; p = 0.514	Lesser benefit/added benefit not proven
Weight	Mean change: 2.34 vs. 0.21–3.62 Hedges' g: −0.06 [−0.30; 0.18]; p = 0.623	Lesser benefit/added benefit not proven
Health-related quality of life (CFQ-R)		
Physical functioning	Mean change: 2.01 vs. −0.97–0.54 Hedges' g: 0.17 [−0.06; 0.40]; p = 0.146	Lesser benefit/added benefit not proven
Emotional functioning	Mean change: −0.02 vs. 1.46–1.97 Hedges' g: −0.11 [−0.34; 0.12]; p = 0.343	Lesser benefit/added benefit not proven
Vitality	Mean change: −0.61 vs. −1.17–0.70 Hedges' g: 0.05 [−0.19; 0.29]; p = 0.694	Lesser benefit/added benefit not proven
Social functioning	Mean change: 0.82 vs. −1.74–(−1.40) Hedges' g: 0.12 [−0.10; 0.35]; p = 0.288	Lesser benefit/added benefit not proven

(continued)

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

Outcome category **Outcome**	**Ivacaftor + tezacaftor/ivacaftor[a] vs. lumacaftor/ivacaftor[a]** **Event rate or mean change or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Health-related quality of life (CFQ-R)		
Role functioning	Mean change: 1.73 vs. 0.69–0.72 Hedges' g: −0.04 [−0.28; 0.20]; p = 0.756	Lesser benefit/added benefit not proven
Body image	Mean change: 0.05 vs. 1.51–2.05 Hedges' g: −0.10 [−0.32; 0.13]; p = 0.406	Lesser benefit/added benefit not proven
Eating problems	Mean change: −0.63 vs. −1.67–0.36 Hedges' g: 0.01 [−0.22; 0.24]; p = 0.911	Lesser benefit/added benefit not proven
Treatment burden	Mean change: 2.88 vs. 2.56–3.43 Hedges' g: 0.28 [0.05; 0.51][e]; p = 0.018	Lesser benefit/added benefit not proven
Health perceptions	Mean change: 1.82 vs. 0.67–1.12 Hedges' g: 0.10 [−0.14; 0.34]; p = 0.404	Lesser benefit/added benefit not proven
Side effects		
SAEs	No usable data	Greater/lesser harm not proven
Discontinuation due to AEs	2.8% vs. 3.3–5.9% RR: 0.35 [0.09; 1.40] p = 0.134	Greater/lesser harm not proven
Rash (PT, AE)	1.6% vs. 3.8–9.6% RR: 0.09 [0.02; 0.35]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects lesser harm, extent: "considerable"

a: Treatment was against the background of concomitant symptomatic treatment.
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.

AE: adverse event; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; CI_u: upper limit of confidence interval; MD: mean difference; PT: Preferred Term; 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 ivacaftor + tezacaftor/ivacaftor in comparison with lumacaftor/ivacaftor

Positive effects	**Negative effects**
–	Serious/severe symptoms/late complications ▪ hospitalization due to pulmonary exacerbations: hint of lesser benefit – extent "minor"
Non-serious/non-severe side effects ▪ rash (PT, AE): hint of lesser harm – extent: "considerable"	–
No usable data on SAEs available	
AE: adverse event; SAE: serious adverse event; PT: Preferred Term; vs.: versus	

Overall, there is one positive effect of ivacaftor + tezacaftor/ivacaftor in the outcome category of non-serious/non-severe side effects with the extent "considerable", and one negative effect of tezacaftor/ivacaftor in the outcome category of serious/severe symptoms/late complications, each in comparison with the ACT lumacaftor/ivacaftor.

The lack of usability of the outcome "SAEs" (see Section 2.7.5.2 of the full dossier assessment) was taken into account when balancing the results. Overall, this resulted in a hint of lesser benefit of ivacaftor + tezacaftor/ivacaftor versus the ACT lumacaftor/ivacaftor for patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

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

Table 18: Ivacaftor + tezacaftor/ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor	Hint of lesser benefit
a: Presentation of the respective 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 assessment described above deviates from that of the company, which claimed an indication of a minor added benefit for patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

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

VX12-809-103

Elborn JS, Ramsey BW, Boyle MP, Konstan MW, Huang X, Marigowda G et al. Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. Lancet Respir Med 2016; 4(8): 617-626.

McColley SA, Konstan MW, Ramsey BW, Elborn JS, Boyle MP, Wainwright CE et al. Lumacaftor/Ivacaftor reduces pulmonary exacerbations in patients irrespective of initial changes in FEV1. J Cyst Fibros 2018; 18(1): 94-101.

Solem CT, Vera-Llonch M, Tai M, O'Callaghan L. Pulmonary exacerbations, lung dysfunction, and EQ-5D measures in adolescents and adults with cystic fibrosis and homozygous for the F508del-CFTR mutation. Value Health 2016; 19(3): A116-A117.

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Vertex Pharmaceuticals. A phase 3, randomized, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous for the F508del CFTR mutation: clinical study results [online]. In: EU Clinical Trials Register. 14.07.2016 [Accessed: 16.09.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-003989-40/results.

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Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med 2015; 373(3): 220-231.

VX12-809-104

Elborn JS, Ramsey BW, Boyle MP, Konstan MW, Huang X, Marigowda G et al. Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. Lancet Respir Med 2016; 4(8): 617-626.

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VX14-661-106

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Please see full dossier assessment for full reference list.

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