IQWiG Reports – Commission No. A20-54

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

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Tezacaftor/Ivacaftor (Kombination mit Ivacaftor; zystische Fibrose, ab 12 Jahre, F508del-Mutation, homozygot) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 September 2020). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
FEV1	forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model repeated measures
N	number of randomized patients
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 combination of tezacaftor/ivacaftor in combination with ivacaftor. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 29 June 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is to assess the added benefit of tezacaftor/ivacaftor in combination with 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.

For the present benefit assessment, the G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of tezacaftor/ivacaftor + 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. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company designated lumacaftor/ivacaftor as the ACT. This concurs with the G-BA's specification. The company also stated that the ACT of lumacaftor/ivacaftor, like tezacaftor/ivacaftor + ivacaftor, i.e. the drug being assessed here, was used in addition to individually optimized symptomatic therapy, and this was included in the presentation of added benefit.

This benefit assessment was conducted using lumacaftor/ivacaftor, the ACT specified by the G-BA. Providing additional symptomatic treatment for the patient population is reasonable.

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 added benefit.

Results

Study pool and study characteristics

No directly comparative RCTs were found to assess the added benefit of tezacaftor/ivacaftor + ivacaftor in comparison with the ACT lumacaftor/ivacaftor. In this benefit assessment, the added benefit was derived on the basis of an adjusted indirect comparison. For this purpose, 1 study for tezacaftor/ivacaftor and 2 studies for lumacaftor/ivacaftor were included. The 2 latter studies were included in the indirect comparison as a metaanalytical summary. The comparison was conducted using placebo as the common comparator. Treatment in all arms of the 3 studies was conducted against the background of concomitant symptomatic treatment.

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

The VX14-661-106 study was a randomized, double-blind, parallel-group study in which patients were either treated with tezacaftor/ivacaftor + ivacaftor or received matching placebo, each administered 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 CF diagnosis, defined as a sweat chloride value ≥ 60 mmol/L. In addition, 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 tezacaftor/ivacaftor + ivacaftor (N = 251) or 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 tezacaftor/ivacaftor in combination with ivacaftor was largely in compliance with the specifications of the Summary of Product Characteristics (SPC).

The 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 administered 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.

In the studies VX12-809-103 and VX12-809-104, CF 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 either study 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

In both studies, VX12-809-103 and VX12-809-104, patients 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 approved only at a dosage of 400 mg every 12 hours. The study arms of both studies in which lumacaftor were 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 specifications of the SPC.

The 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 drug (tezacaftor/ivacaftor + 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 drug. However, the

information provided shows that individual adjustments to the concomitant treatment were made in all 3 studies. A marked increase in concomitant medication was demonstrated after the first intake of the study drug in all arms of the 3 studies, 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 terms 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 in terms of their design and included patient populations.

The demographic and clinical characteristics of the patients were both balanced 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 severity of disease between the studies. Regarding concomitant medication, there were no noticeable differences between the studies, and the drugs were administered in largely similar proportions. The suitability of the studies VX14-661-106, VX12-809-103, and VX14-661-104 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 outcomes of all-cause mortality, pulmonary exacerbations, hospitalization due to pulmonary exacerbations, symptoms (recorded with the Cystic Fibrosis Questionnaire – Revised [CFQ-R]), health-related quality of life (measured using the CFQ-R) and the AE outcome of rash was rated as low for all 3 studies.

Events which can be both side effects and symptoms of the underlying disease were included in the recording of AEs. As a result, the risk of bias of the results for the outcomes of serious adverse events (SAEs) and discontinuation due to AEs from the studies included in the adjusted indirect comparison was rated as high.

Mortality

All-cause mortality

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

Morbidity

Pulmonary exacerbations

For pulmonary exacerbations, the adjusted indirect comparison based on the event rate showed no statistically significant difference between tezacaftor/ivacaftor + ivacaftor and lumacaftor/ivacaftor. This resulted in no hint of added benefit of tezacaftor/ivacaftor + ivacaftor in comparison with lumacaftor/ivacaftor.

Hospitalization due to pulmonary exacerbations

For hospitalization due to pulmonary exacerbations, the adjusted indirect comparison based on the event rate showed a statistically significant difference to the disadvantage of tezacaftor/ivacaftor + ivacaftor versus lumacaftor/ivacaftor. This resulted in a hint of lesser benefit of tezacaftor/ivacaftor + ivacaftor in comparison with lumacaftor/ivacaftor.

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.

"Respiratory symptoms" domain

In the "respiratory symptoms" domain, the adjusted indirect comparison showed a statistically significant difference in favour of tezacaftor/ivacaftor + 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 used to assess the relevance of the result. The 95% confidence interval (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 added benefit of tezacaftor/ivacaftor + ivacaftor in comparison with lumacaftor/ivacaftor for the CFQ-R domain of respiratory symptoms; an added benefit is therefore not proven.

"Digestive symptoms" and "weight" domains

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 tezacaftor/ivacaftor + 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 tezacaftor/ivacaftor + ivacaftor in comparison with lumacaftor/ivacaftor for either of the two 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 tezacaftor/ivacaftor + 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 tezacaftor/ivacaftor + ivacaftor in comparison with lumacaftor/ivacaftor for each of these domains; an added benefit is therefore not proven.

"Treatment burden" domain

The company presented solely SMDs with a 95% CI in the form of Hedges' g for the "treatment burden" domain. The adjusted indirect comparison showed a statistically significant difference in favour of tezacaftor/ivacaftor + ivacaftor versus lumacaftor/ivacaftor regarding the changes between the respective measurement time 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 tezacaftor/ivacaftor + ivacaftor in comparison with lumacaftor/ivacaftor; an added benefit is therefore not proven.

AEs

SAEs and discontinuation due to AEs

For the outcomes of SAEs and discontinuation due to AEs, there is only 1 study each, which additionally has a high risk of bias of 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. For each of the outcomes of SAEs (disregarding the PT of infectious pulmonary exacerbation of CF) and discontinuation due to AEs, this resulted in no hint of greater or lesser harm from tezacaftor/ivacaftor + ivacaftor in comparison with lumacaftor/ivacaftor; greater or lesser harm is therefore not proven.

Specific AEs

Rash

The adjusted indirect comparison showed a statistically significant difference in favour of tezacaftor/ivacaftor + ivacaftor versus lumacaftor/ivacaftor for the outcome of rash. This results in a hint of lesser harm of tezacaftor/ivacaftor + 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 added benefit of the drug tezacaftor/ivacaftor in comparison with the ACT are assessed as follows:

All things considered, there is 1 favourable effect of tezacaftor/ivacaftor + ivacaftor in the outcome category of non-serious/non-severe AEs with the extent "considerable" and 1 unfavourable effect of tezacaftor/ivacaftor + ivacaftor in the outcome category of serious/severe symptoms / late complications, each in comparison with the ACT of lumacaftor/ivacaftor.

Overall, this results in a hint of lesser benefit of tezacaftor/ivacaftor + ivacaftor versus the ACT of 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 the probability and extent of added benefit of tezacaftor/ivacaftor.

Table 3: Tezacaftor/ivacaftor + 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. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

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

Supplementary note

The result of the assessment deviates from the G-BA's assessment issued in the context of the market launch in 2018. In it, the G-BA had found considerable added benefit of tezacaftor/ivacaftor. However, in that assessment, the added benefit was viewed as being backed by the marketing authorization on the basis of the special status of orphan drugs, regardless of the underlying data.

[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 to assess the added benefit of tezacaftor/ivacaftor in combination with ivacaftor in comparison with the ACT of lumacaftor/ivacaftor in patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

For the present benefit assessment, the G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of tezacaftor/ivacaftor + 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. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company designated lumacaftor/ivacaftor as the ACT. This concurs with the G-BA's specification. The company also stated that the ACT of lumacaftor/ivacaftor, like tezacaftor/ivacaftor + ivacaftor, i.e. the drug being assessed here, was used in addition to individually optimized symptomatic therapy, and this was included in the presentation of added benefit.

This benefit assessment was conducted using lumacaftor/ivacaftor, the ACT specified by the G-BA. Providing additional symptomatic treatment for the patient population is sensible.

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

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- study lists on tezacaftor/ivacaftor (status: 1 April 2020)
- bibliographic literature search on tezacaftor/ivacaftor (most recent search on 1 April 2020)
- search in trial registries / study results databases on tezacaftor/ivacaftor (most recent search on 18 May 2020)
- search on the G-BA website for tezacaftor/ivacaftor (most recent search on 1 April 2020)
- bibliographic literature search on the ACT (most recent search on 1 April 2020)

- search in trial registries or results databases on the ACT (most recent search on 18 May 2020)
- search on the G-BA website for the ACT (most recent search on 1 April 2020)

To check the completeness of the study pool:

- search in trial registries on tezacaftor/ivacaftor (most recent search on 13 July 2020)
- search in trial registries on lumacaftor/ivacaftor (most recent search on 13 July 2020)

Concurring with the company, no relevant RCT on the direct comparison of tezacaftor/ivacaftor + ivacaftor versus the ACT was identified from the check.

The company identified 3 studies for an adjusted indirect comparison based on RCTs. These studies have already been presented for the early benefit assessment of ivacaftor in combination with tezacaftor/ivacaftor in the same therapeutic indication [3,4]. For the indirect comparison presented by the company (see Section 2.3.1), no additional relevant studies were identified from the check of completeness of the study pool.

VX15-809-112 study

In its study list, the company identifies the RCT VX15-809-112 [5-8], which investigates lumacaftor/ivacaftor (VX15-809-112) in CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. The company excluded this study from the benefit assessment. This approach is persuasive. The VX15-809-112 study is deemed insufficiently similar to the studies included in the indirect comparison, VX12-809-103 and VX12-809-104 (see Section 2.4.1) (for a more detailed justification, see dossier assessment A19-70 on the drug ivacaftor in combination with tezacaftor/ivacaftor [3]). The results of these studies are therefore disregarded hereinbelow.

Further investigations

The company did not conduct any information retrieval for further investigations. It presented study VX14-661-110 from the study list merely as supplementary evidence. The study included both patients with homozygous F508del mutation (studies VX13-661-103, VX14-661-106, and VX14-9661-111) and patients with heterozygous F508del mutation (studies VX14-661-107, VX14-661-108, and VX14-661-109) in the CFTR gene. Patients received tezacaftor/ivacaftor + ivacaftor + best supportive care or were able to participate in the study in an observation arm without the administration of a study drug. Since the company itself disregarded the study in its assessment of added benefit, the absence of information retrieval is of no consequence. Irrespective of the above, this study is unsuitable for the assessment of added benefit of tezacaftor/ivacaftor + ivacaftor versus lumacaftor/ivacaftor because the study's results are unsuitable for deriving any conclusions on added benefit of tezacaftor/ivacaftor + ivacaftor in comparison with the ACT of lumacaftor/ivacaftor.

2.3.1 Included studies

In the present benefit assessment, the added benefit was derived on the basis of an adjusted indirect comparison. For this purpose, 1 study for tezacaftor/ivacaftor and 2 studies for lumacaftor/ivacaftor were included. The 2 latter studies were included in the indirect comparison as a metaanalytical summary. The comparison was conducted using placebo as the common comparator. Treatment in all arms of the 3 studies was conducted against the background of concomitant symptomatic treatment.

The studies included in the benefit assessment are listed in Table 5 below. The study pool is consistent 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: tezacaftor/ivacaftor + ivacaftor vs. lumacaftor/ivacaftor

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication and other sources[c] (yes/no [reference])
Study with tezacaftor/ivacaftor + ivacaftor[d] vs. placebo[d]						
VX14-661-106	Yes	Yes	No	No[e]	Yes [9-12]	Yes [3,4,13-18]
Studies with lumacaftor/ivacaftor[d] vs. placebo[d]						
VX12-809-103	No	Yes	No	No[e]	Yes [19-22]	Yes [3,4,16-18,23-29]
VX12-809-104	No	Yes	No	No[e]	Yes [30-33]	Yes [3,4,16-18,23-29]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website.
d. Treatment was administed against the background of concomitant symptomatic treatment.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

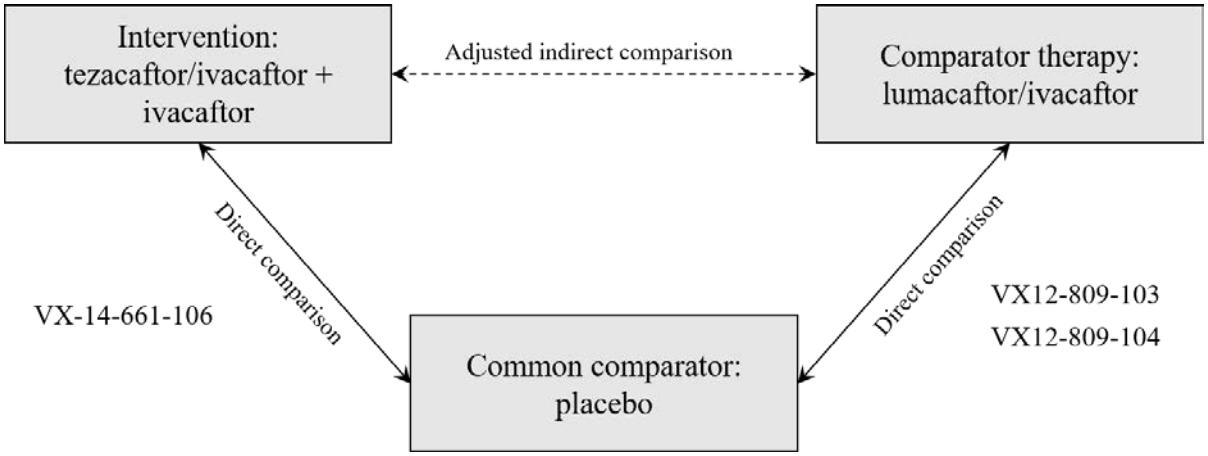

Figure 1: Study pool for the indirect comparison between tezacaftor/ivacaftor + ivacaftor and the ACT of lumacaftor/ivacaftor. Treatment in all arms of the 3 studies was administered against the background of concomitant symptomatic treatment

2.3.2 Study characteristics

Table 6 and Table 7 present the studies used in the benefit assessment.

Table 6: Characterization of the included studies – RCT, indirect comparison: tezacaftor/ivacaftor + ivacaftor vs. lumacaftor/ivacaftor (multi-page table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
Study with tezacaftor/ivacaftor + ivacaftor[b] vs. placebo[b]						
VX14-661-106	RCT, double-blind, parallel-group	CF patients aged ≥ 12 years with F508del mutation in both alleles of the CFTR gene (homozygous) and FEV1[c] ≥ 40% and ≤ 90% at screening	Tezacaftor/ivacaftor + 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-group	CF patients aged ≥ 12 years with F508del mutation in both alleles of the CFTR gene (homozygous) and 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, Ireland, Italy, Netherlands, Sweden, United Kingdom, 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-group	CF patients aged ≥ 12 years with F508del mutation in both alleles of the CFTR gene (homozygous) and 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, Spain, United Kingdom, USA 4/2013–4/2014	Primary: change in FEV1[c] Secondary: all-cause mortality, symptoms, health-related quality of life, AEs

Table 6: Characterization of the included studies – RCT, indirect comparison: tezacaftor/ivacaftor + ivacaftor vs. lumacaftor/ivacaftor (multi-page table)

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

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Treatment was administered against the background of concomitant symptomatic treatment.
c. In % of predicted normal.
d. During the visit at week 24, patients had the opportunity to be enrolled in the tezacaftor/ivacaftor + 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 tezacaftor/ivacaftor + ivacaftor arm of the extension study or who decided against enrolment were able to 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 VX14-661-110 extension study 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 presented in the tables below.
g. During the visit at week 24, patients who had completed the visits in the treatment phase had the option to be switched either to the treatment arm or 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 or 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

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

Study	Tezacaftor/ivacaftor + ivacaftor or lumacaftor/ivacaftor	Placebo
Tezacaftor/ivacaftor + ivacaftor or placebo		
VX14-661-106	Tezacaftor/ivacaftor 100 mg/150 mg orally, in tablet form, in the morning + ivacaftor 150 mg orally, in tablet form, 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 Disallowed: ▪ moderate and strong CYP3A inducers and inhibitors, including certain fruit and fruit juices, certain herbal remedies (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, in tablet form, 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 Disallowed: ▪ Moderate and strong CYP3A inducers and inhibitors, including certain fruit and fruit juices, certain herbal remedies (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, in tablet form, 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 data on study 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 allowed only if approved by the clinical monitor.
b. Treatment administered 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

Study design

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

The VX14-661-106 study was a randomized, double-blind, parallel-group study in which patients were treated with tezacaftor/ivacaftor + ivacaftor or received matching placebo, each against the background of concomitant symptomatic treatment (see section on prior and concomitant medication 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 ≥ 60 mmol/L. In addition, patients had to have an 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 tezacaftor/ivacaftor + ivacaftor (N = 251) or 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 tezacaftor/ivacaftor in combination with ivacaftor (see Table 7) was largely in compliance with the specifications of the SPC [34], according to which the dose should be adjusted when co-administered with strong or moderate CYP3A inhibitors. This was not mandated in the study. However, this is not believed to have 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 tezacaftor/ivacaftor + 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, were eligible for participating 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 VX12-809-103 and VX12-809-104 studies were randomized, double-blind, parallel-group studies in which patients were treated with lumacaftor/ivacaftor or received matching placebo, each administered against the background of concomitant symptomatic treatment (see section on prior and concomitant medication 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. In the VX12-809-103 and VX12-809-104 studies, CF 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 either study 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 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 approved only at a dosage of 400 mg every 12 hours [35]. 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 specifications of the SPC [35], according to which 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. However, this is not believed to have had a relevant influence on the study results.

The 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 opportunity 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: Characterization of the study populations – RCT, indirect comparison: tezacaftor/ivacaftor + ivacaftor vs. lumacaftor/ivacaftor (multi-page table)

Study Characteristics Category	VX14-661-106		VX12-809-103		VX12-809-104	
	TEZA/IVA + IVA[a]	Placebo[a]	LUMA/IVA[a]	Placebo[a]	LUMA/IVA[a]	Placebo[a]
	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

Table 8: Characterization of the study populations – RCT, indirect comparison: tezacaftor/ivacaftor + ivacaftor vs. lumacaftor/ivacaftor (multi-page table)

Study	**VX14-661-106**		**VX12-809-103**		**VX12-809-104**	
Characteristics	**TEZA/IVA + 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**
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 administered against the background of concomitant symptomatic treatment.
b. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
c. IQWiG calculations; 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: tezacaftor/ivacaftor + ivacaftor: n = 80 and placebo: n = 76; study VX12-809-103: lumacaftor/ivacaftor: n = 62 and placebo: n = 72; study VX12-809-104: lumacaftor + ivacaftor: n = 61 and placebo: n = 57)
f. Medication which started up to 28 days before the first study medication and continued during treatment with the study medication.
g. IQWiG calculations.

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

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

Most patients in all 3 studies were of Caucasian descent; the mean age was between 25 and 27 years. The proportions of men and women were balanced in all study arms. At 75%, most patients in the VX14-661-106 study were from Europe, whereas the proportion of patients from Europe was lower, at 26% to 41%, in the VX12-809-103 and VX12-809-104 studies.

The studies' inclusion criteria required patients to have an FEV1 (in % of predicted normal) of ≥ 40% and ≤ 90% at screening. Notwithstanding the above, all 3 studies also included patients with an FEV1 < 40% at baseline (VX14-661-106: n = 47 [9.3%]; VX12-809-103: n = 23 [6.3%]; VX12-809-104: n = 34 [9.1%]). The proportions within and between the 3 studies were each below 10%. However, the marketing authorizations of lumacaftor/ivacaftor and tezacaftor/ivacaftor + ivacaftor contain no restrictions with regard to FEV1..

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 severity of 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 the first administration of study treatment and concomitant medication (≥ 15% in at least 1 study arm) – RCT, indirect comparison: tezacaftor/ivacaftor + ivacaftor vs. lumacaftor/ivacaftor (multi-page table)

Medicinal treatment	VX14-661-106				VX12-809-103				VX12-809-104			
	TEZA/IVA + 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)
Cholecalciferol	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)

Table 9: Medication before the first administration of study treatment and concomitant medication (≥ 15% in at least 1 study arm) – RCT, indirect comparison: tezacaftor/ivacaftor + ivacaftor vs. lumacaftor/ivacaftor (multi-page table)

Medicinal treatment	VX14-661-106				VX12-809-103				VX12-809-104			
	TEZA/IVA + 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)

Table 9: Medication before the first administration of study treatment and concomitant medication (≥ 15% in at least 1 study arm) – RCT, indirect comparison: tezacaftor/ivacaftor + ivacaftor vs. lumacaftor/ivacaftor (multi-page table)

Medicinal treatment	VX14-661-106				VX12-809-103				VX12-809-104			
	TEZA/IVA + 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 (%)
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-medicinal treatment												
Physiotherapy	120 (47.8)[f]	122 (48.6)[f,g]	124 (48.1)[f]	129 (50.0)[f,g]	ND	ND	ND	ND	ND	ND	ND	ND

a. Treatment was administered 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 1 dose of the study medication (safety population) (tezacaftor/ivacaftor + ivacaftor N = 251; placebo N = 258).
g. IQWiG calculations.

FAS: full analysis set; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; LUMA: lumacaftor; N: number of randomized patients; RCT: randomized controlled trial; TEZA: tezacaftor

Administration of symptomatic treatment in addition to the study drug (tezacaftor/ivacaftor + ivacaftor or lumacaftor/ivacaftor) was allowed in the VX14-661-106, VX12-809-103, and VX12-809-104 studies. 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 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 any of the 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 marked increase in concomitant medication after the first intake of the study drug in all arms of the 3 studies was shown, for example, for antibiotics (including ciprofloxacin) and analgesics (ibuprofen and paracetamol). However, there is generally no information on whether the concomitant treatment was adjusted, e.g. by increasing the dose or frequency in the course of the study, and if so, for how many patients this was the case. In contrast to the VX14-661-106 study, no information is available for the VX12-809-103 and VX12-809-104 studies as to whether physiotherapy was allowed 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.

Similarity of the studies for the indirect comparison

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

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 + ivacaftor vs. lumacaftor/ivacaftor

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of results	No additional aspects	Risk of bias at study level
			Patients	Providers			
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							

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

Transferability of the study results to the German healthcare context

For all 3 studies, the company stated that almost all included patients were of Caucasian descent and that the studies were conducted exclusively in European and North American centres, with VX12-809-103 and VX12-809-104 also including Australian centres. Hence, the company assumed very good transferability of results to the German healthcare context.

For the VX12-809-103 and VX12-809-104 studies, the company additionally stated that the transferability of results to the German healthcare context is supported by the results of a Vertex-commissioned survey to characterize patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. This survey was reportedly based on retrospective data from 63 CF patients at 4 German centres. According to the company, the results of the survey show that the patients included in the two RCTs are well comparable with those of seen in routine care with regard to demographic characteristics, severity of disease, concomitant diseases, and medications. For this purpose, the company presented the following selected characteristics of the retrospective survey:

- Sex [percentage of male patients]: 52.4%
- Age [mean ± standard deviation in years]: 27.4 ± 11.2
- Body mass index (BMI) [mean ± standard deviation in kg/m²]: 20.3 ± 2.8
- FEV1 % [mean ± standard deviation in %]: 62.1 ± 28.0
- Use of antibiotics: 61.9%
- Inhalation of hypertonic saline solution 50.8%
- Colonization with *Pseudomonas aeruginosa*: 71.4%
- Pancreatic insufficiency: 92.1%

The company did not present any further information on the transferability of study results to the German healthcare context.

2.4 Results on added benefit

2.4.1 Outcomes included

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

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

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

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

Table 11: Matrix of outcomes – RCT, indirect comparison: tezacaftor/ivacaftor + 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 which 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). These outcomes are therefore not listed in the table and are not considered further hereinbelow.
b. Events related to the underlying disease were included in the recording of AEs.

AE: adverse event; CFQ-R: Cystic Fibrosis Questionnaire – Revised; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event

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

- Lung function using FEV1

The outcome of FEV1 (in % of predicted normal) is a lung function parameter. Relevant aspects for benefit assessment are patient-noticeable symptoms associated with a change in FEV1 or the associated reduction in health-related quality of life; the studies directly surveyed these outcomes.

Like in Module 4 A on the assessment of ivacaftor in combination with tezacaftor/ivacaftor, the company used FEV1 as a surrogate for CF-related mortality [16]. However, the sources cited by the company did not demonstrate the validity of FEV1 as a surrogate. In its current dossier on tezacaftor/ivacaftor + ivacaftor, the company does not discuss any new aspects. For a detailed rationale for the outcome of FEV1 not qualifying as a valid surrogate outcome for mortality, see dossier assessment A19-70 on the drug ivacaftor in combination with tezacaftor/ivacaftor, Section 2.7.5.3.2 [3]).

- BMI

Body weight or BMI is highly relevant in the present indication since developmental issues and nutrient malabsorption are typical signs of CF. In its assessment, the company uses BMI as a

measure for developmental status or as a parameter for the extent of a developmental disorder in patients.

In the present situation, the importance of the BMI as a measure of malnutrition is not directly evident, since the mean BMI of patients in the included VX14-661-106, VX12-809-103, and VX12-809-104 studies was in the normal range both at baseline and after 24 weeks of treatment.

2.4.2 Risk of bias

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

Table 12: Risk of bias at the study and outcome levels – RCT, indirect comparison: tezacaftor/ivacaftor + 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[a]	Discontinuation due to AEs[a]	Rash (PT, AE)
VX14-661-106	L	L	L	L	L	L	H	H	L
VX12-809-103	L	L	L	L	L	L	H	H	L
VX12-809-104	L	L	L	L	L	L	H	H	L

a. When recording AEs, events related to the underlying disease were included.

AE: adverse event; CFQ-R: Cystic Fibrosis Questionnaire – Revised; H: high; L: low; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event

The company's planned methodological approach for rating the risk of bias is largely appropriate. In Annex 4-F of Module 4 A, for each study, the company collectively assessed the risk of bias of the results for several outcomes. This is inappropriate because these outcomes may be associated with an increased risk of bias of results for different reasons.

Concurring with the company, the risk of bias for the results of the outcomes of all-cause mortality, pulmonary exacerbations, hospitalization due to pulmonary exacerbations, symptoms (measured with the CFQ-R), health-related quality of life (measured with the CFQ-R), and the AE outcome of rash is deemed low for all 3 studies.

For the outcome of SAEs, the risk of bias of results from each of the studies included in the adjusted indirect comparison is rated as high. This assessment departs from that made by the company, which assumed a low risk of bias for the results of this outcome. The analyses of SAEs do not include the preferred term (PT) of infectious pulmonary exacerbation of CF, and

consequently, the majority of events which can be allocated to the underlying disease were excluded from analysis. However, further events occurred which might potentially be allocated to the underlying disease, such as the PTs of haemoptoe/haemoptysis, pneumonia or distal intestinal obstruction syndrome / ileus (see Annex B of commission A20-05 [4] [addendum of dossier assessment A19-70]). The company did not comment on the influence of potential further events on effect estimators attributable to the symptoms of the underlying disease.

The results of the outcome of discontinuation due to AEs include events which are attributable to the symptoms of the underlying disease or which might be either an AE or a symptom of the underlying disease (see Table 25, Table 28, and Table 31 of the full report). This concurs with the company's approach in the dossier on ivacaftor + tezacaftor/ivacaftor in the same therapeutic indication. This approach is inadequate. Due to the low total number of events leading to discontinuation of the study drug, the events associated with the symptoms of the underlying disease may considerably alter the effect estimator. The risk of bias for the results of the outcome of discontinuation due to AEs was therefore rated as low. For the results of this outcome, the company assumed a low risk of bias.

2.4.3 Results

Table 13 to Table 15 summarize the results on the comparison of tezacaftor/ivacaftor + ivacaftor versus lumacaftor/ivacaftor in CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. Where necessary, the data from the company's dossier are supplemented by IQWiG calculations. They present results on patient-relevant outcomes, which were surveyed on both sides of the indirect comparison.

To assess clinical relevance, the company used standardized mean differences (Hedges' g) based on a mixed-effects model repeated measures (MMRM), with an irrelevance threshold of 0.2. No formula was specified; in particular, no explanation was provided as to what is used in place of the estimate of the standard deviation pooled across treatment groups, which was used in the original Hedges' g. The company's results were therefore checked by IQWiG calculations. For this purpose, Hedges' g was calculated using the mean difference estimated from the MMRM analysis and the associated confidence interval (CI), with the goal of maintaining consistency between Hedges' g and the initial analysis (MMRM) with regard to the conclusions on significance. While the resulting values were numerically different, they did lead to the same qualitative conclusion. The values calculated by the company are presented.

Tables on common AEs are shown in Appendix A of the full report. Overall, the company's presentation of common AEs, SAEs, and all events on discontinuation due to AEs for system organ classes (SOCs) and PTs in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) is incomplete. The company presented the common AEs and common SAEs without the PT of infectious pulmonary exacerbation of CF. For the events which led to discontinuation, SOCs and PTs were not presented at all. Due to the identical evidence base, this benefit assessment presents common AEs, common SAEs, and discontinuations due to AEs, including the PT of infectious pulmonary exacerbations of CF, in accordance with the

dossier assessment of ivacaftor in the present therapeutic indication in order to reflect the total burden [3].

Table 13: Results (mortality, AEs, dichotomous) – RCT, indirect comparison using common comparators: tezacaftor/ivacaftor + ivacaftor vs. lumacaftor/ivacaftor (multi-page table)

Outcome category Outcome	TEZA/IVA + IVA[a] or LUMA/IVA[a]		Placebo[a]		Group difference
Comparison Study	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality					
Tezacaftor/ivacaftor + 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)	–
AEs					
AEs[b] (presented as supplementary information)					
Tezacaftor/ivacaftor + ivacaftor[a] vs. placebo[a]					
VX14-661-106	251	222 (88.5)	258	242 (93.8)	–
Lumacaftor/ivacaftor[a] vs. placebo[a]					
VX12-809-103	182	171 (94.0)	184	167 (90.8)	–
VX12-809-104	187	173 (92.5)	186	175 (94.1)	–
SAEs[b, c]					
Tezacaftor/ivacaftor + ivacaftor[a] vs. placebo[a]					
VX14-661-106	251	14 (5.6)	258	26 (10.1)	0.55 [0.30; 1.04]; 0.064
Lumacaftor/ivacaftor[a] vs. placebo[a]					
VX12-809-103	182	19 (10.4)	184	15 (8.2)	1.28 [0.67; 2.44]; 0.453
VX12-809-104	187	10 (5.3)	186	17 (9.1)	0.59 [0.28; 1.24]; 0.164
Total[d]					0.92 [0.56; 1.50]; 0.738
Indirect comparison using common comparators[e]:					
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]					–[f]
Discontinuation due to AEs[c]					
Tezacaftor/ivacaftor + 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[d]					2.57 [0.99; 6.70]; 0.053
Indirect comparison using common comparators[e]:					
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]					–[f]

Table 13: Results (mortality, AEs, dichotomous) – RCT, indirect comparison using common comparators: tezacaftor/ivacaftor + ivacaftor vs. lumacaftor/ivacaftor (multi-page table)

Outcome category Outcome	TEZA/IVA + IVA[a] or LUMA/IVA[a]		Placebo[a]		Group difference
Comparison Study	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Rash (PT, AE)					
Tezacaftor/ivacaftor + ivacaftor[a] vs. placebo[a]					
VX14-661-106	251	4 (1.6)	258	13 (5.0)	0.32 [0.10; 0.96]; 0.032[g]
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[g]
VX12-809-104	187	18 (9.6)	186	5 (2.7)	3.58 [1.36; 9.44]; 0.005[g]
Total[h]					57 [1.57; 8.13]; 0.002
Indirect comparison using common comparators[e]:					
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]					0.09 [0.02; 0.35]; < 0.001

a. Treatment was administered against the background of concomitant symptomatic treatment.
b. Without recording of the PT "infectious pulmonary exacerbation of CT".
c. Events of the underlying disease were included in the recording of AEs; a high risk of bias was found in each case.
d. Fixed-effect model.
e. Indirect comparison according to Bucher [36].
f. No presentation of effect estimates as there is only 1 study with outcome-specific high risk of bias on the intervention side, and thus no hint of greater or lesser harm is derived.
g. IQWiG calculation, unconditional exact test (CSZ method according to [37]).
h. Metaanalysis, fixed-effect model, Mantel-Haenszel method.

AE: adverse event; CI: confidence interval; IVA: ivacaftor; LUMA: lumacaftor; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; ND: no data; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TEZA: tezacaftor

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

Outcome category **Outcome** **Comparison** **Study**	**TEZA/IVA + IVA[a] or LUMA/IVA[a]** **N**	**Number of events (n_E/patient years)[b]**	**Placebo[a]** **N**	**Number of events (n_E/patient years)[b]**	**Group difference** **Rate ratio [95% CI]; p-value[c]**
Morbidity					
Pulmonary exacerbations[d]					
Tezacaftor/ivacaftor + 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:					
Tezacaftor/ivacaftor + 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:					
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]					2.02 [1.03; 3.95]; 0.040[g]

a. Treatment was administered 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. IQWiG calculation.
f. IQWiG calculation; metaanalysis with fixed effect; inverse variance method.
e. IQWiG calculation; indirect comparison according to Bucher [36].

CI: confidence interval; IVA: ivacaftor; LUMA: lumacaftor; N: number of analysed patients; n_E: number of events; RCT: randomized controlled trial; TEZA: tezacaftor

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

Outcome category Outcome Domain Comparison Study	TEZA/IVA + 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 system							
Tezacaftor/ivacaftor + 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]:							
Tezacaftor/ivacaftor + 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 systems							
Tezacaftor/ivacaftor + 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]:							
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: 0.08 [−0.15, 0.30]; 0.514[i]

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

Outcome category Outcome Domain Comparison Study	TEZA/IVA + 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]
Weight							
Tezacaftor/ivacaftor + 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)	0.5 [−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]:							
Tezacaftor/ivacaftor + 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							
Tezacaftor/ivacaftor + 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]:							
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: 0.17 [−0.06, 0.40]; 0.146[i]

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

Outcome category Outcome Domain Comparison Study	TEZA/IVA + 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]
Emotional functioning							
Tezacaftor/ivacaftor + 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)	0.5 [−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]:							
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: −0.11 [−0.34, 0.12]; 0.343[i]
Vitality							
Tezacaftor/ivacaftor + 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]:							
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: 0.05 [−0.19, 0.29]; 0.694[i]

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

Outcome category Outcome Domain Comparison Study	TEZA/IVA + 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]
Social functioning							
Tezacaftor/ivacaftor + 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]:							
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]							0.12 [−0.10, 0.35]; 0.288[i]
Role functioning							
Tezacaftor/ivacaftor + 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]:							
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: −0.04 [−0.28, 0.20]; 0.756[i]

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

Outcome category Outcome Domain Comparison Study	TEZA/IVA + 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]
Body image							
Tezacaftor/ivacaftor + 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]:							
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: −0.10 [−0.32, 0.13]; 0.406[i]
Eating problems							
Tezacaftor/ivacaftor + 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]:							
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: 0.01 [−0.22, 0.24]; 0.911[i]

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

Outcome category **Outcome** **Domain** **Comparison** **Study**	**TEZA/IVA + 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]**
Therapy burden							
Tezacaftor/ivacaftor + 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]:							
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: 0.28 [0.05, 0.51]; 0.018[i]
Health perceptions							
Tezacaftor/ivacaftor + 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]:							
Tezacaftor/ivacaftor + ivacaftor[a] vs. lumacaftor/ivacaftor[a]							Hedges' g: 0.10 [−0.14, 0.34]; 0.404[i]

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

Outcome category Outcome	TEZA/IVA + IVA[a] or LUMA/IVA[a]			Placebo[a]			Group difference
Domain Comparison Study	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]

a. Treatment was administered 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, while 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 presented only if they were provided by the company.
e. Higher values indicate better health-related quality of life or symptoms; a positive difference between groups indicates an advantage for tezacaftor/ivacaftor.
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 baseline. Model: sex, age at screening, CFQ-R score at baseline, treatment, time point of study, treatment x time point of study, CFQ-R score at baseline x 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 baseline. 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 [36].
i. IQWiG calculation of p-value under the assumption of asymptotic normal distribution.
j. IQWiG calculation; indirect comparison according to Bucher [36].
k. Metaanalysis with fixed effect using the Hedges' g effect measure; no information on MD.
l. Indirect comparison according to Bucher [36] using the Hedges' g effect measure; no information on MD.

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

Only 1 study is available on the intervention side of the indirect comparison. Hence, the homogeneity for tezacaftor/ivacaftor + ivacaftor versus placebo was not checked. Since there is no directly comparative study for the comparison of tezacaftor/ivacaftor + ivacaftor versus lumacaftor/ivacaftor, it is impossible to check the consistency of the results. The adjusted indirect comparisons therefore have a maximum of 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. For the outcome of discontinuation due to AEs, there is a high risk of bias in all 3 studies of the indirect comparison (Section 2.4.2). Since there is only 1 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.

Mortality

All-cause mortality

No deaths occurred in the course of any of the 3 studies of the indirect comparison. There was no hint of an added benefit of tezacaftor/ivacaftor + 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

Operationalization

In the VX14-661-106, VX12-809-103, and VX12-809-104 studies, pulmonary exacerbations were defined as new, or changed, antibiotic therapy (intravenous, inhaled, or oral) for any 4 or more of the following signs or symptoms:

- change in sputum
- new or increased haemoptysis
- increased cough
- increased dyspnoea
- malaise, fatigue, or lethargy
- temperature > 38°C
- anorexia or weight loss
- sinus pain or tenderness
- change in sinus discharge
- change in physical examination of the chest
- decrease in pulmonary function by 10%
- radiographic changes indicative of pulmonary infection

This definition of pulmonary exacerbations is deemed adequate.

The company classifies pulmonary exacerbations in 3 operationalizations:

- pulmonary exacerbations
- hospitalization due to pulmonary exacerbations
- pulmonary exacerbations requiring intravenous antibiotic treatment

For the present dossier assessment, pulmonary exacerbations and hospitalization due to pulmonary exacerbations were each analysed using the event quantity and event rate (number

of events/patient years) in order to consider not only the occurrence, but also the frequency of pulmonary exacerbations over the entire course of the study. In this process, hospitalization due to pulmonary exacerbations represents the occurrence of serious exacerbations.

Results

Pulmonary exacerbations

For pulmonary exacerbations, the adjusted indirect comparison based on the event rate showed no statistically significant difference between tezacaftor/ivacaftor + ivacaftor and lumacaftor/ivacaftor. This resulted in no hint of added benefit of tezacaftor/ivacaftor + ivacaftor in comparison with lumacaftor/ivacaftor.

This deviates from the assessment of the company, which derived an indication of lesser benefit for the subgroup of patients < 18 years of age 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 hospitalization due to pulmonary exacerbations, the adjusted indirect comparison based on the event rate showed a statistically significant difference to the disadvantage of tezacaftor/ivacaftor + ivacaftor versus lumacaftor/ivacaftor. This resulted in a hint of lesser benefit of tezacaftor/ivacaftor + ivacaftor in comparison with lumacaftor/ivacaftor.

This deviates from the assessment of the company, which derived an indication of lesser benefit of tezacaftor/ivacaftor + ivacaftor versus lumacaftor/ivacaftor 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

Operationalization

To assess symptoms and health-related quality of life, the VX14-661-106, VX12-809-103, and VX12-809-104 studies used the instrument CFQ-R. This instrument comprises multiple versions: a patient version for various age groups (6 to 11 years, 12 to 13 years, and ≥ 14 years) and a parent/guardian version.

In adolescents and adults (≥ 14 years of age), the instrument consists of 3 domains on symptoms, while for children from 12 to 13 years of age, the domain of weight is excluded from the questionnaire. In addition, the CFQ-R for adolescents and adults contains 9 domains on health-related quality of life. For children from 12 to 13 years of age, the domains of vitality, role functioning, and health perceptions are not included. Concurring with the company's approach, IQWiG used the results of the patient versions of the CFQ-R while disregarding the parent/guardian version for children 12 to 13 years of age.

In the present dossier assessment, the MMRM analyses are examined for all domains of the CFQ-R.

Results

“Respiratory symptoms” domain

In the “respiratory symptoms” domain, the adjusted indirect comparison showed a statistically significant difference in favour of tezacaftor/ivacaftor + 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 added benefit of tezacaftor/ivacaftor + ivacaftor in comparison with lumacaftor/ivacaftor for the CFQ-R domain of respiratory symptoms; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of added benefit for this outcome on the basis of the responder analyses and the mean differences.

“Gastrointestinal symptoms” and “weight” domains

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 tezacaftor/ivacaftor + 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 tezacaftor/ivacaftor + 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.

Results

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 tezacaftor/ivacaftor + 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 tezacaftor/ivacaftor + 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.

"Treatment burden" domain

The company presented solely SMDs with a 95% CI in the form of Hedges' g for the "treatment burden" domain. The adjusted indirect comparison showed a statistically significant difference in favour of tezacaftor/ivacaftor + ivacaftor versus lumacaftor/ivacaftor regarding the changes between the respective measurement time 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 tezacaftor/ ivacaftor + ivacaftor in comparison with lumacaftor/ivacaftor; 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".

AEs

SAEs and discontinuation due to AEs

For the outcomes of SAEs and discontinuation due to AEs, only 1 study each exists on the intervention side of the indirect comparison; these two studies also come with a high risk of bias of results. As a result, an effect estimation for the indirect comparison has no sufficient certainty of results. For each of the outcomes of SAEs (disregarding the PT of infectious pulmonary exacerbation of CF) and discontinuation due to AEs, this resulted in no hint of greater or lesser harm from tezacaftor/ivacaftor + ivacaftor in comparison with lumacaftor/ ivacaftor; greater or lesser harm is therefore not proven.

This concurs with the assessment by 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 outcomes of SAEs and discontinuation due to AEs.

Specific AEs

Rash

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

This deviates from the assessment by the company insofar as the company derived an indication of added benefit for this outcome.

2.4.4 Subgroups and other effect modifiers

As already noted in dossier assessment A19-70 on the drug of ivacaftor in combination with tezacaftor/ivacaftor [3], the methods used by the company for the investigation of potential effect modifiers were inadequate.

A procedure by which potential subgroup effects are analysed differently does not lend itself to a consistent interpretation of results. The company calculated interaction tests separately for the VX12-809-106 study and for the metaanalysis of the VX12-809-103 and VX12-809-104 studies. The company presented indirect comparisons for subgroups only where at least 1 of the 2 interaction tests showed interaction at a significance level $\alpha = 0.05$. This approach is inadequate because the interactions identified in the 106 study or in the metaanalysis of the VX12-809-103 and VX12-809-104 studies each relate to treatment comparisons (i.e. versus placebo), which are not part of the benefit assessment. Any relevant interactions which would be revealed by the indirect comparison of tezacaftor/ivacaftor + ivacaftor versus lumacaftor/ ivacaftor might therefore be overlooked.

In situations where there was an interaction in a treatment comparison versus placebo, the company did also report the result of the interaction test for the treatment comparison of interest and thereby supplied additional information not available in dossier assessment A19-70. However, these test results are not fully available due to the preselection.

For this reason, the subgroup analyses were excluded from the benefit assessment.

2.5 Probability and extent of added benefit

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

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

Determination of the outcome category for the outcome of rash

Not for all outcomes considered in the present benefit assessment does the dossier permit inferences as to whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

The specific AE of rash was allocated to the outcome category of non-serious/non-severe AEs as it occurred almost exclusively as a non-serious/non-severe AE.

This concurs with the company's assessment.

Table 16: Extent of added benefit at outcome level: tezacaftor/ivacaftor + ivacaftor vs. lumacaftor/ivacaftor (multi-page table)

Outcome category **Outcome**	**Tezacaftor/ivacaftor + 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		
All-cause mortality	0% vs. 0% RR: –	Lesser/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/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 system	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/added benefit not proven
Digestive systems	Mean change: −0.52 vs. −1.18–(−0.23) Hedges' g: 0.08 [−0.15; 0.30]; p = 0.514	Lesser/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/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/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/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/added benefit not proven
Social functioning	Mean change: 0.82 vs. −1.74–(−1.40) Hedges' g: 0.12 [−.10; 0.35]; p = 0.288	Lesser/added benefit not proven

Table 16: Extent of added benefit at outcome level: tezacaftor/ivacaftor + ivacaftor vs. lumacaftor/ivacaftor (multi-page table)

Outcome category **Outcome**	**Tezacaftor/ivacaftor + 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/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/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/added benefit not proven
Therapy burden	Mean change: 2.88 vs. 2.56–3.43 Hedges' g: 0.28 [0.05; 0.51][e]; p = 0.018	Lesser/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/added benefit not proven
AEs		
SAEs	5.6% vs. 5.3–10.4% _[f]	Greater/lesser harm not proven
Discontinuation due to AEs	2.8% vs. 3.3–5.9% _[f]	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 adverse events Lesser harm; extent: considerable

a. Treatment was administered against the background of concomitant symptomatic treatment.
b. Probability is stated 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. IQWiG calculation, reversed direction of effect to enable use of limits to derive the extent of 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.
f. No presentation of effect estimates as there is only 1 study with outcome-specific high risk of bias on the intervention side, and thus no hint of greater or lesser harm is derived.

AE: adverse event; CFQ-R: Cystic Fibrosis Questionnaire – Revised; CI: confidence interval; CI_u: upper limit of CI; MD: mean difference; PT: preferred term; RR: relative risk; SAE: serious adverse event

2.5.2 Overall conclusion on added benefit

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

Table 17: Favourable and unfavourable effects from the assessment of tezacaftor/ivacaftor + ivacaftor in comparison with lumacaftor/ivacaftor

Favourable effects	**Unfavourable effects**
–	Serious/severe symptoms / late complications ▪ hospitalization due to pulmonary exacerbations: hint of lesser benefit – extent: minor
Non-serious/non-severe AEs ▪ Rash (PT, AE): Hint of lesser harm – extent: considerable	–
AE: adverse event; PT: preferred term	

All things considered, there is 1 favourable effect of tezacaftor/ivacaftor + ivacaftor in the outcome category of non-serious/non-severe AEs, with an extent of considerable, and 1 unfavourable effect of tezacaftor/ivacaftor + ivacaftor in the outcome category of serious/severe symptoms / late complications, each in comparison with the ACT of lumacaftor/ivacaftor.

Overall, this results in a hint of lesser benefit of tezacaftor/ivacaftor + ivacaftor versus the ACT of lumacaftor/ivacaftor for patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

Table 18: Tezacaftor/ivacaftor + 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. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The assessment described above deviates from that made by 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 added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the G-BA's assessment issued in the context of the market launch in 2018. In it, the G-BA had found considerable added benefit of tezacaftor/ivacaftor. However, in that assessment, the added benefit was viewed as being backed by the marketing authorization on the basis of the special status of orphan drugs, regardless of the underlying data.

References for English extract

Please see full dossier assessment for full reference list.

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

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