Ivacaftor/tezacaftor/elexacaftor (combination with ivacaftor; cystic fibrosis, ≥ 2 years, at least one non-Class I mutation, excluding F508del and gating mutations)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Ivacaftor/Tezacaftor/Elexacaftor (Kombination mit Ivacaftor; zystische Fibrose, ≥ 2 Jahren, mindestens 1 Nicht-Klasse-I-Mutation, exklusive F508del- und Gating-Mutation) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone:+49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

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Medical and scientific advice

No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

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

IQWiG thanks the respondent and the patient organization ‘Mukoviszidose e. V.’ for participating in the written exchange and for their support. The respondent and ‘Mukoviszidose e. V.’ were not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Anja Reinartz
- Merlin Bittlinger
- Charlotte Guddat
- Lisa Junge
- Stefan Kobza
- Ulrike Lampert
- Mattea Patt
- Daniela Preukschat
- Min Ripoll
- Yvonne Zens

Part I: Benefit assessment

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

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
BSC	best supportive care
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
FEV1	forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model with repeated measures
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SmPC	summary of product characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ivacaftor/tezacaftor/elexacaftor (in combination with ivacaftor). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 2 May 2025.

Research question

The aim of this report is to assess the added benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (hereinafter referred to as ivacaftor/tezacaftor/elexacaftor + ivacaftor) in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, excluding an F508del and gating mutation, in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

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

Therapeutic indication	**ACT**[a]
Patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, excluding an F508del and gating mutation, in the CFTR gene	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (in particular antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [as outlined in the German Remedies Directive] – while making full use of all possible dietary interventions).

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

The company followed the ACT specified.

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

Results

Transfer of the results of the study VX21-445-124 to the entire therapeutic indication not possible

The company identified the RCT VX21-445-124 as a relevant study in the given therapeutic indication. The study included patients aged 6 years and older with cystic fibrosis who had at least one ivacaftor/tezacaftor/elexacaftor-responsive mutation on the CFTR gene. For inclusion in the study, patients also had to have at least 1 of 18 qualifying mutations, with neither allele having an F508del or gating mutation. The therapeutic indication in question covers notably more mutations than the mutations qualifying for participation in the VX21-445-124 study. The company did not conduct an information retrieval for non-comparative studies with the intervention or the ACT in patients aged 6 years and older that might be available for the other mutations covered by the therapeutic indication.

Due to the lack of studies of direct comparison for patients aged 2 to 5 years, the company conducted an additional information retrieval for further investigations with the intervention in patients aged 2 to 5 years, but did not identify any relevant studies. The company did not conduct an information retrieval for the ACT.

The company transferred the results of the RCT VX21-445-124 across ages and mutations to the patients in the therapeutic indication who were not covered by the study. The company's approach is described and evaluated below.

Transfer to other age groups

The company assumed transferability of the results from patients with cystic fibrosis aged 6 years and older with at least one non-Class I mutation, excluding an F508del and gating mutation, to children aged 2 to 5 years. The company did not present any study results on ivacaftor/tezacaftor/elexacaftor + ivacaftor in patients aged 2 to 5 years. The company justified the transferability on the basis of what it considered to be sufficient comparability of the mechanism of action, the clinical picture of the disease, and consistent pharmacokinetic exposure between patients in different age groups. The company added that the European Medicines Agency (EMA) assumed comparable efficacy and safety of ivacaftor/tezacaftor/elexacaftor + ivacaftor in different age groups.

In the given data situation, it was not possible to transfer the results of patients aged 6 years and older to the age group 2 to 5 years. As the company also described in its reasoning, cystic fibrosis is a progressive disease. This means that younger patients can generally be expected to have less pronounced symptoms. A comparison of the patient characteristics (< 18 years versus ≥ 18 years) in VX21-445-124 showed a less pronounced restriction of lung function in patients < 18 years with regard to the lung parameter forced expiratory volume in 1 second (FEV1) and the respiratory system domain of the instrument Cystic Fibrosis Questionnaire-

Revised (CFQ-R). In addition, there were effect modifications by the characteristic age that were relevant to the conclusion; in patients aged between 6 and 17 years there were no statistically significant effects with notably smaller point estimates, while large effects were observed in older patients. Since no data were available for the age group 2 to 5 years in the given therapeutic indication that could be used to support the assessment, the effects of the study VX21-445-124 were not transferable to the younger age group.

Transfer to other mutations

In the 'further investigations' section, the company listed the single-arm studies VX21-445-125, VX22-CFD-016, VX20-CFD-007, HEOR-23-445-014, Burgel 2024 and Cromwell 2024 as additional evidence for ivacaftor/tezacaftor/elexacaftor + ivacaftor. The company used these studies in particular for its argumentation that the results of the RCT VX21-445-124 were transferable to patients with mutations other than those investigated in the study. However, the company did not conduct an information retrieval for further studies for patients aged 6 years and older with mutations other than those investigated in VX21-445-124. According to the company, it used the study VX21-445-125 as supplementary information, it being the extension study of the RCT VX21-445-124. The company presented as supplementary information the studies Burgel 2024 and Cromwell 2024 identified in another therapeutic indication and the studies VX22-CFD-016, VX20-CFD-007 and HEOR-23-445-014 sponsored by the company, as it considered these to provide valuable results on patient-relevant outcomes in everyday treatment and thus contribute to an informative assessment. The company also used these observational studies as supporting information because, according to the company, these studies considered patients with a total of 94 additional non-Class I mutations that were not investigated in the RCT VX21-445-124. The company also pointed out that the majority of patients whose mutations responded to ivacaftor/tezacaftor/elexacaftor in in vitro trials also achieved an improvement in vivo.

The data from the studies VX21-445-125, VX22-CFD-016, VX20-CFD-007, HEOR-23-445-014, Burgel 2024 and Cromwell 2024, presented as supplementary information in the company's dossier, were not considered further in this assessment, as the completeness of the study pool for further investigations was not ensured due to the lack of information retrieval for patients aged 6 years and older. In addition, the studies VX22-CFD-016, HEOR-23-445-014, Burgel 2024 and Cromwell 2024 also investigated patients with gating mutations that are not covered by the therapeutic indication at hand. Separate analyses for the patients of the given research question were not available.

For inclusion in the VX21-445-124 study, patients had to have at least one of the following mutations: 2789+5G>A, 3272-26A>G, 3849+10kbC>T, P5L, R117C, L206W, V232D, T338I, R347H, A455E, S945L, L997F, R1066H, D1152H, G85E, R347P, L1077P, M1101K. In principle, it was possible for the 2nd allele to contain an additional mutation covered by the given

therapeutic indication but not mandatory for inclusion in the study. It can be assumed that some of the patients included in the study had some other mutations on the 2nd allele covered by the therapeutic indication. Overall, due to the large number of mutations associated with the research question at hand and their rarity, it was deemed unlikely that all mutations relevant to the research question can be investigated in a single study. However, uncertainty remained as to whether the results were transferable to patients who do not have any of the mutations, excluding an F508del mutation and a gating mutation, investigated in the VX21-445-124 study relevant to this benefit assessment. The uncertainties described were considered in the assessment of the certainty of conclusions of the results.

Study pool and study design

The study pool for this benefit assessment consisted of the randomized double-blind study VX21-445-124 comparing ivacaftor/tezacaftor/elexacaftor + ivacaftor with placebo, each in addition to basic therapy for cystic fibrosis. The study included patients aged 6 years and older with cystic fibrosis who had at least one ivacaftor/tezacaftor/elexacaftor-responsive mutation on the CFTR gene. Patients with at least 1 of the 18 mutations listed above were eligible. No F508del mutation or gating mutation was allowed to be present on either allele. The patients additionally had to have an FEV1 of ≥ 40% to ≤ 100% of predicted normal for age, sex, and height at screening. In the assessment of the investigator, the disease had to be stable.

In the VX21-445-124 study, a total of 307 patients were randomly assigned in a 2:1 ratio to receive treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor (N = 205) or placebo (N = 102). Stratification factors were FEV1 at the time of screening (< 70% versus ≥ 70% of predicted normal), age (< 18 years versus ≥ 18 years) and CFTR mutation group (no residual function-like mutation versus ≥ 1 residual function-like mutation). Treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor was carried out according to the summary of product characteristics (SmPC). Patients in the comparator arm received placebo to maintain blinding. Patients in both study arms additionally received concomitant basic therapy.

The primary outcome of the study was the absolute change in FEV1 (in% of predicted normal) after 24 weeks. Patient-relevant secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

Implementation of the ACT

The G-BA specified BSC as the ACT for ivacaftor/tezacaftor/elexacaftor + ivacaftor for the treatment of patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation in the CFTR gene, excluding an F508del and gating mutation.

According to the study protocol, patients had to be on stable medication for the treatment of cystic fibrosis, particularly for sinopulmonary disease, for at least 28 days before the start of the study. Furthermore, concomitant treatment associated with cystic fibrosis – primarily

inhaled antibiotics – was to be maintained until the end of the study if possible. There were no further restrictions regarding concomitant medication for the treatment of cystic fibrosis.

The information on prior and concomitant treatment showed that patients received antibiotics, inhaled medications (including saline), digestive enzymes, vitamins and physiotherapy for the symptomatic treatment of cystic fibrosis at baseline. The company also provided detailed information on the number of concomitant therapies in the course of the study for the different concomitant medications. This information showed that with regard to antibiotic treatment, adjustments were made during the course of the study. For example, 46% of patients in the intervention arm and 65% in the comparator arm who did not receive antibiotic therapy at baseline received at least one antibiotic during the course of the study. With regard to the use of other therapies, the information showed that a small number of patients started a new treatment during the study. It should be taken into account that a large proportion of the patients included were already receiving treatment with inhaled medication (91% vs. 88%), including mucolytics and bronchodilators, at baseline. Around a third of patients received physiotherapy (33% versus 36%). The available data did not indicate whether and for how many patients concomitant treatment was adjusted, for example in terms of an increase in dosage or in the frequency of drug treatment or non-drug treatment. It was also unclear whether and how many patients discontinued concomitant treatment during the course of the study.

Overall, the concomitant treatments used in the VX21-445-124 study were considered to be a sufficient approximation to the implementation of the ACT BSC.

Risk of bias and certainty of conclusions

The risk of bias across outcomes and the risk of bias of the results of all patient-relevant outcomes were assessed as low for the study VX21-445-124. For the outcome severe adverse events (AEs), however, the certainty of conclusions was reduced due to uncertainties in the operationalization.

Overall, uncertainties remained as to whether the results of the VX21-445-124 study were transferable to patients who do not have any non-Class I mutations, excluding a F508del mutation and gating mutation, as investigated in the study. The certainty of conclusions of the study results for the given research question was therefore reduced. Based on the information from the VX21-445-124 study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented.

Results

Mortality

All-cause mortality

In the VX21-445-124 study, there was only one death in the intervention arm. There is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for the outcome all-cause mortality; an added benefit is therefore not proven.

Morbidity

Pulmonary exacerbations

For the outcome pulmonary exacerbations, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC based on event rates (number of events per patient per year). There is a hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for the outcome pulmonary exacerbations.

Severe pulmonary exacerbations

Based on the analysis of patients with at least one event, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC for the outcome severe exacerbations. Analyses based on event rates (number of events per patient per year) were not available for study VX21-445-124. There is a hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for the outcome severe pulmonary exacerbations.

Symptoms (CFQ-R)

Respiratory symptoms

For the respiratory symptoms domain of the CFQ-R, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. The standardized mean difference (SMD) was analysed to assess the relevance of the result. The 95% confidence interval (95% CI) was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. For the respiratory symptoms domain of the CFQ-R, there is a hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC.

Digestive symptoms and weight

For the CFQ-R domains digestive symptoms and weight, no statistically significant differences were shown between the treatment groups. In each case, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC; an added benefit is therefore not proven for either of the 2 domains.

Health-related quality of life (CFQ-R)

Physical wellbeing, health perceptions

For the CFQ-R domains physical wellbeing and health perceptions (the latter domain was only recorded in patients aged 14 years and older), there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. However, there were effect modifications due to the characteristics age and FEV1 for both domains. Within the subgroups, the significance and then, if applicable, the relevance of the result was assessed using the 95% CI associated with the SMD. For patients ≥ 18 years of age or with an FEV1 < 70%, there is a hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for each of these CFQ-R domains. For patients < 18 years of age or with an FEV1 ≥ 70%, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for either of these CFQ-R domains; an added benefit is therefore not proven.

The data presented in the dossier showed that the patients aged 18 years or older included in the VX21-445-124 study tended to have a lower FEV1 at baseline. It was therefore assumed that the subgroup of patients under 18 years of age was more likely to include patients with an FEV1 ≥ 70% and that the subgroup of patients aged 18 years or older was more likely to include patients with an FEV1 < 70%. Due to the progressive course of cystic fibrosis, only age is considered below.

Vitality, role functioning

For the CFQ-R domains vitality and role functioning (which were only recorded in patients aged 14 years and older), there was a statistically significant difference in favour of ivacaftor/ tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. The SMD was considered to assess the relevance of the result. In each case, the 95% CI was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. For each of these CFQ-R domains, there is a hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC.

Social functioning

For the social functioning domain of the CFQ-R, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. However, there is an effect modification by the characteristic of sex. Within the subgroups, the significance and then, if applicable, the relevance of the result was assessed using the 95% CI associated with the SMD. For this domain, there is a hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for female patients. For this domain, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for male patients; an added benefit is therefore not proven.

Emotional functioning, body image, eating problems, treatment burden

For each of the CFQ-R domains of emotional functioning, body image, eating problems and treatment burden, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. The SMD was considered to assess the relevance of the result. The 95% CI was not fully outside the irrelevance range [−0.2; 0.2] in any of the domains. The effect can therefore not be inferred to be relevant. For each of these domains, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC; an added benefit is therefore not proven for any of them.

Side effects

Serious AEs (SAEs), severe AEs, and discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs. There is no hint of greater or lesser harm of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for these outcomes; an added benefit is therefore not proven.

Specific AEs

Rash (AEs)

For the outcome rash (AEs), there was a statistically significant difference to the disadvantage of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. There is a hint of greater harm of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for this outcome.

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

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

The given research question covers patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, excluding an F508del and gating mutation, in the CFTR

[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].

gene. Results from the VX21-445-124 study were available for patients aged 6 years and older. The company did not present any data for patients aged 2 to 5 years.

The characteristic age was an effect modifier for 2 domains of the CFQ-R. Due to the progressive course of cystic fibrosis, it can generally be assumed that younger patients (< 18 years) are at a less advanced disease stage. Therefore, the results on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT are derived separately by age below. For the CFQ-R domain of social functioning, the characteristic sex was an effect modifier. Since male and female patients are equally affected by the disease and this effect modification was only evident in one domain of the CFQ-R, this characteristic was not considered further in the overall assessment.

Patients aged 18 years and older

For patients aged 18 years and older, the overall assessment of the results showed several positive effects of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC. For severe pulmonary exacerbations, there is a hint of a major added benefit. In addition, there is a hint of considerable added benefit for the outcome pulmonary exacerbations. It should be noted that this outcome included events that were already included in the outcome of severe pulmonary exacerbations, so these were not completely independent outcomes. There are hints of a major, considerable or minor added benefit in several CFQ-R domains on symptoms and health-related quality of life. This contrasts with a negative effect in the non-serious/non-severe side effects category based on a specific AE with considerable extent. This does not call into question the positive effects, in particular the major added benefit in severe pulmonary exacerbations and in several domains of health-related quality of life.

In summary, there is a hint of a major added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT BSC for patients with cystic fibrosis aged 18 years and older who have at least one non-Class I mutation, excluding an F508del and gating mutation, in the CFTR gene.

Patients aged 6 to 17 years

For patients aged 6 to 17 years, in terms of positive effects, there is a hint of a major added benefit for severe pulmonary exacerbations and a hint of a considerable added benefit for pulmonary exacerbations in the morbidity category. As described above, this outcome included events that were already included in the outcome of severe pulmonary exacerbations, so these were not completely independent outcomes. There are hints of a major, considerable or minor added benefit in several CFQ-R domains on symptoms and health-related quality of life. The domains of vitality and role functioning for health-related quality of life only applied to patients aged 14 to 17. It was unclear whether these effects were also transferable to younger patients, as the respective domains of the CFQ-R are not provided

for younger age groups. The positive effects contrast with a negative effect in the non-serious/non-severe side effects category based on a specific AE with considerable extent.

The positive effects outweigh the negative effects. Besides the improvements in the outcomes on morbidity, there were positive effects in health-related quality of life. However, the CFQ-R domains of vitality and role functioning only allowed conclusions to be drawn for adolescents and thus only for a subpopulation of the age group < 18 years considered here. When balancing the results, it must be taken into account that younger patients generally have less pronounced symptoms due to the progressive course of cystic fibrosis. This was confirmed by the study results. It therefore remained unclear whether patients aged 6 to 17 years benefit from the treatment in the short term (i.e. within the usual study duration in the therapeutic indication) to the same extent as patients aged 18 years and older. Data on the long-term course were also not available. Therefore, the overall extent was rated as non-quantifiable.

In summary, there is a hint of a non-quantifiable added benefit of ivacaftor/tezacaftor/ elexacaftor + ivacaftor versus the ACT BSC for patients with cystic fibrosis aged 6 to 17 years who have at least one non-Class I mutation, excluding an F508del and gating mutation, in the CFTR gene.

Patients aged 2 to 5 years

In its dossier, the company did not present any data for the assessment of the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with the ACT BSC for patients aged 2 to 5 years. There is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT for these patients; an added benefit is therefore not proven.

Table 3 presents a summary of the probability and extent of the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor.

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

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, excluding an F508del and gating mutation, in the CFTR gene	BSC[b]	▪ Patients aged 2 to 5 years: added benefit not proven ▪ Patients aged 6 to 17 years: hint of a non-quantifiable added benefit[c] ▪ Patients 18 years of age and older: hint of major added benefit[c]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (in particular antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [as outlined in the German Remedies Directive] – while making full use of all possible dietary interventions).
c. Only patients aged 6 years and older with the following mutations were included in the VX21-445-124 study: 2789+5G>A, 3272-26A>G, 3849+10kbC>T, P5L, R117C, L206W, V232D, T338I, R347H, A445E, S945L, L997F, D1152H, G85E, R347P, L1077P, M1101K. It remains unclear whether the observed effects can be transferred to patients with other mutations.

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

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

I 2 Research question

The aim of this report is to assess the added benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (hereinafter referred to as ivacaftor/tezacaftor/elexacaftor + ivacaftor) in comparison with BSC as the ACT in patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, excluding an F508del and gating mutation, in the CFTR gene.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

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

Therapeutic indication	**ACT[a]**
Patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, excluding an F508del and gating mutation, in the CFTR gene	BSC[b]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (in particular antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [as outlined in the German Remedies Directive] – while making full use of all possible dietary interventions).

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

The company followed the ACT specified.

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

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study lists on ivacaftor/tezacaftor/elexacaftor + ivacaftor (status: 6 March 2025)
- Bibliographic literature search for ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 28 February 2025)
- Search of trial registries/trial results databases for studies on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 28 February 2025)
- Search on the G-BA website for ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 11 March 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 19 May 2025); see I Appendix A of the full dossier assessment for the search strategies

The review did not identify any additional relevant studies of direct comparison of ivacaftor/ tezacaftor/elexacaftor + ivacaftor versus the ACT BSC in the given therapeutic indication.

The RCT VX21-445-124 relevant for this benefit assessment included patients aged 6 years and older with cystic fibrosis who had at least one ivacaftor/tezacaftor/elexacaftor-responsive mutation on the CFTR gene. For inclusion in the study, patients also had to have at least 1 of 18 qualifying mutations, with neither allele having an F508del or gating mutation. The therapeutic indication in question covers notably more mutations than the mutations qualifying for participation in the VX21-445-124 study. The company did not conduct an information retrieval for non-comparative studies with the intervention or the ACT in patients aged 6 years and older that might be available for the other mutations covered by the therapeutic indication.

Due to the lack of studies of direct comparison for patients aged 2 to 5 years, the company conducted an additional information retrieval for non-comparative studies with the intervention in patients aged 2 to 5 years, but did not identify any relevant studies. The company did not conduct an information retrieval for the ACT.

Approach of the company for the derivation of an added benefit for the entire therapeutic indication

As described above, the RCT VX21-445-124 used for this benefit assessment included patients aged 6 years and older with cystic fibrosis who had at least one ivacaftor/tezacaftor/elexacaftor-responsive mutation on the CFTR gene. For inclusion in the study, patients had to have at least 1 of 18 qualifying mutations, with neither allele having an F508del or gating mutation.

However, the therapeutic indication in question also covers the age group 2 to 5 years and a large number of other mutations. For this reason, the company transferred the results of the RCT VX21-445-124 across ages and mutations to the patients in the therapeutic indication who were not covered by the study. The company's approach is described and evaluated below.

Transfer to other age groups

The company assumed transferability of the results from patients with cystic fibrosis aged 6 years and older with at least one non-Class I mutation, excluding an F508del and gating mutation, to children aged 2 to 5 years. The company did not present any study results on ivacaftor/tezacaftor/elexacaftor + ivacaftor in patients aged 2 to 5 years.

The company justified the transferability on the basis of what it considered to be adequate comparability of the mechanism of action, the clinical picture of the disease, and consistent pharmacokinetic exposure between patients in different age groups. One of the sources referred to by the company was the data presented in the assessment report of the EMA on safety and pharmacokinetics in children aged 2 to 5 years with cystic fibrosis in another therapeutic indication (at least one F508del mutation in the CFTR gene [3]). The company added that, in the assessment report on this therapeutic indication, the EMA assumed comparable efficacy and safety of ivacaftor/tezacaftor/elexacaftor + ivacaftor in different age groups [3]. In addition, from the company's point of view, the supplementary studies used by the company showed consistent results in various outcomes for patients in different age groups starting at 6 years (see section *Transfer to other mutations*). According to the company, the comparable pharmacokinetic exposure and the common underlying disease process were also decisive for the EMA's assessment of the present therapeutic indication [4].

The company further explained the comparability of the clinical picture of the disease by stating that, without therapeutic intervention, the disease progresses unhindered and the symptoms become more pronounced with increasing age due to the clinical course of the disease. Accordingly, the company expected age-dependent differences in the clinical picture. From the company's perspective, there were no effect modifications relevant to the conclusion for the characteristic age (< 18 years versus ≥ 18 years) in study VX21-445-124.

In the given data situation, it was not possible to transfer the results of patients aged 6 years and older to the age group 2 to 5 years. As the company also described in its reasoning, cystic fibrosis is a progressive disease. This means that younger patients can generally be expected to have less pronounced symptoms. A comparison of the patient characteristics (< 18 years versus ≥ 18 years) in VX21-445-124 showed a less pronounced restriction of lung function in patients < 18 years with regard to the lung parameter FEV1 and the respiratory system domain of the instrument CFQ-R. In addition, there were effect modifications by the characteristic age that were relevant to the conclusion; in patients aged between 6 and 17 years there were no statistically significant effects with notably smaller point estimates, while large effects were observed in older patients (see Section I 4.4). Since no data were available for the age group 2 to 5 years in the given therapeutic indication that could be used to support the assessment, the effects of the study VX21-445-124 were not transferable to the younger age group.

Irrespective of this, it is fundamentally understandable that it is more difficult to prove the added benefit in younger age groups with even less pronounced symptoms if the study duration is the same as for older participants. This problem could be addressed, for example, by long-term observations under the intervention, e.g. in registries and non-randomized comparisons with the natural course of the disease.

Transfer to other mutations

In the 'further investigations' section, the company listed the single-arm studies VX21-445-125 [5], VX22-CFD-016 [6], VX20-CFD-007 [6], HEOR-23-445-014 [6], Burgel 2024 [7] and Cromwell 2024 [8] as additional evidence for ivacaftor/tezacaftor/elexacaftor + ivacaftor. The company used these studies in particular for its argumentation that the results of the RCT VX21-445-124 were transferable to patients with mutations other than those investigated in the study. However, the company did not conduct an information retrieval for further studies for patients aged 6 years and older with mutations other than those investigated in VX21-445-124. According to the company, it used the study VX21-445-125 as supplementary information, it being the extension study of the RCT VX21-445-124. The company presented as supplementary information the studies Burgel 2024 and Cromwell 2024 identified in another therapeutic indication (see dossier assessment A25-62 [9]) and the studies VX22-CFD-016, VX20-CFD-007 and HEOR-23-445-014 sponsored by the company, as it considered these to provide valuable results on patient-relevant outcomes in everyday treatment and thus contribute to an informative assessment. The company also used these observational studies as supporting information because, according to the company, these studies considered patients with a total of 94 additional non-Class I mutations that were not investigated in the RCT VX21-445-124 (see Section I 3.2). The company also pointed out that the majority of patients whose mutations responded to ivacaftor/tezacaftor/elexacaftor in in vitro trials also achieved an improvement in vivo.

The VX21-445-125 study is an ongoing extension study of the RCT VX21-445-124, in which patients from both treatment arms had the opportunity to be treated with ivacaftor/ tezacaftor/elexacaftor + ivacaftor for a further 96 weeks. VX22-CFD-016, VX20-CFD-007 and HEOR-23-445-014 are registry-based retrospective observational studies based on the US Cystic Fibrosis Foundation Patient Registry (US CFFPR; VX22-CFD-016, VX20-CFD-007) and the UK Cystic Fibrosis Registry (UK CFR; HEOR-23-445-014), with the company being the responsible sponsor for each of the underlying registries. The studies included patients with cystic fibrosis aged 6 years and older (VX22-CFD-016, HEOR-23-445-014), or 12 years and older (VX20-CFD-007), who had at least one ivacaftor/tezacaftor/elexacaftor-responsive mutation, excluding an F508del mutation, in the CFTR gene. The Cromwell 2024 study was also based on data from the US registry and was a retrospective observation of patients with cystic fibrosis aged 6 years and older who had at least one ivacaftor/tezacaftor/elexacaftor-responsive mutation, excluding an F508del mutation, in the CFTR gene. Burgel 2024 study is a prospective observational study initiated by the French drug agency, which included patients with cystic fibrosis aged 6 years and older without F508del mutation in the CFTR gene.

The data from the studies VX21-445-125, VX22-CFD-016, VX20-CFD-007, HEOR-23-445-014, Burgel 2024 and Cromwell 2024, presented as supplementary information in the company's dossier, were not considered further in this assessment, as the completeness of the study pool for further investigations was not ensured due to the lack of information retrieval for patients aged 6 years and older. In addition, the studies VX22-CFD-016, HEOR-23-445-014, Burgel 2024 and Cromwell 2024 also investigated patients with gating mutations that are not covered by the therapeutic indication at hand. Separate analyses for the patients of the given research question were not available.

For inclusion in the VX21-445-124 study, patients had to have at least one of the following mutations: 2789+5G>A, 3272-26A>G, 3849+10kbC>T, P5L, R117C, L206W, V232D, T338I, R347H, A455E, S945L, L997F, R1066H, D1152H, G85E, R347P, L1077P, M1101K (see also Section I 3.2). In principle, it was possible for the 2nd allele to contain an additional mutation covered by the given therapeutic indication but not mandatory for inclusion in the study. The EMA assessment report showed that 20 patients had an N1303K mutation on the 2nd allele. There was no further information regarding mutations on the 2nd allele that were covered by the given therapeutic indication but were not mandatory for study inclusion. It can be assumed that some of the patients included in the study had some other mutations on the 2nd allele covered by the therapeutic indication. Overall, due to the large number of mutations associated with the research question at hand and their rarity, it was deemed unlikely that all mutations relevant to the research question can be investigated in a single study. However, uncertainty remained as to whether the results were transferable to patients who do not have any of the non-Class I mutations, excluding an F508del mutation and a gating mutation, investigated in the VX21-445-124 study relevant to this benefit assessment. The

uncertainties described were considered in the assessment of the certainty of conclusions of the results (see Section I 4.2).

I 3.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

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

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
VX21-445-124	Yes	Yes	No	Yes [10,11]	Yes [12,13]	Yes [4]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.

ACT: appropriate comparator therapy; CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
VX21-445-124	RCT, double-blind, parallel	Patients with cystic fibrosis aged 6 years and older with ▪ ≥ 1 ivacaftor/tezacaftor/elexacaftor-responsive mutation[b] on the CFTR gene, excluding a gating and F508del mutation[c] ▪ FEV1 ≥ 40% and ≤ 100% (of predicted normal for age, sex and height) at screening	ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC (N = 205) Placebo + BSC (N = 102)	Screening: ≤ 28 days Treatment: 24 weeks Observation: 28 ± 7 days[d]	84 centres in: Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland 5/2022–7/2023	Primary: absolute change in FEV1 (in% of predicted normal) from baseline to Week 24 Secondary: mortality, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. At least one of the following mutations: 2789+5G>A, 3272-26A>G, 3849+10kbC>T, P5L, R117C, L206W, V232D, T338I, R347H, A455E, S945L, L997F, R1066H, D1152H, G85E, R347P, L1077P, M1101K.
c. None of the following mutations: F508del, G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or R117H.
d. Follow-up was not required for patients who participated in the open-label single-arm extension study VX21-445-125 [5] after completion of 24 weeks of treatment.

AE: adverse event; CFTR: cystic fibrosis transmembrane conductance regulator; FEV1: forced expiratory volume in 1 second; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial

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

Study	Intervention	Comparison
VX21-445-124	Ivacaftor/tezacaftor/elexacaftor, morning, oral ▪ ≥ 6 years to < 12 years ▫ 75 mg/50 mg/100 mg (< 30 kg body weight on Day 1) ▫ 150 mg/100 mg/200 mg (≥ 30 kg body weight on Day 1) ▪ ≥ 12 years ▫ 150 mg/100 mg/200 mg + ivacaftor, evening, oral ▫ 75 mg (< 30 kg body weight on Day 1) ▫ 150 mg (≥ 30 kg body weight on Day 1) + BSC[a]	placebo, morning and evening, oral + BSC[a]
	No dose modification allowed[b]	
	Allowed prior treatment ▪ Stable medication for the treatment of cystic fibrosis from 28 days before study start **Allowed concomitant treatment** ▪ If possible, continuation of stable treatment with inhaled antibiotics until the end of the study ▪ prednisone or prednisolone ≤ 10 mg permanently, or ≤ 60 mg for ≤ 5 days **Prohibited prior and concomitant treatment** ▪ Moderate and strong CYP3A inducers or inhibitors (except ciprofloxacin) within 2 weeks prior to study start until the end of the study ▪ CFTR modulators excluding the study medication within 28 days before the start of the study until the end of the study	

a. In the study, basic medication for the treatment of cystic fibrosis was given in addition to ivacaftor/tezacaftor/elexacaftor + ivacaftor or placebo.
b. Study drug administration had to be interrupted in case of a generalized rash (SAE or severe AE [CTCAE grade ≥ 3]) or markedly elevated liver enzymes (ALT or AST); if the interruption lasted > 72 hours, the study drug could only be continued in clinically stable patients after a thorough investigation.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; CTCAE: Common Terminology Criteria for Adverse Events; CYP: cytochrome P450; RCT: randomized controlled trial; SAE: serious adverse event

The VX21-445-124 study is a randomized, double-blind study comparing ivacaftor/tezacaftor/elexacaftor + ivacaftor with placebo, each in addition to basic therapy for cystic fibrosis. The study included patients aged 6 years and older with cystic fibrosis who had at least one ivacaftor/tezacaftor/elexacaftor-responsive mutation on the CFTR gene. Patients with at least one of the following mutations were eligible: 2789+5G>A, 3272-26A>G, 3849+10kbC>T, P5L, R117C, L206W, V232D, T338I, R347H, A455E, S945L, L997F, R1066H, D1152H, G85E, R347P, L1077P, M1101K. No F508del mutation or gating mutation (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or R117H) was allowed to be present on either allele. As part of the approval process, the L997F mutation was classified as not causing cystic fibrosis. A total of 4 patients in the VX21-445-124 study had this mutation. It is unclear

whether the mutation was also homozygous. In this case, the patients would not be covered by the given therapeutic indication. Since a maximum of 4 patients in total were not covered by this therapeutic indication, this had no consequences for this benefit assessment. The patients additionally had to have an FEV1 of ≥ 40% to ≤ 100% of predicted normal for age, sex, and height at screening. In the assessment of the investigator, the disease had to be stable. Patients with an acute upper or lower respiratory infection or pulmonary exacerbation within 28 days before the first dose of the study drug, as well as patients with a lung infection with organisms associated with a more rapid decline in pulmonary status within the last 12 months before study inclusion, were excluded. In addition, baseline medication for the treatment of sinopulmonary disease associated with cystic fibrosis had to be stable for at least 28 days before the start of the study medication.

In the VX21-445-124 study, a total of 307 patients were randomly assigned in a 2:1 ratio to receive treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor (N = 205) or placebo (N = 102). Stratification factors were FEV1 at the time of screening (< 70% versus ≥ 70% of predicted normal), age (< 18 years versus ≥ 18 years) and CFTR mutation group (no residual function-like mutation versus ≥ 1 residual function-like mutation). All patients who were treated with the study medication until the end of the study or who had completed all planned visits planned in the treatment period despite medication interruptions could switch to the single-arm, open-label extension study VX21-445-125.

Treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor was carried out according to the SmPC [14]. Patients in the comparator arm received placebo to maintain blinding. Patients in both study arms additionally received concomitant basic therapy (see section on the implementation of the ACT).

The primary outcome of the study was the absolute change in FEV1 (in% of predicted normal) after 24 weeks. Patient-relevant secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC (multipage table)

Study **Characteristic** **Category**	**IVA/TEZ/ELX + IVA + BSC** **N[a] = 205**	**Placebo + BSC** **N[a] = 102**
VX21-445-124		
Age [years], median [min; max]	33 [6; 73]	34 [7; 87]
Age at screening, n (%)		
< 18 years	44 (22)	20 (20)
≥ 18 years	161 (79)	82 (80)
Sex [F/M], %	55/45	51/49
Family origin, n (%)		
Caucasian	172 (84)	87 (85)
Not recorded according to local regulations	26 (13)	12 (12)
Asian and others	7 (3)[b]	4 (4)[b]
Region, n (%)		
Europe	191 (93)	92 (90)
North America	14 (7)	10 (10)
Body weight [kg], mean (SD)	61.9 (18.5)	63.2 (16.7)
BMI [kg/m²]		
Mean (SD)	22.5 (4.6)	22.5 (4.2)
Sweat chloride concentration [mmol/L], median [min; max]	89.5 [10.0; 126.0]	79.5 [13.0; 133.0]
FEV1 [% of predicted normal], median [min; max]	69.5 [35.8; 108.7]	69.2 [34.0; 107.6]
FEV1 [% of predicted normal], n (%)		
< 40	5 (2)	5 (5)
≥ 40 to < 70	99 (48)	47 (46)
≥ 70 to ≤ 90	78 (38)	38 (37)
> 90	23 (11)	12 (12)
CFTR mutation group, n (%)		
≥ 1 RF-like mutation	151 (74)	74 (73)
No RF-like mutation	54 (26)	28 (28)
Treatment discontinuation, n (%)[c]	9 (4)	0 (0)
Study discontinuation, n (%)[d]	8 (4)	0 (0)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC (multipage table)

Study Characteristic Category	IVA/TEZ/ELX + IVA + BSC N[a] = 205	Placebo + BSC N[a] = 102

a. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. Common reasons for treatment discontinuation in the intervention vs. the control arm were the following (percentages based on randomized patients): AEs (2% vs. 0), further dosing refused (1% vs. 0), pregnancy (1% vs. 0). All randomized patients started treatment. Furthermore, 96% vs. 100% of the patients completed treatment as planned.
d. Common reasons for study discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): AEs (2% vs. 0), withdrawal of consent (1% vs.0), other (1% vs. 0). The data additionally include patients who died during the course of the study (intervention arm: 1% vs. control arm: 0).

AE: adverse event; BMI: body mass index; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; ELX: elexacaftor; F: female; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; RF: residual function; SD: standard deviation; TEZ: tezacaftor

The demographic and clinical characteristics of the patients were largely balanced between the 2 study arms. The median age of the patients was 33 and 34 years, respectively, the majority were of Caucasian family origin (84%). Patients aged 6 years and older were included in the VX21-445-124 study. 79% of the study participants were at least 18 years old. The mean height and body weight, or body mass index (BMI), were within the normal range.

The patients had a median FEV1 of just under 70 (in% of predicted normal). According to the inclusion criteria of the VX21-445-124 study, patients had to have an FEV1 of ≥ 40% at the time of screening. However, a few patients had an FEV1 of < 40% at baseline.

Implementation of the ACT

The G-BA specified BSC as the ACT for ivacaftor/tezacaftor/elexacaftor + ivacaftor for the treatment of patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation in the CFTR gene, excluding an F508del and gating mutation. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (in particular antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [as outlined in the German Remedies Directive] – while making full use of all possible dietary interventions).

According to the study protocol, patients had to be on stable medication for the treatment of cystic fibrosis, particularly for sinopulmonary disease, for at least 28 days before the start of

the study. Furthermore, concomitant treatment associated with cystic fibrosis – primarily inhaled antibiotics – was to be maintained until the end of the study if possible. There were no further restrictions regarding concomitant medication for the treatment of cystic fibrosis (see also Table 7).

The available information on prior and concomitant treatment from the study showed that the majority of patients in the study received concomitant treatment for the symptomatic treatment of cystic fibrosis both at baseline and during the study.

Table 9 shows the prior and concomitant treatment of the patients in VX21-445-124.

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

Study	IVA/TEZ/ELX + IVA + BSC		Placebo + BSC	
	Treatment before 1st dose of study medication n (%)	Concomitant medication[a] n (%)	Treatment before 1st dose of study medication n (%)	Concomitant medication[a] n (%)
VX21-445-124	**N = 205**		**N = 102**	
Drug treatment				
Antibiotics	122 (59.5)[b]	160 (78.0)[b]	53 (52.0)[b]	85 (83.3)[b]
Intravenous antibiotics	1 (0.5)	15 (7.3)[b]	0	19 (18.6)
Inhaled medication	187 (91.2)[b]	188 (91.7)[b]	90 (88.2)[b]	91 (89.2)[b]
Mucolytics	151 (73.7)[b]	152 (74.1)[b]	75 (73.5)[b]	77 (75.5)[b]
Bronchodilators	174 (84.9)[b]	176 (85.9)[b]	78 (76.5)[b]	80 (78.4)[b]
Inhaled saline	110 (53.7)[c]	116 (56.6)	61 (59.8)[c]	63 (61.8)
Digestives, incl. enzymes	79 (38.5)[c]	81 (39.5)	36 (35.3)[c]	37 (36.3)
Pancreatin	52 (25.4)[c]	53 (25.9)	26 (25.5)[c]	27 (26.5)
Pancrelipase	20 (9.8)[c]	20 (9.8)	8 (7.8)[c]	8 (7.8)
Vitamins	157 (76.6)[c]	161 (78.5)	79 (77.5)[c]	81 (79.4)
Non-drug treatment				
Physiotherapy	67 (32.7)[b]	68 (33.2)[b]	37 (36.3)[b]	37 (36.3)[b]

a. Total number of patients who received treatment at baseline and who started treatment during the study. It is unclear whether and how many patients discontinued concomitant treatment during the course of the study.
b. Institute's calculation.
c. Number of patients with therapy within 56 days before the 1st dose of the study medication

BSC: best supportive care; ELX: elexacaftor; IVA: ivacaftor; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; TEZ: tezacaftor

The information on prior and concomitant treatment showed that patients received antibiotics, inhaled medications (including saline), digestive enzymes, vitamins and physiotherapy for the symptomatic treatment of cystic fibrosis at baseline.

The company also provided detailed information on the number of concomitant therapies in the course of the study for the different concomitant medications (see Table 21 in I Appendix C of the full dossier assessment). Information on individual drugs can be found in the clinical study report (CSR). The data presented by the company in Module 4 A showed that with regard to antibiotic treatment, adjustments were made during the course of the study. For example, 46% of patients in the intervention arm and 65% in the comparator arm who did not receive antibiotic therapy at baseline received at least one antibiotic during the course of the study. The information in the CSR additionally showed that adjustments were also made to the commonly used inhaled antibiotics tobramycin and colistin during the course of the study, regardless of the recommendation to keep them stable. At baseline, 13% of patients in the intervention arm and 9% comparator arm received tobramycin, while this proportion increased to 17% and 23%, respectively, over the course of the study. At baseline, 25% and 23% of patients received colistin, compared with 28% and 27%, respectively, over the course of the study. With regard to the use of other therapies, the detailed information showed that a small number of patients started a new treatment during the study. It should be taken into account that a large proportion of the patients included were already receiving treatment with inhaled medication (91% vs. 88%), including mucolytics and bronchodilators, at baseline. Around a third of patients received physiotherapy (33% versus 36%). The available data did not indicate whether and for how many patients concomitant treatment was adjusted, for example in terms of an increase in dosage or in the frequency of drug treatment or non-drug treatment. It was also unclear whether and how many patients discontinued concomitant treatment during the course of the study.

According to current guidelines, various antibiotics can be used individually or as combination therapy in different treatment regimens to eradicate various pathogens that cause lung infections (especially Pseudomonas aeruginosa) and to treat pulmonary exacerbations. The choice of drugs or drug combinations, the route of administration, and the duration of therapy must be determined on an individual basis for each patient [15,16]. In addition, supportive therapies should be provided as maintenance treatment regardless of the respective bacterial colonization of the airways. These include, in particular, inhaled therapies with mucolytics, bronchodilators and salines. In addition, the guidelines recommend physiotherapy, in particular learning techniques for secretion drainage and chest mobilization (so that physiotherapy can be conducted independently at home), as well as nutritional therapy, if indicated for the individual patient [15].

In summary, the concomitant treatments used in the VX21-445-124 study were considered to be a sufficient approximation to the implementation of the ACT BSC.

Risk of bias across outcomes (study level)

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

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

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
VX21-445-124	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the VX21-445-124 study.

Transferability of the study results to the German health care context

The company described that the non-Class I mutations of the patients included in the study concurred with the mutations in the majority of patients with cystic fibrosis in Germany with at least one non-Class I mutation, excluding an F508del mutation and gating mutation. It also stated that the majority of the patients included were of Caucasian family origin, 12% of whom were German patients, and that the study was primarily conducted in specialized European or North American centres. According to the company, treatment in Germany is also primarily provided in specialized practices and hospital outpatient clinics. Furthermore, the study medication was administered in addition to the patients' basic drug and non-drug therapy, which, according to company, also corresponded to the procedure for treating these patients in Germany. Overall, the company presumed very good transferability of the results to the German health care context.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - All-cause mortality
- Morbidity
  - Pulmonary exacerbations
  - Severe pulmonary exacerbations
  - Symptoms measured using the symptom domains of the CFQ-R instrument
- Health-related quality of life
  - measured using the health-related quality of life domains of the CFQ-R instrument
- Side effects
  - SAEs
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Other specific AEs, if any

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

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

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

Study	Outcomes								
	All-cause mortality[a]	Pulmonary exacerbations	Severe pulmonary exacerbations[b]	Symptoms (CFQ-R)	Health-related quality of life (CFQ-R)	SAEs[c]	Severe AEs[c,d]	Discontinuation due to AEs	Rash (PT, AEs)
VX21-445-124	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalized as hospitalization due to pulmonary exacerbations.
c. Without PT 'infective pulmonary exacerbation of cystic fibrosis'.
d. Severe AEs are operationalized as CTCAE grade 3 or 4. To assess the severity of an AE in paediatric patients, the reference ranges for paediatric clinical laboratory parameters used by the investigator could differ from those of the CTCAE (see body text).

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CTCAE: Common Terminology Criteria for Adverse Events; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event

Notes on outcomes

Pulmonary exacerbations

In the study, pulmonary exacerbations were defined as new, or changed, antibiotic therapy (intravenous, inhaled or oral) being required 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
- Fever > 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 was deemed adequate.

The company classified pulmonary exacerbations in the following:

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

Pulmonary exacerbations and hospitalization due to pulmonary exacerbations were used for this dossier assessment. For this benefit assessment, pulmonary exacerbations were analysed based on the proportion of patients with event and the event rate (number of events per patient per year) in order to take into account not only the occurrence but also the frequency of pulmonary exacerbations over the entire course of the study for this key outcome.

Hospitalization due to pulmonary exacerbations represented the occurrence of severe pulmonary exacerbations. The analysis was carried out post hoc. It should be noted that events of severe pulmonary exacerbation were also included in the outcome pulmonary exacerbations. The number of patients with at least one severe pulmonary exacerbation was only about one-third of the number of patients with any pulmonary exacerbations (see Table 13). Since this outcome exclusively represented severe pulmonary exacerbations and thus a higher severity grade, it was appropriate to reconsider these events in the given data situation. This aspect was taken into account in the overall assessment of the added benefit (see Section I 5.2). For the outcome severe pulmonary exacerbations, analyses were only available on the proportion of patients with event.

Pulmonary exacerbations requiring treatment with intravenous antibiotics were already represented by pulmonary exacerbations leading to hospitalization and were therefore not considered further.

CFQ-R

The CFQ-R instrument was used in the study to assess symptoms and health-related quality of life. The instrument includes several versions: a patient version for different age groups (6 to 11 years, 12 to 13 years, and ≥ 14 years) and a parent/caregiver version (6 to 13 years).

The patient versions for children of the age groups of 6 to 11 years and 12 to 13 years consist of 2 domains relating to symptoms (respiratory symptoms, digestive symptoms) and 6 domains relating to health-related quality of life (physical wellbeing, emotional functioning, social limitations, body image, eating problems and treatment burden). For children aged 6 to 11, the questions are asked by an interviewer, while children aged 12 or 13 complete the questionnaire themselves. In addition to the domains in the versions for children, the patient version for adolescents aged 14 and older and adults contains one more domain on symptoms (weight) and 3 additional domains on health-related quality of life (vitality, role functioning and health perceptions). In addition, a parent/caregiver version of the CFQ-R was also used in the study for the age group of 6 to 13 years, which asks parents or caregivers to assess the symptoms and health-related quality of life. The patient version of the questionnaire was used for the assessment of the added benefit. The parent/caregiver version is presented as supplementary information.

The company presented only joint (pooled) analyses for domains that are included in all patient-reported questionnaire versions. This type of analysis was predefined. The pooled analysis of patients of different age groups (6 to 11 years, 12 to 13 years, ≥ 14 years) for the domains included in all questionnaire versions was appropriate. Although there are differences in the type and number of items included in each domain in the questionnaire versions for the 6 to 11 years and 12 to 13 years age groups compared with the version for the age group of 14 years and above, the corresponding items measure the same domain for each age group. Analyses of domains that, according to the questionnaire system, are only recorded for adolescents aged 14 and over and adults (vitality, role functioning and health perceptions) were only used for this age group.

This dossier assessment considered the analyses based on a mixed-effects model with repeated measures (MMRM) for all domains of the CFQ-R. These analyses enabled an evaluation of all domains of the CFQ-R and thus a meaningful interpretation of the validated instrument, taking into account all changes in symptoms and health-related quality of life over the course of the study in the context of a potentially progressive disorder.

In Appendix 4 G, the company additionally presented responder analyses on the absolute change by ≥ 15 points over 24 weeks (scale range 0 to 100), which were not prespecified. The response criteria of 15 points, which were used in the analyses presented by the company, met the requirements for response criteria for reflecting with sufficient certainty a change that is perceivable for patients, as described in the *General Methods* of the Institute [1]. The company did not provide any further information on the operationalization. It was not clear from the information provided whether the change referred to by the company was either an improvement or a deterioration, or whether any change by at least 15 points, i.e. both an improvement and a deterioration, was analysed as an event. Furthermore, due to a lack of

information, it can only be assumed that the patients recorded as responders were patients who exceeded the response threshold at some point up to Week 24. For the progressive disease in question, responder analyses at Week 24 would have been desirable.

Severe AEs

In the VX21-445-124 study, severity was classified according to the CTCAE, with a severe AE being defined as a grade ≥ 3 AE. When assessing the severity of an AE in paediatric patients, the investigator took into account that the reference ranges for paediatric clinical laboratory parameters may deviate from those of the CTCAE. It remained unclear which reference ranges were used instead for the respective severity classification and whether all investigators used the same reference ranges as a basis.

Overall, only a few severe AEs occurred in the study, and the results were consistent with the SAEs that occurred (see also Table 13). The results on severe AEs were used, but due to the uncertainties described, the certainty of conclusions for this outcome was reduced (see also Section I 4.2).

Outcomes presented as supplementary information in I Appendix B of the full dossier assessment

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

- Lung function using FEV1

The outcome FEV1 (in% of predicted normal) is a lung function parameter. Relevant for a benefit assessment are patient-noticeable symptoms associated with a change in FEV1 or the associated reduction in health-related quality of life, which were directly recorded in the studies. The results of the absolute change in FEV1 (in% of predicted normal) over 24 weeks from baseline are presented as supplementary information.

- BMI and z-score of the BMI

Body weight and BMI are very important for the given therapeutic indication, as developmental disorders and nutrient malabsorption are typical signs of cystic fibrosis. In its assessment, the company used the BMI as a measure for developmental status or as a parameter for the extent of a developmental disorder in the patients.

In the given situation, the importance of the BMI as a measure of malnutrition was not directly evident since the mean BMI of the patients in the VX21-445-124 study included was in the normal range both at the start of therapy and after 24 weeks of treatment. The results on the

absolute change in BMI and the absolute change in the age-dependent z-score of the BMI over 24 weeks compared to baseline are presented as supplementary information.

I 4.2 Risk of bias

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

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

Study	Study level	Outcomes								
		All-cause mortality[a]	Pulmonary exacerbations	Severe pulmonary exacerbations[b]	Symptoms (CFQ-R)	Health-related quality of life (CFQ-R)	SAEs[c]	Severe AEs[c, d]	Discontinuation due to AEs	Rash (PT, AEs)
VX21-445-124	L	L	L	L	L	L	L[e]	L	L	L

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalized as hospitalization due to pulmonary exacerbations.
c. Without PT 'infective pulmonary exacerbation of cystic fibrosis'.
d. Severe AEs are operationalized as CTCAE grade 3 or 4. To assess the severity of an AE in paediatric patients, the reference ranges for paediatric clinical laboratory parameters used by the investigator could differ from those of the CTCAE (see Section I 4.1).
e. Despite the low risk of bias, the certainty of conclusions is reduced for the outcome severe AEs (see Section I 4.1).

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: Low; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event

The risk of bias of the results of all patient-relevant outcomes was rated as low. For the outcome severe AEs, however, the certainty of conclusions was reduced due to the reasons mentioned in Section I 4.1.

Overall, an uncertainty remained for this benefit assessment as to whether the results of the VX21-445-124 study were transferable to patients who do not have any non-Class I mutations, excluding a F508del mutation and gating mutation, as investigated in the study (for an explanation, see Chapter I 3). The certainty of conclusions of the study results for the given research question was therefore reduced. Based on the information from the VX21-445-124 study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented.

I 4.3 Results

Table 13, Table 14 and Table 15 summarize the results of the comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC in patients with cystic fibrosis aged 6 years and older who have at least one non-Class I mutation, excluding an F508del and gating mutation, in the CFTR gene. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Tables on common AEs, common SAEs, common severe AEs and discontinuations due to AEs are presented in I Appendix D of the full dossier assessment.

Table 13: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC

Study Outcome category	IVA/TEZ/ELX + IVA + BSC		Placebo + BSC		IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
VX21-445-124					
Mortality					
All-cause mortality[a]	205	1 (0.5)	102	0 (0)	–
Morbidity					
Pulmonary exacerbations[b]	205	18 (8.8)	102	26 (25.5)	0.34 [0.20; 0.58]; < 0.001[c]
Severe pulmonary exacerbations[d]	205	3 (1.5)	102	11 (10.8)	0.13 [0.04; 0.45]; 0.001[c]
Side effects					
AEs (supplementary information)[e]	205	192 (93.7)	102	94 (92.2)	–
SAEs[e]	205	14 (6.8)	102	3 (2.9)	2.32 [0.68;7.90]; 0.171[f]
Severe AEs[e, g]	205	14 (6.8)	102	2 (2.0)	3.48 [0.81;15.03]; 0.075[f]
Discontinuation due to AEs[e]	205	5 (2.4)	102	0 (0)	–[h]; 0.120[f]
Rash (PT, AEs)	205	45 (22.0)	102	1 (1.0)	22.39 [3.13; 160.13]; < 0.001[f]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. For the definition of pulmonary exacerbations, see Section I 4.1.
c. RR, CI and p-value: generalized linear model (binomial distribution with log link); adjusted for FEV1%, age (< 18 years vs. ≥ 18 years) and CFTR mutation group (≥ 1 RF-like mutation vs. no RF-like mutation).
d. Operationalized as hospitalization due to pulmonary exacerbations, for definition see Section I 4.1.
e. Without PT 'infective pulmonary exacerbation of cystic fibrosis'.
f. Institute's calculation of p-value (unconditional exact test, CSZ method according to [17]).
g. Operationalized as CTCAE grade 3 and 4. To assess the severity of an AE in paediatric patients, the reference ranges for paediatric clinical laboratory parameters used by the investigator could differ from those of the CTCAE (see Section I 4.1).
h. No presentation of RR and CI, as these are not informative.

AE: appropriate comparator therapy; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ELX elexacaftor; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RF: residual function; RR: relative risk; SAE: serious adverse event; TEZ: tezacaftor

Table 14: Results (morbidity number of events per time) – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC

Study Outcome category Outcome	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC
	N	n_E / patient-years[a]	Events per patient per year[b]	N	n_E / patient-years[a]	Events per patient per year[b]	Rate ratio [95% CI]; p-value[b]
VX21-445-124							
Morbidity							
Pulmonary exacerbations[c]	205	21/101.2	0.17	102	40/51.5	0.63	0.28 [0.15; 0.51]; < 0.001
Severe pulmonary exacerbations[d]					ND		

a. Patient years: sum of the observation periods of all patients in days, divided by 336 (1 year is defined as 336 days).
b. Rate (per treatment group) as well as rate ratio, CI and p-value (group comparison): negative binomial model; adjusted for FEV1%, age (< 18 years vs. ≥ 18 years) and CFTR mutation group (≥ 1 RF-like mutation vs. no RF-like mutation), logarithmized patient years as offset.
c. For the definition of pulmonary exacerbations, see Section I 4.1.
d. Operationalized as hospitalization due to pulmonary exacerbations, for definition see Section I 4.1.

AE: adverse event; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; CI: confidence interval; ELX: elexacaftor; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; ND: no data; nE: number of events (sum of all patients); N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RF: residual function; TEZ: tezacaftor

Table 15: Results (morbidity health-related quality of life, continuous) – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC (multipage table)

Study Outcome category Outcome	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Mean change over 24 weeks mean[b] (SE)	N[a]	Values at baseline mean (SD)	Mean change over 24 weeks mean[b] (SE)	Mean difference [95% CI]; p-value[b]
VX21-445-124							
Morbidity							
Symptoms (CFQ-R, children [6–11 years, 12–13 years] and adolescents or adults – pooled)[c]							
Respiratory symptoms	202	64.1 (20.7)	17.5 (1.2)	102	65.8 (21.3)	-2.0 (1.6)	19.49 [15.52; 23.46]; < 0.001 SMD [95% CI]: 1.17 [0.91; 1.43]
Digestive symptoms	202	80.1 (19.8)	0.0 (1.0)	102	84.4 (18.3)	-2.7 (1.4)	2.73 [-0.64; 6.09]; 0.113
Weight[d]	173	83.4 (29.6)	2.2 (1.9)	92	83.3 (30.7)	-2.8 (2.7)	4.94 [-1.55; 11.42]; 0.135
Symptoms (CFQ-R, parent/caregiver version [children 6–13 years]; supplementary information)[c]							
Respiratory symptoms	*29*	*82.5 (15.8)*	*6.5 (2.7)*	*10*	*83.1 (12.7)*	*0.7 (4.7)*	*5.83 [-5.19; 16.85]; 0.290*
Digestive symptoms	*29*	*90.4 (12.1)*	*-2.4 (2.2)*	*10*	*87.8 (17.7)*	*-1.8 (3.8)*	*-0.63 [-9.48; 8.21]; 0.885*
Weight	*29*	*62.1 (36.4)*	*8.5 (4.3)*	*10*	*60.0 (34.4)*	*-3.9 (7.5)*	*12.30 [-5.18; 29.78]; 0.162*
Health-related quality of life							
Health-related quality of life (CFQ-R, children [6–11 years, 12–13 years] and adolescents or adults – pooled)[c]							
Physical wellbeing	202	67.6 (26.4)	9.8 (1.1)	102	67.6 (26.3)	-2.9 (1.6)	12.70 [8.92; 16.47]; < 0.001 SMD [95% CI]: 0.80 [0.56; 1.05]
Emotional functioning	202	76.7 (17.7)	3.1 (0.8)	102	78.2 (18.3)	-0.5 (1.1)	3.54 [0.85; 6.24]; 0.010 SMD [95% CI]: 0.31 [0.07; 0.55]
Vitality[d]	173	55.8 (21.8)	9.4 (1.2)	92	58.6 (20.8)	-4.5 (1.7)	13.82 [9.76; 17.87]; < 0.001 SMD [95% CI]: 0.86 [0.60; 1.13]

Table 15: Results (morbidity health-related quality of life, continuous) – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC (multipage table)

Study Outcome category	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC
Outcome	N[a]	Values at baseline mean (SD)	Mean change over 24 weeks mean[b] (SE)	N[a]	Values at baseline mean (SD)	Mean change over 24 weeks mean[b] (SE)	Mean difference [95% CI]; p-value[b]
Social functioning	202	66.1 (19.1)	5.7 (0.9)	102	68.6 (18.4)	-2.6 (1.2)	8.31 [5.34; 11.28]; < 0.001 SMD [95% CI]: 0.67 [0.42; 0.91]
Role functioning[d]	170	79.0 (20.2)	5.2 (1.0)	91	81.0 (20.0)	-1.2 (1.4)	6.39 [2.98; 9.80]; < 0.001 SMD [95% CI]: 0.48 [0.22; 0.74]
Body image	202	78.1 (22.4)	2.7 (1.1)	102	81.1 (22.3)	-2.1 (1.5)	4.84 [1.28; 8.39]; 0.008 SMD [95% CI]: 0.32 [0.08; 0.56]
Eating problems	202	87.8 (20.1)	2.5 (1.0)	102	89.5 (17.6)	-1.3 (1.4)	3.73 [0.40; 7.06]; 0.028 SMD [95% CI]: 0.27 [0.03; 0.51]
Treatment burden	202	60.9 (21.6)	6.7 (1.1)	102	60.1 (23.9)	1.8 (1.5)	4.86 [1.21; 8.51]; 0.009 SMD [95% CI]: 0.32 [0.08; 0.56]
Health perceptions[d]	173	55.8 (23.6)	12.1 (1.2)	92	59.5 (20.9)	-2.9 (1.7)	15.01 [10.89; 19.13]; < 0.001 SMD [95% CI]: 0.92 [0.66; 1.19]
Health-related quality of life (CFQ-R, parent/caregiver version [children 6–13 years]; supplementary information)[c]							
Physical wellbeing	*29*	*87.1 (15.1)*	*2.8 (2.3)*	*10*	*92.9 (5.9)*	*-5.3 (4.0)*	*8.14 [-1.17; 17.45]; 0.085*
Emotional functioning	*29*	*83.9 (15.5)*	*0.5 (2.0)*	*10*	*83.3 (10.1)*	*-1.5 (3.5)*	*1.97 [-6.13; 10.06]; 0.625*
Vitality	*29*	*77.9 (17.1)*	*-1.0 (2.2)*	*10*	*76.0 (11.8)*	*-0.5 (3.8)*	*-0.55 [-9.44; 8.34]; 0.901*
Social functioning	*Domain not provided for parents/caregivers*						
Role functioning	*Domain not provided for parents/caregivers*						

Table 15: Results (morbidity health-related quality of life, continuous) – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC (multipage table)

Study Outcome category Outcome	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Mean change over 24 weeks mean[b] (SE)	N[a]	Values at baseline mean (SD)	Mean change over 24 weeks mean[b] (SE)	Mean difference [95% CI]; p-value[b]
Body image	*29*	*79.3 (22.4)*	*4.4 (3.0)*	*10*	*71.1 (30.6)*	*-1.0 (5.2)*	*5.40 [-6.73; 17.52]; 0.372*
Eating problems	*29*	*82.8 (22.5)*	*-0.4 (2.8)*	*10*	*75.0 (33.6)*	*-1.9 (5.0)*	*1.45 [-10.13; 13.02]; 0.801*
Treatment burden	*29*	*69.0 (19.6)*	*2.6 (2.8)*	*10*	*70.0 (23.5)*	*-10.4 (4.9)*	*13.01 [1.58; 24.44]; 0.027* *SMD [95% CI]: 0.84 [0.09; 1.59]*
Health perceptions	*29*	*72.6 (18.8)*	*9.7 (2.7)*	*10*	*77.8 (12.8)*	*2.6 (4.8)*	*7.06 [-4.02; 18.13]; 0.204*
School performance[e]	*29*	*77.0 (19.5)*	*1.1 (2.6)*	*10*	*83.3 (14.2)*	*-0.7 (4.6)*	*1.83 [-8.95; 12.60]; 0.733*

a. Number of patients taken into account in the effect estimation; baseline values may be based on different patient numbers.
b. Mean and SE (per treatment group) as well as MD, CI and p-value (group comparison): MMRM; adjusted for FEV1%, age (< 18 years vs. ≥ 18 years) and CFTR mutation group (≥ 1 RF-like mutation vs. no RF-like mutation). The effect represents the difference in the changes (from baseline) averaged over 24 weeks between the treatment groups.
c. Higher (increasing) values indicate better symptoms/health-related quality of life; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100).
d. Domain for adolescents (≥ 14 years) or adults; not provided for children [6 bis 11 years, 12 to 13 years].
e. Domain for parents or caregivers; not provided for patients.

BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane conductance regulator; CI: confidence interval; ELX: elexacaftor; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; MMRM: mixed-effects model with repeated measures; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; RF: residual function; SD: standard deviation; SE: standard error; SMD: standardized mean difference; TEZ: tezacaftor

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 4.1).

Mortality

All-cause mortality

In the VX21-445-124 study, there was only one death in the intervention arm. There is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for the outcome all-cause mortality; an added benefit is therefore not proven.

Morbidity

Pulmonary exacerbations

For the outcome pulmonary exacerbations, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC based on event rates (number of events per patient per year). There is a hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for the outcome pulmonary exacerbations.

Severe pulmonary exacerbations

Based on the analysis of patients with at least one event, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC for the outcome severe exacerbations. Analyses based on event rates (number of events per patient per year) were not available for study VX21-445-124. There is a hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for the outcome severe pulmonary exacerbations.

Symptoms (CFQ-R)

Respiratory symptoms

For the respiratory symptoms domain of the CFQ-R, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. The SMD was analysed to assess the relevance of the result. The 95% 95% CI was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. For the respiratory symptoms domain of the CFQ-R, there is a hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC.

Digestive symptoms and weight

For the CFQ-R domains digestive symptoms and weight, no statistically significant differences were shown between the treatment groups. In each case, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC; an added benefit is therefore not proven for either of the 2 domains.

Health-related quality of life (CFQ-R)

Physical wellbeing, health perceptions

For the CFQ-R domains physical wellbeing and health perceptions (the latter domain was only recorded in patients aged 14 years and older), there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. However, there were effect modifications due to the characteristics age and FEV1 for both domains (see Section I 4.4). Within the subgroups, the significance and then, if applicable, the relevance of the result was assessed using the 95% CI associated with the SMD. For patients ≥ 18 years of age or with an FEV1 < 70%, there is a hint of an added benefit of ivacaftor/tezacaftor/ elexacaftor + ivacaftor in comparison with BSC for each of these CFQ-R domains. For patients < 18 years of age or with an FEV1 ≥ 70%, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for either of these CFQ-R domains; an added benefit is therefore not proven.

Vitality, role functioning

For the CFQ-R domains vitality and role functioning (which were only recorded in patients aged 14 years and older), there was a statistically significant difference in favour of ivacaftor/ tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. The SMD was considered to assess the relevance of the result. In each case, the 95% CI was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. For each of these CFQ-R domains, there is a hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC.

Social functioning

For the social functioning domain of the CFQ-R, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. There was an effect modification by the characteristic of sex, however (see Section I 4.4). Within the subgroups, the significance and then, if applicable, the relevance of the result was assessed using the 95% CI associated with the SMD. For this domain, there is a hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for female patients. For this domain, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for male patients; an added benefit is therefore not proven.

Emotional functioning, body image, eating problems, treatment burden

For each of the CFQ-R domains of emotional functioning, body image, eating problems and treatment burden, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. The SMD was considered to assess the relevance of the result. The 95% CI was not fully outside the irrelevance range [−0.2; 0.2] in any of the domains. The effect can therefore not be inferred

to be relevant. For each of these domains, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC; an added benefit is therefore not proven for any of them.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs. There is no hint of greater or lesser harm of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for these outcomes; an added benefit is therefore not proven.

Specific AEs

Rash (AEs)

For the outcome rash (AEs), there was a statistically significant difference to the disadvantage of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC. There is a hint of greater harm of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for this outcome.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account in this assessment:

- Age (< 18 years versus ≥ 18 years)
- Sex (female versus male)
- FEV1 (in% of predicted normal) at baseline, (< 70% versus ≥ 70%)

All mentioned subgroup characteristics and cut-off values were prespecified for the primary outcome of absolute change in FEV1 from baseline to Week 24.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there have to be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

The results are presented in Table 16.

Table 16: Subgroups (morbidity health-related quality of life) – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC (multipage table)

Study Outcome Characteristic Subgroup	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Mean change over 24 weeks mean[b] (SE)	N[a]	Values at baseline mean (SD)	Mean change over 24 weeks mean[b] (SE)	Mean difference [95% CI]; p-value[b]
VX21-445-124							
Health-related quality of life							
Health-related quality of life (CFQ-R, children [6 to 11 years, 12 to 13 years] and adolescents or adults – pooled)[c]							
Physical wellbeing							
Age							
< 18 years	42	85.3 (17.4)	3.2 (3.0)	20	84.5 (18.2)	-1.4 (4.1)	4.56 [-3.95; 13.08]; 0.288
≥ 18 years	160	63.0 (26.4)	11.3 (1.3)	82	63.5 (26.4)	-3.4 (1.8)	14.78 [10.56; 19.00]; < 0.001 SMD [95% CI]: 0.92 [0.65; 1.20]
Total						Interaction:	p-value = 0.015[d]
FEV_1							
< 70%	102	56.5 (27.5)	16.6 (1.7)	52	60.7 (27.1)	-3.3 (2.3)	19.97 [14.36; 25.58]; < 0.001 SMD [95% CI]: 1.19 [0.83; 1.56]
≥ 70%	100	79.0 (19.5)	2.9 (1.4)	50	74.8 (23.7)	-2.8 (2.0)	5.70 [0.89; 10.51]; 0.020 SMD [95% CI]: 0.40 [0.06; 0.75]
Total						Interaction:	p-value = < 0.001[d]

Table 16: Subgroups (morbidity health-related quality of life) – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC (multipage table)

Study Outcome Characteristic Subgroup	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Mean change over 24 weeks mean[b] (SE)	N[a]	Values at baseline mean (SD)	Mean change over 24 weeks mean[b] (SE)	Mean difference [95% CI]; p-value[b]
Social functioning							
Sex							
Male	91	71.6 (16.1)	2.6 (1.1)	50	70.8 (18.5)	-2.5 (1.5)	5.04 [1.34, 8.74]; 0.008 SMD [95% CI]: 0.47 [0.12; 0.82]
Female	111	61.5 (20.1)	8.2 (1.3)	52	66.5 (18.2)	-2.7 (1.9)	10.87 [6.33; 15.40]; <0.001 SMD [95% CI]: 0.79 [0.45; 1.13]
Total						Interaction:	p-value = 0.032[d]
Health perceptions[e]							
Age							
< 18 years	13	72.7 (16.7)	16.7 (6.1)	10	64.4 (18.0)	12.6 (7.1)	4.02 [-13.58; 21.62]; 0.640
≥ 18 years	160	54.4 (23.6)	12.6 (1.3)	82	58.9 (21.3)	-3.9 (1.7)	16.49 [12.27; 20.71]; < 0.001 SMD [95% CI]: 1.04 [0.76; 1.32]
Total						Interaction:	p-value = 0.020[d]
FEV1							
< 70%	100	48.9 (23.5)	16.8 (1.6)	49	55.6 (22.7)	-4.0 (2.3)	20.77 [15.25; 26.3]; < 0.001 SMD [95% CI]: 1.29 [0.92; 1.66]
≥ 70%	73	65.3 (20.4)	5.8 (1.9)	43	64.1 (18.0)	-2.1 (2.4)	7.89 [1.83; 13.94]; 0.011 SMD [95% CI]: 0.49 [0.11; 0.88]
Total						Interaction:	p-value = 0.003[d]

Table 16: Subgroups (morbidity health-related quality of life) – RCT, direct comparison: ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC vs. placebo + BSC (multipage table)

Study Outcome Characteristic Subgroup	IVA/TEZ/ELX + IVA + BSC			Placebo + BSC			IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Mean change over 24 weeks mean[b] (SE)	N[a]	Values at baseline mean (SD)	Mean change over 24 weeks mean[b] (SE)	Mean difference [95% CI]; p-value[b]
a. Number of patients taken into account in the effect estimation; baseline values may be based on different patient numbers. b. Mean and SE (per treatment group) as well as MD, CI and p-value (group comparison): MMRM; adjusted for FEV1%, age (< 18 years vs. ≥ 18 years) and CFTR mutation group (≥ 1 RF-like mutation vs. no RF-like mutation); no corresponding adjustment in the subgroups divided by age. The effect represents the difference in the changes (from baseline) averaged over 24 weeks between the treatment groups. c. Higher (increasing) values indicate better symptoms/health-related quality of life; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100). b. MMRM with corresponding interaction term; adjusted for FEV1%, age (< 18 years vs. ≥ 18 years) and CFTR mutation group (≥ 1 RF-like mutation vs. no RF-like mutation). No corresponding adjustment was made when investigating the characteristic age. e. Domain for adolescents or adults; not provided for children [6 bis 11 years, 12 to 13 years]. BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane conductance regulator; CI: confidence interval; ELX: elexacaftor; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; MMRM: mixed-effects model with repeated measures; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; RF: residual function; SD: standard deviation; SE: standard error; SMD: standardized mean difference; TEZ: tezacaftor						

Health-related quality of life

Physical wellbeing, health perceptions

There were effect modifications by the characteristics age and FEV1 for each of the CFQ-R domains of physical functioning and health perceptions.

For patients ≥ 18 years of age or with an FEV1 < 70%, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with placebo + BSC for each of the CFQ-R domains of physical wellbeing and health perceptions. The SMD was considered to assess the relevance of the result. In each case, the 95% CI was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect in each case. For patients ≥ 18 years of age or with an FEV1 < 70%, there is a hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for each of these domains.

For patients with an FEV1 ≥ 70%, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with placebo + BSC for each of the CFQ-R domains of physical wellbeing and health perceptions. The SMD was considered

to assess the relevance of the result. The 95% CI was not fully outside the irrelevance range [−0.2; 0.2] in any of the domains. The effect could therefore not be inferred to be relevant in each case. For patients with an FEV1 ≥ 70%, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for either of these domains; an added benefit is therefore not proven in each case.

For patients < 18 years of age, there was no statistically significant difference between the treatment groups for the CFQ-R domains of physical wellbeing and health perceptions. For patients with < 18 years of age, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for either of these domains; an added benefit is therefore not proven in each case.

The company did not provide any information on possible dependencies between the subgroup characteristics. However, the data presented in the dossier showed that the patients aged 18 years or older included in the VX21-445-124 study tended to have a lower FEV1 at baseline. It was therefore assumed that the subgroup of patients under 18 years of age was more likely to include patients with an FEV1 ≥ 70% and that the subgroup of patients aged 18 years or older was more likely to include patients with an FEV1 < 70%. Due to the progressive course of cystic fibrosis, only age is considered below.

Social functioning

There was an effect modification by the characteristic of sex for the CFQ-R domain of social functioning.

For the social functioning domain of the CFQ-R, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC for female patients. The SMD was considered to assess the relevance of the result. The 95% CI was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. For this domain, there is a hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for female patients.

For the social functioning domain of the CFQ-R, there was a statistically significant difference in favour of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC versus placebo + BSC for male patients. The SMD was considered to assess the relevance of the result. The 95% CI was not fully outside the irrelevance range [−0.2; 0.2]. The effect can therefore not be inferred to be relevant. For this domain, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC for male patients; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, The different outcome categories and effect sizes were 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.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 17).

Determination of the outcome category for the morbidity outcomes

For the morbidity outcomes below, it could not be inferred from the dossier whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Morbidity

Pulmonary exacerbations

Based on the definition for the outcome pulmonary exacerbations (see Section I 4.1), both non-severe or non-serious events and severe or serious events were recorded. It can be assumed that pulmonary exacerbations that were defined as requiring new, or changed, antibiotic therapy and could be treated on an outpatient basis were less severe than pulmonary exacerbations that led to hospitalization. The number of patients with at least one severe pulmonary exacerbation was only about one-third of the number of patients with any kind of pulmonary exacerbation. Therefore, the outcome was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Severe pulmonary exacerbations

The outcome severe pulmonary exacerbations was operationalized as hospitalization due to pulmonary exacerbations. Hospitalization is a serious event. The outcome severe pulmonary exacerbations was assigned to the outcome category of serious/severe symptoms/late complications.

Symptoms (CFQ-R)

Respiratory symptoms

For the CFQ-R domain of respiratory symptoms, insufficient severity data were available for a classification as serious/severe. The respiratory symptoms domain of the CFQ-R was therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 17: Extent of added benefit at outcome level: ivacaftor/tezacaftor/elexacaftor + ivacaftor vs. BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC** **Event rate or proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0.5% vs. 0 RR: –	Lesser benefit not proven / added benefit not proven
Morbidity		
Pulmonary exacerbations	Event rate: 0.17 vs. 0.63 Rate ratio: 0.28 [0.15; 0.51] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: considerable
Severe pulmonary exacerbations	1.5% vs. 10.8% RR: 0.13 [0.04; 0.45] p = 0.001 Probability: hint	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% Added benefit, extent: major
Symptoms (CFQ-R)		
Respiratory symptoms	Mean change: 17.5 vs. -2.0 MD: 19.49 [15.52; 23.46] p < 0.001 SMD: 1.17 [0.91; 1.43][c] Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications 0.40 < CI_u Added benefit, extent: considerable
Digestive symptoms	Mean change: 0.0 vs. -2.7 MD: 2.73 [-0.64; 6.09] p = 0.113	Lesser benefit not proven / added benefit not proven
Weight (≥ 14 years)	Mean change: 2.2 vs. -2.8 MWD: 4.94 [-1.55; 11.42]; p = 0.135	Lesser benefit not proven / added benefit not proven

Table 17: Extent of added benefit at outcome level: ivacaftor/tezacaftor/elexacaftor + ivacaftor vs. BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC** **Event rate or proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life (CFQ-R)		
Physical wellbeing Age		
< 18 years	Mean change: 3.2 vs. -1.4 MD: 4.56 [-3.95; 13.08] p = 0.288	Lesser benefit not proven / added benefit not proven
≥ 18 years	Mean change: 11.3 vs. -3.4 MD: 14.78 [10.56; 19.00] p < 0.001 SMD: 0.92 [0.65; 1.20][c] Probability: hint	Outcome category: health-related quality of life $0.50 < CI_u$ Added benefit, extent: major
Emotional functioning	Mean change: 3.1 vs. -0.5 MD: 3.54 [0.85; 6.24] p = 0.010 SMD: 0.31 [0.07; 0.55][c]	Lesser benefit not proven / added benefit not proven
Vitality (≥ 14 years)	Mean change: 9.4 vs. -4.5 MD: 13.82 [9.76; 17.87] p < 0.001 SMD: 0.86 [0.60; 1.13][c] Probability: hint	Outcome category: health-related quality of life $0.50 < CI_u$ Added benefit, extent: major
Social functioning Sex		
Male	Mean change: 2.6 vs. -2.5 MD: 5.04 [1.34; 8.74] p = 0.008 SMD: 0.47 [0.12; 0.82][c]	Lesser benefit not proven / added benefit not proven
Female	Mean change: 8.2 vs. -2.7 MD: 10.87 [6.33; 15.40] p < 0.001 SMD: 0.79 [0.45; 1.13][c] Probability: hint	Outcome category: health-related quality of life $0.30 < CI_L \leq 0.50$ Added benefit, extent: considerable
Role functioning (≥ 14 years)	Mean change: 5.2 vs. -1.2 MD: 6.39 [2.98; 9.80] p < 0.001 SMD: 0.48 [0.22; 0.74][c] Probability: hint	Outcome category: health-related quality of life $0.20 < CI_L \leq 0.30$ Added benefit, extent: minor

Table 17: Extent of added benefit at outcome level: ivacaftor/tezacaftor/elexacaftor + ivacaftor vs. BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC** **Event rate or proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Body image	Mean change: 2.7 vs. -2.1 MD: 4.84 [1.28; 8.39] p = 0.008 SMD: 0.32 [0.08; 0.56][c]	Lesser benefit not proven / added benefit not proven
Eating problems	Mean change: 2.5 vs. -1.3 MD: 3.73 [0.40; 7.06] p = 0.028 SMD: 0.27 [0.03; 0.51][c]	Lesser benefit not proven / added benefit not proven
Treatment burden	Mean change: 6.7 vs. 1.8 MD: 4.86 [1.21; 8.51] p = 0.009 SMD: 0.32 [0.08; 0.56][c]	Lesser benefit not proven / added benefit not proven
Health perceptions (≥ 14 years) Age		
< 18 years	Mean change: 16.7 vs. 12.6 MD: 4.02 [-13.58; 21.62] p = 0.640	Lesser benefit not proven / added benefit not proven
≥ 18 years	Mean change: 12.6 vs. -3.9 MD: 16.49 [12.27; 20.71] p < 0.001 SMD: 1.04 [0.76; 1.32][c] Probability: hint	Outcome category: health-related quality of life 0.50 < CI_u Added benefit, extent: major
Side effects		
SAEs	6.8% vs. 2.9% RR: 2.32 [0.68; 7.90] p = 0.171	Greater/lesser harm not proven
Severe AEs	6.8% vs. 2.0% RR: 3.48 [0.81; 15.03] p = 0.075	Greater/lesser harm not proven
Discontinuation due to AEs	2.4% vs. 0% RR: –[d] p = 0.120	Greater/lesser harm not proven

Table 17: Extent of added benefit at outcome level: ivacaftor/tezacaftor/elexacaftor + ivacaftor vs. BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**IVA/TEZ/ELX + IVA + BSC vs. placebo + BSC** **Event rate or proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Rash (AEs)	22.0% vs. 1.0% RR: 22.39 [3.13; 160.13] RR: 0.04 [0.01; 0.32][e] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: considerable

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale of the outcome, the effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. If the CI for the SMD 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.
d. No presentation of RR and CI, as these are not informative.
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; CI_L: lower limit of confidence interval; CI_u: upper limit of confidence interval; ELX: elexacaftor; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; MD: mean difference; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference; TEZ: tezacaftor

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 18: Positive and negative effects from the assessment of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ Severe pulmonary exacerbations: hint of an added benefit – extent: major	
Non-serious/non-severe symptoms/late complications ▪ Pulmonary exacerbations: hint of an added benefit – extent: considerable ▪ Respiratory symptoms (symptoms CFQ-R): hint of an added benefit – extent: considerable	
Health-related quality of life (CFQ-R) ▪ Physical wellbeing ▫ Age (≥ 18 years): hint of an added benefit – extent: major ▪ Vitality (≥ 14 years): hint of an added benefit – extent: major ▪ Social functioning ▫ Sex (female): hint of an added benefit – extent: considerable ▪ Role functioning (≥ 14 years): hint of an added benefit – extent: minor ▪ Health perceptions (≥ 14 years) ▫ Age (≥ 18 years): hint of an added benefit – extent: major	
	Non-serious/non-severe side effects: ▪ Rash (AEs): hint of greater harm – extent: considerable
Only data on patients aged 6 years and older are available. No data are available for patients between 2 and 5 years of age.	
AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised	

The given research question covers patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, excluding an F508del and gating mutation, in the CFTR gene. Results from the VX21-445-124 study were available for patients aged 6 years and older. The company did not present any data for patients aged 2 to 5 years.

The characteristic age was an effect modifier for 2 domains of the CFQ-R. Due to the progressive course of cystic fibrosis, it can generally be assumed that younger patients (< 18 years) are at a less advanced disease stage. Therefore, the results on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT are derived separately by age below. For the CFQ-R domain of social functioning, the characteristic sex was an effect modifier. Since male and female patients are equally affected by the disease and

this effect modification was only evident in one domain of the CFQ-R, this characteristic was not considered further in the overall assessment.

Patients aged 18 years and older

For patients aged 18 years and older, the overall assessment of the results showed several positive effects of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC. For severe pulmonary exacerbations, there is a hint of a major added benefit. In addition, there is a hint of considerable added benefit for the outcome pulmonary exacerbations. It should be noted that this outcome included events that were already included in the outcome of severe pulmonary exacerbations, so these were not completely independent outcomes. There are hints of a major, considerable or minor added benefit in several CFQ-R domains on symptoms and health-related quality of life. This contrasts with a negative effect in the non-serious/non-severe side effects category based on a specific AE with considerable extent. This does not call into question the positive effects, in particular the major added benefit in severe pulmonary exacerbations and in several domains of health-related quality of life.

In summary, there is a hint of a major added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT BSC for patients with cystic fibrosis aged 18 years and older who have at least one non-Class I mutation, excluding an F508del and gating mutation, in the CFTR gene.

Patients aged 6 to 17 years

For patients aged 6 to 17 years, in terms of positive effects, there is a hint of a major added benefit for severe pulmonary exacerbations and a hint of a considerable added benefit for pulmonary exacerbations in the morbidity category. As described above, this outcome included events that were already included in the outcome of severe pulmonary exacerbations, so these were not completely independent outcomes. There are hints of a major, considerable or minor added benefit in several CFQ-R domains on symptoms and health-related quality of life. The domains of vitality and role functioning for health-related quality of life only applied to patients aged 14 to 17. It was unclear whether these effects were also transferable to younger patients, as the respective domains of the CFQ-R are not provided for younger age groups. The positive effects contrast with a negative effect in the non-serious/non-severe side effects category based on a specific AE with considerable extent.

The positive effects outweigh the negative effects. Besides the improvements in the outcomes on morbidity, there were positive effects in health-related quality of life. However, the CFQ-R domains of vitality and role functioning only allowed conclusions to be drawn for adolescents and thus only for a subpopulation of the age group < 18 years considered here. When balancing the results, it must be taken into account that younger patients generally have less pronounced symptoms due to the progressive course of cystic fibrosis. This was confirmed by the study results. It therefore remained unclear whether patients aged 6 to 17 years benefit

from the treatment in the short term (i.e. within the usual study duration in the therapeutic indication) to the same extent as patients aged 18 years and older. Data on the long-term course were also not available. Therefore, the overall extent was rated as non-quantifiable.

In summary, there is a hint of a non-quantifiable added benefit of ivacaftor/tezacaftor/ elexacaftor + ivacaftor versus the ACT BSC for patients with cystic fibrosis aged 6 to 17 years who have at least one non-Class I mutation, excluding an F508del and gating mutation, in the CFTR gene.

Patients aged 2 to 5 years

In its dossier, the company did not present any data for the assessment of the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor + BSC in comparison with the ACT BSC for patients aged 2 to 5 years. There is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT for these patients; an added benefit is therefore not proven.

The result of the assessment of the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT is summarized in Table 19.

Table 19: Ivacaftor/tezacaftor/elexacaftor + ivacaftor – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Patients with cystic fibrosis aged 2 years and older who have at least one non-Class I mutation, excluding an F508del and gating mutation, in the CFTR gene	BSC[b]	▪ Patients aged 2 to 5 years: added benefit not proven ▪ Patients aged 6 to 17 years: hint of a non-quantifiable added benefit[c] ▪ Patients 18 years of age and older: hint of major added benefit[c]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (in particular antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [as outlined in the German Remedies Directive] – while making full use of all possible dietary interventions).
c. Only patients aged 6 years and older with the following mutations were included in the VX21-445-124 study: 2789+5G>A, 3272-26A>G, 3849+10kbC>T, P5L, R117C, L206W, V232D, T338I, R347H, A445E, S945L, L997F, D1152H, G85E, R347P, L1077P, M1101K. It remains unclear whether the observed effects can be transferred to patients with other mutations.

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

The assessment described above deviates from that of the company, which derived an indication of a major added benefit across all age groups.

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

I 6 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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