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Ivacaftor/tezacaftor/elexacaftor and ivacaftor (cystic fibrosis, 6 to 11 years, F508del mutation, homozygous) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ivacaftor/Tezacaftor/Elexacaftor und Ivacaftor (zystische Fibrose, 6 bis 11 Jahre, F508del-Mutation, homozygot) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 May 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire—Revised
CFTR	cystic fibrosis transmembrane conductance regulator
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MF	minimal function
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination of ivacaftor/tezacaftor/elexacaftor plus ivacaftor as well as the benefit of the drug combination of ivacaftor plus ivacaftor/tezacaftor/elexacaftor. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 8 February 2022.

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) versus the appropriate comparator therapy (ACT) of lumacaftor/ivacaftor or tezacaftor/ivacaftor in combination with ivacaftor (hereinafter referred to as tezacaftor/ivacaftor + ivacaftor) in cystic fibrosis (CF) patients 6 to 11 years of age who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

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

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

Therapeutic indication	**ACT[a]**
CF patients 6 to 11 years of age who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor or tezacaftor/ivacaftor in combination with ivacaftor
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company designated both lumacaftor/ivacaftor and tezacaftor/ivacaftor + ivacaftor as the ACT, thus following the G-BA's specification.

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

Results

Evidence provided by the company

The check of completeness of the study pool revealed no relevant randomized controlled trial (RCT) for the comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT (lumacaftor/ivacaftor or tezacaftor/ivacaftor + ivacaftor) in the present therapeutic indication. Due to the absence of studies offering a direct comparison with the ACT, the company conducted an additional information retrieval for further investigations. For the ACT, however, the company has not submitted any information retrieval on nonrandomized studies.

As part of the information retrieval for additional investigations on the intervention, the company identifies the single-arm study VX18-445-106 as well as its single-arm extension study VX19-445-107. The VX18-445-106 study is a single-arm, open-label study on ivacaftor/tezacaftor/elexacaftor + ivacaftor treatment in CF patients 6 to 11 years of age who are either homozygous for the F508del mutation in the CFTR gene or heterozygous for the F508del mutation in the CFTR gene with a minimal function (MF) mutation on the 2nd allele. The company primarily uses the results of VX18-445-106 participants homozygous for the F508del mutation in the CFTR gene for its derivation of added benefit. It presents results from the VX19-445-107 study as supplementary information.

Furthermore, the company takes into account additional studies it conducted for the therapeutic indication. In Module 4 B, the company includes some of these studies in the analyses described below, which were submitted as supplementary information, as well as in its reasoning regarding the derivation of added benefit.

For an unadjusted indirect comparison of individual arms without common comparator, the company includes the single-arm study VX18-445-106 on the intervention as well as the VX15-661-113, VX13-809-011, and VX14-809-109 studies on the ACT options.

The company additionally bases its reasoning on the VX18-445-109 and VX17-445-103 studies enrolling older CF patients (≥ 12 years) who are homozygous for the F508del mutation in the CFTR gene, presuming that the results in the therapeutic indication are transferable from patients 12 years and older to children 6 to 11 years of age. The company mentions results from the VX18-445-109 study only in its reasoning for the derivation of added benefit, citing the associated benefit assessment procedure in the age group 12 years and older. The company has not submitted any analysis of this study's relevant information and results for the present benefit assessment.

In addition, the company carried out an adjusted indirect comparison across mutation types, where patients on either side of the comparison differed in mutation type. For the intervention, the company took into account the VX19-445-116 RCT, which investigates patients with heterozygous F508del mutation and an MF mutation on the 2nd allele and is the subject of benefit assessments A22-15 and A22-21. On the comparator side, the company took into account the VX14-809-109 RCT on lumacaftor/ivacaftor treatment in patients homozygous for

the F508del mutation in the CFTR gene. The comparator arms of both studies administered placebo in addition to basic CF therapy. On the basis of these studies, the company carried out an adjusted indirect comparison across mutation types, using placebo as the common comparator.

Usability of the presented analyses for the benefit assessment

Overall, the analyses presented by the company are unusable for the benefit assessment.

Single-arm study unsuitable for deriving an added benefit

Since they do not allow any comparison with the ACT, the single-arm study VX18-445-106 and its extension study VX19-445-107 are unsuitable for deriving an added benefit of ivacaftor/tezacaftor/elexacaftor+ ivacaftor.

Analyses submitted by the company as supplementary information for deriving added benefit are incomplete in content and have been inadequately evaluated

The analyses and information submitted by the company as supplementary information on the studies it included for comparing ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT are incomplete in content and have been inadequately evaluated. In particular, the company submitted incomplete and inadequately evaluated information on the comparability of (1) the patients included in the studies and (2) study results. However, a comparative analysis of patient characteristics and results from the different studies would be necessary for evaluating the relevance of the unadjusted indirect comparison of individual arms without common comparator as well as the transfer of results from older patients to the population of the present research question, in part to adequately discuss and take into account potential confounders (e.g. age, origin, period of study conduct, severity of disease, number of pulmonary exacerbations prior to study start, or prior and accompanying treatment). Furthermore, each of the company's analyses take into account the results for only some of the patient-relevant outcomes surveyed in the studies. Yet, evaluating the relevance of the submitted analyses for the benefit assessment requires analysing all available study data necessary for the evaluation. Irrespective of the completeness of the submitted results, the adjusted indirect comparison across mutation types is unusable for the benefit assessment because the company has not submitted any data supporting the transferability of effects (intervention versus comparator therapy) across mutation types.

Overall, the analyses submitted as supplementary information on the basis of the company's analysis are therefore deemed unsuitable for the benefit assessment.

Results on added benefit

No suitable data are available for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT in CF patients aged 6 to 11 years who are homozygous for the F508del mutation in the CFTR gene. Consequently, there is no

hint of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3 shows a summary of the probability and extent of 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**
CF patients 6 to 11 years of age who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor or tezacaftor/ivacaftor in combination with ivacaftor	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The result of this benefit assessment equally applies to ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor.

The G-BA decides on the added benefit.

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

2.2 Research question

The aim of this report is to assess the added benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (hereinafter referred to as ivacaftor/tezacaftor/elexacaftor + ivacaftor) versus the ACT of lumacaftor/ivacaftor or tezacaftor/ivacaftor in combination with ivacaftor (hereinafter referred to as tezacaftor/ivacaftor + ivacaftor) in CF patients 6 to 11 years of age who are homozygous for the F508del mutation in the CFTR gene.

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

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

Therapeutic indication	**ACT[a]**
CF patients 6 to 11 years of age who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor or tezacaftor/ivacaftor in combination with ivacaftor
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company has designated both lumacaftor/ivacaftor and tezacaftor/ivacaftor + ivacaftor as the ACT, thus following the G-BA's specification. The company additionally reports that the ACT as well as the drug to be assessed, ivacaftor/tezacaftor/elexacaftor + ivacaftor, were used in addition to individualized therapy to alleviate symptoms and improve the quality of life as in best supportive care. The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. Providing additional symptomatic treatment for the patient population is appropriate.

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on ivacaftor/tezacaftor/elexacaftor + ivacaftor (status: 15 November 2021)
- bibliographic literature search on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 15 November 2021)
- search in trial registries / study results databases on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 15 November 2021)

- search on the G-BA website for ivacaftor/tezacaftor/ivacaftor + ivacaftor (last search on 15 November 2021)
- bibliographical literature search on ACTs (last search on 15 November 2021)
- search in trial registries / trial results databases for studies on ACTs (last search on 15 November 2021)
- searches on the G-BA website for the ACTs (last search on 15 November 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 24 February 2022); see Appendix A of the full dossier assessment for the search strategies.

Concurring with the company, the check of completeness of the study pool revealed no relevant RCT for the comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT (lumacaftor/ivacaftor or tezacaftor/ivacaftor + ivacaftor) in the present therapeutic indication.

Due to the absence of studies offering a direct comparison with the ACT, the company conducted an additional information retrieval for further investigations. However, the company carried out a complete information retrieval for RCTs and nonrandomized studies only for the intervention. For the ACT, in contrast, the company conducted only an information retrieval for RCTs not taking into account any nonrandomized studies. Having conducted further studies with respect to the therapeutic indication, the company also included said studies in several of the analyses it submitted as supplementary information, taking into account nonrandomized studies both for the intervention and for the ACT (see Table 5). The company did not carry out a systematic literature search in this area, reasoning that, to date, it is the only company to offer CFTR modulators and that all relevant phase III studies are its own. Therefore, the company deems any systematic literature searches to be unlikely to deliver additional relevant insights.

Irrespective of the described shortcomings in information retrieval, the data presented in the company's dossier do not allow deriving any added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT in CF patients 6 to 11 years old who are homozygous for the F508del mutation in the CFTR gene. This is particularly due to the analyses presented in the company's dossier on the comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT being incomplete in content and having been inadequately evaluated and therefore being deemed unsuitable for the benefit assessment according to the company's evaluation. For each of the various analyses, the company has failed to submit a complete evaluation of all relevant information on potentially relevant studies. Furthermore, each of its analyses take into account only results from some of the patient-relevant outcomes surveyed in the studies. Yet, evaluating the relevance of the submitted analyses for the benefit assessment requires analysing

all available study data necessary for the evaluation. The analyses presented by the company as well as their usability for the benefit assessment are discussed in more detail below.

Evidence provided by the company

In the context of the information retrieval on further investigations on the intervention, the company identifies the single-arm study VX18-445-106 [3] as well as its single-arm extension study VX19-445-107 [4]. The company uses the VX18-445-106 study for deriving added benefit. It has presented results from the VX19-445-107 study as supplementary information.

Furthermore, the company takes into account additional studies it conducted for the therapeutic indication. In Module 4 B, the company has included these studies in some of the analyses which it subsequently described and submitted as supplementary information, and in its reasoning regarding the derivation of added benefit.

To carry out an unadjusted indirect comparison of individual arms without common comparator, the company included the single-arm study VX18-445-106 with the intervention as well as the studies VX15-661-113 [5], VX13-809-011 [6], and VX14-809-109 [7] on the ACT options. These analyses presented by the company are based on individual patient data surveyed in the studies on ivacaftor/tezacaftor/elexacaftor + ivacaftor treatment or on the ACT.

The company additionally bases its reasoning on the VX18-445-109 [8] and VX17-445-103 [9] studies on older CF patients (≥ 12 years) who are homozygous for the F508del mutation in the CFTR gene because the company assumes the results in the therapeutic indication to be transferable from patients 12 years and older to children 6 to 11 years. The company mentions results from the VX18-445-109 study only in its reasoning for the derivation of added benefit, citing the associated benefit assessment procedure in the age group 12 years and older [10]. The company has not submitted any analysis of this study's relevant information or results for the present benefit assessment.

In addition, the company has carried out an adjusted indirect comparison across mutation types, where patients on either side of the comparison differed in mutation type. For the intervention side, the company took into account the VX19-445-116 RCT [11], which investigates patients with heterozygous F508del mutation and an MF mutation on the 2nd allele and is the subject of benefit assessments A22-15 and A22-21 [12,13]. On the comparator side, the company takes into account the VX14-809-109 RCT [7] on lumacaftor/ivacaftor treatment of patients homozygous for the F508del mutation in the CFTR gene. The comparator arms of both studies administered placebo in addition to basic CF therapy. On the basis of these studies, the company carried out an adjusted indirect comparison across mutation types, using placebo as the common comparator.

Table 5 provides an overview of the studies taken into account by the company in the analyses presented as supplementary information or cited in its reasoning.

Table 5: Studies included by the company in supplementary analyses or cited in its reasoning

Study	Design	Treatment duration	Interventions	Period of study	Mutation type	Age group
Unadjusted indirect comparison of individual arms without common comparator						
Study on the intervention						
VX18-445-106[a]	Single-arm	24 weeks	IVA/TEZ/ELX+IVA (N = 29[b])	10/2018–8/2020	▪ F508del mutation, homozygous	6–11 years
Information on the ACT						
VX15-661-113[a, c]	Single-arm	24 weeks	TEZ/IVA+IVA (N = 61[b])	11/2017–9/2018	▪ F508del mutation, homozygous	6–11 years
VX13-809-011[a]	Single-arm	24 weeks	LUM/IVA (N = 58)	1/2015–10/2015	▪ F508del mutation, homozygous	6–11 years
VX14-809-109[d]	RCT[e]	24 weeks	LUM/IVA (N = 104) vs. placebo (N = 102)	7/2015–9/2016	▪ F508del mutation, homozygous	6–11 years
Transfer of results from older patients (≥ 12 years) to the target population (6 to 11 years)						
VX18-445-109[f]	RCT	24 weeks	IVA/TEZ/ELX+IVA (N = 88) vs. IVA/TEZ+IVA (N = 88)	10/2019–7/2020	▪ F508del mutation, homozygous	≥ 12 years
VX17-445-103[g]	RCT	4 weeks	IVA/TEZ/ELX+IVA (N = 56) TEZ/IVA+IVA (N = 52)	8/2018–12/2019	▪ F508del mutation, homozygous	≥ 12 years
Adjusted indirect comparison across mutations (placebo as a common comparator)						
Study on the intervention						
VX19-445-116[h]	RCT	24 weeks	IVA/TEZ/ELX+IVA (N = 60) vs. placebo (N = 61)	6/2020–5/2021	▪ F508del, MF mutation, heterozygous	6–11 years
Study on the ACT						
VX14-809-109[d]	RCT	24 weeks	LUM/IVA (N = 104) vs. placebo (N = 102)	7/2015–9/2016	▪ F508del mutation, homozygous	6–11 years

a. Information relates to the study's Part B.
b. Subpopulation of patients who are homozygous for the F508del mutation in the CFTR gene.
c. For 18 of the 61 children (29.5%), the dosage of the intervention departed from the specifications of the Summary of Product Characteristics (SPC) (see discussion in benefit assessment A20-107 [14]).
d. The study is the subject of the benefit assessment A18-08 [15].
e. For the unadjusted comparison of individual arms, the company took into account only the study's intervention arm (LUM/IVA).
f. The study is the subject of the addendum on Commission A21-03 [16] (addendum to the benefit assessment for Commission A20-77 [17].
g. With a randomized treatment phase of 4 weeks, the study is unsuitable for transferring results in the benefit assessment (also see benefit assessment on Commission A20-77 [17]).
h. The study is the subject of the benefit assessment on Commissions A22-15/A22-21 [12,13].

CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; MF: minimal function; N: number of included patients; RCT: randomized controlled trial; TEZ: tezacaftor

Usability of the presented analyses for the benefit assessment

Overall, the analyses presented by the company are unusable for the benefit assessment. The primary study used by the company to derive added benefit, VX18-445-106, is unusable on the grounds of being a single-arm study which does not allow any comparison with the ACT. The analyses presented as supplementary information in Module 4 B of the company's dossier regarding the comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT are unusable particularly due to the fact that they are incomplete in content and have been inadequately evaluated. For each of the various analyses, the company has failed to submit a complete evaluation of all relevant information on potentially relevant studies. Furthermore, each of its analyses take into account only results from some of the patient-relevant outcomes surveyed in the studies. Yet, evaluating the relevance of the submitted analyses for the benefit assessment requires analysing all available study data necessary for the evaluation. For the cross-mutations approach, the company has not submitted any data supporting the transferability of effects (intervention versus comparator therapy) across different mutation types. Overall, the analyses submitted as supplementary information on the basis of the company's analysis are therefore deemed unsuitable for the benefit assessment.

Details on the usability of the analyses presented by the company are discussed in more detail below.

Single-arm study unsuitable for deriving an added benefit

The VX18-445-106 study is a single-arm, open-label study on ivacaftor/tezacaftor/elexacaftor + ivacaftor treatment in CF patients 6 to 11 years of age who are either homozygous for the F508del mutation in the CFTR gene or heterozygous for the F508del mutation in the CFTR gene, with an MF mutation on the 2nd allele. The study was conducted in 2 parts (Part A and Part B) which differ in treatment duration (Part A: 15 days; Part B: 24 weeks). For its benefit assessment, the company used results from Part B of the study on the subpopulation of children who are homozygous for the F508del mutation in the CFTR gene. The single-arm study VX19-445-107 is an ongoing extension study of VX18-445-106. The company presents as supplementary information results of an interim analysis at Week 24 of this extension study (corresponding to treatment week 48 overall), based on the entire study population, irrespective of mutation type.

Since they do not allow a comparison with the ACT, the single-arm study VX18-445-106 and its extension study VX19-445-107 are unsuitable for deriving an added benefit of ivacaftor/tezacaftor/elexacaftor+ ivacaftor.

Analyses submitted by the company as supplementary information for deriving added benefit incomplete in content and have been inadequately evaluated

As described above, the company failed to submit complete information regarding each of the potentially relevant studies for the analyses submitted as supplementary information, and it used results only from some of the patient-relevant outcomes surveyed in the studies. Yet evaluating

the relevance of the presented analyses for the benefit assessment requires an analysis of all available data necessary for the evaluation.

The information submitted by the company on the comparability of study participants and results is incomplete in content and inadequately evaluated. However, a comparative analysis of patient characteristics and results of the different studies is needed, particularly for evaluating the relevance of the unadjusted indirect comparison of individual arms without common comparator as well as the transfer of results from older patients to the population of the present research question. This is a prerequisite for adequately discussing and taking into account potential confounders, i.e. factors which are related to both treatment and outcomes and hence might distort treatment effects. Potential confounders may include age, sex, origin, period of study conduct, severity of disease, number of pulmonary exacerbations prior to study start, or prior and concomitant treatment. On the basis of the incomplete and inadequately evaluated information presented by the company, it is impossible to assess the extent to which the results of the submitted analyses have been influenced by potential confounders.

Furthermore, each of the company's analyses submitted as supplementary information take into account only results for some of the patient-relevant outcomes surveyed in the studies. Table 6 below provides an overview of the patient-relevant outcomes taken into account by the company in the analyses. Patient-relevant outcomes which were generally surveyed in the respective relevant studies but were disregarded in Module 4 B of the company's dossier are marked as "no". Patient-relevant outcomes from which the company's analyses used (some) results are marked as "yes".

Table 6: Results on patient-relevant outcomes taken into account in the company's supplementary analyses

Outcome	Unadjusted indirect comparison of individual arms without common comparator	Transfer of results from older patients (≥ 12 years) to the target population (6 to 11 years)[a]	Adjusted indirect comparison across mutation types (common comparator of placebo)
Mortality			
All-cause mortality	No	No	No
Morbidity			
Pulmonary exacerbations			
Definition 1[b]	No[c]	-[d]	-[d]
Definition 2[e] (AEs)	No	No	Yes
Definition 2[e] (SAEs)	No	No	No
CFQ-R: respiratory domain	Yes[f]	No	Yes[f, g]
CFQ-R: further symptoms domains	No	No	No
Health-related quality of life			
CFQ-R: health-related quality of life domains	No	No	No
Side effects			
AEs	No	No	Yes
SAEs	No	No	Yes
Discontinuation due to AEs	No	No	Yes

a. The company has presented only the results from the single-arm VX18-445-106 study (6–11 years), arguing that the prerequisites for transferring the results from the VX18-445-109 RCT (≥ 12 years) are generally met and results are sufficiently similar. The company has not presented an analysis of the results.
b. At least 4 predefined symptoms/signs had to occur which required new or changed antibiotic therapy (e.g. change in sputum, new/worsened haemoptysis, increased dyspnoea, fever > 38°C). For this definition, the company's dossier presents analyses both on the number of patients with pulmonary exacerbations and on the number of patients hospitalized due to pulmonary exacerbations.
c. The company has presented only a descriptive comparison of the number of pulmonary exacerbations for the VX18-445-106 study (IVA/TEZ/ELX + IVA) versus the VX14-809-109 study (LUM/IVA), without providing an effect estimator. In the VX13-809-011 (LUM/IVA) and VX15-661-113 (TEZ/IVA + IVA) studies, the outcome was not surveyed in this operationalization (definition 1).
d. Not all studies surveyed the outcome in this definition.
e. Recorded through the analysis of the PT "infective pulmonary exacerbation of cystic fibrosis".
f. Continuous analyses (MMRM method).
g. In addition to continuous analyses, the company has presented responder analyses on an MID of 4 points. The company has not submitted any analyses on the response criterion of ≥ 15 points (corresponding to 15% of the scale range).

AE: adverse event; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire – Revised; ELX: elexacaftor; IVA: ivacaftor; LUM: lumacaftor; MID: minimal important difference; MMRM: mixed model repeated measurement; PT: preferred term; SAE: serious adverse event; TEZ: tezacaftor

For the unadjusted indirect comparison of individual arms without common comparator, the company used only individual selected outcomes from the morbidity category. An analysis of the results for their transfer from older patients (≥ 12 years) to the population in the present

therapeutic indication is completely missing. The company has not presented complete results for the adjusted indirect comparison across mutations, which is unusable irrespective of the completeness of the presented results for the benefit assessment. In particular, no complete analyses on symptoms and health-related quality of life have been provided; such analyses could have been prepared based on the studies' surveys using the Cystic Fibrosis Questionnaire – Revised (CFQ-R).

Below, details on the inadequate evaluation of data as well as any further aspects precluding the use of the data in the benefit assessment are discussed separately for the various analyses submitted by the company as supplementary information.

Unadjusted indirect comparison of individual arms without common comparator

Deriving added benefit on the basis of single-arm studies is possible only in case of very large (dramatic) effects in comparison with the ACT. Yet this would require a complete analysis and discussion of the data from the single-arm studies on the intervention and the ACT (see discussion above). Module 4 B of the company's dossier, however, fails to include a complete analysis of all relevant information on the potentially relevant studies. For instance, patient characteristics, including information on prior and concomitant therapies, have been inadequately evaluated for the potentially relevant studies. The company has submitted comprehensive information in this regard only for the single-arm study VX18-445-106 on ivacaftor/tezacaftor/elexacaftor + ivacaftor treatment. For the studies on the ACT (VX15-661-113, VX13-809-011, and VX14-809-109), the company limits its discussion to what are, in its opinion, the "most important parameters on demographics and baseline characteristics" (see Module 4 B, Section 4.3.2.3.2.1, Table 4-47) and assumes the study populations to be comparable. The company does not discuss possible confounders. But even a superficial look at the single-arm studies reveals that they differ, e.g. with regard to the period of study conduct (see Table 5). This difference can result in dissimilarities regarding prior treatment (e.g. with CFTR modulators), which in turn might be associated with a divergent baseline risk for the occurrence of pulmonary exacerbations. The influence of this and other potential confounders cannot be assessed due to the inadequate evaluation of the study data in the dossier.

Another aspect of the inadequate appraisal of data relates to the VX15-661-113 study presented by the company. From this study, the company includes in its analyses the entire subpopulation of patients homozygous for the F508del mutation in the CFTR gene (N = 61). However, as already pointed out in dossier assessment A20-107, 18 out of the 61 patients (29.5%) in the study were treated in departure from approval, being underdosed [14]. Hence, analysing the data on patients treated in compliance with approval would have been both necessary for the present benefit assessment and feasible for the company.

In addition, the company has submitted results only for the 2 patient-relevant outcomes from the morbidity category, pulmonary exacerbations as well as the respiratory symptoms domain

from the CFQ-R (see Table 6). Analyses of results on further morbidity outcomes, health-related quality of life, and adverse events (AEs) are completely missing.

For the outcome of pulmonary exacerbations, the company has presented results only from the studies VX18-445-106 and VX14-809-109, arguing that pulmonary exacerbations were surveyed as a morbidity outcome only by these 2 studies. Although these 2 studies exhibit a numeric difference in favour of the intervention (see Module 4 B, Table 4-82), the company provides only a descriptive comparison of the percentages of patients with event, not discussing or taking into account potential confounders. For this outcome, the company has not provided any results on an operationalization which would be comparable across all studies. However, an analysis of the preferred term (PT) "infectious pulmonary exacerbations of cystic fibrosis" would have been possible on the basis of the AEs and serious adverse events (SAEs) across all single-arm studies because results on this operationalization are available for all studies.

Overall, the company's approach of carrying out an unadjusted indirect comparison of individual arms without common comparator for the benefit assessment is plausible due to the lack of directly comparative studies in children 6 to 11 years of age, but on the basis of the company's analysis, the unadjusted comparison of individual arms is deemed unsuitable for the benefit assessment.

Transfer of results from older patients (≥ 12 years) to the target population (6 to 11 years)

In the company's view, the results on ivacaftor/tezacaftor/elexacaftor + ivacaftor treatment in comparison with the ACT can be transferred to the age group of the present benefit assessment and used for deriving added benefit, particularly from the VX18-445-109 study (subject matter of the addendum to commission A21-03 [16]). Based on this study, the G-BA has derived an indication of major added benefit for CF patients 12 years and older who are homozygous for the F508del mutation in the CFTR gene [18]. The company reasons that results are transferable due to a mechanism of action it deems comparable, the clinical picture of the disease, and sufficiently similar results being found in patients from the different age groups. However, the company has not presented an analysis of the data relevant for transferring the results (see Table 6). The company would have been able to compare study data since for both age groups, data from studies conducted by the company are available on both the intervention and the ACT (see Table 5). Nevertheless, the company has submitted neither such an analysis of the study, intervention, and patient characteristics nor of the results on all patient-relevant outcomes for the 2 age groups. This approach would additionally require discussing and taking into account potential confounders which might affect the transferability of results.

In the present indication, it would further be useful to analyse the youngest age stratum of the VX18-445-109 study (12 to 18 years) because CF is a progressive disorder and transferability seems more questionable as the age difference between the population to be investigated and the population from which the data are to be transferred increases. In its reasoning on the derivation of added benefit, however, the company mentions results only from the total population of the VX18-445-109 study.

While overall, the company's approach of transferring study results from older patients to the population of the present research question is plausible in view to the lack of comparative studies in children aged 6 to 11 years, this approach is deemed unsuitable for the benefit assessment on the basis of the company's analyses.

Adjusted indirect comparison across mutation types

Furthermore, the company has submitted an adjusted indirect comparison across mutation types, taking into account the VX19-445-116 and VX19-809-109 studies using placebo as the common comparator (see Table 5). Both studies enrolled CF patients 6 to 11 years of age, but participants differed with regard to their mutation types: While children in the VX14-809-109 study were homozygous for the F508del mutation in the CFTR gene and therefore corresponded to the target population, the VX19-445-116 study included children who were heterozygous for the F508del mutation and had an MF mutation on the 2nd allele.

Regarding the transferability of added benefit between different mutation types, the company's dossier makes a primarily qualitative argument through the intervention's principle of action. In its discussion of the transferability of added benefit between different mutation types, the company argues that the effect of ivacaftor/tezacaftor/elexacaftor + ivacaftor treatment is based on the protein product of the CFTR allele with the F508del mutation and is largely independent from the mutation on the 2nd allele of the CFTR gene. The company maintains that study results for patients with heterozygous F508del mutation and an MF mutation on the 2nd allele can be transferred as a "conservative estimate" to patients with at least one F508del mutation because the protein product of the CFTR allele with the MF mutation is not affected by ivacaftor/tezacaftor/elexacaftor + ivacaftor treatment. The company argues that due to the effectiveness of ivacaftor/tezacaftor/elexacaftor + ivacaftor being dependent on F508del-CFTR, the effect of ivacaftor/tezacaftor/elexacaftor + ivacaftor is presumably no stronger in children with heterozygous F508del mutation and an MF mutation on the 2nd allele than in children homozygous for the F508del mutation in the CFTR gene. Furthermore, the company cites (1) the broad approval for ivacaftor/tezacaftor/elexacaftor + ivacaftor for all patients with at least one F508del mutation, (2) clinical studies on the intervention in patients aged 12 years and older, and (3) evaluation by clinical experts.

The company has not submitted any data on the patients relevant for transfer of evidence given the currently available data to support the transferability of effects (intervention versus comparator therapy) across different mutation types. Consequently, the information submitted by the company does not allow transferring study results from patients who are heterozygous for the F508del mutation and have an MF mutation on the 2nd allele to the patient group in the present research question. Irrespective of the above, the company has also not submitted a complete analysis of results on patient-relevant outcomes from the adjusted indirect comparison across mutation types (see Table 6).

Summary

Overall, the data presented in the company's dossier are unsuitable for deriving any conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor. This is due, firstly, to only single-arm studies being available on ivacaftor/tezacaftor/elexacaftor + ivacaftor treatment in the population of the present research question and these studies not allowing any comparison versus the ACT. Secondly, the analyses presented as supplementary information by the company, comparing ivacaftor/tezacaftor/elexacaftor + ivacaftor with the ACT, are incomplete in content and have been inadequately evaluated. For each of the various analyses, the company has failed to submit a complete evaluation of all relevant information on potentially relevant studies. Furthermore, each of its analyses take into account results only from some of the patient-relevant outcomes surveyed in the studies. The data submitted in the company's dossier do not permit an adequate evaluation of the relevance of the results or of the analyses presented as supplementary information for the benefit assessment. For the adjusted indirect comparison across mutation types, the company has not submitted any data supporting the transferability of effects (intervention versus comparator therapy) across different mutation types. Overall, the analyses presented as supplementary information by the company are therefore unusable for the benefit assessment.

2.4 Results on added benefit

No suitable data are available for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT in CF patients aged 6 to 11 years who are homozygous for the F508del mutation in the CFTR gene. Consequently, there is no hint of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 7 summarizes the result of the assessment of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT.

Table 7: Ivacaftor/tezacaftor/elexacaftor + ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients 6 to 11 years of age who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor or tezacaftor/ivacaftor in combination with ivacaftor	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The result of this benefit assessment equally applies to ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor.

The assessment described above deviates from the assessment by the company, which derived, overall, a hint of considerable added benefit on the basis of the data from the single-arm study VX18-445-106 and the extension study VX19-445-107 as well as on the analyses presented as supplementary information.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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