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

Addendum to Commission A20-77[1]

Addendum

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[1] Translation of addendum A21-03 *Ivacaftor (Kombination mit Ivacaftor/Tezacaftor/Elexacaftor; zystische Fibrose, ab 12 Jahre, F508del-Mutation, homozygot) – Addendum zum Auftrag A20-77* (Version 1.0; Status: 1 February 2021). 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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Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

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

IQWiG employees involved in the addendum

- Erika Penner
- Katharina Biester
- Petra Kohlepp
- Daniela Preukschat
- Anke Schulz

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	cystic fibrosis transmembrane conductance regulator
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)
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SOC	System Organ Class
SPC	Summary of Product Characteristics

1 Background

On 12 January 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-77 (Ivacaftor – Benefit assessment according to §35a Social Code Book V) [1].

No suitable data were available for the research question of dossier assessment A20-77 for the assessment of the added benefit of ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor (hereinafter referred to as "ivacaftor + ivacaftor/tezacaftor/elexacaftor") in comparison with the appropriate comparator therapy (ACT) in patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") had identified with its search the randomized controlled trial (RCT) VX18-445-109 [3,4], which was sponsored by the company and compared ivacaftor + ivacaftor/tezacaftor/elexacaftor with ivacaftor + tezacaftor/ivacaftor in CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. According to the company, the results of this study had not yet been available by the time the dossier for the benefit assessment of ivacaftor was submitted to the G-BA on 26 August 2020. In the commenting procedure, the company subsequently submitted the results of this study, as announced in the dossier [5-9].

The G-BA commissioned IQWiG with the assessment of study VX18-445-109 (including the subgroup analyses) and the responder analyses subsequently submitted, taking into account the information provided in the dossier.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

In accordance with the commission, the VX18-445-109 study listed in Table 1 is assessed in the sections below. This study is relevant for the benefit assessment of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with the ACT (ivacaftor + ivacaftor/tezacaftor) in patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

Table 1: Study pool – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
VX18-445-109	No	Yes	No	Yes [7]	Yes [3,4]	No

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.

CSR: clinical study report; RCT: randomized controlled trial; vs.: versus

2.1 Study design and study characteristics

Table 2 and Table 3 describe the study used for the benefit assessment.

Table 2: Characteristics of the included study – RCT, direct comparison: – ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
VX18-445-109	RCT, double-blind, parallel	Patients with CF ≥ 12 years with homozygous F508del mutation in the CFTR gene und FEV1[b] ≥ 40% and ≤ 90% at screening	▪ Ivacaftor + ivacaftor/tezacaftor/ elexacaftor[c] (N = 88) ▪ Ivacaftor + ivacaftor/tezacaftor[c] (N = 88)	▪ Screening: 28 days ▪ TEZ/IVA run-in: 28 days ▪ Treatment: 24 weeks[d] ▪ Follow-up observation of AEs[e]: 28 days	35 centres in Australia, Belgium, Germany and United Kingdom 10/2019–7/2020	Primary: change in CFQ-R respiratory domain Secondary: all-cause mortality, symptoms, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. In% of predicted normal.
c. Treatment was against the background of basic medication.
d. At the week 24 visit, patients who had completed the study visits in the treatment phase had the option of either remaining in the treatment arm and conducting the follow-up visit for the observation of AEs, or switching to an open-label extension study. In principle, patients who discontinued the study medication during the treatment phase also had this option. However, in the VX18-445-109 study, all patients with discontinuation of the study medication during the treatment phase discontinued participation in the study and therefore did not switch to the open-label extension study.
e. For study participants who were included in the open-label extension study after completion of the 24-week treatment, participation in the AE follow-up observation was not required.

AE: adverse event; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis-Questionnaire Revised; CFTR: cystic fibrosis transmembrane conductance regulator; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; N: number of randomized patients; RCT: randomized controlled trial; TEZ: tezacaftor; vs.: versus

Table 3: Characteristics of the intervention – RCT, direct comparison: – ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor

Study	Intervention	Comparison
VX18-445-109	Ivacaftor 150 mg, orally, 1 tablet daily (evening)[a, b] + ivacaftor/tezacaftor/elexacaftor (75 mg/50 mg/100 mg), orally, 2 tablets daily (morning)[a, b] + placebo for ivacaftor/tezacaftor, orally, 1 tablet daily (morning)	Ivacaftor 150 mg, orally, 1 tablet daily (evening)[a, b] + ivacaftor/tezacaftor (150 mg/100 mg), orally, 1 tablet daily (morning)[a, b] + placebo for ivacaftor/tezacaftor/elexacaftor , orally, 2 tablets daily (morning)
	Allowed prior and concomitant treatment ▪ stable medication for the treatment of CF 28 days before the start of the study until the end of the study ▪ prednisone or prednisolone ≤ 10 mg/day permanently or ≤ 60 mg/day for up to 5 days **Non-permitted pretreatment** ▪ changes in therapy (including antibiotics) for pulmonary disease within 28 days prior to the start of the run-in phase ▪ continued or previous participation in a study of an investigational therapy within the last 28 days or 5 half-lives (whichever is longer) prior to screening **Non-permitted concomitant treatment** ▪ moderate and strong CYP3A inducers and inhibitors (except ciprofloxacin) ▪ other CFTR modulators (except study medication)[c] ▪ start of long-term therapy with new medication	

a. Treatment was against the background of basic medication (see allowed prior and concomitant treatment in this table).
b. No dose adjustments were allowed, dose interruptions were possible.
c. The use of CFTR modulators from the company Vertex was allowed until the start of the run-in phase.

CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; CYP3A: cytochrome P450 3A; RCT: randomized controlled trial; vs.: versus

Study design

Study VX18-445-109 is a randomized, double-blind study comparing ivacaftor + ivacaftor/ tezacaftor/elexacaftor with ivacaftor + ivacaftor/tezacaftor.

The study included CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. The diagnosis of CF had to be confirmed by the investigator, but it is unclear what criteria were used to make the diagnosis. The patients additionally had to have a forced expiratory volume in 1 second (FEV1) of ≥ 40% and ≤ 90% of predicted normal for age, sex, and height at screening. Patients with infection of the lungs with organisms associated with a more rapid decline in pulmonary status were excluded.

In the study, a total of 176 patients were randomized in a 1:1 ratio either to treatment with ivacaftor + ivacaftor/tezacaftor/elexacaftor (N = 88) or to ivacaftor + ivacaftor/tezacaftor

(N = 88). Randomization was stratified according to FEV1 (< 70%/≥ 70%), age (< 18/≥ 18 years) and use of a CFTR modulator (yes/no).

In the run-in phase, all patients received ivacaftor + ivacaftor/tezacaftor. Following the run-in phase, patients in both treatment arms were treated with either ivacaftor + ivacaftor/tezacaftor/ elexacaftor or ivacaftor + ivacaftor/tezacaftor in compliance with the Summary of Product Characteristics (SPC) [10]. The patients also received matching placebo tablets in both study arms. In addition, concomitant therapy for CF was administered in both study arms.

The primary outcome was operationalized using the absolute change in the respiratory symptoms domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R). Patient-relevant secondary outcomes were all-cause mortality and outcomes of the categories of symptoms, health-related quality of life, and adverse events (AEs).

Following the 24-week treatment phase, patients had the option of participating in an open-label extension study.

Characteristics of the study population

Table 4 shows the characteristics of the patients in the study included.

Table 4: Characteristics of the study population – RCT, direct comparison: – ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor (multipage table)

Study Characteristic Category	**IVA + IVA/TEZA/ELEXA[a] N[b] = 87**	**IVA + IVA/TEZA[a] N[b] = 88**
VX18-445-109		
Age [years], mean (SD)	28 (12)	28 (11)
Age group, n (%)		
< 18 years	25 (29)	27 (31)
≥ 18 years	62 (71)	61 (69)
Sex [F/M], %	49/51	51/49
Family origin, n (%)		
White	85 (98)	88 (100)
Other	3 (3)	0 (0)
Region, n (%)		
Europe	74 (84)	71 (82)
Australia	14 (16)	16 (18)
FEV_1[c] at baseline, n (%)		
< 40%	6 (7)	2 (2)
≥ 40 to < 70%	50 (58)	52 (59)
≥ 70 to ≤ 90%	26 (30)	29 (33)
> 90%	5 (6)	5 (6)
BMI [kg/m^2], mean (SD)	21.2 (3.4)	21.9 (3.9)
BMI z-score, mean (SD)	ND	ND
Sweat chloride concentration [mmol/L], mean (SD)	89.0 (12.2)	89.8 (11.7)
Treatment before study inclusion[d], n (%)		
Inhaled antibiotics	51 (59)	57 (65)
Inhaled bronchodilators	75 (86)	79 (90)
Inhaled hypertonic saline solution	53 (61)	52 (59)
Inhaled corticosteroids	56 (64)	58 (66)
Pseudomonas aeruginosa infection[e], n (%)	59 (68)	58 (66)
Treatment discontinuation, n (%)	1 (1)	2 (2)
Study discontinuation, n (%)	1 (1)	2 (2)

a. Treatment was against the background of basic medication for the treatment.
b. Number of patients in the FAS population, randomization of 88 vs. 88 patients.
c. In % of predicted normal.
d. Medication inhaled up to 56 days before first dose of study medication.
e. Within 2 years before screening.

BMI: body mass index; ELEXA: elexacaftor; F: female; FAS: full analysis set; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; M: male; n: number of patients in the category; N: number of patients who had received at least one dose of the study medication (full analysis set); ND: no data; RCT: randomized controlled trial; SD: standard deviation; TEZA: tezacaftor; vs.: versus

The demographic and clinical characteristics of the patients were largely balanced between the 2 study arms. Almost all patients were white; the mean age was 28 years. The proportion of men and women was balanced. The majority (83%) of patients included were from Europe.

According to the inclusion criteria of the study, patients had to have an FEV1 (in % of predicted normal) of ≥ 40% and ≤ 90% at screening. In deviation from this, the study also included patients who had an FEV1 of < 40% or > 90% at baseline. The proportion of patients outside the predefined range was 13% in the intervention arm and 8% in the comparator arm.

Approximately 2 thirds of the patients had *Pseudomonas aeruginosa* infection at study entry. Most of the included patients had been treated with inhaled symptomatic therapy prior to study entry.

Concomitant symptomatic treatment

Table 5 shows the symptomatic medication before the first dose of the study treatment and the concomitant symptomatic treatment used during the study.

Table 5: Treatment before first dose of study treatment and concomitant treatment (≥ 15% in at least one study arm) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor/tezacaftor

VX18-445-109	IVA + IVA/TEZA/ELEXA[a]		IVA + IVA/TEZA[a]	
	N[b] = 87	N[b] = 87	N[b] = 88	N[b] = 88
	Treatment before start of study[c] n (%)	Concomitant treatment (%)	Treatment before start of study[c] n (%)	Concomitant treatment n (%)
Drug therapy[d]				
Pancreatin	80 (92.0)	80 (92.0)	84 (95.5)	84 (95.5)
Dornase alfa	62 (71.3)	62 (71.3)	72 (81.8)	72 (81.8)
Sodium chloride	65 (74.7)	65 (74.7)	67 (76.1)	67 (76.1)
Salbutamol	56 (64.4)	57 (65.5)	57 (64.8)	57 (64.8)
Azithromycin	49 (56.3)	48 (55.2)	44 (50.0)	47 (53.4)
Colistimethate sodium	35 (40.2)	36 (41.4)	28 (31.8)	28 (31.8)
Ursodeoxycholic acid	26 (29.9)	28 (32.2)	27 (30.7)	27 (30.7)
Tobramycin	23 (26.4)	26 (29.9)	28 (31.8)	36 (40.9)
Colecalciferol	22 (25.3)	22 (25.3)	27 (30.7)	28 (31.8)
Omeprazole	26 (29.9)	26 (29.9)	21 (23.9)	24 (27.3)
Ciprofloxacin	3 (3.4)	15 (17.2)	1 (1.1)	29 (33.0)
Tocopherol	20 (23.0)	20 (23.0)	21 (23.9)	21 (23.9)
Paracetamol	21 (24.1)	27 (31.0)	19 (21.6)	31 (35.2)
Fluticasone propionate, salmeterol xinafoate	20 (23.0)	20 (23.0)	19 (21.6)	18 (20.5)
Ibuprofen	12 (13.8)	22 (25.3)	6 (6.8)	16 (18.2)
Budesonide, formoterol fumarate	16 (18.4)	16 (18.4)	11 (12.5)	11 (12.5)
Insulin aspart	17 (19.5)	17 (19.5)	10 (11.4)	10 (11.4)
Aztreonam lysine	11 (12.6)	11 (12.6)	14 (15.9)	15 (17.0)
Non-drug therapy				
Physiotherapy	37 (42.5)	35 (40.2[e])	46 (52.3)	44 (50.0[e])

a. Treatment was against the background of basic medication.
b. Number of patients in the FAS population.
c. Treatment within 56 days before the treatment phase (including 28-day run-in phase).
d. Drugs coded according to WHODrug Global March 2020 (Preferred Term).
e. Institute's calculation.

ELEXA: elexacaftor; FAS: full analysis set; IVA: ivacaftor; n: number of patients in the category; N: number of patients who had received at least one dose of the study medication (full analysis set); RCT: randomized controlled trial; TEZA: tezacaftor; vs.: versus

Administration of symptomatic treatment in addition to the study medication (ivacaftor + ivacaftor/tezacaftor/elexacaftor or ivacaftor + ivacaftor/tezacaftor) was allowed in the VX18-445-109 study. However, according to the study protocol, this therapy had to be continued at a stable dosage from 28 days before the start of the study (i.e. from the start of the

run-in phase) until the end of the study. Long-term treatment with new drugs was not to be started during this period.

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

It can be inferred from the study documents that patients received the regularly used medication for symptomatic treatment of CF (see Table 5). These included, among others, dornase alfa, bronchodilators, antibiotics, analgesics and vitamin preparations. Treatment with inhaled saline solution was not excluded.

The proportion of patients under the respective concomitant medication remained largely unchanged before and after the first intake of the study medication (see Table 5). A clear increase in concomitant medication after the first intake of the study medication was shown, for example, for antibiotics (tobramycin and ciprofloxacin) and analgesics (ibuprofen and paracetamol). The information provided by the company shows how many patients started new physiotherapy or therapy with antibiotics, inhaled drugs, mucolytics and bronchodilators during the study. It can be inferred from this information that the proportion of patients who started antibiotic therapy during the study was 10% in the intervention arm and 16% in the comparator arm (Institute's calculation). However, new physiotherapy or therapy with inhaled drugs or mucolytics was not started in any patient during the course of the study.

However, there was generally no information on whether and how many patients had their concomitant treatment adjusted, for example in the sense of an increase in dose or frequency in the course of the study.

In summary, the information provided shows that individual adjustments to the concomitant treatment were made in the study. Nevertheless, there is a lack of data on increased dose or frequency of the respective therapies in the course of the study.

Risk of bias across outcomes (study level)

Table 6 shows the risk of bias across outcomes (risk of bias at study level).

Table 6: Risk of bias across outcomes (study level) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
VX18-445-109	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the VX18-445-109 study.

2.2 Results

2.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - pulmonary exacerbations
  - serious 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
  - serious AEs (SAEs)
  - discontinuation due to AEs
  - further specific AEs, if any

Table 7 shows for which outcomes data were available in the study included.

Table 7: Matrix of outcomes – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor

Study	Outcomes							
	All-cause mortality	Pulmonary exacerbations	Serious pulmonary exacerbations[a]	Symptoms (CFQ-R symptom scales)	Health-related quality of life (CFQ-R quality of life scales)	SAEs[b]	Discontinuation due to AEs[b]	Skin and subcutaneous tissue disorders (SOC, AE)
VX18-445-109	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	Yes

a. Recorded as "infective pulmonary exacerbation of cystic fibrosis" (PT, SAE); the operationalization of the PT as serious event is comparable to the operationalization "hospitalization due to pulmonary exacerbations" used in previous benefit assessments, which is why this is used as an alternative morbidity outcome in the present benefit assessment.
b. Without PT "infective pulmonary exacerbation of cystic fibrosis".
c. No suitable operationalization available.

AE: adverse event; CFQ-R: Cystic Fibrosis Questionnaire-Revised; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Pulmonary exacerbations

In contrast to the studies previously sponsored and submitted by the company for benefit assessments of ivacaftor, for example, the outcomes "pulmonary exacerbations" and "hospitalization due to pulmonary exacerbations" were not operationalized in the VX18-445-109 study as a symptom outcome and recorded accordingly in the study (see, for example, A20-83 [11] on the operationalization defined regularly to date in the studies of the company). Instead, for study VX18-445-109, only analyses are available for events documented using the recording of AEs and SAEs (PT "infective pulmonary exacerbation of cystic fibrosis"). The reason given by the company that the recording of this outcome would have increased the size of the study population so that the study could hardly have been conducted is not appropriate [12]. In the absence of an adequate operationalization and thus also recording of the outcome "pulmonary exacerbations", the events for the PT "infective pulmonary exacerbation of cystic fibrosis" recorded via the SAE were used for the present assessment. It is assumed for this operationalization that the events that were also recorded using the previously used operationalization of hospitalizations due to pulmonary exacerbations were recorded with sufficient certainty.

The outcomes "lung function" (using FEV1) and body mass index (BMI) are presented as supplementary information in Appendix B. As in previous dossiers for the assessment of ivacaftor, the company did not present any new aspects on these outcomes (e.g. [13]).

2.2.2 Risk of bias

Table 8 describes the risk of bias for the results of the relevant outcomes.

Table 8: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor

Study		Outcomes							
	Study level	All-cause mortality	Pulmonary exacerbations	Serious pulmonary exacerbations[a]	Symptoms (CFQ-R symptom scales)	Health-related quality of life (CFQ-R quality of life scales)	SAEs[b]	Discontinuation due to AEs[b]	Skin and subcutaneous tissue disorders (SOC, AE)
VX18-445-109	L	L	-[c]	L	L	L	L	L	L

a. Recorded as "infective pulmonary exacerbation of cystic fibrosis" (PT, SAE).
b. Without PT "infective pulmonary exacerbation of cystic fibrosis".
c. No suitable operationalization available.

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

The risk of bias of all outcomes with suitable operationalization included in the present benefit assessment was rated as low.

2.2.3 Results

Table 9 summarizes the results of the comparison of ivacaftor + ivacaftor/tezacaftor/elexacaftor with ivacaftor + ivacaftor/tezacaftor in patients with CF aged 12 years and older who are homozygous for the F508del mutation. Where necessary, calculations by the Institute are provided in addition to the data.

Tables on common AEs, common SAEs and discontinuation due to AEs are presented in Appendix A.

Table 9: Results (mortality, side effects, dichotomous) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor (multipage table)

Study Outcome category Outcome	IVA + IVA/TEZA/ELEXA[a] N	 Patients with event n (%)	IVA + IVA/TEZA[a] N	 Patients with event n (%)	Group difference RR [95% CI]; p-value[b]
VX18-445-109					
Mortality					
All-cause mortality	87	0 (0)	88	0 (0)	–
Morbidity					
Pulmonary exacerbations	No usable data[c]				
Serious pulmonary exacerbations[d]	87	1 (1.1)	88	9 (10.2)	0.11 [0.01; 0.87]; 0.010[e]
Symptoms (CFQ-R, symptom domains, children [12 to 13 years] and adolescents or adults – pooled); improvement by ≥ 15 points[f]					
Respiratory symptoms	87	40 (46.0)	88	9 (10.2)	4.50 [2.32; 8.69]; < 0.001
Digestive symptoms	87	8 (9.2)	88	9 (10.2)	0.90 [0.36; 2.22]; 0.818
Weight[f]	78	22 (28.2)	80	8 (10.0)	2.82 [1.34; 5.95]; 0.007
Health-related quality of life					
Health-related quality of life (CFQ-R, health-related quality of life domains, children [12 to 13 years] and adolescents or adults – pooled); improvement by ≥ 15 points[f]					
Physical functioning	87	24 (27.6)	88	7 (8.0)	3.47 [1.58; 7.63]; 0.002
Emotional functioning	87	8 (9.2)	88	6 (6.8)	1.35 [0.49; 3.73]; 0.564
Vitality[g]	78	25 (32.1)	80	13 (16.3)	1.97 [1.09; 3.57]; 0.025
Social functioning	87	10 (11.5)	88	3 (3.4)	3.37 [0.96; 11.84]; 0.058
Role functioning[g]	78	16 (20.5)	80	5 (6.3)	3.28 [1.26; 8.52]; 0.015
Body image	87	11 (12.6)	88	8 (9.1)	1.39 [0.59; 3.29]; 0.453
Eating problems	87	11 (12.6)	88	5 (5.7)	2.23 [0.81; 6.14]; 0.122
Treatment burden	87	19 (21.8)	88	8 (9.1)	2.40 [1.11; 5.19]; 0.026
Health perceptions[g]	78	26 (33.3)	80	8 (10.0)	3.33 [1.61; 6.91]; 0.001
Side effects					
AEs (supplementary information)[h]	87	77 (88.5)	88	75 (85.2)	–
SAEs[h]	87	4 (4.6)	88	6 (6.8)	0.67 [0.20; 2.31]; 0.558[d]
Discontinuation due to AEs[h]	87	1 (1.1)	88	2 (2.3)	0.51 [0.05; 5.48]; 0.682[d]
Skin and subcutaneous tissue disorders (SOC, AE)	87	20 (23.0)	88	4 (4.5)	5.06 [1.80; 14.19]; < 0.001[d]

Table 9: Results (mortality, side effects, dichotomous) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor (multipage table)

Study Outcome category	IVA + IVA/TEZA/ELEXA[a]		IVA + IVA/TEZA[a]		Group difference
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[b]
a. Treatment was against the background of basic medication. b. Analysis of the CFQ-R by generalized linear model (GLM) using the binomial distribution and a log-link function. c. No suitable operationalization available. d. Recorded as "infective pulmonary exacerbation of cystic fibrosis" (PT) using SAEs. e. Institute's calculation, unconditional exact test, CSZ method according to [14]. f. Improvement, defined as an increase in CFQ-R score of at least 15 points from baseline; it is unclear whether this improvement existed at one documentation time during the course of the study over 24 weeks or at several documentation times. g. Domain for adolescents or adults; not intended for children [12 to 13 years]. h. Without recording of the PT "infective pulmonary exacerbation of cystic fibrosis". AE: adverse event; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; CSZ: convexity, symmetry, z-score; ELEXA: elexacaftor; IVA: ivacaftor; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; TEZA: tezacaftor; vs.: versus					

Based on the VX18-445-109 study, at most indications, e.g. of an added benefit, can be derived for all outcomes presented.

Mortality

All-cause mortality

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

Morbidity

Pulmonary exacerbations

For the outcome "pulmonary exacerbations", there were no usable data from study VX18-445-109 for a comparison of ivacaftor + ivacaftor/tezacaftor/elexacaftor with ivacaftor + ivacaftor/tezacaftor. This resulted in no hint of an added benefit of ivacaftor + ivacaftor/ tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor; an added benefit is therefore not proven.

Serious pulmonary exacerbations

For the outcome "serious pulmonary exacerbations" (recorded using SAEs via the PT "infective pulmonary exacerbation of cystic fibrosis"), there was a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor versus ivacaftor + ivacaftor/tezacaftor.

This resulted in an indication of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor for serious pulmonary exacerbations.

Symptoms measured using the CFQ-R

Operationalization

The CFQ-R instrument was used in the study to assess the outcomes of 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.

For adolescents and adults (≥ 14 years), the instrument consists of 3 domains on symptoms; for children aged 12 to 13 years, the weight domain is not part of the questionnaire. In addition, the CFQ-R for adolescents and adults contains 9 domains on health-related quality of life. For children aged 12 to 13 years, these do not include the domains of vitality, role functioning and health perceptions.

In accordance with the Institute's *General Methods* [15,16], the company presented post hoc analyses on 15% of the scale range conducted for the CFQ-R. For the CFQ-R with a scale range of 0 to 100 [17], the 15% corresponds exactly to 15 points (responder analysis presented by the company: improvement by ≥ 15 points). According to the company [12], the response existed over the 24 weeks, i.e. in the course of the study, and it was not a single time point. It is unclear whether the improvement existed at one documentation time during the course of the study or at several documentation times.

Results

Domain "respiratory symptoms"

In the domain "respiratory symptoms", the responder analysis (improvement of at least 15 points) showed a statistically significant difference in favour of ivacaftor + ivacaftor/ tezacaftor/elexacaftor versus ivacaftor + ivacaftor/tezacaftor. There was an effect modification by the characteristic "sex". However, the results of the 2 subgroups did not differ in direction of effect and extent from the result of the total study population (see Section 2.2.4), so that the characteristic was not considered further for the respiratory symptoms domain. This resulted in an indication of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor for the CFQ-R domain "respiratory symptoms".

Domain "digestive symptoms"

In the domain "digestive symptoms", the responder analysis (improvement of at least 15 points) showed no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor for the CFQ-R domain "digestive symptoms"; an added benefit is therefore not proven.

Domain "weight"

In the domain "weight", the responder analysis (improvement of at least 15 points) showed a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor versus ivacaftor + ivacaftor/tezacaftor. There was an effect modification by the characteristic "sex". This resulted in an indication of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor for the CFQ-R domain "weight" for male patients. For female patients, in contrast, no added benefit was shown (see Section 2.2.4).

Health-related quality of life measured with the CFQ-R

Operationalization

Health-related quality of life was recorded using the domains of physical functioning, emotional functioning, vitality, social functioning, role functioning, body image, eating problems, treatment burden, and health perceptions of the CFQ-R. As already described above for the symptoms, the company presented post hoc analyses on 15% of the scale range also for the CFQ-R domains on health-related quality of life.

Results

Domains of physical functioning, vitality, role functioning, treatment burden, and health perceptions

The responder analysis (improvement of at least 15 points) showed a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor versus ivacaftor + ivacaftor/tezacaftor for each of the domains of physical functioning, vitality, role functioning, treatment burden, and health perceptions. This resulted in an indication of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor for each of these CFQ-R domains.

Domains of emotional functioning, social functioning, body image, and eating problems

The responder analysis (improvement of at least 15 points) showed no statistically significant difference between the treatment arms for any of the domains of emotional functioning, social functioning, body image, and eating problems. This resulted in no hint of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor for any of these CFQ-R domains; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

There was no statistically significant difference between the treatment groups for either of the outcomes "SAEs" and "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm from ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor for either of the outcomes "SAEs" and "discontinuation due to AEs"; greater or lesser harm is therefore not proven.

Specific AEs

Skin and subcutaneous tissue disorders

There was a statistically significant difference to the disadvantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor for the outcome "skin and subcutaneous tissue disorders". There was an effect modification by the characteristic "sex". This resulted in an indication of greater harm from ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor for the outcome "skin and subcutaneous tissue disorders" for male patients. For female patients, in contrast, no greater or lesser harm was shown (see Section 2.2.4).

2.2.4 Subgroups and other effect modifiers

The following subgroups were used for the present assessment:

- age (< 18 years/≥ 18 years)
- sex (female/male)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there must be 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.

Table 10 presents the subgroup results for the comparison of ivacaftor + ivacaftor/tezacaftor/elexacaftor with ivacaftor + ivacaftor/tezacaftor.

Table 10: Subgroups (morbidity, side effects) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor

Study Outcome	IVA + IVA/TEZA/ELEXA[a]		IVA + IVA/TEZA[a]		Group difference	
Characteristic Subgroup	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][b]	p-value
VX18-445-109						
Morbidity: symptoms: CFQ-R domain "respiratory symptoms", children [12 to 13 years] and adolescents or adults – pooled; improvement by ≥ 15 points[c]						
Sex						
Male	44	19 (43.2)	43	1 (2.3)	18.57 [2.60; 132.68]	0.004
Female	43	21 (48.8)	45	8 (17.8)	2.75 [1.37; 5.53]	0.005
Total					Interaction:	0.026[d]
Morbidity: Symptoms: CFQ-R domain "weight", adolescents or adults[e]; improvement by ≥ 15 points[c]						
Sex						
Male	39	13 (33.3)	38	1 (2.6)	12.67 [1.74; 92.13]	0.012
Female	39	9 (23.1)	42	7 (16.7)	1.38 [0.57; 3.36]	0.472
Total					Interaction:	0.015[d]
Side effects: skin and subcutaneous tissue disorders (SOC, AE)						
Sex						
Male	44	12 (27.3)	43	0 (0.0)	24.44 [1.49; 400.4]	< 0.001[f]
Female	43	8 (18.6)	45	4 (8.9)	2.09 [0.68; 6.45]	0.241[f]
Total					Interaction	0.011[d]

a. Treatment was against the background of basic medication.
b. Analysis of the CFQ-R by generalized linear model (GLM) using the binomial distribution and a log-link function.
c. Improvement, defined as an increase in CFQ-R score of at least 15 points from baseline; it is unclear whether this improvement existed at one documentation time during the course of the study over 24 weeks or at several documentation times.
d. From generalized linear model (GLM) using the binomial distribution and a log-link function.
e. Domain for adolescents or adults; not intended for children [12 to 13 years].
f. Institute's calculation, unconditional exact test (CSZ method according to [14]).

AE: adverse event; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; CSZ: convexity, symmetry, z-score; ELEXA: elexacaftor; IVA: ivacaftor; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SOC: System Organ Class; TEZA: tezacaftor; vs.: versus

Morbidity

Symptoms measured using the CFQ-R

Domain "respiratory symptoms"

There was an effect modification by the characteristic "sex" for the domain "respiratory symptoms". The responder analysis (improvement of at least 15 points) showed a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor versus ivacaftor +

ivacaftor/tezacaftor for each of both subgroups. The extent for both subgroups is consistent with the result of the total study population (see Section 2.3). The characteristic "sex" was therefore not considered further for the CFQ-R domain "respiratory symptoms".

Domain "weight"

There was an effect modification by the characteristic "sex" for the domain "weight". The responder analysis (improvement of at least 15 points) showed a statistically significant difference in favour of ivacaftor + ivacaftor/tezacaftor/elexacaftor versus ivacaftor + ivacaftor/tezacaftor for male patients. This resulted in an indication of an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor for the CFQ-R domain "weight" for male patients. For female patients, in contrast, there was no statistically significant difference between the treatment groups; an added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor is therefore not proven for female patients.

Side effects

Specific AEs

Skin and subcutaneous tissue disorders

There was an effect modification by the characteristic "sex" for the outcome "skin and subcutaneous tissue disorders". There was a statistically significant difference to the disadvantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor versus ivacaftor + ivacaftor/tezacaftor for male patients. This resulted in an indication of greater harm from ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor for the outcome "skin and subcutaneous tissue disorders" for male patients. For female patients, in contrast, there was no statistically significant difference between the treatment groups; greater or lesser harm of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor is therefore not proven for female patients.

2.3 Extent and probability of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [15].

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

2.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.2 (see Table 11).

Determination of the outcome category for symptom outcomes

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

The company did not state whether the information on the symptom domains of the CFQ-R referred to severe/serious events. These CFQ-R domains were assigned to the outcome category "non-serious/non-severe symptoms/late complications" in the present assessment.

Table 11: Extent of added benefit at outcome level: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: -	Lesser benefit/added benefit not proven
Morbidity		
Pulmonary exacerbations	No usable data	Lesser benefit/added benefit not proven
Serious pulmonary exacerbations	1.1% vs. 10.2% RR: 0.11 [0.01; 0.87]; p = 0.010 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.75 < CI_u < 0.90$ added benefit, extent: "considerable"
Symptoms (CFQ-R domains on symptoms, improvement of ≥ 15 points)		
Respiratory symptoms	46.0% vs. 10.2% RR: 4.50 [2.32; 8.69]; RR: 0.22 [0.12; 0.43][c]; p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Digestive symptoms	9.2% vs. 10.2% RR: 0.90 [0.36; 2.22]; p = 0.818	Lesser benefit/added benefit not proven
Weight Sex Male	33.3% vs. 2.6% RR: 12.67 [1.74; 92.13] RR: 0.08 [0.01; 0.57][c]; p = 0.012 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Female	23.1% vs. 16.7% RR: 1.38 [0.57; 3.36]; p = 0.472	Lesser benefit/added benefit not proven
Health-related quality of life (CFQ-R domains on health-related quality of life, improvement of ≥ 15 points)		
Physical functioning	27.6% vs. 8.0% RR: 3.47 [1.58; 7.63] RR: 0.29 [0.13; 0.63][c]; p = 0.002 probability: "indication"	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"
Emotional functioning	9.2% vs. 6.8% RR: 1.35 [0.49; 3.73]; p = 0.564	Lesser benefit/added benefit not proven
Vitality	32.1% vs. 16.3% RR: 1.97 [1.09; 3.57]; RR: 0.51 [0.28; 0.92][c]; p = 0.025 probability: "indication"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"

Table 11: Extent of added benefit at outcome level: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor** **Proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Social functioning	11.5% vs. 3.4% RR: 3.37 [0.96; 11.84]; p = 0.058	Lesser benefit/added benefit not proven
Role functioning	20.5% vs. 6.3% RR: 3.28 [1.26; 8.52]; RR: 0.30 [0.12; 0.79][c]; p = 0.015 probability: "indication"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Body image	12.6% vs. 9.1% RR: 1.39 [0.59; 3.29]; p = 0.453	Lesser benefit/added benefit not proven
Eating problems	12.6% vs. 5.7% RR: 2.23 [0.81; 6.14]; p = 0.122	Lesser benefit/added benefit not proven
Treatment burden	21.8% vs. 9.1% RR: 2.40 [1.11; 5.19] RR: 0.42 [0.19; 0.9009][c]; p = 0.026 probability: "indication"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Health perceptions	33.3% vs. 10.0% RR: 3.33 [1.61; 6.91]; RR: 0.30 [0.14; 0.62][c]; p = 0.001 probability: "indication"	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"
Side effects		
SAEs	4.6% vs. 6.8% RR: 0.67 [0.20; 2.31]; p = 0.558	Greater/lesser harm not proven
Discontinuation due to AEs	1.1% vs. 2.3% RR: 0.51 [0.05; 5.48]; p = 0.682	Greater/lesser harm not proven
Skin and subcutaneous tissue disorders (SOC, AE) Sex Male	27.3% vs. 0.0% RR: 24.44 [1.49; 400.4] RR: 0.04 [0.00; 0.67][c]; p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Female	18.6% vs. 8.9% RR: 2.09 [0.68; 6.45]; p = 0.241	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; CI_u: upper limit of confidence interval; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.3.2 Overall conclusion on added benefit

Table 12 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 12: Positive and negative effects from the assessment of ivacaftor + ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ Serious pulmonary exacerbations: indication of an added benefit – extent: "considerable"	-
Non-serious/non-severe symptoms/late complications ▪ Symptoms ▫ Domain "respiratory symptoms": indication of an added benefit – extent: "considerable" ▫ Domain "weight"[a]: - Male patients: indication of an added benefit – extent: "considerable"	-
Health-related quality of life ▪ Domains "physical functioning" and "health perceptions"[a]: indication of an added benefit – extent: "major" ▪ Domain "role functioning"[a]: indication of an added benefit – extent: "considerable" ▪ Domains "vitality"[a] and "treatment burden": indication of an added benefit – extent: "minor"	-
-	Non-serious/non-severe side effects: ▪ Specific AEs: skin and subcutaneous tissue disorders: ▫ Male patients: indications of greater harm – extent: "considerable"
a. Domain was only recorded for adolescents or adults, as it is not intended for children [12 to 13 years]. AE: adverse event	

Overall, there are several positive effects and one negative effect. On the side of positive effects, there are indications of considerable added benefit of ivacaftor + ivacaftor/tezacaftor/ elexacaftor in comparison with ivacaftor + ivacaftor/tezacaftor both in non-serious/non-severe and in serious/severe symptoms/late complications. In addition, positive effects were shown in health-related quality of life, in some cases with the extent "major". There are isolated effect modifications by the characteristic "sex", including one negative effect for male patients in non-serious/non-severe side effects.

In summary, since the positive effects described above for serious/severe symptoms/late complications and health-related quality of life are present for all patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene, there is an

indication of a major added benefit of ivacaftor + ivacaftor/tezacaftor/elexacaftor in comparison with the ACT ivacaftor + tezacaftor/ivacaftor.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of ivacaftor from dossier assessment A20-77.

The following Table 13 shows the result of the benefit assessment of ivacaftor + ivacaftor/ tezacaftor/elexacaftor.

Table 13: Ivacaftor + ivacaftor/tezacaftor/elexacaftor – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**[b]
CF patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor or **tezacaftor/ivacaftor in combination with ivacaftor**	**Indication of major added benefit**

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. Changes in comparison with dossier assessment A20-77 are printed in **bold**.

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

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

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Appendix A – Results on side effects

The following tables present events for the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs) and Preferred Terms (PTs) for the overall rates of AEs and SAEs on the basis of the following criteria:

- overall rate of AEs (irrespective of the severity grade): events that occurred in at least 10% of the patients in one study arm
- SAEs: events that occurred in at least 5% of the patients in one study arm
- in addition for all events irrespective of the severity grade: events that occurred in at least 10 patients and in at least 1% of the patients in one study arm

For the outcome "discontinuation due to AEs", a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 14: Common AEs[a] – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**IVA + IVA/TEZA/ELEXA** **N = 87**	**IVA + IVA/TEZA** **N = 88**
VX18-445-109		
Overall AE rate	77 (88.5)	81 (82.0)
Infections and infestations	48 (55.2)	51 (58.0)
Nasopharyngitis	17 (19.5)	13 (14.8)
Infective pulmonary exacerbation of cystic fibrosis	10 (11.5)	36 (40.9)
Upper respiratory tract infection	9 (10.3)	5 (5.7)
Respiratory, thoracic and mediastinal disorders	45 (51.7)	44 (50.0)
Cough	11 (12.6)	23 (26.1)
Oropharyngeal pain	11 (12.6)	7 (8.0)
Sputum increased	10 (11.5)	16 (18.2)
Nervous system disorders	30 (34.5)	23 (26.1)
Headache	25 (28.7)	18 (20.5)
Gastrointestinal disorders	25 (28.7)	25 (28.4)
Skin and subcutaneous tissue disorders	20 (23.0)	4 (4.5)
Investigations	13 (14.9)	18 (20.5)
Musculoskeletal and connective tissue disorders	13 (14.9)	13 (14.8)
General disorders and administration site conditions	8 (9.2)	12 (13.6)
Psychiatric disorders	5 (5.7)	10 (11.4)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 23.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 15: Common SAEs[a] – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**IVA + IVA/TEZA/ELEXA** **N = 87**	**IVA + IVA/TEZA** **N = 88**
VX18-445-109		
Overall SAE rate	5 (5.7)	14 (15.9)
Infections and infestations	1 (1.1)	10 (11.4)
Infective pulmonary exacerbation of cystic fibrosis	1 (1.1)	9 (10.2)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 23.0.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 16: Discontinuation due to AEs[a] – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**IVA + IVA/TEZA/ELEXA** **N = 87**	**IVA + IVA/TEZA** **N = 88**
VX18-445-109		
Overall rate of discontinuations due to AEs	1 (1.1)	2 (2.3)
Psychiatric disorders	1 (1.1)	2 (2.3)
Anxiety	1 (1.1)	0 (0)
Depression	1 (1.1)	0 (0)
Obsessive-compulsive disorder	0 (0)	1 (1.1)
Psychosis	0 (0)	1 (1.1)

a. MedDRA version 23.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Appendix B – Results for the outcomes "FEV1" (in% of predicted normal) and "BMI"

Table 17: Results for the outcomes "FEV1" (in % of predicted normal) and "BMI" (continuous) – RCT, direct comparison: ivacaftor + ivacaftor/tezacaftor/elexacaftor vs. ivacaftor + ivacaftor/tezacaftor

Study Outcome category	IVA + IVA/TEZA/ELEXA[a]			IVA + IVA/TEZA[a]			Group difference
Outcome	N[b]	Values at baseline mean (SD)	Change at week 24 mean (SD)	N[b]	Values at baseline mean (SD)	Change at week 24 mean (SD)	MD [95% CI]; p-value[c]
VX18-445-109							
Morbidity							
FEV1[d] (absolute change)	86	63.00 (16.72)	11.96 (8.41)[e]	87	64.21 (15.11)	1.98 (5.37)[e]	10.15 [8.18; 12.12]; < 0.001[f]
BMI [kg/m²]	61	21.17 (3.43)	1.70 (1.38)	62	21.92 (3.89)	0.15 (0.78)	1.44 [1.07; 1.82]; < 0.001[g]
BMI (age-dependent z-score)[h]	19	−0.79 (0.98)	0.52 (0.47)	16	−0.33 (0.95)	−0.01 (0.48)	0.51 [0.20; 0.82]; 0.002[g]

a. Treatment was against the background of basic medication.
b. Number of patients who were included in the analysis according to the information provided by the company. For the BMI and the age-dependent BMI analysis, however, these are presumably patients for whom values were available at least at baseline and week 24; the estimation of the parameters of the MMRM models could be based on higher patient numbers. At least the values at baseline are based on 28 vs. 30 patients for the age-dependent BMI analysis (presumably the patients who were ≤ 20 years at screening) and 87 vs. 88 patients for the BMI. Overall, it is unclear for the age-dependent BMI analysis whether ≥ 70% of the patients contribute to the estimation of the parameters of the MMRM model.
c. MMRM; dependent variable is the absolute change from baseline; adjusted for age (< 18 vs. ≥ 18 years at screening), baseline FEV1% and use of a CFTR modulator at screening; additionally treatment, study time point, treatment×study time point as fixed effects in the model.
d. The values at baseline are based on 87 vs. 88 patients, values at the change at week 24 are based on 52 vs. 53 patients.
e. Higher values indicate better symptoms; a positive group difference indicates an advantage of ivacaftor + ivacaftor/tezacaftor/elexacaftor.
f. Effect represents the difference between the treatment groups of the adjusted mean difference of absolute changes over 24 weeks. Week 15 is excluded.
g. Effect presents the difference between the treatment groups of the changes from the start of the study until week 24.
h. According to information provided by the company in Module 4 B, only for patients ≤ 20 years of age; the required weight measurements after screening were planned for patients ≤ 21 years of age

BMI: body mass index; CFTR: cystic fibrosis transmembrane conductance regulator; CI: confidence interval; ELEXA: elexacaftor; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; TEZA: tezacaftor; vs.: versus