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

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

Extract

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

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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

Medical and scientific advice

- Thomas O. F. Wagner, FRZSE, University Hospital Frankfurt/Main, Germany

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.

IQWiG employees involved in the dossier assessment

- Anne Hüning
- Lars Beckmann
- Katharina Biester
- Lisa Junge
- Marco Knelangen
- Stefan Kobza
- Petra Kohlepp
- Min Ripoll

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
BSC	best supportive care
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
FEV1	forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLMM	generalized linear mixed models
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed model for repeated measures
RCT	randomized controlled trial
RF	residual function
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination of tezacaftor/ivacaftor in combination with ivacaftor. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 29 June 2020.

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

Research question

The aim of the present report is to assess the added benefit of tezacaftor/ivacaftor in combination with ivacaftor in comparison with the appropriate comparator therapy (ACT) of best supportive care (BSC) in patients with cystic fibrosis (CF) aged 12 years and older who are heterozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The patients have one of the following mutations on the second allele: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G und 3849+10 kbC→T. Tezacaftor/ivacaftor is assessed as a treatment administered in combination with ivacaftor 150 mg tablets.

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

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

Therapeutic indication	**ACT[a]**
Patients with CF aged 12 years and older who are heterozygous for the F508del mutation and have one of the following 14 mutations on the second allele in the CFTR gene[b]: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10 kbC→T	BSC
a. Presented is the ACT specified by the G-BA. b. These are RF mutations. ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; RF: residual function	

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

Study included by the company

In its dossier, the company used the study VX14-661-108 with a study duration of 8 weeks for the assessment of added benefit. Using a crossover design, the VX14-661-108 study compared 3 treatments: the combination therapy of ivacaftor + tezacaftor/ivacaftor, ivacaftor, and placebo. During the study, patients received concomitant medication largely within the context of BSC. For the present dossier assessment, the company considered the comparison of the combination therapy of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC.

Due to a treatment phase of only 8 weeks, the VX14-661-108 study included by the company is unsuitable for a benefit assessment in the therapeutic indication of CF – a chronic disease requiring lifelong treatment. No conclusions can be drawn on the basis of short-term studies as to whether short-term effects persist in the longer term. Effects that do not appear until later will also be missed, e.g. in case of adverse events (AEs) or pulmonary exacerbations and their sequelae.

The company justified its inclusion criterion of 8 weeks by stating that this was the maximum treatment duration used in the lone randomized approval study and that the basis for the approval decision was also the basis for the assessment of the added benefit. The company's rationale was not followed.

Overall, studies of at least 24 weeks' duration are necessary to compare benefit and harm in the therapeutic indication of CF. Hence, the VX14-661-108 study was too short to be included in the present benefit assessment. The company additionally presented, among others, results from the 24-week RCT VX14 661 106, which was conducted with CF patients who are homozygous for the F508del mutation. The company claims that it cited these results as supplementary information to make the case for transferability. However, the data presented by the company to be transferred from patients with homozygous F508del mutation to patients with heterozygous F508del mutation are unsuitable for such projection, i.e. transfer. For deriving an added benefit, the company did in fact exclusively consider the VX14-661-108 study.

Due to the rarity of the mutations to be investigated and the fact that children are affected in the present therapeutic indication, the VX14-661-108 study and the corresponding short-term results are presented as supplementary information in the present dossier assessment. No conclusion on added benefit is derived from them.

Special features of the crossover study design

A crossover design produces meaningful results only if certain conditions are met:

1) Carry-over effects are negligible.
2) Period effects are considered adequately in the statistical analyses.

Assuming that both of the above conditions are sufficiently fulfilled for the VX14-661-108 study, the short-term results of this study are presented as supplementary information in the

present dossier assessment. Further information on the period effect and specific consequences of possible carry-over effects are considered in the assessment of the risk of bias of the short-term results.

A crossover design is usually inadequate for irreversible outcomes. This concerns the outcomes of all-cause mortality and discontinuation due to AEs (if the discontinuation did not allow participation in the following treatment periods). However, no deaths and only 1 discontinuation due to AEs occurred in the VX14-661-108 study.

Implementation of the ACT

In the VX14-661-108 study, patients were to continue their ongoing symptomatic treatment at the same time as treatment with tezacaftor/ivacaftor + ivacaftor or placebo. According to the study protocol, however, the concomitant medication had to be stable from 4 weeks before the start of the study until the end of the study. Additionally, an inclusion criterion of the VX14-661-108 study required that participants were willing to keep the concomitant treatment associated with CF stable over the entire study period.

The available information suggests that patients received a variety of drugs for symptomatic treatment of CF (including dornase alfa as well as pancreatin and antibiotic therapy and sodium chloride) at the time point of study entry. The available data also suggest that some patients started concomitant medication after the first intake of the study medication (e.g. antibiotic therapy and physiotherapy). It cannot be inferred from the data, however, whether the concomitant treatment was adjusted, e.g. by increasing the dose or frequency in the course of the study, and if so, for how many patients this was the case.

In summary, the available data leave unclear whether increases in dose or frequency of the concomitant medication were possible, but in view of the short duration of the study, it is assumed that the concomitant treatment used was largely carried out in the sense of BSC.

Short-term results of the study included by the company

The risk of bias at study level was rated as low. For the short-term results of the considered outcomes, the risk of bias is rated as high, except for the outcome of discontinuation due to AEs. The results of the outcome of discontinuation due to AEs are rated as having a low risk of bias.

Morbidity

Pulmonary exacerbations, hospitalization due to pulmonary exacerbations

For each of the outcomes of pulmonary exacerbation and hospitalization due to pulmonary exacerbations, no statistically significant difference between the treatment groups was found.

Symptoms measured with the Cystic Fibrosis Questionnaire – Revised (CFQ-R)

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

- "Respiratory symptoms" domain

In the "respiratory symptoms" domain, a statistically significant difference was found in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC for the change from baseline. The standardized mean difference (SMD) in the form of Hedges' g was considered to assess the relevance of the result. The 95% confidence interval (95% CI) was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect. However, there was an effect modification by the attribute of age. For adults (aged 18 years and older), there was an advantage of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC.

- "Digestive symptoms" domain

There was a statistically significant effect to the disadvantage of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC. The SMD in the form of Hedges' g was considered to assess the relevance of these results. The 95% CI was not completely above or below the irrelevance threshold of 0.2 or −0.2. It can therefore not be inferred that this effect was relevant.

- "Weight" domain

There was a statistically significant effect in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC. The SMD in the form of Hedges' g was considered to assess the relevance of these results. The 95% CI was not completely above or below the irrelevance threshold of 0.2 or −0.2. It can therefore not be inferred that the effect was relevant.

Health-related quality of life

Health-related quality of life (measured using the CFQ-R domains)

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

- "Physical functioning" domain

A statistically significant difference in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC was shown in the "physical functioning" domain. The 95% CI of the SMD in the form of Hedges' g was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect.

- "Vitality" domain

A statistically significant difference in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC was shown for the change from baseline in the "vitality" domain. The 95% CI of the SMD in the form of Hedges' g was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect.

- "Health perceptions" domain

A statistically significant difference in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC was shown in the "health perceptions" domain. The 95% CI of the SMD in the form of Hedges' g was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect. However, there was an effect modification by the attribute of age. For adults (aged 18 years and older), there was an advantage of ivacaftor/tezacaftor + ivacaftor + BSC versus placebo + BSC.

- Domains "emotional functioning", "social functioning", "role functioning", "body image", and "treatment burden"

In addition, statistically significant effects in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC were shown in the "emotional functioning", "social functioning", "role functioning", "body image", and "treatment burden" domains. The 95% CI of the SMD in the form of Hedges' g was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that these effects were relevant.

- "Eating disorders" domain

In the "eating disorders" domain, no statistically significant difference between the treatment groups was found.

Health-related quality of life measured using the physical and mental summary scores of the SF-12 v2

Both the physical and the mental health summary score showed statistically significant effects in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC. For the physical health summary score, the 95% CI of the SMD in the form of Hedges' g was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect. However, there was an effect modification by age. For adults (aged 18 years and older), there was an advantage of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC.

For the mental health summary score, however, the 95% CI of the SMD in the form of Hedges' g was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that this effect was relevant.

AEs

Serious adverse events (SAEs) and discontinuation due to AEs

For the outcome of SAEs (excluding the PT of infectious pulmonary exacerbation of CF), no statistically significant difference between the treatment groups was found.

There was 1 discontinuation due to AEs. This resulted in no statistically significant difference between the treatment groups.

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

On the basis of the results presented, the probability and extent of added benefit of the drug combination of tezacaftor/ivacaftor in combination with ivacaftor in comparison with the ACT are assessed as follows:

Studies with a minimum duration of 24 weeks are necessary for the benefit assessment in the therapeutic indication of CF. In the present therapeutic indication, the company presented only comparative data collected over a period of 8 weeks. These show only short-term effects, however, which are unsuitable for the derivation of an added benefit in the present therapeutic indication.

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

Table 3: Tezacaftor/ivacaftor + ivacaftor + BSC – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with CF aged 12 years and older who are heterozygous for the F508del mutation and have 1 of the following 14 mutations in the CFTR gene[b]: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10 kbC→T	BSC	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. These are RF mutations. ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; RF: residual function		

The G-BA decides on the added benefit.

Supplementary note

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

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

2.2 Research question

The aim of the present report is to assess the added benefit of tezacaftor/ivacaftor in combination with ivacaftor in comparison with the ACT of BSC in patients with CF aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene. The patients have one of the following mutations on the second allele: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G und 3849+10 kbC→T. The assessment of tezacaftor/ivacaftor was conducted for combination treatment with ivacaftor 150 mg tablets.

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

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

Therapeutic indication	**ACT**[a]
Patients with CF aged 12 years and older who are heterozygous for the F508del mutation and have one of the following 14 mutations on the second allele in the CFTR gene[b]: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10 kbC→T	BSC
a. Presented is the ACT specified by the G-BA. b. These are RF mutations. ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; RF: residual function	

The company named BSC as ACT and thus followed 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. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This deviates from the company's inclusion criteria, which specified a minimum duration of 8 weeks.

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

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

To check the completeness of the study pool:

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

No relevant study was identified from the check.

Evidence provided by the company

VX14-661-108 study

In its dossier, the company used the VX14-661-108 study [3-7] for the assessment of the added benefit. This study had already been presented for the early benefit assessment of ivacaftor in combination with tezacaftor/ivacaftor in the same therapeutic indication [8,9]. Using a crossover design, the VX14-661-108 study compared 3 treatments. The patients received concomitant medication, largely in the sense of BSC, during the study (see Section 2.3.2). The comparison of the tezacaftor/ivacaftor + ivacaftor + BSC combination therapy with placebo + BSC is relevant for the present dossier assessment.

Due to a treatment phase of only 8 weeks, the VX14-661-108 study included by the company is unsuitable for a benefit assessment in the therapeutic indication of CF – a chronic disease requiring lifelong treatment. In the therapeutic indication of CF, short-term studies (with a treatment duration of less than 24 weeks) are unsuitable for the benefit assessment since tezacaftor/ivacaftor in combination with ivacaftor is a long-term treatment. The European Medicines Agency (EMA) guideline recommends a minimum duration of 6 months for the investigation of a clinical outcome [10]. IQWiG's *General Methods 5.0* also considers long-term studies to be necessary for the benefit assessment of chronic diseases [1]. No conclusions can be drawn on the basis of short-term studies as to whether short-term effects persist in the longer term. Effects that do not appear until later will also be missed, e.g. in case of AEs or pulmonary exacerbations and their sequelae. Pulmonary exacerbations are a common cause of lung damage or death in patients with CF [11-14]. In Module 4 B, the company justified its inclusion criterion of 8 weeks with the explanation that this was the maximum treatment duration in the only randomized approval study and that the basis of the approval decision was also the basis of the assessment of the added benefit. The company's rationale was not followed.

Overall, studies of at least 24 weeks' duration are necessary to compare benefit and harm for the benefit assessment in the therapeutic indication of CF. Hence, the VX14-661-108 study was too short to be included in the present benefit assessment. However, due to the rarity of the mutations to be investigated and the fact that children are affected in the present therapeutic indication, the VX14-661-108 study and the corresponding short-term results are presented as supplementary information in the present dossier assessment. No conclusion on added benefit is derived from them.

Further supplementary evidence presented by the company

Study VX14-661-110

In its dossier, the company presented the VX14-661-110 open-label extension study as supplementary evidence. The study included both patients with homozygous F508del mutation

(from the studies VX13-661-103, VX14-661-106, and VX14-9661-111) and patients with heterozygous F508del mutation (from the studies VX14-661-107, VX14-661-108, and VX14-661-109) in the CFTR gene. The included patients either received tezacaftor/ivacaftor + ivacaftor + BSC or were allowed to participate in the study in an observation arm without a study drug being administered. The results from this study are irrelevant for the present benefit assessment since no data are available for an assessment of tezacaftor/ivacaftor + ivacaftor in comparison with the ACT. Hereinbelow, these results are not presented as supplementary information any further.

VX14-661-106 study with patients with homozygous F508del mutation for a transfer of results to the patient population with heterozygous F508del mutation

In addition, the company presented results from the RCT VX14-661-106 [15-19] with patients with CF who are homozygous for the F508del mutation. In this study, either tezacaftor/ivacaftor + ivacaftor + BSC or placebo + BSC was administered for 24 weeks. The company stated that it took into account the results from the population of patients with homozygous F508del mutation as supplementary evidence in the sense of a transfer because the G-BA rated the 8-week study VX14-661-108 as too short in the benefit assessment procedure on the drug ivacaftor in combination with tezacaftor/ivacaftor [20]. In an effort to demonstrate appropriate comparability between the two patient populations, the company assumed the criteria it employed (identical mechanism of action, no differences in the clinical picture of the disease, and transferability of efficacy and safety) to be met and hence transferability to be possible. Yet ultimately, the company did not transfer the data for deriving an added benefit (see below).

However, the data presented by the company regarding the transferability of the results from patients with homozygous F508del mutation to patients with heterozygous F508del mutation are not conducive to be transferred. The reasoning is provided below.

The literature as well as the European Public Assessment Report on tezacaftor/ivacaftor show that the clinical picture and course of disease typically differ between patients with heterozygous versus homozygous mutation. For instance, patients with homozygous F508del mutation exhibit earlier disease manifestation than patients with heterozygous F508del mutation. Further, patients with homozygous F508del mutation are characterized by more rapid progression of disease and a more severe course of disease [21,22]. Corresponding differences in disease severity are also found in the patient characteristics at baseline, as presented by the company for VX14-661-106 (homozygous F508del mutation) and VX14-661-108 (heterozygous F508del mutation). For instance, in the VX14-661-106 study, about twice as many patients with homozygous F508del mutation had received prior treatment with inhaled antibiotics (homozygous: 58.7% versus heterozygous: 30.0%) and about 11% more patients exhibited colonization with *Pseudomonas aeruginosa* within 2 years prior to screening (homozygous: 72.8% versus heterozygous: 61.3%). Overall, a greater severity of disease is derived from these data for patients with homozygous F508del mutation.

Due to insufficient available data, it is not possible to estimate the extent to which the results of patients with homozygous F508del mutation could nevertheless be transferred to patients with heterozygous F508del mutation. The company did not conduct any information retrieval on the ACT with a treatment duration of ≥ 24 weeks for the population of interest with heterozygous mutation. This information is necessary, however, to estimate the disease course of the two populations over a sufficiently long and therefore meaningful time period.

As far as chronic diseases are concerned, transferring the results from an 8-week investigation to a 24-week period is seen as inappropriate for two reasons: (1) the 8-week treatment/observation period being too short and (2) the markedly different lengths of treatment/observation in the given therapeutic indication.

Nevertheless, the company selectively presented week-8 data of patients with homozygous/heterozygous F508del mutation, largely in different operationalizations. Hence, an adequate comparison of patients with heterozygous versus homozygous mutation is impossible even for this treatment duration, which is too short for the benefit assessment.

Ultimately, the company ended up not using the results of patients with homozygous F508del mutation for deriving an added benefit, but instead based the added benefit of tezacaftor/ivacaftor on the 8-week data of the VX14-661-108 study.

Since the results of the VX14-661-106 study are unsuitable for the present benefit assessment, they are not presented as supplementary information any further.

2.3.1 Study included by the company

The study included by the company is shown in the following table.

Table 5: Study pool of the company – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication and other sources[c] (yes/no [reference])
VX14-661-108	Yes	Yes	No	No[d]	Yes [4-7]	Yes [3,8,9,23-28]

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

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

2.3.2 Study characteristics of the study included by the company

Table 6 and Table 7 describe the VX14-661-108 study included by the company.

Table 6: Characterization of the study included by the company – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC (multi-page table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
VX14-661-108	RCT, double-blind, crossover study	Patients with CF aged 12 years or older who ▪ are heterozygous for the F508del mutation and ▪ have an RF[b] mutation on the second allele of the CFTR gene and ▪ have an FEV1 (in % of predicted normal) at baseline of ≥ 40% and ≤ 90%	N = 248 randomized[c] (to 6 treatment sequences: 1) tezacaftor/ivacaftor + ivacaftor → washout period → ivacaftor (N = 41) 2) ivacaftor → washout period → tezacaftor/ivacaftor + ivacaftor (N = 42) 3) placebo → washout period → tezacaftor/ivacaftor + ivacaftor (N = 41) 4) tezacaftor/ivacaftor + ivacaftor → washout period → placebo (N = 43) 5) ivacaftor →washout period → placebo (N = 40) 6) placebo → washout period → ivacaftor (N = 41) Patients per treatment in treatment period 1[d] ▪ tezacaftor/ivacaftor + ivacaftor (N = 83) ▪ placebo (n = 80) Patients per treatment in treatment period 2 ▪ tezacaftor/ivacaftor + ivacaftor (N = 78) ▪ placebo (n = 81) Patients per treatment group during the study (treatment period 1 + 2)[d] ▪ tezacaftor/ivacaftor + ivacaftor (N = 161) ▪ placebo (n = 161)	▪ Screening: 4 weeks ▪ Treatment period 1: 8 weeks ▪ Washout period: 8 weeks ▪ Treatment period 2: 8 weeks ▪ Observation[e]: 4 weeks	81 study centres in Australia, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, United Kingdom, USA 3/2015–2/2017	Primary: FEV1 in % of predicted normal Secondary: symptoms, health-related quality of life, AEs

Table 6: Characterization of the study included by the company – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC (multi-page table)

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

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes contain information exclusively on relevant available outcomes from the information provided by the company in Module 4 B of the dossier.
b. This inclusion criterion was met by 25 mutations: 2789+5G→A, R74W, R352Q, R1070W,3849+10 kbC→T, D110E, A455E, F1074L, 3272-26A→G, D110H, D579G, D1152H, 711+3A→G, R117C, S945L, D1270N, E56K, E193K, S977F, P67L, L206W, F1052V, E831X, R347H, K1060T (these are CFTR mutations which are likely to develop an RF: participants were included for 17 of these mutations).
c. Stratification by age (< 18 years versus ≥ 18 years), FEV1 (< 70%, ≥ 70% of predicted normal), and type of RF mutation on the second CFTR allele (class V non-canonical splice mutation vs. classes II to IV missense RF mutation).
d. Two patients had not received any study treatment and were therefore disregarded in the analysis of all outcomes. Two further patients had CFTR mutations which were excluded according to the inclusion criteria. These patients were included in the analysis of AEs, but not for further outcomes. This results in the following numbers of analysed patients: placebo (FAS): 39 (sequence 3; period 1) + 41 (sequence 4; period 2) + 40 (sequence 5; period 2) + 41 (sequence 6; period 1) = 161 (for AEs +1 patient); tezacaftor/ivacaftor + ivacaftor + BSC: 40 (sequence 1; period 1) + 39 (sequence 2; period 2) + 39 (sequence 3; period 2) + 43 (sequence 4; period 1) = 161 (for AEs +1 patient)
e. After completion of treatment period 2, patients could receive tezacaftor/ivacaftor in combination with ivacaftor for 96 weeks as part of the 1-arm study VX14-661-110.

ACT: appropriate comparator therapy; AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire – Revised; CFTR: cystic fibrosis transmembrane conductance regulator; FAS: full analysis set; FEV1: forced expiratory volume in 1 second; N: number of randomized patients; RCT: randomized controlled trial; RF: residual function

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

Study	Intervention	Comparison
VX14-661-108	Tezacaftor/ivacaftor[a] + ivacaftor[a] + BSC[b] ▪ in the morning: tezacaftor 100 mg / ivacaftor 150 mg or placebo, orally, tablet, with a high-fat meal ▪ in the evening: ivacaftor 150 mg or placebo, orally, tablet, with a high-fat meal	Placebo[a] + BSC[b]
	Non-permitted prior treatment ▪ transplantation **Non-permitted concomitant treatment** ▪ CYP3A inducers and inhibitors had to be discontinued 14 days before start of treatment	

a. Dose adjustments were not allowed. Dose interruptions after AE occurrence were permissible after consultation with the clinical monitor.
b. In the study, basic medication for the treatment of CF was given in addition to ivacaftor or placebo. The basic medication had to be stable from 4 weeks before the start of treatment until the end of the observation.

AE: adverse event; BSC: best supportive care; CF: cystic fibrosis; CYP: cytochrome P450; RCT: randomized controlled trial

Study design

The VX14-661-108 study was a randomized, controlled, double-blind study with crossover design (see below for details on the crossover design). It included 248 patients with CF aged 12 years and older who were heterozygous for the F508del mutation on the first allele of the CFTR gene and who had a residual function (RF) mutation on the second allele (see Table 9). According to the inclusion criteria of the study, patients had to additionally have a sweat chloride value of ≥ 60 mmol/L or, in case of a lower sweat chloride value, additionally chronic sinopulmonary disease. Patients had to have a forced expiratory volume in 1 second (FEV1) of ≥ 40% and ≤ 90% of predicted normal for age, sex, and body height at screening.

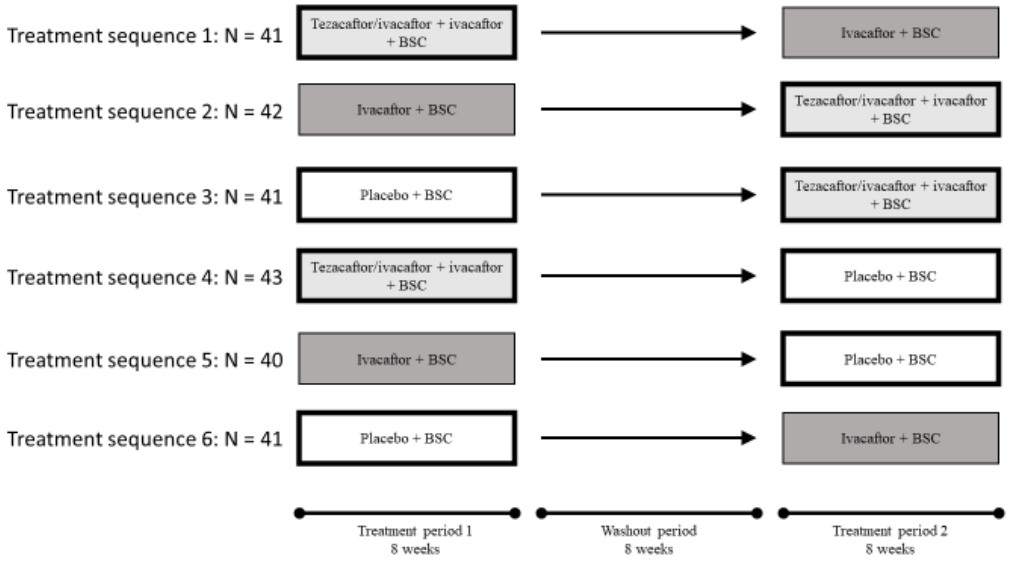
Using a crossover study design, VX14-661-108 compared 3 treatments:

- tezacaftor/ivacaftor + ivacaftor combination therapy
- ivacaftor
- placebo

Patients received continuous concomitant treatment largely in the sense of treatment with BSC (see Section: Implementation of the ACT).

A total of 248 patients were randomly allocated to 6 treatment sequences, each of which involved 2 treatments administered one after the other (see Figure 1).

Figure 1 shows the treatment sequences of the VX14-661-108 study.



Adapted according to Rowe 2017 [3]. The 2 treatment groups of tezacaftor/ivacaftor + ivacaftor + BSC and placebo + BSC presented as supplementary information in the present dossier assessment are outlined in bold.

N: number of randomized patients. Stable-dose concomitant medication in the sense of treatment with BSC was given in the washout period and in the treatment periods.

Figure 1: Treatment sequences of the VX14-661-108 study

Stratification was by age (< 18 versus ≥ 18 years), FEV1 (< 70% versus ≥ 70%), and type of RF mutation. After 8 weeks of treatment in treatment period 1, treatment was discontinued for 8 weeks (washout period). The washout period was followed by an 8-week second treatment period. Hence, the total treatment duration was 8 weeks. The present dossier assessment shows the short-term results for the comparison of the combination therapy of tezacaftor/ivacaftor + ivacaftor + BSC with placebo + BSC as supplementary information.

Treatment with tezacaftor/ivacaftor in combination with ivacaftor was in compliance with the specifications of the summary of product characteristics [29,30].

The second treatment period was followed by a 4-week observation period for AEs. This follow-up observation was not conducted in patients enrolled in the VX14-661-110 extension study.

In Module 4 B, the company presented analyses in which all patients who had received the combination therapy or placebo during the study were considered. This means that it included those patients who had received both relevant treatments, tezacaftor/ivacaftor + ivacaftor + BSC and placebo + BSC (treatment sequences 3 and 4). In addition, the company included in its analyses those patients from the other sequences (treatment sequences 1, 2, 5, 6) who had received either tezacaftor/ivacaftor + ivacaftor + BSC or placebo + BSC during the course of the study. The company did not present results separately by treatment period and treatment sequence.

Primary outcome of the study was FEV1. Patient-relevant secondary outcomes were symptoms, health-related quality of life, and AEs.

Special features of the crossover study design

A crossover design allows the intra-individual comparison of an experimental intervention with a control therapy since all participants receive both therapies (see Figure 1). In rare diseases such as CF, using a crossover design is a way to achieve power even with smaller sample sizes which, in a parallel-group design, would be attainable only with greater sample size. However, a crossover design produces meaningful results only if certain conditions are met [31]:

1) Carry-over effects are negligible.

   Carry-over effects occur when the therapies in treatment period 1 influence the effects in treatment period 2, so that there is an interaction between period and therapy. Washout periods between the treatment periods are used to prevent carry-over effects.

2) Period effects must be considered adequately in the statistical analyses.

   Period effects are effects which lead to different effects being observed in treatment period 1 than in treatment period 2 due to external circumstances. This applies equally to both therapies. In addition to rapid disease progression, e.g. a strong seasonal impact on the observed outcomes might lead to period effects. In a rapidly progressive disease, period effects would be inevitable.

The extent to which both conditions are met is not adequately addressed by the company.

It cannot be inferred from the available data for the VX14-661-108 study that the course of disease in this study was insufficiently stable over the duration of the study (condition 2). However, only data on the course of the outcome of FEV1 are available to check this condition. When looking at the placebo group, no particularly large decrease in FEV1 can be found over a period of 8 weeks (−0.37 in % of predicted normal, absolute change at week 8). In addition, stable disease was an inclusion criterion of the VX14-661-108 study.

Assuming that both of the above conditions are sufficiently fulfilled for the VX14-661-108 study, the short-term results of this study are presented as supplementary information in the present dossier assessment. Further information on the period effect and specific consequences of possible carry-over effects are described and considered below in the assessment of the risk of bias regarding the short-term results.

Crossover designs are usually ill-suited for irreversible outcomes [32]. This concerns the outcomes of all-cause mortality and discontinuation due to AEs (if the discontinuation did not allow participation in the following treatment periods). However, no deaths and only 1 discontinuation due to AEs occurred in the VX14-661-108 study.

Analysis method for the crossover design

For the effect measures of relative risk (RR) and rate ratio, the statistical analysis of the data is based on generalized linear mixed models (GLMMs), and for the effect measure of mean difference over the course of the study, on a mixed model for repeated measures (MMRM). For the MMRM, the program code for the primary outcome of change in FEV1, based on the SAS procedure proc mixed, is found in the statistical analysis plan (SAP) of the VX14-661-108 study. For the GLMMs, the SAS procedure proc glimmix is mentioned in SAP for the analysis of pulmonary exacerbations. However, no program code is available for the assessment of the corresponding analyses.

The mixed models described by the company, GLMM and MMRM, and the SAS procedures are in principle suitable for the statistical analysis of crossover studies which appropriately consider the intra-individual dependence of data [33]. In the present case, for about 2/3 of the considered patients, values are available from only 1 treatment period. The absence of values in a second treatment period is due to the randomization to the 6 sequences. Therefore, the missing values meet the assumption of missing at random (MAR), which is required for the mixed models. The company's approach does not lead to potential bias of results, but it can reduce the precision of effect estimators, i.e. reduce statistical power.

Patient characteristics

Table 8 and Table 9 show the characteristics of the patients in the VX14-661-108 study. The presentation in Table 8 is broken down by treatment period. Table 9 shows the 17 RF mutations of the patients on the second allele.

Table 8: Characteristics of the study populations at baseline – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC (multi-page table)

Study Characteristics Category	Treatment period 1		Treatment period 2	
	TEZA/IVA + IVA + BSC	Placebo + BSC	TEZA/IVA + IVA + BSC	Placebo + BSC
	N[a] = 83	N[a] = 80	N[a] = 78	N[a] = 81
VX14-661-108				
Age [years], mean (SD)	36 (14)	33 (14)	35.6 (16)	37 (15)
Age group [years], n (%)				
< 18 years	11 (13)	11 (14)	10 (13)	13 (16)
≥ 18 years	72 (87)	69 (86)	68 (87)	68 (84)
Sex [f/m], %	58/42	58 / 42	53/47	54/46
Family origin, n (%)				
White	80 (96.4)	77 (96.3)	77 (98.7)	80 (98.8)
Other[b]	3 (3.6)[c]	3 (3.8)[c]	1 (1.3)	1 (1.2)
Region, n (%)				
North America	45 (54.2)	39 (48.8)	36 (46.2)	43 (53.1)
Europe[d]	38 (45.8)	41 (51.3)	42 (53.8)	38 (46.9)
FEV1 (in % of predicted normal) at baseline, n (%)				
< 70%	52 (62.7)	51 (63.8)	49 (62.8)	51 (63.0)
≥ 70%	31 (37.3)	29 (36.3)	29 (37.2)	29 (35.8)
FEV1 (in % of predicted normal) before start of treatment, n (%)				
< 40%	8 (9.6)	6 (7.5)	8 (10.3)	9 (11.1)
≥ 40% to < 70%	48 (57.8)	48 (60.0)	42 (53.8)	47 (58.0)
≥ 70% to ≤ 90%	25 (30.1)	25 (31.3)	28 (35.9)	23 (28.4)
> 90%	2 (2.4)	1 (1.3)	0 (0)	2 (2.5)
Height [cm]				
Mean (SD)	168.8 (9.6)	168.0 (9.0)	169.0 (9.4)	169.6 (9.7)
Median (min; max)	168.0 (150.0; 190.0)	168.0 (146.0;190.0)	168.5 (146.0;195.0)	169.0 (150.0;190.0)
Body weight [kg]				
Mean (SD)	67.7 (16.5)	69.7 (16.7)	70.3 (15.9)	71.6 (19.9)
Median (min; max)	67.0 (43.0;127.0)	67.5 (42.0;112.0)	69.0 (42.0;112.0)	70.0 (40.0;156.9)
BMI [kg/m²], mean (SD)	23.6 (4.6)	24.6 (5.0)	24.5 (4.9)	24.7 (5.8)
Type of the RF mutation				
Class V non-canonical splice mutations	50 (60.2)	48 (60.0)	45 (57.7)	49 (60.5)
Classes II to IV missense RF mutations	33 (39.8)	32 (40.0)	33 (42.3)	32 (39.5)
Treatment before study inclusion[e], n (%)				
Inhaled antibiotics	26 (31.3)	23 (28.8)	23 (29.5)	27 (33.3)
Inhaled bronchodilators	74 (89.2)	71 (88.8)	67 (85.9)	70 (86.4)
Inhaled hypertonic saline	43 (51.8)	39 (48.8)	35 (44.9)	45 (55.6)

Table 8: Characteristics of the study populations at baseline – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC (multi-page table)

Study Characteristics Category	Treatment period 1		Treatment period 2	
	TEZA/IVA + IVA + BSC	Placebo + BSC	TEZA/IVA + IVA + BSC	Placebo + BSC
	N[a] = 83	N[a] = 80	N[a] = 78	N[a] = 81
VX14-661-108				
Inhaled corticosteroids	50 (60.2)	45 (56.3)	48 (61.5)	45 (55.6)
Dornase alfa	47 (56.6)	54 (67.5)	50 (64.1)	50 (61.7)
Pseudomonas aeruginosa infection within 2 years before baseline, n (%)	52 (62.7)	48 (60.0)	44 (56.4)	44 (54.3)
Treatment discontinuation, n (%)	1 (1.2)	2 (2.5)	0 (0)	0 (0)
Study discontinuation, n (%)	2 (2.4)[f]	6 (7.4)[g]	0 (0)	0 (0)

a. Number of analysed patients. Patients from all 6 treatment sequences are included in the analysis with the values from the respective treatment periods: 83 (40 from sequence 1 + 43 from sequence 2), 80 (39 from sequence 3 + 41 from sequence 6), 78 (39 from sequence 2 + 39 from sequence 3), 81 (41 from sequence 4 + 40 from sequence 5). Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Black/African American or other or not recorded.
c. IQWiG calculations.
d. Patients from Israel and Australia (1 patient in each case) were recorded under Europe.
e. Medication started up to 28 days before the first study medication and continued during treatment with the study medication.
f. Reasons: other, non-compliance (n = 1) and other (n = 1).
g. Reasons: AEs (n = 2), withdrawal of consent not due to AEs (n = 2), other or non-compliance (n = 1), lost to follow-up (n = 1).

AE: adverse event; BMI: body mass index; f: female; FAS: full analysis set; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; m: male; max: maximum; min.: minimum; n: number of patients in the category; N: number of analysed patients of the FAS population; RCT: randomized controlled trial; RF: residual function; SD: standard deviation; TEZA: tezacaftor

Table 9: Mutations on the second allele of the CFTR gene – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC

Study	**N[a] = 244**
VX14-661-108	n (%[b])
Mutations	
Class V non-canonical splice mutations, n (%)	
2789+5G→A	37 (15.2)
3849+10 kbC→T	69 (28.3)
3272-26A→G	36 (14.8)
711+3A→G	3 (1.2)
Classes II to IV missense RF mutations, n (%)	
P67L	17 (7.0)
E831X[c]	1 (0.4)
D110H[c]	1 (0.4)
R117C	1 (0.4)
L206W	5 (2.0)
R347H[c]	4 (1.6)
R352Q	3 (1.2)
R1070W	3 (1.2)
A455E	20 (8.2)
D579G	3 (1.2)
D1152H	26 (10.7)
S945L	13 (5.3)
S977F	2 (0.8)

a. Number of analysed patients from all 6 treatment sequences.
b. IQWiG calculations.
c. Excluded from the therapeutic indication of tezacaftor/ivacaftor [29].

BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; FAS: full analysis set; n: number of patients with event; N: number of analysed patients of the FAS population; RCT: randomized controlled trial; RF: residual function

The demographic characteristics between the patients included in the respective treatment groups were largely balanced. Over 80% of the patients were adults. About 60% of the patients had an FEV1 of < 70%.

At 28.3%, patients with the 3849+10 kbC→T mutation are most frequently represented in the VX14-661-108 study. According to the approval, the therapeutic indication relevant for this dossier assessment comprises only 14 RF mutations; 6 (2.5%) of the patients included in the study therefore do not belong to the target population in the therapeutic indication.

Implementation of the ACT

The G-BA specified BSC as the ACT in the context of appropriate combination treatment for tezacaftor/ivacaftor for patients with CF aged 12 years and older who are heterozygous for the F508del mutation and have 1 of the following mutations in the CFTR gene[b]: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10 kbC→T. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

In the VX14-661-108 study, patients were to continue their ongoing symptomatic treatment at the same time as treatment with tezacaftor/ivacaftor + ivacaftor or placebo. According to the study protocol, however, the concomitant medication had to be stable from 4 weeks before the start of the study until the end of the study. An additional inclusion criterion of the VX14-661-108 study was that participants were willing to keep the concomitant treatment associated with CF stable over the entire study period.

Medication taken within 28 days before the first intake of the study medication was recorded as prior reatment. Information on prior and concomitant treatment is listed in Table 10. Medication taken after the first dose of the study medication was recorded as concomitant treatment. Concomitant treatment was recorded throughout the study duration. Table 11 shows the concomitant treatments of patients over the entire study duration, broken down by treatment group per treatment period in which the patients were considered. Medication which was taken both within the 28 days before the first dose of the study medication and during the study treatment is shown in both tables.

Table 10: Treatment before first administration of study medication (≥ 15% in at least 1 study arm), RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC

Study	Treatment period 1		Treatment period 2	
	TEZA/IVA + IVA + BSC	Placebo + BSC	TEZA/IVA + IVA + BSC	Placebo + BSC
	n (%)	n (%)	n (%)	n (%)
VX14-661-108	**N[a] = 83**	**N[a] = 80**	**N[a] = 78**	**N[a] = 81**
Medicinal treatment[b]				
Salbutamol	51 (61.4)	44 (55.0)	40 (51.3)	52 (64.2)
Dornase alfa	47 (56.6)	54 (67.5)	50 (64.1)	50 (61.7)
Sodium chloride	43 (51.8)	45 (56.3)	39 (50.0)	53 (65.4)
Azithromycin	32 (38.6)	38 (47.5)	30 (38.5)	32 (39.5)
Colecalciferrol	23 (27.7)	24 (30.0)	22 (28.2)	26 (32.1)
Seretide	23 (27.7)	18 (22.5)	18 (23.1)	28 (34.6)
Pancreatin	18 (21.7)	10 (12.5)	18 (23.1)	18 (22.2)
Budesonid w/ formeterol fumarate	17 (20.5)	10 (12.5)	15 (19.2)	10 (12.3)
Fluticasone propionate	17 (20.5)	12 (15.0)	12 (15.4)	12 (14.8)
Vitamins NOS	17 (20.5)	14 (17.5)	15 (19.2)	16 (19.8)
Tobramycin	16 (19.3)	13 (16.3)	13 (16.7)	14 (17.3)
Montekulast sodium	15 (18.1)	8 (10.0)	5 (6.4)	11 (13.6)
Omeprazole	15 (18.1)	13 (16.3)	15 (19.2)	14 (17.3)
Vitamin D NOS	15 (18.1)	9 (11.3)	12 (15.4)	15 (18.5)
Aztreonam lysinate	13 (15.7)	12 (15.0)	12 (15.4)	11 (13.6)
Ibuprofen	13 (15.7)	8 (10.0)	7 (9.0)	15 (18.5)
Salbutamol sulfate	10 (12.0)	13 (16.3)	8 (10.3)	11 (13.6)
Non-medicinal treatment				
Physiotherapy[c]	44 (52.4)	44 (54.3)	ND	ND

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Started within 28 days before the first dose of the study medication, irrespective of the end date. PT, coded according to WHO-DD, December 2007.
c. Ongoing physiotherapy at start of treatment.

BSC: best supportive care; FAS: full analysis set; IVA: ivacaftor; n: number of patients with the administration of the respective medication; N: number of analysed patients of the FAS population; ND: no data; PT: preferred term; RCT: randomized controlled trial; TEZA: tezacaftor; WHO-DD: World Health Organization Drug Dictionary

Table 11: Concomitant treatment (≥ 15% in at least 1 study arm) – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC

Study	**TEZA/IVA + IVA + BSC**	**Placebo + BSC**
	n (%)	**n (%)**
VX14-661-108	N[a] = 161	N[a] = 161
Medicinal treatment[b]		
Dornase alfa	97 (60.2)	106 (65.8)
Salbutamol	92 (57.1)	101 (62.7)
Sodium chloride	83 (51.6)	101 (62.7)
Azithromycin	63 (39.1)	73 (45.3)
Colecalciferrol	50 (31.1)	52 (32.3)
Seretide	41 (25.5)	47 (29.2)
Pancreatin	37 (23.0)	28 (17.4)
Budesonid w/ formeterol fumarate	33 (20.5)	21 (13.0)
Tobramycin	33 (20.5)	40 (24.8)
Vitamins NOS	32 (19.9)	31 (19.3)
Aztreonam lysinate	31 (19.3)	28 (17.4)
Omeprazole	31 (19.3)	25 (15.5)
Fluticasone propionate	30 (18.6)	27 (16.8)
Ibuprofen	29 (18.0)	35 (21.7)
Vitamin D NOS	28 (17.4)	27 (16.8)
Paracetamol	20 (12.4)	28 (17.4)
Ciprofloxacin	16 (9.9)	33 (20.5)
Bactrim	11 (6.8)	28 (17.4)
Non-medicinal treatment		
Physiotherapy	ND[c]	ND[c]

a. Number of analysed patients. Patients from all 6 treatment sequences are included in the analysis with the values from the respective treatment periods.
b. Continued concomitant medication or concomitant medication initiated during treatment with the study medication until the end of observation. PT, coded according to WHO-DD, December 2007.
c. In treatment period 1, no patient in the tezacaftor/ivacaftor + ivacaftor + BSC group and 1 patient in the placebo + BSC group started physiotherapy. No data are available on treatment period 2 or on discontinuations of physiotherapy which was ongoing (at the start of treatment).

BSC: best supportive care; IVA: ivacaftor; n: number of patients with administration of the respective medication; N: number of analysed patients of the FAS population; ND: no data; PT: preferred term; RCT: randomized controlled trial; TEZA: tezacaftor; WHO-DD: World Health Organization Drug Dictionary

The available information suggests that patients received a variety of drugs for symptomatic treatment of CF (including dornase alfa as well as pancreatin and antibiotic therapy and sodium chloride) at the time point of study entry. The available data and the data provided by the company in Module 4 B with respect to treatment period 1 also suggest that individual patients started taking concomitant medication after the first dose of the study medication (e.g. antibiotic therapy and physiotherapy). It cannot be inferred from the data, however, whether the

concomitant treatment was adjusted, e.g. by increasing the dose or frequency in the course of the study, and if so, for how many patients this was the case.

In summary, the available data leave unclear whether increases in dose or frequency of the concomitant medication were possible, but in view of the short duration of the study, it is assumed that the concomitant treatment used was largely carried out in the sense of BSC.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of results	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
VX14-661-108	Yes	Yes	Yes	Yes	Yes	No[a]	Low

a. Insufficient information on carry-over and period effects.

BSC: best supportive care; RCT: randomized controlled trial

The risk of bias at study level was rated as low. This concurs with the company's assessment.

The following additional aspects came to bear in the study with crossover design:

With reference to the 8-week washout period, the company ruled out a carry-over effect. Furthermore, the company made reference to the comparability of the observed baseline values in period 1 and period 2 for the outcomes "FEV1", "CFQ-R domain of respiratory symptoms" and "sweat chloride concentration". The problem here is that the company merged data aggregated over different sequences; thus, not the same patients were included in the analysis (see Section 2.4.2).

Overall, however, information is missing on baseline characteristics and, for each period and each sequence, on the patient-relevant outcomes on symptoms (pulmonary exacerbations and measured using the CFQ-R) and health-related quality of life (measured using the CFQ-R and Short Form 12-Items Health Survey Version 2 [SF-12 v2]) [31,32]. Period-specific effect estimations for these outcomes are also necessary for an assessment of period effects [31,32]. A statistical test for a period effect showed no statistically significant result for the primary outcome "absolute change in FEV1".

The effects of the missing data on carry-over and period effects are considered in the assessment of the outcome-specific risk of bias (see Section 2.4.2).

Transferability of the study results to the German healthcare context

The company stated that 95% of included patients were of Caucasian descent and that their further characteristics also suggested very good comparability to the German healthcare context.

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

2.4 Short-term results of the study included by the company

2.4.1 Patient-relevant outcomes in the VX14-661-108 study

The following patient-relevant outcomes are presented as supplementary information on the VX14-661-108 study included by the company:

- Morbidity
  - pulmonary exacerbations
  - hospitalization due to 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
  - measured using the physical and mental health summary scores of the SF-12 v2
- AEs
  - SAEs
  - discontinuation due to AEs
  - further specific AEs, if any

Since the crossover design does not permit a meaningful investigation of the outcome "mortality", the latter is left out of the following tables. No deaths occurred in the VX14-661-108 study. Regarding the outcome "discontinuation due to AEs", it is assumed in the present dossier assessment that the discontinuation principally allowed participation in subsequent treatment periods.

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

Table 13 shows for which outcomes data are available.

Table 13: Matrix of outcomes – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC

Study	Outcomes						
	Pulmonary exacerbations	Hospitalization due to pulmonary exacerbations	Symptoms (CFQ-R)	Health-related quality of life (CFQ-R)	Health-related quality of life (SF-12 v2)	SAEs[a]	Discontinuation due to AEs
VX14-661-108	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Without recording of the PT "infectious pulmonary exacerbation of CT".

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SF-12 v2: 12-Item Short Form Health Survey Version 2

Beyond the patient-relevant outcomes, the following outcomes are presented as supplementary information and without considering subgroup characteristics, but without being included in the consideration of short-term results (see Section 2.4.3):

- Lung function using FEV1

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

Like in Module 4 B on the assessment of ivacaftor in combination with tezacaftor/ivacaftor, the company used FEV1 as a surrogate for CF-associated mortality [23]. However, the sources cited by the company did not demonstrate the validity of FEV1 as a surrogate. In its current dossier on tezacaftor/ivacaftor + ivacaftor, the company does not discuss any new aspects. For a detailed rationale on the outcome of FEV1 not qualifying as a valid surrogate outcome for mortality, see dossier assessment A19-71 on the drug ivacaftor in combination with tezacaftor/ivacaftor, Section 2.7.5.3.2 [8]).

- Body mass index (BMI)

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

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

In the present situation, the importance of the BMI as a measure of malnutrition is not directly evident since the mean BMI of patients in the VX14-661-108 study was in the normal range both at baseline and after 8 weeks of treatment.

2.4.2 Risk of bias

Table 14 presents the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias at study and outcome levels – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC

Study	Study level	Outcomes						
		Pulmonary exacerbations	Hospitalization due to pulmonary exacerbations	Symptoms (CFQ-R)	Health-related quality of life (CFQ-R)	Health-related quality of life (SF-12 v2)	SAEs[a]	Discontinuation due to AEs
VX14-661-108	L	H[b]	H[b]	H[b]	H[b]	H[b]	H[b]	L

a. Without recording of the PT "infectious pulmonary exacerbation of CT".
b. Insufficient data for the assessment of carry-over and period effects.

AE: adverse event; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; H: high; L: low; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SF-12 v2: 12-Item Short Form Health Survey Version 2

The results on pulmonary exacerbations, hospitalization due to pulmonary exacerbations, symptoms (measured using the CFQ-R), health-related quality of life (measured using the CFQ-R and SF-12 v2), and on the outcome of SAEs are rated as potentially highly biased since carry-over and period effects with regard to patient-relevant outcomes were insufficiently discussed by the company in Module 4 B (see Section 2.4.2). This departs from the assessment by the company, which rated the risk of bias of the results from all company-selected outcomes as low.

For the results on discontinuation due to AEs, the risk of bias is rated as low. There were 0 versus 1 event. Hence, no effect estimation is required for this outcome.

2.4.3 Results

Table 15, Table 16, and Table 17 present the short-term results of the comparison of tezacaftor/ivacaftor + ivacaftor + BSC with BSC in patients with CF aged 12 years and older who are heterozygous for the F508del mutation and have 1 of the following 14 mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10 kbC→T as supplementary information. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier. As described above, the company did not present any results broken down by treatment period and treatment sequence.

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

The results on common AEs, SAEs, and discontinuation due to AEs are presented in Appendix A of the full report. The company presented common AEs as well as common SAEs without the PT of infectious pulmonary exacerbation of CF. Due to the identical evidence base, this benefit assessment presents common AEs, common SAEs, including the PT of infectious pulmonary exacerbations of CF, in accordance with the dossier assessment of ivacaftor in the present therapeutic indication in order to reflect the total burden [8].

Table 15: Results, treatment duration of 8 weeks (AEs, dichotomous) – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC

Study Outcome category Outcome	TEZA/IVA + IVA + BSC		Placebo + BSC		TEZA/IVA + IVA + BSC vs. placebo + BSC
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value
VX14-661-108					
AEs					
AEs (supplementary information)[b]	162	111 (68.5)		122 (75.3)	–
SAEs[b]	162	4 (2.5)		9 (5.6)	0.44 [0.14; 1.42]; p = 0.169
Discontinuation due to AEs	162	0 (0.0)	162	1 (0.6)	–[c]

a. Number of analysed patients. Patients from all 6 treatment sequences are included in the analysis with the values from the respective treatment periods.
b. Without recording of the PT "infectious pulmonary exacerbation of CT".
c. No meaningful calculation possible.

AE: adverse event; BSC: best supportive care; CI: confidence interval; IVA: ivacaftor; n: number of patients with (at least 1) event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TEZA: tezacaftor

Table 16: Results, treatment duration of 8 weeks (morbidity, dichotomous) – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC

Study Outcome category Outcome	TEZA/IVA + IVA + BSC		Placebo + BSC		TEZA/IVA + IVA + BSC vs. placebo + BSC
	N[a]	Number of events n_E (n_E / patient years)[b]	N[a]	Number of events n_E (n_E / patient years)[b]	Rate ratio [95% CI]; p-value[c]
VX14-661-108					
Morbidity					
Pulmonary exacerbations	161	11 (0.39[d])	161	20 (0.71[d])	0.53 [0.26; 1.12]; 0.096
Hospitalization due to pulmonary exacerbations	161	3 (0.11[d])	161	5 (0.18[d])	0.79 [0.19; 3.23]; 0.737

a. Number of analysed patients. Patients from all 6 treatment sequences are included in the analysis with the values from the respective treatment periods.
b. Event rate (nE / patient years) is calculated from the total number of events divided by the total number of years (sum of the observation period of all patients included in the analysis).
c. Effect estimate and p-value: negative binomial model in a generalized linear mixed model. Fixed effects are treatment, period, and FEV1 at baseline, patient as random effect; log(study time) as offset.
d. IQWiG calculations.

BSC: best supportive care; CI: confidence interval; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; N: number of analysed patients; nE: number of events; RCT: randomized controlled trial; TEZA: tezacaftor

Table 17: Results, treatment duration of 8 weeks (morbidity, health-related quality of life, continuous) – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC (multi-page table)

Study **Outcome category** **Outcome**	**TEZA/IVA + IVA + BSC**			**Placebo + BSC**			**TEZA/IVA + IVA + BSC vs. placebo + BSC**
	N[a]	**Values at baseline mean (SD)**	**Change at end of study mean[b] (SD)**	**N[a]**	**Values at baseline mean (SD)**	**Change at end of study mean[b] (SD)**	**MD[c] [95% CI]; p-value**
VX14-661-108							
Morbidity							
Symptoms (CFQ-R, symptom domains, children [12 to 13 years] and adolescents or adults – pooled)[d]							
Respiratory symptoms	161	68.20 (17.51)	9.82 (16.79)	160	68.75 (18.29)	−2.35 (17.29)	10.82 [8.30; 13.33]; < 0.001 Hedges' g: 0.84 [0.61; 1.07]
Digestive symptoms	161	84.20 (16.51)	−0.69 (14.35)	160	83.57 (17.13)	2.11 (12.17)	−2.57 [−4.77; −0.36]; 0.023 Hedges' g: −0.24 [−0.46; −0.02]
Weight[e]	155	87.10 (24.73)	4.10 (21.60)	155	87.82 (21.78)	−0.43 (18.27)	3.58 [0.42; 6.74]; 0.026 Hedges' g: 0.245 [0.02; 0.47]
FEV1 (in % of predicted normal; absolute change)[f]	*159*	*62.15 (14.74)*	*6.69 (7.03)*	*160*	*62.22 (14.28)*	*−0.37 (6.58)*	*6.67 [5.49; 7.84]; < 0.001*
FEV1 (in % of predicted normal, relative change)[f]	*159*	*62.15 (14.74)*	*11.40 (12.86)*	*160*	*62.22 (14.28)*	*−0.20 (10.88)*	*11.16 [9.15; 13.16]; < 0.001*
BMI ([kg/m²], absolute change)	*158*	*24.06 (4.74)*	*0.34 (0.96)*	*160*	*24.63 (5.41)*	*0.18 (0.81)*	*0.15 [−0.00; 0.31]; 0.052*

Table 17: Results, treatment duration of 8 weeks (morbidity, health-related quality of life, continuous) – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC (multi-page table)

Study Outcome category Outcome	TEZA/IVA + IVA + BSC			Placebo + BSC			TEZA/IVA + IVA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	MD[c] [95% CI]; p-value
VX14-661-108							
Health-related quality of life							
CFQ-R (health-related quality of life domains, children [12 to 13 years] and adolescents or adults – pooled)[d]							
Physical functioning	161	73.30 (22.31)	3.25 (18.38)	160	70.21 (23.01)	−4.29 (17.67)	6.76 [4.01; 9.50]; < 0.001 Hedges' g: 0.49 [0.26; 0.71]
Emotional functioning	161	82.00 (15.78)	1.16 (10.68)	160	80.23 (15.93)	−0.44 (12.21)	2.51 [0.84; 4.19]; 0.004 Hedges' g: 0.28 [0.06; 0.50]
Vitality[e]	155	60.54 (17.72)	4.03 (19.31)	155	59.24 (19.91)	−4.27 (18.92)	7.86 [5.20; 10.53]; < 0.001 Hedges' g: 0.57 [0.34; 0.79]
Social functioning	161	69.93 (17.65)	3.62 (12.46)	161	67.42 (18.32)	−0.43 (11.82)	2.80 [1.04; 4.57]; 0.002 Hedges' g: 0.29 [0.07; 0.51]
Role functioning[e]	155	83.92 (16.56)	0.48 (14.35)	155	82.98 (16.23)	−3.79 (14.82)	3.14 [0.81; 5.47]; 0.009 Hedges' g: 0.26 [0.04; 0.49]
Body image	161	82.88 (17.30)	4.14 (12.84)	161	84.13 (18.03)	−0.35 (12.61)	2.17 [0.48; 3.85]; 0.006 Hedges' g: 0.22 [0.00; 0.44]
Eating disorders	161	93.03 (14.48)	-0.62 (13.68)	160	93.37 (12.93)	−2.80 (13.17)	1.42 [-0.55; 3.38]; 0.156
Treatment burden	161	63.98 (21.79)	3.31 (15.66)	161	62.73 (21.78)	−1.22 (15.19)	2.86 [0.85; 4.87]; 0.007 Hedges' g: 0.24 [0.02; 0.46]
Health perceptions[e]	155	65.95 (20.56)	5.59 (15.11)	156	63.89 (21.37)	−3.01 (15.11)	8.93 [6.69, 11.16]; < 0.001 Hedges' g: 0.74 [0.51; 0.97]

Table 17: Results, treatment duration of 8 weeks (morbidity, health-related quality of life, continuous) – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC (multi-page table)

Study Outcome category Outcome	TEZA/IVA + IVA + BSC			Placebo + BSC			TEZA/IVA + IVA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	MD[c] [95% CI]; p-value
VX14-661-108							
Health-related quality of life							
SF-12 v2[d]							
Physical Component Summary[g]	160	49.99 (7.78)	1.21 (6.49)	158	49.64 (7.21)	−1.28 (6.18)	2.40 [1.47; 3.33]; < 0.001 Hedges' g: 0.50 [0.27; 0.72]
Mental Component Summary[g]	160	52.55 (7.09)	0.22 (6.53)	158	51.56 (8.98)	−0.77 (8.08)	1.35 [0.31; 2.38]; 0.011 Hedges' g: 0.25 [0.03; 0.47]

Results presented in italics: no interpretation of the advantages and disadvantages of treatment.

a. Number of patients considered in the analysis for the calculation of the effect estimation. The values at the start of the study may be based on other patient numbers. Patients from all 6 treatment sequences are included in the analysis with the values from the respective treatment periods.

b. Refers to the change from baseline to the last time point of measurement.

c. MMRM: effect presents the difference between the treatment groups of the changes averaged over the course of the study between the respective time points of measurement and the start of the study. Model: dependent variable absolute change from baseline; period and treatment as fixed effects; adjusted for baseline values of the respective SF-12 domain; patient as random effect.

d. Higher values indicate better quality of life or symptoms; a positive group difference corresponds to an advantage of tezacaftor/ivacaftor.

e. Domain for adolescents or adults; not intended for children [12 to 13 years].

f. Higher values correspond to better lung function; a positive difference between groups corresponds to an advantage for tezacaftor/ivacaftor.

g. Data are available on 2 of the 8 subscales in total. Since data are not available on all subscales, the 2 available subscales are not presented.

BSC: best supportive care; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; MD: mean difference; MMRM: mixed effect model repeated measurement; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SF-12 v2: 12-Item Short Form Health Survey Version 2; TEZA: tezacaftor

The short-term results from the study included by the company are described below. Except for the outcome of discontinuation due to AEs, the risk of bias is high for all results (see Section 2.4.2).

Morbidity

Pulmonary exacerbations

Operationalization

In the study, pulmonary exacerbations were defined as new, or changed, antibiotic therapy (intravenous, inhaled, or oral) being required for any 4 or more of the following signs or symptoms:

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

This definition of pulmonary exacerbations is deemed adequate.

The company classified pulmonary exacerbations in 3 operationalizations:

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

For the present dossier assessment, pulmonary exacerbations and hospitalization due to pulmonary exacerbations were each analysed using the event quantity and event rate (number of events / patient years) in order to consider not only the occurrence, but also the frequency of pulmonary exacerbations over the entire course of the study. In this process, hospitalization due to pulmonary exacerbations marks the occurrence of serious exacerbations.

Results

For each of the operationalizations of pulmonary exacerbation and hospitalization due to pulmonary exacerbations, no statistically significant difference between the treatment groups was found.

Symptoms measured using the CFQ-R

Operationalization

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

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

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

Results

"Respiratory symptoms" domain

In the "respiratory symptoms" domain, a statistically significant difference was found in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC for the change from baseline. The SMD in the form of Hedges' g was employed to assess the relevance of the result. The 95% CI was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect. However, there was an effect modification by the attribute of age. In adults (18 years and older), an advantage of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC is found (see Section 2.4.4).

"Digestive symptoms" domain

In the "digestive symptoms" domain, a statistically significant effect to the disadvantage of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC was found. The SMD in the form of Hedges' g was employed to assess the relevance of these results. The 95% CI was not completely above or below the irrelevance threshold of 0.2 or −0.2. It can therefore not be inferred that this effect was relevant.

"Weight" domain

In the "weight" domain, a statistically significant effect was found in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC. The SMD in the form of Hedges' g was employed to assess the relevance of these results. The 95% CI was not completely above or below the irrelevance threshold of 0.2 or -0.2. It can therefore not be inferred that the effect was relevant.

Health-related quality of life

Health-related quality of life (measured using the CFQ-R domains)

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

Results

"Physical functioning" domain

In the "physical functioning" domain, a statistically significant difference in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC was found. The SMD in the form of Hedges' g was considered to assess the relevance of the results. The 95% CI was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect. However, there were effect modifications by each of the characteristics of FEV1 (in % of predicted normal) and *Pseudomonas aeruginosa* infection within 2 years before the start of the study. On the other hand, due to missing data on the investigation of potential dependencies between the subgroup characteristics, the subgroups results cannot be interpreted (see Section 2.4.4).

"Vitality" domain

A statistically significant difference in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC was shown for the change from baseline in the domain "vitality". The SMD in the form of Hedges' g was considered to assess the relevance of the results. The 95% CI was completely above the irrelevance threshold of 0.2. Hence, there were relevant effects in each case. There were, however, effect modifications by the characteristics of FEV1 (in % of predicted normal) and *Pseudomonas aeruginosa* infection within 2 years before the baseline for the "vitality" domain. On the other hand, due to missing data on the investigation of potential dependencies between the subgroup characteristics, the subgroups results cannot be interpreted (see Section 2.4.4).

"Health perceptions" domain

A statistically significant difference in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC was shown in the "health perceptions" domain. The SMD in the form of Hedges' g was considered to assess the relevance of the results. The 95% CI was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect.

There was an effect modification by the attribute of age. In adults (18 years and older), an advantage of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC was found.

Domains "emotional functioning", "social functioning", "role functioning", "body image", and "treatment burden"

In addition, statistically significant effects in favour of tezacaftor/ivacaftor + ivacaftor + BSC were shown in the domains of emotional functioning, social functioning, role functioning, body image, and treatment burden. The SMD in the form of Hedges' g was considered to assess the

relevance of the results. The 95% CI was not completely above the irrelevance threshold of 0.2 in any of the outcomes. It can therefore not be inferred that these effects were relevant.

"Eating disorders" domain

In the "eating disorders" domain, no statistically significant difference between the treatment groups was found.

Health-related quality of life measured using the physical and mental health summary scores of the SF-12 v2

Operationalization

The SF-12 is a short form of the validated generic questionnaire SF-36. All 12 items are also found in the SF-36. According to the manual, the SF-12 still covers the 8 underlying concepts of the SF-36, with 1 to 2 items each [34].

Like in the SF-36, the two summary scores (physical and mental) are formed for the analysis. In addition to the two summary scores, the company's dossier provides analyses of 2 out of the 8 subscales. Since data are not available for all subscales, no supplementary presentation of the 2 available subscales is provided.

Results

Both the physical and mental health summary score showed statistically significant effects in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC. The SMD in the form of Hedges' g was considered in each case to assess the relevance of the results.

For the Physical Component Summary, the 95% CI of the SMD in the form of Hedges' g was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect. In the Physical Component Summary, there was an effect modification by age, however. For adults (aged 18 years and older), there was an advantage of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC (see Section 2.4.4).

For the Mental Component Summary, however, the 95% CI of the SMD in the form of Hedges' g was not completely above the irrelevance threshold of 0.2. It can therefore not be inferred that this effect was relevant.

AEs

SAEs and discontinuation due to AEs

For the outcome of SAEs (excluding the preferred term of infectious pulmonary exacerbation of CF), no statistically significant difference between the treatment groups was found.

There was 1 discontinuation due to AEs. This resulted in no statistically significant difference between the treatment groups.

2.4.4 Subgroups and other effect modifiers (study included by the company)

The following subgroup characteristics were employed for the presentation of results of the VX14-661-108 study:

- age (< 18, ≥ 18 years)
- sex (female, male)
- region (North America, Europe [including Israel and Australia])
- FEV1 (in % of predicted normal) at baseline (< 70%, ≥ 70%)
- *Pseudomonas aeruginosa* infection within 2 years before baseline (yes, no)
- RF mutation (class V non-canonical splice mutation, classes II to IV missense RF mutation)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. For binary data, there must be 10 events in at least 1 subgroup.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

Table 18 presents the subgroup results of subgroup characteristics with a statistically significant and relevant effect in at least 1 subgroup.

Table 18: Subgroups, treatment duration of 8 weeks (morbidity, health-related quality of life, continuous) – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC (multi-page table)

Study Outcome Character-istic Subgroup	TEZA/IVA + IVA + BSC			Placebo + BSC			TEZA/IVA + IVA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	MD [95% CI]; p-value[c]
VX14-661-108							
Morbidity: symptoms: CFQ-R "respiratory symptoms" domain, children [12 to 13 years] and adolescents or adults – pooled							
Age							
< 18 years	21	81.22 (11.38)	3.44 (13.23)	24	82.29 (14.37)	−2.17 (15.67)	1.78 [−3.38; 6.94]; 0.472
≥ 18 years	140	66.25 (17.47)	10.78 (17.09)	136	66.37 (17.91)	−2.38 (17.61)	12.30 [9.58; 15.03]; < 0.001 Hedges' g: 0.95 [0.70; 1.20]
Total						Interaction:	0.004
Health-related quality of life: CFQ-R "health perceptions" domain, adolescents or adults[d]							
Age							
< 18 years	15	67.41 (21.19)	5.19 (10.17)	19	73.68 (21.34)	1.85 (17.15)	−0.94 [−9.02; 7.14]; 0.804
≥ 18 years	140	65.79 (20.56)	5.63 (15.57)	137	62.53 (21.09)	−3.65 (14.77)	10.28 [8.00; 12.56]; < 0.001 Hedges' g: 0.86 [0.62; 1.11]
Total						Interaction:	0.002
Health-related quality of life: CFQ-R "physical functioning" domain, children [12 to 13 years] and adolescents or adults – pooled							
FEV1 (in % of predicted normal) at baseline							
< 70	106	69.10 (22.69)	4.33 (19.51)	109	66.24 (23.11)	−6.28 (18.95)	9.10 [5.57; 12.64]; < 0.001 Hedges' g: 0.61 [0.34; 0.89]
≥ 70	55	81.38 (19.32)	1.17 (15.94)	51	78.79 (20.51)	0.06 (13.67)	1.94 [−2.13; 6.01]; 0.342
Total						Interaction:	0.012

Table 18: Subgroups, treatment duration of 8 weeks (morbidity, health-related quality of life, continuous) – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC (multi-page table)

Study Outcome Character-istic Subgroup	TEZA/IVA + IVA + BSC			Placebo + BSC			TEZA/IVA + IVA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	MD [95% CI]; p-value[c]
VX14-661-108							
Health-related quality of life: CFQ-R "physical functioning" domain, children [12 to 13 years] and adolescents or adults – pooled							
Pseudomonas aeruginosa infection within 2 years before baseline							
Yes	96	70.28 (21.66)	2.39 (20.95)	92	68.84 (22.25)	−7.46 (20.05)	9.31 [5.51; 13.11]; < 0.001 Hedges' g 0.64 [0.34; 0.93]
No	65	77.75 (22.69)	4.51 (13.79)	68	72.04 (24.03)	−0.04 (12.82)	3.42 [−0.49; 7.33] 0.086
Total						Interaction:	0.036
Health-related quality of life: CFQ-R "vitality" domain, adolescents or adults[d]							
FEV1 (in % of predicted normal) at baseline							
< 70	105	61.90 (16.86)	3.17 (19.96)	106	58.26 (18.90)	−6.68 (19.70)	9.91 [6.51; 13.32]; < 0.001 Hedges' g: 0.71 [0.43; 0.99]
≥ 70	50	57.67 (19.26)	5.83 (17.92)	49	61.39 (22.03)	1.04 (16.00)	4.12 [0.14; 8.11]; 0.043 Hedges' g: 0.31 [−0.09; 0.71]
Total						Interaction:	0.029
Pseudomonas aeruginosa infection within 2 years before baseline							
Yes	95	60.44 (16.26)	4.21 (19.02)	92	58.70 (18.94)	−6.59 (19.66)	10.29 [6.76; 13.81]; < 0.001 Hedges' g 0.74 [0.44; 1.03]
No	60	60.69 (19.95)	3.75 (19.91)	63	60.03 (21.37)	−0.93 (17.40)	4.59 [0.49, 8.68] 0.029 Hedges' g 0.33 [−0.02; 0.69]
Total						Interaction:	0.033

Table 18: Subgroups, treatment duration of 8 weeks (morbidity, health-related quality of life, continuous) – RCT, direct comparison: tezacaftor/ivacaftor + ivacaftor + BSC vs. placebo + BSC (multi-page table)

Study Outcome Character-istic Subgroup	TEZA/IVA + IVA + BSC			Placebo + BSC			TEZA/IVA + IVA + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SD)	MD [95% CI]; p-value[c]
VX14-661-108							
Health-related quality of life: SF-12 v2 Physical Component Summary							
Age							
< 18 years	21	53.27 (4.75)	0.57 (3.51)	23	53.86 (4.64)	0.30 (3.92)	−0.29 [−1.25, 0.67] 0.518
≥ 18 years	139	49.49 (8.04)	1.31 (6.83)	135	48.92 (7.34)	−1.55 (6.46)	2.91 [1.86, 3.95] < 0.001 Hedges' g: 0.58 [0.34; 0.83]
Total						Interaction:	0.009

a. Number of patients included in the analysis for the calculation of the effect estimation. The values at the start of the study may be based on other patient numbers. Patients from all 6 treatment sequences are included in the analysis with the values from the respective treatment periods.
b. Refers to the change from baseline to the last time point of measurement.
c. MMRM: effect presents the difference between the treatment groups of the changes averaged over the course of the study between the respective time point of measurement and baseline. Model: dependent variable absolute change from baseline; period, treatment, and treatment x subgroup as fixed effects; adjusted for baseline values and the respective CFQ-R domain; patient as random effect.
d. Domain for adolescents or adults; not intended for children [12 to 13 years].

CI: confidence interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; MD: mean difference; MMRM: mixed effect model repeated measurement; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; TEZA: tezacaftor

Morbidity

Symptoms measured using the CFQ-R

"Respiratory symptoms" domain

There was an effect modification by the attribute of age in the "respiratory symptoms" domain. There was no statistically significant difference between the treatment groups for patients from 12 to 17 years of age. For adults (18 years and older), however, there was a statistically significant difference in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC. The SMD in the form of Hedges' g was considered to assess the relevance of the results. The 95% CI was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect.

Health-related quality of life

Health-related quality of life (measured using the CFQ-R domains)

"Health perceptions" domain

There was an effect modification by the attribute of age. There was no statistically significant difference between the treatment groups for patients from 12 to 17 years of age. There was a statistically significant effect in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC for adults. The SMD in the form of Hedges' g was considered to assess the relevance of the results. The 95% CI was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect.

"Physical functioning" domain

In the "physical functioning" domain, there were effect modifications by the characteristic of FEV1 (in % of predicted normal) at baseline as well as by the characteristic of *Pseudomonas aeruginosa* infection within 2 years before baseline.

There was no statistically significant difference between the treatment groups for patients with an FEV1 ≥ 70% at baseline. There was a statistically significant effect in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC for patients with an FEV1 < 70% at baseline. The 95% CI of the SMD in the form of Hedges' g was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect.

There was no statistically significant effect between the treatment groups for patients without *Pseudomonas aeruginosa* infection within 2 years before baseline in this domain. There was a statistically significant difference in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC for patients with *Pseudomonas aeruginosa* infection within 2 years before baseline. The 95% CI of the SMD in the form of Hedges' g was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect.

The subgroup results could not be interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing.

"Vitality" domain

In the "vitality domain", there were effect modifications by the characteristic of FEV1 (in % of predicted normal) at baseline and by the characteristic of *Pseudomonas aeruginosa* infection within 2 years before baseline.

In the "vitality" domain, there was a statistically significant effect in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC for patients with an FEV1 ≥ 70% at baseline. The 95% CI of the SMD in the form of Hedges' g was not completely above or below the irrelevance threshold of 0.2 or −0.2. It can therefore not be inferred that the effect was relevant. For patients with an FEV1 < 70% at baseline, the effect was statistically significant in favour of tezacaftor/ivacaftor + ivacaftor + BSC. The 95% CI of the SMD in the

form of Hedges' g was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect.

There was a statistically significant effect in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC for patients without *Pseudomonas aeruginosa* infection within 2 years before baseline in this domain. The 95% CI of the SMD in the form of Hedges' g was not completely above or below the irrelevance threshold of 0.2 or −0.2. It can therefore not be inferred that the effect was relevant. For patients with *Pseudomonas aeruginosa* infection within 2 years before baseline, the effect was statistically significant in favour of tezacaftor/ivacaftor + ivacaftor + BSC. The 95% CI of the SMD in the form of Hedges' g was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect.

The subgroup results could not be interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing.

Health-related quality of life measured using the Physical Component Summary of the SF-12 v2

There was an effect modification by the characteristic of age for the "health-related quality of life" outcome measured using the Physical Component Summary of the SF-12 v2. There was no statistically significant difference between the treatment groups for patients from 12 to 17 years of age. For adults (aged 18 years and older), however, there was a statistically significant effect in favour of tezacaftor/ivacaftor + ivacaftor + BSC versus placebo + BSC. The 95% CI of the SMD in the form of Hedges' g was completely above the irrelevance threshold of 0.2. Hence, there was a relevant effect.

2.4.5 Summary

Studies with a minimum duration of 24 weeks are necessary for the benefit assessment in the therapeutic indication of CF. In the present therapeutic indication, the company presented only comparative data collected over a period of 8 weeks. These show only short-term effects, however, which are unsuitable for the derivation of an added benefit in the present therapeutic indication. Nevertheless, due to the rarity of the mutations to be investigated and the fact that children are affected, the study is described in the present dossier assessment, and the short-term effects are described.

Overall, no disadvantages of tezacaftor/ivacaftor + ivacaftor + BSC in comparison with placebo + BSC resulted from the short-term results of the VX14-661-108 study (8-week period). The following advantages of tezacaftor/ivacaftor + ivacaftor + BSC were shown in comparison with placebo + BSC:

- Morbidity: advantage for adults (≥ 18 years) in favour of tezacaftor/ivacaftor + ivacaftor + BSC in comparison with placebo + BSC in the "respiratory symptoms" domain recorded using the CFQ-R

- Health-related quality of life:
  - advantage in favour of tezacaftor/ivacaftor + ivacaftor + BSC in comparison with placebo + BSC in the “physical functioning” and “vitality” domains, each recorded using the CFQ-R
  - advantage for adults (≥ 18 years) in favour of tezacaftor/ivacaftor + ivacaftor + BSC in comparison with placebo + BSC in the “health perceptions” domain recorded using the CFQ-R and in the Physical Component Summary of the SF-12 v2

2.5 Probability and extent of added benefit

Table 19 presents the results of the assessment of added benefit of tezacaftor/ivacaftor + BSC in comparison with the ACT.

Table 19: Tezacaftor/ivacaftor + ivacaftor + BSC – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with CF aged 12 years and older who are heterozygous for the F508del mutation and have 1 of the following 14 mutations in the CFTR gene[b]: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10 kbC→T	BSC	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. These are RF mutations. ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; RF: residual function		

The assessment described above deviates from that submitted by the company, which derived an indication of considerable added benefit on the basis of the 8-week data of the VX14-661-108 study.

The G-BA decides on the added benefit.

Supplementary note

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

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Please see full dossier assessment for full reference list.

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

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