IQWiG

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

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

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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:

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

IQWiG employees involved in the dossier assessment:

- Claudia Selbach

- Christiane Balg

- Lars Beckmann

- Katharina Biester

- Petra Kohlepp

- Ulrike Lampert

- Daniela Preukschat

- Min Ripoll

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
EMA	European Medicines Agency
FEV1	forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
RF	residual function
SAE	serious adverse event
SF-12	Short Form 12-Items Health Survey Version 2
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ivacaftor in combination with tezacaftor/ivacaftor. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 28 August 2019.

Research question

The aim of the present report is the assessment of the added benefit of ivacaftor in combination with tezacaftor/ivacaftor in comparison with the appropriate comparator therapy (ACT) 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 and 3849+10kbC→T.

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

Therapeutic indication	ACT[a]
Patients with cystic fibrosis 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+10kbC→T	BSC
a: Presentation of the ACT specified by the G-BA. b: These are RF mutations.	
ACT: appropriate comparator therapy; BSC: best supportive care; 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 the added benefit.

Study included by the company

In its dossier, the company used the RCT VX14-661-108 with a study duration of 8 weeks for the assessment of the added benefit. The VX14-661-108 study compared 3 interventions in a crossover design: ivacaftor, combination therapy of ivacaftor + tezacaftor/ivacaftor and placebo. The patients received continuous concomitant treatment largely in the sense of treatment with BSC. For the benefit assessment, the company considered the comparison of ivacaftor in combination with tezacaftor/ivacaftor + BSC versus placebo + BSC.

Due to the study duration 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. CF is 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. It is also not possible to record any effects that only become apparent in the longer term, such as for pulmonary exacerbations and their consequences or for adverse events (AEs).

The company justified the inclusion criterion of 8 weeks used by the company 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 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. A conclusion on the added benefit is not derived from it.

Special features of the crossover study design
A crossover design only produces informative results if certain conditions are met:

1) Carry-over effects are negligible.

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

Assuming that the 2 conditions described above 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 not adequate for irreversible outcomes. This concerns the outcomes "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 one discontinuation due to AEs occurred in the VX14-661-108 study.

Implementation of the appropriate comparator therapy
In the VX14-661-108 study, patients were to continue their ongoing symptomatic treatment at the same time as treatment with ivacaftor + tezacaftor/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. It was also an inclusion criterion of the

VX14-661-108 study that the participants were willing to keep the concomitant treatment associated with CF stable over the entire study period.

The available information suggests that the patients were given 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 individual patients initiated 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 and how many patients had their concomitant treatment adjusted, for example in the sense of an increase in dose or frequency.

In summary, it remains unclear on the basis of the available data 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 a BSC.

Short-term results of the study included by the company

Overall, the results from the VX14-661-108 study had a high risk of bias. The results on serious AEs (SAEs) are not usable, as events attributable to the underlying disease were also recorded for the recording of side effects.

Morbidity

Pulmonary exacerbations, hospitalization due to pulmonary exacerbations

There was no statistically significant difference between the treatment groups for the outcomes "pulmonary exacerbations" and "hospitalization due to pulmonary exacerbations".

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

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

▪ Domain "respiratory symptoms"

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

▪ Domain "digestive symptoms"

There was a statistically significant effect to the disadvantage of ivacaftor + tezacaftor/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.

- Domain "weight"

There was a statistically significant effect in favour of ivacaftor + tezacaftor/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 problems, treatment burden and health perceptions of the CFQ-R.

- Domain "physical functioning"

A statistically significant difference in favour of ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC was shown in the domain "physical functioning". 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.

- Domain "vitality"

A statistically significant difference in favour of ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC was shown for the change from baseline in the domain "vitality". 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.

- Domain "health perceptions"

A statistically significant difference in favour of ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC was shown in the domain "health perceptions". 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 characteristic "age". For adults (aged 18 years and older), there was an advantage of ivacaftor + ivacaftor/tezacaftor + BSC versus placebo + BSC.

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

In addition, statistically significant effects in favour of ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC were shown in the domains of emotional functioning, social functioning, role functioning, body image and treatment burden. 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.

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

Both the physical and the mental sum score showed statistically significant effects in favour of ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC. 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. However, there was an effect modification by age. For adults (aged 18 years and older), there was an advantage of ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC.

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.

Side effects
Serious adverse events and discontinuation due to adverse events
The results on SAEs are not usable.

There was one 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 the added benefit of the drug ivacaftor in combination with tezacaftor/ivacaftor compared with the ACT is assessed as follows:

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

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[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].

Table 3: Ivacaftor in combination with tezacaftor/ivacaftor + BSC – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Patients with cystic fibrosis aged 12 years and older who are heterozygous for the F508del mutation and have one 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+10kbC→T	BSC	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. b: These are RF mutations. ACT: appropriate comparator therapy; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; RF: residual function		

The G-BA decides on the added benefit.

2.2   Research question

The aim of the present report is the assessment of the added benefit of ivacaftor in combination with tezacaftor/ivacaftor in comparison with the ACT 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 and 3849+10kbC→T. The assessment of ivacaftor was conducted for a combination treatment with tezacaftor 100 mg/ivacaftor 150 mg tablets.

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

Therapeutic indication	ACT[a]
Patients with cystic fibrosis 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+10kbC→T	BSC
a: Presentation of the ACT specified by the G-BA. b: These are RF mutations. ACT: appropriate comparator therapy; BSC: best supportive care; 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 the 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 of the company in the dossier:

- study list on ivacaftor + tezacaftor/ivacaftor (status: 6 June 2019)

- bibliographical literature search on ivacaftor + tezacaftor/ivacaftor (last search on 6 June 2019)

- search in trial registries for studies on ivacaftor + tezacaftor/ivacaftor (last search on 6 June 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ivacaftor + tezacaftor/ivacaftor (last search on 4 September 2019)

No relevant study was identified from the check.

Evidence provided by the company

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

Due to the 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. CF is a chronic disease requiring lifelong treatment. The European Medicines Agency (EMA) guideline recommends a minimum duration of 6 months for the investigation of a clinical outcome [8]. IQWiG's *General Methods 5.0* also consider long-term studies to be necessary for the benefit assessment in chronic diseases [1]. In the therapeutic indication of CF, short-term studies (with a treatment duration of less than 24 weeks) are unsuitable for the benefit assessment because ivacaftor in combination with tezacaftor/ivacaftor is a long-term treatment. No conclusions can be drawn on the basis of short-term studies as to whether short-term effects persist in the longer term. It is also not possible to record any effects that only become apparent in the longer term, such as for pulmonary exacerbations and their consequences or for AEs. Pulmonary exacerbations are a common cause of lung damage or death in patients with CF [9-12]. In Module 4 B, the company justified the inclusion criterion of 8 weeks used by the company 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 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. A conclusion on the added benefit is not derived from it.

In addition, the company presented the open-label extension study VX14-661-110 in its dossier as supplementary information. The study included both patients with homozygous F508del mutation (studies VX13-661-103, VX14-661-106, VX14-9661-111) and patients with heterozygous F508del mutation (studies VX14-661-107, VX14-661-108, VX14-661-109) in the CFTR gene. These results are not relevant for the present benefit assessment, as there are no data for an assessment of ivacaftor + tezacaftor/ivacaftor in comparison with the ACT. These results are not presented below as supplementary information (see also Section 2.7.8.1 of the full dossier assessment).

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: ivacaftor + tezacaftor/ivacaftor + BSC vs. placebo + BSC

Study	Study category		
	Study for approval of the drug to be assessed **(yes/no)**	**Sponsored study[a]** **(yes/no)**	**Third-party study** **(yes/no)**
VX14-661-108	Yes	Yes	No
a: Study sponsored by the company.			
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus			

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: Characteristics of the study included by the company – RCT, direct comparison: ivacaftor + tezacaftor/ivacaftor + BSC vs. placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
VX14-661-108	RCT, double-blind, crossover study	Patients with CF aged 12 years and 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 $\geq 40\%$ and $\leq 90\%$	$N = 248$ randomized[c] (to 6 treatment sequences): ▪ 1) ivacaftor + tezacaftor/ivacaftor $\rightarrow$ washout period $\rightarrow$ ivacaftor ($N = 41$) ▪ 2) ivacaftor $\rightarrow$ washout period $\rightarrow$ ivacaftor + tezacaftor/ivacaftor ($N = 42$) ▪ 3) placebo $\rightarrow$ washout period $\rightarrow$ ivacaftor + tezacaftor/ivacaftor ($N = 41$) ▪ 4) ivacaftor + tezacaftor/ivacaftor $\rightarrow$ washout period $\rightarrow$ placebo ($N = 43$) ▪ 5) ivacaftor $\rightarrow$ washout period $\rightarrow$ placebo ($N = 40$) ▪ 6) placebo $\rightarrow$ washout period $\rightarrow$ ivacaftor ($N = 41$) Patients per treatment in treatment period 1[d] ▪ ivacaftor + tezacaftor/ivacaftor ($N = 83$) ▪ placebo ($N = 80$) Patients per treatment in treatment period 2 ▪ ivacaftor + tezacaftor/ivacaftor ($N = 78$) ▪ placebo ($N = 81$) Patients per treatment group during the study (treatment period 1 + 2)[d] ▪ ivacaftor + tezacaftor/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

(continued)

Table 6: Characteristics of the study included by the company – RCT, direct comparison: ivacaftor + tezacaftor/ivacaftor + BSC vs. placebo + BSC (continued)

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes contain exclusively information 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+10kbC→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 that 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. class II to IV missense RF mutation).

d: 2 patients had not received any study treatment and were therefore not considered in the analysis of all outcomes. 2 further patients had CFTR mutations that were excluded according to the inclusion criteria. These patients were considered in the analysis of side effects, 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 side effects + 1 patient) ivacaftor + tezacaftor/ivacaftor + BSC: 40 (sequence 1; period 1) + 39 (sequence 2; period 2) + 39 (sequence 3; period 2) + 43 (sequence 4; period 1) = 161 (for side effects + 1 patient).

e: After completion of treatment period 2, patients could receive ivacaftor in combination with tezacaftor/ivacaftor for 96 weeks in the framework of the single-arm study VX14-661-110.

ACT: appropriate comparator therapy; AE: adverse event; BSC: best supportive care; CF: cystic fibrosis; 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; vs.: versus

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

Study	Intervention	Comparison
VX14-661-108	Ivacaftor[a] + tezacaftor/ivacaftor[a] + BSC[b]	Placebo[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	
	Non-permitted pretreatment	
	▪ 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 were allowed in case of side effects after
consultation with the clinical monitor.
b: In the study, basic medication for the treatment of cystic fibrosis was given in addition to tezacaftor/ivacaftor
or placebo. The basic medication had to be stable for 4 weeks before the start of treatment until the end of the
observation.
BSC: best supportive care; CYP: cytochrome P450; RCT: randomized controlled trial; vs.: versus

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, diagnosis of CF was defined by the presence of
chronic sinopulmonary disease. In addition, the patients had to have a sweat chloride value of
≥ 60 mmol/L. The patients had to have a forced expiratory volume in 1 second (FEV1) of
$\geq 40\%$ and $\leq 90\%$ of predicted normal for age, sex, and height at screening.

The VX14-661-108 study compared 3 treatments in a crossover study design:

▪ ivacaftor

▪ ivacaftor + tezacaftor/ivacaftor combination therapy

▪ placebo

The patients received continuous concomitant treatment largely in the sense of treatment with
BSC (see Section *Implementation of the appropriate comparator therapy* for details).

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

Figure 1 shows the treatment sequences of the VX14-661-108 study.
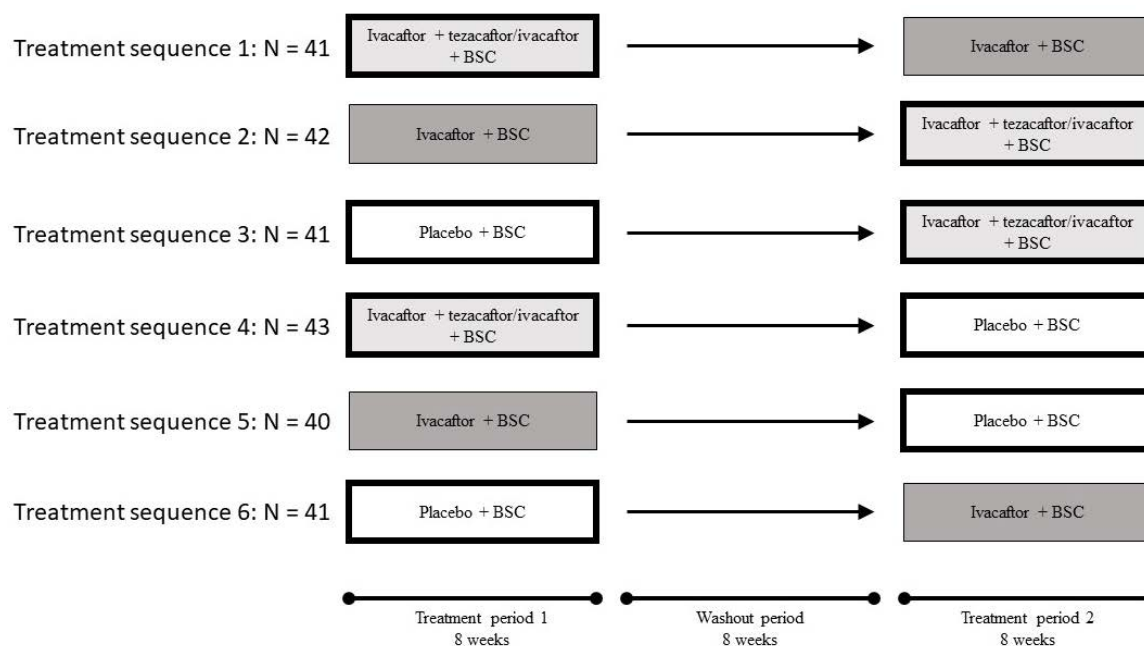
Adapted according to Rowe 2017 [4]. The 2 treatment groups of ivacaftor + tezacaftor/ivacaftor + BSC and placebo + BSC presented as supplementary information in the present dossier assessment are outlined in bold. N: Number of randomized patients. Stable concomitant medication in the sense of treatment 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 years versus ≥ 18 years), FEV1 ($< 70\%$ versus $\geq 70\%$) 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 overall treatment duration was 8 weeks. The present dossier assessment shows the short-term results for the comparison of the combination therapy of ivacaftor + tezacaftor/ivacaftor + BSC with placebo + BSC as supplementary information.

Treatment with ivacaftor in combination with tezacaftor/ivacaftor was in compliance with the recommendations of the Summary of Product Characteristics (SPC) [13,14].

The second treatment period was followed by a 4-week observation period for side effects. 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, on the one hand, those patients who had received both relevant treatments, ivacaftor + tezacaftor/ivacaftor + BSC and placebo + BSC (treatment sequences 3 and 4). In addition, the company also included in its analyses those patients from the other sequences (treatment sequences 1, 2, 5, 6) who had received either ivacaftor + tezacaftor/ivacaftor + BSC or placebo + BSC during the course of the study.

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 intra-individual comparison of an experimental intervention with a control therapy, since all participants receive both therapies (see Figure 1). In a rare disease such as CF, a crossover design is a possibility to achieve a power even with smaller sample sizes, which in a parallel group design could only be achieved with greater sample sizes. However, a crossover design only produces informative results if certain conditions are met [15]:

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 that 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 a rapid progression of the disease, a strong influence of the season on the observed outcomes could also lead to period effects, for example. Period effects would be unavoidable in a rapidly progressive disease.

The company did not provide sufficient information on the extent to which both conditions are fulfilled.

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

Assuming that the 2 conditions described above 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 in the assessment of the risk of bias of the short-term results below.

A crossover design is usually not adequate for irreversible outcomes [16]. This concerns the outcomes "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 one discontinuation due to AEs occurred in the VX14-661-108 study.

Patient characteristics

Table 8 and Table 9 show the characteristics of the patients included in the VX14-661-108 study. The presentation in Table 8 is made separated 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: ivacaftor + tezacaftor/ivacaftor + BSC vs. placebo + BSC

Study Characteristics Category	Treatment period 1		Treatment period 2	
	IVA + TEZA/IVA + BSC	Placebo + BSC	IVA + TEZA/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)

(continued)

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

Study Characteristics Category	Treatment period 1		Treatment period 2	
	IVA + TEZA/IVA + BSC	Placebo + BSC	IVA + TEZA/IVA + BSC	Placebo + BSC
	N^a = 83	N^a = 80	N^a = 78	N^a = 81
VX14-661-108				
Type of the RF mutation				
Class V non-canonical splice mutations	50 (60.2)	48 (60.0)	45 (57.7)	49 (60.5)
Class 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)
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 that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

b: Black/African American or others or not recorded.

c: Institute's calculation.

d: Patients from Israel and Australia (one patient in each case) were recorded as Europe.

e: Medication started until 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; BSC: best supportive care; 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; vs.: versus

Table 9: Mutations on the second allele of the CFTR gene – RCT, direct comparison: ivacaftor + tezacaftor/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+10kbC→T	69 (28.3)
3272-26A→G	36 (14.8)
711+3A→G	3 (1.2)
Class 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: Institute's calculation.	
c: Not comprised by the therapeutic indication of ivacaftor [13].	
BSC: best supportive care; 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; vs.: versus	

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+10kbC→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 appropriate comparator therapy

The G-BA specified BSC as ACT for ivacaftor, in the framework of a combination treatment with tezacaftor/ivacaftor, for patients with CF aged 12 years and older who are heterozygous

for the F508del mutation and have one of the following 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+10kbC→T. BSC refers to the therapy that 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 ivacaftor + tezacaftor/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. It was also an inclusion criterion of the VX14-661-108 study that the 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 pretreatment. Information on prior and concomitant treatment is listed in Table 10. Medication taken after the first intake of the study medication was recorded as concomitant treatment. Concomitant treatment was recorded during the total study duration. Table 11 shows the concomitant treatments of the patients during the total study duration separated by treatment group per treatment period in which the patients were considered. Medication that was taken both within the 28 days before the first intake of the study medication and during the study treatment is shown in both tables.

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

Study	Treatment period 1		Treatment period 2	
	IVA + TEZA/IVA + BSC	Placebo + BSC	IVA + TEZA/IVA + BSC	Placebo + BSC
	n (%)	n (%)	n (%)	n (%)
VX14-661-108	N^a = 83	N^a = 80	N^a = 78	N^a = 81
Drug 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)
Colecalciferol	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)
Budesonide w/formoterol 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 lysine	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-drug treatment				
Physiotherapy[c]	44 (52.4)	44 (54.3)	ND	ND

a: Number of randomized patients. Values that are based on other 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 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 administration of the respective medication; N: number of analysed patients of the FAS population; ND: no data; NOS: not otherwise specified; PT: Preferred Term; RCT: randomized controlled trial; TEZA: tezacaftor; vs.: versus; WHO-DD: World Health Organization Drug Dictionary

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

Study	IVA + TEZA/IVA + BSC	Placebo + BSC
	n (%)	n (%)
VX14-661-108	N[a] = 161	N[a] = 161
Drug 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)
Colecalciferol	50 (31.1)	52 (32.3)
Seretide	41 (25.5)	47 (29.2)
Pancreatin	37 (23.0)	28 (17.4)
Budesonide w/formoterol fumarate	33 (20.5)	21 (13.0)
Tobramycin	33 (20.5)	40 (24.8)
Vitamins NOS	32 (19.9)	31 (19.3)
Aztreonam lysine	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-drug 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 the observation. PT, coded according to WHO-DD, December 2007.
c: In treatment period 1, no patient in the ivacaftor + tezacaftor/ivacaftor + BSC group and one patient in the placebo + BSC group initiated physiotherapy. No data are available on treatment period 2 and on discontinuations of physiotherapy that was ongoing (at the start of treatment).
BSC: best supportive care; FAS: full analysis set; IVA: ivacaftor; n: Number of patients with administration of the respective medication; N: number of analysed patients of the FAS population; ND: no data; NOS: not otherwise specified; PT: Preferred Term; RCT: randomized controlled trial; TEZA: tezacaftor; vs.: versus; WHO-DD: World Health Organization Drug Dictionary

The available information suggests that the patients were given 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 on treatment period 1 also suggest that individual patients initiated 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

and how many patients had their concomitant treatment adjusted, for example in the sense of an increase in dose or frequency.

In summary, it remains unclear on the basis of the available data 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 a BSC.

Risk of bias across outcomes (study level, for the study included by the company)

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: ivacaftor + tezacaftor/ivacaftor + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
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; vs.: versus							

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

There were the following additional aspects for the study in the crossover design:

With reference to the 8-week washout period, the company excluded a carry-over effect. Furthermore, it referred 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, and 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]) [15,16]. Period-specific effect estimations for these outcomes are also necessary for an assessment of period effects [15,16]. A statistical test for a period effect showed no statistically significant result for the primary outcome "absolute change in FEV1" [5].

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).

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 for the VX14-661-108 study included by the company (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- 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 sum scores of the SF-12 v2
- Side effects
    - SAEs
    - discontinuation due to AEs
    - if applicable, further specific AEs

No meaningful investigation of the outcome "mortality" is possible in the crossover design. It is therefore not taken into account in 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 of the company, which used further outcomes in the dossier (Module 4 B) (see Section 2.7.4.3.2 of the full dossier assessment).

Table 13 shows for which outcomes data are available.

Table 13: Matrix of outcomes – RCT, direct comparison: ivacaftor + tezacaftor/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	Discontinuation due to AEs
VX14-661-108	Yes	Yes	Yes	Yes	Yes	–[a]	Yes

a: No usable data available (see Section 2.7.4.3.2 of the full dossier assessment).

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

2.4.2 Risk of bias

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

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ivacaftor + tezacaftor/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	Discontinuation due to AEs
VX14-661-108	L	H[a]	H[a]	H[a]	H[a]	H[a]	–[b]	L

a: Insufficient data for the assessment of carry-over and period effects.
b: No usable data available (see Section 2.4.3).

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

The risk of bias of the results on pulmonary exacerbations, hospitalization due to pulmonary exacerbations, symptoms (measured using the CFQ-R) and health-related quality of life (measured using the CFQ-R and SF-12) was rated as high, since carry-over and period effects

with regard to patient-relevant outcomes were not sufficiently discussed by the company in Module 4 B (see Section 2.3.2).

The risk of bias for the results on these outcomes was therefore rated as high. This deviates from the assessment of the company, which assessed the risk of bias as low for the results of all outcomes it included.

No usable data are available for the outcome "SAEs", as the Preferred Term (PT) "infective pulmonary exacerbation of cystic fibrosis", which is to be allocated to the progression of the underlying disease, was recorded to a relevant extent. Hence, no conclusion on side effects can be drawn on the basis of the available results.

The risk of bias for the results on discontinuation due to AEs was 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 ivacaftor + tezacaftor/ivacaftor + BSC with BSC in patients with CF aged 12 years and older who are heterozygous for the F508del mutation and have one 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+10kbC→T, as supplementary information. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Table 15: Short-term results (treatment duration of 8 weeks) (side effects, dichotomous) – RCT, direct comparison: ivacaftor + tezacaftor/ivacaftor + BSC vs. placebo + BSC

Study Outcome category Outcome	IVA + TEZA/IVA + BSC		Placebo + BSC		IVA + TEZA/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					
Side effects					
AEs (supplementary information)	162	117 (72.2)	162	126 (77.8)	–
SAEs				Not usable[c]	
Discontinuation due to AEs	162	0 (0.0)	162	1 (0.6)	–[b]
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: No meaningful calculation possible. c: Data are not usable, as they contain a large proportion of patients with events of the PT "cystic fibrosis lung" and events that can be both side effects and symptoms of the disease.					
AE: adverse event; BSC: best supportive care; CI: confidence interval; IVA: ivacaftor; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TEZA: tezacaftor; vs.: versus					

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

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

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

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

Study Outcome category Outcome	IVA + TEZA/IVA + BSC			Placebo + BSC			IVA + TEZA/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)	–0.64 (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)[d]	*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)[d]	*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*

(continued)

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

Study Outcome category Outcome	IVA + TEZA/IVA + BSC			Placebo + BSC			IVA + TEZA/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 problems	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]

(continued)

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

Study Outcome category Outcome	IVA + TEZA/IVA + BSC			Placebo + BSC			IVA + TEZA/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[f]	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[f]	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 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 ivacaftor.
e: Domain for adolescents or adults; not intended for children [12 to 13 years].
f: 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.
BMI: body mass index; BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire Revised; CI: confidence interval; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; MD: mean difference, MMRM: mixed-effects model repeated measures; 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; vs.: versus

The short-term results of the study included by the company are described below. There was a high risk of bias for all results, except for the outcome "discontinuation due to AEs".

Morbidity

Pulmonary exacerbations

No statistically significant difference was shown between the treatment groups for the outcome "pulmonary exacerbations".

Hospitalization due to pulmonary exacerbations

No statistically significant difference was shown between the treatment groups for the outcome "hospitalization due to pulmonary exacerbations".

Symptoms measured using the CFQ-R

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

Domain "respiratory symptoms"

A statistically significant difference in favour of ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC was shown for the change from baseline in the domain "respiratory symptoms". The SMD in the form of Hedges' g was considered 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 characteristic "age". For adults (aged 18 years and older), there was an advantage of ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC (see Section 2.4.4).

Domain "digestive symptoms"

A statistically significant effect to the disadvantage of ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC was shown in the domain "digestive symptoms". 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.

Domain "weight"

A statistically significant effect in favour of ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC was shown in the domain "weight". 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 problems, treatment burden and health perceptions of the CFQ-R.

Domain "physical functioning"

A statistically significant difference in favour of ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC was shown in the domain "physical functioning". 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 the characteristics of FEV1 (in % of predicted normal) and *Pseudomonas aeruginosa* infection within 2 years before baseline. A meaningful interpretation of the subgroup results was not possible, however, because data for the investigation of possible dependencies between the subgroup characteristics were missing (see Section 2.4.4).

Domain "vitality"

A statistically significant difference in favour of ivacaftor + tezacaftor/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. However, there were effect modifications by the characteristics of FEV1 (in % of predicted normal) and *Pseudomonas aeruginosa* infection within 2 years before baseline for the domain "vitality". A meaningful interpretation of the subgroup results was not possible, however, because data for the investigation of possible dependencies between the subgroup characteristics were missing (see Section 2.4.4).

Domain "health perceptions"

A statistically significant difference in favour of ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC was shown in the domain "health perceptions". 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 characteristic "age". For adults (aged 18 years and older), there was an advantage in favour of ivacaftor + ivacaftor/tezacaftor + BSC versus placebo + BSC.

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

In addition, statistically significant effects in favour of ivacaftor + tezacaftor/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.

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

Both the physical and the mental sum score showed statistically significant effects in favour of ivacaftor + tezacaftor/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 ivacaftor + tezacaftor/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.

Side effects

Serious adverse events and discontinuation due to adverse events

The results on SAEs are not usable to draw a conclusion on this outcome (see Section 2.7.4.3.2 of the full dossier assessment).

There was one 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 are considered for the presentation of the results of the VX14-661-108 study:

- age ($< 18/\geq 18$ years)

- sex (female, male)

- region (North America, Europe [including Israel and Australia])

- FEV1 (in % of predicted normal) at baseline ($< 70\%, \geq 70\%$)

- *Pseudomonas aeruginosa* infection within 2 years before baseline (yes, no)

- RF mutation (class V non-canonical splice mutation, class II to IV missense RF mutation)

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

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

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

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

Study Outcome Characteristic Subgroup	IVA + TEZA/IVA + BSC			Placebo + BSC			IVA + TEZA/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 domain "respiratory symptoms", 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 domain "health perceptions", 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 domain "physical functioning", 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

(continued)

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

Study Outcome Characteristic Subgroup	IVA + TEZA/IVA + BSC			Placebo + BSC			IVA + TEZA/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 domain "physical functioning", 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 domain "vitality", 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

(continued)

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

Study Outcome Characteristic Subgroup	IVA + TEZA/IVA + BSC			Placebo + BSC			IVA + TEZA/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 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, 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].

BSC: best supportive care; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; FEV1: forced expiratory volume in 1 second; IVA: ivacaftor; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; TEZA: tezacaftor; vs.: versus

Morbidity

Symptoms measured using the CFQ-R

Domain "respiratory symptoms"

There was an effect modification by the characteristic "age" in the domain "respiratory symptoms". 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 difference in favour of ivacaftor + tezacaftor/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

Domain "health perceptions"

There was an effect modification by the characteristic "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 ivacaftor + ivacaftor/tezacaftor + 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.

Domain "physical functioning"

In the domain "physical functioning", 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.

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 ivacaftor + tezacaftor/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 ivacaftor + tezacaftor/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.

Domain "vitality"

In the domain "vitality", 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 domain "vitality", there was a statistically significant effect in favour of ivacaftor + tezacaftor/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 ivacaftor + tezacaftor/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 ivacaftor + tezacaftor/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 ivacaftor + tezacaftor/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 "age" for the outcome "health-related quality of life" 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 ivacaftor + tezacaftor/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. The company only presented comparative data over a period of 8 weeks. These only show short-term effects, however, which are unsuitable for the derivation of an added benefit in the present therapeutic indication. However, due to the rarity of the mutations to be investigated and the fact that children are affected, the study is presented in the present dossier assessment and the short-term effects are described.

Overall, no disadvantages of ivacaftor + tezacaftor/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 ivacaftor + tezacaftor/ivacaftor + BSC were shown in comparison with placebo + BSC:

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

- Health-related quality of life:

  ▫ advantage in favour of ivacaftor + tezacaftor/ivacaftor + BSC in comparison with placebo + BSC in the domains "physical functioning" and "vitality", each recorded using the CFQ-R

  ▫ advantage for adults (≥ 18 years) in favour of ivacaftor + tezacaftor/ivacaftor + BSC in comparison with placebo + BSC in the domain "health perceptions" recorded using the CFQ-R and in the Physical Component Summary of the SF-12 v2

2.5 Probability and extent of added benefit

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

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

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Patients with cystic fibrosis aged 12 years and older who are heterozygous for the F508del mutation and have one 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+10kbC→T	BSC	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. b: These are RF mutations.		
ACT: appropriate comparator therapy; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee; RF: residual function		

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

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company did not present any relevant data for the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical

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