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

Addendum to Commission A19-71[1]

Addendum

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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
CSR	clinical study report
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
SAE	serious adverse event
SF-12	Short Form 12-Items Health Survey Version 2

1 Background

On 7 January 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-71 (Ivacaftor – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented results of the randomized controlled trial (RCT) VX14-661-108 with a treatment duration of 8 weeks for the assessment of the added benefit of ivacaftor in combination with tezacaftor/ivacaftor 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. Due to the treatment duration of only 8 weeks, the study was not included in the benefit assessment, but the short-term results were presented as supplementary information. For the outcome "serious adverse events (SAEs)", the company had presented analyses that included events that can be both symptoms of the underlying disease and side effects. The results for the outcome "SAEs" were therefore not usable in dossier assessment A19-71. For the outcome "discontinuation due to adverse events (AEs)", an effect estimation was not carried out for other reasons.

In addition to the results of the 8-week treatment duration of the VX14-661-108 study, the company presented supplementary data of the single-arm extension study to the VX14-661-108 study – study VX14-661-110 – on treatment with ivacaftor + tezacaftor/ivacaftor + concomitant treatment for individual outcomes over a total period of at least 24 weeks in its dossier. The VX14-661-110 study was not included in the benefit assessment, as it did not allow to conduct a comparison with the appropriate comparator therapy (ACT) best supportive care (BSC).

The G-BA commissioned IQWiG to present and assess the analyses of the VX14-661-108 study on the outcomes "SAEs" and "discontinuation due to AEs" without pulmonary exacerbations presented by the company in the comments. In addition, the data of the single-arm extension study VX14-661-110 with data cut-off at week 96 subsequently submitted were to be presented and assessed.

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

2 Assessment

2.1 Studies VX14-661-108 and VX14-661-110

Study VX14-661-108

The company presented analyses of the VX14-661-108 study in its dossier for the assessment of ivacaftor in combination with tezacaftor/ivacaftor in patients with CF aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene.

The VX14-661-108 study compared 3 treatments in a crossover study design: ivacaftor as monotherapy, combination therapy of ivacaftor + tezacaftor/ivacaftor and placebo, each + BSC. A total of 248 patients were randomly allocated to 6 treatment sequences, in which 2 treatments were administered one after the other. 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 (see dossier assessment A19-71 for details).

Study VX14-661-110 (extension study to study VX14-661-108)

The VX14-661-110 study was a single-arm extension study, in which patients received ivacaftor in combination with tezacaftor/ivacaftor + concomitant treatment for up to 96 weeks. It included both patients with homozygous F508del mutation (extension of the studies VX13-661-103, VX14-661-106, VX14-9661-111) and patients with heterozygous F508del mutation (extension of the studies VX14-661-107, VX14-661-108, VX14-661-109) in the CFTR gene.

Of a total of 248 randomized patients of the VX14-661-108 study, 227 (91.5%) were enrolled in the single-arm extension study.

2.2 AE outcomes in the VX14-661-108 study without Preferred Term “infective pulmonary exacerbation of cystic fibrosis”

For the outcome “SAEs”, the company in its dossier had shown analyses of the VX14-661-108 study that contained events forming part of the symptoms of the underlying disease or that can be both side effects and symptoms of the underlying disease. As already described in dossier assessment A19-71, an adequate operationalization of the outcome “SAEs” is an analysis without events of the underlying disease. The Preferred Term (PT) “infective pulmonary exacerbation of cystic fibrosis” was mentioned in dossier assessment A19-71 [1] because here the allocation to the underlying disease is clear and this PT was rated to a relevant extent as SAE in the studies.

With its comments [3], the company presented additional analyses on SAEs without the PT “infective pulmonary exacerbation of cystic fibrosis”.

2.2.1 Risk of bias

The risk of bias for the results was rated as high for the outcome "SAEs". This was largely due to the still insufficient data for the assessment of carry-over and period effects (see dossier assessment A19-71 for details). The analyses on SAEs subsequently submitted by the company did not contain the PT "infective pulmonary exacerbation of cystic fibrosis", and therefore a large proportion of events that can be allocated to the underlying disease are not included in the analysis. However, neither in Module 4 B of its dossier nor in its comments did the company address the influence possible further events that can be allocated to symptoms of the underlying disease might have on the effect estimations.

The assessment of the risk of bias of the results on the outcome "discontinuation due to AEs" was already described in the dossier assessment on Commission A19-71. It was rated as low.

2.2.2 Results

Serious adverse events

The following table shows the results for the outcome "SAEs" without consideration of the PT "infective pulmonary exacerbation of cystic fibrosis" in the VX14-661-108 study for the comparison of ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC in patients with CF aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene. The results presented are short-term results after a treatment duration of 8 weeks, which are unsuitable for a benefit assessment in the therapeutic indication of CF.

Table 1: Short-term results (treatment duration of 8 weeks) (side effects, 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]**	**Patients with event n (%)**	**N[a]**	**Patients with event n (%)**	**RR [95% CI] p-value**
VX14-661-108					
Side effects					
SAEs[b]	162	4 (2.5)	162	9 (5.6)	0.44 [0.12; 1.54]; 0.26

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 "infective pulmonary exacerbation of cystic fibrosis".

CI: confidence interval; BSC: best supportive care; 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

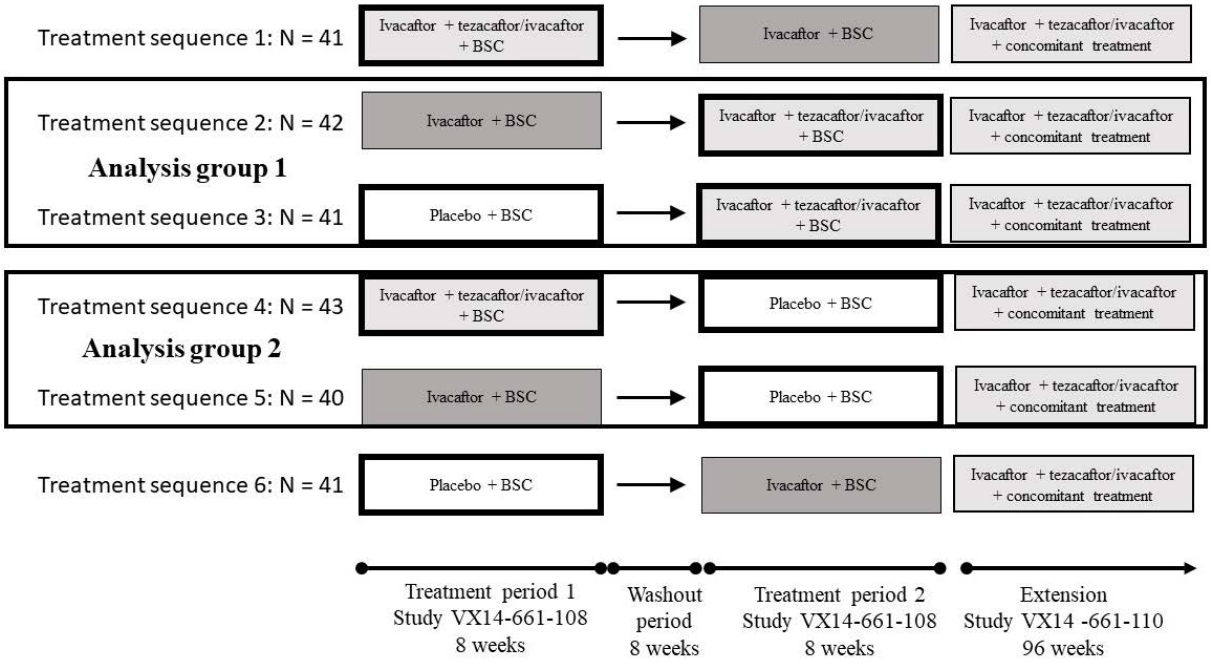
There was no statistically significant difference between the treatment groups for the outcome "SAEs" (without consideration of the PT "infective pulmonary exacerbation of cystic fibrosis").

Discontinuation due to adverse events

As already described in the dossier assessment, there was 1 discontinuation due to AEs. Hence, no effect estimation is required for this outcome. There was no statistically significant difference between the treatment groups.

2.3 Analyses of the single-arm extension study VX14-661-110 at week 96

Figure 1 shows the treatment sequences of the VX14-661-108 study and the analyses of the VX14-661-110 extension study for which the company showed data in its comments (designated "analysis groups 1 and 2" in the present assessment).



Adapted according to Rowe 2017 [4]. The 2 treatment groups of the VX14-661-108 study shown in the present addendum (ivacaftor + tezacaftor/ivacaftor + BSC versus placebo + BSC) are outlined in bold. In addition, the analyses groups of the single-arm extension study VX14-661-110 for which the company presented data in its comments are outlined.
BSC: best supportive care; N: Number of randomized patients

Figure 1: Treatment sequences of the VX14-661-108 study and analysis groups of the VX14-661-110 extension study

Analyses presented by the company in its comments

In its comments [3], the company provided analyses on the VX14-661-110 study over a period of 96 weeks for 2 analysis groups of patients already included in the VX14-661-108 study:

- Analysis group 1: patients who had received ivacaftor + tezacaftor/ivacaftor + BSC in treatment period 2 of study VX14-661-108 (treatment sequences 2 and 3) and remained on ivacaftor + tezacaftor/ivacaftor + concomitant treatment in the extension study

- Analysis group 2: patients who had received placebo + BSC (treatment sequences 4 and 5) in treatment period 2 of study VX14-661-108 and switched to ivacaftor + tezacaftor/ivacaftor + concomitant treatment in the extension study

With its comments, the company transmitted the following analyses for the 2 analysis groups described:

- Change at week 96 of the VX-14-661-110 extension study from baseline in the VX-14-661-108 study for the following outcomes:
  - forced expiratory volume in 1 second (FEV1) (in % of predicted normal, absolute and relative change
  - body mass index (BMI)
  - domain “respiratory symptoms” of the Cystic Fibrosis Questionnaire-Revised (CFQ-R)
- Event rates considering the time under ivacaftor + tezacaftor/ivacaftor from treatment period 2 of the VX-14-661-108 study until week 96 of the VX-14-661-110 study for the following outcomes:
  - pulmonary exacerbations
  - hospitalization due to pulmonary exacerbations
  - pulmonary exacerbations requiring treatment with intravenous antibiotics

As a result of the analyses on the event rates of the company, the time from entry into treatment period 2 of the VX-14-661-108 study plus 96 weeks of the extension study was included in the analysis for analysis group 1, and the time from entry into the extension study was included in the analysis for analysis group 2.

The analyses of the VX-14-661-110 study subsequently submitted by the company in the comments were incomplete for several reasons:

- As already described in the dossier assessment on Commission A19-71 for the 24-week data presented in the dossier, the company again only presented a choice of outcomes. There were no analyses on AE outcomes, analyses on the 2 further symptom domains of the CFQ-R, and analyses for the outcome “health-related quality of life” on the 9 CFQ-R domains and on the Short Form 12-Items Health Survey (SF-12).
- The clinical study report (CSR) on data at week 96 [5] presented by the company in the commenting procedure was incomplete, as the tables and figures at the end of the CSR (Chapter 14, end-of-text tables and figures), as well as any appendices (Chapter 16) were missing. It was therefore unclear whether data relevant for the assessment of the single-arm study were missing.

Regardless of this, the presented results of the single-arm VX14-661-110 study are unsuitable to draw conclusions on the added benefit of ivacaftor + tezacaftor/ivacaftor + BSC versus BSC in the present therapeutic indication. There were no data on the ACT. Thus, even if all data for all relevant outcomes at week 96 were available, an assessment of the sustainability of effects beyond a period of 8 weeks of treatment would not be possible due to the lack of comparative data.

In accordance with the G-BA's commission, the data on the VX14-661-110 extension study subsequently submitted by the company are presented in Appendix A.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of ivacaftor in combination with tezacaftor/ivacaftor from dossier assessment A19-71.

The following Table 2 shows the result of the benefit assessment of ivacaftor + tezacaftor/ ivacaftor under consideration of dossier assessment A19-71 and the present addendum.

Table 2: Ivacaftor + tezacaftor/ivacaftor – 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.

3 References

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Appendix A – Analyses of the single-arm extension study VX14-661-110 at week 96 presented by the company in the comments

Note: The exacerbation rates of the VX14-661-110 study presented by the company in the comments (see Table 3 of the company below) are the rates estimated from a negative binomial model in relation to 48 weeks (336 days); the rates presented in the dossier assessment for the VX14-661-108 study, however, are the observed rates in relation to 1 year (365.25 days).

Table 3: Table of the company from the comments: results of the VX14-661-110 study for patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene

Study VX14-661-110 **Subgroup analysis of only the patients of the RCT VX14-661-108**	**Change at week 96 of the extension phase[a] versus baseline[b]** **N** **LS mean [95% CI]** **or number of patients with event (%)**	
Outcome	**Stratum** **placebo → IVA (+ TEZ/IVA)**	**Stratum** **IVA (+ TEZ/IVA) → IVA (+ TEZ/IVA)**
FEV1% absolute, mean change	N = 68 4.1 [2.2 ; 6.0]	N = 67 7.5 [5.6 ; 9.4]
FEV1% relative, mean change	N = 68 7.9 [4.7 ; 11.1]	N = 67 13.0 [9.7 ; 16.2]
BMI, mean change	N = 75 1.07 [0.59 ; 1.55]	N = 68 1.05 [0.56 ; 1.55]
CFQ “respiratory symptoms”, mean change	N = 74 10.3 [7.4 ; 13.6]	N = 68 13.8 [10.3 ; 17.2]
Number of patients with at least one pulmonary exacerbation[c] Event rate/year [95% CI]	N = 81 40 (49.4) 0.44 [0.29 ; 0.66]	N = 78 28 (35.9) 0.22 [0.14 ; 0.35]
Number of patients with at least one pulmonary exacerbation requiring hospitalization[c] Event rate/year [95% CI]	n = 81 12 (14.8) 0.07 [0.03 ; 0.18]	n = 78 9 (11.5) 0.05 [0.02 ; 0.13]
Number of patients with at least one pulmonary exacerbation requiring administration of IV antibiotics[c]: Event rate/year [95% CI]	n = 81 14 (17.3) 0.09 [0.04 ; 0.22]	n = 78 12 (15.4) 0.05 [0.02 ; 0.13]

Source: Clinical study report of the VX14-661-110 study (3)

Abbreviations: IVA = ivacaftor, TEZ/IVA = tezacaftor/ivacaftor, N = number, CI = confidence interval, FEV1% = proportion of forced expiratory volume in 1 second of predicted normal in percent, BMI = body mass index, CFQ-R = Cystic Fibrosis Questionnaire-Revised

a. Corresponds to 104 weeks of treatment with IVA (+ TEZ/IVA) for patients who had received IVA (+ TEZ/IVA) in treatment period 2 of the VX14-661-108 study (IVA (+ TEZ/IVA) → IVA (+ TEZ/IVA)), and to 96 weeks of treatment with IVA (+ TEZ/IVA) for patients who had received placebo in treatment period 2 of the VX14-661-108 study (placebo → IVA (+ TEZ/IVA)).

b. Baseline corresponds to baseline of study VX14-661-108.

c. For this outcome, the individual total duration of treatment with IVA (+ TEZ/IVA) for each patient is considered, i.e.: in the studies VX14-661-108 and VX14-661-110 for patients in the stratum „IVA (+ TEZ/IVA) → IVA (+ TEZ/IVA)“, and only the treatment duration in the VX14-661-110 study for patients in the stratum „placebo → IVA (+ TEZ/IVA)“. This duration (accumulated per stratum) represents the “time at risk” for the occurrence of pulmonary exacerbations, on which the calculations of event rates/year are based.

Note: „Stratum placebo → IVA (+ TEZ/IVA)“ concurs with analysis group 2 presented in Figure 1; „stratum IVA (+ TEZ/IVA) → IVA (+ TEZ/IVA)“ concurs with analysis group 1