Ivacaftor/tezacaftor/elexacaftor (combination with ivacaftor; cystic fibrosis, 2 to 5 years of age, F508del mutation, MF mutation, heterozygous 1)

Addendum to Project A23-122 (dossier assessment)[1]

ADDENDUM

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[1] Translation of the addendum *Ivacaftor/Tezacaftor/Elexacaftor (Kombination mit Ivacaftor; zystische Fibrose, 2 bis 5 Jahre, F508del-Mutation, MF-Mutation, heterozygot) – Addendum zum Projekt A23-122 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	best supportive care
CFTR	cystic fibrosis transmembrane conductance regulator
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MF	minimal function
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 15 April 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-122 (Ivacaftor/tezacaftor/elexacaftor – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the following analyses presented by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [2] (including the documents subsequently submitted following the oral hearing [3]), taking into account the information in the dossier [4]:

- The company's arguments regarding the study Stahl 2021 [5] on the appropriate comparator therapy (ACT) "best supportive care (BSC)" in patients with cystic fibrosis who are heterozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and have a minimal function (MF) mutation on the second allele

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 Background of the addendum and data situation in the dossier assessment

For the assessment of the added benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (hereinafter referred to as ivacaftor/tezacaftor/elexacaftor + ivacaftor) in comparison with BSC as ACT in patients from 2 to 5 years of age with cystic fibrosis who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele (hereinafter referred to as F508del/MF mutation), the company primarily used the results of the single-arm study VX20-445-111 [6] and the associated extension study VX20-445-112 [7] in Module 4 A for the treatment with ivacaftor/tezacaftor/alexacaftor. However, as describedin dossier assessment A23-122 [1], these studies do not allow a comparison versus the ACT due to the single-arm design and are therefore not suitable for the assessment of the added benefit of ivacaftor/tezacaftor/ivacaftor + ivacaftor in comparison with the ACT.

Furthermore, in Module 4 A, the company sought to transfer study results from older patient groups in the therapeutic indication to the population of children aged 2 to 5 years which is relevant for the benefit assessment. For this purpose, the company referred to previous benefit assessments on ivacaftor/tezacaftor/ivacaftor + ivacaftor in patients of different age groups with F508del/MF mutation [8,9] - in particular to results from the randomized controlled trials (RCTs) VX19-445-116 (6 to 11 years) [10] and VX17-445-102 (12 years and older) [11]. However, for the following reasons, the implementation by the company (at the time of the dossier assessment) was not suitable for the transfer of the study results:

- The company had not presented any information on non-comparative studies for the ACT. Thus, the dossier also does not include any studies or other information for evaluating the course of disease under the ACT, BSC, for the population of the present research question in the age group of 2 to 5 years.

  According to comments made by clinicians during the oral hearing on the early benefit assessment procedure for lumacaftor/ivacaftor [12] (dossier assessment for Commission A23-72 [13]), it also remained unclear from IQWiG's point of view whether there are data on treatment with BSC for the age group of the present research question, i.e. patients from 2 to 5 years of age, which the company could have analysed to evaluate the course of the disease under BSC for this patient group.
- In addition, the company had not presented any analysed data for the transfer for the higher age groups in the present therapeutic indication for the relevant studies. The company only mentioned results for the RCTs VX19-445-116 and VX17-445-102 in the higher age groups in its argumentation on the derivation of added benefit.
- A comprehensive evaluation of all results on intervention and comparator therapy relevant for the transfer is therefore not available either for the age group of the

present research question or for the older age groups (in particular the adjacent age group of patients from 6 to 11 years).

The company only partially addressed these points of criticism with the analyses [2] submitted in the context of the commenting procedure (including the documents subsequently submitted following the oral hearing [3]), so that the data are still not suitable for the transfer of the study results. This is explained in more detail in Section 2.3; at first, the analyses subsequently submitted by the company are described in Section 2.2.

2.2 Analyses subsequently submitted by the company

Subsequent submissions in the context of the comments

With its comments [2], the company subsequently submitted a tabular comparison of the study, intervention and patient characteristics as well as the results, including the operationalization of the outcomes, for the studies (VX20-445-111, VX19-445-116 and VX17-445-102) on treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor in patients with F508del/MF mutation in the various age groups .

In addition, the company conducted an information retrieval for the ACT of BSC. A review of the information retrieval was waived, as the company still did not present a complete analysis of the available data following the oral hearing, but only 1 individual data item from a study identified by it (for a detailed explanation, see Section 2.3).

The company stated that it had identified the publication Stahl 2021 [5], which was already subject of discussion in the oral hearing in the early benefit assessment procedure on lumacaftor/ivacaftor [12], via its information retrieval. However, the company excluded this study in its comments with criterion A1 "other population" because, according to the company, the study population did not exactly represent the patients of the present research question in terms of age group and mutation type.

Subsequent submissions following the oral hearing

Contrary to the company's initial assessment in Module 4 A and in the comments, the oral hearing on the present procedure [14] and the company's explanations subsequently submitted following the oral hearing on the study Stahl 2021 [3] show that the study could generate data on the course of the disease under BSC for patients with F508del/MF mutation aged 2 to 5 years.

The company stated that due to the submission deadline of the supplement to the oral hearing, a complete analysis of the data from the study for the population of 2- to 5-year-old patients with F508del/MF mutation relevant in the present therapeutic indication was not possible, and described in its supplement a personal communication with Prof. Stahl that had taken place after the oral hearing. On the basis of this communication, the company stated

that, according to Prof. Stahl, data on the annualized rate of the patient-relevant outcome "pulmonary exacerbations" were available from the study for the population of 2- to 5-year-olds with F508del/MF mutation relevant in the present therapeutic indication. This rate would be an average of 1.2 pulmonary exacerbations/patient year [3]. In its subsequent submission, the company compares this information with the results of the VX20-445-111 study, in which the mean rate was 0.23 pulmonary exacerbations/patient year, and points out that, based on the information in the Stahl 2021 publication [5], it can be assumed that the same definition of pulmonary exacerbations was used in both studies, which means that the values can be assumed to be comparable. The company concludes that pulmonary exacerbations occur about 5 times more frequently under therapy with BSC alone than under therapy with ivacaftor/tezacaftor/elexacaftor + ivacaftor, that this difference cannot be explained by confounding variables alone and therefore justified a considerable added benefit. A calculation of an effect estimate based on the study data, e.g. a rate ratio, with a presentation of a confidence interval is not available.

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

Although the company addressed some of the points of criticism mentioned in the dossier assessment in the commenting procedure (e.g. the company now presents an information retrieval for the ACT), the analysis is still incomplete. In addition, the company's conclusion described in the previous section and the derivation of an added benefit with reference exclusively to data on the mean, annualized rate of pulmonary exacerbations is not appropriate.

Further data processing would be necessary to assess whether the data on the course under BSC support a transfer of the study results from older patients to this age group. In addition to the complete analysis of the data on the population of the present research question from the Stahl 2021 study, this includes the following points in particular:

- for the intervention and the ACT, a comparative analysis of study, intervention and patient characteristics of the studies on the different age groups (2 to 5 years, 6 to 11 years, if necessary additionally ≥ 12 years). Although the company presented an analysis of data with this in the comments, it only included treatment with the intervention for the age group of 2 to 5-year-olds,
- for the intervention and the ACT, a comparative analysis of the results on all patient-relevant outcomes and their operationalization for the studies for the different age groups (2 to 5 years, 6 to 11 years, if necessary additionally ≥ 12 years). There is still a lack of complete data analysis on course under BSC for the age group of 2 to 5-year-olds, e.g. on the basis of the Stahl 2021 study [5] considered by the company.

A comprehensive analysis and comparison of all available data on the intervention and comparator side would be necessary for the benefit assessment, including adequate discussion and consideration of potential confounders in the comparison of individual arms or across age groups.

On the basis of the insufficiently analysed data presented by the company, it is still not possible to assess overall whether a transfer of the added benefit from higher age groups to the population relevant in the present therapeutic indication is possible.

2.4 Summary

On the basis of the analyses subsequently submitted by the company with the comments (including the documents subsequently submitted following the oral hearing), there was no change in the conclusion on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with BSC as an ACT compared with dossier assessment A23-122 [1] in patients with cystic fibrosis aged 2 to 5 years who are heterozygous for the F508del mutation in the CFTR gene and have an MF mutation on the 2nd allele.

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