Ivacaftor/tezacaftor/elexacaftor (combination with ivacaftor; cystic fibrosis, 2 to 5 years, F508del mutation, homozygous1)

Addendum to Project A23-123 (dossier assessment)[1]

ADDENDUM

Project: A24-44 Version: 1.0 Status: 26 Apr 2024 DOI: 10.60584/A24-44_en

[1] Translation of the addendum *Ivacaftor/Tezacaftor/Elexacaftor (Kombination mit Ivacaftor; zystische Fibrose, 2 bis 5 Jahre, F508del-Mutation, homozygot) – Addendum zum Projekt A23-123 (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.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Ivacaftor/tezacaftor/elexacaftor (combination with ivacaftor; cystic fibrosis, 2 to 5 years, F508del mutation, homozygous1) – Addendum to Project A23-123

Commissioning agency

Federal Joint Committee

Commission awarded on

15 April 2024

Internal Project No.

A24-44

DOI-URL

https://doi.org/10.60584/A24-44_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

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

IQWiG employees involved in the addendum

- Selver Altin
- Kirsten Janke
- Ulrike Lampert
- Jona Lilienthal
- Daniela Preukschat

Keywords

Ivacaftor, Tezacaftor, Elexacaftor, Cystic fibrosis, Child - Preschool, Benefit Assessment

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
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)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
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 A23-123 (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]:

- Comparison of the results of study VX20-445-111 with ivacaftor/tezacaftor/elexacaftor versus results of the individual studies on the appropriate comparator therapy (ACT) lumacaftor/ivacaftor (VX15-809-115 and VX16-809-121) in the therapeutic indication of cystic fibrosis in patients aged 2 to 5 years, who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

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 lumacaftor/ivacaftor as ACT in patients from 2 to 5 years of age with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene, the company primarily used the results of the single-arm study VX20-445-111 [5,6] and the associated extension study VX20-445-112 [7] in Module 4 B for the treatment with ivacaftor/tezacaftor/elexacaftor. However, as described in dossier assessment A23-123 [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/elexacaftor + ivacaftor in comparison with the ACT.

Furthermore, 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 in Module 4 B. For this purpose, the company referred to previous benefit assessments of ivacaftor/tezacaftor/elexacaftor + ivacaftor in patients of higher age groups (6 to 11 years [8] and 12 years and older [9]) who are also homozygous for the F508del mutation in the CFTR gene. For its reasoning, the company used the single-arm VX18-445-106 study [10] and the associated extension study VX19-445-107 [11] for the age group from 6 to 11 years, and the randomized controlled trial (RCT) VX18-445-109 [12] for the age group 12 years and older. 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, lumacaftor/ivacaftor, for the population of the present research question in the age group of 2 to 5 years.

  However, as described in dossier assessment A23-123 [1], results on treatment with lumacaftor/ivacaftor from numerous studies conducted by the company itself are available for the patient group of the present research question, such as RCT VX16-809-121 [13], which was the subject of the early benefit assessment procedure for lumacaftor/ivacaftor in patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene [14]. Although the company itself conducted these studies, it did not present an evaluation of the information and results on treatment with the ACT lumacaftor/ivacaftor from these studies in the dossier.

  As described in the dossier assessment for commissions A22-16 and A22-22 [15] , data from studies conducted by the company on treatment with lumacaftor/ivacaftor in

patients who are homozygous for the F508del mutation in the CFTR gene are also available for the age group of 6- to 11-year-olds. The data preparation in the dossier [16] was already incomplete for this age group, so that it was not possible to assess whether the results of older patient groups could be transferred to this age group. For the age group 12 years and older, the company also did not include any data on treatment with the ACT of lumacaftor/ivacaftor in the present dossier. For this age group, the company only mentions textual results comparing the intervention with tezacaftor/ivacaftor in combination with ivacaftor (hereinafter referred to as tezacaftor/ivacaftor + ivacaftor).

- In addition, the company had also not presented fully analysed data on the treatment with the intervention for the higher age groups in the present therapeutic indication for the transfer. In the dossier, the company mentioned the results for the studies VX18-445-106 and VX19-445-107 in the age group 6 to 11 years and for the RCT VX18-445-109 comparing the intervention with tezacaftor/ivacaftor + ivacaftor in the age group 12 years and older exclusively in its argumentation on the derivation of the 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.

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.

A (descriptive) comparison of individual arms from different studies on the basis of the analyses subsequently submitted by the company was also not suitable for the benefit assessment. This is explained in more detail in Section 2.4 in accordance with the G-BA's commission.

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, VX18-445-106 and VX18-445-109 on treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor in patients in the various age groups who are homozygous for the F508del mutation in the CFTR gene.

In addition, the company conducted an information retrieval for the ACT “lumacaftor/ivacaftor”. A review of the information retrieval was waived, as there is still

neither a complete analysis of the available data to assess whether a transfer of study results from higher age groups is possible (for a detailed explanation, see Section 2.3), nor a comparison of individual arms from different studies suitable for the benefit assessment (for a detailed explanation, see Section 2.4).

In its information retrieval, the company identified the RCT VX16-809-121 [17,18] (this study was the subject of the dossier assessment for commission A21-122 [19]) and the single-arm study VX15-809-115 [20,21] (this study was the subject of the dossier assessment for commission A19-13 [22]) as well as its extension study VX16-809-116 [23]. However, in its comments on the ACT lumacaftor/ivacaftor, the company did not present an analysis of the data on the studies it had identified via the information retrieval.

Subsequent submissions following the oral hearing

Following the oral hearing [24], the company summarized the study, intervention and patient characteristics as well as results, including the operationalization of the outcomes, for the RCT VX16-809-121 and the single-arm study VX15-809-115 in tabular form and compared them with the data of study VX20-445-111 on treatment with the intervention. The company described this comparison of the studies for the intervention (VX20-445-111) with the studies for the ACT lumacaftor/ivacaftor (VX16-809-121 and VX15-809-115) in text form and discussed possible confounders, such as sex and pretreatment of patients in the respective studies. The company points out, for example, that the values of the lung clearance $index_{2.5}$ and faecal elastase-1 at baseline for both studies on lumacaftor/ivacaftor indicated that the disease was already more advanced. In the company's view, this discrepancy can be explained by the pretreatment with CFTR modulators in around 43% of patients in the study on the intervention versus no corresponding pretreatment in the studies on lumacaftor/ivacaftor.

Based on the descriptive comparison, the company nevertheless categorized the patient populations as sufficiently similar overall and drew conclusions from the descriptive comparison of the results. For the key outcome of pulmonary exacerbations in the present indication, the company concluded that these occur less frequently under treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor than under treatment with lumacaftor/ivacaftor. The company describes that pulmonary exacerbations occur up to 1.8 times more frequently under treatment with lumacaftor/ivacaftor than under treatment with the triple combination [3]. From the company's point of view, the descriptive comparison overall supports the transfer of the study results from higher age groups to the age group of 2 to 5-year-olds.

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 context of the commenting procedure (e.g. the company now presents an

information retrieval for the ACT, compares the results of the intervention with those of the ACT and discusses individual confounders), the analysis is still incomplete. In addition, the company's conclusion described in the previous section that the subsequently submitted descriptive comparison of the studies VX16-809-121 and VX15-809-115 on lumacaftor/ivacaftor and the study VX20-445-111 on ivacaftor/tezacaftor/elexacaftor + ivacaftor support a transfer of the study results from older patients to the present age group is not appropriate.

As described in detail in the dossier assessment for commission A23-123 [1] and the dossier assessment for commissions A22-16 and A22-22 [15], an assessment of whether the data on the course of treatment with lumacaftor/ivacaftor support a transfer of the study results from older patients to the present age group also requires a consideration across the different age groups for the ACT. However, the company presented no data on the course of disease under lumacaftor/ivacaftor for the age groups 6 to 11 years and ≥ 12 years, neither in the dossier nor in its comments or following the oral hearing. Overall, it would be necessary to analyse the following data to assess whether a transfer of the study results from older patients to this age group is possible:

- 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, ≥ 12 years)
- for the intervention and the ACT, a comparative analysis of the results on all patient-relevant outcomes and their operationalization for the studies on the different age groups (2 to 5 years, 6 to 11 years, ≥ 12 years)

In particular, the following points of criticism continue to exist:

- The company's analysis of the data on the ACT remains inadequate, as the age groups 6 to 11 years and ≥ 12 years were not considered by the company. This means that there is still no data available on the course under treatment with lumacaftor/ivacaftor for these age groups.

  The analysis of the evidence on the next higher age group of 6 to 11-year-old patients relevant for transfer would also be of particular importance here, as tezacaftor/ivacaftor + ivacaftor was used as comparator therapy in RCT VX18-445-109 for the age group ≥ 12 years. However, in the age group of the present assessment, tezacaftor/ivacaftor + ivacaftor is not an option of the ACT. However, as described in the dossier assessment for commissions A22-16 and A22-22 [15], evidence is available for the age group of 6- to 11-year-olds on both the course under treatment with lumacaftor/ivacaftor as well as on the course under treatment with tezacaftor/ivacaftor + ivacaftor, which would be necessary to assess the possibility of a transfer in this data situation.

- The descriptive comparison of individual arms for the age group of 2 to 5-year-olds presented by the company is not suitable to support a transfer of the study results from older patients to the present age group (see Section 2.4).
- The company still does not present a complete analysis of the necessary data on all patient-relevant outcomes. For outcomes in the category of side effect, the company describes in its comments that a direct comparison of the proportions of patients with adverse events (AEs) between the studies is not possible due to discrepancies in the operationalization. The company stated, among other things, that events of the preferred term (PT) "infective pulmonary exacerbation of cystic fibrosis" were excluded from the analysis in study VX20-445-111, but not in study VX15-809-115, and that a direct comparison was therefore not meaningful. However, it should be noted that it would have been possible for the company to conduct standardized analyses excluding the PT mentioned, as the identified studies were conducted by the company itself.

A comprehensive analysis and comparison of all available data on the intervention and comparator side across all age groups 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. In addition, analyses on all patient-relevant outcomes would be necessary if the company is able to conduct analyses on comparable operationalizations (e.g. analyses for the overall rates of serious AEs [SAEs] excluding the PT "infectious pulmonary exacerbation of cystic fibrosis").

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 Analyses on the descriptive comparison of individual arms from different studies subsequently submitted by the company not suitable

The descriptive comparison of individual arms from different studies is not suitable for supporting the transfer of study results from higher age groups to the age group of 2 to 5-year-olds. This is explained in more detail below by considering the key outcome (pulmonary exacerbations) of the present indication.

Table 1 shows a comparison of the results for the outcome "pulmonary exacerbations" from study VX20-445-111 for the intervention and from studies VX15-809-115 and VX16-809-121 for the ACT.

Table 1: Results on the outcome of pulmonary exacerbations: comparison of the results from studies VX20-445-111, VX15-809-115 and VX16-809-121 (multipage table)

Operationalization outcome	**VX20-445-111 (2-5 years, hF508del, 24 weeks)**		**VX15-809-115 (2-5 years, hF508del, 24 weeks)**		**VX16-809-121 (2-5 years, hF508del, 48 weeks)**	
	ivacaftor/tezacaftor/ elexacaftor + ivacaftor + BSC		**lumacaftor/ivacaftor + BSC**		**lumacaftor/ivacaftor + BSC**	
	N	**number of nE events (nE/patient-years)**	**N**	**number of events nE (nE/patient-years)**	**N**	**number of events nE (nE/patient-years)**
Recording as morbidity outcome						
Pulmonary exacerbation[a]	23	6 (0.51)[b]	60	25 (0.86)[c]	35	26 (0.75)[b]
Hospitalization due to pulmonary exacerbations[a]	23	1 (0.09)[b, d]	60	4 (0.14)[c, e]	35	5 (0.14)[b, d]
	Ivacaftor/tezacaftor/ elexacaftor + ivacaftor + BSC		**Lumacaftor/ivacaftor + BSC**		**Lumacaftor/ivacaftor + BSC**	
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**N**	**patients with event n (%)**
Pulmonary exacerbation[a]	23	6 (26.1)	60	18 (30.0)	35	15 (42.9)
Hospitalization due to pulmonary exacerbations[a]	23	1 (4.3)[d]	60	4 (6.7)[e]	35	5 (14.3)[d]
Recording via AEs						
Infective pulmonary exacerbation of cystic fibrosis (AE, PT)	23	3 (13.0)	60	4 (6.7)[f]	35	18 (51.4)[f]
Infective pulmonary exacerbation of cystic fibrosis (SAE, PT)	23	1 (4.3[f])	60	2 (3.3)[f]	35	3 (8.6)

Table 1: Results on the outcome of pulmonary exacerbations: comparison of the results from studies VX20-445-111, VX15-809-115 and VX16-809-121 (multipage table)

Operationalization outcome	VX20-445-111 (2-5 years, hF508del, 24 weeks)		VX15-809-115 (2-5 years, hF508del, 24 weeks)		VX16-809-121 (2-5 years, hF508del, 48 weeks)	
	ivacaftor/tezacaftor/ elexacaftor + ivacaftor + BSC		lumacaftor/ivacaftor + BSC		lumacaftor/ivacaftor + BSC	
	N	number of nE events (nE/patient-years)	N	number of events nE (nE/patient-years)	N	number of events nE (nE/patient-years)

a. Defined as the need for antibiotic treatment (IV, by inhalation or orally) and the occurrence of at least one of the criteria from list A or at least two criteria from list B between a maximum of 3 days before the start of antibiotic administration and the end of antibiotic administration.
list A:
- decrease in the pulmonary function (FEV1%) by ≥ 10% from the highest value within the last 6 months
- oxygen saturation < 90% in closed rooms or ≥ 5% decrease from baseline
- new lobar infiltrate or atelectasis on X-ray
- haemoptysis
- list B:
- increased respiratory effort or increased respiratory rate (for at least 3 days).
- new or increased breathing sounds on lung examination (for at least 3 days).
- weight loss by ≥ 5% from the highest weight measured or decrease by a full percentile by age during the previous 6 months.
- increased cough (for at least 3 days).
- increased strain from breathing during physical exertion (for at least 3 days).
- increased chest tightness or change in sputum (for at least 3 days).

b. The company calculates the event rate (nE/patient years) from the total number of events divided by the total number of years (sum of the follow-up period of all patients included in the analysis in days, divided by 336).
c. Institute's calculation of the event rate (nE/patient years) from the total number of pulmonary events divided by the number of patient years. The company did not specify the exact calculation formula for patient years.
d. It remains unclear whether this outcome includes planned besides unplanned hospitalizations.
e. The outcome comprises both unplanned hospitalizations due to CF events and planned hospitalizations (e.g. prophylactic antibiotic therapy).
f. Institute's calculation.

AE: adverse event; CF: cystic fibrosis; FEV1%: forced expiratory volume in 1 second; IV: intravenous; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; nE: number of events; PT: Preferred Term; SAE: serious adverse event

The outcome of pulmonary exacerbations was recorded in all study as a morbidity outcome as well as in the context of AEs and SAEs via the PT “infectious pulmonary exacerbation of cystic fibrosis”. Results on Week 24 are available for studies VX20-445-111 and VX15-809-115. Results on Week 48 are available for the VX16-809-121 study. Thus, a direct comparison of the results for the outcome “pulmonary exacerbations” based on the proportion of patients with an event between the intervention study VX20-445-111 and the RCT VX16-809-121 is not

possible due to the different observation periods. However, since study VX16-809-121 was conducted by the company itself, an analysis for a comparable observation period would basically have been possible for the company. It remains unclear why the company did not present such an analysis.

When recording the proportion of patients with a pulmonary exacerbation as a morbidity outcome, the VX20-445-111 and VX15-809-115 studies show roughly comparable proportions. Although the event rates are numerically lower under treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor compared to treatment with lumacaftor/ivacaftor, there are no clear differences for which it can be ruled out with sufficient certainty that they are not based solely on systematic bias due to confounders. If the outcome had been recorded as AE, a reverse trend was observed after 24 weeks. The proportion of patients under treatment with the ACT lumacaftor/ivacaftor (study VX15-089-115) was lower than under treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor in study VX20-445-111 (AE: 6.7% for lumacaftor/ivacaftor vs. 13.0% for ivacaftor/tezacaftor/elexacaftor + ivacaftor or SAE: 3.3% for lumacaftor/ivacaftor vs. 4.3% for ivacaftor/tezacaftor/elexacaftor + ivacaftor).

2.5 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 lumacaftor/ivacaftor as ACT compared with dossier assessment A23-123 [1] in patients with cystic fibrosis aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ivacaftor/Tezacaftor/Elexacaftor (Kombination mit Ivacaftor; zystische Fibrose, 2 bis 5 Jahre, F508del-Mutation, homozygot); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2024 [Accessed: 04.03.2024]. URL: https://doi.org/10.60584/A23-123.

2. Vertex Pharmaceuticals. Stellungnahme zum IQWiG-Bericht Nr. 1726: Ivacaftor/Tezacaftor/Elexacaftor (Kombination mit Ivacaftor; zystische Fibrose, 2 bis 5 Jahre, F508del-Mutation, homozygot); Nutzenbewertung gemäß § 35a SGB V. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1030/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Vertex Pharmaceuticals. Nachtrag zur mündlichen Anhörung am 8. April 2024 (Nutzenbewertung nach § 35a SGB V) [unpublished]. 2024.

4. Vertex Pharmaceuticals. Ivacaftor/Tezacaftor/Elexacaftor (Kaftrio); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2023 [Accessed: 22.04.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1030/#dossier.

5. Goralski JL, Hoppe JE, Mall MA et al. Phase 3 Open-Label Clinical Trial of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged 2-5 Years with Cystic Fibrosis and at Least One F508del Allele. Am J Respir Crit Care Med 2023; 208(1): 59-67. https://doi.org/10.1164/rccm.202301-0084OC.

6. Vertex Pharmaceuticals. Clinical Study Report; Protocol VX20-445-111; A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis sbjects 2 Through 5 Years of Age [unpublished]. 2022.

7. Vertex Pharmaceuticals. Evaluation of Long-term Safety and Efficacy of ELX/TEZ/IVA in Cystic Fibrosis (CF) Participants 2 Years and Older [online]. 2023 [Accessed: 09.01.2024]. URL: https://clinicaltrials.gov/study/NCT05153317.

8. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Ivacaftor/Tezacaftor/Elexacaftor (Neues Anwendungsgebiet: Zystische Fibrose, Kombinationsbehandlung mit Ivacaftor, 6 bis ≤ 11 Jahre (homozygot bzgl. F508del-Mutation)) [online]. 2022 [Accessed: 24.01.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/794/.

9. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Ivacaftor/Tezacaftor/Elexacaftor (Zystische Fibrose, Kombinationsbehandlung mit Ivacaftor bei Patienten ab 12 Jahren (homozygot bzgl. F508del-Mutation)) [online]. 2020 [Accessed: 29.01.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/584/.

10. Zemanick ET, Taylor-Cousar JL, Davies J et al. A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele. Am J Respir Crit Care Med 2021; 203(12): 1522-1532. https://doi.org/10.1164/rccm.202102-0509OC.

11. Vertex Pharmaceuticals. Evaluation of Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older [online]. 2022 [Accessed: 25.04.2022]. URL: https://ClinicalTrials.gov/show/NCT04183790.

12. Sutharsan S, McKone EF, Downey DG et al. Efficacy and safety of elexacaftor plus tezacaftor plus ivacaftor versus tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for F508del-CFTR: a 24-week, multicentre, randomised, double-blind, active-controlled, phase 3b trial. Lancet Respir Med 2022; 10(3): 267-277. https://doi.org/10.1016/S2213-2600(21)00454-9.

13. Stahl M, Roehmel J, Eichinger M et al. Effects of Lumacaftor/Ivacaftor on Cystic Fibrosis Disease Progression in Children 2 through 5 Years of Age Homozygous for F508del-CFTR: A Phase 2 Placebo-controlled Clinical Trial. Ann Am Thorac Soc 2023; 20(8): 1144-1155. https://doi.org/10.1513/AnnalsATS.202208-684OC.

14. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Lumacaftor/Ivacaftor (Neubewertung nach Fristablauf: zystische Fibrose, homozygot F508del-Mutation im CFTR-Gen, ≥ 2 bis ≤ 5 Jahre) [online]. 2021. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/743/.

15. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ivacaftor/Tezacaftor/Elexacaftor und Ivacaftor (zystische Fibrose, 6 bis 11 Jahre, F508del-Mutation, homozygot); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a22-16-und-a22-22_ivacaftor-tezacaftor-elexacaftor-und-ivacaftor_nutzenbewertung-35a-sgb-v_v1-0.pdf.

16. Vertex Pharmaceuticals. Ivacaftor/Tezacaftor/Elexacaftor (Kaftrio); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2022 [Accessed: 22.04.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/794/#dossier.

17. Vertex Pharmaceuticals. Dossier zur Nutzenbewertung gemäß § 35a SGB V, Lumacaftor/Ivacaftor (Orkambi) Modul 4 A; Behandlung der zystischen Fibrose bei Patienten von 2 bis 5 Jahren, die homozygot bezüglich der F508del-Mutation im CFTR-Gen sind [online]. 2021 [Accessed: 29.01.2024]. URL: https://www.g-ba.de/downloads/92-975-5148/2021_09_27_Modul4A_Lumacaftor_Ivacaftor.pdf.

18. Vertex Pharmaceuticals. A Study to Explore the Impact of Lumacaftor/Ivacaftor on Disease Progression in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for F508del [online]. 2022 [Accessed: 22.04.2024]. URL: https://classic.clinicaltrials.gov/ct2/show/results/NCT03625466?view=results.

19. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Lumacaftor/Ivacaftor (zystische Fibrose, 2 bis 5 Jahre, F508del-Mutation, homozygot); Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung); Dossierbewertung [online]. 2022 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a21-122_lumacaftor-ivacaftor_nutzenbewertung-35a-sgb-v_v1-0.pdf.

20. Vertex Pharmaceuticals (Europe). Dossier zur Nutzenbewertung gemäß § 35a SGB V; Lumacaftor/Ivacaftor (Orkambi); Modul 4 A; Behandlung der zystischen Fibrose bei Patienten zwischen 2 und 5 Jahren, die homozygot bezüglich der F508del-Mutation im CFTR-Gen sind [online]. 2019 [Accessed: 22.04.2024]. URL: https://www.g-ba.de/downloads/92-975-2943/2019-02-08_Modul4A_Lumacaftor-Ivacaftor.pdf.

21. Vertex Pharmaceuticals. Safety and Pharmacokinetic Study of Lumacaftor/Ivacaftor in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for F508del [online]. 2018 [Accessed: 22.04.2024]. URL: https://classic.clinicaltrials.gov/ct2/show/results/NCT02797132.

22. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Lumacaftor/Ivacaftor (zystische Fibrose bei Kindern zwischen 2 und 5 Jahren); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2019 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a19-13_lumacaftor-lvacaftor_nutzenbewertung-35a-sgb-v_v1-0.pdf.

23. Hoppe JE, Chilvers M, Ratjen F et al. Long-term safety of lumacaftor-ivacaftor in children aged 2-5 years with cystic fibrosis homozygous for the F508del-CFTR mutation; a multicentre, phase 3, open-label, extension study. Lancet Respir Med 2021; 9(9): 977-988. https://doi.org/10.1016/S2213-2600(21)00069-2.

24. Gemeinsamer Bundesausschuss. Mündliche Anhörung gemäß § 35 a Abs. 3 Satz 2 SGB V des Gemeinsamen Bundesausschusses; hier: Ivacaftor/Tezacaftor/Elexacaftor (D-985, D-1018, D-1019, D-1020, D-1021); Stenografisches Wortprotokoll [online]. 2024. URL: https://www.g-ba.de/downloads/91-1031-1030/2024-04-08_Wortprotokoll_Ivacaftor-Tezacaftor-Elexacaftor_D-1018.pdf.