IQWiG Reports – Commission No. A19-13

Lumacaftor/ivacaftor (cystic fibrosis in children aged 2 to 5 years) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Lumacaftor/Ivacaftor (zystische Fibrose bei Kindern zwischen 2 und 5 Jahren) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 May 2019). 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	best supportive care
CF	cystic fibrosis
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)
LCI	lung clearance index (measurement for assessment of ventilation inhomogeneity of the lung using the gas washout test) A subscript number after the abbreviation indicates the target concentration of the tracer gas.
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination lumacaftor/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 11 February 2019.

Research question

The aim of the present report was the assessment of the added benefit of lumacaftor/ivacaftor in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in the treatment of cystic fibrosis (CF) in patients aged 2 to 5 years who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Table 2 shows the therapeutic indication to be assessed and the corresponding ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of lumacaftor/ivacaftor

Research question	Therapeutic indication	ACT[a]
1	Patients with CF aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene	BSC[b]

a: Presentation of the ACT specified by the G-BA.
b: 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 (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [in the sense of the "Heilmittel Richtlinie", Remedies Directive] under exhaustion of all possible dietary measures).
ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee

The company cited BSC as ACT without mentioning concrete therapeutic measures specified by the G-BA as components of BSC.

The present benefit assessment was conducted in comparison with the G-BA's ACT. The implementation of the BSC (concurring with the G-BA's specification) was examined in the studies. 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.

Results

The company identified no RCTs with available results in the population to be assessed (children aged 2 to 5 years). For this reason, the company presented the single-arm

VX15-809-115 study, in which children with the disease under assessment were treated with lumacaftor/ivacaftor (in addition to their basic therapy) for 24 weeks.

The company derived an indication of a non-quantifiable added benefit from the results of the VX15-809-115 study. It justified this with the transferability of the added benefit of lumacaftor/ivacaftor determined by the G-BA for children aged 6 to 11 years and patients aged 12 years and older due to the same underlying genetic disease and advantages of the earliest possible start of causal treatment. For this purpose, the company presented the results from the single-arm study as proportions of patients with events or as the number of events per patient years (outcomes with binary data) or as a before-after comparison (outcomes with continuous data).

The company's approach to transfer study results from older patients to the population to be assessed is comprehensible due to the lack of comparative data in children aged 2 to 5 years. The concrete approach adopted by the company was unsuitable, however. An added benefit of lumacaftor/ivacaftor versus the ACT in children aged 2 to 5 years cannot be derived from the data presented by the company for the following reasons:

- The derivation of an added benefit on the basis of single-arm studies would only be possible in case of very large (dramatic) effects in comparison with the ACT. This would require data from studies with the ACT, however. These were not presented by the company. Besides, the single-arm VX15-809-115 study did not show such dramatic results, which would justify the derivation of an added benefit without comparison with the ACT.
- Regardless of whether the requirements formulated by the company for the transfer of study results were sufficient and also fulfilled, it should be noted that CF is a progressive disease. The greater the age difference between the population to be assessed and the population from which the transfer is to be made, the more questionable the transferability. Hence, data on patients aged 12 years and older appear even less suitable for being transferred to children aged 2 to 5 years than data on children aged 6 to 11 years.
- Transferring the added benefit from children aged 6 to 11 years to children aged 2 to 5 years is not possible. In IQWiG's assessment A18-08, the RCT VX14-809-109 used for the assessment of the added benefit in children aged 6 to 11 years showed neither positive nor negative effects of lumacaftor/ivacaftor in comparison with the ACT in patient-relevant outcomes. The determination of a non-quantifiable added benefit by the G-BA was based on the outcome "lung clearance index $(LCI)_{2.5}$", which the G-BA itself had rated as an unvalidated surrogate outcome. Apart from the fact that no results on this outcome were available for children aged 2 to 5 years for the comparator therapy, the results on lumacaftor/ivacaftor from the single-arm VX15-809-115 study on this outcome were not usable because a very high proportion of children were not included in the analysis, i.e. 54% of the children aged 3 years and older, for whom the $LCI_{2.5}$ was measured in a substudy. Consequently, the results for children aged 6 to 11 years cannot be compared with the results from the present VX15-809-115 study.

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 lumacaftor/ivacaftor compared with the ACT is assessed as follows:

Table 3 presents a summary of the probability and extent of the added benefit of lumacaftor/ivacaftor.

Table 3: Lumacaftor/ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with CF aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene	BSC[b]	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: 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 (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [in the sense of the "Heilmittel Richtlinie", Remedies Directive] under exhaustion of all possible dietary measures). ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

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

2.2 Research question

The aim of the present report was the assessment of the added benefit of lumacaftor/ivacaftor in comparison with BSC as ACT in the treatment of CF in patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene.

Table 4 shows the therapeutic indication to be assessed and the corresponding ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of lumacaftor/ivacaftor

Research question	Therapeutic indication	ACT[a]
1	Patients with CF aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene	BSC[b]

a: Presentation of the ACT specified by the G-BA.
b: 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 (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [in the sense of the "Heilmittel Richtlinie", Remedies Directive] under exhaustion of all possible dietary measures).
ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee

The company cited BSC, which it referred to as "best possible symptomatic therapy" in its dossier, as ACT without mentioning concrete therapeutic measures specified by the G-BA as components of BSC.

The present benefit assessment was conducted in comparison with the G-BA's ACT. The implementation of the BSC (concurring with the G-BA's specification) was examined in the studies. 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 largely concurs with the company's inclusion criteria. However, it also used non-randomized studies to assess the added benefit.

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 lists on lumacaftor/ivacaftor (status: 26 November 2018)
- bibliographical literature search on lumacaftor/ivacaftor (last search on 26 November 2018)
- search in trial registries for studies on lumacaftor/ivacaftor (last search on 26 November 2018)

To check the completeness of the study pool:

- search in trial registries for studies on lumacaftor/ivacaftor (last search on 25 February 2019)

Concurring with the company, the check of the completeness of the study pool produced no RCTs with available results in the population to be assessed (children aged 2 to 5 years). The potentially relevant RCT VX16-809-121 was identified, but no results from this RCT have become available yet [3].

Since no directly comparative data were available, the company presented the single-arm VX15-809-115 study (NCT02797132), in which children with the disease under assessment were treated with lumacaftor/ivacaftor (in addition to their basic therapy) for 24 weeks. This treatment phase was followed by a 2-week washout phase (see Appendix A of the full dossier assessment for additional information on the study).

The company derived an indication of a non-quantifiable added benefit from the results of this study. It justified this with the transferability of the added benefit of lumacaftor/ivacaftor from children aged 6 to 11 years [4] and patients aged 12 years and older [5]. For this purpose, the company presented the results from the single-arm study as proportions of patients with events or as the number of events per patient years (outcomes with binary data) or as a before-after comparison (outcomes with continuous data).

The company's approach to transfer study results from older patients to the population to be assessed is comprehensible due to the lack of comparative data in children aged 2 to 5 years. The concrete approach adopted by the company was unsuitable, however. An added benefit of lumacaftor/ivacaftor versus the ACT in children aged 2 to 5 years cannot be derived from the data presented by the company. This is justified below.

No comparison with the appropriate comparator therapy; effects not large enough

The derivation of an added benefit on the basis of single-arm studies would only be possible in case of very large (dramatic) effects in comparison with the ACT [1]. This would require data from studies with the ACT, however. These were not presented by the company. Consequently, the company also presented no comparison between treatment with lumacaftor/ivacaftor and BSC, so that treatment effects of lumacaftor/ivacaftor versus the ACT cannot be estimated.

Besides, the single-arm VX15-809-115 study did not show such dramatic results, which would justify the derivation of an added benefit without comparison with the ACT. None of the outcomes presented by the company showed a dramatic change after 24 weeks of treatment compared with baseline or after 2 weeks after the end of treatment (week 26) compared with week 24 [6].

Transfer of the added benefit not possible

The company transferred the added benefit established for patients aged 12 years and older and the added benefit established for children aged 6 to 11 years to the patient population of children aged 2 to 5 years to be assessed. It considered the transferability of the results on the added benefit based on the RCTs with older patients to be plausible due to the same mutation in the CFTR gene and the desirable early start of treatment.

Regardless of whether the requirements formulated by the company for the transfer of study results were sufficient and also fulfilled, it should be noted that CF is a progressive disease. The greater the age difference between the population to be assessed and the population from which the transfer is to be made, the more questionable the transferability. Hence, data on patients aged 12 years and older appear even less suitable for being transferred to children aged 2 to 5 years than data on children aged 6 to 11 years.

Transferring the added benefit from children aged 6 to 11 years to children aged 2 to 5 years is not possible for the following reason: In IQWiG's assessment, the RCT VX14-809-109 used for the assessment of the added benefit in children aged 6 to 11 years showed neither positive nor negative effects of lumacaftor/ivacaftor in comparison with the ACT in patient-relevant outcomes [7]. The determination of a non-quantifiable added benefit by the G-BA was based on the outcome "$LCI_{2.5}$", which the G-BA itself had rated as an unvalidated surrogate outcome [7-9]. Apart from the fact that no results on this outcome were available for children aged 2 to 5 years for the comparator therapy, the results on lumacaftor/ivacaftor from the single-arm VX15-809-115 study on this outcome were not usable. The $LCI_{2.5}$ was measured in a substudy within the VX15-809-115 study in children aged 3 years and older in selected centres. Only 37 of the 60 children included in the VX15-809-115 study participated in this substudy. Hence, only data of 17 children were included in the analysis of the change at week 24 compared with baseline. Consequently, a very high proportion of 54% of the children participating in the substudy were not considered in the analysis. Hence, the results on this outcome were not usable and could not be compared with the results of children aged 6 to 11 years.

2.4 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of lumacaftor/ivacaftor versus the ACT BSC in children with CF aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene. This resulted in no hint of an added benefit of lumacaftor/ivacaftor in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of lumacaftor/ivacaftor in comparison with the ACT is summarized in Table 5.

Table 5: Lumacaftor/ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with CF aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene	BSC[b]	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: 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 (particularly antibiotics for pulmonary infection, mucolytics, pancreatic enzymes for pancreatic insufficiency, physiotherapy [in the sense of the "Heilmittel Richtlinie", Remedies Directive] under exhaustion of all possible dietary measures). ACT: appropriate comparator therapy; BSC: best supportive care; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived an indication of non-quantifiable added benefit.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no 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 information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-13-lumacaftor-ivacaftor-cystic-fibrosis-in-children-aged-2-to-5-years-benefit-assessment-according-to-35a-social-code-book-v.11764.html.