IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Lumacaftor/ivacaftor (cystic fibrosis) –

Addendum to Commission A18-08[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
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)
LCI	lung clearance index
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
RCT	randomized controlled trial

1 Background

On 13 June 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A18-08 (Lumacaftor/ivacaftor – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier, the pharmaceutical company (hereinafter referred to as "the company") had presented results of the randomized controlled trial (RCT) VX14-809-109 for the assessment of the added benefit of lumacaftor/ivacaftor in the treatment of cystic fibrosis (CF) in patients between 6 and 11 years of age who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This study was included for the benefit assessment. However, it was unclear whether the study adequately implemented the appropriate comparator therapy (ACT) specified by the G-BA (best symptomatic treatment, 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). This uncertainty was considered in the assessment of the certainty of conclusions of the results. In its comment, the company presented additional information on the implementation of the ACT in the VX14-809-109 study, which went beyond the information provided in the dossier [2].

In its dossier [3], the company had presented analyses for the outcomes "lung clearance index ($LCI_{2.5}$)" and "forced expiratory volume in 1 second (FEV1)". These outcomes were not included in the benefit assessment as they are surrogate outcomes whose validity had not been shown in the company's dossier.

The G-BA commissioned IQWiG with the assessment of the analyses regarding intensification of treatment in the VX14-809-109 study submitted by the company in the commenting procedure under consideration of the information provided in the dossier. In addition, the G-BA commissioned IQWiG with the analysis of the outcomes on lung function using $LCI_{2.5}$ and FEV1 under consideration of the information provided in the dossier and, if applicable, supplementary explanations in the comment.

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 Implementation of the appropriate comparator therapy in the VX14-809-109 study

The G-BA specified best symptomatic treatment as ACT for the assessment of the added benefit of lumacaftor/ivacaftor in the treatment of CF in patients between 6 and 11 years of age who are homozygous for the F508del mutation in the CFTR gene. It further specified that this is understood to include, in particular, 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.

In its dossier, the company presented results of the RCT VX14-809-109 to prove the added benefit. This study investigated lumacaftor/ivacaftor in comparison with placebo, each in addition to basic therapy (see dossier assessment A18-08 [1] for a description of the study). It was checked whether the basic therapy administered in the study concurred with the G-BA's specifications for the ACT.

The company provided no information in Module 4 A of the dossier for the check of the implementation of the ACT. It only presented the proportion of children with inhaled treatments at baseline. This information alone is insufficient for assessing whether the ACT was adequately implemented in the study, however. The information from the clinical study report (CSR) was therefore used for the benefit assessment.

In accordance with the study protocol, it was recommended to maintain a stable level of the basic medication that the children had been receiving already 4 weeks before randomization. There were no explicit requirements for physiotherapy and dietary measures.

It was inferred from the documentation of the drug treatments administered before the first dose of the study medication and in the course of the study that the children were receiving comprehensive symptomatic drug treatment at the time point of study inclusion. It was visible that some adjustments to treatment, particularly regarding antibiotic treatment, were made in the course of the study. However, more detailed information on the intensification of further drug treatment measures comprised by the ACT was missing. The company's dossier contained no information at all on physiotherapy and dietary measures. In summary, it was uncertain whether the concomitant treatment used in the VX14-809-109 study constituted an adequate best symptomatic treatment in the sense of the ACT specified by the G-BA. As a result of this uncertainty, at most hints, e.g. of an added benefit, could be derived on the basis of the study. Detailed reasons can be found in the dossier assessment [1].

With its comment, the company submitted additional information on the implementation of the ACT in the VX14-809-109 study (see Table 1).

Table 1: Additional information subsequently submitted by the company regarding the switching of basic therapy in the course of the study, direct comparison: lumacaftor/ivacaftor + BST vs. placebo + BST

Study **Type of symptomatic treatment**	**Lumacaftor/ivacaftor + BST** **n (%)**	**Placebo + BST** **n (%)**
VX14-809-109	N[a] = 103	N[a] = 101
Antibiotic treatment[b]		
No antibiotic treatment at baseline	63 (61.2)	46 (45.5)
Antibiotic treatment at baseline		
1 continued antibiotic	29 (28.2)	38 (37.6)
≥ 2 continued antibiotics	11 (10.7)[c]	17 (16.8)[c]
Initiation of antibiotic treatment between baseline and week 24		
Not initiated	27 (26.2)	18 (17.8)
Initiation of 1 antibiotic	26 (25.2)	22 (21.8)
Initiation of ≥ 2 antibiotics	50 (48.5)[c]	61 (60.4)[c]
Treatment with IV antibiotics between baseline and week 24		
IV antibiotic at baseline	0 (0)	0 (0)
Initiation of treatment with IV antibiotics	16 (15.5)[c]	10 (9.9)[c]
Mucolytics		
The company presented no additional information.		
Pancreatic enzymes		
The company presented no additional information.		
Physiotherapy[d]		
No physiotherapy at baseline	10 (9.7)	16 (15.8)
Physiotherapy at baseline	93 (90.3)[c]	85 (84.2)[c]
Physiotherapy at week 24	89 (86.4)[c]	84 (83.2)[c]
Initiation of physiotherapy between baseline and week 24	2 (1.9)[c, e]	4 (4.0)[c]
Dietary measures		
	Not reported	Not reported[f]

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: Systemic antibiotics and drugs for mycobacteria, including all with any of the following methods of application: intramuscular, IV, IV bolus injection, nasal, oral, or inhaled.
c: Institute's calculation from the information provided by the company in the comment.
d: Summary of the following MedDRA PTs by the company: positive expiratory pressure therapy, positive end-expiratory pressure, airway secretion clearance therapy, physiotherapy chest.
e: Additional physiotherapy was added to the treatment of one child in the lumacaftor/ivacaftor arm during the course of the study.
f: One study patient required percutaneous gastrostomy placement for nutritional supplementation.
BST: best symptomatic treatment; IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients in the category; N: number of randomized patients; PT: Preferred Term; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The information subsequently submitted by the company regarding basic therapy comprised further information on antibiotic treatment as well as information on physiotherapy and dietary measures.

The supplementary information provided by the company on antibiotic treatment confirmed that, as already described in the dossier assessment, adjustments to the antibiotic treatment were made in the course of the study. Treatment with a systemic antibiotic was initiated in about 74% of the children in the lumacaftor/ivacaftor arm and in about 82% in the placebo arm.

For the area of physiotherapy, the company presented an analysis based on a selection of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs). This analysis was not mandated in the VX14-809-109 study. Instead, according to the company, it was prepared specifically for the present procedure on the basis of the data on non-pharmacological measures in the study from the patient listings. The listings themselves were not transmitted by the company. The analyses presented by the company on physiotherapy showed that the majority of the patients (about 87%) were receiving physiotherapeutic basic therapy already at baseline. The proportion of children receiving physiotherapy at week 24 remained largely stable in both study arms (about 85%).

Regarding dietary measures, the company noted that patients were on a stable diet programme before study inclusion and that the necessity for a rapid medical nutritional intervention at the time point of treatment start was excluded per inclusion criterion. Only one study patient in the placebo arm required percutaneous gastrostomy placement for nutritional supplementation. Further medical nutritional interventions were not reported in the framework of the study.

Regarding treatment with mucolytics and pancreatic enzymes, the company presented no information that went beyond the information provided in the dossier assessment. It would have been possible for the company to prepare information for these drug groups in the same way as it prepared information for antibiotics. However, Table 9 and Table 10 of dossier assessment A18-08 [1] show that most patients received inhaled mucolytics such as dornase alfa (about 85%) or hypertonic saline (about 59%) before the study and in the course of the study. Pancreatic enzymes were also administered to at least 2 thirds of the children before the study and in the course of the study (pancreatin: about 69%; pancrelipase: about 25%). Overall, it can be assumed that patients received an at least adequate (stable) basic therapy with these substances.

In the overall assessment of the information available in the dossier and subsequently submitted by the company, basic therapy in the VX14-809-109 study was considered to be an adequate implementation of best symptomatic treatment. Outcome-specific, at most indications, e.g. of an added benefit, can therefore be derived on the basis of the study.

2.2 Lung function measured with $LCI_{2.5}$ and FEV1

Comment on the outcomes "$LCI_{2.5}$" and "FEV1"

In its dossier [3], the company had presented analyses for the outcomes "$LCI_{2.5}$" and "FEV1 (as proportion of the standardized normal value in per cent FEV1 %])". It considered both outcomes to be patient-relevant and, at the same time, to be surrogate outcomes for symptoms/morbidity ($LCI_{2.5}$) and morbidity (FEV1 %). Both in the dossier and again in the comment, the company presented a number of publications it regarded as proof of patient relevance and validity of the $LCI_{2.5}$ as surrogate outcome [4-10]. The company did not address the issue of validity of the outcome "FEV1 %" in its comment.

As already described in the dossier assessment, both outcomes "$LCI_{2.5}$" and "FEV1 %" are not considered patient-relevant and were not included in the assessment of the added benefit. It is plausible that both parameters can be of diagnostic and prognostic importance. However, this statement does not mean that parameters used for measuring lung function are suitable per se to describe a patient-relevant treatment effect of a drug in comparison with the ACT.

As already described in the dossier assessment [1], both outcomes "$LCI_{2.5}$" and "FEV1 %" are surrogate outcomes. The studies presented by the company were unsuitable for answering the question of surrogate validation. In particular, these studies did not consider treatment effects, whose investigation is necessary for surrogate validation. In addition, these publications partly investigated correlations on outcomes that are not patient-relevant (such as the Bhalla score, which is based on radiographic examinations). Kent 2014 [11] also concluded in the current review on the LCI that LCI could be a potential surrogate outcome, but that further investigation is required.

In compliance with the commission, the outcomes "$LCI_{2.5}$" and "FEV1 %" are analysed in the following section.

Analysis of the outcomes "$LCI_{2.5}$" and "FEV1 %"

For the outcome "$LCI_{2.5}$", the company presented analyses on the absolute change from baseline to week 24.

For the outcome "FEV1 %", the company presented analyses on the absolute change from baseline to week 24 and on the relative change to week 24. These 2 analyses for FEV1 % were predefined. The company presented additional responder analyses on 2 criteria defined post hoc. The company defined children with an increase in FEV1 % by at least 3 percentage points or by at least 5 percentage points from baseline as responders. The company presented no publications describing the validity of these response criteria.

In compliance with the commission, Table 2 presents the results for the outcomes "$LCI_{2.5}$" and "FEV1". It only shows the analyses planned a priori in the VX14-809-109 study.

Table 2: Results for the outcomes "LCI2.5" and "FEV1 %" (continuous) – RCT, direct comparison: lumacaftor/ivacaftor + BST vs. placebo + BST

Study Outcome	Lumacaftor/ivacaftor + BST			Placebo + BST			Lumacaftor/ ivacaftor + BST vs. placebo + BST
	N[a]	Values at baseline mean (SD)	Change at end of study mean (SD)	N[a]	Values at baseline mean (SD)	Change at end of study mean (SD)	MD[b] [95% CI]; p-value
VX14-809-109							
$LCI_{2.5}$ (absolute change)	99	10.30 (2.36)	−1.00 (1.41)	99	10.26 (2.24)	0.08 (1.41)	−1.09 [−1.43; −0.75]; < 0.001
FEV1 % (absolute change)	101	88.82 (13.75)	0.50 (8.08)	100	90.73 (10.80)	−1.91 (6.83)	2.42 [0.42; 4.43]; 0.018
FEV1 % (relative change)	101	88.82 (13.75)	1.46 (11.10)	100	90.73 (10.80)	−1.71 (7.82)	3.16 [0.64; 5.68]; 0.014

a: Number of patients considered in the analysis for the calculation of the effect; the values at baseline may be based on other patient numbers.
b: Least squares estimation of the mean difference from MMRM; treatment, time point of study and treatment x time point of study as fixed effects, patient as random effect; adjusted for weight (< 25 kg vs. ≥ 25 kg) and FEV1 % (< 90 vs. ≥ 90) at time point of screening (for the outcome "$LCI_{2.5}$" additionally $LCI_{2.5}$ at baseline).
BST: best symptomatic treatment; CI: confidence interval; LCI: lung clearance index; MD: mean difference, MMRM: mixed-effects model repeated measures; N: number of analysed patients; FEV1 %: proportion of forced expiratory volume in 1 second from the standardized normal value in per cent; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

For the **outcome "$LCI_{2.5}$"** (absolute change), a statistically significant difference was shown in favour of lumacaftor/ivacaftor.

For the **outcome "FEV1 %"**, a statistically significant difference was shown in favour of lumacaftor/ivacaftor, both for absolute and for relative change.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of lumacaftor/ivacaftor from dossier assessment A18-08.

The following Table 3 shows the result of the benefit assessment of lumacaftor/ivacaftor under consideration of dossier assessment A18-08 and the present addendum.

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CF patients between 6 and 11 years of age who are homozygous for the F508del mutation in the CFTR gene	Best symptomatic treatment (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	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

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