IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Elbasvir/grazoprevir (chronic hepatitis C) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment Elbasvir/Grazoprevir *(chronische Hepatitis C) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 10 March 2017). 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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[3] 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
CHC	chronic hepatitis C
CKD	chronic kidney disease
DSV	dasabuvir
EBR/GZR	elbasvir/grazoprevir
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IU	international units
LDV	ledipasvir
NS5A RAV	nonstructural protein 5A resistance-associated variant
OBV/PTV/R	ombitasvir/paritaprevir/ritonavir
peg-IFN	pegylated interferon
RBV	ribavirin
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SOF	Sofosbuvir
SVR	sustained virologic response

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 elbasvir/grazoprevir (EBR/GZR). 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 14 December 2016.

Research question

The aim of this report was to assess the added benefit of EBR/GZR compared with the appropriate comparator therapy (ACT) in the treatment of adult patients with chronic hepatitis C (CHC).

Two research questions resulted from the G-BA's specification of the ACT for patients with CHC genotype 1 and genotype 4.

Table 2: Research questions of the benefit assessment of elbasvir/grazoprevir

Research question	Subindication	Appropriate comparator therapy[a]
1	CHC genotype 1	Ledipasvir/sofosbuvir[b] or ombitasvir/paritaprevir/ritonavir plus dasabuvir (if applicable, plus ribavirin)[c]
2	CHC genotype 4	Ledipasvir/sofosbuvir[b] or ombitasvir/paritaprevir/ritonavir plus ribavirin[c]

a: Presentation of the respective ACT specified by the G-BA. The G-BA's ACT also contains information on genotype 3 and 6 – however, the use of elbasvir/grazoprevir for these genotypes is not recommended in the SPC.
b: Patients without cirrhosis/with compensated cirrhosis; according to the SPC of ledipasvir/sofosbuvir, the combination of ledipasvir/sofosbuvir plus ribavirin is an alternative option in patients infected with genotype 1, 4, 5 or 6 without cirrhosis or with compensated cirrhosis. The G-BA currently does not consider this combination as ACT.
c: Patients without cirrhosis.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

In its dossier, the company derived 6 research questions, justifying them with different CHC (sub)genotypes and their different treatment regimens according to the Summary of Product Characteristics (SPC) of EBR/GZR:

- 3 research questions for CHC genotype 1:
  - CHC genotype 1a
  - CHC genotype 1a and baseline viral load of > 800 000 international units [IU]/mL and/or presence of specific nonstructural protein 5A resistance-associated variants (NS5A RAVs) causing at least a 5-fold reduction in antiviral activity of elbasvir
  - CHC genotype 1b
- 2 research questions for CHC genotype 4:
  - CHC genotype 4
  - CHC genotype 4 and baseline viral load of > 800 000 IU/mL
- 1 research question for CHC genotype 1 or 4:
  - CHC genotype 1 or 4 and stage 4 and 5 chronic kidney disease (CKD)

The differentiation by subgenotypes and baseline viral load or presence of specific NS5A RAVs is principally comprehensible, but not relevant for the assessment because no suitable studies on the comparison with the ACT were available for any of the subpopulations (including patients with CHC and CKD).

The differentiation into 2 research questions in the present benefit assessment was based on the G-BA's specification of the ACT.

The company followed the G-BA regarding the ACT for some of the research questions defined by the company and specified ledipasvir/sofosbuvir (LDV/SOF) as ACT. In addition, the company searched for suitable evidence for the comparison with ombitasvir/paritaprevir/ritonavir (OBV/PTV/R) in cases in which it considered there to be no suitable evidence versus LDV/SOF.

Deviating from the G-BA, the company additionally cited sofosbuvir (SOF) + pegylated interferon (peg-IFN) + ribavirin (RBV) as ACT for patients with CHC genotype 1a and 1b, as well as best supportive care (BSC) for patients with CHC genotype 1 or 4 and stage 4 and 5 CKD. These therapies do not concur with the G-BA's ACT and were therefore not relevant for the present benefit assessment.

An overview of the data presented by the company is shown in Table 3.

Table 3: Data presented by the company on the research questions

Research question	Subindication of the company	Intervention of the company	Comparator therapy of the company	Data presented by the company
1	CHC in adults – genotype 1			
	CHC genotype 1a	EBR/GZR	SOF + peg-IFN + RBV	RCT
			LDV/SOF (+ RBV)	Use of individual arms from different studies
	CHC genotype 1a and baseline viral load[a] of > 800 000 IU/mL and/or presence of specific NS5A RAVs[b]	EBR/GZR + RBV	OBV/PTV/R + DSV + RBV	Use of individual arms from different studies
	CHC genotype 1b	EBR/GZR	SOF + peg-IFN + RBV	RCT
			LDV/SOF (+ RBV)	Use of individual arms from different studies
	CHC genotype 1 (or 4) and stage 4 and 5 CKD	EBR/GZR	BSC	RCT
2	CHC in adults – genotype 4			
	CHC genotype 4	EBR/GZR	OBV/PTV/R + RBV	Use of individual arms from different studies
	CHC genotype 4 and baseline viral load[a] of > 800 000 IU/mL	EBR/GZR + RBV	LDV/SOF (+ RBV) or OBV/PTV/R + RBV	No studies with comparator therapy LDV/SOF (+ RBV) or OBV/PTV/R + RBV identified
	CHC genotype (1 or) 4 and stage 4 and 5 CKD	EBR/GZR	BSC	RCT

a: Determined with measurement of HCV RNA plasma levels.
b: NS5A RAVs causing at least a 5-fold reduction in antiviral activity of elbasvir.

BSC: best supportive care; CHC: chronic hepatitis C; CKD: chronic kidney disease; DSV: dasabuvir; EBR/GZR: elbasvir/grazoprevir; HCV: hepatitis C virus; IU: international units; LDV/SOF: ledipasvir/sofosbuvir; NS5A RAV: nonstructural protein 5A resistance-associated variant; OBV/PTV/R: ombitasvir/paritaprevir/ritonavir; peg-IFN: pegylated interferon; RBV: ribavirin; RNA: ribonucleic acid; RCT: randomized controlled trial; SOF: sofosbuvir

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Research question 1: patients with CHC genotype 1

Direct comparison

The company presented 2 RCTs, the studies C-EDGE H2H and C-SURFER, for research question 1 (CHC genotype 1). Both studies were unsuitable to derive conclusions on the added benefit of EBR/GZR in comparison with the ACT. The reasons are described below.

Study C-EDGE H2H

The company used the C-EDGE H2H study for the subpopulations of CHC genotype 1a patients and of CHC genotype 1b patients. The study was a randomized, controlled, open-label phase 3 study on the comparison of EBR/GZR with SOF + peg-IFN + RBV.

However, the C-EDGE H2H study was unsuitable to derive conclusions on the added benefit of EBR/GZR versus the ACT specified by the G-BA. The combination therapy SOF + peg-IFN + RBV did not concur with the ACT specified by the G-BA. The company presented no evidence that justified the use of SOF + peg-IFN + RBV as ACT. Guidelines also do not recommend SOF + peg-IFN + RBV because interferon-free treatments have at least equivalent rates in sustained virologic response (SVR) with better tolerability and partly shorter treatment duration.

Study C-SURFER

The company used the C-SURFER study for CHC genotype 1 patients with stage 4 and 5 CKD. The study was a randomized, double-blind, placebo-controlled phase 2/3 study. Patients in the intervention arm ("immediate" arm) received EBR/GZR for 12 weeks. Patients in the control arm received placebo for 12 weeks, followed by a 4-week unblinding phase and, subsequently (from week 16) EBR/GZR for 12 weeks in the open-label design ("deferred" arm).

However, the C-SURFER study was unsuitable to derive conclusions on the added benefit of EBR/GZR versus the ACT.

The company specified BSC as ACT for patients with stage 4 and 5 CKD and argued that the 12-week placebo phase in the "deferred" arm of the C-SURFER study corresponded to BSC. However, the company presented no evidence that justified the use of BSC as ACT.

The G-BA specified no separate ACT for CKD patients (stage 4 and 5 CKD).

One of the options of the ACT specified by the G-BA for genotype 1 patients was the combination therapy OBV/PTV/R (+ DSV) (+ RBV). According to the SPCs, neither ribavirin nor OBV/PTV/R is contraindicated in patients with severe renal function disorder. Guidelines also additionally recommend OBV/PTV/R with/without dasabuvir and with/without ribavirin for CHC genotype 1 or 4 patients with severe renal insufficiency.

Comparison using individual arms from different studies

The company presented further comparisons besides the 2 studies of direct comparisons. Using individual arms from different studies, it compared EBR/GZR with the ACT specified by the G-BA. No added benefit of EBR/GZR in comparison with the ACT could be derived from the data presented by the company, however.

Conclusions on the added benefit based on the use of individual arms from different studies are only possible if the observed effect is so large that it can be excluded that it is caused by systematic bias alone (so-called dramatic effect). In the present case, the comparison using individual arms from different studies showed no effects that can be considered dramatic; hence an added benefit could not be derived.

Research question 2: patients with CHC genotype 4

Direct comparison

As for the subpopulation of CHC genotype 1 patients with CKD, the company presented the C-SURFER study for the subpopulation of CHC genotype 4 patients with CKD (stage 4 and 5 CKD). The study was unsuitable to derive conclusions on the added benefit of EBR/GZR versus the ACT because the comparator of the study did not concur with the ACT (see research question 1). In addition, only patients with CHC genotype 1, but not with CHC genotype 4, were included in the study. The company assumed transferability of the results to genotype 4 patients, but provided no adequate justification for this.

Comparison using individual arms from different studies

Besides the C-SURFER study of direct comparison, the company presented further comparisons using individual arms from different studies for CHC genotype 4 patients.

The comparisons presented by the company using individual arms from different studies showed no effects that can be considered dramatic; hence no added benefit of EBR/GZR in comparison with the ACT could be derived from the data.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug combination EBR/GZR compared with the ACT is assessed as follows:

[4] 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, no added benefit, or less benefit). For further details see [1,2].

Table 4 presents a summary of the extent and probability of the added benefit of EBR/GZR

Table 4: Elbasvir/grazoprevir – extent and probability of added benefit

Subindication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
CHC genotype 1	Ledipasvir/sofosbuvir[b] or ombitasvir/paritaprevir/ritonavir plus dasabuvir (if applicable, plus ribavirin)[c]	Added benefit not proven
CHC genotype 4	Ledipasvir/sofosbuvir[b] or ombitasvir/paritaprevir/ritonavir plus ribavirin[c]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. The G-BA's ACT also contains information on genotype 3 and 6 – however, the use of elbasvir/grazoprevir for these genotypes is not recommended in the SPC.
b: Patients without cirrhosis/with compensated cirrhosis; according to the SPC of ledipasvir/sofosbuvir, the combination of ledipasvir/sofosbuvir plus ribavirin is an alternative option in patients infected with genotype 1, 4, 5 or 6 without cirrhosis or with compensated cirrhosis. The G-BA currently does not consider this combination as ACT.
c: Patients without cirrhosis.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of EBR/GZR compared with the ACT in the treatment of adult patients with CHC.

Two research questions resulted from the G-BA's specification of the ACT for patients with CHC genotype 1 and genotype 4.

Table 5: Research questions of the benefit assessment of elbasvir/grazoprevir

Research question	Subindication	Appropriate comparator therapy[a]
1	CHC genotype 1	Ledipasvir/sofosbuvir[b] or ombitasvir/paritaprevir/ritonavir plus dasabuvir (if applicable, plus ribavirin)[c]
2	CHC genotype 4	Ledipasvir/sofosbuvir[b] or ombitasvir/paritaprevir/ritonavir plus ribavirin[c]

a: Presentation of the respective ACT specified by the G-BA. The G-BA's ACT also contained information on genotype 3 and 6 – however, the use of elbasvir/grazoprevir for these genotypes is not recommended in the SPC.
b: Patients without cirrhosis/with compensated cirrhosis; according to the SPC of ledipasvir/sofosbuvir, the combination of ledipasvir/sofosbuvir plus ribavirin is an alternative option in patients infected with genotype 1, 4, 5 or 6 without cirrhosis or with compensated cirrhosis. The G-BA currently does not consider this combination as ACT.
c: Patients without cirrhosis.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

In its dossier, the company derived 6 research questions, justifying them with different CHC (sub)genotypes and their different treatment regimens according to the SPC of EBR/GZR [3]:

- 3 research questions for CHC genotype 1:
  - CHC genotype 1a
  - CHC genotype 1a and baseline viral load of > 800 000 IU/mL and/or presence of specific NS5A RAVs causing at least a 5-fold reduction in antiviral activity of elbasvir
  - CHC genotype 1b
- 2 research questions for CHC genotype 4:
  - CHC genotype 4
  - CHC genotype 4 and baseline viral load of > 800 000 IU/mL
- 1 research question for CHC genotype 1 or 4:
  - CHC genotype 1 or 4 and stage 4 and 5 CKD

The differentiation into 2 research questions in the present benefit assessment was based on the G-BA's specification of the ACT. The different research questions of the company are investigated within the sections on genotypes 1 and 4.

The company followed the G-BA regarding the ACT for some of the research questions defined by the company and specified LDV/SOF as ACT. In addition, the company searched for suitable evidence for the comparison with OBV/PTV/R in cases in which it considered there to be no suitable evidence versus LDV/SOF.

Deviating from the G-BA, the company additionally cited SOF + peg-IFN + RBV as ACT for patients with CHC genotype 1a and 1b, as well as BSC for patients with CHC genotype 1 or 4 and stage 4 and 5 CKD. These therapies do not concur with the G-BA's ACT and were therefore not relevant for the present benefit assessment (see Section 2.3.1 and Section 2.6.1 of the full dossier assessment).

An overview of the data presented by the company is shown in Table 6.

Table 6: Data presented by the company on the research questions

Research question	Subindication of the company	Intervention of the company	Comparator therapy of the company	Data presented by the company
1	CHC in adults – genotype 1			
	CHC genotype 1a	EBR/GZR	SOF + peg-IFN + RBV	RCT
			LDV/SOF (+ RBV)	Use of individual arms from different studies
	CHC genotype 1a and baseline viral load[a] of > 800 000 IU/mL and/or presence of specific NS5A RAVs[b]	EBR/GZR + RBV	OBV/PTV/R + DSV + RBV	Use of individual arms from different studies
	CHC genotype 1b	EBR/GZR	SOF + peg-IFN + RBV	RCT
			LDV/SOF (+ RBV)	Use of individual arms from different studies
	CHC genotype 1 (or 4) and stage 4 and 5 CKD	EBR/GZR	BSC	RCT
2	CHC in adults – genotype 4			
	CHC genotype 4	EBR/GZR	OBV/PTV/R + RBV	Use of individual arms from different studies
	CHC genotype 4 and baseline viral load[a] of > 800 000 IU/mL	EBR/GZR + RBV	LDV/SOF (+ RBV) or OBV/PTV/R + RBV	No studies with comparator therapy LDV/SOF (+ RBV) or OBV/PTV/R + RBV identified
	CHC genotype (1 or) 4 and stage 4 and 5 CKD	EBR/GZR	BSC	RCT

a: Determined with measurement of HCV RNA plasma levels.
b: NS5A RAVs causing at least a 5-fold reduction in antiviral activity of elbasvir.

BSC: best supportive care; CHC: chronic hepatitis C; CKD: chronic kidney disease; DSV: dasabuvir; EBR/GZR: elbasvir/grazoprevir; HCV: hepatitis C virus; IU: international units; LDV/SOF: ledipasvir/sofosbuvir; NS5A RAV: nonstructural protein 5A resistance-associated variant; OBV/PTV/R: ombitasvir/paritaprevir/ritonavir; peg-IFN: pegylated interferon; RBV: ribavirin; RNA: ribonucleic acid; RCT: randomized controlled trial; SOF: sofosbuvir

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Research question 1: patients with CHC genotype 1

2.3.1 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 EBR/GZR (status: 21 November 2016)
- bibliographical literature search on EBR/GZR (last search on 2 October 2016)
- search in trial registries for studies on EBR/GZR (last search on 29 September 2016)
- bibliographical literature search on ACTs (last search on 2 November 2016)
- search in trial registries for studies on ACTs (last search on 3 November 2016)

To check the completeness of the study pool:

- search in trial registries for studies on EBR/GZR (last search on 22 December 2016)

No randomized controlled trials (RCTs) of direct comparisons for CHC genotype 1 patients comparing EBR/GZR with the ACT were identified from the check.

Table 7 presents the studies included by the company for research question 1 (CHC genotype 1 patients), separated by studies for the direct comparison and for the comparison of individual arms from different studies presented by the company. The table also shows the subpopulations for CHC genotype 1 patients considered by the company in the dossier: genotype 1a, genotype 1b, genotype 1a with high baseline viral load and/or presence of specific NS5A RAVs as well as patients with CKD.

Table 7: Study pool of the company – CHC genotype 1 patients (research question 1)

Comparison Genotype Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Direct comparison			
Genotype 1a/1b			
Studies with EBR/GZR			
NCT02358044 (C-EDGE H2H[b]) [4-6]	No	Yes	No
Genotype 1 with CKD (stage 4 and 5)			
Studies with EBR/GZR			
NCT02092350 (C-SURFER[b]) [7-10]	Yes	Yes	No
Comparison using individual arms from different studies			
Genotype 1a			
Studies with EBR/GZR			
NCT02251990 (C-CORAL[b]) [11,12]	No	Yes	No
NCT02358044 (C-EDGE H2H[b])	No	Yes	No
NCT02105701 (C-EDGE TE[b]) [13-16]	Yes	Yes	No
NCT02105467 (C-EDGE TN[b]) [17-20]	Yes	Yes	No
NCT01717326 (C-WORTHY[b]) [21-25]	Yes	Yes	No
Studies with LDV/SOF			
NCT01260350 (ELECTRON [Part 6][b]) [26,27]	No	No	Yes
NCT01826981 (ELECTRON-2[b]) [28,29]	No	No	Yes
NCT01701401 (ION-1[b]) [30,31]	No	No	Yes
NCT01768286 (ION-2[b]) [32,33]	No	No	Yes
NCT01851330 (ION-3[b]) [34,35]	No	No	Yes
NCT01726517 (LONESTAR[b]) [36,37]	No	No	Yes
NCT01965535 (SIRIUS[b]) [38-40]	No	No	Yes
Genotype 1b			
Studies with EBR/GZR			
NCT02251990 (C-CORAL[b])	No	Yes	No
NCT02358044 (C-EDGE H2H[b])	No	Yes	No
NCT02105701 (C-EDGE TE[b])	Yes	Yes	No
NCT02105467 (C-EDGE TN[b])	Yes	Yes	No
NCT01717326 (C-WORTHY[b])	Yes	Yes	No
Studies with LDV/SOF			
NCT01260350 (ELECTRON [Part 6][b])	No	No	Yes
NCT01826981 (ELECTRON-2[b])	No	No	Yes
NCT01975675 (GS-US-337-0113[b]) [41,42]	No	No	Yes

(continued)

Table 7: Study pool of the company – CHC genotype 1 patients (research question 1) (continued)

Comparison Genotype Study	Study category Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Comparison using individual arms from different studies			
Genotype 1b			
Studies with LDV/SOF			
NCT01701401 (ION-1[b])	No	No	Yes
NCT01768286 (ION-2[b])	No	No	Yes
NCT01851330 (ION-3[b])	No	No	Yes
NCT01726517 (LONESTAR[b])	No	No	Yes
NCT01965535 (SIRIUS[b])	No	No	Yes
Genotype 1a (with baseline viral load[a] of > 800 000 IU/mL and/or presence of specific NS5A RAVs[c])			
Studies with EBR/GZR			
NCT02105701 (C-EDGE TE[b])	Yes	Yes	No
Studies with LDV/SOF	No studies identified		
Studies with OBV/PTV/R			
NCT01833533 (PEARL-IV[b]) [43,44]	No	No	Yes
NCT01715415 (SAPPHIRE-II[b]) [45,46]	No	No	Yes

a: Study for which the company was sponsor.
b: Hereinafter, the study is referred to with this abbreviated form.
c: NS5A RAVs that result in an at least 5-fold decrease of the antiviral activity of elbasvir.
CHC: chronic hepatitis C; CKD: chronic kidney disease; EBR/GZR: elbasvir/grazoprevir; IU: international units; LDV/SOF: ledipasvir/sofosbuvir; NS5A RAV: nonstructural protein 5A resistance-associated variant; OBV/PTV/R: ombitasvir/paritaprevir/ritonavir

Direct comparison

The company presented 2 RCTs, the studies C-EDGE H2H and C-SURFER, for research question 1 (CHC genotype 1). Table 13 and Table 14 (Appendix A.1 of the full dossier assessment) describe the study characteristics and interventions. Both studies were unsuitable to derive conclusions on the added benefit of EBR/GZR in comparison with the ACT. The reasons are described below.

Study C-EDGE H2H

The company used the C-EDGE H2H study for the subpopulations of CHC genotype 1a patients and of CHC genotype 1b patients. The study was a randomized, controlled, open-label phase 3 study. Adult patients with CHC genotype 1, 4 or 6 were enrolled. The patients in the intervention arm received EBR/GZR for 12 weeks (N = 129). The dosing scheme was in compliance with the requirements of the SPCs [3]. The patients in the comparator arm received SOF + peg-IFN + RBV for 12 weeks (N = 128).

However, the C-EDGE H2H study was unsuitable to derive conclusions on the added benefit of EBR/GZR versus the ACT. The combination therapy SOF + peg-IFN + RBV did not concur with the ACT specified by the G-BA. The company presented no evidence that justified the use of SOF + peg-IFN + RBV as ACT. Guidelines also do not recommend SOF + peg-IFN + RBV because interferon-free treatments have at least equivalent rates in SVR with better tolerability and partly shorter treatment duration [47-50].

Study C-SURFER

The company used the C-SURFER study for CHC genotype 1 patients with stage 4 and 5 CKD. The study was a randomized, double-blind, placebo-controlled phase 2/3 study. Adult patients with CHC genotype 1 and CKD (defined by means of a glomerular filtration rate of ≤ 29 mL/min) were enrolled. Patients were randomly assigned to 2 treatment arms. In addition, further patients were treated in a separate open-label pharmacokinetics arm. Hereinafter, only the 2 randomized, double-blind treatment arms considered by the company in the dossier are described. Patients in the intervention arm ("immediate" arm) received EBR/GZR for 12 weeks (N = 112). Patients in the control arm received placebo for 12 weeks, followed by a 4-week unblinding phase. Subsequently (from week 16), the patients in the control arm received EBR/GZR for 12 weeks in an open-label design ("deferred" arm) (N = 114).

The C-SURFER study was unsuitable to derive conclusions on the added benefit of EBR/GZR versus the ACT.

The company specified BSC as ACT for patients with stage 4 and 5 CKD and argued that the 12-week placebo phase in the "deferred" arm of the C-SURFER study corresponded to BSC (see Table 14 in Appendix A.1 of the full dossier assessment for information on the allowed concomitant treatment in the C-SURFER study). However, the company presented no evidence that justified the use of BSC as ACT.

The G-BA specified no separate ACT for CKD patients (stage 4 and 5 CKD).

One of the options of the ACT specified by the G-BA for genotype 1 patients was the combination therapy OBV/PTV/R (+ dasabuvir [DSV]) (+ RBV). According to the SPCs, neither ribavirin nor OBV/PTV/R is contraindicated in patients with severe renal function disorder [51,52]. Guidelines also additionally recommend OBV/PTV/R with/without dasabuvir and with/without ribavirin for CHC genotype 1 or 4 patients with severe renal insufficiency [47,48].

Since treatment in the comparator arm of the C-SURFER study (placebo in the first 12 weeks) did not concur with the ACT, the implementation of BSC in the placebo arm of the C-SURFER study is not further commented on.

Comparison using individual arms from different studies

The company presented further comparisons besides the 2 studies of direct comparisons. Using individual arms from different studies, it compared EBR/GZR with the ACT specified by the G-BA. Table 15 and Table 16 (Appendix A.2 of the full dossier assessment) describe the study characteristics and interventions of these studies. No added benefit of EBR/GZR in comparison with the ACT could be derived from the data presented by the company, however.

Conclusions on the added benefit based on the use of individual arms from different studies are only possible if the observed effect is so large that it can be excluded that it is caused by systematic bias alone (so-called dramatic effect). The simulation results of Glasziou 2007 [53] cited in the IQWiG methods paper serve as an orientation for the classification of a dramatic effect. In an approach, an effect is regarded as sufficiently large if it is statistically significant at the level of 1% and, expressed as the estimated relative risk [RR], has a value of 10 or higher (or 1/10 or lower) [1]. Moreover, the risk of the examined event should be at least 5% in at least one of the groups compared. In the present case, the comparison using individual arms from different studies showed no effects that can be considered dramatic; hence an added benefit could not be derived. The company also claimed no added benefit on the basis of this comparison.

Subpopulations considered by the company

For CHC genotype 1 patients, the company defined the following 4 subpopulations, for each of which it derived the added benefit separately:

- CHC genotype 1a
- CHC genotype 1a with high baseline viral load of > 800 000 IU/mL and/or presence of specific NS5A RAVs causing at least a 5-fold reduction in antiviral activity of elbasvir
- CHC genotype 1b
- CHC genotype 1 or 4 and stage 4 and 5 CKD

The company justified the differentiation into subpopulations with different CHC (sub)genotypes and their different treatment regimens according to the SPC of EBR/GZR. For patients with CHC genotype 1a and 1b, the SPC recommends treatment with EBR/GZR (without RBV) for 12 weeks [3]. In addition, for CHC genotype 1a, treatment for 16 weeks in combination with RBV should be considered in patients with baseline viral load of > 800 000 IU/mL and/or the presence of specific NS5A RAVs causing at least a 5-fold reduction in antiviral activity of elbasvir. The differentiation is principally comprehensible, but not relevant for the assessment because there were no suitable studies on the comparison with the ACT for any of the subpopulations.

The subpopulation of CHC wit CKD considered by the company has already been addressed in this Section (see Section 2.3.1, Study C-SURFER).

2.3.2 Results on added benefit

On the basis of the direct comparisons presented by the company and the comparisons using individual arms from different studies for research question 1 (CHC genotype 1), no added benefit of EBR/GZR in comparison with the ACT could be derived. There was no hint of an added benefit of EBR/GZR in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

No hint of added benefit of EBR/GZR in comparison with the ACT was derived from the available data for CHC genotype 1 patients. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

This assessment deviates from that of the company, which, based on the C-EDGE H2H study, separately derived an indication of considerable added benefit for patients with CHC genotype 1a and an indication of major added benefit for patients with CHC genotype 1b in comparison with SOF + peg-IFN + RBV. For the subpopulation of CHC genotype 1a with baseline viral load of > 800 000 IU/mL and/or presence of specific NS5A RAVs causing at least a 5-fold reduction in antiviral activity of elbasvir considered by the company, no hint of an added benefit or harm can be derived, according to the company. In addition, the company derived an indication of considerable added benefit in comparison with BSC for patients with CHC genotype 1 or 4 and stage 4 and 5 CKD from the C-SURFER study.

2.3.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.4 Research question 2: patients with CHC genotype 4

2.4.1 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 EBR/GZR (status: 21 November 2016)
- bibliographical literature search on EBR/GZR (last search on 2 October 2016)
- search in trial registries for studies on EBR/GZR (last search on 29 September 2016)
- bibliographical literature search on ACTs (last search on 2 November 2016)
- search in trial registries for studies on ACTs (last search on 3 November 2016)

To check the completeness of the study pool:

- search in trial registries for studies on EBR/GZR (last search on 22 December 2016)

No RCTs of direct comparisons for CHC genotype 4 patients comparing EBR/GZR with the ACT were identified from the check.

Study pool of the company

Table 8 shows the studies included by the company for research question 2 (patients with CHC genotype 4).

Table 8: Study pool of the company – CHC genotype 4 patients (research question 2)

Comparison Genotype Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Direct comparison			
Genotype 4 with CKD (stage 4 and 5)			
Studies with EBR/GZR			
NCT02092350 (C-SURFER[b])	Yes	Yes	No
Comparison using individual arms from different studies			
Genotype 4			
Studies with EBR/GZR			
NCT02251990 (C-CORAL[b])	No	Yes	No
NCT02358044 (C-EDGE H2H[b])	No	Yes	No
NCT02105701 (C-EDGE TE[b])	Yes	Yes	No
NCT02105467 (C-EDGE TN[b])	Yes	Yes	No
NCT01932762 (C-SCAPE[b]) [54,55]	Yes	Yes	No
Studies with LDV/SOF	No studies identified		
Study with OBV/PTV/R			
NCT01685203 (PEARL-I[b]) [56-58]	No	No	Yes
Genotype 4 (baseline viral load of > 800 000 IU/mL)			
Studies with EBR/GZR			
NCT02105701 (C-EDGE TE[b])	Yes	Yes	No
Studies with LDV/SOF or OBV/PTV/R	No studies identified		

a: Study for which the company was sponsor.
b: Hereinafter, the study is referred to with this abbreviated form.
CHC: chronic hepatitis C; CKD: chronic kidney disease; EBR/GZR: elbasvir/grazoprevir; IU: international units; LDV/SOF: ledipasvir/sofosbuvir; OBV/PTV/R: ombitasvir/paritaprevir/ritonavir

Direct comparison

As for the subpopulation of CHC genotype 1 patients with CKD, the company presented the C-SURFER study for the subpopulation of CHC genotype 4 patients with CKD (stage 4 and 5 CKD). Table 13 and Table 14 (Appendix A.1 of the full dossier assessment) describe the study characteristics and interventions. The study was unsuitable to derive conclusions on the added benefit of EBR/GZR versus the ACT because the comparator of the study did not concur with the ACT (see Section 2.3.1). In addition, only patients with CHC genotype 1, but

not with CHC genotype 4, were included in the study. The company assumed transferability of the results to CHC genotype 4 patients, but provided no adequate justification for this.

Comparison using individual arms from different studies

Besides the C-SURFER study of direct comparison, the company presented further comparisons using individual arms from different studies for CHC genotype 4 patients. Table 15 and Table 16 (Appendix A.2 of the full dossier assessment) describe the study characteristics and interventions. No added benefit of EBR/GZR in comparison with the ACT could be derived from the data presented by the company.

Conclusions on the added benefit based on the use of individual arms from different studies are only possible if the observed effect is so large that it can be excluded that it is caused by systematic bias alone (so-called dramatic effect) (see Section 2.3.1). There were no effects that can be considered dramatic in the comparisons presented by the company using individual arms from different studies; an added benefit could therefore not be derived from these data. The company also claimed no added benefit on the basis of this comparison.

Subpopulations considered by the company

For CHC genotype 4 patients, the company defined the following 3 subpopulations, for each of which it derived the added benefit separately:

- CHC genotype 4
- CHC genotype 4 with high baseline viral load of > 800 000 IU/mL
- CHC genotype 1 or 4 and stage 4 and 5 CKD

The company justified the differentiation into subpopulations with different CHC (sub)genotypes and their different treatment regimens according to the SPC of EBR/GZR. According to the SPC of EBR/GZR, patients with CHC genotype 4 are treated for 12 weeks. A longer treatment regimen (16 weeks) with RBV should be considered for patients with CHC genotype 4 and baseline viral load of > 800 000 IU/mL [3]. The differentiation is principally comprehensible, but not relevant for the assessment because there were no suitable studies on the comparison with the ACT for any of the subpopulations.

See Section 2.3.1, Study C-SURFER, for the subpopulation of CHC with CKD.

2.4.2 Results on added benefit

On the basis of the direct comparison presented by the company and the comparison using individual arms from different studies for research question 2 (CHC genotype 4), no added benefit of EBR/GZR in comparison with the ACT could be derived. There was no hint of an added benefit of EBR/GZR in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

No hint of added benefit of EBR/GZR in comparison with the ACT was derived from the available data for CHC genotype 4 patients. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

This assessment partly deviates from the approach of the company. For patients with CHC genotype 4 and CHC genotype 4 with baseline viral load > 800 000 IU/mL, the company also derived no hint of an added benefit. Deviating from the present benefit assessment, the company derived an indication of considerable added benefit in comparison with BSC for patients with CHC genotype 1 or 4 and stage 4 and 5 CKD from the C-SURFER study.

2.4.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.5 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of EBR/GZR in comparison with the ACT is summarized in Table 9.

Table 9: Elbasvir/grazoprevir – extent and probability of added benefit

Subindication	Appropriate comparator therapy[a]	Extent and probability of added benefit
CHC genotype 1	Ledipasvir/sofosbuvir[b] or ombitasvir/paritaprevir/ritonavir plus dasabuvir (if applicable, plus ribavirin)[c]	Added benefit not proven
CHC genotype 4	Ledipasvir/sofosbuvir[b] or ombitasvir/paritaprevir/ritonavir plus ribavirin[c]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. The G-BA's ACT also contained information on genotype 3 and 6 – however, the use of elbasvir/grazoprevir for these genotypes is not recommended in the SPC.
b: Patients without cirrhosis/with compensated cirrhosis; according to the SPC of ledipasvir/sofosbuvir, the combination of ledipasvir/sofosbuvir plus ribavirin is an alternative option in patients infected with genotype 1, 4, 5 or 6 without cirrhosis or with compensated cirrhosis. The G-BA currently does not consider this combination as ACT.
c: Patients without cirrhosis.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The G-BA decides on the added benefit.

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Please see full dossier assessment for full reference list.

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