IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Sofosbuvir – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 April 2014). 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
AE	adverse event
BSC	best supportive care
CHC	chronic hepatitis C
FAS	full analysis set
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
PEG	peginterferon alfa
RBV	ribavirin
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOF	sofosbuvir
SPC	Summary of Product Characteristics
SVR	sustained virologic response
TVR	telaprevir

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 sofosbuvir. 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 21 January 2014.

Research question

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

The G-BA specified different ACTs for different subindications. These are shown in Table 2.

Table 2: Overview of the ACT specified by the G-BA for sofosbuvir

Subindication CHC	ACT specified by the G-BA
Genotype 1 (treatment-naive without cirrhosis, and treatment-experienced with and without cirrhosis)	Dual therapy (combination of peginterferon and ribavirin) or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)[a]
Genotype 1 treatment-naive patients with cirrhosis	Dual therapy (combination of peginterferon and ribavirin)[b]
Genotype 2-6 (treatment-naive and treatment-experienced)	Dual therapy (combination of peginterferon and ribavirin)
Patients with HIV coinfection	Dual therapy (combination of peginterferon and ribavirin)[c]

a: The information provided in the SPCs of the combination partners of the ACTs are to be taken into account, particularly with regard to the approved therapeutic indications, dosages, treatment duration and prognostic factors. The necessity of using triple therapy has to be considered when favourable prognostic factors are present.
b: Data currently available prove no superiority of triple therapy for treatment-naive patients with cirrhosis. Dual therapy is therefore to be regarded as ACT in these situations.
c: Only very few data for triple therapy are currently available for patients with HIV coinfection. Dual therapy is therefore to be regarded as ACT in these situations.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus; SPC: Summary of Product Characteristics

The company largely followed the G-BA with regard to the ACT. For genotype 1 patients it chose triple therapy as ACT (as supplementary presentation for treatment-naive patients with cirrhosis). In addition, the company presented studies on sofosbuvir in patients who are not eligible for interferon. According to a separate commission by the G-BA, these studies were also assessed (see Appendix A of the full dossier assessment).

Different research questions arose from the different ACTs and the company's processing of the different subindications in the dossier. The company conducted separate assessments according to genotypes for the patient group with genotype 2 to 6 specified by the company, summarizing patients with genotypes 4, 5 and 6. Genotype 4 patients are presented separately in the benefit assessment because the company only presented data for these patients in its research question (see Sections 2.11.2.3.2.5 and 2.11.2.3.2.6 of the full dossier assessment). Table 3 shows the research questions of the present assessment.

Table 3: Research questions of the benefit assessment of sofosbuvir

Research question	Therapeutic indication CHC	Approved treatment regimen	ACT
1	Genotype 1, treatment-naive without cirrhosis, and treatment-experienced with and without cirrhosis	SOF + PEG + RBV	PEG + RBV or[a] BOC + PEG + RBV or TVR + PEG + RBV
1b	Genotype 1, treatment-naive patients with cirrhosis	SOF + PEG + RBV	PEG + RBV
2	Genotype 2	SOF + RBV	PEG + RBV
3	Genotype 3	SOF + PEG + RBV or SOF + RBV	PEG + RBV
4	Genotype 4	SOF + PEG + RBV	PEG + RBV
5	Genotype 5 or 6	SOF + PEG + RBV	PEG + RBV
6	Patients with HIV coinfection (genotype 1–6)	According to genotype	PEG + RBV

a: Under consideration of the necessity of using triple therapy when favourable prognostic factors are present.
ACT: appropriate comparator therapy; BOC: boceprevir; CHC: chronic hepatitis C; PEG: peginterferon alfa; RBV: ribavirin; SOF: sofosbuvir; TVR: telaprevir

The assessment was based on patient-relevant outcomes.

Results

No adequate analyses were available for this benefit assessment except for treatment-naive genotype 2 patients, for which the company presented one direct comparative study. This deviates from the company's approach, which summarized further investigations, in which the respective comparator therapy was investigated in at least one study arm, in so-called "historical comparisons" for the remaining research questions. These historical comparisons were unadjusted indirect comparisons. On the sofosbuvir side, it included arms from randomized controlled trials (RCTs) and one-arm studies, whereas on the comparator side, it only included arms from RCTs. The company only justified this inadequate limitation with regard to content by claiming that it wanted to reduce the number of hits. As a result, the methodological approach of all "historical comparisons" presented (unadjusted indirect

comparisons) is inadequate because the underlying database for the treatments to be compared differs systematically.

A simplified search conducted by the Institute already showed that a relevant amount of data was not considered by the company due to this approach. The unadjusted indirect comparisons are therefore incomplete with regard to content and unsuitable for the benefit assessment.

Direct comparison: treatment-naive genotype 2 patients (research question 2)

The company presented one direct comparative study (FISSION) for treatment-naive genotype 2 patients within research question 2. This study was an open-label RCT, in which treatment-naive adults with chronic hepatitis C virus (HCV) genotype 2 or 3 infection were treated. The patients in the intervention arm were treated with sofosbuvir in combination with ribavirin (SOF + RBV) for 12 weeks, and in the comparator arm with peginterferon in combination with RBV (PEG + RBV) for 24 weeks.

The use of the study medications limited the usability of the data of the FISSION study.

Study medication

The administration of SOF + RBV in the FISSION study was only approval-compliant for genotype 2 patients: These patients were treated in compliance with the Summary of Product Characteristics (SPC) of sofosbuvir in the intervention arm for 12 weeks. The proportion of these patients was below 30% of the study population. In contrast, the SPC of sofosbuvir specifies a treatment duration of 24 weeks for the SOF + RBV combination for treatment-naive genotype 3 patients. Hence the treatment conducted in the intervention arm over a period of 12 weeks was not compliant with the approval for genotype 3 patients. However, these patients constituted the majority of the study population of the FISSION study. The company itself did not consider the FISSION study for genotype 3 patients because of this.

The results on the basis of the total population from the FISSION study are not applicable to the patients of the relevant subpopulation (genotype 2). The results on the subpopulation with genotype 2 patients were used for the present benefit assessment.

Risk of bias

Due to an inadequate implementation of the intention to treat (ITT) principle, the risk of bias at study level was rated as high for all outcomes because the proportion of patients that was not considered in the assessment population was relevantly different between the treatment arms. This led to a risk of bias that was also rated as high for the following outcomes: sustained virologic response (SVR), serious adverse events (SAEs) and discontinuation due to adverse events (AEs). The different observation periods for AEs between the study arms were also included in the assessment of the risk of bias at outcome level for SAEs and discontinuation due to AEs. No relevant data were available for health-related quality of life so that no outcome-specific rating of the risk of bias was conducted. As no deaths occurred in

the relevant subpopulation, no effect estimation for the outcome "all-cause mortality" was possible and an outcome-specific rating of the risk of bias was also not conducted.

Results

Mortality (all-cause mortality)

In the FISSION study, no deaths occurred in the relevant subpopulation. Hence an added benefit of SOF + RBV in comparison with PEG + RBV with regard to the outcome "all-cause mortality" is not proven.

Morbidity

The company presented the outcome "SVR", which was regarded as a sufficiently valid surrogate for the patient-relevant outcome "occurrence of hepatocellular carcinoma (HCC)" in this benefit assessment. There was a statistically significant advantage of SOF + RBV versus the appropriate comparator therapy PEG + RBV (RR: 1.28; 95% CI: [1.11; 1.47]; $p < 0.001$) for the SVR 24 (SVR at the time point of 24 weeks after the end of treatment). The Institute conducted its own sensitivity analyses because in the assessment of the outcome the ITT principle was violated to a relevant extent, and, moreover, no information on the SVR 24 was available for 2 patients of the SOF + RBV arm for other reasons. Different imputation strategies for missing values showed the stability of the results in favour of SOF + RBV. Due to the stability of the results, a high certainty of results can be assumed for the SVR 24 despite the high risk of bias.

Overall, there is therefore an indication of an added benefit of SOF + RBV compared with the ACT PEG + RBV for the SVR 24 as sufficiently valid surrogate for the patient-relevant outcome "HCC".

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life for the relevant subpopulation of treatment-naive genotype 2 patients. Hence an added benefit of SOF + RBV in comparison with PEG + RBV with regard to the outcome "health-related quality of life" is not proven.

Adverse events

The area of AEs could only be assessed to a limited extent. The company presented the data on AEs on the basis of the proportions of patients with at least one event. These results were no adequate analysis because of the different observation periods between the 2 treatment arms. If there is no statistically significant effect to the disadvantage of the shorter observation period and no dramatic effect, only qualitative conclusions based on the proportion of patients with at least one event are drawn.

One SAE occurred in each of the 2 treatment arms. Overall, there is therefore no proof of greater or lesser harm from sofosbuvir versus the ACT.

There was a statistically significant result in favour of SOF + RBV versus PEG + RBV for the outcome "treatment discontinuation due to AEs". Because of the inadequate implementation of the ITT principle and the additional aspect that – contrary to the company's assessment – they were observations on a subjective outcome from an open-label study, the overall result is so uncertain that no advantage of sofosbuvir can be inferred from it. For the assessment of the extent and probability of the added benefit, however, the events are (qualitatively) interpreted that, due to the existing results (no events in the intervention arm compared with 8 events in the comparator arm), an effect to the disadvantage of sofosbuvir would be unlikely even in case of approximately the same observation period in both treatment arms.

No quantitative conclusion on harm from sofosbuvir versus the ACT can be derived in the overall assessment of AEs for the relevant subpopulation. Greater or lesser harm from SOF + RBV versus the ACT PEG + RBV is not proven for the outcomes "SAEs" and "discontinuation due to AEs" for treatment-experienced genotype 2 patients.

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 sofosbuvir compared with the ACT is assessed as follows:

In the overall assessment for treatment-naive genotype 2 patients, a positive effect of SOF + RBV remains for the outcome category "serious late complications" (probability: "indication"). The extent of added benefit for the outcome "HCC", which was assessed with the surrogate "SVR", is non-quantifiable.

The area of AEs could only be assessed to a limited extent. Based on the event rates, greater harm from SOF + RBV in case of the same treatment durations is assumed to be unlikely. It therefore does not seem justified to downgrade the added benefit of SOF + RBV versus the ACT for the outcome "HCC".

Overall, there is an indication of a non-quantifiable added benefit of sofosbuvir versus the ACT for treatment-naive genotype 2 patients.

There is no added benefit of sofosbuvir versus the ACT for any of the other research questions because the company presented no adequate analyses.

[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), see [1]. 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), see [2].

The result of the assessment of the added benefit of sofosbuvir in comparison with the ACT for the research questions investigated is summarized in Table 4.

Table 4: Sofosbuvir – extent and probability of added benefit

Research question	**Patient group with CHC**	**ACT**[a]	**Extent and probability of added benefit**
1	Genotype 1, treatment-naive without cirrhosis, and treatment-experienced with and without cirrhosis	PEG + RBV or[b] **BOC + PEG + RBV or** **TVR + PEG + RBV**	Added benefit not proven
1b	Genotype 1, treatment-naive patients with cirrhosis	PEG + RBV	Added benefit not proven
2	Genotype 2	PEG + RBV	Treatment-naive patients: indication of added benefit of sofosbuvir (extent "non-quantifiable")
			Treatment-experienced patients: added benefit not proven
3	Genotype 3	PEG + RBV	Added benefit not proven
4	Genotype 4	PEG + RBV	Added benefit not proven
5	Genotype 5 or 6	PEG + RBV	Added benefit not proven
6	Patients with HIV coinfection (genotype 1–6)	PEG + RBV	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The information provided in the SPCs of the combination partners of the ACTs are to be taken into account, particularly with regard to the approved therapeutic indications, dosages, treatment duration and prognostic factors. The necessity of using triple therapy has to be considered when favourable prognostic factors are present.
BOC: boceprevir; CHC: chronic hepatitis C; HIV: human immunodeficiency virus; PEG: peginterferon alfa; RBV: ribavirin; SOF: sofosbuvir; TVR: telaprevir

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Additional presentation of data presented on patients who are not (or no longer) eligible for interferon treatment

According to the supplementary commission by the G-BA, studies presented by the company for patients who are not (or no longer) eligible for interferon treatment were assessed. The company specified best supportive care (BSC) as comparator therapy for these patients. For this comparison, the company presented, on the one hand, a placebo-controlled RCT, and on the other hand, single study arms with sofosbuvir without conducting a comparison with BSC. The further investigations were therefore unsuitable for the assessment of sofosbuvir versus BSC.

The following points should be given particular consideration in the assessment of the RCTs:

- In principle, interferon treatment would have been (still) possible for a relevant proportion of included patients.
- Genotype 3 patients were not treated in compliance with the approval.
- It is unclear whether the patients in the BSC control group were treated according to the company's own definition.

The results of the RCTs are presented in Appendix A of the full dossier assessment.

2.2 Research questions of the dossier assessment

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

The G-BA specified different ACTs for the different subindications. These are shown in Table 5.

Table 5: Overview of the ACT specified by the G-BA for sofosbuvir

Therapeutic indication CHC	**ACT specified by the G-BA**
Genotype 1 (treatment-naive without cirrhosis, and treatment-experienced with and without cirrhosis)	Dual therapy (combination of peginterferon and ribavirin) or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)[a]
Genotype 1 treatment-naive patients with cirrhosis	Dual therapy (combination of peginterferon and ribavirin)[b]
Genotype 2-6 (treatment-naive and treatment-experienced)	Dual therapy (combination of peginterferon and ribavirin)
Patients with HIV coinfection	Dual therapy (combination of peginterferon and ribavirin)[c]
a: The information provided in the SPCs of the combination partners of the ACTs are to be taken into account, particularly with regard to the approved therapeutic indications, dosages, treatment duration and prognostic factors. The necessity of using triple therapy has to be considered when favourable prognostic factors are present. b: Data currently available prove no superiority of triple therapy for treatment-naive patients with cirrhosis. Dual therapy is therefore to be regarded as ACT in these situations. c: Only very few data for triple therapy are currently available for patients with HIV coinfection. Dual therapy is therefore to be regarded as ACT in these situations. ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus; SPC: Summary of Product Characteristics	

The company largely followed the G-BA with regard to the ACT. For genotype 1 patients it chose triple therapy as ACT (as supplementary presentation for treatment-naive patients with cirrhosis). In addition, the company presented studies on sofosbuvir in patients who are not eligible for interferon. According to a separate commission by the G-BA, these studies were also assessed (see Appendix A of the full dossier assessment).

Table 6 shows the research questions of the present assessment.

Table 6: Research questions of the benefit assessment of sofosbuvir

Research question	**Therapeutic indication CHC**	**Approved treatment regimen**	**ACT**
1	Genotype 1, treatment-naive without cirrhosis, and treatment-experienced with and without cirrhosis	SOF + PEG + RBV	PEG + RBV or[a] BOC + PEG + RBV or TVR + PEG + RBV
1b	Genotype 1, treatment-naive patients with cirrhosis	SOF + PEG + RBV	PEG + RBV
2	Genotype 2	SOF + RBV	PEG + RBV
3	Genotype 3	SOF + PEG + RBV or SOF + RBV	PEG + RBV
4	Genotype 4	SOF + PEG + RBV	PEG + RBV
5	Genotype 5 or 6	SOF + PEG + RBV	PEG + RBV
6	Patients with HIV coinfection (genotype 1–6)	According to genotype	PEG + RBV
a: Under consideration of the necessity of using triple therapy when favourable prognostic factors are present. ACT: appropriate comparator therapy; BOC: boceprevir; CHC: chronic hepatitis C; PEG: peginterferon alfa; RBV: ribavirin; SOF: sofosbuvir; TVR: telaprevir			

The assessment was conducted based on patient-relevant outcomes.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.11.1 and 2.11.2.1 of the full dossier assessment.

2.3 Research question 1: CHC genotype 1 (except treatment-naive patients with cirrhosis)

2.3.1 Information retrieval and study pool (research question 1)

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 sofosbuvir (studies completed up to 19 November 2013)
- bibliographical literature search on sofosbuvir (last search on 4 December 2013)
- search in trial registries for studies on sofosbuvir (last search on 4 December 2013)
- bibliographical literature search on the ACT (last search on 15 November 2013)
- search in trial registries for studies on the ACT (last search on 15 October 2013)

The Institute's own search:

- to check the completeness of the study pool: search in trial registries for studies on sofosbuvir (last search on 12 February 2014)
- simplified search on whether a relevant amount of data was not considered by the company in the unadjusted indirect comparisons (last search on 7 April 2014)

Direct comparison

There were no direct comparative studies on SOF + PEG + RBV versus the ACT for genotype 1 patients.

Indirect comparison (unadjusted)

The unadjusted indirect comparison of SOF + PEG + RBV versus the ACT presented by the company was incomplete with regard to content and therefore unsuitable for the benefit assessment (see Section 2.11.2.3.2.1 of the full dossier assessment).

Regardless of this, even in the study pool presented by the company, there was no dramatic effect in SVR, which would have been necessary for the derivation of an added benefit on the basis of the unadjusted indirect comparison.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.11.2.1 and 2.11.2.3 of the full dossier assessment. Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.3 of the dossier, and in Sections 2.11.2.3.1 and 2.11.2.3.2 of the full dossier assessment.

2.3.2 Results on added benefit (research question 1)

There were no adequate analyses on research question 1. Hence the added benefit of sofosbuvir versus the ACT is not proven for genotype 1 patients (except treatment-naive patients with cirrhosis).

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3, 4.3.2.1.3, 4.3.2.3.7.1 and 4.3.2.3.7.2 of the dossier, and in Sections 2.11.2.4.2, 2.11.2.4.3 and 2.11.2.5 of the full dossier assessment.

2.3.3 Extent and probability of added benefit (research question 1)

No proof of added benefit of sofosbuvir versus the ACT specified by the G-BA could be derived for genotype 1 patients from the available data. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

In contrast, the company derived a considerable added benefit of sofosbuvir.

2.4 Research question 1b: treatment-naive CHC genotype 1 patients with cirrhosis

2.4.1 Information retrieval and study pool (research question 1b)

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 sofosbuvir (studies completed up to 19 November 2013)
- bibliographical literature search on sofosbuvir (last search on 4 December 2013)
- search in trial registries for studies on sofosbuvir (last search on 4 December 2013)
- bibliographical literature search on the ACT (last search on 15 November 2013)
- search in trial registries for studies on the ACT (last search on 15 October 2013)

The Institute's own search:

- to check the completeness of the study pool: search in trial registries for studies on sofosbuvir (last search on 12 February 2014)
- simplified search with regard to a relevant amount of data not considered by the company in the unadjusted indirect comparisons (last search on 7 April 2014)

Direct comparison

There were no direct comparative studies on SOF + PEG + RBV versus the ACT for treatment-naive genotype 1 patients with cirrhosis.

Indirect comparison (unadjusted)

The unadjusted comparison of SOF + PEG + RBV versus the ACT was incomplete with regard to content and therefore unsuitable for the benefit assessment (see Section 2.11.2.3.2.2 of the full dossier assessment).

Regardless of this, even in the study pool presented by the company, there was no dramatic effect in SVR, which would have been necessary for the derivation of an added benefit on the basis of the unadjusted indirect comparison.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.11.2.1 and 2.11.2.3 of the full dossier assessment. Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.3 of the dossier, and in Sections 2.11.2.3.1 and 2.11.2.3.2 of the full dossier assessment.

2.4.2 Results on added benefit (research question 1b)

There were no adequate analyses on research question 1b. Hence the added benefit of sofosbuvir versus the ACT is not proven for treatment-naive genotype 1 patients with cirrhosis.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3, 4.3.2.1.3, 4.3.2.3.7.1 and 4.3.2.3.7.2 of the dossier, and in Sections 2.11.2.4.2, 2.11.2.4.3 and 2.11.2.5 of the full dossier assessment.

2.4.3 Extent and probability of added benefit (research question 1b)

No proof of added benefit of sofosbuvir versus the ACT specified by the G-BA could be derived for treatment-naive genotype 1 patients with cirrhosis from the available data. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

In contrast, the company derived a considerable added benefit of sofosbuvir.

2.5 Research question 2: CHC genotype 2

2.5.1 Information retrieval and study pool (research question 2)

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 sofosbuvir (studies completed up to 19 November 2013)
- bibliographical literature search on sofosbuvir (last search on 4 December 2013)
- search in trial registries for studies on sofosbuvir (last search on 4 December 2013)
- bibliographical literature search on the ACT (last search on 15 November 2013)
- search in trial registries for studies on the ACT (last search on 15 October 2013)

The Institute's own search:

- to check the completeness of the study pool: search in trial registries for studies on sofosbuvir (last search on 12 February 2014)
- simplified search with regard to a relevant amount of data not considered by the company in the unadjusted indirect comparisons (last search on 7 April 2014)

For treatment-naive genotype 2 patients, the check produced no deviations from the study pool presented in the dossier. The RCT FISSION was included.

The company's search for indirect comparisons on treatment-experienced genotype 2 patients was incomplete with regard to content and therefore unsuitable for the benefit assessment (see Section 2.11.2.3.2.3 of the full dossier assessment).

Regardless of this, even in the study pool presented by the company, there was no dramatic effect in SVR, which would have been necessary for the derivation of an added benefit on the basis of the unadjusted indirect comparison.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.11.2.1 and 2.11.2.3 of the full dossier assessment.

2.5.2 Studies included

The company presented one RCT (FISSION) for the assessment of the added benefit of SOF + RBV versus the ACT in treatment-naive genotype 2 patients. The study included in the benefit assessment is presented in Table 7.

Table 7: Study pool – RCT, direct comparison: SOF + RBV vs. PEG + RBV (treatment-naive CHC genotype 2 patients)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
FISSION	Yes	Yes	No

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
CHC: chronic hepatitis C; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; vs.: versus

The study pool concurred with the study pool of the company. However, only the subpopulation of genotype 2 patients (less than 30% of the study population) of the FISSION study was relevant for the assessment. Detailed reasons for this are presented in the following Section 2.5.3.

Section 2.5.6 contains a reference list for the study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.3 of the dossier, and in Sections 2.11.2.3 and 2.11.2.3.2 of the full dossier assessment.

2.5.3 Study characteristics

Table 8 and Table 9 describe the study used for the benefit assessment; Table 10 shows the characteristics of the patients of the FISSION study.

Table 8: Characteristics of the studies included – RCT, direct comparison: SOF + RBV vs. PEG + RBV (treatment-naive CHC genotype 2 patients)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
FISSION	RCT, open-label, parallel, multicentre, phase 3	Previously untreated adults (≥ 18 years) with chronic GT 2 or 3 HCV infection without or with cirrhosis (up to 20% of the patients)	group 1: SOF + RBV (N = 263[b]) group 2: PEG + RBV (N = 264[b]) relevant subpopulation thereof[c]: group 1: SOF + RBV (n = 73) group 2: PEG + RBV (n = 77)	Treatment duration: group 1: 12 weeks group 2: 24 weeks follow-up observation[d]: 4–24 weeks	Australia, Canada, Italy, Netherlands, New Zealand, Sweden, United States 12/2011–04/2013	Primary: proportion of patients with sustained virologic response 12 weeks after stopping all study drugs (SVR 12), defined as HCV RNA < LLOQ Secondary: SVR 24, health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for this benefit assessment.
b: Of the randomized patients, 7 patients in the sofosbuvir arm and 21 patients in the control arm were not included in the analyses.
c: Treatment-naive genotype 2 patients.
d: The follow-up observation for AEs was conducted up to 30 days, for the outcome "SVR" up to 24 weeks after administration of the last study medication.

AE: adverse event; CHC: chronic hepatitis C; HCV: hepatitis C virus; GT: genotype; HCV-RNA: hepatitis C virus ribonucleic acid; LLOQ: lower limit of quantitation; N: number of randomized patients; n: relevant subpopulation; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; SVR: sustained virologic response; vs.: versus

Table 9: Characteristics of the interventions – RCT, direct comparison: SOF + RBV vs. PEG + RBV (treatment-naive CHC genotype 2 patients)

Study	Intervention	Comparison	Concomitant medication
FISSION	12 weeks oral SOF 400 mg/day (2 × 200 mg tablets) once daily plus oral RBV 1000 to 1200 mg/day (5 or 6 x 200 mg tablets) based on weight (< 75 kg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) daily, divided into 2 doses	24 weeks PEG 180 µg (subcutaneously) once weekly plus oral RBV 800 mg (4 x 200 mg tablets) daily, divided into 2 doses	Treatment with the following drugs was prohibited for 28 days before the first study visit up to the end of the study: ▪ systemic immunosuppressants (including corticosteroids) ▪ strong P-glycoprotein inhibitors (including cyclosporin, quinidine, dronedarone, itraconazole, verapamil or ritonavir) ▪ antiarrhythmics and cardiac drugs (including amiodarone, felodipine, ranolazine, verapamil) ▪ anticonvulsants (including phenytoin, carbamazepine, oxcarbazepine) ▪ herbal agents (including milk thistle, St. John's Wort) ▪ modafinil Patients who had antineoplastic treatment or radiotherapy within 6 months before the first dose of the study medication or who might need it during the study were excluded.
CHC: chronic hepatitis C; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; vs.: versus			

Table 10: Characteristics of the study populations – RCT, direct comparison: SOF + RBV vs. PEG + RBV (treatment-naive CHC genotype 2 patients)

Study group	N	Age [years] median (range)	Sex [F/M] %	Cirrhosis [with/ without] %	Genotype 1/2/3 %	Viral load [< 800 000/ ≥ 800 000 IU/mL] %	Ethnicity [white/ black/ other] %
FISSION							
total study population							
SOF + RBV	256	50 (20–72)	33.2[a]/66.8[a]	19.5[a]/80.1[a, b]	1.2/27.3/71.5	37.9[a]/62.1[a]	87.1/4.7/ 8.2[a]
PEG + RBV	243	50 (19-77)	35.8[a]/64.2[a]	20.6[a]/77.8[a, c]	0/27.6/72.4	40.3[a]/59.7[a]	87.2/2.1/ 10.7[a]
Relevant subpopulation							
SOF + RBV	70	ND	ND	ND	0/100/0	ND	ND
PEG + RBV	67	ND	ND	ND	0/100/0	ND	ND

a: Institute's calculation.
b: There was no information on the cirrhosis status at baseline for 1 patient.
c: There was no information on the cirrhosis status at baseline for 4 patients.
CHC: chronic hepatitis C; F: female; IU: international units; M: male; N: number of randomized patients who received at least one dose of the allocated study medication; ND: no data; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; SOF: sofosbuvir; vs.: versus

FISSION was an open-label RCT, in which treatment-naive adults with hepatitis C virus (HCV) genotype 2 or 3 infection were treated. The patients in the intervention arm were treated with SOF + RBV for 12 weeks, and in the comparator arm with PEG + RBV for 24 weeks. The proportion of patients with cirrhosis was up to 20%. The treatment duration of the respective study arm was followed by a follow-up observation period of up to 24 weeks to determine the outcome "SVR at a time point of 24 weeks after the end of treatment (SVR 24)".

The characteristics for the FISSION study were only available for the total population. The study was balanced between the study arms. As patients in the study were stratified by genotype 2 and 3, it can be assumed that the group structure in the relevant subpopulation was comparable.

The use of study medications and the open-label study design limited the usability of the data of the FISSION study.

Study medication

The administration of SOF + RBV in the FISSION study was only approval-compliant for genotype 2 patients: These patients were treated in compliance with the SPC of sofosbuvir [3] in the intervention arm for 12 weeks. The proportion of these patients was below 30% of the study population. In contrast, the SPC of sofosbuvir specifies a treatment duration of 24

weeks for the SOF + RBV combination for treatment-naive genotype 3 patients. Hence the treatment conducted in the intervention arm over a period of 12 weeks was not compliant with the approval for genotype 3 patients. However, these patients constituted the majority of the study population of the FISSION study.

The company presented results of the analyses on the genotype (2 or 3) subgroup for the outcome "SVR 24" in Module 4, Section 4.3.1.3.4.1. These provided proof of an interaction from which it can be inferred that genotype 3 patients respond less well to treatment with SOF + RBV than genotype 2 patients (55.2% versus 97.1%).

The results on the basis of the total population from the FISSION study are not applicable to the patients of the relevant subpopulation (genotype 2). The results on the subpopulation with genotype 2 patients were used for the present benefit assessment.

Table 11 shows the risk of bias at study level. All analyses for the outcomes included in the present benefit assessment were based on the full analysis set (FAS), i.e. on the randomized genotype 2 patients who have received at least one dose of their allocated study medication. A total of 9% of the randomized genotype 2 patients were not considered. The difference of the proportions of patients who were not considered was greater than 5% between the study arms. Hence the ITT principle was not implemented to a relevant extent. For this reason, the risk of bias at study level was rated as high for the FISSION study (see Section 2.11.2.4.2 of the full dossier assessment).

This does not concur with the company's assessment, which rated the risk of bias at study level as low. It did not consider the analysis of the outcomes based on the FAS as potentially biasing factor.

Table 11: Risk of bias at study level – SOF + RBV vs. PEG + RBV (treatment-naive CHC genotype 2 patients)

Study	**Adequate random sequence generation**	**Allocation concealment**	**Blinding**		**Reporting independent of the results**	**No additional aspects**	**Risk of bias at study level**
			Patient	**Treating staff**			
FISSION	Yes	Yes	No	No	Yes	No[a]	High[b]

a: All analyses are based on the FAS population, i.e. on the patients who have received at least one dose of their allocated study medication. A total of 13 of the 150 randomized GT2 patients (9%) were not considered. The difference of the proportions of patients who were not considered was greater than 5% between the study arms (SOF+RBV: 3 of 73 [4%] vs. PEG+RBV: 10 of 77 [13%]). Hence the ITT principle was not implemented adequately in any of the outcomes used in the benefit assessment.
b: Due to the inadequate implementation of the ITT principle.

CHC: chronic hepatitis C; FAS: full analysis set; GT2: genotype 2; ITT: intention to treat; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; vs.: versus

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and Appendix 4-G of the dossier, in Sections 2.11.2.4.1 and 2.11.2.4.2 of the full dossier assessment and in Section 2.5.3.

2.5.4 Results on added benefit (research question 2)

2.5.4.1 Direct comparison: treatment-naive genotype 2 patients

The following patient-relevant outcomes and surrogates were considered in this assessment (for reasons, see Section 2.11.2.4.3 of the full dossier assessment):

- Mortality (all-cause mortality)
- Morbidity
  - SVR 24 as sufficiently valid surrogate for the patient-relevant outcome "HCC"
- Adverse events
  - SAEs
  - treatment discontinuation due to AEs

There were no analyses on health-related quality of life, measured with the Short Form (36) Health Survey (SF-36), for the relevant subpopulation.

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.11.2.4.3 of the full dossier assessment).

Data availability and risk of bias

Table 12 shows for which outcomes included data were available in the FISSION study. Table 13 shows the risk of bias for these outcomes.

Table 12: Matrix of outcomes – RCT, direct comparison: SOF + RBV vs. PEG + RBV (treatment-naive CHC genotype 2 patients)

Study	Outcomes				
	All-cause mortality	SVR 24	Health-related quality of life (generic instrument)	Serious adverse events	Discontinuation due to adverse events
FISSION	Yes	Yes	No[a]	Yes	Yes

a: No evaluable data available because there were no analyses for the relevant subpopulation. See Section 2.11.2.4.3 of the full dossier assessment for reasons.

CHC: chronic hepatitis C; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; SVR: sustained virologic response; vs.: versus

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: SOF + RBV vs. PEG + RBV (treatment-naive CHC genotype 2 patients)

Study	Study level	Outcomes				
		Mortality/overall survival	SVR	Health-related quality of life	Serious adverse events	Discontinuation due to adverse events
FISSION	H	–[a]	H[b]	–[c]	H[d]	H[e]

a: No effect estimation possible because no deaths occurred.
b: Due to the high risk of bias at study level (inadequate implementation of the ITT principle).
c: No data for the relevant subpopulation.
d: Due to the high risk of bias at study level (inadequate implementation of the ITT principle) and the great difference in observation period between the treatment arms.
e: Due to the high risk of bias at study level (inadequate implementation of the ITT principle), subjective recording of outcomes and lack of blinding, and the great difference in observation period between the treatment arms.

CHC: chronic hepatitis C; H: high; ITT: intention to treat; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; SVR: sustained virologic response; vs.: versus

Data for the relevant subpopulation were available for the outcome "all-cause mortality". An effect estimation was not possible because no deaths occurred; the risk of bias was not estimated.

The specifications of the respective SPCs resulted in fixed treatment durations for the combination of SOF + RBV and PEG + RBV [3-7]. Due to a 30-day follow-up observation period of AEs, there were considerable differences in observation periods of 12 weeks between the treatment arms, because the observation periods referred to a time point after the end of treatment both for SVR and for AEs. This difference in treatment durations and observation periods constituted a potentially biasing factor for the outcome-specific assessment of the risk of bias for all further outcomes. For each outcome, the consequences are mentioned below.

There were no separate analyses on the relevant subpopulation for the outcome "health-related quality of life". Hence the data on this outcome could not be interpreted in the framework of the present research question. Therefore there was no outcome-specific assessment of the risk of bias. The different observation periods were relevant for the assessment of health-related quality of life. An adequate assessment of health-related quality of life could only be

conducted on the basis of time-adjusted results (for example 12 weeks after the end of treatment for SOF + RBV versus end of treatment for PEG + RBV). If time-adjusted results were available for both treatment arms, they would be an adequate analysis for the outcome "health-related quality of life" with different treatment durations in the 2 study arms. However, it would have to be investigated also in case of time-adjusted results whether sufficient data were available for the analyses on the basis of the relevant subpopulation (the response rate of the questionnaires in the total population was approximately 30% in each of the groups).

The risk of bias was rated as high for all outcomes for which data for the relevant subpopulation were available in the dossier (SVR 24, SAEs and discontinuation due to AEs). The high risk of bias at study level was decisive for this at first because the ITT principle was not adequately implemented to a relevant extent in the analysis of all outcomes included in the benefit assessment. A total of 9% of the randomized genotype 2 patients were not included in the assessment of the outcomes. The difference of the proportions of patients who were not considered was greater than 5% between the treatment arms (see Section 2.11.2.4.2 of the full dossier assessment). Sensitivity analyses with different imputation strategies for missing values could address this risk of bias. The company did not present any corresponding analyses.

Because of the permanence of the SVR, the outcome "SVR 24" can be also compared between study arms with different treatment durations without causing important bias. For reasons, see Section 2.11.2.2 of the full dossier assessment.

Further biasing aspects are included in the assessment of the risk of bias for the interpretation of the outcomes "SAEs" and "discontinuation due to AEs". The different observation periods between the study arms are relevant here: In the FISSION study, AEs were recorded up to 30 days after administration of the last study medication. Because of this, the observation period of AEs was approximately 16 weeks for the intervention arm, and approximately 28 weeks for the comparator arm. Analyses of results on AEs based on proportions of patients with at least one event, as the ones conducted by the company, are usually inadequate and potentially highly biased in case of great differences in observation duration (see Section 2.11.2.4.2 of the full dossier assessment).

Moreover, the outcome "discontinuation due to AEs" is a subjectively reported outcome. There was no blinding of the patients or of the treating staff in the FISSION study because of the open-label design. This problem is additionally considered in the assessment of the outcome-specific risk of bias. This is because the knowledge of the treatment administered may influence the decision for or against discontinuation of treatment after the occurrence of an AE.

Overall, the assessment of the risk of bias does not concur with that of the company, which assumed a low risk of bias for all outcomes it used.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier, in Sections 2.11.2.4.2 and 2.11.2.4.3 of the full dossier assessment, and in Section 2.5.4.1.

Reporting of results

Table 14 summarizes the results on the comparison of SOF + RBV with PEG + RBV in treatment-naive genotype 2 patients. Where necessary, the data from the company's dossier were supplemented by the Institute's own calculations.

Table 14: Results (dichotomous outcomes) – RCT, direct comparison: SOF + RBV vs. PEG + RBV (treatment-naive CHC genotype 2 patients)

Study outcome category outcome	SOF + RBV		PEG + RBV		SOF + RBV vs. PEG + RBV
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value[a]
FISSION					
Mortality					
All-cause mortality	70	0 (0)	67	0 (0)	
Morbidity					
SVR, 24 weeks after the end of treatment (SVR 24)[b]					
Responders[c]	70	68[d] (97.1)	67	51 (76.1)	1.28 [1.11; 1.47]; < 0.001
Health-related quality of life	No evaluable data available[e]				
Adverse events[f]					
AEs	70	60 (85.7[g])	67	61 (91.0[g])	
SAEs	70	1 (1.4[g])	67	1 (1.5[g])	
Discontinuation due to AEs[h]	70	0 (0[g])	67	8[f] (11.9[g])	

a: Institute's calculation, unconditional exact test (CSZ method according to [8]).
b: As sufficiently valid surrogate for the patient-relevant outcome "HCC".
c: Different strategies for the imputation of missing values were used for patients who did not receive any of the allocated study medication and who were not considered in the company's analysis (SOF + RBV: 3; PEG +RBV: 10), as well as for patients for whom the missing SVR 24 value was imputed with the virologic response observed after 12 weeks (SOF + RBV: 2; PEG + RBV: 0). The imputation to the disadvantage of SOF + RBV also showed the stability of the results in favour of SOF + RBV.
d: In 2 patients, the missing SVR 24 value was imputed with the virologic response observed after 12 weeks.
e: No results for the relevant subpopulation.
f: Due to the great difference in observation period between the 2 treatment arms, conclusions are only derived from the results in case of the exceptions described in Section 2.11.2.4.2 of the full dossier assessment.
g: Institute's calculation.
h: Institute's calculation of estimate and corresponding 95% CI with continuity correction of 0.5 in both treatment arms due to missing events in one of the treatment arms: 0.06 [0.00; 0.96]. Institute's calculation, unconditional exact test (CSZ method according to [8]): p = 0.004.

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; HCC: hepatocellular carcinoma; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOF: sofosbuvir; SVR: sustained virologic response; vs.: versus

Only the FISSION study was available for the assessment of sofosbuvir in treatment-naive genotype 2 patients. The risk of bias was rated as high. Hence, if no outcome-specific aspects result in an increase of the certainty of results, the maximum that can be inferred from the data are "hints", e.g. of an added benefit. This assessment deviates from that of the company, which principally rated the informative value of the FISSION study as "indication".

Mortality (all-cause mortality)

In the FISSION study, no deaths occurred in the relevant subpopulation. Hence an added benefit of SOF + RBV in comparison with PEG + RBV with regard to the outcome "all-cause mortality" is not proven.

Morbidity

SVR 24 as sufficiently valid surrogate for the patient-relevant outcome "HCC"

The proportion of treatment-naive genotype 2 patients with an SVR 24 after a 12-week treatment with SOF + RBV was significantly higher than after a 24-week treatment with PEG + RBV. The Institute conducted its own sensitivity analyses because in the assessment of the outcome the ITT principle was violated to a relevant extent (see Section 2.11.2.4.2 of the full dossier assessment), and, moreover, no information on the SVR 24 was available for 2 patients of the SOF + RBV arm for other reasons. Two strategies for the imputation of missing values were used for patients who did not receive any of the allocated study medication and who were not considered in the company's analysis (SOF + RBV: 3; PEG +RBV: 10), as well as for patients for whom the missing SVR 24 value was imputed with the virologic response observed after 12 weeks (SOF + RBV: 2; PEG + RBV: 0). Both the imputation with "virologic response" and the imputation according to the observed risk in the PEG + RBV arm showed the stability of the results in favour of SOF + RBV, because of which a high certainty of results is assumed despite the high risk of bias for the outcome "SVR 24".

Overall, there is therefore an indication of an added benefit of SOF + RBV compared with the ACT PEG + RBV for the outcome "SVR 24".

In contrast, the company used the results of the total population of the FISSION study and derived an indication of an added benefit of sofosbuvir for the outcome "SVR 24" from it.

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life for the relevant subpopulation of treatment-naive genotype 2 patients. Hence an added benefit of SOF + RBV in comparison with PEG + RBV with regard to the outcome "health-related quality of life" is not proven.

This assessment deviates from that of the company, which derived a hint of a minor added benefit of SOF + RBV for the outcome "health-related quality of life measured with the SF-36" on the basis of the data of the study population.

Adverse events

The area of AEs of sofosbuvir could only be assessed to a limited extent. The company presented the data on AEs on the basis of the proportions of patients with at least one event. Due to the different observation durations between the 2 treatment arms (SOF + RBV: approximately 16 weeks; PEG + RBV: approximately 28 weeks), these results constituted no adequate analysis (see Section 2.11.2.4.2 of the full dossier assessment).

These analyses were only used for the derivation of a conclusion on harm in the present benefit assessment if there was either a statistically significant effect to the disadvantage of the shorter observation period or if the observed effect was rated as dramatic. Otherwise only qualitative conclusions based on the proportions of patients with at least one event were drawn.

SAEs

One SAE occurred in each of the 2 treatment arms. Overall, there is therefore no proof of greater or lesser harm from sofosbuvir versus the ACT.

Discontinuation due to AEs

The 2 operationalizations "discontinuation of one of the 2 study medications" and "discontinuation of both study medications" were available for the outcome "discontinuation due to AEs" in the FISSION study (see Section 2.11.2.4.3 of the full dossier assessment). Data on the operationalization "discontinuation of both study medications" were used for the benefit assessment.

The confidence interval associated with the effect is only slightly below the null effect. Because of the inadequate implementation of the ITT principle (3 patients from the SOF + RBV arm and 10 patients from the PEG + RBV arm were not included in the analysis) and the aspect that – contrary to the company's assessment – they were observations on a subjective outcome from an open-label study, the overall result is so uncertain that no advantage of sofosbuvir can be inferred from it. For the assessment of the extent and probability of the added benefit, however, the results are (qualitatively) interpreted that, due to the existing results (no events in the intervention arm compared with 8 events in the comparator arm), an effect to the disadvantage of sofosbuvir would be unlikely even in case of approximately the same observation periods in both treatment arm.

Adverse events: summary of the results

No quantitative conclusion on harm from sofosbuvir versus the ACT can be derived in the overall assessment of AEs for the relevant subpopulation. Greater or lesser harm from SOF + RBV versus the ACT PEG + RBV is not proven for the outcomes "SAEs" and "discontinuation due to AEs" for treatment-experienced genotype 2 patients.

In contrast, the company used the results of the total population on the basis of the proportions of patients with at least one event to derive conclusions on harm from

SOF + RBV. It derived no added benefit for the outcome "SAEs", and it derived a considerable added benefit for the outcome "discontinuation due to AEs".

Subgroup analyses

The company presented no subgroup analyses for the relevant subpopulation of treatment-naive genotype 2 patients.

2.5.4.2 Indirect comparison (unadjusted): treatment-experienced genotype 2 patients

There were no adequate analyses for treatment-experienced genotype 2 patients. Hence the added benefit of SOF + RBV versus the ACT is not proven for treatment-experienced genotype 2 patients.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3, 4.3.2.1.3, 4.3.2.3.7.1 and 4.3.2.3.7.2 of the dossier, and in Sections 2.11.2.4.2, 2.11.2.4.3 and 2.11.2.5 of the full dossier assessment.

2.5.5 Extent and probability of added benefit (research question 2)

2.5.5.1 Direct comparison: treatment-naive genotype 2 patients

The derivation of extent and probability of the added benefit of SOF + RBV for treatment-naive genotype 2 patients at outcome level is presented below, taking into account the various outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of the Institute [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.5.1.1 Assessment of added benefit at outcome level

The data presented in Section 2.5.4.1 results in an added benefit of sofosbuvir for the outcome "SVR 24". There is no added benefit of sofosbuvir with regard to all-cause mortality and health-related quality of life, SAEs and treatment discontinuations due to AEs. The extent of the respective added benefit at outcome level was estimated from these results (see Table 15).

Table 15: Extent of added benefit at outcome level: SOF + RBV vs. PEG + RBV (treatment-naive CHC genotype 2 patients)

Outcome category **outcome**	**SOF + RBV vs. PEG + RBV** **Effect estimate [95% CI]** **proportion of events** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
HCC, assessed with the surrogate SVR[c]	RR: 1.28 [1.11; 1.47] 97.1% vs. 76.1% p < 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"
Health-related quality of life		
SF-36	No evaluable data available	Added benefit not proven
Adverse events		
SAEs	1.4% vs. 1.5%	Lesser/greater harm not proven[d]
Discontinuation due to AEs	0 % vs. 11.9 %	Lesser/greater harm not proven[d]

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: SVR is used as surrogate for a patient-relevant outcome (HCC). It is regarded as sufficiently valid to be considered in the benefit assessment (see Section 2.11.2.2 of the full dossier assessment).
d: Qualitative interpretation of the results, see Section 2.5.4.1.

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CI_u: upper limit of the CI; HCC: hepatocellular carcinoma; PEG: peginterferon alfa; RBV: ribavirin; RR: relative risk; SAE: serious adverse event; SOF: sofosbuvir; SVR: sustained virologic response; vs.: versus

2.5.5.1.2 Overall conclusion on added benefit

Table 16 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of SOF + RBV compared with PEG + RBV (treatment-naive CHC genotype 2 patients)

Positive effects	**Negative effects**
Indication of added benefit – extent: "non-quantifiable" (serious late complications: HCC, assessed with the surrogate SVR)	–

CHC: chronic hepatitis C; HCC: hepatocellular carcinoma; PEG: peginterferon alfa; RBV: ribavirin; SOF: sofosbuvir; SVR: sustained virologic response; vs.: versus

Based on the available results, one positive effect (probability: "indication") of SOF + RBV remains for the outcome category "serious late complications" in the overall assessment. The extent of added benefit for the outcome "HCC", which was assessed with the surrogate "SVR", is non-quantifiable.

The area of AEs could only be assessed to a limited extent. However, based on the event rates, greater harm from SOF + RBV in case of the same treatment durations appears to be unlikely. It therefore does not seem justified to downgrade the added benefit of SOF + RBV versus the ACT for the outcome "HCC".

Overall, there is an indication of a non-quantifiable added benefit of sofosbuvir versus the ACT.

2.5.5.2 Indirect comparison (unadjusted): treatment-experienced genotype 2 patients

No proof of added benefit of SOF + RBV versus the ACT specified by the G-BA could be derived for treatment-experienced genotype 2 patients from the available data.

2.5.5.3 Summary

Table 17 shows the summary on extent and probability of the added benefit of SOF + RBV versus the ACT for genotype 2 patients. There is an indication of a non-quantifiable added benefit of sofosbuvir for treatment-naive patients. For treatment-experienced patients an added benefit is not proven.

Table 17: Patient groups, ACT and extent and probability of the added benefit of SOF + RBV for CHC genotype 2 patients

Patient group	ACT	Extent and probability of added benefit
Treatment-naive CHC genotype 2 patients	PEG + RBV	Indication of a non-quantifiable added benefit
Treatment-experienced CHC genotype 2 patients	PEG + RBV	Added benefit not proven
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; PEG: peginterferon alfa; RBV: ribavirin; SOF: sofosbuvir		

The assessment deviates from that of the company, which derived a considerable added benefit for the total population of genotype 2 patients.

2.5.6 List of included studies

FISSION

Gilead. A phase 3, multicenter, randomized, active-controlled study to investigate the safety and efficacy of PSI-7977 and ribavirin for 12 weeks compared to pegylated interferon and ribavirin for 24 weeks in treatment-naïve patients with chronic genotype 2 or 3 HCV infection: study no P7977-1231 (FISSION); interim clinical study report [unpublished]. 2013.

2.6 Research question 3: CHC genotype 3

2.6.1 Information retrieval and study pool (research question 3)

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 sofosbuvir (studies completed up to 19 November 2013)
- bibliographical literature search on sofosbuvir (last search on 4 December 2013)
- search in trial registries for studies on sofosbuvir (last search on 4 December 2013)
- bibliographical literature search on the ACT (last search on 15 November 2013)
- search in trial registries for studies on the ACT (last search on 15 October 2013)

The Institute's own search:

- to check the completeness of the study pool: search in trial registries for studies on sofosbuvir (last search on 12 February 2014)
- simplified search with regard to a relevant amount of data not considered by the company in the unadjusted indirect comparisons (last search on 7 April 2014)

Direct comparison

There were no direct comparative studies on SOF + RBV or SOF+ PEG + RBV versus the ACT for genotype 3 patients.

Indirect comparison (unadjusted)

The unadjusted indirect comparisons of SOF + RBV and SOF + PEG + RBV versus the ACT presented by the company were incomplete with regard to content and therefore unsuitable for the benefit assessment (see Section 2.11.2.3.2.4 of the full dossier assessment).

Regardless of this, even in the study pool presented by the company, there was no dramatic effect in SVR, which would have been necessary for the derivation of an added benefit on the basis of the unadjusted indirect comparisons.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.11.2.1 and 2.11.2.3 of the full dossier assessment. Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.3 of the dossier, and in Sections 2.11.2.3.1 and 2.11.2.3.2 of the full dossier assessment.

2.6.2 Results on added benefit (research question 3)

There were no adequate analyses on research question 3. Hence the added benefit of sofosbuvir versus the ACT is not proven for genotype 3 patients.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3, 4.3.2.1.3, 4.3.2.3.7.1 and 4.3.2.3.7.2 of the dossier, and in Sections 2.11.2.4.2, 2.11.2.4.3 and 2.11.2.5 of the full dossier assessment.

2.6.3 Extent and probability of added benefit (research question 3)

No proof of added benefit of sofosbuvir versus the ACT specified by the G-BA could be derived for genotype 3 patients from the available data. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

In contrast, the company derived a considerable added benefit of sofosbuvir.

2.7 Research question 4: CHC genotype 4

2.7.1 Information retrieval and study pool (research question 4)

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 sofosbuvir (studies completed up to 19 November 2013)
- bibliographical literature search on sofosbuvir (last search on 4 December 2013)
- search in trial registries for studies on sofosbuvir (last search on 4 December 2013)
- bibliographical literature search on the ACT (last search on 15 November 2013)
- search in trial registries for studies on the ACT (last search on 15 October 2013)

The Institute's own search:

- to check the completeness of the study pool: search in trial registries for studies on sofosbuvir (last search on 12 February 2014)
- simplified search with regard to a relevant amount of data not considered by the company in the unadjusted indirect comparisons (last search on 7 April 2014)

Direct comparison

There were no direct comparative studies on SOF + PEG + RBV versus the ACT for genotype 4 patients.

Indirect comparison (unadjusted)

The unadjusted indirect comparison of SOF + PEG + RBV versus the ACT presented by the company was incomplete with regard to content and therefore unsuitable for the benefit assessment (see Section 2.11.2.3.2.5 of the full dossier assessment).

There was a dramatic effect in SVR in the study pool presented by the company. Due to the underlying unsuitable unadjusted indirect comparison, no added benefit of sofosbuvir can be derived from it.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.11.2.1 and 2.11.2.3 of the full dossier assessment. Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.3 of the dossier, and in Sections 2.11.2.3.1 and 2.11.2.3.2 of the full dossier assessment.

2.7.2 Results on added benefit (research question 4)

There were no adequate analyses on research question 4. Hence the added benefit of sofosbuvir versus the ACT is not proven for genotype 4 patients.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3, 4.3.2.1.3, 4.3.2.3.7.1 and 4.3.2.3.7.2 of the dossier, and in Sections 2.11.2.4.2, 2.11.2.4.3 and 2.11.2.5 of the full dossier assessment.

2.7.3 Extent and probability of added benefit (research question 4)

No proof of added benefit of sofosbuvir versus the ACT specified by the G-BA could be derived for genotype 4 patients from the available data. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

In contrast, the company derived a considerable added benefit of sofosbuvir.

2.8 Research question 5: CHC genotype 5 or 6

2.8.1 Information retrieval and study pool (research question 5)

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 sofosbuvir (studies completed up to 19 November 2013)
- bibliographical literature search on sofosbuvir (last search on 4 December 2013)
- search in trial registries for studies on sofosbuvir (last search on 4 December 2013)
- bibliographical literature search on the ACT (last search on 15 November 2013)
- search in trial registries for studies on the ACT (last search on 15 October 2013)

The Institute's own search:

- to check the completeness of the study pool: search in trial registries for studies on sofosbuvir (last search on 12 February 2014)
- simplified search with regard to a relevant amount of data not considered by the company in the unadjusted indirect comparisons (last search on 7 April 2014)

In its research question, the company considered genotype 4 patients together with genotype 5 or 6 patients. However, it excluded studies from its research question that included exclusively genotype 5 or 6 patients. Hence the present research question was not investigated systematically by the company. (Section 2.11.2.3.2.6 of the full dossier assessment).

Moreover, the unadjusted indirect comparison presented by the company was incomplete with regard to content and therefore unsuitable for the benefit assessment.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.11.2.1 and 2.11.2.3 of the full dossier assessment. Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.3 of the dossier, and in Sections 2.11.2.3.1 and 2.11.2.3.2 of the full dossier assessment.

2.8.2 Results on added benefit (research question 5)

No relevant data were available for research question 5, neither for a direct comparison nor for an indirect comparison. Hence the added benefit of sofosbuvir versus the ACT is not proven for genotype 5 or 6 patients.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3, 4.3.2.1.3, 4.3.2.3.7.1 and 4.3.2.3.7.2 of the dossier, and in Sections 2.11.2.4.2, 2.11.2.4.3 and 2.11.2.5 of the full dossier assessment.

2.8.3 Extent and probability of added benefit (research question 5)

Since no relevant data were presented for the benefit assessment, there is no proof of an added benefit of sofosbuvir in comparison with the ACT specified by the G-BA. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

In contrast, the company derived a considerable added benefit of sofosbuvir.

2.9 Research question 6: CHC patients with HIV coinfection

2.9.1 Information retrieval and study pool (research question 6)

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 sofosbuvir (studies completed up to 19 November 2013)
- bibliographical literature search on sofosbuvir (last search on 4 December 2013)
- search in trial registries for studies on sofosbuvir (last search on 4 December 2013)
- bibliographical literature search on the ACT (last search on 15 November 2013)
- search in trial registries for studies on the ACT (last search on 15 October 2013)

The Institute's own search:

- to check the completeness of the study pool: search in trial registries for studies on sofosbuvir (last search on 12 February 2014)
- simplified search with regard to a relevant amount of data not considered by the company in the unadjusted indirect comparisons (last search on 7 April 2014)

Direct comparison

There were no direct comparative studies on SOF + RBV versus the ACT for CHC patients with HIV coinfection.

Indirect comparison (unadjusted)

The unadjusted indirect comparisons of SOF + RBV versus the ACT presented by the company for **treatment-naive genotype 2 patients** and HIV coinfection as well as **treatment-experienced genotype 2 or 3 patients** and HIV coinfection were incomplete with regard to content and therefore unsuitable for the benefit assessment (see Section 2.11.2.3.2.7 of the full dossier assessment).

Regardless of this, in the study pool for treatment-naive genotype 2 patients presented by the company, there was no dramatic effect in SVR, which would have been necessary for the derivation of an added benefit on the basis of the unadjusted indirect comparison. The company presented no analyses for SVR for treatment-experienced genotype 2 or 3 patients.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.11.2.1 and 2.11.2.3 of the full dossier assessment. Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.3 of the dossier, and in Sections 2.11.2.3.1 and 2.11.2.3.2 of the full dossier assessment.

2.9.2 Results on added benefit (research question 6)

There were no adequate analyses on research question 6. Hence the added benefit of sofosbuvir versus the ACT is not proven for CHC patients with HIV coinfection.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3, 4.3.2.1.3, 4.3.2.3.7.1 and 4.3.2.3.7.2 of the dossier, and in Sections 2.11.2.4.2, 2.11.2.4.3 and 2.11.2.5 of the full dossier assessment.

2.9.3 Extent and probability of added benefit (research question 6)

No proof of added benefit of sofosbuvir versus the ACT specified by the G-BA could be derived for CHC patients with HIV coinfection from the available data. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

In contrast, the company derived a considerable added benefit of sofosbuvir.

2.10 Extent and probability of added benefit – summary

An overview of the extent and probability of added benefit for the different subindications of sofosbuvir in comparison with the relevant ACTs is given below.

Table 18: Sofosbuvir – extent and probability of added benefit

Research question	Patient group with CHC	ACT[a]	Extent and probability of added benefit
1	Genotype 1, treatment-naive without cirrhosis, and treatment-experienced with and without cirrhosis	PEG + RBV or[b] **BOC + PEG + RBV or** **TVR + PEG + RBV**	Added benefit not proven
1b	Genotype 1, treatment-naive patients with cirrhosis	PEG + RBV	Added benefit not proven
2	Genotype 2	PEG + RBV	Treatment-naive patients: indication of added benefit of sofosbuvir (extent "non-quantifiable")
			Treatment-experienced patients: added benefit not proven
3	Genotype 3	PEG + RBV	Added benefit not proven
4	Genotype 4	PEG + RBV	Added benefit not proven
5	Genotype 5 or 6	PEG + RBV	Added benefit not proven
6	Patients with HIV coinfection (genotype 1–6)	PEG + RBV	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The information provided in the SPCs of the combination partners of the ACTs are to be taken into account, particularly with regard to the approved therapeutic indications, dosages, treatment duration and prognostic factors. The necessity of using triple therapy has to be considered when favourable prognostic factors are present.
BOC: boceprevir; CHC: chronic hepatitis C; HIV: human immunodeficiency virus; PEG: peginterferon alfa; RBV: ribavirin; SOF: sofosbuvir; TVR: telaprevir

The G-BA decides on the added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.11.2.8 of the full dossier assessment.

References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a14_05_sofosbuvir_nutzenbewertung_gemass_35a_sgb_v_dossierbewertung.6009.html.