IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-48

Sofosbuvir/velpatasvir (chronic hepatitis C) –

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

Extract

[1] Translation of Sections 2.1 to 2.13 of the dossier assessment *Sofosbuvir/Velpatasvir (chronische Hepatitis C) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 October 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Sofosbuvir/velpatasvir (chronic hepatitis C) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

13 July 2016

Internal Commission No.:

A16-48

Address of publisher:

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Keywords: sofosbuvir, velpatasvir, hepatitis C – chronic, benefit assessment

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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
CI	confidence interval
CLDQ-HCV	Chronic Liver Disease Questionnaire-Hepatitis C
CPT	Child-Pugh-Turcotte
CSR	clinical study report
CSZ	convexity, symmetry, z score
DSV	dasabuvir
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IL28B	interleukin 28B
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDV	ledipasvir
MCS	Mental Component Summary
OBV/PTV/R	ombitasvir/paritaprevir/ritonavir
PEG	peginterferon alfa
PCS	Physical Component Summary
PT	Preferred Term
RBV	ribavirin
RCT	randomized controlled trial
RNA	ribonucleic acid
RR	relative risk
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SOF	sofosbuvir
SPC	Summary of Product Characteristics

Abbreviation	Meaning
SVR	sustained virologic response
SVR 12	sustained virologic response 12 weeks after the end of treatment
SVR 24	sustained virologic response 24 weeks after the end of treatment
VEL	velpatasvir
WPAI	Work Productivity and Activity Impairment

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 sofosbuvir/velpatasvir (SOF/VEL). 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 13 July 2016.

Research question

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

Eight research questions initially resulted from the ACTs specified by the G-BA for different patient groups. The company additionally subdivided research questions 1 and 4 into patients without cirrhosis (research question 1.1 or 4.1) and patients with compensated cirrhosis (research question 1.2 or 4.2).

The research questions and the corresponding ACTs are shown in the following Table 2.

Table 2: Research questions of the benefit assessment of sofosbuvir/velpatasvir

Research question	**Subindication**	**Appropriate comparator therapy**[a]
1	CHC genotype 1	
1.1	Patients without cirrhosis	Ledipasvir/sofosbuvir or ombitasvir/paritaprevir/ritonavir plus dasabuvir (if applicable, plus ribavirin)
1.2	Patients with compensated cirrhosis	Ledipasvir/sofosbuvir
2	CHC genotype 2	
	Patients without cirrhosis or with compensated cirrhosis	Sofosbuvir plus ribavirin
3	CHC genotype 3	
	Patients without cirrhosis or with compensated cirrhosis	Sofosbuvir plus ribavirin
4	CHC genotype 4	
4.1	Patients without cirrhosis	Ledipasvir/sofosbuvir or ombitasvir/paritaprevir/ritonavir plus ribavirin
4.2	Patients with compensated cirrhosis	Ledipasvir/sofosbuvir
5	CHC genotype 5	
	Patients without cirrhosis or with compensated cirrhosis	Peginterferon alfa and ribavirin
6	CHC genotype 6	
	Patients without cirrhosis or with compensated cirrhosis	Peginterferon alfa and ribavirin
7	CHC genotype 1	
	Patients with decompensated cirrhosis	Ledipasvir/sofosbuvir plus ribavirin
8	CHC genotype 2–6	
	Patients with decompensated cirrhosis	Best supportive care
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee		

The company concurred with the ACT specified by the G-BA for all research questions.

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	Intervention	Comparator therapy of the company	Data presented by the company
1	CHC genotype 1			
1.1	Patients without cirrhosis	SOF/VEL for 12 weeks	LDV/SOF for 12 weeks[a]	Further investigations: unadjusted historical comparison
1.2	Patients with compensated cirrhosis	SOF/VEL for 12 weeks	LDV/SOF for 24 weeks[b]	Further investigations: unadjusted historical comparison
2	CHC genotype 2			
	Patients without cirrhosis or with compensated cirrhosis	SOF/VEL for 12 weeks	SOF + RBV for 12 weeks[c]	RCT (ASTRAL-2)
3	CHC genotype 3			
	Patients without cirrhosis or with compensated cirrhosis	SOF/VEL for 12 weeks[d]	SOF + RBV for 24 weeks	RCT (ASTRAL-3)
4	CHC genotype 4			
4.1	Patients without cirrhosis	SOF/VEL for 12 weeks	OBV/PTV/R + RBV for 12 weeks	Further investigations: unadjusted historical comparison
4.2	Patients with compensated cirrhosis	SOF/VEL for 12 weeks	LDV/SOF for 24 weeks[b]	Further investigations: consideration of individual treatment arms of the studies on SOF/VEL without presentation of the evidence on the ACT
5	CHC genotype 5			
	Patients without cirrhosis or with compensated cirrhosis	SOF/VEL for 12 weeks	PEG + RBV for 48 weeks	Further investigations: consideration of individual treatment arms of the studies on SOF/VEL without systematic presentation of the evidence on the ACT (only as examples)
6	CHC genotype 6			
	Patients without cirrhosis or with compensated cirrhosis	SOF/VEL for 12 weeks	PEG + RBV for 48 weeks	Further investigations: consideration of individual treatment arms of the studies on SOF/VEL without systematic presentation of the evidence on the ACT (only as examples)

(continued)

Table 3: Data presented by the company on the research questions (continued)

Research question	Subindication	Intervention	Comparator therapy of the company	Data presented by the company
7	CHC genotype 1			
	Patients with decompensated cirrhosis	SOF/VEL + RBV for 12 weeks	LDV/SOF + RBV for 12 weeks	Further investigations: unadjusted historical comparison
8	CHC genotype 2–6			
	Patients with decompensated cirrhosis	SOF/VEL + RBV for 12 weeks	BSC	Further investigations: consideration of individual treatment arms of the studies on SOF/VEL without presentation of the evidence on the ACT
The company presented no relevant data on patients with HIV coinfection for all research questions.				

a: According to the approval of LDV/SOF, treatment for 8 weeks in treatment-naive patients and treatment for 24 weeks in pretreated patients with uncertain subsequent retreatment options may be considered [3]. The company did not consider these options in the dossier.
b: According to the approval of LDV/SOF, treatment for 12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have uncertain subsequent retreatment options [3]. The company did not consider this option in the dossier.
c: According to the approval of SOF consideration should be given to potentially extending the duration of therapy with SOF + RBV beyond 12 weeks and up to 24 weeks for certain patient groups [4]. The company did not consider this option in the dossier.
d: According to the approval of SOF/VEL, addition of RBV may be considered for patients with compensated cirrhosis [5]. The company did not consider this option in the dossier.

ACT: appropriate comparator therapy; BSC: best supportive care; CHC: chronic hepatitis C; HIV: human immunodeficiency virus; LDV: ledipasvir; OBV/PTV/R: ombitasvir/paritaprevir/ritonavir; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir

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

Results

The results are presented below, categorized by type of the data presented by the company for the individual research questions.

Research question 2 (patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis): study of direct comparison

Study pool and study characteristics

The study ASTRAL-2 was included in the benefit assessment for research question 2. This was a completed, randomized, open-label phase 3 study with an active control. Adult CHC genotype 2 patients without cirrhosis or with compensated cirrhosis were included in the study. About 20% treatment-experienced patients and 20% patients with compensated cirrhosis were to be included in the study. Patients with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) coinfection were excluded from the study.

Stratified by pretreatment and cirrhosis status, the patients were randomly allocated to the treatment arms: 135 patients to the intervention arm, and 134 patients to the comparator arm.

The patients in the intervention arm received SOF/VEL over a period of 12 weeks. The patients in the comparator arm received SOF in combination with ribavirin (RBV) also for 12 weeks.

According to the approval of SOF, treatment with SOF + RBV can be extended up to 24 weeks for certain patients with CHC genotype 2. This particularly applies to patients with one or more negative predictive factors historically associated with lower response rates to interferon-based therapies. The vast majority of the patients included in the study fulfilled one or more of these criteria. The option of 24-week treatment was not available in the ASTRAL-2 study, however. This reduced the informative value of the results, particularly for the outcome "sustained virologic response 12 weeks after the end of treatment (SVR 12)".

The planned maximum duration of follow-up for the outcome "sustained virologic response (SVR)" was 24 weeks after the end of treatment. Health-related quality of life was also recorded until at most 24 weeks after the end of treatment. Adverse events (AEs) were followed-up in the study for 30 days after the end of treatment. Results of the interim clinical study report (CSR) from 11 August 2015 presented by the company, in which only results on the time point of follow-up 12 weeks after the end of treatment were considered, were included in the present benefit assessment, however. The company did not present the results on SVR 24 weeks after the end of treatment (SVR 24), although a data cut-off 10/2015 would have been sufficient for this and the company also presented concordance analyses using data on the SVR 24. It remained unclear why it did not report the SVR 24 results themselves.

Risk of bias and certainty of conclusions

The risk of bias at study level was rated as low.

The informative value of the results from the ASTRAL-2 study was reduced. This was due to the fact that the study mainly included patients who fulfilled one or more criteria according to which extended treatment with SOF + RBV for 24 weeks may be considered, according to the Summary of Product Characteristics (SPC) of SOF. Since this treatment option was not available in the ASTRAL-2 study, estimation of effects of the comparator therapy can be potentially wrong. This is mainly relevant for the SVR 12, particularly because the absolute difference between SOF/VEL and SOF + RBV for the outcome "SVR 12" was small. Overall, at most hints can therefore be derived from the ASTRAL-2 study.

Results

All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of SOF/VEL in comparison

with SOF + RBV; an added benefit for the outcome "all-cause mortality" is therefore not proven.

Morbidity

Sustained virologic response (SVR 12 and SVR 24) as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

A statistically significant difference in favour of SOF/VEL in comparison with SOF + RBV was shown for the outcome "SVR 12". The company presented no data for the outcome "SVR 24".

In addition, there was an indication of an effect modification by the characteristic "sex" for the outcome "SVR 12". For women, there was no hint of an added benefit of SOF/VEL in comparison with SOF + RBV; an added benefit for the outcome "SVR 12" for women is therefore not proven. For men, there was a hint of an added benefit of SOF/VEL in comparison with SOF + RBV for the outcome "SVR 12".

Health-related quality of life recorded with the SF-36

The physical and mental sum scores were considered individually for the Short Form (36) Health Survey (SF-36). The mean difference of the change from the start of the study until 12 weeks after the end of treatment was considered in each case.

No statistically significant difference between the treatment groups was shown in the consideration of the mean differences of the change from the start of the study until 12 weeks after the end of treatment for the physical or the mental sum score. This resulted in no hint of an added benefit of SOF/VEL in comparison with SOF + RBV; an added benefit for the outcome "SF-36" is therefore not proven.

Side effects

Serious adverse events, discontinuation due to adverse events

No statistically significant difference between the treatment groups was shown for the outcomes "serious adverse events (SAEs)" and "discontinuation due to AEs". Greater or lesser harm from SOF/VEL in comparison with SOF + RBV for the outcomes "SAEs" and "discontinuation due to AEs" is therefore not proven.

Fatigue

A statistically significant difference in favour of SOF/VEL in comparison with SOF + RBV was shown for the outcome "fatigue". There was a hint of lesser harm from SOF/VEL in comparison with SOF + RBV for the outcome "fatigue".

Psychiatric disorders

A statistically significant difference in favour of SOF/VEL in comparison with SOF + RBV was shown for the outcome "psychiatric disorders". There was a hint of lesser harm from SOF/VEL in comparison with SOF + RBV for the outcome "psychiatric disorders".

Skin and subcutaneous tissue disorders

A statistically significant difference in favour of SOF/VEL in comparison with SOF + RBV was shown for the outcome "skin and subcutaneous tissue disorders". The extent of the effect for this outcome from the category "non-serious/non-severe side effects" was no more than marginal, however. Greater or lesser harm from SOF/VEL in comparison with SOF + RBV is thus not proven for the outcome.

Research question 3 (patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis): study of direct comparison

Study pool and study characteristics

The study ASTRAL-3 was included in the benefit assessment for research question 3. This was a completed, randomized, open-label phase 3 study with an active control. Adult CHC genotype 3 patients without cirrhosis or with compensated cirrhosis were included in the study. About 20% treatment-experienced patients and 20% patients with compensated cirrhosis were to be included in the study. Patients with HIV or HBV coinfection were excluded from the study.

Stratified by pretreatment and cirrhosis status, the patients were randomly allocated to the treatment arms: 278 patients to the intervention arm, and 280 patients to the comparator arm.

The patients in the intervention arm received SOF/VEL over a period of 12 weeks. The patients in the comparator arm received SOF in combination with RBV for 24 weeks.

According to the approval of SOF/VEL, addition of RBV may be considered for CHC genotype 3 patients with compensated cirrhosis. The ASTRAL-3 study did not investigate this treatment regimen for the subpopulation of patients with compensated cirrhosis, however. No data for the comparison of SOF/VEL with addition of RBV with SOF + RBV were available for the present benefit assessment.

Results of the interim CSR from 8 October 2015 presented by the company, in which only results on the time point of follow-up 12 weeks after the end of treatment were considered, were included in the present benefit assessment. The company did not present the results of the time point of follow-up 24 weeks after the end of treatment, although a data cut-off 12/2015 would have been sufficient for this.

Risk of bias and certainty of conclusions

The risk of bias at study level was rated as low.

The risk of bias of the outcome "hepatocellular carcinoma", which was included using the surrogate "sustained virologic response" (SVR 12), was rated as high because neither data on the SVR 24 nor concordance analyses between SVR 12 and SVR 24 were available.

Due to the different observation periods in the intervention and comparator arm of the ASTRAL-3 study, the data on AEs (including mortality recorded using AEs) and health-related quality of life were largely not meaningfully interpretable. Except for the outcome "discontinuation due to AEs", the results on AEs were therefore not conclusively interpretable in quantitative terms. A comprehensive choice of further specific AEs was also not possible for this reason. The company presented no usable data for health-related quality of life on a comparable time period.

The outcome "discontinuation due to AEs" also had a high risk of bias due to the open-label study design.

In summary, at most hints, e.g. of an added benefit, can be derived from the ASTRAL-3 study for all outcomes.

Results

All-cause mortality

Few patients died in the study, 3 patients in the comparator arm and no patient in the intervention arm. Overall, there was no hint of an added benefit of SOF/VEL in comparison with SOF + RBV; an added benefit for the outcome "all-cause mortality" is therefore not proven.

Morbidity

Sustained virologic response (SVR 12 and SVR 24) as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

The company's analysis showed a statistically significant difference in favour of SOF/VEL in comparison with SOF + RBV for the outcome "SVR 12". Patients who discontinued treatment prematurely for other reasons than virologic failure were counted as non-responders in this analysis. The Institute therefore conducted its own sensitivity analysis (worst case analysis) to check the robustness of the results of the company's analysis. In this analysis, all patients in the comparator arm who discontinued treatment for other reasons than virologic failure were counted as responders. The result of this analysis also showed a statistically significant difference in favour of SOF/VEL versus SOF + RBV and supported the result of the primary analysis.

The company presented no data for the outcome "SVR 24".

Overall, there was a hint of an added benefit of SOF/VEL in comparison with SOF + RBV for the outcome "SVR 12".

Health-related quality of life recorded with the SF-36

The company presented no usable analysis with comparable time periods for both treatment groups for the SF-36.

Side effects

Serious adverse events

In the intervention arm, at least one SAE was observed in 2.2% of the patients, whereas in the comparator arm, at least one SAE was observed in 5.5% of the patients. The available data allowed no quantitative conclusion for this outcome.

Discontinuation due to adverse events

A statistically significant difference in favour of SOF/VEL in comparison with SOF + RBV was shown for the outcome "discontinuation due to AEs". There was a hint of lesser harm from SOF/VEL in comparison with SOF + RBV.

Specific adverse events

Due to the available data, no comprehensive choice of specific AEs was possible.

Research questions 1.1, 1.2, 4.1 and 7: unadjusted historical comparisons

For research questions 1.1, 1.2, 4.1 and 7, the company compared data from individual arms of randomized controlled trials (RCTs) on SOF/VEL with data from individual arms of RCTs on the respective ACT to conduct unadjusted historical comparisons. Based on the comparisons presented, no added benefit of SOF/VEL versus the ACT can be derived for all 4 research questions.

Conclusions on the added benefit based on unadjusted historical comparisons 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).

For research questions 1.1 (patients with CHC genotype 1 without cirrhosis), 4.1 (patients with CHC genotype 4 without cirrhosis) and 7 (patients with CHC genotype 1 with decompensated cirrhosis), such an effect was not achieved for any of the relevant outcomes analysed by the company (mortality, SVR 12, SAEs and discontinuation due to AEs). Instead, no statistically significant differences between the treatment groups were shown for all outcomes except for the outcome "discontinuation due to AEs" for research question 7. Overall, an added benefit is therefore not proven for research questions 1.1, 4.1 and 7.

For research question 1.2 (patients with CHC genotype 1 with compensated cirrhosis), the company derived a hint of a minor added benefit of SOF/VEL in comparison with ledipasvir/sofosbuvir (LDV/SOF). The company's assessment was solely based on the effect for the outcome "severe AEs" (grade ≥ 3) (relative risk [RR] [95% confidence interval (CI)]:

0.10 [0.01; 0.77]; p = 0.027[4]). The operationalization of the outcome "severe AEs" used by the company was unsuitable, however. Irrespective of this, the postulated difference was potentially caused solely by the notably shorter observation period for SOF/VEL (about 16 weeks) than for LDV/SOF (about 28 weeks). This also applied to the outcome "SAEs", for which a statistically significant effect in favour of SOF/VEL was found in the Institute's calculation, but not in the company's calculation.

There were no statistically significant differences between the treatment groups for any further relevant outcomes analysed by the company (mortality, SVR 12 and discontinuation due to AEs).

Overall, an added benefit is therefore not proven also for research question 1.2.

Research questions 4.2, 5, 6 and 8: consideration of individual treatment arms of the studies on SOF/VEL

For research questions 4.2, 5, 6 and 8, the company only presented data on SOF/VEL without comparing these with (suitable) comparative data on the ACT. For research question 8, the company conducted no information retrieval for studies with the ACT at all because this constituted no antiviral therapy, according to the company.

Overall, no added benefit is proven for any of these research questions.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[5]

On the basis of the results presented, the extent and probability of the added benefit of the drug SOF/VEL in comparison with the ACT is assessed as follows.

Table 4 presents a summary of the extent and probability of the added benefit of SOF/VEL.

[4] p-value from the company's calculations; the Institute's calculation using the convexity, symmetry, z score (CSZ) test resulted in a p-value of p = 0.005.

[5] 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: Sofosbuvir/velpatasvir – extent and probability of added benefit

Subindication	**ACT**[a]	**Extent and probability of added benefit**
Patients with CHC genotype 1 without cirrhosis	Ledipasvir/sofosbuvir or ombitasvir/paritaprevir/ritonavir plus dasabuvir (if applicable, plus ribavirin)	Added benefit not proven
Patients with CHC genotype 1 with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
Patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis	Sofosbuvir plus ribavirin	Hint of considerable added benefit[b]
Patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis	Sofosbuvir plus ribavirin	Hint of non-quantifiable added benefit[b]
Patients with CHC genotype 4 without cirrhosis	Ledipasvir/sofosbuvir or ombitasvir/paritaprevir/ritonavir plus ribavirin	Added benefit not proven
Patients with CHC genotype 4 with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
Patients with CHC genotype 5 without cirrhosis or with compensated cirrhosis	Peginterferon alfa and ribavirin	Added benefit not proven
Patients with CHC genotype 6 without cirrhosis or with compensated cirrhosis	Peginterferon alfa and ribavirin	Added benefit not proven
Patients with CHC genotype 1 with decompensated cirrhosis	Ledipasvir/sofosbuvir plus ribavirin	Added benefit not proven
Patients with CHC genotype 2–6 with decompensated cirrhosis	BSC	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: The added benefit is not proven for patients with HIV coinfection because the company presented no relevant data for these patients.
ACT: appropriate comparator therapy; BSC: best supportive care; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus

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

2.2 Research question

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

Eight research questions initially resulted from the ACTs specified by the G-BA for different patient groups. The company additionally subdivided research questions 1 and 4 into patients without cirrhosis (research question 1.1 or 4.1) and patients with compensated cirrhosis (research question 1.2 or 4.2). For reasons of clarity of the present benefit assessment, the subdivision and the numbering of the research questions used by the company were maintained, resulting in a total of 10 research questions for the benefit assessment.

The research questions and the corresponding ACTs are shown in the following Table 5.

Table 5: Research questions of the benefit assessment of sofosbuvir/velpatasvir

Research question	Subindication	Appropriate comparator therapy[a]
1	CHC genotype 1	
1.1	Patients without cirrhosis	Ledipasvir/sofosbuvir or ombitasvir/paritaprevir/ritonavir plus dasabuvir (if applicable, plus ribavirin)
1.2	Patients with compensated cirrhosis	Ledipasvir/sofosbuvir
2	CHC genotype 2	
	Patients without cirrhosis or with compensated cirrhosis	Sofosbuvir plus ribavirin
3	CHC genotype 3	
	Patients without cirrhosis or with compensated cirrhosis	Sofosbuvir plus ribavirin
4	CHC genotype 4	
4.1	Patients without cirrhosis	Ledipasvir/sofosbuvir or ombitasvir/paritaprevir/ritonavir plus ribavirin
4.2	Patients with compensated cirrhosis	Ledipasvir/sofosbuvir
5	CHC genotype 5	
	Patients without cirrhosis or with compensated cirrhosis	Peginterferon alfa and ribavirin
6	CHC genotype 6	
	Patients without cirrhosis or with compensated cirrhosis	Peginterferon alfa and ribavirin
7	CHC genotype 1	
	Patients with decompensated cirrhosis	Ledipasvir/sofosbuvir plus ribavirin
8	CHC genotype 2–6	
	Patients with decompensated cirrhosis	Best supportive care

a: Presentation of the respective ACT specified by the G-BA.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee

The company concurred with the ACT specified by the G-BA for all research questions.

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	Intervention	Comparator therapy of the company	Data presented by the company
1	CHC genotype 1			
1.1	Patients without cirrhosis	SOF/VEL for 12 weeks	LDV/SOF for 12 weeks[a]	Further investigations: unadjusted historical comparison
1.2	Patients with compensated cirrhosis	SOF/VEL for 12 weeks	LDV/SOF for 24 weeks[b]	Further investigations: unadjusted historical comparison
2	CHC genotype 2			
	Patients without cirrhosis or with compensated cirrhosis	SOF/VEL for 12 weeks	SOF + RBV for 12 weeks[c]	RCT (ASTRAL-2)
3	CHC genotype 3			
	Patients without cirrhosis or with compensated cirrhosis	SOF/VEL for 12 weeks[d]	SOF + RBV for 24 weeks	RCT (ASTRAL-3)
4	CHC genotype 4			
4.1	Patients without cirrhosis	SOF/VEL for 12 weeks	OBV/PTV/R + RBV for 12 weeks	Further investigations: unadjusted historical comparison
4.2	Patients with compensated cirrhosis	SOF/VEL for 12 weeks	LDV/SOF for 24 weeks[b]	Further investigations: consideration of individual treatment arms of the studies on SOF/VEL without presentation of the evidence on the ACT
5	CHC genotype 5			
	Patients without cirrhosis or with compensated cirrhosis	SOF/VEL for 12 weeks	PEG + RBV for 48 weeks	Further investigations: consideration of individual treatment arms of the studies on SOF/VEL without systematic presentation of the evidence on the ACT (only as examples)
6	CHC genotype 6			
	Patients without cirrhosis or with compensated cirrhosis	SOF/VEL for 12 weeks	PEG + RBV for 48 weeks	Further investigations: consideration of individual treatment arms of the studies on SOF/VEL without systematic presentation of the evidence on the ACT (only as examples)

(continued)

Table 6: Data presented by the company on the research questions (continued)

Research question	Subindication	Intervention	Comparator therapy of the company	Data presented by the company
7	CHC genotype 1			
	Patients with decompensated cirrhosis	SOF/VEL + RBV for 12 weeks	LDV/SOF + RBV for 12 weeks	Further investigations: unadjusted historical comparison
8	CHC genotype 2–6			
	Patients with decompensated cirrhosis	SOF/VEL + RBV for 12 weeks	BSC	Further investigations: consideration of individual treatment arms of the studies on SOF/VEL without presentation of the evidence on the ACT
The company presented no relevant data on patients with HIV coinfection for all research questions.				

a: According to the approval of LDV/SOF, treatment for 8 weeks in treatment-naive patients and treatment for 24 weeks in pretreated patients with uncertain subsequent retreatment options may be considered [3]. The company did not consider these options in the dossier.
b: According to the approval of LDV/SOF, treatment for 12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have uncertain subsequent retreatment options [3]. The company did not consider this option in the dossier.
c: According to the approval of SOF consideration should be given to potentially extending the duration of therapy with SOF + RBV beyond 12 weeks and up to 24 weeks for certain patient groups [4]. The company did not consider this option in the dossier.
d: According to the approval of SOF/VEL, addition of RBV may be considered for patients with compensated cirrhosis [5]. The company did not consider this option in the dossier.

ACT: appropriate comparator therapy; BSC: best supportive care; CHC: chronic hepatitis C; HIV: human immunodeficiency virus; LDV: ledipasvir; OBV/PTV/R: ombitasvir/paritaprevir/ritonavir; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir

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 1.1: CHC genotype 1, patients without cirrhosis

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 SOF/VEL (status: 17 May 2016)
- bibliographical literature search on SOF/VEL (last search on 19 May 2016)
- search in trial registries for studies on SOF/VEL (last search on 17 May 2016)
- study list on the ACT (status: 17 May 2016)
- bibliographical literature search on the ACT (last search on 19 May 2016)
- search in trial registries for studies on the ACT (last search on 17 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on SOF/VEL (last search on 22 July 2016)

In its information retrieval, the company identified no studies of direct comparison of SOF/VEL versus the ACT for this research question. The Institute's check of completeness also identified no RCTs of direct comparison of SOF/VEL for patients with CHC genotype 1 without cirrhosis.

Since the company identified no studies of direct comparison for this research question and there were no common comparators for an adjusted indirect comparison, it searched for further investigations for an unadjusted historical comparison. The company initially searched for studies with the comparator therapy LDV/SOF. Since this search identified studies on this comparator therapy, it conducted no further searches for the alternative comparator therapy ombitasvir/paritaprevir/ritonavir (OBV/PTV/R) + dasabuvir (DSV) (if applicable + RBV).

Table 7 shows the studies included by the company in its unadjusted historical comparison.

Table 7: Study pool of the company – further investigations: patients with CHC genotype 1 without cirrhosis, SOF/VEL vs. LDV/SOF

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Studies with SOF/VEL			
GS-US-342-1138 (ASTRAL-1[b])	Yes	Yes	No
GS-US-342-0102	Yes	Yes	No
GS-US-342-0109	Yes	Yes	No
Studies with the ACT LDV/SOF			
GS-US-337-0102 (ION-1[b])	No	Yes	No
GS-US-337-0109 (ION-2[b])	No	Yes	No
GS-US-337-0108 (ION-3[b])	No	Yes	No
GS-US-337-0118 (LONESTAR[b])	No	Yes	No
GS-US-337-0113 (Japan)	No	Yes	No

a: Study for which the company was sponsor.
b: In the benefit assessment, the study is referred to with this abbreviated form.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; LDV: ledipasvir; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus

The company identified 3 RCTs on SOF/VEL: ASTRAL-1 [6], GS-US-342-0102 [7] and GS US-342-0109 [8]. On the comparator therapy LDV/SOF, the company identified the RCTs ION-1 [9], ION-2 [10], ION-3 [11], LONESTAR [12] and GS-US-337-0113 (Japan) [13]. For the unadjusted historical comparison, the company included subpopulations of individual arms of these studies, namely patients with genotype 1 without cirrhosis, for SOF/VEL and LDV/SOF.

In the study arms considered by the company, SOF/VEL and LDV/SOF were administered in compliance with the approval over a period of 12 weeks [3,5]. The company conducted no comparison for further treatment options possible according to the SPC of LDV/SOF, i.e. treatment of patients for 8 or 24 weeks [3].

The company included a total of 301 patients on SOF/VEL and 623 patients on LDV/SOF in its comparison.

The 8 studies included by the company in the unadjusted historical comparison are described in Tables 48 and 49 in Appendix B.1 of the full dossier assessment.

No added benefit of SOF/VEL in comparison with LDV/SOF could be derived from the historical comparison presented by the company. Conclusions on the added benefit based on historical comparisons are only possible in the presence of very large effects (so-called

dramatic effects). Such an effect was not achieved for any of the relevant outcomes analysed by the company (mortality, SVR 12, SAEs and discontinuation due to AEs). Instead, no statistically significant differences between the treatment groups were shown for all outcomes.

2.3.2 Results on added benefit

No added benefit of SOF/VEL in comparison with the ACT could be derived on the basis of the unadjusted historical comparison presented by the company. There was no hint of an added benefit of SOF/VEL in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

No proof of added benefit of SOF/VEL in comparison with the ACT was derived from the available data for CHC genotype 1 patients without cirrhosis. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

This concurs with the company’s assessment.

2.4 Research question 1.2: CHC genotype 1, patients with compensated cirrhosis

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 SOF/VEL (status: 17 May 2016)
- bibliographical literature search on SOF/VEL (last search on 19 May 2016)
- search in trial registries for studies on SOF/VEL (last search on 17 May 2016)
- study list on the ACT (status: 17 May 2016)
- bibliographical literature search on the ACT (last search on 19 May 2016)
- search in trial registries for studies on the ACT (last search on 17 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on SOF/VEL (last search on 22 July 2016)

In its information retrieval, the company identified no studies of direct comparison of SOF/VEL versus the ACT for this research question. The Institute's check of completeness also identified no RCTs of direct comparison of SOF/VEL for patients with CHC genotype 1 with compensated cirrhosis.

Since the company identified no studies of direct comparison for this research question and there were no common comparators for an adjusted indirect comparison, it searched for further investigations for an unadjusted historical comparison.

Table 8 shows the studies included by the company in its unadjusted historical comparison.

Table 8: Study pool of the company – further investigations: patients with CHC genotype 1 with compensated cirrhosis, SOF/VEL vs. LDV/SOF

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Studies with SOF/VEL			
GS-US-342-1138 (ASTRAL-1[b])	Yes	Yes	No
GS-US-342-0109	Yes	Yes	No
Studies with the ACT LDV/SOF			
GS-US-337-0102 (ION-1[b])	No	Yes	No
GS-US-337-0109 (ION-2[b])	No	Yes	No
GS-US-337-0121 (SIRIUS[b])	No	Yes	No

a: Study for which the company was sponsor.
b: In the benefit assessment, the study is referred to with this abbreviated form.
CHC: chronic hepatitis C; LDV: ledipasvir; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus

The company identified 2 RCTs on SOF/VEL: ASTRAL-1 [6] and GS-US-342-0109 [8]. On the comparator therapy LDV/SOF, the company identified the RCTs ION-1 [9], ION-2 [10] und SIRIUS [14,15]. For the unadjusted historical comparison, the company included subpopulations of individual arms of these studies, namely patients with genotype 1 with compensated cirrhosis, for SOF/VEL and LDV/SOF.

In the arms of the SOF/VEL studies considered by the company, SOF/VEL was administered in compliance with the approval [5] over a period of 12 weeks. In the studies on the comparator therapy, the patients received LDV/SOF also in compliance with the approval [3] over a period of 24 weeks. The company conducted no comparison for a further treatment option possible in certain patients according to the SPC of LDV/SOF, i.e. the shorter treatment period of 12 weeks.

The company included a total of 80 patients on SOF/VEL and 132 patients on LDV/SOF in its comparison.

The 5 studies included by the company in the unadjusted historical comparison are described in Tables 50 and 51 in Appendix B.2 of the full dossier assessment.

The company derived a hint of a minor added benefit of SOF/VEL in comparison with LDV/SOF on the basis of its unadjusted historical comparison. The company's assessment was solely based on the effect for the outcome "severe AEs" (grade $\geq$ 3) (RR [95% CI]: 0.10 [0.01; 0.77]; p = 0.027[6]). The company considered this effect to be dramatic in the sense

[6] p-value from the company's calculations; the Institute's calculation using the CSZ test [16] resulted in a p-value of p = 0.005.

of a 10-fold improvement. The company's assessment on the added benefit was not followed. This is justified below.

Prerequisite for the derivation of an added benefit based on historical comparisons

Conclusions on the added benefit based on unadjusted historical comparisons 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 [17] 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 RR, has a value of 10 or higher (or 1/10 or lower). Moreover, the risk of the examined event should be at least 5% in at least one of the groups compared [1]. The certainty of conclusions based on the unadjusted historical comparisons is generally very limited. For this reason, there should be no methodological aspects that may cause such a high additional bias to the results that they can no longer be regarded as "dramatic" with sufficient certainty.

Systematic bias of the results on side effects

The RR [95% CI] for the outcome "severe AEs" (grade ≥ 3) calculated by the company was 0.10 [0.01; 0.77] ($p = 0.027$[6]) and showed a statistically significant difference in favour of SOF/VEL versus LDV/SOF. The effect for the outcome "severe AEs" (grade ≥ 3) was based on 1 patient with event for SOF/VEL (1.3%) and 16 patients with event for LDV/SOF [12%]. According to the Institute's calculation, the effect principally reached the magnitude of a dramatic effect (according to the criteria mentioned above). According to the Institute's calculation, the effect for the outcome "SAEs" (RR [95% CI]: 0.06 [–[7]]; $p = 0.004$), which was based on 0 patients with event for SOF/VEL and 13 [9.8%] patients for LDV/SOF, also principally reached the magnitude of a dramatic effect.

For both outcomes, no dramatic effect in favour of SOF/VEL versus LDV/SOF could be assumed with sufficient certainty, however.

On the one hand, the outcome "severe AEs" (grade ≥ 3), which was recorded in the studies using the Gilead Sciences, Inc. (Gilead) Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, was not relevant for the present benefit assessment. This scale had originally been developed for HIV infection and was now used by the company in a modified form for CHC. The company provided no information on the changes between the versions (see Section 2.14.2.4.3 of the full dossier assessment).

Irrespective of this, consideration should be given in the present situation to the different observation periods for intervention and comparator therapy in the interpretation of the results of AEs.

[7] 95% CI not meaningfully interpretable

In the comparison presented by the company, patients were treated with SOF/VEL for 12 weeks, whereas patients with LDV/SOF were treated for 24 weeks. In all studies included by the company, AEs were followed-up for 30 days after the end of treatment. This resulted in markedly different observation periods for AEs with a difference of 12 weeks. As a result, the effect estimations for AEs (including mortality recorded using AEs) on the basis of naive proportions presented by the company constituted no adequate analysis. Due to the longer observation period alone, more events can be observed for the comparator therapy than for the intervention, without this being necessarily caused by the comparator therapy itself. In addition to the high uncertainty of the unadjusted historical comparison, this causes additional bias due to the different observation periods. Moreover, low numbers of events were observed for the outcome "SAEs". Some of the events observed for LDV/SOF were hepatic events, such as hepatocellular carcinoma and hepatic encephalopathy, that may be associated with the underlying disease. These events were possible recorded due to the longer observation period for LDV/SOF alone so that bias to the disadvantage of the comparator therapy can be assumed for the outcome "SAEs" (without recording of the symptoms of the underlying disease). Overall, the uncertainty of the unadjusted historical comparison in conjunction with the different observation periods in the treatment arms alone is to be regarded as so high that a dramatic effect in favour of SOF/VEL versus LDV/SOF cannot be assumed with sufficient certainty for the outcomes "severe AEs" (grade ≥ 3) and "SAEs".

There were no statistically significant differences between the treatment groups for any further relevant outcomes analysed by the company (mortality, SVR 12 and discontinuation due to AEs).

2.4.2 Results on added benefit

No added benefit of SOF/VEL in comparison with the ACT could be derived on the basis of the unadjusted historical comparison presented by the company. There was no hint of an added benefit of SOF/VEL in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

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

This deviates from the assessment of the company, which derived a hint of a minor added benefit of SOF/VEL for patients with CHC genotype 1 with compensated cirrhosis.

2.5 Research question 2: CHC genotype 2, patients without cirrhosis or with compensated cirrhosis

2.5.1 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 list on SOF/VEL (status: 17 May 2016)
- bibliographical literature search on SOF/VEL (last search on 19 May 2016)
- search in trial registries for studies on SOF/VEL (last search on 17 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on SOF/VEL (last search on 22 July 2016)

No additional relevant study was identified from the check.

2.5.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 9: Study pool – RCT, direct comparison: patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
GS-US-342-1139 (ASTRAL-2[b])	Yes	Yes	No

a: Study for which the company was sponsor.
b: In the benefit assessment, the study is referred to with this abbreviated form.
CHC: chronic hepatitis C; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus

Section 2.5.4 contains a reference list for the study included.

2.5.1.2 Study characteristics

Table 10 and Table 11 describe the study used for the benefit assessment.

Table 10: Characteristics of the study included – RCT, direct comparison: patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ASTRAL-2	RCT (stratified by cirrhosis status and pretreatment), open-label, parallel	Treatment-naive and treatment-experienced[b] adults with CHC genotype 2 without cirrhosis or with compensated cirrhosis[c]	SOF/VEL (12W) (N = 135) SOF + RBV (12W) (N = 134)	Screening: up to 42 days Treatment: 12 weeks Follow-up: up to 24 weeks[d] (AEs up to 30 days)	51 study centres in the USA 9/2014–9/2015 Data cut-off for the interim analysis of SVR 12: 22 July 2015[e]	Primary: SVR 12 Secondary: SVR 24[f], health-related quality of life, AEs (including deaths)

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on relevant (available) outcomes.
b: Previous treatment failure of interferon-based therapy with or without RBV.
c: About 20% of the study population could be treatment-experienced, and about 20% of the study population could have compensated cirrhosis.
d: In HCV-RNA ≥ LLOQ 12 weeks after the end of treatment or confirmed relapse at a later time point, no further follow-up until 24 weeks was conducted.
e: According to the information provided by the company in the dossier, only an interim CSR from 11 August 2015 and no final CSR was available at the time of submission of the dossier.
f: According to the company, data on the SVR 24 were not yet available at the time of submission of the dossier.

AE: adverse event; CHC: chronic hepatitis C; CSR: clinical study report; HCV: hepatitis C virus; LLOQ: lower limit of quantification; N: number of randomized patients; RBV: ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; SVR 24: sustained virologic response 24 weeks after the end of treatment; VEL: velpatasvir; vs.: versus; W: weeks

Table 11: Characteristics of the intervention – RCT, direct comparison: patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study	Intervention	Comparison
ASTRAL-2	SOF/VEL (400 mg/100 mg) once daily, orally, for 12 weeks	SOF 400 mg once daily, orally + RBV 1000 or 1200 mg/day, distributed to 2 doses, orally, (depending on weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg), for 12 weeks
	Dose adjustment not allowed	Dose adjustment of SOF not allowed; dose adjustments of RBV allowed according to the approval of SOF; in case of discontinuation of the RBV treatment, SOF also had to be discontinued.
	Prior and concomitant medication: Treatment with the following drugs was prohibited for 28 days before the first study visit up to the end of the treatment: ▪ systemic immunosuppressants (including corticosteroids, azathioprine, monoclonal antibodies) ▪ blood cell stimulating drugs ▪ drugs or herbal agents that may influence the pharmacokinetics of the medication (e.g. p-glycoprotein inhibitors, St. John's Wort) ▪ antacids (proton pump inhibitors), anticonvulsants (phenobarbital, phenytoin, carbamazepine, oxcarbazepine), antimycotics (rifabutin, rifapentine, rifampin)	

CHC: chronic hepatitis C; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus

The included ASTRAL-2 study was a completed, randomized, open-label, active-controlled phase 3 study. Adult CHC genotype 2 patients without cirrhosis or with compensated cirrhosis were included in the study. About 20% treatment-experienced patients and 20% patients with compensated cirrhosis were to be included in the study. Patients with HIV or HBV coinfection were excluded from the study.

Stratified by pretreatment and cirrhosis status, the patients were randomly allocated to the treatment arms: 135 patients to the intervention arm, and 134 patients to the comparator arm.

The patients in the intervention arm received SOF/VEL over a period of 12 weeks. The patients in the comparator arm received SOF in combination with RBV also for 12 weeks. Dosage and type of use of the drugs administered complied with their respective approval [4,5]. Drugs contraindicated according to the SPCs were not allowed to be used as concomitant medication in the study.

According to the approval of SOF, treatment with SOF + RBV can be extended up to 24 weeks for certain patients with CHC genotype 2 [4]. According to the SPC, this particularly applies to patients with one or more negative predictive factors historically associated with lower response rates to interferon-based therapies (e.g. cirrhosis, high baseline viral load, or interleukin 28B [IL28B] non-CC genotype).

The planned duration of follow-up for the outcome “SVR” was based on the detection of hepatitis C virus ribonucleic acid (HCV RNA) 12 weeks after the last administration of the study medication. Patients with HCV RNA below the limit of detection 12 weeks after the end of treatment were followed-up until week 24. Patients with detection of HCV RNA at this time point were not followed-up beyond week 12 after the end of treatment. Patients with demonstrated relapse between week 12 and week 24 after the end of treatment were also not followed-up for SVR. Health-related quality of life was recorded until at most 24 weeks after the end of treatment. AEs were followed-up in the study for 30 days after the end of treatment.

According to the information provided by the company, only an interim CSR from 11 August 2015 was available at the time of submission of the dossier. Results on the time point of follow-up 12 weeks after the end of treatment were included in this interim CSR. The results of the time point of follow-up 24 weeks after the end of treatment were not available for the present benefit assessment, although a data cut-off 10/2015 would have been sufficient for this. In addition, the company presented concordance analyses using data on the SVR 24 (see Section 2.14.2.4.3 of the full dossier assessment). It remained unclear why it did not present the SVR 24 results themselves.

Table 12 shows the characteristics of the patients in the study included.

Table 12: Characteristics of the study population – RCT, direct comparison: patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study **Characteristics** **Category**	**SOF/VEL (12W)**	**SOF + RBV (12W)**
ASTRAL-2	N = 134	N = 132
Age [years], mean (SD)	57 (11)	57 (9)
Sex [F/M], %	36/64	46/54
Ethnicity		
White	124 (92.5)	111 (84.1)
Black	6 (4.5)	12 (9.1)
Asian	1 (0.7)	5 (3.8)
Other/unknown	3 (2.2)[a]	4 (3.1)[a]
HCV subgenotype, n (%)		
GT 2 (not further specified)	13 (9.7)	12 (9.1)
GT 2a	2 (1.5)	4 (3.0)
GT 2a or 2c	16 (11.9)	12 (9.1)
GT 2b	103 (76.9)	104 (78.8)
Cirrhosis, n (%)		
Compensated cirrhosis	19 (14.2)	19 (14.4)
No cirrhosis	115 (85.8)	112 (84.8)
No data	0 (0)	1 (0.8)
IL28B genotype, n (%)		
CC	55 (41.0)	46 (34.8)
Non-CC	79 (59.0)	86 (65.2)
CT	61 (77.2)	64 (74.4)
TT	18 (22.8)	22 (25.6)
Baseline HCV RNA viral load [IU/mL], n (%)		
< 800 000	23 (17.2)	31 (23.5)
≥ 800 000	111 (82.8)	101 (76.5)
Pretreatment, n (%)		
Treatment-naive	115 (85.8)	112 (84.8)
Pretreated	19 (14.2)	20 (15.2)
Pretreatment with:		
PEG + RBV	16 (84.2)	15 (75.0)
Other treatments	3 (15.8)	5 (25.0)
Response to prior therapy		
No response	3 (15.8)	3 (15.0)
Relapse	16 (84.2)	17 (85.0)
Treatment discontinuation, n (%)	1 (0.7)	1 (0.8)
Study discontinuation, n (%)	1 (0.7)	2 (1.5)

(continued)

Table 12: Characteristics of the study population – RCT, direct comparison: patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV (continued)

a: Institute's calculation.
CHC: chronic hepatitis C; F: female; GT: genotype; HCV: hepatitis C virus; IL28B: interleukin 28B; IU: international units; M: male; n: number of patients in the category; N: number of randomized and treated patients; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus; W: weeks

The mean age of the patients in the ASTRAL-2 study was 57 years. The sex ratio in the intervention arm was 36% women and 64% men. The ratio in the comparator arm was more balanced (46% women and 54% men). More than 80% of the patients in both study arms were white.

About 14% of the patients in both study arms had compensated cirrhosis. About 60% of the study participants had IL28B genotype non-CC. The HCV RNA viral load at the start of the study was high (≥ 800 000 IU/mL) in more than 75% of the patients in both study arms with the majority of the patients being treatment-naive (about 85%). According to this, the vast majority of the patients fulfilled one or more criteria according to which, treatment with SOF + RBV for 24 weeks may be considered, according to the SPC of SOF [4]. This treatment option was not available in the ASTRAL-2 study, however. This had an influence on the certainty of conclusions of the results of the ASTRAL-2 study (see Section 2.5.2.2).

The number of patients who discontinued the study or the treatment was below 2% in both study arms and did not differ substantially between the study arms.

Table 13 shows the risk of bias at study level.

Table 13: Risk of bias at study level – RCT, direct comparison: patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

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			
ASTRAL-2	Yes	Yes	No	No	Yes	Yes	Low

CHC: chronic hepatitis C; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus

The risk of bias at study level was rated as low. This concurs with the company's assessment.

Limitations resulting from the open-label study design and the missing option of SOF + RBV treatment for 24 weeks are described in Section 2.5.2.2.

2.5.2 Results on added benefit

2.5.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.14.2.4.3 of the full dossier assessment):

- Mortality
  - All-cause mortality
- Morbidity
  - sustained virologic response (SVR 12 and SVR 24) as sufficiently valid surrogate for the patient-relevant outcome “hepatocellular carcinoma”
- Health-related quality of life
  - SF-36
- Side effects
  - SAEs
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

The company used a total of 4 instruments to measure health-related quality of life. Besides the generic questionnaire SF-36 mentioned above, these were the Chronic Liver Disease Questionnaire-Hepatitis C (CLDQ-HCV), the instrument Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and the questionnaire Work Productivity and Activity Impairment (WPAI: hepatitis C). These instruments were only partly included in the benefit assessment. The validity of the instrument CLDQ-HCV was not conclusively clear from the information presented by the company. The validity of the instrument FACIT-F for CHC patients was not proven by the company. The WPAI: hepatitis C is not regarded as instrument for measuring health-related quality of life. A detailed comment can be found in Section 2.14.2.4.3 of the full dossier assessment.

In addition, the company used the outcome “severe AEs” (grade ≥ 3) for its assessment. Deviating from the company, this outcome was regarded as not relevant (see Section 2.14.2.4.3 of the full dossier assessment).

Furthermore, the choice of the specific AEs relevant for the benefit assessment deviated from the company's choice. Based on common events, the company included the outcomes "fatigue", "insomnia" and "anaemia", each as Preferred Term (PT), in its assessment. In the present benefit assessment, in contrast, the outcomes "fatigue" (PT), "psychiatric disorders" (System Organ Class [SOC]) and "skin and subcutaneous tissue disorders" (SOC) were included. Thus insomnia was considered with the SOC "psychiatric disorders". Anaemia was not considered in the present benefit assessment because the patient relevance of the outcome in the operationalization chosen in the study remained unclear. A detailed comment on the choice of specific AEs can be found in Section 2.14.2.4.3 of the full dossier assessment.

Table 14 shows for which outcomes data were available in the study included.

Table 14: Matrix of outcomes – RCT, direct comparison: patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study	Outcomes							
	All-cause mortality	Sustained virologic response (SVR 12 and SVR 24)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Fatigue (PT)	Psychiatric disorders (SOC)	Skin and subcutaneous tissue disorders (SOC)
ASTRAL-2	Yes	Yes[a]	Yes	Yes	Yes	Yes	Yes	Yes

a: Data on the SVR 24 are not available for the present benefit assessment.

AE: adverse event; CHC: chronic hepatitis C; PT: Preferred Term; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; SVR 24: sustained virologic response 24 weeks after the end of treatment; VEL: velpatasvir; vs.: versus

2.5.2.2 Risk of bias

Table 15 shows the risk of bias for the relevant outcomes.

Table 15: Risk of bias at study and outcome level – RCT, direct comparison: patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study		Outcomes							
	Study level	All-cause mortality	Sustained virologic response (SVR 12 and SVR 24)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Fatigue (PT)	Psychiatric disorders (SOC)	Skin and subcutaneous tissue disorders (SOC)
ASTRAL-2	L	L	H[a]	H[b, c]	L	H[b]	H[b]	H[b]	H[b]

a: Data on the SVR 24 are not available for the present benefit assessment. A high risk of bias is assumed for the outcome "SVR 12" because it remains unclear why the company did not present data on the SVR 24, although these must have been available to the company for conducting the concordance analysis.
b: Open-label study design.
c: Proportion of missing values > 10%.

AE: adverse event; CHC: chronic hepatitis C; H: high; L: low; PT: Preferred Term; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; SVR 24: sustained virologic response 24 weeks after the end of treatment; VEL: velpatasvir; vs.: versus

The risk of bias of the outcome "hepatocellular carcinoma", which was included using the surrogate "sustained virologic response" (SVR 12), was rated as high because it remained unclear why the company did not present data on the SVR 24. A data cut-off 10/2015 would have been sufficient for this. In addition, the company presented results of a concordance analysis between SVR 12 and SVR 24 using SVR 24 data. It was therefore assumed that the data on the SVR 24 were available to the company (see Section 2.14.2.4.3 of the full dossier assessment). This deviates from the company's assessment, which rated the risk of bias for SVR 12 as low.

The risk of bias for the outcomes "all-cause mortality" and "SAEs" was classed as low. This concurs with the company's assessment.

The risk of bias of the outcomes "SF-36", "discontinuation due to AEs", "fatigue", "psychiatric disorders" and "skin and subcutaneous tissue disorders" was regarded as high because these are subjective outcomes that are generally to be rated as having a high risk of bias in an open-label study design. In addition, the proportion of missing values for the SF-36 was over 10%.

The company also assumed a high risk of bias for the outcome "SF-36". It justified its assessment exclusively with the open-label study design, however.

The assessment of the risk of bias for the outcome “discontinuation due to AEs” and the specific AE “fatigue” deviates from the assessment of the company, which rated the risk of bias as low. The company did not include the further specific AEs (psychiatric disorders and skin and subcutaneous tissue disorders) in its assessment. It assumed a low risk of bias for all outcomes from the category “side effects”, however.

Assessment of the certainty of conclusions of the results of the ASTRAL-2 study

The informative value of the results from the ASTRAL-2 study was reduced. This was due to the fact that the study mainly included patients who fulfilled one or more criteria according to which extended treatment with SOF + RBV for 24 weeks may be considered, according to the SPC of SOF. Since this treatment option was not available in the ASTRAL-2 study, estimation of effects of the comparator therapy can be potentially wrong. This is mainly relevant for the SVR 12, particularly because the absolute difference between SOF/VEL and SOF + RBV for the outcome “SVR 12” was small (see following Table 16). Overall, at most hints can therefore be derived from the ASTRAL-2 study.

2.5.2.3 Results

Table 16 and Table 17 summarize the results on the comparison of SOF/VEL with SOF + RBV in patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis. Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations.

Table 16: Results (mortality, morbidity, side effects) – RCT, direct comparison: patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study Outcome category Outcome	SOF/VEL (12W)		SOF + RBV (12W)		SOF/VEL (12W) vs. SOF + RBV (12W)
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
ASTRAL-2					
Mortality					
All-cause mortality	134	2 (1.5)	132	0 (0)	4.93 [0.24; 101.64]; 0.302
Morbidity					
SVR 12[a]	134	133 (99.3)	132	124 (93.9)	1.06 [1.01; 1.11]; 0.018
SVR24[a, b]	134	ND	132	ND	–
Side effects					
AEs (supplementary information)	134	92 (68.7)	132	101 (76.5)	–
SAEs	134	2 (1.5)	132	2 (1.5)	0.99 [0.14; 6.89]; 0.988
Discontinuation due to AEs	134	1 (0.7)	132	0 (0)	2.96 [0.12; 71.90]; 0.506
Fatigue	134	20 (14.9)	132	47 (35.6)	0.42 [0.26; 0.67]; < 0.001
Psychiatric disorders	134	19 (14.2)	132	38 (28.8)	0.49 [0.30; 0.81]; 0.004[c]
Skin and subcutaneous tissue disorders	134	10 (7.5)	132	21 (15.9)	0.47 [0.23; 0.96]; 0.033[c]

a: Sufficiently valid surrogate for the patient-relevant outcome “hepatocellular carcinoma”.
b: Data on the SVR 24 are not available for the present benefit assessment.
c: Effect estimate; CI and p-value (CSZ test [16]): Institute’s calculation.

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; SVR 24: sustained virologic response 24 weeks after the end of treatment; VEL: velpatasvir; vs.: versus; W: weeks

Table 17: Results (health-related quality of life) – RCT, direct comparison: patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study Outcome category Outcome	SOF/VEL (12W)			SOF + RBV (12W)			SOF/VEL (12W) vs. SOF + RBV (12W)
	N[a]	Baseline values mean (SD)	Change at FU 12 mean[b] (SD)	N[a]	Baseline values mean (SD)	Change at FU 12 mean[b] (SD)	MD [95% CI]; p-value
ASTRAL-2							
Health-related quality of life							
SF-36 PCS[c]	97	49.6 (9.5)	1.8 (7.5)	101	48.7 (10.8)	3.6 (7.3)	−1.80 [−3.87; 0.27]; 0.088
Physical functioning	97	80.6 (23.3)	1.9 (19.4)	101	75.6 (27.6)	6.4 (18.0)	NC
Physical role functioning	97	77.7 (27.3)	3.3 (21.9)	101	77.2 (28.9)	8.8 (20.0)	NC
Bodily pain	97	66.7 (24.7)	7.7 (22.4)	101	67.4 (28.9)	7.6 (20.3)	NC
General health perception	97	69.4 (20.4)	1.2 (17.2)	101	71.3 (20.1)	5.5 (16.7)	NC
SF-36 MCS[c]	97	51.1 (9.9)	0.2 (8.7)	101	52.6 (9.5)	0.7 (8.0)	–0.50 [–2.83; 1.83]; 0.674
Vitality	97	60.4 (21.0)	2.8 (21.6)	101	61.3 (23.0)	8.6 (19.3)	NC
Social functioning	97	80.9 (23.3)	4.0 (20.8)	101	83.2 (24.7)	3.5 (20.5)	NC
Emotional role functioning	97	85.7 (22.4)	–1.2 (21.5)	101	87.8 (20.3)	0.3 (16.9)	NC
Mental wellbeing	97	75.4 (18.1)	1.2 (14.6)	101	77.0 (18.6)	2.5 (16.3)	NC

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Analysis without imputation of missing values.
c: Positive effect estimate indicates advantage for the intervention.
CHC: chronic hepatitis C; CI: confidence interval; FU 12: week 12 after the end of treatment; MCS: Mental Component Summary; MD: mean difference; N: number of analysed patients; NC: not calculated; PCS: Physical Component Summary; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form (36) Health Survey; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus; W: weeks

Outcome-specific, at most hints, e.g. of an added benefit, can be derived from the ASTRAL-2 study.

Mortality

All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of SOF/VEL in comparison

with SOF + RBV; an added benefit for the outcome "all-cause mortality" is therefore not proven.

This concurs with the company's assessment.

Morbidity

Sustained virologic response (SVR 12 and SVR 24) as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

A statistically significant difference in favour of SOF/VEL in comparison with SOF + RBV was shown for the outcome "SVR 12". The company presented no data for the outcome "SVR 24".

In addition, there was an indication of an effect modification by the characteristic "sex" for the outcome "SVR 12" (see Section 2.5.2.4). For women, there was no hint of an added benefit of SOF/VEL in comparison with SOF + RBV; an added benefit for the outcome "SVR 12" for women is therefore not proven. For men, there was a hint of an added benefit of SOF/VEL in comparison with SOF + RBV for the outcome "SVR 12".

This deviates from the assessment of the company, which considered the subgroup results not to be relevant and derived an indication of an added benefit of SOF/VEL for the outcome "SVR 12" at the level of the total population.

Health-related quality of life

SF-36

The Physical Component Summary (PCS) and the Mental Component Summary (MCS) of the SF-36 were considered individually. The mean difference of the change from the start of the study until 12 weeks after the end of treatment was considered in each case.

There was no statistically significant difference between the treatment groups for the PCS or for the MCS in the consideration of the mean differences. This resulted in no hint of an added benefit of SOF/VEL in comparison with SOF + RBV; an added benefit for the outcome "SF-36" is therefore not proven.

This concurs with the assessment of the company, which additionally considered a further period of analysis (change from the start of study until the end of the treatment) and also derived no added benefit for this period.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". Greater or lesser harm from SOF/VEL in comparison with SOF + RBV is thus not proven for the outcome.

This concurs with the company's assessment.

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". Greater or lesser harm from SOF/VEL in comparison with SOF + RBV is thus not proven for the outcome.

This concurs with the company's assessment.

Fatigue

A statistically significant difference in favour of SOF/VEL in comparison with SOF + RBV was shown for the outcome "fatigue". Due to the open-label study design, the risk of bias for the outcome was high (see Section 2.5.2.2). This resulted in a hint of lesser harm from SOF/VEL in comparison with SOF + RBV for the outcome "fatigue".

This deviates from the assessment of the company, which considered the outcome not to have a high risk of bias and, instead of a hint, derived an indication of lesser harm from SOF/VEL in comparison with SOF + RBV.

Psychiatric disorders

A statistically significant difference in favour of SOF/VEL in comparison with SOF + RBV was shown for the outcome "psychiatric disorders". Due to the open-label study design, the risk of bias for the outcome was high (see Section 2.5.2.2). This resulted in a hint of lesser harm from SOF/VEL in comparison with SOF + RBV for the outcome "psychiatric disorders".

The company did not consider the outcome "psychiatric disorders" in its assessment.

Skin and subcutaneous tissue disorders

A statistically significant difference in favour of SOF/VEL in comparison with SOF + RBV was shown for the outcome "skin and subcutaneous tissue disorders". The extent of the effect for this outcome from the category "non-serious/non-severe side effects" was no more than marginal, however. Greater or lesser harm from SOF/VEL in comparison with SOF + RBV is thus not proven for the outcome.

The company did not consider the outcome "skin and subcutaneous tissue disorders" in its assessment.

2.5.2.4 Subgroups and other effect modifiers

The following effect modifiers were considered in the present benefit assessment:

- age (< 65 years/≥ 65 years)
- sex (female/male)
- ethnicity (white/other)
- cirrhosis (compensated cirrhosis/no cirrhosis/no data)
- IL28B genotype (CC/non-CC [CT or TT])
- HCV RNA viral load at the start of the study (< 800 000 IU/mL/≥ 800 000 IU/mL)
- pretreatment (treatment-naive/pretreated)

Only for treatment-experienced patients additionally:

- response to prior therapy (no response/relapse)

Only the results are presented, in which there was at least an indication of an interaction between treatment effect and subgroup characteristic. The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The company chose potentially relevant effect modifiers with the same method. However, it considered the CIs of the subgroups to assess the relevance of the effect modification for the conclusion. The company excluded an effect modification relevant for the conclusion as soon as the CIs of the subgroups investigated for a characteristic were overlapping. This method was not followed for the present benefit assessment.

Table 18: Subgroups (morbidity and side effects) – RCT, direct comparison: patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study Outcome category Outcome Characteristic Subgroup	SOF/VEL (12W) N	SOF/VEL (12W) Patients with event n (%)	SOF + RBV (12W) N	SOF + RBV (12W) Patients with event n (%)	SOF/VEL (12W) vs. SOF + RBV (12W) RR [95% CI]	p-value
ASTRAL-2						
Morbidity						
SVR 12						
Sex						
Women	48	48 (100)	60	59 (98.3)	1.01 [0.97; 1.07]	0.558
Men	86	85 (98.8)	72	65 (90.3)	1.09 [1.01; 1.19]	0.025
					Interaction:	0.053[a]
Side effects						
Fatigue						
Age						
< 65 years	106	17 (16.0)	110	32 (29.1)	0.55 [0.33; 0.93]	0.026
≥ 65 years	28	3 (10.7)	22	15 (68.2)	0.16 [0.05; 0.48]	0.001
					Interaction:	0.043[a]
Pretreatment						
Treatment-naive	115	14 (12.2)	112	38 (33.9)	0.36 [0.21; 0.62]	< 0.001
Pretreated	19	6 (31.6)	20	9 (45.0)	0.70 [0.31; 1.59]	0.397
					Interaction:	0.179[a]

a: Cochran's Q test.

CHC: chronic hepatitis C; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; VEL: velpatasvir; vs.: versus; W: weeks

Morbidity

Sustained virologic response (SVR 12 and SVR 24) as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

There was an indication of an effect modification by the characteristic "sex" for the outcome "SVR 12". Since there was only an indication of an interaction, the result of the total population (statistically significant difference in favour of SOF/VEL) was considered in the interpretation of the results.

For women, there was no statistically significant difference between the treatment groups. Due to the indication of interaction with the same direction of the effect as in the total population, it was assumed in the interpretation of the result that there was an effect in the subgroup of women nonetheless. Nevertheless, the certainty of results in the subgroup is downgraded compared with the total population in such cases. Due to the reduced certainty of

conclusions for this outcome, at most the derivation of a hint was possible already in the total population (see Section 2.5.2.2). Overall, this resulted in no hint of an added benefit of SOF/VEL in comparison with SOF + RBV for women.

For men (as in the total population), there was a statistically significant difference in favour of SOF/VEL in comparison with SOF + RBV. This resulted in a hint of an added benefit of SOF/VEL in comparison with SOF + RBV for men.

This deviates from the assessment of the company, which considered the subgroup results not to be relevant because the CIs of the effects in the subgroups were overlapping.

The company presented no data for the outcome “SVR 24” for the present benefit assessment.

Side effects

Fatigue

There was proof of an effect modification by the characteristic “age” and an indication of an effect modification by the characteristic “pretreatment” for the outcome “fatigue”.

The subgroup results could not be meaningfully interpreted because no data were available for the investigation of possible dependencies between the subgroup characteristics. Moreover, the direction of the effect of the results for all subgroups concurred with the one of the total population. The added benefit for the outcome “fatigue” was therefore derived for the total population (see Section 2.5.2.3).

Apart from the justification that the subgroup results were not relevant because the CIs of the effects were overlapping, this assessment concurs with that of the company.

2.5.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [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.

2.5.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.5.2 resulted in an indication of an effect modification by the characteristic “sex” for the outcome “hepatocellular carcinoma” (assessed with the surrogate “SVR 12”). For SVR 12, there is a hint of an added benefit for men, whereas no added benefit is proven for women. In addition, there are hints of lesser harm for the outcomes “fatigue” and “psychiatric disorders” for the total population. The extent of the respective added benefit at outcome level was estimated from these results (see Table 19).

As sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma", the SVR 12 was allocated to the outcome category "serious/severe symptoms or late complications". The outcomes "fatigue", "psychiatric disorders" and "skin and subcutaneous tissue disorders" were allocated to the category "non-serious/non-severe side effects" because only individual or no SAEs within these outcomes had occurred in the ASTRAL-2 study (see Table 43 of the full dossier assessment).

Table 19: Extent of added benefit at outcome level: patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Outcome category **Outcome** **Effect modifier** **Subgroup**		**SOF/VEL vs. SOF + RBV** **Proportion of events or MD** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality			
All-cause mortality		1.5% vs. 0% RR: 4.93 [0.24; 101.64] p = 0.302	Lesser benefit/added benefit not proven
Morbidity			
Hepatocellular carcinoma, assessed with the surrogate SVR 12		99.3% vs. 93.9% RR: 1.06 [1.01; 1.11] p = 0.018	
Sex	Women	100% vs. 98.3% RR: 1.01 [0.97; 1.07] p = 0.558	Lesser benefit/added benefit not proven
	Men	98.8% vs. 90.3% RR: 1.09 [1.01; 1.19] p = 0.025 probability: "hint"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"
Health-related quality of life			
SF-36 PCS		MD: −1.80 [−3.87; 0.27][c] p = 0.088	Lesser benefit/added benefit not proven
SF-36 MCS		MD: −0.50 [−2.83; 1.83][c] p = 0.674	Lesser benefit/added benefit not proven

(continued)

Table 19: Extent of added benefit at outcome level: patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**SOF/VEL vs. SOF + RBV** **Proportion of events or MD** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	1.5% vs. 1.5% RR: 0.99 [0.14; 6.89] p = 0.988	Greater/lesser harm not proven
Discontinuation due to adverse events	0.7% vs. 0% RR: 2.96 [0.12; 71.90] p = 0.506	Greater/lesser harm not proven
Fatigue	14.9% vs. 35.6% RR: 0.42 [0.26; 0.67] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Psychiatric disorders	14.2% vs. 28.8% RR: 0.49 [0.30; 0.81] p = 0.004 probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ lesser harm, extent: "minor"
Skin and subcutaneous tissue disorders	7.5% vs. 15.9% RR: 0.47 [0.23; 0.96] p = 0.033	Outcome category: non-serious/non-severe side effects $0.9 < CI_u < 1$ Greater/lesser harm not proven[d]

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Positive effect estimate indicates advantage for the intervention.
d: Lesser benefit or added benefit is not proven because the effect size was only marginal.
AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CI_u: upper limit of confidence interval; MCS: Mental Component Summary; MD: mean difference; PCS: Physical Component Summary; RBV: ribavirin; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; VEL: velpatasvir; vs.: versus

2.5.3.2 Overall conclusion on added benefit

Table 20 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 20: Positive and negative effects from the assessment of SOF/VEL in comparison with SOF + RBV (patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis)

Positive effects	**Negative effects**
Morbidity – serious/severe symptoms/late complications ▪ Hepatocellular carcinoma, assessed with the surrogate SVR 12 ▫ Men hint of an added benefit: extent: “non-quantifiable”	-
Non-serious/non-severe side effects ▪ Fatigue hint of lesser harm; extent: “considerable” ▪ Psychiatric disorders hint of lesser harm; extent: “minor”	-
CHC: chronic hepatitis C; RBV: ribavirin; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; VEL: velpatasvir	

Only positive effects for SOF/VEL resulted in the overall assessment. In the outcome category “serious/severe symptoms or late complications”, there was a hint of an added benefit for the outcome “hepatocellular carcinoma” for men. The extent of this added benefit could not be quantified, however, because the outcome was assessed with the surrogate SVR 12. In addition, there were hints of lesser harm for 2 outcomes on non-serious/non-severe side effects for the total population; the extent was “considerable” for fatigue and “minor” for psychiatric disorders.

Since the effect on the surrogate “SVR 12” was only shown for men and, furthermore, was not large enough to determine the overall conclusion, the overall conclusion on the added benefit was mostly determined by the outcome “fatigue”. Overall, there is therefore a hint of considerable added benefit of SOF/VEL versus the ACT for patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis.

The result of the assessment of the added benefit of SOF/VEL in comparison with the ACT is summarized in Table 21.

Table 21: Sofosbuvir/velpatasvir– extent and probability of added benefit for patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis

Subindication	ACT specified by the G-BA	Extent and probability of added benefit
Patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis	Combination of sofosbuvir plus ribavirin	Hint of considerable added benefit[a]
a: The added benefit is not proven for patients with HIV coinfection because the company presented no relevant data for these patients. ACT: appropriate comparator therapy; BSC: best supportive care; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus		

This deviates from the approach of the company, which derived an indication of considerable added benefit of SOF/VEL for patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG.

2.5.4 List of included studies

ASTRAL-2

Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med 2015; 373(27): 2608-2617.

Gilead. A phase 3, multicenter, randomized, open-label study to compare the efficacy and safety of sofosbuvir/GS-5816 fixed dose combination for 12 weeks with sofosbuvir and ribavirin for 12 weeks in subjects with chronic genotype 2 HCV infection: study GS-US-342-1139 (ASTRAL-2); interim clinical study report [unpublished]. 2015.

Gilead. A phase 3, multicenter, randomized, open-label study to compare the efficacy and safety of sofosbuvir/GS-5816 fixed dose combination for 12 weeks with sofosbuvir and ribavirin for 12 weeks in subjects with chronic genotype 2 HCV infection: study GS-US-342-1139 (ASTRAL-2); Zusatzanalysen [unpublished]. 2016.

Gilead Sciences. Comparison of sofosbuvir/velpatasvir fixed dose combination for 12 weeks with sofosbuvir and ribavirin for 12 weeks in adults with chronic genotype 2 HCV infection (ASTRAL-2): full text view [online]. In: ClinicalTrials.gov. 08.04.2016 [Accessed: 29.07.2016]. URL: https://ClinicalTrials.gov/show/NCT02220998.

2.6 Research question 3: CHC genotype 3, patients without cirrhosis or with compensated cirrhosis

2.6.1 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 list on SOF/VEL (status: 17 May 2016)
- bibliographical literature search on SOF/VEL (last search on 19 May 2016)
- search in trial registries for studies on SOF/VEL (last search on 17 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on SOF/VEL (last search on 22 July 2016)

No additional relevant study was identified from the check.

2.6.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 22: Study pool – RCT, direct comparison: patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
GS-US-342-1140 (ASTRAL-3[b])	Yes	Yes	No

a: Study for which the company was sponsor.
b: In the benefit assessment, the study is referred to with this abbreviated form.
CHC: chronic hepatitis C; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus

Section 2.6.4 contains a reference list for the study included.

2.6.1.2 Study characteristics

Table 23 and Table 24 describe the study used for the benefit assessment.

Table 23: Characteristics of the study included – RCT, direct comparison: patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ASTRAL-3	RCT (stratified by cirrhosis status and pretreatment), open-label, parallel	Treatment-naive and treatment-experienced[b] adults with CHC genotype 3 without cirrhosis or with compensated cirrhosis[c]	SOF/VEL (12W) (N = 278) SOF + RBV (24W) (N = 280)	Screening: up to 42 days Treatment: 12 or 24 weeks Follow-up: up to 24 weeks[d] (AEs up to 30 days)	76 study centres in Australia, Canada, France, Germany, Italy, New Zealand, United Kingdom, USA 7/2014–12/2015 Data cut-off for the interim analysis of SVR 12: 11 Sep 2015[e]	Primary: SVR 12 Secondary: SVR 24[f], health-related quality of life, AEs (including deaths)

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on relevant (available) outcomes.
b: Previous treatment failure of interferon-based therapy with or without RBV.
c: About 20% of the study population could be treatment-experienced, and about 20% of the study population could have compensated cirrhosis.
d: In HCV-RNA ≥ LLOQ 12 weeks after the end of treatment or confirmed relapse at a later time point, no further follow-up until 24 weeks was conducted.
e: According to the information provided by the company in the dossier, only an interim CSR from 8 October 2015 and no final CSR was available at the time of submission of the dossier.
f: According to the company, data on the SVR 24 were not yet available at the time of submission of the dossier.

AE: adverse event; CHC: chronic hepatitis C; CSR: clinical study report; HCV: hepatitis C virus; LLOQ: lower limit of quantification; N: number of randomized patients; RBV: ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; SVR 24: sustained virologic response 24 weeks after the end of treatment; VEL: velpatasvir; vs.: versus; W: weeks

Table 24: Characteristics of the intervention – RCT, direct comparison: patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study	Intervention	Comparison
ASTRAL-3	SOF/VEL (400 mg/100 mg) once daily, orally, for 12 weeks	SOF 400 mg once daily, orally + RBV 1000 or 1200 mg/day, distributed to 2 doses, orally, (depending on weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg), for 24 weeks
	Dose adjustment not allowed	Dose adjustment of SOF not allowed; dose adjustments of RBV allowed according to the approval of SOF; in case of discontinuation of the RBV treatment, SOF also had to be discontinued.
	Prior and concomitant medication: Treatment with the following drugs was prohibited for 28 days before the first study visit up to the end of the treatment: ▪ systemic immunosuppressants (including corticosteroids, azathioprine, monoclonal antibodies) ▪ blood cell stimulating drugs ▪ drugs or herbal agents that may influence the pharmacokinetics of the medication (e.g. p-glycoprotein inhibitors, St. John's Wort) ▪ antacids (proton pump inhibitors), anticonvulsants (phenobarbital, phenytoin, carbamazepine, oxcarbazepine), antimycotics (rifabutin, rifapentine, rifampin)	

CHC: chronic hepatitis C; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus

The included ASTRAL-3 study was a completed, randomized, open-label, active-controlled phase 3 study. Adult CHC genotype 3 patients without cirrhosis or with compensated cirrhosis were included in the study. About 20% treatment-experienced patients and 20% patients with compensated cirrhosis were to be included in the study. Patients with HIV or HBV coinfection were excluded from the study.

Stratified by pretreatment and cirrhosis status, the patients were randomly allocated to the treatment arms: 278 patients to the intervention arm, and 280 patients to the comparator arm.

The patients in the intervention arm received SOF/VEL over a period of 12 weeks. The patients in the comparator arm received SOF in combination with RBV for 24 weeks. Dosage and type of use of the drugs administered complied with their respective approval [4,5]. Drugs contraindicated according to the SPCs were not allowed to be used as concomitant medication in the study.

According to the approval of SOF/VEL, addition of RBV may be considered for CHC genotype 3 patients with compensated cirrhosis [5]. The ASTRAL-3 study did not investigate this treatment regimen for the subpopulation of patients with compensated cirrhosis, however.

No data for the comparison of SOF/VEL with addition of RBV with SOF + RBV were available for the present benefit assessment.

The planned duration of follow-up for the outcome "SVR" was based on the detection of HCV RNA 12 weeks after the last administration of the study medication. Patients with HCV RNA below the limit of detection 12 weeks after the end of treatment were followed-up until week 24. Patients with detection of HCV RNA at this time point were not followed-up beyond week 12 after the end of treatment. Patients with demonstrated relapse between week 12 and week 24 after the end of treatment were also not followed-up for SVR. Health-related quality of life was recorded until at most 24 weeks after the end of treatment. AEs were followed-up in the study for 30 days after the end of treatment.

According to the information provided by the company, only an interim CSR from 08/10/2015 was available at the time of submission of the dossier. Results on the time point of follow-up 12 weeks after the end of treatment were included in this interim CSR. The results of the time point of follow-up 24 weeks after the end of treatment were not available for the present benefit assessment, although a data cut-off 12/2015 would have been sufficient for this.

Treatment duration/observation period in the study

The specifications of the respective SPCs resulted in fixed treatment durations for SOF/VEL and SOF + RBV. Accordingly, patients in the intervention arm (SOF/VEL) were treated for 12 weeks, whereas patients in the comparator arm (SOF + RBV) were treated for 24 weeks.

Despite the different treatment periods in the intervention and the comparator arm of the study, a valid interpretation of the results for the outcome "SVR" was possible because durability of the SVR over this period of time was assumed. The results for the SVR 12 were subject to uncertainty, however (see Section 2.6.2.2).

The interpretation of the results for AEs and health-related quality of life was complicated due to the different requirements placed on the treatment duration, however.

AEs were followed-up in the study for 30 days after the end of treatment. This resulted in markedly different observation periods with a difference of 12 weeks. As a result, the effect estimations for AEs (including mortality recorded using AEs) on the basis of naive proportions constituted no adequate analysis. In its dossier, the company provided no time-adjusted analysis required for the effect estimation. With the exception of the outcome "discontinuation due to AEs", the data on AEs overall were not conclusively interpretable due to the differences in observation periods. As a result, no final quantitative conclusion on the harm of SOF/VEL was drawn in the overall consideration of side effects. For the outcome "discontinuation due to AEs", the RRs estimated using naive proportions were interpretable despite the different observation periods because, deviating from the other outcomes, the

event (treatment discontinuation) can only occur during the treatment duration with planned limitation.

Different observation periods with a difference of 12 weeks also resulted for health-related quality of life, which was recorded in the study at most 24 weeks after the end of treatment. For the benefit assessment, the company presented no usable analysis with time periods (treatment plus follow-up) comparable for both treatment groups (see Section 2.14.2.4.3 of the full dossier assessment). The change in health-related quality of life from the start of the study until the end of the treatment is shown as additional information in the present benefit assessment.

Table 25 shows the characteristics of the patients in the study included.

Table 25: Characteristics of the study population – RCT, direct comparison: patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study **Characteristics** **Category**	**SOF/VEL (12W)**	**SOF + RBV (24W)**
ASTRAL-3	N = 277	N = 275
Age [years], mean (SD)	49 (10)	50 (10)
Sex [F/M], %	39/61	37/63
Ethnicity, n (%)		
White	250 (90.3)	239 (86.9)
Black	3 (1.1)	1 (0.4)
Asian	23 (8.3)	29 (10.5)
Other/unknown	1 (0.4)[a]	6 (2.2)[a]
HCV subgenotype, n (%)		
GT 3 (not further specified)	9 (3.2)	18 (6.5)
GT 3a	265 (95.7)	250 (90.9)
GT 3b	2 (0.7)	5 (1.8)
GT 3h	0 (0)	2 (0.7)
GT 3k	1 (0.4)	0 (0)
Cirrhosis, n (%)		
Compensated cirrhosis	80 (28.9)	83 (30.2)
No cirrhosis	197 (71.1)	187 (68.0)
No data	0 (0)	5 (1.8)
IL28B genotype, n (%)		
CC	105 (37.9)	111 (40.4)
Non-CC	172 (62.1)	164 (59.6)
CT	148 (86.0[a])	133 (81.1[a])
TT	24 (14.0[a])	31 (18.9[a])
Baseline HCV RNA viral load [IU/mL], n (%)		
< 800 000	86 (31.0)	81 (29.5)
≥ 800 000	191 (69.0)	194 (70.5)
Pretreatment, n (%)		
Treatment-naive	206 (74.4)	204 (74.2)
Pretreated	71 (25.6)	71 (25.8)
Pretreatment with:		
PEG/RBV	64 (90.1)	65 (91.5)
Other treatments	7 (9.9[a])	6 (8.5[a])
Response to prior therapy		
No response	20 (28.2)	24 (33.8)
Relapse	51 (71.8)	47 (66.2)
Treatment discontinuation, n (%)	2 (0.7)	21 (7.6)
Study discontinuation, n (%)	2 (0.7)	18 (6.5)

(continued)

Table 25: Characteristics of the study population – RCT, direct comparison: patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV (continued)

a: Institute's calculation.
CHC: chronic hepatitis C; F: female; GT: genotype; HCV: hepatitis C virus; IL28B: interleukin 28B; IU: international units; M: male; n: number of patients in the category; N: number of randomized and treated patients; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus; W: weeks

The mean age of the patients in the ASTRAL-3 study was about 50 years. The sex ratio in the intervention and in the comparator arm was about 40% women to 60% men in each case. More than 86% of the patients in both study arms were white.

The predominant subgenotype in the study was genotype 3a, which was present in more than 90% of the patients in the comparator arm and in more than 95% of the patients in the intervention arm. About 30% of the patients in both study arms had compensated cirrhosis. About 60% of the study participants had IL28B genotype non-CC. The HCV RNA viral load at the start of the study was high (≥ 800 000 IU/mL) in approximately 70% of the patients in both study arms. Treatment-experienced patients (about 25%) were evenly distributed to the intervention and comparator arm.

The number of patients who discontinued the study and the treatment was below 1% in the intervention arm, whereas in the comparator arm, about 8% of the patients discontinued treatment and 7% discontinued participation in the study.

Table 26 shows the risk of bias at study level.

Table 26: Risk of bias at study level – RCT, direct comparison: patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

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			
ASTRAL-3	Yes	Yes	No	No	Yes	Yes	Low

CHC: chronic hepatitis C; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus

The risk of bias at study level was rated as low. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.6.2.2 with the outcome-specific risk of bias.

2.6.2 Results on added benefit

2.6.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.14.2.4.3 of the full dossier assessment):

- Mortality
  - All-cause mortality
- Morbidity
  - sustained virologic response (SVR 12 and SVR 24) as sufficiently valid surrogate for the patient-relevant outcome “hepatocellular carcinoma”
- Health-related quality of life
  - SF-36
- Side effects
  - SAEs
  - Discontinuation due to adverse events
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.14.2.4.3 of the full dossier assessment).

The company used a total of 4 instruments to measure health-related quality of life. Besides the generic questionnaire SF-36 mentioned above, these were the questionnaire CLDQ-HCV, the instrument FACIT-F and the questionnaire WPAI: hepatitis C. These instruments were only partly included in the benefit assessment. The validity of the instrument CLDQ-HCV was not conclusively clear from the information presented by the company. The validity of the instrument FACIT-F for CHC patients was not proven by the company. The WPAI: hepatitis C is not regarded as instrument for measuring health-related quality of life. A detailed comment can be found in Section 2.14.2.4.3 of the full dossier assessment. The company presented no usable analysis with time periods (treatment plus follow-up) comparable for both treatment groups for the SF-36 (see Section 2.14.2.4.3 of the full dossier assessment). The change in health-related quality of life from the start of the study until the end of the treatment is shown only as additional information in the present benefit assessment.

In addition, the company used the outcome "severe AEs" (grade ≥ 3) in its assessment. Deviating from the company, this outcome was regarded as not relevant (see Section 2.14.2.4.3 of the full dossier assessment).

Deviating from the company, no further specific AEs were included in the present benefit assessment because no comprehensive identification of the relevant specific AEs of SOF/VEL versus SOF + RBV was possible due to the different observation periods for intervention and ACT. The company, in contrast, included the outcomes "dry skin" and "anaemia" (each as PT) based on the common events in its assessment (see Section 2.14.2.4.3 of the full dossier assessment).

Table 27 shows for which outcomes data were available in the study included.

Table 27: Matrix of outcomes – RCT, direct comparison: patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study	Outcomes					
	All-cause mortality	Sustained virologic response (SVR 12 and SVR 24)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Specific AEs
ASTRAL-3	–[a]	Yes[b]	–[a]	–[a]	Yes	–[a]

a: Due to the different observation periods in the intervention and comparator arm, data are not meaningfully interpretable. The company provided no adequate analyses in the dossier.
b: Data on the SVR 24 are not available for the present benefit assessment.
AE: adverse event; CHC: chronic hepatitis C; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; SVR 24: sustained virologic response 24 weeks after the end of treatment; VEL: velpatasvir; vs.: versus

2.6.2.2 Risk of bias

Table 28 shows the risk of bias for the relevant outcomes.

Table 28: Risk of bias at study and outcome level – RCT, direct comparison: patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study	Study level	Outcomes					
		All-cause mortality	Sustained virologic response (SVR 12 and SVR 24)	Health-related quality of life (SF-36)	SAEs	Discontinuation due to AEs	Specific AEs
ASTRAL-3	L	–[a]	H[b]	–[a]	–[a]	H[c]	–[a]

a: Due to the different observation periods in the intervention and comparator arm, data are not meaningfully interpretable. The company provided no adequate analyses in the dossier.
b: Data on the SVR 24 are not available for the present benefit assessment.
c: Open-label study design.

AE: adverse event; CHC: chronic hepatitis C; H: high; L: low; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; SVR 24: sustained virologic response 24 weeks after the end of treatment; VEL: velpatasvir; vs.: versus

The risk of bias of the outcome "hepatocellular carcinoma", which was included using the surrogate "sustained virologic response" (SVR 12), was rated as high because no data on the SVR 24 were available. In addition, it remained unclear why the company presented no concordance analysis for the ASTRAL-3 study as it did for the ASTRAL-2 study (see Section 2.14.2.4.3 of the full dossier assessment). This deviates from the company's assessment, which rated the risk of bias for SVR 12 as low.

Due to the different observation periods in the intervention and comparator arm of the ASTRAL-3 study, the data on AEs (including mortality recorded using AEs) and health-related quality of life were largely not meaningfully interpretable (see Section 2.14.2.4.3). Except for the outcome "discontinuation due to AEs", the results on AEs were therefore not conclusively interpretable in quantitative terms. The company presented no usable data for health-related quality of life on a comparable time period. Hence the risk of bias for the outcomes "all-cause mortality", "SAEs" and "SF-36" was not assessed. A comprehensive choice of further specific AEs was also not possible for this reason so that the risk of bias was not assessed. This deviates from the approach of the company, which regarded the risk of bias of the outcomes mentioned as high.

The risk of bias of the outcome "discontinuation due to AEs" was regarded as high because it is a subjective outcome, which is generally rated as having a high risk of bias in an open-label study design. This deviates from the company's assessment, which assessed the risk of bias for this outcome as low.

2.6.2.3 Results

Table 29 and Table 30 summarize the results on the comparison of SOF/VEL with SOF + RBV in patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations.

Table 29: Results (mortality, morbidity, side effects) – RCT, direct comparison: patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study Outcome category Outcome	SOF/VEL (12W)		SOF + RBV (24W)		SOF/VEL (12W) vs. SOF + RBV (24W)
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
ASTRAL-3					
Mortality					
All-cause mortality	277	0 (0)	275	3 (1.1)	NC
Morbidity					
SVR 12[a]	277	264 (95.3)	275	221 (80.4)	1.19 [1.11; 1.26]; < 0.001[b]
SVR24[a, c]	277	ND	275	ND	–
Side effects					
AEs (supplementary information)	277	245 (88.4)	275	260 (94.5)	–
SAEs	277	6 (2.2)	275	15 (5.5)	NC
Discontinuation due to AEs	277	0 (0)	275	9 (3.3)	0.05 [0.00; 0.89]; 0.042

a: Sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma".
b: Patients who discontinued treatment for other reasons than virologic failure were counted as non-responders by the company. A sensitivity analysis conducted by the Institute, in which all 20 patients in the control group who did not discontinue due to virologic failure were rated as responders (worst case analysis) still provided a significant result: RR [95% CI] = 1.09 [1.03; 1.15] p = 0.001 (unconditional exact test, CSZ method according to [16]).
c: Data on the SVR 24 are not available for the present benefit assessment.

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculated; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; SVR 24: sustained virologic response 24 weeks after the end of treatment; VEL: velpatasvir; vs.: versus; W: weeks

Table 30: Results (health-related quality of life) – RCT, direct comparison: patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study Outcome category Outcome	SOF/VEL (12W)			SOF + RBV (24W)			SOF/VEL (12W) vs. SOF + RBV (24W)
	N[a]	Baseline values mean (SD)	Change at end of treatment mean (SD)	N[a]	Baseline values mean (SD)	Change at end of treatment mean (SD)	MD [95% CI]; p-value
ASTRAL-3							
Supplementary information: health-related quality of life (under treatment)[b]							
SF-36 PCS[c]	220	51.2 (9.3)	1.3 (6.0)	215	50.2 (8.9)	0.1 (7.4)	1.20 [–0.07; 2.47]; 0.063
Physical functioning	220	82.8 (22.4)	1.9 (15.0)	215	81.5 (22.9)	-2.2 (19.9)	NC
Physical role functioning	220	76.6 (28.2)	2.7 (19.7)	215	75.6 (26.3)	-4.9 (25.2)	NC
Bodily pain	220	73.6 (26.4)	3.2 (20.6)	215	72.2 (25.7)	1.1 (23.4)	NC
General health perception	220	64.8 (21.2)	6.6 (16.4)	215	61.3 (21.0)	3.2 (18.0)	NC
SF-36 MCS[c]	220	47.1 (10.8)	1.6 (8.4)	215	47.5 (10.6)	-1.3 (10.8)	2.90 [1.08; 4.72]; 0.002 Hedges' g: 0.30 [0.11; 0.49]
Vitality	220	54.7 (23.4)	5.2 (19.8)	215	55.1 (22.1)	-0.8 (22.2)	NC
Social functioning	220	76.6 (25.2)	2.4 (23.2)	215	77.6 (24.1)	-3.5 (25.5)	NC
Emotional role functioning	220	79.6 (25.0)	2.2 (18.7)	215	79.5 (25.1)	-3.2 (26.6)	NC
Mental wellbeing	220	70.0 (20.1)	3.3 (16.0)	215	69.8 (19.1)	-2.2 (18.8)	NC

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: SOF/VEL: Change from the start of the study until the end of treatment (week 12); SOF + RBV: change from the start of the study until the end of treatment (week 24).
c: Positive effect estimate indicates advantage for the intervention.

CHC: chronic hepatitis C; CI: confidence interval; MCS: Mental Component Summary; MD: mean difference; N: number of analysed patients; NC: not calculated; PCS: Physical Component Summary; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form (36) Health Survey; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus; W: weeks

At most hints, e.g. of an added benefit, can be derived from the ASTRAL-3 study for all outcomes.

Mortality

All-cause mortality

Few patients died in the study, 3 patients in the comparator arm and no patient in the intervention arm.

Overall, there was no hint of an added benefit of SOF/VEL in comparison with SOF + RBV; an added benefit for the outcome "all-cause mortality" is therefore not proven.

This concurs with the company's assessment.

Morbidity

Sustained virologic response (SVR 12 and SVR 24) as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

The company's analysis showed a statistically significant difference in favour of SOF/VEL in comparison with SOF + RBV for the outcome "SVR 12". Patients who discontinued treatment prematurely for other reasons than virologic failure were counted as non-responders in this analysis. The proportion of these patients differed notably between the groups (intervention arm 0.4%, comparator arm 7.3%). As a result of this approach, the responder rate in the comparator arm can be substantially underestimated. The Institute therefore conducted its own sensitivity analysis (worst case analysis) to check the robustness of the results of the company's analysis. In this analysis, all patients in the comparator arm who discontinued treatment for other reasons than virologic failure were counted as responders. The result of this analysis also showed a statistically significant difference in favour of SOF/VEL versus SOF + RBV and supported the result of the primary analysis.

The company presented no data for the outcome "SVR 24".

Overall, there was a hint of an added benefit of SOF/VEL in comparison with SOF + RBV for the outcome "SVR 12".

This deviates from the company's assessment, which derived proof of an added benefit of SOF/VEL.

Health-related quality of life

SF-36

The company presented no usable analysis with time periods (treatment plus follow-up) comparable for both treatment groups for the SF-36 (see Section 2.14.2.4.3 of the full dossier assessment).

Side effects

Serious adverse events

In the intervention arm, at least one SAE was observed in 2.2% of the patients, whereas in the comparator arm, at least one SAE was observed in 5.5% of the patients.

As described in Section 2.6.2.2, the available data allowed no quantitative conclusion for this outcome.

This assessment concurred with that of the company, but the company conducted a quantitative assessment.

Discontinuation due to adverse events

A statistically significant difference in favour of SOF/VEL in comparison with SOF + RBV was shown for the outcome "discontinuation due to AEs". Due to the open-label study design, the risk of bias for the outcome was high (see Section 2.6.2.2). This resulted in a hint of lesser harm from SOF/VEL in comparison with SOF + RBV.

This deviates from the assessment of the company, which considered the outcome not to have a high risk of bias and, instead of a hint, derived an indication of lesser harm from SOF/VEL in comparison with SOF + RBV.

Specific adverse events

Due to the available data, no comprehensive choice of specific AEs was possible.

This assessment deviates from that of the company, which derived a hint of an added benefit of SOF/VEL for each of the specific AEs "dry skin" and "anaemia".

2.6.2.4 Subgroups and other effect modifiers

The following effect modifiers were considered in the present benefit assessment:

- age (< 65 years/≥ 65 years)
- sex (female/male)
- ethnicity (white/other)
- cirrhosis (compensated cirrhosis/no cirrhosis/no data)
- IL28B genotype (CC/non-CC [CT or TT])
- HCV RNA viral load at the start of the study (< 800 000 IU/mL/≥ 800 000 IU/mL)
- pretreatment (treatment-naive/pretreated)

Only for treatment-experienced patients additionally:

- response to prior therapy (no response/relapse)

Only the results are presented, in which there was at least an indication of an interaction between treatment effect and subgroup characteristic. The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The company chose potentially relevant effect modifiers with the same method. However, it considered the CIs of the subgroups to assess the relevance of the effect modification for the conclusion. The company excluded an effect modification relevant for the conclusion as soon as the CIs of the subgroups investigated for a characteristic were overlapping. This method was not followed for the present benefit assessment.

Table 31: Subgroups (morbidity) – RCT, direct comparison: patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Study Outcome category Outcome Characteristic Subgroup	SOF/VEL (12W)		SOF + RBV (24W)		SOF/VEL (12W) vs. SOF + RBV (24W)	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
ASTRAL-3						
Morbidity						
SVR 12						
Sex						
Women	107	105 (98.1)	101	89 (88.1)	1.11 [1.03; 1.20]	0.006
Men	170	159 (93.5)	174	132 (75.9)	1.23 [1.12; 1.35]	< 0.001
					Interaction:	0.074[a]
Cirrhosis						
Compensated cirrhosis	80	73 (91.2)	83	55 (66.3)	1.38 [1.16; 1.63]	< 0.001
No cirrhosis	197	191 (97)	187	163 (87.2)	1.11 [1.05; 1.18]	< 0.001
No data	0	0 (0)	5	3 (60.0)	NC	NC
					Interaction:	0.010[a]
Baseline HCV RNA viral load						
< 800 000 IU/mL	86	85 (98.8)	81	72 (88.9)	1.11 [1.03; 1.20]	0.010
≥ 800 000 IU/mL	191	179 (93.7)	194	149 (76.8)	1.22 [1.12; 1.33]	< 0.001
					Interaction:	0.093[a]
Pretreatment						
Treatment-naive	206	200 (97.1)	204	176 (86.3)	1.13 [1.06; 1.19]	< 0.001
Pretreated	71	64 (90.1)	71	45 (63.4)	1.42 [1.17; 1.72]	< 0.001
					Interaction:	0.012[a]
Ethnicity						
White	250	238 (95.2)	239	187 (78.2)	1.22 [1.13; 1.31]	< 0.001
Other	27	26 (96.3)[c]	35	33 (94.3)[c]	1.02 [0.91; 1.14][c]	0.755[b]
					Interaction:	0.005[c]

a: Cochran's Q test.
b: Institute's calculation, unconditional exact test (CSZ method according to [16]).
c: Institute's calculation.
CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; HCV: hepatitis C virus; n: number of patients with event; N: number of analysed patients; RBV: ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; VEL: velpatasvir; vs.: versus; W: weeks

Morbidity

Sustained virologic response (SVR 12 and SVR 24) as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

For the outcome "SVR 12", there was proof of an effect modification for the characteristics "cirrhosis", "pretreatment" and "ethnicity", and indications of an effect modification by the characteristics "sex" and "HCV RNA viral load at the start of the study".

The subgroup results could not be meaningfully interpreted because no data were available for the investigation of possible dependencies between the subgroup characteristics. In addition, the results for all subgroups, except for a subgroup by ethnicity, concurred with the results of the total population regarding direction of the effect and statistical significance. The only subgroup without statistically significant difference between the treatment groups comprised non-white patients, which do not correspond to the decisive patient population in the German health care context. The proportion of this patient group from the total population of the study was below 15% (see Table 25). The added benefit was therefore derived for the total population (see Section 2.6.2.3).

Apart from the justification that the subgroup results were not relevant because the CIs of the effects were overlapping, this assessment concurs with that of the company.

The company presented no data for the outcome "SVR 24" for the present benefit assessment.

2.6.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [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.

2.6.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.6.2 resulted in a hint of added benefit for the outcome "hepatocellular carcinoma" (assessed with the surrogate "SVR 12"). In addition, there was a hint of a lesser harm for the outcome "discontinuation due to AEs". The extent of the respective added benefit at outcome level was estimated from these results (see Table 32).

As sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma", the SVR 12 was allocated to the outcome category "serious/severe symptoms or late complications". The outcome "discontinuation due to AEs" was allocated to the category "non-serious/non-severe side effects" because there were no signs that the discontinuations were mostly caused by serious events.

Table 32: Extent of added benefit at outcome level: patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis, SOF/VEL vs. SOF + RBV

Outcome category **Outcome** **Effect modifier** **Subgroup**	**SOF/VEL vs. SOF + RBV** **Proportion of events or MD** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 1.1%	Lesser benefit/added benefit not proven
Morbidity		
Hepatocellular carcinoma, assessed with the surrogate SVR 12	95.3% vs. 80.4% RR: 1.19 [1.11; 1.26] $p < 0.001$ probability: "hint"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"
Health-related quality of life		
	No usable data available	
Side effects		
Serious adverse events	2.2% vs. 5.5%	Greater/lesser harm not proven
Discontinuation due to adverse events	0% vs. 3.3% RR: 0.05 [0.00; 0.89] $p = 0.042$ probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ lesser harm, extent: "minor"
Specific adverse events	Comprehensive choice and quantitative assessment not possible	Greater/lesser harm not proven

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CI_u: upper limit of confidence interval; MCS: Mental Component Summary; MD: mean difference; PCS: Physical Component Summary; RBV: ribavirin; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; VEL: velpatasvir; vs.: versus

2.6.3.2 Overall conclusion on added benefit

Table 33 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 33: Positive and negative effects from the assessment of SOF/VEL in comparison with SOF + RBV (patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis)

Positive effects	**Negative effects**
Morbidity – serious/severe symptoms/late complications ▪ hepatocellular carcinoma, assessed with the surrogate SVR 12 hint of added benefit; extent: non-quantifiable	-
Non-serious/non-severe side effects ▪ discontinuation due to AEs: hint of lesser harm; extent "minor"	-
AE: adverse event; CHC: chronic hepatitis C; RBV: ribavirin; SOF: sofosbuvir; SVR 12: sustained virologic response 12 weeks after the end of treatment; VEL: velpatasvir	

Only positive effects for SOF/VEL resulted in the overall assessment. In the outcome category "serious/severe symptoms or late complications", there was a hint of an added benefit for the outcome "hepatocellular carcinoma". The extent of this added benefit could not be quantified, however, because the outcome was assessed with the surrogate SVR 12.

Regarding harm from SOF/VEL in comparison with SOF + RBV, a quantitative conclusion was only possible for the outcome "discontinuation due to AEs". For this outcome, there was a hint of lesser harm with the extent "minor" in the category "non-serious/non-severe side effects". The available data allowed no quantitative conclusions for further outcomes in the category "side effects". A weakening of the positive effects of SOF/VEL for this reason did not seem justified, however.

In summary, there is a hint of a non-quantifiable added benefit of SOF/VEL versus the ACT for patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis.

The result of the assessment of the added benefit of SOF/VEL in comparison with the ACT is summarized in Table 34.

Table 34: Sofosbuvir/velpatasvir– extent and probability of added benefit for patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis

Subindication	**ACT specified by the G-BA**	**Extent and probability of added benefit**
Patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis	Combination of sofosbuvir plus ribavirin	Hint of a non-quantifiable added benefit[a]
a: The added benefit is not proven for patients with HIV coinfection because the company presented no relevant data for these patients. ACT: appropriate comparator therapy; BSC: best supportive care; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus		

This deviates from the approach of the company, which derived proof of considerable added benefit of SOF/VEL for patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG.

2.6.4 List of included studies

ASTRAL-3

Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med 2015; 373(27): 2608-2617.

Gilead. A phase 3, multicenter, randomized, open-label study to compare the efficacy and safety of sofosbuvir/GS-5816 fixed dose combination for 12 weeks with sofosbuvir and ribavirin for 24 weeks in subjects with chronic genotype 3 HCV infection: study GS-US-342-1140 (ASTRAL-3); interim clinical study report [unpublished]. 2015.

Gilead. A phase 3, multicenter, randomized, open-label study to compare the efficacy and safety of sofosbuvir/GS-5816 fixed dose combination for 12 weeks with sofosbuvir and ribavirin for 24 weeks in subjects with chronic genotype 3 HCV infection: study GS-US-342-1140 (ASTRAL-3); Zusatzanalysen [unpublished]. 2016.

Gilead Sciences. A phase 3, multicenter, randomized, open-label study to compare the efficacy and safety of sofosbuvir/GS-5816 fixed dose combination for 12 weeks with sofosbuvir and ribavirin for 24 weeks in subjects with chronic genotype 3 hcv infection [online]. In: EU Clinical Trials Register. [Accessed: 29.07.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001682-27.

Gilead Sciences. Comparison of sofosbuvir/velpatasvir fixed dose combination for 12 weeks with sofosbuvir and ribavirin for 24 weeks in adults with chronic genotype 3 HCV infection (ASTRAL-3): full text view [online]. In: ClinicalTrials.gov. 08.12.2015 [Accessed: 29.07.2016]. URL: https://ClinicalTrials.gov/show/NCT02201953.

2.7 Research question 4.1: CHC genotype 4, patients without cirrhosis

2.7.1 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 SOF/VEL (status: 17 May 2016)
- bibliographical literature search on SOF/VEL (last search on 19 May 2016)
- search in trial registries for studies on SOF/VEL (last search on 17 May 2016)
- study list on the ACT (status: 17 May 2016)
- bibliographical literature search on ACTs (last search on 19 May 2016)
- search in trial registries for studies on ACTs (last search on 18 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on SOF/VEL (last search on 22 July 2016)

In its information retrieval, the company identified no studies of direct comparison of SOF/VEL versus the ACT for this research question. The Institute's check of completeness also identified no RCTs of direct comparison of SOF/VEL for patients with CHC genotype 4 without cirrhosis.

Since the company identified no studies of direct comparison for this research question and there were no common comparators for an adjusted indirect comparison, it searched for further investigations for an unadjusted historical comparison. The company initially searched for studies with the comparator therapy LDV/SOF. Since, according to the company, this search identified no relevant studies with LDV/SOF, the company conducted a search for the alternative comparator therapy OBV/PTV/R + RBV.

Table 35 shows the studies included by the company in its unadjusted historical comparison.

Table 35: Study pool of the company – further investigations: patients with CHC genotype 4 without cirrhosis, SOF/VEL vs. OBV/PTV/R + RBV

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Studies with SOF/VEL			
GS-US-342-1138 (ASTRAL-1[b])	Yes	Yes	No
GS-US-342-0102	Yes	Yes	No
Studies with the ACT OBV/PTV/R + RBV			
PEARL-I substudy 1	No	No	Yes

a: Study for which the company was sponsor.
b: In the benefit assessment, the study is referred to with this abbreviated form.
CHC: chronic hepatitis C; OBV/PTV/R: ombitasvir/paritaprevir/ritonavir; RBV: ribavirin; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus

The company identified 2 RCTs on SOF/VEL: ASTRAL-1 [6] and GS-US-342-0102 [7]. The company identified the RCT PEARL-I substudy 1 [18] on the comparator therapy OBV/PTV/R + RBV. For the unadjusted historical comparison, the company included subpopulations of individual arms of these studies, namely patients with genotype 4 without cirrhosis, for SOF/VEL and OBV/PTV/R + RBV.

In the study arms considered by the company, both SOF/VEL and OBV/PTV/R + RBV were administered in compliance with the approval over a period of 12 weeks [5,19].

The company included a total of 96 patients on SOF/VEL and 91 patients on OBV/PTV/R + RBV in its comparison.

The 3 studies included by the company in the unadjusted historical comparison are described in Tables 52 and 53 in Appendix B.3 of the full dossier assessment.

No added benefit of SOF/VEL in comparison with OBV/PTV/R + RBV could be derived from the historical comparison presented by the company. Conclusions on the added benefit based on historical comparisons are only possible in the presence of very large effects (so-called dramatic effects). Such an effect was not achieved for any of the relevant outcomes analysed by the company (mortality, SVR 12, SAEs and discontinuation due to AEs). Instead, no statistically significant differences between the treatment groups were shown for all outcomes.

2.7.2 Results on added benefit

No added benefit of SOF/VEL in comparison with the ACT could be derived on the basis of the unadjusted historical comparison presented by the company. There was no hint of an

added benefit of SOF/VEL in comparison with the ACT; an added benefit is therefore not proven.

2.7.3 Extent and probability of added benefit

No proof of added benefit of SOF/VEL in comparison with the ACT was derived from the available data for CHC genotype 4 patients without cirrhosis. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

This concurs with the company's assessment.

2.8 Research question 4.2: CHC genotype 4, patients with compensated cirrhosis

2.8.1 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 SOF/VEL (status: 17 May 2016)
- bibliographical literature search on SOF/VEL (last search on 19 May 2016)
- search in trial registries for studies on SOF/VEL (last search on 17 May 2016)
- study list on the ACT (status: 17 May 2016)
- bibliographical literature search on the ACT (last search on 19 May 2016)
- search in trial registries for studies on the ACT (last search on 17 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on SOF/VEL (last search on 22 July 2016)

In its information retrieval, the company identified no studies of direct comparison of SOF/VEL versus the ACT for this research question. The Institute's check of completeness also identified no RCTs of direct comparison of SOF/VEL for patients with CHC genotype 4 with compensated cirrhosis.

Since the company identified no studies of direct comparison for this research question and there were no common comparators for an adjusted indirect comparison, it searched for further investigations for an unadjusted historical comparison. The company presented the results of a subpopulation of a study arm of the RCT ASTRAL-1 [6] (n = 27) for the intervention with SOF/VEL. The company identified no relevant RCTs on the comparator therapy LDV/SOF. Overall, the company therefore presented no comparative data.

Nonetheless, it described in Section 4.4 of the dossier that an added benefit for this research question could be shown also without directly or indirectly comparative evidence. According to the company, the non-quantifiable added benefit resulted from the shorter treatment duration of SOF/VEL (12 weeks) in comparison with LDV/SOF (24 weeks), which, on the one hand, offered an advantage for the SVR 12, and, on the other, led to a relevant avoidance of AEs.

The company's assumption that SOF/VEL had an advantage for SVR 12 and led to a relevant avoidance of AEs in comparison with LDV/SOF was not followed without underlying evidence on the comparator therapy. Based on a shorter treatment duration alone (without processing of data on SVR 12 and side effect rates under the comparator therapy LDV/SOF), no added benefit of SOF/VEL can be assumed per se (see also Section 2.14.2.8.2 of the full

dossier assessment). Overall, the added benefit of SOF/VEL in comparison with LDV/SOF is not proven for patients with CHC genotype 4 with compensated cirrhosis.

2.8.2 Results on added benefit

The company provided no suitable data for the assessment of the added benefit of SOF/VEL in comparison with the ACT for patients with CHC genotype 4 with compensated cirrhosis. This resulted in no hint of an added benefit of SOF/VEL in comparison with the ACT; an added benefit is therefore not proven.

2.8.3 Extent and probability of added benefit

Since the company presented no suitable data for the assessment of the added benefit of SOF/VEL for patients with CHC genotype 4 with compensated cirrhosis, an added benefit of SOF/VEL in comparison with the ACT for these patients is not proven.

This deviates from the approach of the company, which derived a hint of a non-quantifiable added benefit for these patients due to the shorter treatment duration of SOF/VEL in comparison with the ACT.

2.9 Research question 5: CHC genotype 5, patients without cirrhosis or with compensated cirrhosis

2.9.1 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 SOF/VEL (status: 17 May 2016)
- bibliographical literature search on SOF/VEL (last search on 19 May 2016)
- search in trial registries for studies on SOF/VEL (last search on 17 May 2016)
- bibliographical literature search on the ACT (last search on 19 May 2016)
- search in trial registries for studies on the ACT (last search on 18 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on SOF/VEL (last search on 22 July 2016)

In its information retrieval, the company identified no studies of direct comparison of SOF/VEL versus the ACT for this research question. The Institute's check of completeness also identified no RCTs of direct comparison of SOF/VEL for patients with CHC genotype 5 without cirrhosis or with compensated cirrhosis.

Since the company identified no studies of direct comparison for this research question and there were no common comparators for an adjusted indirect comparison, it searched for further investigations for an unadjusted historical comparison. The company presented the results of a subpopulation of a study arm of the RCT ASTRAL-1 [6] (n = 35) for the intervention with SOF/VEL. The company identified one potentially relevant RCT (Berg et al. [20]) on the comparator therapy peginterferon alfa plus ribavirin (PEG + RBV). Due to the low number of patients in the relevant subpopulation of the study (n = 2), the company appropriately did not calculate effect estimates. Overall, the company therefore presented no comparative data for research question 5.

In Section 4.4.2 of the dossier, the company nonetheless cited evidence from meta-analyses on SVR rates after treatment with PEG + RBV in patients with CHC genotype 5 as examples [21,22]. The meta-analyses included also non-randomized studies. The company derived a dramatic effect for the SVR for SOF/VEL in comparison with PEG + RBV from the comparison of these data with the results of the ASTRAL-1 study. Furthermore, the company saw a major added benefit for SOF/VEL versus the ACT due to the shorter treatment duration (12 weeks versus 48 weeks).

The company's rationale was not accepted. The data from the literature on PEG + RBV cited by the company were not systematically searched and assessed. The completeness of the

comparator data is therefore unclear (see Section 2.14.2.8.2 of the full dossier assessment). Furthermore, the patients with genotype 5 were not randomly enrolled in the ASTRAL-1 study. Hence the relevant subpopulation of the ASTRAL-1 study did not concur with the company's own inclusion criteria for further investigations. Consequently, the further investigations presented by the company were unsuitable for this research question for the benefit assessment. Overall, the added benefit for patients with genotype 5 without cirrhosis or with compensated cirrhosis is not proven.

2.9.2 Results on added benefit

The company provided no suitable data for the assessment of the added benefit of SOF/VEL in comparison with the ACT for patients with CHC genotype 5 without cirrhosis or with compensated cirrhosis. This resulted in no hint of an added benefit of SOF/VEL in comparison with the ACT; an added benefit is therefore not proven.

2.9.3 Extent and probability of added benefit

Since the company presented no suitable data for the assessment of the added benefit of SOF/VEL for patients with CHC genotype 5 without cirrhosis or with compensated cirrhosis, an added benefit of SOF/VEL in comparison with the ACT for these patients is not proven.

This deviates from the approach of the company, which derived a hint of a major added benefit for these patients due to the dramatic effect regarding the SVR and the shorter treatment duration of SOF/VEL in comparison with the ACT.

2.10 Research question 6: CHC genotype 6, patients without cirrhosis or with compensated cirrhosis

2.10.1 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 SOF/VEL (status: 17 May 2016)
- bibliographical literature search on SOF/VEL (last search on 19 May 2016)
- search in trial registries for studies on SOF/VEL (last search on 17 May 2016)
- bibliographical literature search on the ACT (last search on 19 May 2016)
- search in trial registries for studies on the ACT (last search on 18 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on SOF/VEL (last search on 22 July 2016)

In its information retrieval, the company identified no studies of direct comparison of SOF/VEL versus the ACT for this research question. The Institute's check of completeness also identified no RCTs of direct comparison of SOF/VEL for patients with CHC genotype 6 without cirrhosis or with compensated cirrhosis.

Since the company identified no studies of direct comparison for this research question and there were no common comparators for an adjusted indirect comparison, it searched for further investigations for an unadjusted historical comparison. The company presented the results of a subpopulation of a study arm of each of the RCTs ASTRAL-1 [6] (n = 41) and GS-US-342-0102 [7] (n = 5) for the intervention with SOF/VEL. The company identified no relevant RCTs on the comparator therapy PEG + RBV. Overall, it therefore presented no comparative data.

In Section 4.4.2 of the dossier, the company nonetheless cited evidence from a meta-analysis on SVR rates after treatment with PEG + RBV in patients with CHC genotype 6 as examples [23]. The meta-analysis included also non-randomized studies. The company derived a dramatic effect for the SVR for SOF/VEL in comparison with PEG + RBV from the comparison of these data with the results of the studies ASTRAL-1 and GS-US-342-0102. Furthermore, the company saw a major added benefit for SOF/VEL versus the ACT due to the shorter treatment duration (12 weeks versus 48 weeks).

The company's rationale was not accepted. The data from the literature on PEG + RBV cited by the company were not systematically searched and assessed. The completeness of the comparator data is therefore unclear (see Section 2.14.2.8.2 of the full dossier assessment). Consequently, the further investigations presented by the company were unsuitable for this

research question for the benefit assessment. Overall, the added benefit for patients with genotype 6 without cirrhosis or with compensated cirrhosis is not proven.

Irrespective of this, it should be noted that SVR rates of up to 93% are described in the literature cited by the company. Irrespective of the missing systematic assessment of the literature, these data give reason to question the dramatic effect of SOF/VEL regarding the SVR postulated by the company.

2.10.2 Results on added benefit

The company provided no suitable data for the assessment of the added benefit of SOF/VEL in comparison with the ACT for patients with CHC genotype 6 without cirrhosis or with compensated cirrhosis. This resulted in no hint of an added benefit of SOF/VEL in comparison with the ACT; an added benefit is therefore not proven.

2.10.3 Extent and probability of added benefit

Since the company presented no suitable data for the assessment of the added benefit of SOF/VEL for patients with CHC genotype 6 without cirrhosis or with compensated cirrhosis, an added benefit of SOF/VEL in comparison with the ACT for these patients is not proven.

This deviates from the approach of the company, which derived a hint of a major added benefit for these patients due to the dramatic effect regarding the SVR and the shorter treatment duration of SOF/VEL in comparison with the ACT.

2.11 Research question 7: CHC genotype 1, patients with decompensated cirrhosis

2.11.1 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 SOF/VEL (status: 17 May 2016)
- bibliographical literature search on SOF/VEL (last search on 19 May 2016)
- search in trial registries for studies on SOF/VEL (last search on 17 May 2016)
- study list on the ACT (status: 17 May 2016)
- bibliographical literature search on the ACT (last search on 19 May 2016)
- search in trial registries for studies on the ACT (last search on 17 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on SOF/VEL (last search on 22 July 2016)

In its information retrieval, the company identified no studies of direct comparison of SOF/VEL versus the ACT for this research question. The Institute's check of completeness also identified no RCTs of direct comparison of SOF/VEL for patients with CHC genotype 1 with decompensated cirrhosis.

Since the company identified no studies of direct comparison for this research question and there were no common comparators for an adjusted indirect comparison, it searched for further investigations for an unadjusted historical comparison.

Table 36 shows the studies included by the company in its unadjusted historical comparison.

Table 36: Study pool of the company – further investigations: patients with CHC genotype 1 with decompensated cirrhosis, SOF/VEL + RBV vs. LDV/SOF + RBV

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Studies with SOF/VEL + RBV			
GS-US-342-1137 (ASTRAL-4[b])	Yes	Yes	No
Studies with the ACT LDV/SOF + RBV			
GS-US-337-0123 (SOLAR-1[b]), cohort A	No	Yes	No
GS-US-337-0124 (SOLAR-2[b]), cohort A	No	Yes	No

a: Study for which the company was sponsor.
b: In the benefit assessment, the study is referred to with this abbreviated form.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; LDV: ledipasvir; RBV: ribavirin; SOF: sofosbuvir; VEL: velpatasvir; vs.: versus

The company identified the RCT ASTRAL-4 on SOF/VEL [24]. On the comparator therapy LDV/SOF + RBV, the company identified the RCTs SOLAR-1 [25] and SOLAR-2 [26]. For the unadjusted historical comparison, the company included subpopulations of individual arms of these studies for SOF/VEL and LDV/SOF + RBV. The subpopulation of the included studies analysed by the company were patients with CHC genotype 1 and decompensated cirrhosis of Child-Pugh-Turcotte (CPT) class B without a history of liver transplantation. The limitations regarding the CPT classification and the transplantation status resulted from the patient population included in the ASTRAL-4 study. Correspondingly, the company only included patient groups from the studies on the comparator therapy that were comparable with the population in the ASTRAL-4 study.

In the study arms considered by the company, SOF/VEL with addition of RBV was administered in compliance with the approval over a period of 12 weeks [5]. As comparator therapy, the patients included by the company received LDV/SOF + RBV also in compliance with the approval over a period of 12 weeks [3].

The company included a total of 68 patients on SOF/VEL and 53 patients on LDV/SOF + RBV in its comparison.

The 3 studies included by the company in the unadjusted historical comparison are described in Tables 54 and 55 in Appendix B.4 of the full dossier assessment.

No added benefit of SOF/VEL in comparison with LDV/SOF + RBV could be derived from the historical comparison presented by the company. Conclusions on the added benefit based on unadjusted historical comparisons are only possible in the presence of very large effects (so-called dramatic effects). Finally, the effect estimated on the basis of the available data has

to be so large that it can be excluded that it is solely caused by systematic bias. Such an effect was not achieved for any of the relevant outcomes analysed by the company (mortality, SVR 12, SAEs and discontinuation due to AEs). In addition, there were no statistically significant differences between the treatment groups for all outcomes except discontinuation due to AEs. For the outcome "discontinuation due to AEs", the company determined the following effect form the historical comparison: RR [95% CI] (p-value) 7.68 [1.00; 58.80] (0.0498).

2.11.2 Results on added benefit

No added benefit of SOF/VEL in comparison with the ACT could be derived on the basis of the unadjusted historical comparison presented by the company. There was no hint of an added benefit of SOF/VEL in comparison with the ACT; an added benefit is therefore not proven.

2.11.3 Extent and probability of added benefit

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

This concurs with the company's assessment.

2.12 Research question 8: CHC genotype 2 to 6, patients with decompensated cirrhosis

2.12.1 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 list on SOF/VEL (status: 17 May 2016)
- bibliographical literature search on SOF/VEL (last search on 19 May 2016)
- search in trial registries for studies on SOF/VEL (last search on 17 May 2016)

To check the completeness of the study pool:

- search in trial registries for studies on SOF/VEL (last search on 22 July 2016)

In its information retrieval, the company identified no studies of direct comparison of SOF/VEL versus the ACT for this research question. The Institute's check of completeness also identified no RCTs of direct comparison of SOF/VEL for patients with CHC genotype 2 to 6 with decompensated cirrhosis.

For research question 8, the company presented the results of a subpopulation of a study arm of the RCT ASTRAL-4 [24] (n = 19) for SOF/VEL. The company conducted no information retrieval on studies with best supportive care (BSC) and therefore presented no comparative data. Nonetheless, it postulated a major added benefit for SOF/VEL in comparison with "no antiviral treatment" in Section 4.4.2 of the dossier. From the company's point of view, this resulted from an SVR of 90% and a favourable side effect profile of the drug combination SOF/VEL.

The company's rationale was not accepted. For patients in the present research question, who already have decompensated cirrhosis, the SVR is no longer to be regarded as adequate outcome (see Section 2.14.2.9.4 of the full dossier assessment). Hence the company's approach to derive an added benefit due to a dramatic effect regarding the SVR was not followed. In addition, the assessment of harm from SOF/VEL is not possible without systematic assessment of the evidence on the comparator therapy "no antiviral therapy". In the ASTRAL-4 study, 3 (16%) patients with genotype 2 to 4 with decompensated cirrhosis had SAEs; 4 (21%) patients discontinued treatment due to side effects. The ASTRAL-4 study did not investigate the patients with genotype 5 and 6. Overall, the added benefit for patients with genotype 2 to 6 and decompensated cirrhosis is not proven (see Section 2.14.2.8.2 of the full dossier assessment).

2.12.2 Results on added benefit

The company provided no suitable data for the assessment of the added benefit of SOF/VEL in comparison with the ACT for patients with CHC genotype 2 to 6 with decompensated

cirrhosis. This resulted in no hint of an added benefit of SOF/VEL in comparison with the ACT; an added benefit is therefore not proven.

2.12.3 Extent and probability of added benefit

Since the company presented no suitable data for the assessment of the added benefit of SOF/VEL for patients with CHC genotype 2 to 6 with decompensated cirrhosis, an added benefit of SOF/VEL in comparison with the ACT for these patients is not proven.

This deviates from the approach of the company, which postulated a dramatic effect regarding the SVR for these patients and derived a hint of a major added benefit from it.

2.13 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of SOF/VEL in comparison with the ACT is summarized in Table 37.

Table 37: Sofosbuvir/velpatasvir – extent and probability of added benefit

Subindication	Appropriate comparator therapy[a]	Extent and probability of added benefit
Patients with CHC genotype 1 without cirrhosis	Ledipasvir/sofosbuvir or ombitasvir/paritaprevir/ritonavir plus dasabuvir (if applicable, plus ribavirin)	Added benefit not proven
Patients with CHC genotype 1 with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
Patients with CHC genotype 2 without cirrhosis or with compensated cirrhosis	Sofosbuvir plus ribavirin	Hint of considerable added benefit[b]
Patients with CHC genotype 3 without cirrhosis or with compensated cirrhosis	Sofosbuvir plus ribavirin	Hint of non-quantifiable added benefit[b]
Patients with CHC genotype 4 without cirrhosis	Ledipasvir/sofosbuvir or ombitasvir/paritaprevir/ritonavir plus ribavirin	Added benefit not proven
Patients with CHC genotype 4 with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
Patients with CHC genotype 5 without cirrhosis or with compensated cirrhosis	Peginterferon alfa and ribavirin	Added benefit not proven
Patients with CHC genotype 6 without cirrhosis or with compensated cirrhosis	Peginterferon alfa and ribavirin	Added benefit not proven
Patients with CHC genotype 1 with decompensated cirrhosis	Ledipasvir/sofosbuvir plus ribavirin	Added benefit not proven
Patients with CHC genotype 2–6 with decompensated cirrhosis	Best supportive care	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: The added benefit is not proven for patients with HIV coinfection because the company presented no relevant data for these patients.
ACT: appropriate comparator therapy; BSC: best supportive care; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus

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

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