IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-35

Sofosbuvir/velpatasvir/ voxilaprevir (chronic hepatitis C) –

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

Extract

[1] Translation of Sections 2.1 to 2.9 of the dossier assessment *Sofosbuvir/Velpatasvir/Voxilaprevir (chronische Hepatitis C) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 November 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

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

Commissioning agency:

Federal Joint Committee

Commission awarded on:

3 August 2017

Internal Commission No.:

A17-35

Address of publisher:

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Keywords: sofosbuvir, velpatasvir, voxilaprevir, hepatitis C – chronic, benefit assessment, NCT02607800, NCT02639338, NCT02639247

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CHC	chronic hepatitis C
CI	confidence interval
CSR	clinical study report
DAA	direct acting antiviral agent
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HBV	hepatitis B virus
HCV RNA	hepatitis C virus ribonucleic acid
HIV	human immunodeficiency virus
IL28B	interleukin-28B
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IU	international units
LDV	ledipasvir
MCS	Mental Component Summary
NS	non-structural protein
PCS	Physical Component Summary
PT	Preferred Term
RBV	ribavirin
RCT	randomized controlled trial
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
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
VOX	voxilaprevir

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/voxilaprevir (SOF/VEL/VOX). 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 3 August 2017.

Research question

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

Under consideration of the Summary of Product Characteristics (SPC) of SOF/VEL/VOX, 7 research questions initially resulted from the ACTs specified by the G-BA for different patient groups. Research questions 1 to 6 were additionally subdivided for patients without cirrhosis (research questions 1.1, 2.1, 3.1, 4.1, 5.1 and 6.1) and for patients with compensated cirrhosis (research questions 1.2, 2.2, 3.2, 4.2, 5.2 and 6.2).

Hence there were 13 research questions for the benefit assessment; their subindications and ACTs are presented in the following Table 2.

Table 2: Research questions of the benefit assessment of SOF/VEL/VOX

Research question		**Subindication**	**ACT**[a]
Benefit assess-ment	**Module 4 A**		
1	A1	DAA-naive adult patients with CHC genotype 1	
1.1	A1.1	Without cirrhosis	**Ledipasvir/sofosbuvir** or ombitasvir/paritaprevir/ritonavir plus dasabuvir (if applicable, plus ribavirin)
1.2	A1.2	With compensated cirrhosis	Ledipasvir/sofosbuvir
2	A2	DAA-naive adult patients with CHC genotype 2	
2.1	A2.1	Without cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**
2.2	A2.2	With compensated cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**
3	A3	DAA-naive adult patients with CHC genotype 3	
3.1	A3.1	Without cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**
3.2	A3.2	With compensated cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**
4	A4	DAA-naive adult patients with CHC genotype 4	
4.1	A4.1	Without cirrhosis	**Ledipasvir/sofosbuvir** or ombitasvir/paritaprevir/ritonavir plus ribavirin
4.2	A4.2	With compensated cirrhosis	Ledipasvir/sofosbuvir
5	A5	DAA-naive adult patients with CHC genotype 5	
5.1	A5.1	Without cirrhosis	Ledipasvir/sofosbuvir
5.2	A5.2	With compensated cirrhosis	Ledipasvir/sofosbuvir
6	A6	DAA-naive adult patients with CHC genotype 6	
6.1	A6.1	Without cirrhosis	Ledipasvir/sofosbuvir
6.2	A6.2	With compensated cirrhosis	Ledipasvir/sofosbuvir
7	B1.1–B6.2, C[b]	DAA-experienced adult patients with CHC	Individual treatment specified by the physician under consideration of the pretreatment(s), the genotype and the respective approval. Possible cross-resistances must be considered in the choice of the antiviral therapy, particularly in the case of protease inhibitors.[c]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The company subdivided research question 7 according to pretreatment with an NS5A inhibitor and, for NS5A-naive patients, according to genotype and partly cirrhosis status. In the resulting research questions of the company (B1.1–B6.2, C), the company's ACT deviates from the ACT specified by the G-BA for research question 7.
c: In accordance with the G-BA's specification it is assumed that interferon-based regimens are not an option for the patients.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; DAA: direct acting antiviral agent; G-BA: Federal Joint Committee; NS: non-structural protein; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir

For research questions 1.1 to 6.2 (adult patients not pretreated with direct acting antiviral agents [DAAs] – hereinafter referred to as "DAA-naive adults"), the company concurred with the ACTs specified by the G-BA.

For research question 7 (adult patients with DAA pretreatment – hereinafter referred to as "DAA-experienced adults"), the company deviated from the ACT specified by the G-BA.

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[a]
1	DAA-naive adult patients with CHC genotype 1			
1.1	Without cirrhosis	SOF/VEL/VOX for 8 weeks	LDV/SOF for 8 or 12 weeks	Further investigations: consideration of the SOF/VEL/ VOX arm of an RCT (POLARIS-2) without presentation of evidence on the comparator therapy
1.2	With compensated cirrhosis	SOF/VEL/VOX for 12 weeks	LDV/SOF for 12 or 24 weeks	–
2	DAA-naive adult patients with CHC genotype 2			
2.1	Without cirrhosis	SOF/VEL/VOX for 8 weeks	SOF/VEL for 12 weeks	RCT (POLARIS-2: subpopulation)
2.2	With compensated cirrhosis	SOF/VEL/VOX for 12 weeks	SOF/VEL for 12 weeks	–
3	DAA-naive adult patients with CHC genotype 3			
3.1	Without cirrhosis	SOF/VEL/VOX for 8 weeks	SOF/VEL for 12 weeks	RCT (POLARIS-2: subpopulation)
3.2	With compensated cirrhosis	SOF/VEL/VOX for 8 or 12 weeks	SOF/VEL for 12 weeks	RCT (POLARIS-3: total population)
4	DAA-naive adult patients with CHC genotype 4			
4.1	Without cirrhosis	SOF/VEL/VOX for 8 weeks	LDV/SOF for 12 weeks	Further investigations: consideration of the SOF/VEL/ VOX arm of an RCT (POLARIS-2) without presentation of evidence on the comparator therapy
4.2	With compensated cirrhosis	SOF/VEL/VOX for 12 weeks	LDV/SOF for 12 or 24 weeks	–
5	DAA-naive adult patients with CHC genotype 5			
5.1	Without cirrhosis	SOF/VEL/VOX for 8 weeks	LDV/SOF for 12 weeks	Further investigations: consideration of the SOF/VEL/ VOX arm of an RCT (POLARIS-2) without presentation of evidence on the comparator therapy
5.2	With compensated cirrhosis	SOF/VEL/VOX for 12 weeks	LDV/SOF for 12 or 24 weeks	–
6	DAA-naive adult patients with CHC genotype 6			
6.1	Without cirrhosis	SOF/VEL/VOX for 8 weeks	LDV/SOF for 12 weeks	Further investigations: consideration of the SOF/VEL/ VOX arm of an RCT (POLARIS-2) without presentation of evidence on the comparator therapy
6.2	With compensated cirrhosis	SOF/VEL/VOX for 12 weeks	LDV/SOF for 12 or 24 weeks	–

(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[a]
7	DAA-experienced adult patients with CHC	SOF/VEL/VOX for 12 weeks	NS5A-naive	
			▪ Genotypes 1, 4, 5 and 6 ▫ without cirrhosis: LDV/SOF for 12 weeks ▫ with compensated cirrhosis: LDV/SOF for 24 weeks	▪ Genotypes 1 and 4 ▫ further investigations: consideration of the SOF/ VEL/VOX arms of 2 RCTs (for genotype 1: POLARIS-4 and TRILOGY-3; for genotype 4: POLARIS-4) without presentation of evidence on the comparator therapy ▪ Genotypes 5 and 6 ▫ –
			▪ Genotypes 2 and 3: SOF/VEL for 12 weeks	RCT (POLARIS-4: one subpopulation for each genotype)
			NS5A-experienced: SOF/VEL + RBV for 24 weeks	Further investigations: consideration of the SOF/ VEL/VOX arms of 2 RCTs (POLARIS-1 and TRILOGY-3) without presentation of evidence on the comparator therapy

a: The company presented no data on patients with HBV or HIV coinfection for all research questions.
CHC: chronic hepatitis C; DAA: direct acting antiviral agent; HBV: hepatitis B virus; HIV: human immunodeficiency virus; LDV: ledipasvir; NS: non-structural protein; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir

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 questions 2.1 (DAA-naive adults with CHC genotype 2 and without cirrhosis) and 3.1 (DAA-naive adults with CHC genotype 3 and without cirrhosis): study for direct comparisons

Study pool and study characteristics

The POLARIS-2 study was included in the benefit assessment for research questions 2.1 and 3.1. This was a completed, randomized, multicentre, open-label phase 3 study with an active control. DAA-naive adults with CHC of all genotypes were included in the study.

Randomization of the patients with genotype 1, 2, 3 or 4 was stratified by pretreatment, genotype, and cirrhosis status (except for genotype 3, for which only patients without cirrhosis were to be enrolled). The patients were randomly allocated in a ratio of 1:1. Patients with genotype 5 or with undetermined genotype, including genotype 6, were only enrolled in the SOF/VEL/VOX arm. Coinfections with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) were exclusion criteria of the study.

The interventions SOF/VEL/VOX and SOF/VEL were used in compliance with the SPCs in the subpopulations relevant for research questions 2.1 and 3.1 (DAA-naive adults with genotype 2 or genotype 3, each without cirrhosis). The relevant subpopulations for research question 2.1 comprised 49 patients in the SOF/VEL/VOX arm and 40 patients in the SOF/VEL arm; those for research question 3.1 comprised 91 patients in the SOF/VEL/VOX arm and 90 patients in the SOF/VEL arm.

The planned maximum duration of follow-up observation for 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. Follow-up observation of adverse events (AEs) and deaths in the study was planned until 30 days after the end of treatment.

Risk of bias

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

The risk of bias was rated as low for the outcome “hepatocellular carcinoma”, which was included using the surrogate parameter “sustained virologic response” (SVR 12 weeks after the end of treatment 12 [SVR 12] and SVR 24 weeks after the end of treatment [SVR 24]). The risk of bias was rated as high for all other outcomes included.

Results

For research questions 2.1 and 3.1, no statistically significant and relevant difference between the treatment groups was shown for any of the outcomes included (all-cause mortality, hepatocellular carcinoma, health-related quality of life, serious AEs [SAEs], and discontinuation due to AEs). Hence, there was no hint of an added benefit or of greater or lesser harm of SOF/VEL/VOX in comparison with SOF/VEL for any of these outcomes; an added benefit or greater or lesser harm is therefore not proven.

There is an uncertainty regarding specific AEs, however. The company only provided analyses for a choice of Preferred Terms (PTs) for the subpopulations. It did not provide analyses for further PTs or by System Organ Classes (SOCs).

Research question 3.2 (DAA-naive adults with CHC genotype 3 and with compensated cirrhosis): study for direct comparisons

Study pool and study characteristics

The POLARIS-3 study was included in the benefit assessment for research question 3.2. This was a completed, randomized, multicentre, open-label phase 3 study with an active control. DAA-naive adults with CHC genotype 3 and with compensated cirrhosis were included in the study. Coinfections with HIV or HBV were exclusion criteria of the study.

Randomization was stratified by pretreatment and the patients were allocated in a ratio of 1:1. 110 patients were included in each of the treatment arms SOF/VEL/VOX and SOF/VEL.

The interventions were used for 8 weeks (SOF/VEL/VOX) and for 12 weeks (SOF/VEL), which was in compliance with the SPCs. The SPC of SOF/VEL/VOX also allows a treatment duration of 12 weeks for patients with genotype 3 and with compensated cirrhosis. No data were available for a comparison of SOF/VEL/VOX over 12 weeks.

The planned maximum duration of follow-up observation for 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. Follow-up observation of AEs and deaths in the study was planned until 30 days after the end of treatment.

Risk of bias

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

The risk of bias was rated as low for the outcome “hepatocellular carcinoma”, which was included using the surrogate parameter “sustained virologic response” (SVR 12 and SVR 24). The risk of bias was rated as high for all other outcomes included.

Results

All-cause mortality, morbidity, health-related quality of life

No statistically significant difference between the treatment groups was shown for the outcomes included “all-cause mortality”, “hepatocellular carcinoma” and “health-related quality of life” (recorded with the Short Form (36) Health Survey [SF-36]). This resulted in no hint of an added benefit of SOF/VEL/VOX in comparison with SOF/VEL for these outcomes; an added benefit is therefore not proven.

Side effects

- Serious adverse events and discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence for these outcomes, there was no hint of greater or lesser harm from SOF/VEL/VOX in comparison with SOF/VEL; greater or lesser harm is therefore not proven.

- Nausea and diarrhoea

A statistically significant difference to the disadvantage of SOF/VEL/VOX in comparison with SOF/VEL was shown for each of the outcomes "nausea" and "diarrhoea". This resulted in a hint of greater harm from SOF/VEL/VOX in comparison with SOF/VEL for these outcomes.

Research question 7 (DAA-experienced adults with CHC)

After submission of the dossier, the G-BA defined individual treatment specified by the physician as ACT for research question 7. No RCTs for direct comparisons with the ACT were identified.

For DAA-experienced adults, the company's comparator therapies deviated from the ACT specified by the G-BA (see Table 3). For DAA-experienced adults who have not been pretreated with a non-structural protein inhibitor (NS5A) (hereinafter referred to as "NS5A-naive adults") and who have CHC genotype 2 or 3, the company included one RCT for a direct comparison. This was the POLARIS-4 study, in which SOF/VEL/VOX was compared with the company's comparator therapy (SOF/VEL). For further subpopulations, the company included data only for SOF/VEL/VOX – without comparator data – or no data overall.

DAA-experienced, NS5A-naive adults with CHC

For DAA-experienced, NS5A-naive adults, the company included a subpopulation of the randomized controlled trial (RCT) POLARIS-4, in which SOF/VEL/VOX was compared with SOF/VEL, for genotype 2 and for genotype 3. The POLARIS-4 study was unsuitable to derive conclusions on the added benefit of SOF/VEL/VOX in comparison with the ACT because the ACT was not implemented in the POLARIS-4 study. In the study, treatment in the comparator arm was not chosen for the individual patient from one of several available treatment options under consideration of the pretreatment(s), the genotype and possible cross-resistances. Instead, all patients in the comparator arm were treated with SOF/VEL.

For example, the study showed a statistically significant difference in favour of SOF/VEL/ VOX versus SOF/VEL for SVR 12 in patients with genotype 3 and compensated cirrhosis, from which the company derived an indication of a minor added benefit. However, the SPC of SOF/VEL notes that the addition of ribavirin (RBV) should be considered for this patient group. This option was not available in the POLARIS-4 study. It is possible that patients of this patient group would have received SOF/VEL + RBV or another treatment option if

individual treatment specified by the physician had been implemented. This might have had a better result than treatment with SOF/VEL and might not have resulted in significant difference between the treatment arms for SVR 12.

For NS5A-naive adults with genotype 1 and 4, the company only presented data for SOF/VEL/VOX (i.e. without data for the ACT); for genotype 5 and 6, the company presented neither data for SOF/VEL/VOX nor for the ACT.

For the reasons stated above, no suitable data or no data were available for DAA-experienced, NS5A-naive adults to assess the added benefit of SOF/VEL/VOX in comparison with the ACT. This resulted in no hint of an added benefit of SOF/VEL/VOX in comparison with the ACT. An added benefit is therefore not proven.

DAA-experienced, NS5A-experienced adults with CHC

For DAA-experienced adults pretreated with an NS5A inhibitor (hereinafter referred to as "NS5A-experienced adults"), the company only presented data for SOF/VEL/VOX (i.e. not for the ACT).

Although the company presented no comparator data, it claimed a hint of a non-quantifiable added benefit for NS5A-experienced adults. This approach was not followed.

Hence the company presented no suitable data for the assessment of the added benefit of SOF/VEL/VOX in comparison with the ACT for NS5A-experienced adults. This resulted in no hint of an added benefit of SOF/VEL/VOX in comparison with the ACT. An added benefit is therefore not proven.

Research questions 1.1, 1.2, 2.2, 4.1 to 6.2: DAA-naive adults with CHC genotype 1, 4, 5 and 6 (each without cirrhosis or with compensated cirrhosis) and genotype 2 (with compensated cirrhosis): no suitable data or no data

No RCTs for direct comparisons versus the ACT were identified for research questions 1.1, 1.2, 2.2, and 4.1 to 6.2.

For research questions 1.1, 4.1, 5.1 and 6.1, the company only presented data on SOF/ VEL/VOX; data on the ACT were missing. For research questions 1.2, 2.2, 4.2, 5.2 and 6.2, the company presented no data overall (including data on SOF/VEL/VOX). Hence, no suitable data or no data were available for the assessment of the added benefit of SOF/VEL/VOX in comparison with the ACT for research questions 1.1, 1.2, 2.2, and 4.1 to 6.2. This resulted in no hint of an added benefit of SOF/VEL/VOX in comparison with the ACT. An added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

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

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

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

Table 4: Sofosbuvir/velpatasvir/voxilaprevir – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
DAA-naive adult patients with CHC genotype 1, without cirrhosis	**Ledipasvir/sofosbuvir** or ombitasvir/paritaprevir/ritonavir plus dasabuvir (if applicable, plus ribavirin)	Added benefit not proven
DAA-naive adult patients with CHC genotype 1, with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 2, without cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**	Added benefit not proven
DAA-naive adult patients with CHC genotype 2, with compensated cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**	Added benefit not proven
DAA-naive adult patients with CHC genotype 3, without cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**	Added benefit not proven
DAA-naive adult patients with CHC genotype 3, with compensated cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**	Hint of lesser benefit[b, c]
DAA-naive adult patients with CHC genotype 4, without cirrhosis	**Ledipasvir/sofosbuvir** or ombitasvir/paritaprevir/ritonavir plus ribavirin	Added benefit not proven
DAA-naive adult patients with CHC genotype 4, with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 5, without cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 5, with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 6, without cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 6, with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-experienced adult patients with CHC	Individual treatment specified by the physician under consideration of the pretreatment(s), the genotype and the respective approval. Possible cross-resistances must be considered in the choice of the antiviral therapy, particularly in the case of protease inhibitors.[d]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Patients with HBV or HIV coinfection were not included in the study.
c: In the POLARIS-3 study included, sofosbuvir/velpatasvir/voxilaprevir was used for 8 weeks. Conclusions on the added benefit in 12-week treatment with sofosbuvir/velpatasvir/voxilaprevir, which is also in compliance with the approval, are not possible on the basis of the study.
d: In accordance with the G-BA's specification it is assumed that interferon-based regimens are not an option for the patients.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; DAA: direct acting antiviral agent; G-BA: Federal Joint Committee; HBV: hepatitis B virus; HIV: human immunodeficiency virus

Overall, an added benefit of SOF/VEL/VOX versus the respective ACT is not proven for any of the research questions for the treatment of adult patients with CHC. There is a hint of lesser benefit of SOF/VEL/VOX in comparison with SOF/VEL for DAA-naive adults with CHC genotype 3 and with compensated cirrhosis.

The approach for deriving an overall conclusion on the 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/VOX compared with the ACT in the treatment of adult patients with CHC.

Under consideration of the SPC of SOF/VEL/VOX [3], 7 research questions initially resulted from the ACTs specified by the G-BA for different patient groups.

Adult patients without DAA pretreatment (hereinafter referred to as “DAA-naive adults”), subdivided by genotype (1 to 6), constitute the populations of research questions 1 to 6. Adult patients with DAA pretreatment (hereinafter referred to as “DAA-experienced adults”) constitute the population of research question 7.

The company additionally subdivided research questions 1 to 6 in patients without cirrhosis (research questions 1.1, 2.1, 3.1, 4.1, 5.1 and 6.1) and patients with compensated cirrhosis (research questions 1.2, 2.2, 3.2, 4.2, 5.2 and 6.2). This subdivision was maintained in the present benefit assessment for DAA-naive adults due to the differences in treatment durations approved for SOF/VEL/VOX and ACTs.

The company divided research question 7 by pretreatment with an NS5A inhibitor and partly by genotype and cirrhosis status (see Sections 2.10.1 and 2.10.2.1 of the full dossier assessment). This subdivision was not used because the ACT specified by the G-BA (individual treatment specified by the physician) requires no further subdivision of the research question.

Patients with decompensated cirrhosis are not part of the therapeutic indication of SOF/ VEL/VOX [3]. No research question was therefore investigated for these patients. This concurs with the company’s approach.

Hence there were 13 research questions for the benefit assessment; their subindications and ACTs are presented in the following Table 5.

Table 5: Research questions of the benefit assessment of SOF/VEL/VOX

Research question		Subindication	ACT[a]
Benefit assessment	**Module 4 A**		
1	A1	DAA-naive adult patients with CHC genotype 1	
1.1	A1.1	Without cirrhosis	**Ledipasvir/sofosbuvir** or ombitasvir/paritaprevir/ritonavir plus dasabuvir (if applicable, plus ribavirin)
1.2	A1.2	With compensated cirrhosis	Ledipasvir/sofosbuvir
2	A2	DAA-naive adult patients with CHC genotype 2	
2.1	A2.1	Without cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**
2.2	A2.2	With compensated cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**
3	A3	DAA-naive adult patients with CHC genotype 3	
3.1	A3.1	Without cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**
3.2	A3.2	With compensated cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**
4	A4	DAA-naive adult patients with CHC genotype 4	
4.1	A4.1	Without cirrhosis	**Ledipasvir/sofosbuvir** or ombitasvir/paritaprevir/ritonavir plus ribavirin
4.2	A4.2	With compensated cirrhosis	Ledipasvir/sofosbuvir
5	A5	DAA-naive adult patients with CHC genotype 5	
5.1	A5.1	Without cirrhosis	Ledipasvir/sofosbuvir
5.2	A5.2	With compensated cirrhosis	Ledipasvir/sofosbuvir
6	A6	DAA-naive adult patients with CHC genotype 6	
6.1	A6.1	Without cirrhosis	Ledipasvir/sofosbuvir
6.2	A6.2	With compensated cirrhosis	Ledipasvir/sofosbuvir
7	B1.1–B6.2, C[b]	DAA-experienced adult patients with CHC	Individual treatment specified by the physician under consideration of the pretreatment(s), the genotype and the respective approval. Possible cross-resistances must be considered in the choice of the antiviral therapy, particularly in the case of protease inhibitors.[c]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

b: The company subdivided research question 7 according to pretreatment with an NS5A inhibitor and, for NS5A-naive patients, according to genotype and partly cirrhosis status. In the resulting research questions of the company (B1.1–B6.2, C), the company's ACT deviates from the ACT specified by the G-BA for research question 7.

c: In accordance with the G-BA's specification it is assumed that interferon-based regimens are not an option for the patients.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; DAA: direct acting antiviral agent; G-BA: Federal Joint Committee; NS: non-structural protein; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir

For DAA-naive adults (research questions 1.1 to 6.2), the company followed the ACTs specified by the G-BA.

For DAA-experienced adults (research question 7), the company deviated from the ACT specified by the G-BA (see Section 2.10.1 of the full dossier assessment).

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. 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 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/VOX (status: 13 June 2017)
- bibliographical literature search on SOF/VEL/VOX (last search on 2 June 2017)
- search in trial registries for studies on SOF/VEL/VOX (last search on 13 June 2017)
- bibliographical literature search on the ACT for research questions 1.1, 1.2, 4.1 and 6.2 and on the company's comparator therapies for research question 7 (last search on 13 June 2017)
- search in trial registries for studies on the ACT for research questions 1.1, 1.2, 4.1 and 6.2 and on the company's comparator therapies for research question 7 (last search on 13 June 2017)

To check the completeness of the study pool:

- search in trial registries for studies on SOF/VEL/VOX (last search on 24 August 2017)

With its information retrieval, the company identified studies for direct comparisons only for research questions 2.1, 3.1, 3.2 and 7 (thereof adult patients without pretreatment with an NS5A inhibitor – hereinafter referred to as "NS5A-naive adults"). The Institute's check also identified no additional relevant study.

Within research question 7, the company additionally searched for RCTs for adjusted indirect comparisons. In addition, the company aimed at comparisons of individual arms from different RCTs for a subpopulation of research question 7 (adult patients with pretreatment with an NS5A inhibitor – hereinafter referred to as "NS5A-experienced adults").

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[a]
1	DAA-naive adult patients with CHC genotype 1			
1.1	Without cirrhosis	SOF/VEL/VOX for 8 weeks	LDV/SOF for 8 or 12 weeks	Further investigations: consideration of the SOF/VEL/VOX arm of an RCT (POLARIS-2) without presentation of evidence on the comparator therapy
1.2	With compensated cirrhosis	SOF/VEL/VOX for 12 weeks	LDV/SOF for 12 or 24 weeks	–
2	DAA-naive adult patients with CHC genotype 2			
2.1	Without cirrhosis	SOF/VEL/VOX for 8 weeks	SOF/VEL for 12 weeks	RCT (POLARIS-2: subpopulation)
2.2	With compensated cirrhosis	SOF/VEL/VOX for 12 weeks	SOF/VEL for 12 weeks	–
3	DAA-naive adult patients with CHC genotype 3			
3.1	Without cirrhosis	SOF/VEL/VOX for 8 weeks	SOF/VEL for 12 weeks	RCT (POLARIS-2: subpopulation)
3.2	With compensated cirrhosis	SOF/VEL/VOX for 8 or 12 weeks	SOF/VEL for 12 weeks	RCT (POLARIS-3: total population)
4	DAA-naive adult patients with CHC genotype 4			
4.1	Without cirrhosis	SOF/VEL/VOX for 8 weeks	LDV/SOF for 12 weeks	Further investigations: consideration of the SOF/VEL/VOX arm of an RCT (POLARIS-2) without presentation of evidence on the comparator therapy
4.2	With compensated cirrhosis	SOF/VEL/VOX for 12 weeks	LDV/SOF for 12 or 24 weeks	–
5	DAA-naive adult patients with CHC genotype 5			
5.1	Without cirrhosis	SOF/VEL/VOX for 8 weeks	LDV/SOF for 12 weeks	Further investigations: consideration of the SOF/VEL/VOX arm of an RCT (POLARIS-2) without presentation of evidence on the comparator therapy
5.2	With compensated cirrhosis	SOF/VEL/VOX for 12 weeks	LDV/SOF for 12 or 24 weeks	–
6	DAA-naive adult patients with CHC genotype 6			
6.1	Without cirrhosis	SOF/VEL/VOX for 8 weeks	LDV/SOF for 12 weeks	Further investigations: consideration of the SOF/VEL/VOX arm of an RCT (POLARIS-2) without presentation of evidence on the comparator therapy
6.2	With compensated cirrhosis	SOF/VEL/VOX for 12 weeks	LDV/SOF for 12 or 24 weeks	–

(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[a]
7	DAA-experienced adult patients with CHC	SOF/VEL/VOX for 12 weeks	NS5A-naive	
			▪ Genotypes 1, 4, 5 and 6 ▫ without cirrhosis: LDV/SOF for 12 weeks ▫ with compensated cirrhosis: LDV/SOF for 24 weeks	▪ Genotypes 1 and 4 ▫ further investigations: consideration of the SOF/VEL/VOX arms of 2 RCTs (for genotype 1: POLARIS-4 and TRILOGY-3; for genotype 4: POLARIS-4) without presentation of evidence on the comparator therapy ▪ Genotypes 5 and 6 ▫ –
			▪ Genotypes 2 and 3: SOF/VEL for 12 weeks	RCT (POLARIS-4: one subpopulation for each genotype)
			NS5A-experienced: SOF/VEL + RBV for 24 weeks	Further investigations: consideration of the SOF/VEL/VOX arms of 2 RCTs (POLARIS-1 and TRILOGY-3) without presentation of evidence on the comparator therapy

a: The company presented no data on patients with HBV or HIV coinfection for all research questions.
CHC: chronic hepatitis C; DAA: direct acting antiviral agent; HBV: hepatitis B virus; HIV: human immunodeficiency virus; LDV: ledipasvir; NS: non-structural protein; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir

The company did not present any results from direct comparisons for research questions 1.1, 1.2, 2.2, and 4.1 to 6.2. It presented results of treatment with SOF/VEL/VOX for some of the research questions, but did not compare them with results on the ACT and overall claimed no added benefit for these research questions. These research questions are described in summary form below (see Section 2.4). For each of the further research questions, the company included an RCT for a direct comparison or claimed an added benefit on the basis of non-comparative data. The benefit assessment of these further research questions is therefore conducted in individual sections (see Sections 2.5, 2.6, 2.7 and 2.8).

2.4 Research questions 1.1, 1.2, 2.2, 4.1 to 6.2: DAA-naive adults with CHC genotype 1, 4, 5 and 6 (each without cirrhosis or with compensated cirrhosis) and genotype 2 (with compensated cirrhosis)

2.4.1 Results on added benefit (research questions 1.1, 1.2, 2.2, 4.1 to 6.2)

As described in Section 2.3, with its information retrieval, the company identified no studies for direct comparisons with SOF/VEL/VOX versus the respective ACT for research questions 1.1, 1.2, 2.2 and 4.1 to 6.2 (DAA-naive adults with CHC genotype 1, 4, 5 and 6 [each without cirrhosis or with compensated cirrhosis] and genotype 2 [with compensated cirrhosis]). The Institute's check also identified no relevant RCT.

For research questions 1.1, 4.1, 5.1 and 6.1, the company described results of the corresponding subpopulation of the SOF/VEL/VOX arm of the RCT GS-US-367-1172 (hereinafter referred to with its abbreviated form "POLARIS-2") [4]. However, the company did not aim at conducting indirect comparisons or comparisons of individual arms from different studies for these research questions. The company presented no evidence on the comparator therapy. Hence there are no data for the assessment of the added benefit of SOF/VEL/VOX in comparison with the ACT for these research questions.

For research questions 1.2, 2.2, 4.2, 5.2 and 6.2, the company presented no data overall (including data on SOF/VEL/VOX); hence no data for the assessment of the added benefit of SOF/VEL/VOX were available for these research questions either.

In summary, this resulted in no hint of an added benefit of SOF/VEL/VOX in comparison with the ACT for research questions 1.1, 1.2, 2.2, and 4.1 to 6.2. An added benefit is therefore not proven.

2.4.2 Probability and extent of added benefit (research questions 1.1, 1.2, 2.2, 4.1 to 6.2)

The company presented no relevant data or no data for the assessment of the added benefit of SOF/VEL/VOX in DAA-naive patients with CHC genotype 1, 2 (with compensated cirrhosis), 4, 5 and 6. An added benefit of SOF/VEL/VOX in comparison with the ACT is therefore not proven for these patients.

This concurs with the assessment of the company, which claimed no added benefit for these patients.

2.4.3 List of included studies (research questions 1.1, 1.2, 2.2, 4.1 to 6.2)

Not applicable as the company presented no relevant data or no data for research questions 1.1, 1.2, 2.2, and 4.1 to 6.2 for the benefit assessment.

2.5 Research question 2.1: DAA-naive adults with CHC genotype 2, without cirrhosis

2.5.1 Studies included (research question 2.1)

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

Table 7: Study pool – RCT, direct comparison: DAA-naive adults with CHC genotype 2, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 2.1)

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-367-1172 (POLARIS-2[b])	Yes	Yes	No

a: Study for which the company was sponsor.
b: In the following tables, the study is referred to with this abbreviated form.
CHC: chronic hepatitis C; DAA: direct acting antiviral agent; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; vs.: versus

The study pool for the benefit assessment of SOF/VEL/VOX in comparison with the ACT for DAA-naive adults with CHC genotype 2 and without cirrhosis consisted of the RCT POLARIS-2. In the study, SOF/VEL/VOX was compared with SOF/VEL in DAA-naive adults with CHC with different genotypes. The subpopulation of patients with CHC genotype 2 and without cirrhosis was considered for research question 2.1. This concurs with the company's approach.

Section 2.5.5 contains a reference list for the study included.

2.5.2 Study characteristics (research question 2.1)

Table 8 and Table 9 describe the study used for the benefit assessment.

Table 8: Characteristics of the study included – RCT, direct comparison: DAA-naive adults with CHC genotype 2, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 2.1)

Study	Study design	Population	Interventions (numbers of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
POLARIS-2	RCT[b], open-label, parallel	Treatment-naive and treatment-experienced[c] adults with CHC, all genotypes, without cirrhosis or with compensated cirrhosis[d]	SOF/VEL/VOX (8 W) (N = 502) SOF/VEL (12 W) (N = 441) Relevant subpopulation thereof[e]: SOF/VEL/VOX (8 W) (n = 49) SOF/VEL (12 W) (n = 40)	Screening: up to 42 days Treatment: 8 or 12 weeks Follow-up observation: up to 24 weeks[f] (AEs up to 30 days)	117 study centres in Australia, Canada, France, Germany, New Zealand, United Kingdom, USA 11/2015–1/2017 Data cut-off for final analysis: 11 Jan 2017[g]	Primary: SVR 12, AEs leading to treatment discontinuation Secondary: all-cause mortality, SVR 24, health-related quality of life, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant (available) outcomes for this benefit assessment.
b: All patients with genotype 1, 2, 3 or 4 were randomly allocated in a ratio of 1:1; stratification was by genotype, cirrhosis status (without cirrhosis/with compensated cirrhosis) and pretreatment (treatment-naive/pretreated with interferon-containing regimen). Patients with genotype 5 or with undetermined genotype, including genotype 6, were only enrolled in the SOF/VEL/VOX arm.
c: Treatment-experienced with an interferon-containing (but not DAA-containing) regimen; prior therapy must have been completed at least 8 weeks before screening and must not have been discontinued due to AEs or virologic failure due to a lack of adherence.
d: It was planned that at least 20% of the patients included had compensated cirrhosis. Only patients without cirrhosis were to be included for genotype 3.
e: Patients with genotype 2, without cirrhosis.
f: No further follow-up observation was to be conducted if HCV-RNA ≥ LLOQ 12 weeks after the end of treatment.
g: Deviating from the information provided in the final CSR (last observation of the last patient on 11 January 2017), the company presented 26 January 2017 as the corresponding data cut-off date in Module 4 A.

AE: adverse event; CHC: chronic hepatitis C; CSR: clinical study report; DAA: direct acting antiviral agent; HCV: hepatitis C virus; LLOQ: lower limit of quantification; n: relevant subpopulation; N: number of randomized patients; 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; VOX: voxilaprevir; vs.: versus; W: weeks

Table 9: Characteristics of the interventions – RCT, direct comparison: DAA-naive adults with CHC genotype 2, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 2.1)

Study	Intervention	Comparison
POLARIS-2	SOF/VEL/VOX (400 mg/100 mg/100 mg) once daily, orally with a meal, for 8 weeks	SOF/VEL (400 mg/100 mg) once daily, orally independent of meals, for 12 weeks
	Dose reduction not allowed	
	Allowed prior and concomitant medication: Prior interferon-based therapy, which was completed at least 8 weeks before screening **Prohibited prior and concomitant medication:** Pretreatment with approved or investigational HCV-specific DAA During screening and at least 28 days before the first study visit until end of treatment: ▪ systemic immunosuppressants (including corticosteroids, azathioprine, monoclonal antibodies) ▪ blood cell stimulating drugs ▪ investigational drugs or agents for any therapeutic indication Within 60 days before the first study visit until end of treatment: ▪ amiodarone Within 21 days before the first study visit until end of treatment: ▪ antibiotics (clarithromycin, erythromycin), antacids (proton pump inhibitors), anticonvulsants (phenobarbital, phenytoin, carbamazepine, oxcarbazepine), antimycotics (rifabutin, rifapentine, rifampin), cardiac drugs (bosentan, digoxin, diltiazem, dronedarone, olmesartan, quinidine, ranolazine, telmisartan, valsartan, verapamil), herbal or natural supplements (St. John's Wort, echinacea, milk thistle, Chinese herb sho-saikoto [or Xiao-Shai-Hu-Tang]), modafinil, sulfasalazine, methotrexate 1 day before the first study visit until end of treatment: ▪ HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin)	

CHC: chronic hepatitis C; DAA: direct acting antiviral agent; HCV: hepatitis C virus; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme-A; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; vs.: versus

The included POLARIS-2 study was a completed, randomized, multicentre, open-label, active-controlled phase 3 study. DAA-naive adults with CHC of all genotypes were included in the study. Patients with genotype 3 were only included if they had no cirrhosis. Patients with other genotypes were included if they had no cirrhosis or compensated cirrhosis. Coinfections with HIV or HBV were exclusion criteria of the study.

Randomization of the patients with genotype 1, 2, 3 or 4 was stratified by pretreatment, genotype, and cirrhosis status (except for genotype 3, for which only patients without cirrhosis were to be enrolled). The patients were randomly allocated in a ratio of 1:1. Patients

with genotype 5 or with undetermined genotype, including genotype 6, were only enrolled in the SOF/VEL/VOX arm.

The interventions SOF/VEL/VOX and SOF/VEL were used in compliance with the SPCs [3,5] in the subpopulation relevant for research question 2.1 (DAA-naive adults with genotype 2 and without cirrhosis). This relevant subpopulation comprised 49 patients in the SOF/VEL/VOX arm and 40 patients in the SOF/VEL arm.

Primary outcomes of the POLARIS-2 study were SVR 12 and AEs leading to treatment discontinuation. Further patient-relevant outcomes on mortality, morbidity, health-related quality of life and AEs were additionally recorded.

The planned duration of follow-up observation for SVR and health-related quality of life was based on the detection of hepatitis C virus ribonucleic acid (HCV RNA) 12 weeks after the end of treatment. Patients with HCV RNA below the limit of detection 12 weeks after the end of treatment were to be followed-up until week 24. In other cases, there was no further follow-up observation for SVR and health-related quality of life from week 12 after the end of treatment. Documentation of AEs was only until 30 days after the end of treatment, however. Hence the observation period for the outcomes of the category of side effects was systematically shortened. Yet in order to draw conclusions over the total study period, it would be necessary to record these outcomes also over the total study period.

Characteristics of the relevant subpopulation

Table 10 shows the characteristics of the patients in the relevant subpopulation of the study included.

Table 10: Characteristics of the relevant subpopulation – RCT, direct comparison: DAA-naive adults with CHC genotype 2, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 2.1)

Study **Characteristics** **Category**	**SOF/VEL/VOX (8 W)**	**SOF/VEL (12 W)**
POLARIS-2	N[a] = 49	N[a] = 40
Age [years], mean (SD)	53 (12)	54 (12)
Sex [F/M], %	47/53	58/43
Ethnicity, n (%)		
Black or African American	6 (12.2)	4 (10.0)
White	40 (81.6)	32 (80.0)
Asian	2 (4.1)	3 (7.5)
Other[b]	1 (2.0)	1 (2.5)
HCV subgenotype, n (%)	ND	ND
IL28B genotype, n (%)		
CC	11 (22.4)	16 (40.0)
Non-CC	38 (77.6)	24 (60.0)
CT	27 (55.1)	19 (47.5)
TT	11 (22.4)	5 (12.5)
HCV RNA viral load at the start of the study [IU/mL], n (%)		
< 800 000	23 (46.9)	12 (30.0)
≥ 800 000	26 (53.1)	28 (70.0)
Pretreatment, n (%)		
Treatment-naive	43 (87.8)	38 (95.0)
Pretreated (no DAA)	6 (12.2)	2 (5.0)
Pretreatment with, n (%[c])		
PEG + RBV	4 (66.7)	2 (100)
Other	2 (33.3)	0 (0)
Number of prior therapies, n (%[c])		
1	6 (100)	1 (50.0)
≥ 2	0 (0)	1 (50.0)
Response to prior therapy, n (%[c])		
No response	2 (33.3)	0 (0)
Relapse	3 (50.0)	2 (100)
Other	1 (16.7)	0 (0)
Treatment discontinuation, n (%)	0 (0)	0 (0)
Study discontinuation, n (%)	0 (0)	0 (0)

(continued)

Table 10: Characteristics of the relevant subpopulation – RCT, direct comparison: DAA-naive adults with CHC genotype 2, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 2.1) (continued)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Contains the categories of American Indians or native Alaskans and native Hawaiians or pacific islanders.
c: Proportion of pretreated patients.
CHC: chronic hepatitis C; DAA: direct acting antiviral agent; F: female; HCV: hepatitis C virus; IL28B: interleukin 28B; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; vs.: versus; W: weeks

The patient characteristics between the arms of the POLARIS-2 study in the relevant subpopulation showed no relevant differences; minor imbalances in some characteristics were probably due to small patient numbers.

The mean age of the patients was about 53 years. The sex ratio was approximately balanced. There was a major imbalance in the distribution of the characteristic "interleukin-28B (IL28B) genotype". About 22% of the patients in the SOF/VEL/VOX arm and about 40% of the patients in the SOF/VEL arm had IL28B CC genotype. There was a minor imbalance also for the characteristic "HCV RNA": It was high in about 53% of the patients in the SOF/VEL/VOX arm and in about 70% of the patients in the SOF/VEL arm (≥ 800 000 international units [IU]/mL). There were about 12% pretreated patients in the SOF/VEL/VOX arm and about 5% pretreated patients in the SOF/VEL arm.

There were neither treatment nor study discontinuations in the relevant subpopulation in both arms.

Risk of bias at study level

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: DAA-naive adults with CHC genotype 2, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 2.1)

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			
POLARIS-2	Yes	Yes	No	No	Yes	Yes	Low

CHC: chronic hepatitis C; DAA: direct acting antiviral agent; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; vs.: versus

The risk of bias at study level was rated as low for the POLARIS-2 study. This corresponds to the company's assessment.

Limitations resulting from the open-label study design are described with the outcome-specific risk of bias in Section 2.10.2.4.2 of the full dossier assessment.

2.5.3 Results on added benefit (research question 2.1)

2.5.3.1 Outcomes included (research question 2.1)

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.10.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - SVR 12 and SVR 24 as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"
- Health-related quality of life
  - Short Form (36) Health Survey (SF-36)
- Side effects
  - serious adverse events (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) and did not consider the SVR 24 (see Section 2.10.2.4.3 of the full dossier assessment).

Table 12 shows for which outcomes data were available for the relevant subpopulation of the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: DAA-naive adults with CHC genotype 2, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 2.1)

Study	Outcomes					
	All-cause mortality	Sustained virologic response (SVR 12 and SVR 24)	Health-related quality of life (SF-36)[a]	SAEs	Discontinuation due to AEs	Specific AEs
POLARIS-2	Yes	Yes	Yes	Yes	Yes	No[b]

a: For the relevant subpopulation, the company presented analyses for week 12 after the end of treatment (see Section 2.10.2.4.3 of the full dossier assessment).
b: For the relevant subpopulation, the company only provided analyses for a choice of PTs. It did not provide analyses for further PTs or by SOCs. Hence, no specific AEs were chosen (see Section 2.10.2.4.3 of the full dossier assessment).

AE: adverse event; CHC: chronic hepatitis C; DAA: direct acting antiviral agent; PT: Preferred Term; 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; VOX: voxilaprevir; vs.: versus

2.5.3.2 Risk of bias (research question 2.1)

Table 13 describes the risk of bias for the relevant outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: DAA-naive adults with CHC genotype 2, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 2.1)

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	Specific AEs
POLARIS-2	L	H[a]	L	H[b]	H[a]	H[c]	–[d]

a: 4-week difference in treatment duration and therefore in observation period between the SOF/VEL/VOX arm and the SOF/VEL arm.
b: In the available analyses for 12 weeks after the end of treatment: lack of blinding in subjective recording of outcomes and 4-week difference in the documentation times between the SOF/VEL/VOX arm and the SOF/VEL arm.
c: Lack of blinding in subjective decision making.
d: For the relevant subpopulation, the company only provided analyses for a choice of PTs. It did not provide analyses for further PTs or by SOCs. Hence, no specific AEs were chosen (see Section 2.10.2.4.3 of the full dossier assessment).

AE: adverse event; CHC: chronic hepatitis C; DAA: direct acting antiviral agent; H: high; L: low; PT: Preferred Term; 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; VOX: voxilaprevir; vs.: versus

The results on the outcomes “all-cause mortality” and “SAEs” are considered to be potentially highly biased because there was a 4-week difference in treatment duration and therefore observation period between the SOF/VEL/VOX arm and the SOF/VEL arm of the POLARIS-2 study. This concurs with the company’s assessment conducted for the total population of the study.

The risk of bias was rated as low for the outcome “hepatocellular carcinoma”, which was included using the surrogate parameter “sustained virologic response” (SVR 12 and SVR 24). For the SVR 12, this concurs with the company’s assessment conducted for the total population of the study; the SVR 24 was not considered by the company.

The results on the SF-36 and on the outcome “discontinuation due to AEs” were considered to be potentially highly biased because their recording was subjective, which, if unblinded, is to be generally considered as potentially highly biased. For the SF-36, this concurs with the company’s assessment conducted for the total population of the study. Besides, the present benefit assessment identified a 4-week difference in documentation times between the

SOF/VEL/VOX arm and the SOF/VEL arm as an additional potentially biasing factor for this instrument, which was not identified by the company. For the outcome “discontinuation due to AEs”, the company reached a deviating assessment, which rated the risk of bias as low for the total population of the study for this outcome.

Detailed reasons for the assessment of the risk of bias can be found in Section 2.10.2.4.2 of the full dossier assessment.

2.5.3.3 Results (research question 2.1)

Table 14 and Table 15 summarize the results on the comparison of SOF/VEL/VOX with SOF/VEL in DAA-naive adults with CHC genotype 2 and without cirrhosis. Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations.

Table 14: Results (mortality, morbidity, side effects) – RCT, direct comparison: DAA-naive adults with CHC genotype 2, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 2.1)

Study Outcome category	SOF/VEL/VOX (8 W)		SOF/VEL (12 W)		SOF/VEL/VOX vs. SOF/VEL
Outcome	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
POLARIS-2					
Mortality					
All-cause mortality	49	0 (0)	40	0 (0)	–
Morbidity					
SVR 12[b]	49	47 (95.9)[c]	40	40 (100)	0.96 [0.89; 1.03]; 0.225
SVR 24[b, d]	49	47 (95.9)[e]	40	40 (100)	0.96 [0.89; 1.03][f]; 0.225
Side effects					
AEs (supplementary information)	49	26 (53.1)	40	24 (60.0)	–
SAEs	49	3 (6.1)	40	2 (5.0)	1.22 [0.21; 6.97]; 0.865
Discontinuation due to AEs	49	0 (0)	40	0 (0)	–
Specific AEs	No usable data[g]				

a: Institute's calculation, unconditional exact test (CSZ method according to [6]).
b: Sufficiently valid surrogate for the patient-relevant outcome "HCC".
c: No information on the number of imputed values is available for the relevant subpopulation (DAA-naive adults with CHC genotype 2, without cirrhosis). It can be inferred from the information provided in the CSR on all DAA-naive adults with CHC genotype 2 (without cirrhosis or with compensated cirrhosis) that at most 1 (2%) value was missing and was imputed as response (based on SVR 4 and SVR 24).
d: Due to the consistency between the results for SVR 12 and SVR 24, the results on SVR 24 are no longer shown in the following tables.
e: No information on the number of imputed values is available for the relevant subpopulation (DAA-naive adults with CHC genotype 2, without cirrhosis). It can be inferred from the information provided in the CSR on all DAA-naive adults with CHC genotype 2 (without cirrhosis and with compensated cirrhosis) that 2 values were imputed as non-responses; these values were non-responses already at week 12 after the end of treatment. Since there were no further non-responses, both non-responses (4%) in the relevant subpopulation had to be the imputed values.
f: Institute's calculation of RR and CI (asymptotic).
g: For the relevant subpopulation, the company only presented analyses for PTs that occur in at least 5% of the patients in the total population in at least one arm. Based on this selection, comprehensive identification of specific AEs is not guaranteed (see Section 2.10.2.4.3 of the full dossier assessment).

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CSR: clinical study report; CSZ: convexity, symmetry, z score; DAA: direct acting antiviral agent; HCC: hepatocellular carcinoma; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOF: sofosbuvir; SVR 4: sustained virologic response 4 weeks after the end of treatment; 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; VOX: voxilaprevir; vs.: versus; W: weeks

Table 15: Results (health-related quality of life) – RCT, direct comparison: DAA-naive adults with CHC genotype 2, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 2.1)

Study **Outcome category**	**SOF/VEL/VOX (8 W)**			**SOF/VEL (12 W)**			**SOF/VEL/VOX vs. SOF/VEL**
Time point **Outcome**	**N[a]**	**Values at start of study mean (SD)**	**Change at FU 12[b] or FU 24 mean (SD)**	**N[a]**	**Values at start of study mean (SD)**	**Change at FU 12[b] or FU 24 mean (SD)**	**MD [95% CI]; p-value**
POLARIS-2							
Health-related quality of life							
12 weeks after end of treatment							
SF-36 PCS[c]	48	47.5 (11.47)	3.3 (6.78)	39	46.7 (10.07)	3.3 (7.28)	0.00 [−2.98; 2.98]; > 0.999
Physical functioning						ND[d]	
Physical role functioning						ND[d]	
Bodily pain						ND[d]	
General health perception						ND[d]	
SF-36 MCS[c]	48	50.4 (10.98)	0.1 (11.19)	39	46.1 (12.06)	4.9 (11.19)	−4.80 [−9.53; −0.07]; 0.047 Hedges' g: −0.43 [−0.85; 0.00]
Vitality						ND[d]	
Social functioning						ND[d]	
Emotional role functioning						ND[d]	
Mental wellbeing						ND[d]	
24 weeks after end of treatment						ND[d]	

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: A positive change indicates improvement.
d: Analyses are available for the total population, but not for the relevant subpopulation.
CHC: chronic hepatitis C; CI: confidence interval; DAA: direct acting antiviral agent; FU 12: 12 weeks after the end of treatment; FU 24: 24 weeks after the end of treatment; MCS: Mental Component Summary; MD: mean difference; N: number of analysed patients; ND: no data; PCS: Physical Component Summary; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form (36) Health Survey; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; vs.: versus; W: weeks

Based on the available data, at most an indication, e.g. of an added benefit, can be determined for the outcome "hepatocellular carcinoma", included using the surrogate outcome "sustained virologic response" (SVR 12 and SVR 24). Due to the high risk of bias, at most hints, e.g. of

an added benefit, can be determined for the outcomes “all-cause mortality”, “health-related quality of life” (recorded with the SF-36), “SAEs” and “discontinuation due to AEs”.

Mortality

All-cause mortality

In both treatment groups, no deaths occurred in the relevant subpopulation of the POLARIS-2 study. This resulted in no hint of an added benefit of SOF/VEL/VOX in comparison with SOF/VEL; an added benefit is therefore not proven.

This concurs with the assessment of the company, which analysed this outcome in the framework of AEs, using the designation “death”.

Morbidity

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

No statistically significant difference between the treatment groups was shown for SVR 12 or SVR 24. The concordance of the results for the relevant subpopulation of the POLARIS-2 study was 100% in patients with recordings both at week 12 and at week 24 after the end of treatment. Due to this data constellation, the SVR 12, for which the company presented subgroup analyses, is used hereinafter for the derivation of the added benefit for research question 2.1.

Overall, this resulted in no hint of an added benefit of SOF/VEL/VOX in comparison with SOF/VEL for SVR 12; an added benefit is therefore not proven.

This corresponds to the company’s assessment.

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 (for reasons, see Section 2.10.2.4.3 of the full dossier assessment). The company presented no analyses for the relevant subpopulation for the documentation time 24 weeks after the end of treatment, which is also relevant, although an analysis was planned for this time point and was available in the clinical study report (CSR) for the total population.

The consideration of the mean differences showed no statistically significant difference between the treatment groups for the PCS. A statistically significant difference to the disadvantage of SOF/VEL/VOX was shown for the MCS. The standardized mean difference in the form of Hedges’ g was considered to check the relevance of the result. The 95% confidence interval (95% CI) was not completely below the irrelevance threshold of −0.2. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an added

benefit or of lesser benefit of SOF/VEL/VOX in comparison with SOF/VEL; an added benefit is therefore not proven.

This concurs with the assessment of the company, which additionally used a further period of analysis (change from the start of the 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". This resulted in no hint of greater or lesser harm from SOF/VEL/VOX in comparison with SOF/VEL; greater or lesser harm is therefore not proven.

This corresponds to the company's assessment.

Discontinuation due to adverse events

In both treatment groups, no discontinuations due to AEs occurred in the relevant subpopulation of the POLARIS-2 study. This resulted in no hint of greater or lesser harm from SOF/VEL/VOX in comparison with SOF/VEL; greater or lesser harm is therefore not proven.

This corresponds to the company's assessment.

Specific adverse events

For specific AEs, the company only presented a choice of PTs for the relevant subpopulation. It did not provide analyses for further PTs or by SOCs, so that comprehensive identification of specific AEs was not guaranteed (see Section 2.10.2.4.3 of the full dossier assessment). This resulted in no hint of greater or lesser harm from SOF/VEL/VOX in comparison with SOF/VEL; greater or lesser harm is therefore not proven.

This concurs with the company's assessment, which was based on not statistically significant results of the following PTs used by the company, however: headache, fatigue, diarrhoea, nausea, asthenia, insomnia, and arthralgia.

In view of the results of the total population at SOC and PT level (see Table 44 in Appendix A.1 of the full dossier assessment) however, it is possible that effects for specific AEs exist in the relevant subpopulation, which could not be identified based on the company's analyses. For instance, a more pronounced difference between the treatment groups in the total population was shown in the SOC "gastrointestinal disorders" than in the associated PTs. It was unclear whether this pattern of results also occurred in the relevant subpopulation because the company presented no analyses at SOC level for this.

2.5.3.4 Subgroups and other effect modifiers (research question 2.1)

In the present benefit assessment, the following effect modifiers were used for research question 2.1 (for reasons, see Section 2.10.2.4.3 of the full dossier assessment):

- age (< 65 years/≥ 65 years)
- sex (men/women)
- ethnicity (black/non-black)
- IL28B genotype (CC/non-CC [CT or TT])
- HCV RNA viral load at start of study (< 800 000 IU/mL/≥ 800 000 IU/mL)

The chosen cut-off values were prespecified in the POLARIS-2 study.

It was planned to present only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). In addition, subgroup results were only planned to be presented if there was a statistically significant and relevant effect in at least one subgroup.

No relevant effect modification was identified for the present research question. This concurs with the assessment of the company, which presented an effect modification by the characteristic "treatment status" for the SF-36 MCS, but considered it to be irrelevant to the conclusion because of the same direction of the effect in both subgroups. The company's justification was not followed; the characteristic "treatment status" was not used for research question 2.1 for a different reason, however: The subgroup "treatment-experienced" comprised fewer than 10 patients. In this case, there is regularly no subgroup analysis [1].

2.5.4 Probability and extent of added benefit (research question 2.1)

The derivation of probability and extent of the 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.

2.5.4.1 Assessment of added benefit at outcome level (research question 2.1)

The data presented in Section 2.5.3 resulted in no statistically significant and relevant effects of SOF/VEL/VOX compared with SOF/VEL for DAA-naive patients with CHC genotype 2 and without cirrhosis. The extent of the respective added benefit at outcome level was estimated from these results (see Table 16).

Table 16: Extent of added benefit at outcome level: DAA-naive adults with CHC genotype 2, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 2.1)

Outcome category **Outcome**	**SOF/VEL/VOX (8 W) vs. SOF/VEL (12 W)** **Proportion of events or mean change[a] between start of study and FU 12** **Effect [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Hepatocellular carcinoma, assessed with the surrogate SVR 12	95.9% vs. 100% RR: 0.96 [0.89; 1.03]; p = 0.225	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36 PCS	3.3 vs. 3.3 MD: 0.00 [−2.98; 2.98]; p > 0.999	Lesser benefit/added benefit not proven
SF-36 MCS	0.1 vs. 4.9 MD: −4.80 [−9.53; −0.07]; p = 0.047 Hedges' g: −0.43 [−0.85; 0.00][d]	Lesser benefit/added benefit not proven
Side effects		
Serious adverse events	6.1% vs. 5.0% RR: 1.22 [0.21; 6.97]; p = 0.865	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 0%	Greater/lesser harm not proven
Specific AEs	Comprehensive identification of specific AEs not guaranteed	

a: A positive change indicates improvement.
b: Probability provided if a statistically significant and relevant effect is present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, it cannot be derived that a relevant effect is present.

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CI_u: upper limit of confidence interval; DAA: direct acting antiviral agent; FU 12: 12 weeks after the end of treatment; MCS: Mental Component Summary; MD: mean difference; PCS: Physical Component Summary; 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; VOX: voxilaprevir; vs.: versus; W: weeks

2.5.4.2 Overall conclusion on the added benefit (research question 2.1)

Table 17 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of SOF/VEL/VOX in comparison with SOF/VEL (DAA-naive adults with CHC genotype 2, without cirrhosis) (research question 2.1)

Positive effects	**Negative effects**
–	–
Specific AEs – no conclusive assessment possible based on the data presented by the company	
AE: adverse event; CHC: chronic hepatitis C; DAA: direct acting antiviral agent; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir	

Overall, neither positive nor negative effects were found. There is an uncertainty regarding positive and negative effects in specific AEs, however, as the company only presented analyses for a choice of PTs for the relevant subpopulation. It did not provide analyses for further PTs or by SOCs.

In summary, there is no hint of an added benefit of SOF/VEL/VOX versus SOF/VEL for DAA-naive patients with CHC genotype 2 and without cirrhosis. An added benefit is therefore not proven.

This assessment corresponds to that of the company.

2.5.5 List of included studies (research question 2.1)

Gilead. A phase 3, global, multicenter, randomized, open-label study to investigate the safety and efficacy of sofosbuvir/velpatasvir/GS-9857 fixed-dose combination for 8 weeks compared to sofosbuvir/velpatasvir for 12 weeks in direct-acting antiviral-naïve subjects with chronic HCV infection: Study GS-US-367-1172 (POLARIS-2); Zusatzanalysen [unpublished]. 2017.

Gilead Sciences. Safety and efficacy of sofosbuvir/velpatasvir/voxilaprevir and sofosbuvir/velpatasvir in adults with chronic HCV infection who have not previously received treatment with direct-acting antiviral therapy (POLARIS-2): full text view [online]. In: ClinicalTrials.gov. 18.01.2017 [Accessed: 01.09.2017]. URL: https://ClinicalTrials.gov/show/NCT02607800.

Gilead Sciences. A phase 3, global, multicenter, randomized, open-label study to investigate the safety and efficacy of sofosbuvir/velpatasvir/GS-9857 fixed-dose combination for 8 weeks compared to sofosbuvir/velpatasvir for 12 weeks in direct-acting antiviral-naïve subjects with chronic HCV infection [online]. In: EU Clinical Trials Register. [Accessed: 01.09.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003460-36.

Gilead Sciences. A phase 3, global, multicenter, randomized, open-label study to investigate the safety and efficacy of sofosbuvir/velpatasvir/GS-9857 fixed dose combination for 8 weeks compared to sofosbuvir/velpatasvir for 12 weeks in direct-acting antiviral-naïve subjects with chronic HCV infection: study GS-US-367-1172 (POLARIS-2); interim clinical study report [unpublished]. 2016.

Gilead Sciences. A phase 3, global, multicenter, randomized, open-label study to investigate the safety and efficacy of sofosbuvir/velpatasvir/GS-9857 fixed-dose combination for 8 weeks compared to sofosbuvir/velpatasvir for 12 weeks in direct-acting antiviral-naïve subjects with chronic HCV infection: Study GS-US-367-1172 (POLARIS-2); final synoptic clinical study report [unpublished]. 2017.

Jacobson IM, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. Gastroenterology 2017; 153(1): 113-122.

2.6 Research question 3.1: DAA-naive adults with CHC genotype 3, without cirrhosis

2.6.1 Studies included (research question 3.1)

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

Table 18: Study pool – RCT, direct comparison: DAA-naive adults with CHC genotype 3, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.1)

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-367-1172 (POLARIS-2[b])	Yes	Yes	No

a: Study for which the company was sponsor.
b: In the following tables, the study is referred to with this abbreviated form.
CHC: chronic hepatitis C; DAA: direct acting antiviral agent; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; vs.: versus

As for research question 2.1, the study pool for the benefit assessment of SOF/VEL/VOX in comparison with the ACT for DAA-naive adults with CHC genotype 3 and without cirrhosis consisted of the RCT POLARIS-2. The subpopulation of patients with CHC genotype 3 and without cirrhosis was considered for research question 3.1. This concurs with the company's approach.

The reference list for the study included for research question 3.1 is identical to the list for research question 2.1 (see Section 2.5.5).

2.6.2 Study characteristics (research question 3.1)

Table 19 describes the study used for the benefit assessment.

Table 19: Characteristics of the study included – RCT, direct comparison: DAA-naive adults with CHC genotype 3, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.1)

Study	Study design	Population	Interventions (numbers of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
POLARIS-2	RCT[b], open-label, parallel	Treatment-naive and treatment-experienced[c] adults with CHC, all genotypes, without cirrhosis or with compensated cirrhosis[d]	SOF/VEL/VOX (8 W) (N = 502) SOF/VEL (12 W) (N = 441) Relevant subpopulation thereof[e]: SOF/VEL/VOX (8 W) (n = 91) SOF/VEL (12 W) (n = 90)	Screening: up to 42 days Treatment: 8 or 12 weeks Follow-up observation: up to 24 weeks[f] (AEs up to 30 days)	117 study centres in Australia, Canada, France, Germany, New Zealand, United Kingdom, USA 11/2015–1/2017 Data cut-off for final analysis: 11 Jan 2017[g]	Primary: SVR 12, AEs leading to treatment discontinuation Secondary: all-cause mortality, SVR 24, health-related quality of life, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant (available) outcomes for this benefit assessment.
b: All patients with genotype 1, 2, 3 or 4 were randomly allocated in a ratio of 1:1; stratification was by genotype, cirrhosis status (without cirrhosis/with compensated cirrhosis) and pretreatment (treatment-naive/pretreated with interferon-containing regimen). Patients with genotype 5 or with undetermined genotype, including genotype 6, were only enrolled in the SOF/VEL/VOX arm.
c: Treatment-experienced with an interferon-containing (but not DAA-containing) regimen; prior therapy must have been completed at least 8 weeks before screening and must not have been discontinued due to AEs or virologic failure due to a lack of adherence.
d: It was planned that at least 20% of the patients included had compensated cirrhosis. Only patients without cirrhosis were to be included for genotype 3.
e: Patients with genotype 3, without cirrhosis.
f: No further follow-up observation was to be conducted if HCV-RNA ≥ LLOQ 12 weeks after the end of treatment.
g: Deviating from the information provided in the final CSR (last observation of the last patient on 11 January 2017), the company presented 26 January 2017 as the corresponding data cut-off date in Module 4 A.

AE: adverse event; CHC: chronic hepatitis C; CSR: clinical study report; DAA: direct acting antiviral agent; HCV: hepatitis C virus; LLOQ: lower limit of quantification; n: relevant subpopulation; N: number of randomized patients; 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; VOX: voxilaprevir; vs.: versus; W: weeks

The included POLARIS-2 study was a completed, randomized, multicentre, open-label, active-controlled phase 3 study. DAA-naive adults with CHC of all genotypes were included in the study. Patients with genotype 3 were only included if they had no cirrhosis. Patients with other genotypes were included if they had no cirrhosis or compensated cirrhosis.

The subpopulation of DAA-naive adults with CHC genotype 3 and without cirrhosis was relevant for research question 3.1. This relevant subpopulation comprised 91 patients in the SOF/VEL/VOX arm and 90 patients in the SOF/VEL arm.

The detailed characteristics of the POLARIS-2 study, including the characteristics of the interventions (see Table 9), are described in Section 2.5.2 (research question 2.1).

Characteristics of the relevant subpopulation

Table 20 shows the characteristics of the patients in the relevant subpopulation of the study included.

Table 20: Characteristics of the relevant subpopulation – RCT, direct comparison: DAA-naive adults with CHC genotype 3, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.1)

Study **Characteristics** **Category**	**SOF/VEL/VOX (8 W)**	**SOF/VEL (12 W)**
POLARIS-2	N[a] = 91	N[a] = 90
Age [years], mean (SD)	48 (12)	48 (13)
Sex [F/M], %	45/55	48/52
Ethnicity, n (%)		
Black or African American	1 (1.1)	2 (2.2)
White	84 (92.3)	78 (87.6)
Asian	5 (5.5)	8 (9.0)
Other[b]	1 (1.1)	1 (1.1)
HCV subgenotype, n (%)	ND	ND
IL28B genotype, n (%)		
CC	34 (37.4)	38 (42.7)
Non-CC	57 (62.6)	51 (57.3)
CT	46 (50.5)	44 (49.4)
TT	11 (12.1)	7 (7.9)
HCV RNA viral load at start of study [IU/mL], n (%)		
< 800 000	33 (36.3)	25 (28.1)
≥ 800 000	58 (63.7)	64 (71.9)
Pretreatment, n (%)		
Treatment-naive	72 (79.1)	69 (77.5)
Pretreated (no DAA)	19 (20.9)	20 (22.5)
Pretreatment with, n (%[c])		
PEG + RBV	17 (89.5)	16 (80.0)
Other	2 (10.5)	4 (20.0)
Number of prior therapies, n (%[c])		
1	15 (78.9)	14 (70.0)
≥ 2	4 (21.1)	6 (30.0)
Response to prior therapy, n (%[c])		
No response	5 (26.3)	4 (20.0)
Relapse	12 (63.2)	12 (60.0)
Other	2 (10.5)	4 (20.0)
Treatment discontinuation, n (%)	0 (0)	2 (2.2)
Study discontinuation, n (%)	ND[d]	3 (3.4)

(continued)

Table 20: Characteristics of the relevant subpopulation – RCT, direct comparison: DAA-naive adults with CHC genotype 3, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.1) (continued)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Contains the categories of American Indians or native Alaskans and native Hawaiians or pacific islanders.
c: Proportion of pretreated patients.
d: No information on the number of study discontinuations is available for the relevant subpopulation (DAA-naive adults with CHC genotype 3, without cirrhosis). It can be inferred from the information provided in the CSR on all DAA-naive patients with genotype 3 that there were 2 (2.2%) or 3 (3.3%) study discontinuations in the relevant subpopulation.
CHC: chronic hepatitis C; CSR: clinical study report; DAA: direct acting antiviral agent; F: female; HCV: hepatitis C virus; IL28B: interleukin 28B; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; vs.: versus; W: weeks

Overall, the patient characteristics between the arms of the POLARIS-2 study in the relevant subpopulation were balanced. The mean age of the patients was 48 years. The sex ratio was balanced. About 60% of the patients had IL28B genotype non-CC. The HCV RNA viral load at the start of the study was high (≥ 800 000 IU/mL) in over 63% of the patients in both study arms. Patients with pretreatment (except with DAA) were evenly distributed between both study arms (about 20% of the relevant subpopulation).

In the relevant subpopulation, no treatment discontinuations occurred in the SOF/VEL/VOX arm and 2 treatment discontinuations occurred in the SOF/VEL arm. There were 2 or 3 study discontinuations in the SOF/VEL/VOX arm, and 3 study discontinuations in the SOF/VEL arm.

Risk of bias at study level

The risk of bias at study level was rated as low for the POLARIS-2 study (see Table 11 in Section 2.5.2). This corresponds to the company's assessment.

Limitations resulting from the open-label study design are described with the outcome-specific risk of bias in Section 2.10.2.4.2 of the full dossier assessment.

2.6.3 Results on added benefit (research question 3.1)

2.6.3.1 Outcomes included (research question 3.1)

The patient-relevant outcomes listed for research question 2.1 were also to be included in the assessment for research question 3.1 (see Section 2.5.3.1). For both research questions, the choice of patient-relevant outcomes deviates from that of the company in the same way (see Section 2.10.2.4.3 of the full dossier assessment).

The data availability at outcome level for research question 3.1 and research question 2.1 was identical (see Table 12 in Section 2.5.3.1).

2.6.3.2 Risk of bias (research question 3.1)

The risk of bias for the relevant outcomes for research question 3.1 and research question 2.1 was identical (see Table 13 in Section 2.5.3.2). For both research questions, the assessment regarding the risk of bias at outcome level deviates from that of the company in the same way (see Section 2.5.3.2).

Detailed reasons for the assessment of the risk of bias can be found in Section 2.10.2.4.2 of the full dossier assessment.

2.6.3.3 Results (research question 3.1)

Table 21 and Table 22 summarize the results on the comparison of SOF/VEL/VOX with SOF/VEL in DAA-naive adults with CHC genotype 3 and without cirrhosis. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations.

Table 21: Results (mortality, morbidity, side effects) – RCT, direct comparison: DAA-naive adults with CHC genotype 3, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.1)

Study Outcome category Outcome	SOF/VEL/VOX (8 W) N	 Patients with event n (%)	SOF/VEL (12 W) N	 Patients with event n (%)	SOF/VEL/VOX vs. SOF/VEL RR [95% CI]; p-value[a]
POLARIS-2					
Mortality					
All-cause mortality	91	0 (0)	89	0 (0)	–
Morbidity					
SVR 12[b]	92[c]	91 (98.9)[d]	89	86 (96.6)[e]	1.02 [0.98; 1.07]; 0.324
SVR 24[b, f]	92[c]	91 (98.9)[g]	89	86 (96.6)[h]	1.02 [0.98; 1.07][i]; 0.324
Side effects					
AEs (supplementary information)	91	72 (79.1)	89	73 (82.0)	–
SAEs	91	2 (2.2)	89	0 (0)	4.89 [0.24; 100.47][i]; 0.210
Discontinuation due to AEs	91	0 (0)	89	1 (1.1)	0.33 [0.01; 7.90][i]; 0.367
Specific AEs				no usable data[j]	

a: Institute's calculation, unconditional exact test (CSZ method according to [6]).
b: Sufficiently valid surrogate for the patient-relevant outcome "HCC".
c: 1 (1%) patient with cirrhosis was analysed.
d: 1 missing value (1%) was imputed as non-response (lost to follow-up).
e: 3 missing values (3%) were imputed, thereof 1 as response (based on SVR 4 and SVR 24) and 2 as non-response (lost to follow-up).
f: Due to the consistency between the results for SVR 12 and SVR 24, the results on SVR 24 are no longer shown in the following tables.
g: 4 missing values (4%) were imputed, thereof 3 as response (2 based on SVR 12, 1 based on SVR 4 and sustained virologic response after week 24 after the end of treatment) and 1 as non-response (lost to follow-up already 12 weeks after the end of treatment).
h: 5 missing values (6%) were imputed, thereof 2 as response (1 based on SVR 12, 1 based on SVR 4 and sustained virologic response after week 24 after the end of treatment) and 3 as non-response (1 based on non-response already at week 12 after the end of treatment, 2 lost to follow-up already at week 12 after the end of treatment).
i: Institute's calculation of RR and CI (asymptotic).
j: For the relevant subpopulation, the company only presented analyses for PTs that occurred in at least 5% of the patients in the total population in at least 1 arm. Based on this selection, comprehensive identification of specific AEs is not guaranteed (see Section 2.10.2.4.3 of the full dossier assessment).

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; DAA: direct acting antiviral agent; HCC: hepatocellular carcinoma; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOF: sofosbuvir; SVR 4: sustained virologic response 4 weeks after the end of treatment; 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; VOX: voxilaprevir; W: weeks

Table 22: Results (health-related quality of life) – RCT, direct comparison: DAA-naive adults with CHC genotype 3, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.1)

Study **Outcome category**	**SOF/VEL/VOX (8 W)**			**SOF/VEL (12 W)**			**SOF/VEL/VOX vs. SOF/VEL**
Time point **Outcome**	**N[a]**	**Values at start of study mean (SD)**	**Change at FU 12[b] or FU 24 mean (SD)**	**N[a]**	**Values at start of study mean (SD)**	**Change at FU 12[b] or FU 24 mean (SD)**	**MD [95% CI]; p-value**
POLARIS-2							
Health-related quality of life							
12 weeks after end of treatment							
SF-36 PCS[c]	88	50.3 (9.41)	2.0 (6.81)	84	48.9 (9.51)	3.5 (7.73)	−1.50 [−3.68; 0.68]; 0.178
Physical functioning						ND[d]	
Physical role functioning						ND[d]	
Bodily pain						ND[d]	
General health perception						ND[d]	
SF-36 MCS[c]	88	47.4 (11.54)	2.4 (8.14)	84	46.4 (11.88)	4.3 (9.32)	−1.90 [−4.52; 0.72]; 0.155
Vitality						ND[d]	
Social functioning						ND[d]	
Emotional role functioning						ND[d]	
Mental wellbeing						ND[d]	
24 weeks after end of treatment						ND[d]	

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: A positive change indicates improvement.
d: Analyses are available for the total population, but not for the relevant subpopulation.

CHC: chronic hepatitis C; CI: confidence interval; DAA: direct acting antiviral agent; FU 12: 12 weeks after the end of treatment; FU 24: 24 weeks after the end of treatment; MCS: Mental Component Summary; MD: mean difference; N: number of analysed patients; ND: no data; PCS: Physical Component Summary; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form (36) Health Survey; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; vs.: versus; W: weeks

Based on the available data, at most an indication, e.g. of an added benefit, can be determined for the outcome “hepatocellular carcinoma”, included using the surrogate outcome “sustained virologic response” (SVR 12 and SVR 24). Due to the high risk of bias, at most hints, e.g. of an added benefit, can be determined for the outcomes “all-cause mortality”, “health-related quality of life” (recorded with the SF-36), “SAEs” and “discontinuation due to AEs”.

Mortality

All-cause mortality

In both treatment groups, no deaths occurred in the relevant subpopulation of the POLARIS-2 study. This resulted in no hint of an added benefit of SOF/VEL/VOX in comparison with SOF/VEL; an added benefit is therefore not proven.

This concurs with the assessment of the company, which analysed this outcome in the framework of AEs, using the designation “death”.

Morbidity

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

No statistically significant difference between the treatment groups was shown for SVR 12 or SVR 24. The concordance of the results for the relevant subpopulation of the POLARIS-2 study was 100% in patients with recordings both at week 12 and at week 24 after the end of treatment. Due to this data constellation, the SVR 12, for which the company presented subgroup analyses, is used hereinafter for the derivation of the added benefit for research question 3.1.

Overall, this resulted in no hint of an added benefit of SOF/VEL/VOX in comparison with SOF/VEL for SVR 12; an added benefit is therefore not proven.

This corresponds to the company’s assessment.

Health-related quality of life

SF-36

The PCS and the 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 (for reasons, see Section 2.10.2.4.3 of the full dossier assessment). The company presented no analyses for the relevant subpopulation for the documentation time 24 weeks after the end of treatment, which is also relevant, although an analysis was planned for this time point and was available in the CSR for the total population.

The consideration of the mean differences showed no statistically significant difference between the treatment groups for the PCS and the MCS. This resulted in no hint of an added benefit of SOF/VEL/VOX in comparison with SOF/VEL; an added benefit is therefore not proven.

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

Side effects

Serious adverse events and discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence for these outcomes, there was no hint of greater or lesser harm from SOF/VEL/VOX in comparison with SOF/VEL; greater or lesser harm is therefore not proven.

This corresponds to the company's assessment.

Specific adverse events

For specific AEs, the company only presented analyses for a choice of PTs for the relevant subpopulation. It did not provide analyses for further PTs or by SOCs, so that comprehensive identification of specific AEs was not guaranteed (see Section 2.10.2.4.3 of the full dossier assessment). This resulted in no hint of greater or lesser harm from SOF/VEL/VOX in comparison with SOF/VEL; greater or lesser harm is therefore not proven.

This concurs with the company's assessment, which was based on not statistically significant results of the following PTs used by the company, however: headache, fatigue, diarrhoea, nausea, asthenia, insomnia, and arthralgia.

In view of the results of the total population at SOC and PT level (see Table 44 in Appendix A.1 of the full dossier assessment) however, it is possible that effects for specific AEs exist in the relevant subpopulation, which could not be identified based on the company's analyses. For instance, a more pronounced difference between the treatment groups in the total population was shown in the SOC "gastrointestinal disorders" than in the associated PTs. It was unclear whether this pattern of results also occurred in the relevant subpopulation because the company presented no analyses at SOC level for this.

2.6.3.4 Subgroups and other effect modifiers (research question 3.1)

In the present benefit assessment, the following effect modifiers were used for research question 3.1 (for reasons, see Section 2.10.2.4.3 of the full dossier assessment):

- age (< 65 years/≥ 65 years)
- sex (men/women)
- IL28B genotype (CC/non-CC [CT or TT])
- HCV RNA viral load at start of study (< 800 000 IU/mL/≥ 800 000 IU/mL)
- pretreatment (treatment-naive/pretreated)

The chosen cut-off values were prespecified in the POLARIS-2 study.

It was planned to present only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). In addition, subgroup results were only planned to be presented if there was a statistically significant and relevant effect in at least one subgroup.

No relevant effect modification was identified for the present research question. This corresponds to the company's assessment.

2.6.4 Probability and extent of added benefit (research question 3.1)

The derivation of probability and extent of the 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.

2.6.4.1 Assessment of added benefit at outcome level (research question 3.1)

The data presented in Section 2.6.3 resulted in no statistically significant and relevant effects of SOF/VEL/VOX compared with SOF/VEL for DAA-naive patients with CHC genotype 3 and without cirrhosis. The extent of the respective added benefit at outcome level was estimated from these results (see Table 23).

Table 23: Extent of added benefit at outcome level: DAA-naive adults with CHC genotype 3, without cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.1)

Outcome category **Outcome**	**SOF/VEL/VOX (8 W) vs. SOF/VEL (12 W)** **Proportion of events or mean change[a] between start of study and FU 12** **Effect [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Hepatocellular carcinoma, assessed with the surrogate SVR 12	98.9% vs. 96.6% RR: 1.02 [0.98; 1.07]; p = 0.324	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36 PCS	2.0 vs. 3.5 MD: −1.50 [−3.68; 0.68]; p = 0.178	Lesser benefit/added benefit not proven
SF-36 MCS	2.4 vs. 4.3 MD: −1.90 [−4.52; 0.72]; p = 0.155	Lesser benefit/added benefit not proven
Side effects		
SAEs	2.2% vs. 0% RR: 4.89 [0.24; 100.47]; p = 0.210	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 1.1% RR: 0.33 [0.01; 7.90]; p = 0.367	Greater/lesser harm not proven
Specific AEs	Comprehensive identification of specific AEs not guaranteed	

a: A positive change indicates improvement.
b: Probability provided if a statistically significant and relevant effect is present.
c: 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; DAA: direct acting antiviral agent; FU 12: 12 weeks after the end of treatment; MCS: Mental Component Summary; MD: mean difference; PCS: Physical Component Summary; 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; VOX: voxilaprevir; vs.: versus; W: weeks

2.6.4.2 Overall conclusion on the added benefit (research question 3.1)

Table 24 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 24: Positive and negative effects from the assessment of SOF/VEL/VOX in comparison with SOF/VEL (DAA-naive adults with CHC genotype 3, without cirrhosis) (research question 3.1)

Positive effects	Negative effects
–	–
Specific AEs – no conclusive assessment possible based on the data presented by the company	
AE: adverse event; CHC: chronic hepatitis C; DAA: direct acting antiviral agent; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir	

Overall, neither positive nor negative effects were found. There is an uncertainty regarding positive and negative effects in specific AEs, however, as the company only presented analyses for a choice of PTs for the relevant subpopulation. It did not provide analyses for further PTs or by SOCs.

In summary, there is no hint of an added benefit of SOF/VEL/VOX versus SOF/VEL for DAA-naive patients with CHC genotype 3 and without cirrhosis. An added benefit is therefore not proven.

This assessment corresponds to that of the company.

2.6.5 List of included studies (research question 3.1)

The list of included studies was identical for research questions 2.1 and 3.1 (see Section 2.5.5).

2.7 Research question 3.2: DAA-naive adults with CHC genotype 3, with compensated cirrhosis

2.7.1 Studies included (research question 3.2)

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

Table 25: Study pool – RCT, direct comparison: DAA-naive adults with CHC genotype 3, with compensated cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.2)

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-367-1173 (POLARIS-3[b])	Yes	Yes	No
a: Study for which the company was sponsor. b: In the following tables, the study is referred to with this abbreviated form. CHC: chronic hepatitis C; DAA: direct acting antiviral agent; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; vs.: versus			

The study pool for the benefit assessment of SOF/VEL/VOX in comparison with the ACT for DAA-naive adults with CHC genotype 3 and with compensated cirrhosis consisted of the RCT POLARIS-3, which concurred with the study pool of the company.

Section 2.7.5 contains a reference list for the study included.

2.7.2 Study characteristics (research question 3.2)

Table 26 and Table 27 describe the study used for the benefit assessment.

Table 26: Characteristics of the study included – RCT, direct comparison: DAA-naive adults with CHC genotype 3, with compensated cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.2)

Study	Study design	Population	Interventions (numbers of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
POLARIS-3	RCT[b], open-label, parallel	Treatment-naive and treatment-experienced[c] adults with CHC genotype 3, with compensated cirrhosis	SOF/VEL/VOX (8 W) (N = 110) SOF/VEL (12 W) (N = 110)	Screening: up to 42 days Treatment: 8 or 12 weeks Follow-up: up to 24 weeks[d] (AEs up to 30 days)	84 study centres in Australia, Canada, France, Germany, New Zealand, United Kingdom, USA 12/2015–1/2017 Data cut-off for final analysis: 2 Jan 2017	Primary: SVR 12, AEs leading to treatment discontinuation Secondary: all-cause mortality, SVR 24, health-related quality of life, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant (available) outcomes for this benefit assessment.
b: Randomization stratified by pretreatment (treatment-naive/pretreated with interferon-containing regimen).
c: Treatment-experienced with an interferon-containing (but not DAA-containing) regimen; prior therapy must have been completed at least 8 weeks before screening and must not have been discontinued due to AEs or virologic failure due to a lack of adherence.
d: No further follow-up observation was to be conducted if HCV-RNA ≥ LLOQ 12 weeks after the end of treatment.
AE: adverse event; CHC: chronic hepatitis C; DAA: direct acting antiviral agent; HCV: hepatitis C virus; LLOQ: lower limit of quantification; N: number of randomized patients; 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; VOX: voxilaprevir; vs.: versus; W: weeks

Table 27: Characteristics of the interventions – RCT, direct comparison: DAA-naive adults with CHC genotype 3, with compensated cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.2)

Study	Intervention	Comparison
POLARIS-3	SOF/VEL/VOX (400 mg/100 mg/100 mg) once daily, orally with a meal, for 8 weeks	SOF/VEL (400 mg/100 mg) once daily, orally independent of meals, for 12 weeks
	Dose reduction not allowed	
	Allowed prior and concomitant medication: Prior interferon-based therapy, which was completed at least 8 weeks before screening **Prohibited prior and concomitant medication:** Pretreatment with approved or investigational HCV-specific DAA During screening and at least 28 days before the first study visit until end of treatment: ▪ systemic immunosuppressants (including corticosteroids, azathioprine, monoclonal antibodies) ▪ blood cell stimulating drugs ▪ investigational drugs or agents for any therapeutic indication Within 60 days before the first study visit until end of treatment: ▪ amiodarone Within 21 days before the first study visit until end of treatment: ▪ antibiotics (clarithromycin, erythromycin), antacids (proton pump inhibitors), anticonvulsants (phenobarbital, phenytoin, carbamazepine, oxcarbazepine), antimycotics (rifabutin, rifapentine, rifampin), cardiac drugs (bosentan, digoxin, diltiazem, dronedarone, olmesartan, quinidine, ranolazine, telmisartan, valsartan, verapamil), herbal or natural supplements (St. John's Wort, echinacea, milk thistle, Chinese herb sho-saikoto [or Xiao-Shai-Hu-Tang]), modafinil, sulfasalazine, methotrexate 1 day before the first study visit until end of treatment: ▪ HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin)	

CHC: chronic hepatitis C; DAA: direct acting antiviral agent; HCV: hepatitis C virus; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme-A; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; vs.: versus

The included POLARIS-3 study was a completed, randomized, multicentre, open-label, active-controlled phase 3 study. DAA-naive adults with CHC genotype 3 and with compensated cirrhosis were included in the study. Coinfections with HIV or HBV were exclusion criteria of the study.

Randomization was stratified by pretreatment and the patients were allocated in a ratio of 1:1. 110 patients were included in each of the treatment arms SOF/VEL/VOX and SOF/VEL.

The interventions were used for 8 weeks (SOF/VEL/VOX) and for 12 weeks (SOF/VEL), which was in compliance with the SPCs [3,5]. The SPC of SOF/VEL/VOX also allows a

treatment duration of 12 weeks for patients with genotype 3 and with compensated cirrhosis. No data were available for a comparison of SOF/VEL/VOX over 12 weeks.

Primary outcomes of the POLARIS-3 study were SVR 12 and AEs leading to treatment discontinuation. Further patient-relevant outcomes on mortality, morbidity, health-related quality of life and AEs were additionally recorded.

The planned duration of follow-up observation for SVR and health-related quality of life was based on the detection of HCV RNA 12 weeks after the end of treatment. Patients with HCV RNA below the limit of detection 12 weeks after the end of treatment were to be followed-up until week 24. In other cases, there was no further follow-up observation for SVR and health-related quality of life from week 12 after the end of treatment. Documentation of AEs was only until 30 days after the end of treatment, however. Hence the observation period for the outcomes of the category of side effects was systematically shortened. Yet in order to draw conclusions over the total study period, it would be necessary to record these outcomes also over the total study period.

Table 28 shows the characteristics of the patients in the study included.

Table 28: Characteristics of the study population – RCT, direct comparison: DAA-naive adults with CHC genotype 3, with compensated cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.2)

Study **Characteristics** **Category**	**SOF/VEL/VOX (8 W)**	**SOF/VEL (12 W)**
POLARIS-3	N[a] = 110	N[a] = 110
Age [years], mean (SD)	54 (8)	55 (8)
Sex [F/M], %	33/67	24/76
Ethnicity, n (%)		
Black or African American	0 (0)	1 (0.9)
White	100 (90.9)	97 (89.0)
Asian	8 (7.3)	9 (8.3)
Other[b]	2 (1.8)	2 (1.8)
HCV subgenotype, n (%)	ND	ND
IL28B genotype, n (%)		
CC	41 (37.3)	52 (47.7)
Non-CC	69 (62.7)	57 (52.3)
CT	57 (51.8)	44 (40.4)
TT	12 (10.9)	13 (11.9)
HCV RNA viral load at start of study [IU/mL], n (%)		
< 800 000	40 (36.4)	28 (25.7)
≥ 800 000	70 (63.6)	81 (74.3)
Pretreatment, n (%)		
Treatment-naive	75 (68.2)	77 (70.6)
Pretreated (no DAA)	35 (31.8)	32 (29.4)
Pretreatment with, n (%[c])		
PEG + RBV	32 (91.4)	30 (93.8)
Other	3 (8.6)	2 (6.3)
Number of prior therapies, n (%[c])		
1	23 (65.7)	22 (68.8)
≥ 2	12 (34.3)	10 (31.3)
Response to prior therapy, n (%[c])		
No response	16 (45.7)	8 (25.0)
Relapse	16 (45.7)	20 (62.5)
Other	3 (8.6)	4 (12.5)
Treatment discontinuation, n (%)	0 (0)	2 (1.8)
Study discontinuation, n (%)	4 (3.6)	4 (3.7)

(continued)

Table 28: Characteristics of the study population – RCT, direct comparison: DAA-naive adults with CHC genotype 3, with compensated cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.2) (continued)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Contains the categories of American Indians or native Alaskans, native Hawaiians or pacific islanders and others.
c: Proportion of pretreated patients.
CHC: chronic hepatitis C; DAA: direct acting antiviral agent; F: female; HCV: hepatitis C virus; IL28B: interleukin 28B; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; vs.: versus; W: weeks

The patient characteristics between the arms of the POLARIS-3 study were largely balanced. The mean age of the patients was about 54 years. A minor imbalance occurred in the distribution of the characteristics "sex" (proportion of women: 33% in the SOF/VEL/VOX arm, 24% in the SOF/VEL arm) and IL28B genotype (CC: 37% of the patients in the SOF/VEL/VOX arm, 48% in the SOF/VEL arm). There was a minor imbalance also for the characteristic "HCV RNA viral load": It was high in about 64% of the patients in the SOF/VEL/VOX arm and in about 74% of the patients in the SOF/VEL arm (≥ 800 000 IU/mL). There were about 32% pretreated patients in the SOF/VEL/VOX arm and about 29% pretreated patients in the SOF/VEL arm.

No treatment discontinuations occurred in the SOF/VEL/VOX arm, and 2 treatment discontinuations in the SOF/VEL arm. There were 4 study discontinuations each in the SOF/VEL/VOX arm and in the SOF/VEL arm.

Risk of bias at study level

Table 29 shows the risk of bias at study level.

Table 29: Risk of bias at study level – RCT, direct comparison: DAA-naive adults with CHC genotype 3, with compensated cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.2)

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			
POLARIS-3	Yes	Yes	No	No	Yes	Yes	Low

CHC: chronic hepatitis C; DAA: direct acting antiviral agent; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; vs.: versus

The risk of bias at study level was rated as low for the POLARIS-3 study. This corresponds to the company's assessment.

Limitations resulting from the open-label study design are described with the outcome-specific risk of bias in Section 2.10.2.4.2 of the full dossier assessment.

2.7.3 Results on added benefit (research question 3.2)

2.7.3.1 Outcomes included (research question 3.2)

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.10.2.4.3 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) and did not consider the SVR 24 (see Section 2.10.2.4.3 of the full dossier assessment).

Table 30 shows for which outcomes data were available in the study included.

Table 30: Matrix of outcomes – RCT, direct comparison: DAA-naive adults with CHC genotype 3, with compensated cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.2)

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	Nausea (PT)	Diarrhoea (PT)
POLARIS-3	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AE: adverse event; CHC: chronic hepatitis C; DAA: direct acting antiviral agent; PT: Preferred Term; 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; VOX: voxilaprevir; vs.: versus

2.7.3.2 Risk of bias (research question 3.2)

Table 31 describes the risk of bias for the relevant outcomes.

Table 31: Risk of bias at study and outcome level – RCT, direct comparison: DAA-naive adults with CHC genotype 3, with compensated cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.2)

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	Nausea (PT)	Diarrhoea (PT)
POLARIS-3	L	H[a]	L	H[b]	H[a]	H[c]	H[d]	H[d]

a: 4-week difference in treatment duration and therefore in observation period between the SOF/VEL/VOX arm and the SOF/VEL arm.
b: In the analyses for the documentation times 12 and 24 weeks after the end of treatment: lack of blinding in subjective recording of outcomes and 4-week difference in the documentation times between the SOF/VEL/VOX arm and the SOF/VEL arm; in the analysis for the documentation time 24 weeks after the end of treatment, there was also no information on the proportion of imputed values.
c: Lack of blinding in subjective decision making.
d: Lack of blinding in subjective recording of outcomes and 4-week difference in treatment duration and therefore in observation period between the SOF/VEL/VOX arm and the SOF/VEL arm.

AE: adverse event; CHC: chronic hepatitis C; DAA: direct acting antiviral agent; H: high; L: low; PT: Preferred Term; 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; VOX: voxilaprevir; vs.: versus

The results on the outcomes “all-cause mortality”, “SAEs”, “nausea” and “diarrhoea” are considered to be potentially highly biased because there was a 4-week difference in treatment duration and therefore observation period between the SOF/VEL/VOX arm and the SOF/VEL arm of the POLARIS-3 study. This corresponds to the company’s assessment. For the outcomes “nausea” and “diarrhoea”, the present benefit assessment identified subjective recording of outcomes with lack of blinding as an additional potentially biasing factor, which was not identified by the company.

The risk of bias was rated as low for the outcome “hepatocellular carcinoma”, which was included using the surrogate parameter “sustained virologic response” (SVR 12 and SVR 24). For the SVR 12, this concurs with the company’s assessment; the SVR 24 was not considered by the company.

The results on the SF-36 and on the outcome “discontinuation due to AEs” were considered to be potentially highly biased because their recording was subjective, which, if unblinded, is to be generally considered as potentially highly biased. In the case of the SF-36, this corresponds to the company’s assessment. Besides, the present benefit assessment identified a 4-week

difference in documentation times between the SOF/VEL/VOX arm and the SOF/VEL arm as an additional potentially biasing factor for this instrument, which was not identified by the company. For the outcome “discontinuation due to AEs”, the company reached a deviating assessment, which rated the risk of bias as low for this outcome.

Detailed reasons for the assessment of the risk of bias can be found in Section 2.10.2.4.2 of the full dossier assessment.

2.7.3.3 Results (research question 3.2)

Table 32 and Table 33 summarize the results on the comparison of SOF/VEL/VOX with SOF/VEL in DAA-naive adults with CHC genotype 3 and with compensated cirrhosis. Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations.

Table 32: Results (mortality, morbidity, side effects) – RCT, direct comparison: DAA-naive adults with CHC genotype 3, with compensated cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.2)

Study Outcome category	SOF/VEL/VOX (8 W)		SOF/VEL (12 W)		SOF/VEL/VOX vs. SOF/VEL
Outcome	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
POLARIS-3					
Mortality					
All-cause mortality	110	1 (0.9)	109	0 (0)	2.97 [0.12; 72.19]; 0.529
Morbidity					
SVR 12[b]	110	106 (96.4)[c]	109	105 (96.3)[d]	1.00 [0.95; 1.05]; > 0.999
SVR 24[b, e]	110	106 (96.4)[f]	109	105 (96.3)[g]	1.00 [0.95; 1.05][h]; > 0.999
Side effects					
AEs (supplementary information)	110	83 (75.5)	109	81 (74.3)	–
SAEs	110	2 (1.8)	109	3 (2.8)	0.66 [0.11; 3.88]; 0.711
Discontinuation due to AEs	110	0 (0)	109	1 (0.9)	0.33 [0.01; 8.02]; 0.369
Nausea	110	23 (20.9)	109	10 (9.2)	2.28 [1.14; 4.56]; 0.015
Diarrhoea	110	17 (15.5)	109	5 (4.6)	3.37 [1.29; 8.81]; 0.008

a: Institute's calculation, unconditional exact test (CSZ method according to [6]).
b: Sufficiently valid surrogate for the patient-relevant outcome "HCC".
c: 2 missing values (2%) were imputed as non-response (1 patient died, 1 withdrawal of consent).
d: 1 missing value (1%) was imputed as non-response (lost to follow-up).
e: Due to the consistency between the results for SVR 12 and SVR 24, the results on SVR 24 are no longer shown in the following tables.
f: 7 missing values (6%) were imputed, thereof 3 as response (2 based on SVR 12, 1 based on SVR 4 and sustained virologic response after week 24 after the end of treatment) and 4 as non-response (1 patient died, 1 withdrawal of consent; 2 based on non-response already at week 12 after the end of treatment).
g: 8 missing values (7%) were imputed, thereof 4 as response (based on SVR 12) and 4 as non-response (3 based on non-response already at week 12 after the end of treatment, 1 lost to follow-up already at week 12 after the end of treatment).
h: Institute's calculation of RR and CI (asymptotic).

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; DAA: direct acting antiviral agent; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOF: sofosbuvir; SVR 4: sustained virologic response 4 weeks after the end of treatment; 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; VOX: voxilaprevir; vs.: versus; W: weeks

Table 33: Results (health-related quality of life) – RCT, direct comparison: DAA-naive adults with CHC genotype 3, with compensated cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.2)

Study Outcome category Time point Outcome	SOF/VEL/VOX (8 W)			SOF/VEL (12 W)			SOF/VEL/VOX vs. SOF/VEL
	N[a]	Values at start of study mean (SD)	Change at FU 12[b] or FU 24[c] mean (SD)	N[a]	Values at start of study mean (SD)	Change at FU 12[b] or FU 24[c] mean (SD)	MD [95% CI]; p-value
POLARIS-3							
Health-related quality of life							
12 weeks after end of treatment							
SF-36 PCS[d]	99	43.9 (10.64)	2.5 (8.70)	100	47.1 (9.22)	2.4 (8.46)	0.10 [−2.28; 2.48]; 0.935
Physical functioning	102	65.3 (28.62)	5.1 (25.26)	101	72.5 (26.61)	6.1 (25.44)	−
Physical role functioning	102	59.4 (32.22)	9.3 (28.36)	101	65.0 (29.41)	8.6 (28.07)	−
Bodily pain	101	57.8 (28.53)	5.2 (26.55)	101	67.2 (26.28)	2.6 (23.61)	−
General health perception	102	52.4 (23.97)	5.8 (18.98)	101	58.0 (21.19)	7.8 (19.98)	−
SF-36 MCS[d]	99	45.2 (11.76)	3.3 (9.74)	100	46.2 (10.86)	3.4 (9.62)	−0.10 [−2.79; 2.59]; 0.942
Vitality	100	48.2 (23.10)	10.5 (23.19)	100	50.4 (23.34)	11.7 (20.44)	−
Social functioning	102	64.2 (29.61)	9.2 (28.74)	101	71.6 (27.37)	8.0 (24.72)	−
Emotional role functioning	101	68.2 (32.12)	7.1 (28.90)	100	72.7 (24.54)	5.8 (27.61)	−
Mental wellbeing	100	66.6 (20.34)	4.1 (16.60)	100	68.4 (18.39)	4.9 (17.60)	−

(continued)

Table 33: Results (health-related quality of life) – RCT, direct comparison: DAA-naive adults with CHC genotype 3, with compensated cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.2) (continued)

Study Outcome category	SOF/VEL/VOX (8 W)			SOF/VEL (12 W)			SOF/VEL/VOX vs. SOF/VEL
Time point Outcome	N[a]	Values at start of study mean (SD)	Change at FU 12[b] or FU 24[c] mean (SD)	N[a]	Values at start of study mean (SD)	Change at FU 12[b] or FU 24[c] mean (SD)	MD [95% CI]; p-value
POLARIS-3							
Health-related quality of life							
24 weeks after end of treatment							
SF-36 PCS[d]	101	43.9 (10.64)	3.9 (7.86)	102	47.1 (9.22)	2.7 (8.22)	1.20 [−1.03; 3.43]; 0.289[e]
Physical functioning	103	65.3 (28.62)	8.8 (23.03)	102	72.5 (26.61)	5.6 (24.28)	−
Physical role functioning	103	59.4 (32.33)	10.4 (25.68)	102	65.0 (29.41)	9.9 (26.77)	−
Bodily pain	102	57.8 (28.53)	7.3 (24.92)	102	67.2 (26.28)	2.9 (23.56)	−
General health perception	103	52.4 (23.97)	9.2 (19.39)	102	58.0 (21.19)	8.2 (19.86)	−
SF-36 MCS[d]	101	45.2 (11.76)	3.8 (9.43)	102	46.2 (10.86)	3.5 (9.00)	0.30 [−2.25; 2.85]; 0.817[e]
Vitality	102	48.2 (23.10)	12.0 (21.51)	102	50.4 (23.34)	12.8 (21.72)	−
Social functioning	103	64.2 (29.61)	12.7 (25.42)	102	71.6 (27.37)	9.3 (23.31)	−
Emotional role functioning	102	68.2 (32.12)	6.0 (29.46)	101	72.7 (24.54)	4.5 (26.34)	−
Mental wellbeing	102	66.6 (20.34)	5.9 (16.40)	102	68.4 (18.39)	5.2 (16.31)	−

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: LOCF analysis; no information on proportion of imputed values.
d: A positive change indicates improvement.
e: Institute's calculation; MD, CI and p-value (t-test).

CHC: chronic hepatitis C; CI: confidence interval; DAA: direct acting antiviral agent; FU 12: 12 weeks after the end of treatment; FU 24: 24 weeks after the end of treatment; LOCF: last observation carried forward; MCS: Mental Component Summary; MD: mean difference; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form (36) Health Survey; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir; vs.: versus; W: weeks

Based on the available data, at most an indication, e.g. of an added benefit, can be determined for the outcome "hepatocellular carcinoma", included using the surrogate outcome "sustained virologic response" (SVR 12 and SVR 24). Due to the high risk of bias, at most hints, e.g. of

an added benefit, can be determined for the outcomes “all-cause mortality”, “health-related quality of life” (recorded with the SF-36), “SAEs”, “discontinuation due to AEs”, “nausea” and “diarrhoea”.

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/VOX in comparison with SOF/VEL; an added benefit is therefore not proven.

This concurs with the assessment of the company, which analysed this outcome in the framework of AEs, using the designation “death”.

Morbidity

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

No statistically significant difference between the treatment groups was shown for SVR 12 or SVR 24. The concordance of the results for the total population of the POLARIS-3 study was 100% in patients with recordings both at week 12 and at week 24 after the end of treatment. Due to this data constellation, the SVR 12, for which the company presented subgroup analyses, is used hereinafter for the derivation of the added benefit for research question 3.2.

Overall, this resulted in no hint of an added benefit of SOF/VEL/VOX in comparison with SOF/VEL for SVR 12; an added benefit is therefore not proven.

This corresponds to the company’s assessment.

Health-related quality of life

SF-36

The PCS and the MCS of the SF-36 were considered individually. The mean difference of the change from the start of the study until 12 weeks and until 24 weeks after the end of treatment was considered in each case (for reasons, see Section 2.10.2.4.3 of the full dossier assessment). The consideration of the mean differences of the change from the start of study until week 12 and until week 24 after the end of treatment showed no statistically significant difference between the treatment groups for the PCS and the MCS. The results for both documentation times were qualitatively consistent. Due to this data constellation, hereinafter the change from the start of the study until 12 weeks after the end of treatment, for which the company presented subgroup analyses, was used for the derivation of the added benefit for research question 3.2.

Overall, there was no hint of an added benefit of SOF/VEL/VOX in comparison with SOF/VEL; an added benefit is therefore not proven.

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

Side effects

Serious adverse events and discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence for these outcomes, there was no hint of greater or lesser harm from SOF/VEL/VOX in comparison with SOF/VEL; greater or lesser harm is therefore not proven.

This corresponds to the company's assessment.

Nausea and diarrhoea

A statistically significant difference to the disadvantage of SOF/VEL/VOX in comparison with SOF/VEL was shown for each of the outcomes "nausea" and "diarrhoea". This resulted in a hint of greater harm from SOF/VEL/VOX in comparison with SOF/VEL for these outcomes.

This deviates from the assessment of the company, which considered the results on the outcomes "nausea" and "diarrhoea" to be of very little relevance and therefore derived no greater harm. This assessment was not followed (see Section 2.10.2.8.2 of the full dossier assessment).

2.7.3.4 Subgroups and other effect modifiers (research question 3.2)

In the present benefit assessment, the following effect modifiers were used for research question 3.2 (for reasons, see Section 2.10.2.4.3 of the full dossier assessment):

- age (< 65 years/≥ 65 years)
- sex (men/women)
- IL28B genotype (CC/non-CC [CT or TT])
- HCV RNA viral load at start of study (< 800 000 IU/mL/≥ 800 000 IU/mL)
- pretreatment (treatment-naive/pretreated)
- response to prior therapy (no response/relapse/other)

The chosen cut-off values were prespecified in the POLARIS-3 study.

It was planned to present only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). In addition, subgroup results were only planned to be presented if there was a statistically significant and relevant effect in at least one subgroup.

No relevant effect modification was identified for the present research question. This corresponds to the company's assessment.

2.7.4 Probability and extent of added benefit (research question 3.2)

The derivation of probability and extent of the 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.

2.7.4.1 Assessment of added benefit at outcome level (research question 3.2)

For each of the outcomes "nausea" and "diarrhoea", the data presented in Section 2.7.3 resulted in a hint of greater harm of SOF/VEL/VOX compared with SOF/VEL for DAA-naive patients with CHC genotype 3 and with compensated cirrhosis.

Allocation to the outcome categories of the AEs "nausea" and "vomiting", for which greater harm was shown, depended on the severity of the respective AE. The results on SAEs recorded in the POLARIS-3 study were used to assess the severity of these AEs.

The AEs "nausea" and "diarrhoea" did not occur as SAEs. Correspondingly, the results on these AEs were allocated to the outcome category "non-serious/non-severe side effects". This allocation concurs with that of the company.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 34).

Table 34: Extent of added benefit at outcome level: DAA-naive adults with CHC genotype 3, with compensated cirrhosis, SOF/VEL/VOX vs. SOF/VEL (research question 3.2)

Outcome category **Outcome**	**SOF/VEL/VOX (8 W) vs. SOF/VEL (12 W)** **Proportion of events or mean change[a] between start of study and FU 12** **Effect [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	0.9% vs. 0% RR: 2.97 [0.12; 72.19]; p = 0.529	Lesser benefit/added benefit not proven
Morbidity		
Hepatocellular carcinoma, assessed with the surrogate SVR 12	96.4% vs. 96.3% RR: 1.00 [0.95; 1.05]; p < 0.999	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36 PCS	2.5 vs. 2.4 MD: 0.10 [−2.28; 2.48]; p = 0.935	Lesser benefit/added benefit not proven
SF-36 MCS	3.3 vs. 3.4 MD: −0.10 [−2.79; 2.59]; p = 0.942	Lesser benefit/added benefit not proven
Side effects		
SAEs	1.8% vs. 2.8% RR: 0.66 [0.11; 3.88]; p = 0.711	Greater/lesser harm not proven
Discontinuation due to AEs	0% vs. 0.9% RR: 0.33 [0.01; 8.02]; p = 0.369	Greater/lesser harm not proven
Nausea	20.9% vs. 9.2% RR: 2.28 [1.14; 4.56]; p = 0.015 RR[d]: 0.44 [0.22; 0.88] probability: “hint”	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: “minor”
Diarrhoea	15.5% vs. 4.6% RR: 3.37 [1.29; 8.81]; p = 0.008 RR[d]: 0.30 [0.11; 0.78] probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”

a: A positive change indicates improvement.
b: Probability provided if a statistically significant and relevant effect is present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: Institute’s calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CI_u: upper limit of confidence interval; DAA: direct acting antiviral agent; FU 12: 12 weeks after the end of treatment; MCS: Mental Component Summary; MD: mean difference; PCS: Physical Component Summary; 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; VOX: voxilaprevir; vs.: versus; W: weeks

2.7.4.2 Overall conclusion on the added benefit (research question 3.2)

Table 35 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 35: Positive and negative effects from the assessment of SOF/VEL/VOX in comparison with SOF/VEL (DAA-naive adults with CHC genotype 3, with compensated cirrhosis) (research question 3.2)

Positive effects	Negative effects
–	Non-serious/non-severe side effects ▪ Nausea hint of greater harm – extent: "minor" ▪ Diarrhoea hint of greater harm – extent: "considerable"
CHC: chronic hepatitis C; DAA: direct acting antiviral agent; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir	

The overall assessment showed only negative effects of SOF/VEL/VOX. In the outcome category "non-serious/non-severe side effects", a hint of greater harm from SOF/VEL/VOX with the extent "minor" was shown for the outcome "nausea". For the outcome "diarrhoea", there was a hint of greater harm from SOF/VEL/VOX with the extent "considerable". Overall, there is therefore a hint of lesser benefit of SOF/VEL/VOX versus SOF/VEL for DAA-naive patients with CHC genotype 3 and with compensated cirrhosis.

The result of the assessment of the added benefit of SOF/VEL/VOX in DAA-naive adults with CHC genotype 3 and with compensated cirrhosis in comparison with the ACT is summarized in Table 36.

Table 36: Sofosbuvir/velpatasvir/voxilaprevir – probability and extent of added benefit (research question 3.2)

Therapeutic indication	ACT[a]	Probability and extent of added benefit
DAA-naive adult patients with CHC genotype 3, with compensated cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**	Hint of lesser benefit[b, c]
a: Presentation of the ACT specified by the G-BA. Since the pharmaceutical company could choose a comparator therapy from several options because of the G-BA's specification of the ACT, the respective choice of the company is printed in **bold**. b: Patients with HBV or HIV coinfection were not included in the study. c: In the POLARIS-3 study included, sofosbuvir/velpatasvir/voxilaprevir was used for 8 weeks. Conclusions on the added benefit in 12-week treatment with sofosbuvir/velpatasvir/voxilaprevir, which is also in compliance with the approval [3], are not possible on the basis of the study. ACT: appropriate comparator therapy; CHC: chronic hepatitis C; DAA: direct acting antiviral agent; G-BA: Federal Joint Committee; HBV: hepatitis B virus; HIV: human immunodeficiency virus; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir		

This approach deviates from that of the company, which derived no lesser benefit of SOF/VEL/VOX for DAA-naive adults with CHC genotype 3 and with compensated cirrhosis (see Section 2.10.2.8.2).

2.7.5 List of included studies (research question 3.2)

Gilead. A phase 3, global, multicenter, randomized, open-label study to investigate the safety and efficacy of sofosbuvir/velpatasvir/GS-9857 fixed-dose combination for 8 weeks and sofosbuvir/velpatasvir for 12 weeks in subjects with chronic genotype 3 HCV infection and cirrhosis: study GS-US-367-1173 (POLARIS-3); Zusatzanalysen [unpublished]. 2017.

Gilead Sciences. Safety and efficacy of SOF/VEL/VOX FDC for 8 weeks and SOF/VEL for 12 weeks in adults chronic genotype 3 HCV infection and cirrhosis: full text view [online]. In: ClinicalTrials.gov. 12.01.2017 [Accessed: 01.09.2017]. URL: https://ClinicalTrials.gov/show/NCT02639338.

Gilead Sciences. A phase 3, global, multicenter, randomized, open-label study to investigate the safety and efficacy of sofosbuvir/velpatasvir/GS-9857 fixed-dose combination for 8 weeks and sofosbuvir/velpatasvir for 12 weeks in subjects with chronic genotype 3 HCV infection and cirrhosis [online]. In: EU Clinical Trials Register. [Accessed: 01.09.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-002996-12.

Gilead Sciences. A phase 3, global, multicenter, randomized, open-label study to investigate the safety and efficacy of sofosbuvir/velpatasvir/GS-9857 fixed-dose combination for 8 weeks and sofosbuvir/velpatasvir for 12 weeks in subjects with chronic genotype 3 HCV infection and cirrhosis: study GS-US-367-1173 (POLARIS-3); interim clinical study report [unpublished]. 2016.

Gilead Sciences. A phase 3, global, multicenter, randomized, open-label study to investigate the safety and efficacy of sofosbuvir/velpatasvir/GS-9857 fixed-dose combination for 8 weeks and sofosbuvir/velpatasvir for 12 weeks in subjects with chronic genotype 3 HCV infection and cirrhosis: study GS-US-367-1173 (POLARIS-3); final synoptic clinical study report [unpublished]. 2017.

Jacobson IM, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. Gastroenterology 2017; 153(1): 113-122.

2.8 Research question 7: DAA-experienced adults with CHC

2.8.1 Study pool (research question 7)

After submission of the dossier, the G-BA defined individual treatment specified by the physician as ACT for research question 7 (DAA-experienced adults with CHC) [7].

As mentioned in Section 2.2, the company distinguished between NS5A-naive and NS5A-experienced adults in this population. For NS5A-naive patients, the company specified the same comparator therapies as for DAA-naive adults, namely ledipasvir/sofosbuvir (LDV/ SOF) for genotype 1, 4, 5 and 6, and SOF/VEL for genotype 2 and 3. For NS5A-experienced adults, the company considered a treatment consisting of SOF/VEL + ribavirin (RBV) to be appropriate.

The comparator therapies named by the company may be possible treatment options within individual treatment specified by the physician. It was therefore investigated to what extent the studies presented by the company were suitable to draw conclusions on the added benefit of SOF/VEL/VOX in comparison with the ACT.

In accordance with the comparator therapy specified by the company, it presented different data for individual subpopulations of DAA-experienced adults (Table 37).

Table 37: Data presented by the company for DAA-experienced adults

Subpopulation of DAA-experienced adults	Data presented by the company
NS5A-naive	
▪ ▪ Genotypes 1 and 4	Further investigations: consideration of the SOF/VEL/VOX arms of 2 RCTs (for genotype 1: POLARIS-4 and TRILOGY-3; for genotype 4: POLARIS-4) without presentation of evidence on the comparator therapy
▪ Genotypes 2 and 3	RCT (POLARIS-4: one subpopulation for each genotype)
▪ Genotypes 5 and 6	–
NS5A-experienced	Further investigations: consideration of the SOF/VEL/VOX arms of 2 RCTs (POLARIS-1 and TRILOGY-3) without presentation of evidence on the comparator therapy
DAA: direct acting antiviral agent; NS: non-structural protein; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir	

For NS5A-naive adults, the company included a subpopulation of the RCT GS-US-367-1170 (hereinafter referred to with its abbreviated form “POLARIS-4”) [8] for each of the genotypes 2 and 3. Information on this study can be found in Appendix B of the full dossier assessment. This study was also identified in the check of the completeness of the company’s information retrieval.

The company identified no RCTs for direct comparisons of SOF/VEL/VOX versus the respective comparator therapy for NS5A-naive adults with genotype 1, 4, 5 or 6, or for NS5A-

experienced adults (see Section 2.3). The Institute's check of completeness also identified no RCTs for direct comparisons for these patient groups.

All of the data presented by the company for DAA-experienced adults were unsuitable for the derivation of conclusions on the added benefit of SOF/VEL/VOX. Hereinafter, the data for NS5A-naive and NS5A-experienced adults are described separately, presenting the reasons why these data were unsuitable to derive conclusions on the added benefit of SOF/VEL/VOX in comparison with the ACT.

NS5A-naive patients

Direct comparisons

The RCT POLARIS-4 used by the company

The company identified the RCT POLARIS-4, in which SOF/VEL/VOX was compared with SOF/VEL in DAA-experienced, NS5A-naive adults with genotype 1, 2 or 3 and without cirrhosis or with compensated cirrhosis.

Since the company specified LDV/SOF as comparator therapy for patients with genotype 1, but the comparison in the POLARIS-4 study was conducted with SOF/VEL, the company did not consider the stratum of genotype 1. It considered the strata of genotype 2 and 3, however, in which the comparator therapies specified by the company (SOF/VEL) were administered. The company used the subpopulations of genotype 2 and 3 separately for the respective derivation of the added benefit.

Appendix B of the full dossier assessment presents the characteristics of the POLARIS-4 study, of the interventions and of the patients in the subpopulation separated by genotype 1, 2 and 3, the risk of bias at study level, the available patient-relevant outcomes, as well as the risk of bias at outcome level and the corresponding results.

Suitability of the RCT POLARIS-4 for the present benefit assessment

The POLARIS-4 study was unsuitable to derive conclusions on the added benefit of SOF/VEL/VOX in comparison with the ACT because the ACT was not implemented in the POLARIS-4 study. In the study, treatment in the comparator arm was not chosen for the individual patient from one of several available treatment options under consideration of the pretreatment(s), the genotype and possible cross-resistances. Instead, all patients in the comparator arm were treated with SOF/VEL. There are further treatment options, which were not offered in the POLARIS-4 study, however. Daclatasvir [9], SOF + RBV [10] or SOF/VEL + RBV [5] are some of the options available also for DAA-experienced adults, depending on genotype, possibly cirrhosis status, and further factors.

Hence it is possible that effects in the POLARIS-4 study were caused by the fact that individual treatment specified by the physician was not implemented in the study. For example, a statistically significant difference in favour of SOF/VEL/VOX versus SOF/VEL was shown for SVR 12 in patients with genotype 3 and compensated cirrhosis (see Table 61

in Appendix B.2 of the full dossier assessment), from which the company derived an indication of a minor added benefit. However, the SPC of SOF/VEL notes that the addition of RBV should be considered for this patient group. This option was not available in the POLARIS-4 study. It is possible that patients of this patient group would have received SOF/VEL + RBV or another treatment option if individual treatment specified by the physician had been implemented. This might have had a better result than treatment with SOF/VEL and might not have resulted in significant difference between the treatment arms for SVR 12.

The results of the POLARIS-4 study are presented as additional information in Appendix B.2 of the full dossier assessment. Section 2.10.2.8.2 of the full dossier assessment briefly explores individual results.

Further investigations

Since the company identified no RCTs for direct comparisons with the ACT cited by the company for DAA-experienced, NS5A-naive adults with genotype 1, 4, 5 or 6, it searched for RCTs for adjusted indirect comparisons for these patient groups.

The company presented no data for genotype 5 and 6. For SOF/VEL/VOX, it identified 2 RCTs for genotype 1 and 4 (for genotype 1: POLARIS-4 and GS-US-367-1871 [hereinafter referred to with its abbreviated form "TRILOGY-3"] [11]; for genotype 4: POLARIS-4). Since the company identified no RCTs for its comparator therapy SOF/VEL, it conducted no indirect comparisons. It presented the results of the SOF/VEL/VOX arms of the studies POLARIS-4 and TRILOGY-3 in further investigations, however.

The characteristics of the POLARIS-4 study are presented in Appendix B.1 of the full dossier assessment. Patients in the TRILOGY-3 study were treated with SOF/VEL/VOX (N = 24) or – contrary to the SPC [3] – with SOF/VEL/VOX + RBV (N = 25).

Without presentation of the evidence on the ACT, the results of the further investigations are unsuitable for the derivation of conclusions on the added benefit of SOF/VEL/VOX in comparison with the ACT.

The company also derived no added benefit from the results for DAA-experienced, NS5A-naive adults presented under further investigations.

NS5A-experienced patients

The company specified SOF/VEL + RBV as comparator therapy for NS5A-experienced adults. Since the company identified no RCTs for direct comparisons for these patients, it searched for RCTs for adjusted indirect comparisons and for comparisons of individual arms from different RCTs (referred to by the company as "unadjusted indirect comparisons").

For SOF/VEL/VOX, the company identified the RCT TRILOGY-3 for genotype 1 and the RCT GS-US-367-1171 (hereinafter referred to with its abbreviated form "POLARIS-1") [12],

in which patients received SOF/VEL/VOX (N = 264) or placebo (N = 152), for all genotypes. Since the company identified no RCT for its comparator therapy SOF/VEL + RBV, it conducted neither adjusted indirect comparisons nor comparisons of individual arms from different RCTs. It presented the results of the SOF/VEL/VOX arms of the studies TRILOGY-3 and POLARIS-1 in further investigations, however. Overall, the company presented no comparative data.

Nonetheless, the company claimed a hint of a non-quantifiable added benefit for NS5A-experienced adults. This assessment was based on the results of the SOF/VEL/VOX arms presented in further investigations on the following outcomes: SVR 12 (97.5%), SAEs (1.8%), discontinuation due to AEs (0.4%), death (0%), diarrhoea (17.9%), fatigue (20.5%), headache (24.2%) and nausea (13.6%). Furthermore, the company claimed that SOF/VEL + RBV was the only option explicitly approved for these patients. It additionally claimed that, even assuming equivalent efficacy, an added benefit of SOF/VEL/VOX could be assumed due to the shorter treatment duration of SOF/VEL/VOX (12 weeks) in comparison with SOF/VEL + RBV (24 weeks). The company also stated that SOF/VEL/VOX was the only treatment option for NS5A-experienced adults for which a comprehensive and high-quality investigation of efficacy and safety had been conducted.

The company's assessment was not followed. The reasons were as follows:

1) Without presentation of the evidence on the ACT, the results on the RCTs TRILOGY-3 and POLARIS-1 in the further investigations are unsuitable for the derivation of conclusions on the added benefit of SOF/VEL/VOX in comparison with the ACT.
2) The ACT (individual treatment specified by the physician) comprised treatment options beyond SOF/VEL + RBV (see Section 2.10.1 of the full dossier assessment).
3) Even assuming equivalent efficacy, shorter treatment duration per se does not allow the derivation of an added benefit in comparison with SOF/VEL + RBV, particularly as some of the specific side effects mentioned by the company occurred in the SOF/VEL/VOX arms of the studies to an important degree.

Irrespective of this, the company mentioned a publication [13] on a non-comparative study, in which the efficacy and safety of SOF/VEL + RBV was investigated in NS5A-experienced adults (N = 69) without cirrhosis or with compensated cirrhosis and with genotype 1, 2 or 3. In this study, 91% of the patients reached SVR 12. Individual AEs were even more common in the studies on SOF/VEL/VOX than in the study on SOF/VEL + RBV. The company did not include this study in its benefit assessment, however, because it was not randomized (see Section 2.10.2.1 of the full dossier assessment). These data give reason to question the added benefit of SOF/VEL/VOX postulated by the company.

2.8.2 Results on added benefit (research question 7)

The company presented no suitable data for the assessment of the added benefit of SOF/VEL/VOX in comparison with the ACT for DAA-experienced adults. This resulted in no hint of an added benefit of SOF/VEL/VOX in comparison with the ACT. An added benefit is therefore not proven.

2.8.3 Probability and extent of added benefit (research question 7)

Since the company presented no suitable data for the assessment of the added benefit of SOF/VEL/VOX for DAA-experienced adults, an added benefit of SOF/VEL/VOX is not proven for these patients.

2.8.4 List of included studies (research question 7)

Not applicable as the company presented no suitable data for this research question for the benefit assessment.

2.9 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of SOF/VEL/VOX in comparison with the respective ACT is summarized in Table 38.

Table 38: Sofosbuvir/velpatasvir/voxilaprevir – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
DAA-naive adult patients with CHC genotype 1, without cirrhosis	**Ledipasvir/sofosbuvir** or ombitasvir/paritaprevir/ritonavir plus dasabuvir (if applicable, plus ribavirin)	Added benefit not proven
DAA-naive adult patients with CHC genotype 1, with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 2, without cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**	Added benefit not proven
DAA-naive adult patients with CHC genotype 2, with compensated cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**	Added benefit not proven
DAA-naive adult patients with CHC genotype 3, without cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**	Added benefit not proven
DAA-naive adult patients with CHC genotype 3, with compensated cirrhosis	Sofosbuvir plus ribavirin or **sofosbuvir/velpatasvir**	Hint of lesser benefit[b, c]
DAA-naive adult patients with CHC genotype 4, without cirrhosis	**Ledipasvir/sofosbuvir** or ombitasvir/paritaprevir/ritonavir plus ribavirin	Added benefit not proven
DAA-naive adult patients with CHC genotype 4, with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 5, without cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 5, with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 6, without cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-naive adult patients with CHC genotype 6, with compensated cirrhosis	Ledipasvir/sofosbuvir	Added benefit not proven
DAA-experienced adult patients with CHC	Individual treatment specified by the physician under consideration of the pretreatment(s), the genotype and the respective approval. Possible cross-resistances must be considered in the choice of the antiviral therapy, particularly in the case of protease inhibitors.[d]	Added benefit not proven

(continued)

Table 38: Sofosbuvir/velpatasvir/voxilaprevir – probability and extent of added benefit (continued)

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Patients with HBV or HIV coinfection were not included in the study.
c: In the POLARIS-3 study included, sofosbuvir/velpatasvir/voxilaprevir was used for 8 weeks. Conclusions on the added benefit in 12-week treatment with sofosbuvir/velpatasvir/voxilaprevir, which is also in compliance with the approval [3], are not possible on the basis of the study.
d: In accordance with the G-BA's specification it is assumed that interferon-based regimens are not an option for the patients.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; DAA: direct acting antiviral agent; G-BA: Federal Joint Committee; HBV: hepatitis B virus; HIV: human immunodeficiency virus

Overall, an added benefit of SOF/VEL/VOX versus the respective ACT is not proven for any of the research questions for the treatment of adult patients with CHC. There is a hint of lesser benefit of SOF/VEL/VOX in comparison with SOF/VEL for DAA-naive adults with CHC genotype 3 and with compensated cirrhosis.

This assessment deviates from that of the company insofar as the company

- considered the added benefit not to be proven for DAA-naive adults with genotype 3 and with compensated cirrhosis (research question 3.2) and derived no hint of lesser benefit (see Section 2.10.2.8.2 of the full dossier assessment),
- derived an indication of a minor added benefit for DAA-experienced, NS5A-naive adults with genotype 3 and with compensated cirrhosis (patient group within research question 7) (see Section 2.10.2.8.2 of the full dossier assessment), and
- derived a hint of a non-quantifiable added benefit for DAA-experienced, NS5A-experienced adults with genotype 1 to 6 and without cirrhosis or with compensated cirrhosis (patient group within research question 7) (see Section 2.10.2.8.2 of the full dossier assessment).

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

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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