IQWiG Reports – Commission No. A20-86

Sofosbuvir/velpatasvir (chronic hepatitis C in children and adolescents) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Sofosbuvir/Velpatasvir (chronische Hepatitis C bei Kindern und Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 23 December 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IFN	interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PedsQL 4.0 SF15	Pediatric Quality of Life Inventory Version 4.0 Short Form 15
RBV	ribavirin
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOF	sofosbuvir
SPC	Summary of Product Characteristics
SVR 12/SVR 24	sustained virologic response 12/24 weeks after end of treatment
VEL	velpatasvir

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination sofosbuvir/velpatasvir (SOF/VEL). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 22 September 2020.

Research question

The aim of the present report is the assessment of the added benefit of SOF/VEL in comparison with the appropriate comparator therapy (ACT) in children and adolescents aged 6 to < 18 years and weighing at least 17 kg with chronic hepatitis C (CHC).

For the benefit assessment of SOF/VEL, the research questions presented in Table 2 resulted from the ACTs specified by the G-BA.

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

Research questions	Subindication	ACT[a]
1	Children aged 6 to < 12 years with CHC	Watchful waiting[b]
2	Adolescents aged 12 to < 18 years with CHC	
2a	With genotype 1, 4, 5 or 6	Ledipasvir/sofosbuvir or glecaprevir/pibrentasvir
2b	With genotype 2 or 3	Sofosbuvir + ribavirin or glecaprevir/pibrentasvir

a. Presentation of the respective ACT specified by the G-BA.
b. In the present age group, therapy with the approved options (peg)interferon + ribavirin is no longer considered adequate according to the current guideline recommendations and is only used in exceptional cases.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; (peg)interferon: (pegylated) interferon; SOF: sofosbuvir; VEL: velpatasvir

The company followed the G-BA's specification of the ACT.

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

Results for research question 1: children (6 to < 12 years)

Study pool and patient population

The single-arm study G342-1143 (hereinafter referred to as "study 1143") was used for the present benefit assessment. This study investigated the administration of SOF/VEL in children and adolescents aged 3 to < 18 years with CHC of any genotype. The study included 3 different age cohorts. The cohort of 6 to < 12-year-olds relevant to the present research question included 73 children.

All children in the relevant cohort received 200/50 mg SOF/VEL for 12 weeks regardless of their body weight. According to the Summary of Product Characteristics (SPC), the dose of 200/50 mg SOF/VEL is approved for a body weight of ≥ 17 to < 30 kg. From a body weight of 30 kg, the daily dose is 400/100 mg SOF/VEL. Since dosing in the study was adapted to age and not to body weight, the treatment was underdosed in children aged 6 to < 12 years who already weighed > 30 kg. This concerned 28 of the 73 children (38.4%).

In the present data constellation, however, it is assumed that the data of the entire cohort of 6 to 12-year-olds are suitable for deriving conclusions on the added benefit for research question 1 because the described underdosing did not have a relevant effect on the study results.

In the relevant cohort 2 of the study, the majority of the included patients were infected with genotype 1 hepatitis C virus (HCV). Only 2 children had genotype 2 HCV, only 4 children had genotype 4, and none of the children had genotype 5 or 6 HCV.

Risk of bias

Since the present assessment was based on one single-arm study without comparative assessment with the ACT, the aspects of bias were not assessed for the included study or for the included outcomes. On the basis of the limited evidence, at most hints of an added benefit can be determined.

Assessment of the study results

Results from the single-arm study 1143 were available for the assessment of the added benefit of SOF/VEL in children aged 6 to 12 years. Due to the specific data situation, it was still possible to draw conclusions on the added benefit on the basis of the available evidence.

In study 1143, about 93% of the patients aged 6 to < 12 years achieved sustained virologic response 12 (SVR 12) or 24 weeks (SVR 24) after the end of therapy with SOC/VEL. Under the ACT watchful waiting, virus elimination (e.g. by spontaneous virus elimination) is unlikely, however. Thus, an advantage of SOF/VEL in SVR can be deduced even without studies of direct comparison being available.

For the outcome “health-related quality of life” recorded with the Pediatric Quality of Life Inventory Version 4.0 Short Form 15 (PedsQL 4.0 SF15), the change in total score from baseline to follow-up week 24 in the entire cohort was 4.2 points (standard deviation: 13.7 points).

There were also no data for a comparison with the ACT watchful waiting to assess the risk of harm of SOF/VEL. However, no deaths and only individual cases of serious adverse events (SAEs) and discontinuations due to adverse events (AEs) were observed under SOF/VEL (in each case 2 [2.7%]).

Overall, in this particular data constellation (achievement of SVR in > 93% of the patients, no deaths, and SAEs or discontinuations due to AEs each in only 2.7% of the patient population),

a derivation of the added benefit of SOF/VEL is possible. With great certainty, the results in SVR cannot be achieved by the ACT watchful waiting. Furthermore, the risk of harm under SOF/VEL observed in the study does not call into question the advantage this drug combination has in the SVR rate.

In the present situation, there is a hint of a non-quantifiable added benefit of SOF/VEL in children from 6 to < 12 years of age with CHC. Since the study included only 2 children with genotype 2 HCV, 4 children with genotype 4, and none with genotype 5 or 6, the added benefit is determined exclusively for children with genotype 1 or 3.

Results for research questions 2a and 2b: adolescents (12 to < 18 years)

Concurring with the company, the check of the completeness of the study pool produced no randomized controlled trials (RCTs) of direct comparison with SOF/VEL in adolescents aged 12 to < 18 years.

Overall, the company did not present any data for adolescents aged 12 to < 18 years to derive an added benefit of SOF/VEL in comparison with the ACT and claimed no added benefit for SOF/VEL.

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

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

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

Research question 1: children (6 to < 12 years)

On the basis of the limited evidence, at most hints of an added benefit can be determined. The extent of the added benefit cannot be quantified because there was no comparison with the ACT watchful waiting and because SVR was considered as sufficiently valid surrogate for the patient-relevant outcome “hepatocellular carcinoma”.

In the present situation, there is a hint of a non-quantifiable added benefit of SOF/VEL in comparison with the ACT for children with CHC genotype 1 or 3. This added benefit refers

[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, added benefit not proven, or less benefit). For further details see [1,2].

only to children without cirrhosis. Patients with decompensated cirrhosis were not investigated in the included study.

There was no hint of an added benefit of SOF/VEL in comparison with the ACT for children with CHC genotype 2, 4, 5 or 6; an added benefit is therefore not proven.

Research questions 2a and 2b: adolescents (12 to < 18 years)

Since the company presented no data for the assessment of the added benefit of SOF/VEL in comparison with the ACT in adolescents aged 12 to < 18 years with CHC, an added benefit of SOF/VEL in comparison with the ACT is not proven for these patients.

Table 3 shows a summary of probability and extent of the added benefit of SOF/VEL.

Table 3: SOF/VEL – probability and extent of added benefit

Research questions	**Subindication**	**ACT**[a]	**Probability and extent of added benefit**
1	Children aged 6 to < 12 years with CHC		
	▪ Genotype 1 or 3[b]	Watchful waiting	Hint of non-quantifiable added benefit
	▪ Genotype 2, 4, 5 or 6[c]	Watchful waiting	Added benefit not proven
2	Adolescents aged 12 to < 18 years with CHC		
2a	▪ Genotype 1, 4, 5 or 6	Ledipasvir/sofosbuvir or glecaprevir/pibrentasvir	Added benefit not proven
2b	▪ Genotype 2 or 3	Sofosbuvir + ribavirin or glecaprevir/pibrentasvir	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Study 1143 included no children with confirmed cirrhosis and no children with HIV, HAV or HBV coinfection. Hence, no conclusions on the added benefit can be drawn for these populations.
c. Study 1143 included only 2 children with genotype 2, 4 children with genotype 4 and no children with genotype 5 or 6. Therefore, no conclusions on the added benefit can be drawn for CHC infections with these genotypes.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HAV: hepatitis A virus; HBV: hepatitis B virus; HIV: human immunodeficiency virus; SOF: sofosbuvir; VEL: velpatasvir

The approach for the derivation of 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 the present report is the assessment of the added benefit of SOF/VEL in comparison with the ACT in children and adolescents aged 6 to < 18 years and weighing at least 17 kg with CHC.

For the benefit assessment of SOF/VEL, the research questions presented in Table 4 resulted from the ACTs specified by the G-BA.

Table 4: Research questions of the benefit assessment of SOF/VEL

Research questions	Subindication	ACT[a]
1	Children aged 6 to < 12 years with CHC	Watchful waiting[b]
2	Adolescents aged 12 to < 18 years with CHC	
2a	With genotype 1, 4, 5 or 6	Ledipasvir/sofosbuvir or glecaprevir/pibrentasvir
2b	With genotype 2 or 3	Sofosbuvir + ribavirin or glecaprevir/pibrentasvir

a. Presentation of the respective ACT specified by the G-BA.
b. In the present age group, therapy with the approved options (peg)interferon + ribavirin is no longer considered adequate according to the current guideline recommendations and is only used in exceptional cases.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; (peg)interferon: (pegylated) interferon; SOF: sofosbuvir; VEL: velpatasvir

The company followed the G-BA's specification of the ACT.

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

2.3 Research question 1: children (6 to < 12 years)

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on SOF/VEL (status: 24 July 2020)
- bibliographical literature search on SOF/VEL (last search on 17 July 2020)
- search in trial registries/trial results databases for studies on SOF/VEL (last search on 8 July 2020)
- search on the G-BA website for SOF/VEL (last search on 17 July 2020)

To check the completeness of the study pool:

- bibliographical literature search on SOF/VEL (last search on 20 October 2020)
- search in trial registries for studies on SOF/VEL (last search on 6 October 2020)

Concurring with the company, the check of the completeness of the study pool for children aged 6 to < 12 years with CHC produced no RCTs for a direct comparison of SOF/VEL versus the ACT.

The company conducted an additional information retrieval for further investigations with the intervention and identified the single-arm study G342-1143 (hereinafter referred to as "study 1143"). It did not conduct an information retrieval for further investigations with the ACT.

The completeness of the study pool for studies with SOF/VEL was also checked for further investigations. No additional relevant study was identified from the check.

2.3.1.1 Studies included

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

Table 5: Study pool – non-RCT, single-arm study: SOF/VEL

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
G342-1143 (1143[c])	Yes	Yes	No	Yes [3,4]	Yes [5-8]	No

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
CSR: clinical study report; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir

The study 1143 presented by the company is a single-arm study with SOF/VEL without comparison with the ACT. Although this is a single-arm study, conclusions on the added benefit of SOF/VEL in children aged 6 to < 12 years with CHC can still be drawn on the basis of this study due to the special data constellation. The study was therefore used for the assessment of the added benefit. The reasons for this can be found in Section 2.3.2.2.

2.3.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – non-RCT, single-arm study: SOF/VEL

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
1143	Single-arm	Children and adolescents (3 to < 18 years) with CHC (all genotypes[b])	SOF/VEL: ▪ Cohort 1: adolescents aged 12 to < 18 years (N = 102)[c] ▪ Cohort 2: children aged 6 to < 12 years (N = 73) ▪ Cohort 3: children aged 3 to < 6 years (N = 41)[c]	▪ Screening: up to 42 days ▪ PK lead-in phase: 7 days[d] ▪ Treatment: 12 weeks[e] ▪ Follow-up observation[f, g]: 24 weeks	28 centres in Belgium, Italy, United Kingdom, USA 1/2017–2/2020	Primary: AEs, discontinuation due to AEs Secondary: SVR 12, SVR 24, health-related quality of life

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. No patients with genotype 5 were included in the total population of the study. The relevant cohort 2 also included no patients with genotype 6.
c. The cohort is not relevant for the assessment and is not shown in the following tables.
d. The PK lead-in phase comprised only a part of the study population (planned for at least 17 patients of each cohort).
e. Patients who had already participated in the PK lead-in phase continued treatment only until they reached the total planned treatment duration of 12 weeks.
f. Outcome-specific information is provided in Table 8.
g. Long-term follow-up observation (5 years) in the framework of a separate study (GS-US-334-1113) for patients who do not initiate another anti-HCV therapy.

AE: adverse event; CHC: chronic hepatitis C; HCV: hepatitis C virus; N: number of patients included; PK: pharmacokinetics; RCT: randomized controlled trial; SOF: sofosbuvir; SVR 12/SVR 24: sustained virologic response 12/24 weeks after end of treatment; VEL: velpatasvir

Table 7: Characteristics of the intervention – non-RCT, single-arm study: SOF/VEL

Study	Intervention
1143	Cohort 2: children aged 6 to < 12 years[a]: ▪ SOF 200 mg/VEL 50 mg once/day, orally, for 12 weeks[b]
	Pretreatment Allowed: ▪ IFN with or without RBV and with or without a protease inhibitor (completed ≥ 8 weeks before study start) Not allowed: ▪ use of an HCV NS5A inhibitor **Concomitant treatment** Not allowed, e.g.: ▪ 60 days before study start until end of therapy ▫ cardiac medication (amiodarone) ▪ 21 days before study start until end of study ▫ anticonvulsants (phenobarbital, phenytoin, carbamazepine) ▫ antimycotics (rifampicin, rifabutin, rifapentine) ▫ herbal or natural drugs (St. John's Wort, echinacea, milk thistle [silymarin], Chinese medicinal herbs) ▫ other drugs: bosentan, modafinil, sulfasalazine, methotrexate

a. According to the SPC of SOF/VEL [9], the dose is 200/50 mg per day for patients weighing ≥ 17 to < 30 kg, and 400/100 mg per day for patients weighing 30 kg or more.
b. In case of inability to swallow: 4 x 50/12.5 mg granules.

HCV: hepatitis C virus; IFN: interferon; NS5A: nonstructural protein 5A; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; VEL: velpatasvir

Study 1143 is a single-arm study investigating SOF/VEL in children and adolescents aged 3 to < 18 years with CHC of any genotype.

A total of 216 children and adolescents were included in the 3 cohorts of the study depending on their age. For the present research question, the cohort of 6 to < 12-year-olds is relevant, in which 73 children were included. Children with current or prior history of hepatic decompensation or coinfection with human immunodeficiency virus (HIV), hepatitis A virus (HAV), or hepatitis B virus (HBV) were excluded from study participation. Patients had to be either pretreated, treatment-naive or interferon (IFN)-intolerant. Treatment-experienced patients had to have completed a regimen containing IFN with or without ribavirin (RBV) and with or without a protease inhibitor due to treatment failure or intolerance at least 8 weeks before study start.

In the beginning of the study, some of the patients of each age cohort participated in a 7-day pharmacokinetics lead-in phase, which was aimed at confirming the suitability of the SOF/VEL dosing for the respective age group. After this lead-in phase, the patients continued therapy in the treatment phase without interruption until reaching the total planned treatment duration of 12 weeks. Further patients were enrolled directly into the treatment phase after analysis of the pharmacokinetics lead-in phase.

In the study, children between 6 and < 12 years of age received 200/50 mg SOF/VEL daily regardless of body weight. Thus, some of the children were not treated in compliance with the approval, as the approval of SOF/VEL recommends a higher dose for patients weighing 30 kg or more (for a detailed discussion, see below). In addition, SOF/VEL could be administered as granules in case of inability to swallow. The granules are not approved in Germany [9]. However, only 2 of the 73 children (2.7%) in the relevant cohort were treated with the granules.

The primary outcome of study 1143 were AEs, with a particular focus on AEs leading to discontinuation of the study medication. Secondary outcomes were SVR 12 and SVR 24 and health-related quality of life.

Study 1143 was completed in February 2020. The patients could then participate in a separate study on longterm follow-up observation if they did not start another anti-HCV therapy (GS-US-334-1113).

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of follow-up observation – non-RCT, single-arm study: SOF/VEL

Study **Outcome category** **Outcome**	**Planned follow-up observation**
1143	
Mortality	
All-cause mortality	24 weeks after end of treatment[a]
Morbidity	
SVR 12	12 weeks after end of treatment
SVR 24	24 weeks after end of treatment
Health-related quality of life	
PedsQL 4.0 SF15	24 weeks after end of treatment
Side effects	
AEs	4 weeks after end of treatment
SAEs	24 weeks after end of treatment

a. Deaths were recorded in the framework of the SAEs.

AE: adverse event; PedsQL 4.0 SF15: Pediatric Quality of Life Inventory Version 4.0 Short Form 15; RCT: randomized controlled trial; SAE: serious adverse event; SOF: sofosbuvir; SVR 12/SVR 24: sustained virologic response 12/24 weeks after end of treatment; VEL: velpatasvir

Patient populations presented by the company

As described above, according to the SPC, the dose of 200/50 mg SOF/VEL is approved up to a body weight of ≥ 17 to < 30 kg. From a body weight of 30 kg, the daily dose is 400/100 mg SOF/VEL [9]. Since dosing in the study was adapted to age and not to body weight, the treatment was underdosed in children aged 6 to < 12 years who already weighed ≥ 30 kg. This

concerned 28 of the 73 children (38.4%). In addition to the entire cohort of 6 to 12-year-olds (N = 73), the company therefore also presented the data of the subpopulation with a body weight of ≥ 17 to < 30 kg (N = 45) who were treated in compliance with the approval in Module 4 A of the dossier.

In the present data constellation, it is assumed that the data of the entire cohort of 6 to 12-year-olds are suitable for deriving conclusions on the added benefit for research question 1 because the described partial underdosing did not have a relevant effect on the study results. Regarding morbidity, the SVR (SVR 12 and SVR 24) in the entire cohort (93.2% each) is about the same as in children in the subpopulation treated in compliance with the approval (93.3% each). There were also no relevant differences between the 2 populations regarding side effect outcomes (see Section 2.3.2.2). Furthermore, data from cohort 1 of study 1143 are available for adolescents (12 to < 18 years) who received SOF/VEL at the dose of 400/100 mg. In adolescents, no deaths or discontinuations due to AEs and only 2 SAEs (2% of the patients) occurred under this dosage. Therefore, an underestimation of the harm of SOF/VEL in study 1143 is also not assumed for children weighing ≥ 30 kg. The present assessment presents both patient populations for the children, but uses the data of the entire cohort 2 to derive the added benefit.

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – non-RCT, single-arm study: SOF/VEL (multipage table)

Study **Characteristic** **Category**	**SOF/VEL**	
1143	Cohort 2 (6 to < 12 years) N = 73	Cohort 2 (6 to < 12 years; ≥ 17 to < 30 kg body weight) N = 45
Age [years], median [Q1; Q3]	8 [7; 9]	7 [7; 8]
Sex [F/M], %	52/48	49/51
Family origin, n (%)		
White	66 (90.4)	43 (95.6)
Asian	1 (1.4)	0
Black or African American	4 (5.5)	1 (2.2)
Other	2 (2.7)	1 (2.2)
Weight at baseline [kg], median [Q1; Q3]	26.7 [23.0; 35.0]	24.2 [21.8; 26.1]
HCV subgenotype, n (%)		
1	56 (76.7)	36 (80.0)
1a	47 (64.4)	30 (66.7)
1b	9 (12.3)	6 (13.3)
2	2 (2.7)	1 (2.2)
2b	2 (2.7)	1 (2.2)
3	11 (15.1)	6 (13.3)
3a	11 (15.1)	6 (13.3)
4	4 (5.5)	2 (4.4)
4a	2 (2.7)	1 (2.2)
4d	1 (1.4)	0
4p	1 (1.4)	1 (2.2)
Cirrhosis, n (%)		
Yes	0	0
No	31 (42.5)	20 (44.4)
Not determined	42 (57.5)	25 (55.6)
Baseline HCV RNA viral load [IU/mL], n (%)		
< 800 000	38 (52.1)	24 (53.3)
≥ 800 000	35 (47.9)	21 (46.7)
Pretreatment status, n (%)		
Treatment-naive	69 (94.5)	43 (95.6)
Treatment-experienced	4 (5.5)	2 (4.4)
No response	1 (25.0)	1 (50.0)
Relapse	3 (75.0)	1 (50.0)
Treatment discontinuation, n (%)	4 (5.5)	ND
Study discontinuation, n (%)	4 (5.5)	ND

Table 9: Characteristics of the study population – non-RCT, single-arm study: SOF/VEL (multipage table)

Study Characteristic Category	SOF/VEL
F: female; GT: genotype; HCV: hepatitis C virus; IU: international units; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of patients included; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; RNA: ribonucleic acid; SOF: sofosbuvir; VEL: velpatasvir	

The mean age of the children included in the entire cohort (6 to < 12 years) of study 1143 was 8 years. The sex ratio was balanced and the vast majority of the children were of white family origin. Most children (about 95%) were treatment-naive and none had confirmed cirrhosis, with the cirrhosis status being unknown in more than half of the children. In the relevant cohort 2, the majority of the included patients were infected with genotype 1 HCV. Only 2 children had genotype 2 HCV, 4 children had genotype 4, and no child had genotype 5 or 6 HCV.

Transferability of the study results to the German health care context

The company considered the transferability of the study results to everyday health care in Germany to be given due to the comparability of the study populations with the HCV-infected German population. The company described that the proportion of female and male children (6 to < 12 years) was almost identical in study 1143 and comparable with the distribution of sexes reported at the Robert Koch Institute (RKI) over the last few years [10].

The company further explained that the main transmission route in the study was vertical infection and that this was consistent with the transmission routes relevant in Germany, since, according to the guideline relevant for Germany [11], the main transmission route in children and adolescents is vertical transmission. Concurring with the population shares in Germany, the majority of the patients in the study were of white family origin, the company stated.

The company concluded overall that a transferability of the study data of study 1143 to the German health care context can be assumed.

The company did not provide any further data on the transferability of the study results to the German health care context.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - sustained virologic response (SVR 12 and SVR 24) as sufficiently valid surrogate for the patient-individual outcome "hepatocellular carcinoma"
- Health-related quality of life
  - health-related quality of life measured using the PedsQL 4.0 SF15
- Side effects
  - SAEs
  - discontinuation due to AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes concurs with that of the company. For the SVR, the company only presented the data for the time point of 12 weeks after the end of treatment in Module 4 of the dossier. Furthermore, the results on SVR at week 24 after the end of treatment are relevant and are presented in the present assessment.

Table 10 shows for which outcomes data were available in the study included.

Table 10: Matrix of outcomes – non-RCT, single-arm study: SOF/VEL

Study	Outcomes						
	All-cause mortality	SVR 12	SVR 24	Health-related quality of life (PedsQL 4.0 SF15)	SAEs	Discontinuation due to AEs	Specific AEs
1143	Yes	Yes	Yes	Yes	Yes	Yes	No[a]

a. Due to the data situation, no choice of specific AEs is possible.

AE: adverse event; PedsQL 4.0 SF15: Pediatric Quality of Life Inventory Version 4.0 Short Form 15; RCT: randomized controlled trial; SAE: serious adverse event; SOF: sofosbuvir; SVR 12/SVR 24: sustained virologic response 12/24 weeks after end of treatment; VEL: velpatasvir

Outcome "SVR"

In the present benefit assessment, the SVR was not assessed as a directly patient-relevant outcome, but as a sufficiently valid surrogate for the outcome "hepatocellular carcinoma". For detailed justification of the validity of the surrogate, see the benefit assessment of boceprevir [12]. As this assessment is based on data from observational studies, it is subject to increased uncertainty.

Specific AEs

The company presented a choice of specific AEs. It is unclear to what extent this ensures a complete presentation of relevant specific AEs. In addition, due to the lack of data on specific AEs under the ACT, a choice of specific AEs is not possible.

2.3.2.2 Results

Since one single-arm study without comparative assessment of the ACT was used for the present assessment, the aspects of bias were not assessed for the study included or for any of the outcomes included.

Table 11 and Table 12 summarize the results on SOF/VEL in children aged 6 to < 12 years with CHC from study 1143. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Tables with the common AEs are presented in Appendix A of the full dossier assessment.

Table 11: Results (mortality, morbidity, side effects) – non-RCT, single-arm study: SOF/VEL

Study Outcome category Outcome	SOF/VEL			
	Cohort 2 (6 to < 12 years)		Supplementary information: Cohort 2 (6 to < 12 years; ≥ 17 to < 30 kg body weight)	
	N	Patients with event n (%)	N	Patients with event n (%)
1143				
Mortality				
All-cause mortality[a]	73	0 (0)	45	0 (0)
Morbidity				
SVR 12[b]	73	68 (93.2)	45	42 (93.3)
SVR 24[b]	73	68 (93.2)	45	42 (93.3)
Side effects				
AEs (supplementary information)	73	59 (80.8)	45	37 (82.2)
SAEs[c]	73	2 (2.7)	45	2 (4.4)
Discontinuation due to AEs	73	2 (2.7)	45	2 (4.4)

a. Recorded via SAEs.
b. Sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma".
c. The 2 events were the PTs "constipation" and "auditory hallucination", the latter leading to treatment discontinuation. It is not clear from the study documents whether this information is based on a follow-up period of 30 days or 24 weeks.

AE: adverse event; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOF: sofosbuvir; SVR 12/SVR 24: sustained virologic response 12/24 weeks after end of treatment; VEL: velpatasvir

Table 12: Results (health-related quality of life) – non-RCT, single-arm study: SOF/VEL

Study Outcome category Outcome	SOF/VEL					
	Cohort 2 (6 to < 12 years)			Supplementary information: Cohort 2 (6 to < 12 years; ≥ 17 to < 30 kg body weight)		
	N[a]	Values at baseline mean (SD)	Change at FU week 24 mean[b] (SD)	N[a]	Values at baseline mean (SD)	Change at FU week 24 mean[b] (SD)
1143						
Health-related quality of life						
PedsQL (total score, patient-reported)[c]	69	77.9 (13.3)	4.2 (13.7)	42	78.9 (12.0)	0.9 (12.8)

a. Number of patients considered in the analysis; the values at baseline (possibly at other time points) may be based on other patient numbers.
b. If there are no values for FU week 24, the last available value after completion of treatment was imputed.
c. Higher (increasing) values mean better quality of life.

FU: follow-up; N: number of analysed patients; PedsQL 4.0 SF15: Pediatric Quality of Life Inventory Version 4.0 Short Form 15; RCT: randomized controlled trial; SD: standard deviation; SOF: sofosbuvir; VEL: velpatasvir

Results from the single-arm study 1143 were available for the assessment of the added benefit of SOF/VEL in children aged 6 to < 12 years. Due to the specific data situation, it was still possible to draw conclusions on the added benefit on the basis of the available evidence. At most hints, e.g. of an added benefit, can therefore be determined for all outcomes.

In the present study, about 93% of the 6 to < 12-year-old patients achieved SVR 12 or SVR 24 under SOF/VEL, regardless of body weight. Under the ACT watchful waiting, virus elimination (e.g. by spontaneous virus elimination) is unlikely, however. Thus, an advantage of SOF/VEL in SVR can be deduced even without studies of direct comparison being available.

In the entire cohort, 5 of the 73 children did not achieve SVR 12 and SVR 24. 4 of them had genotype 1 HCV and one child had genotype 3 HCV. One 10-year old patient weighing > 30 kg showed no virologic response to treatment. For 4 further patients, no measurement was available at week 12, which is why they were rated as patients without a SVR. Of these, 2 children had no follow-up examination at week 12 or 24 (lost to follow-up). 2 other children had discontinued the study medication, one due to an AE already on day 7 of the treatment phase (Preferred Term [PT]: product use issue) and one at the discretion of the investigator.

For the outcome “health-related quality of life”, the company presented data for the PedsQL 4.0 SF15. The questionnaire comprises 15 questions and measures health-related quality of life using the dimensions of physical functioning, emotional functioning, social functioning and school functioning [13]. In study 1143, the change in total score from baseline to follow-up week 24 in the entire cohort was 4.2 points (standard deviation: 13.7 points).

There were also no data for a comparison with the ACT watchful waiting to assess the risk of harm of SOF/VEL. However, no deaths and only individual cases of SAEs and discontinuations due to AEs (in each case 2 [2.7%]) were observed under SOF/VEL.

Overall, in this particular data constellation (achievement of SVR in > 93% of the patients, no deaths, and SAEs or discontinuations due to AEs each in only 2.7% of the patient population), a derivation of the added benefit of SOF/VEL in comparison with the ACT is possible. With great certainty, the results in SVR cannot be achieved by the ACT watchful waiting. Furthermore, the risk of harm under SOF/VEL observed in the study does not call into question the advantage this drug combination has in the SVR rate.

On the basis of the limited evidence, at most hints of an added benefit can be determined. The extent of the added benefit cannot be quantified because there was no comparative study with the ACT watchful waiting and because SVR was considered as sufficiently valid surrogate for the patient-relevant outcome “hepatocellular carcinoma”.

In the present situation, there is a hint of a non-quantifiable added benefit of SOF/VEL in children from 6 to < 12 years of age with CHC. Since the study included only 2 children with genotype 2 HCV, 4 children with genotype 4, and none with genotype 5 or 6, the added benefit is determined exclusively for children with genotype 1 or 3.

2.3.3 Probability and extent of added benefit

In summary, there is a hint of a non-quantifiable added benefit of SOF/VEL in comparison with the ACT watchful waiting for children aged 6 to < 12 years with genotype 1 or 3 CHC. This added benefit refers only to children without cirrhosis. Patients with decompensated cirrhosis were not investigated in the included study.

This deviates from the assessment of the company, which derived a hint of a major added benefit of SOF/VEL in comparison with the ACT for children aged 6 to < 12 years and weighing < 30 kg, regardless of cirrhosis status and genotype.

2.4 Research questions 2a and 2b: adolescents (12 to < 18 years)

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on SOF/VEL (status: 27 July 2020)
- bibliographical literature search on SOF/VEL (last search on 6 July 2020)
- search in trial registries for studies on SOF/VEL (last search on 8 July 2020)

To check the completeness of the study pool:

- search in trial registries for studies on SOF/VEL (last search on 6 October 2020)

Concurring with the company, the check of the completeness of the study pool produced no RCTs of direct comparison with SOF/VEL in adolescents aged 12 to < 18 years.

The company did not conduct an information retrieval for lower evidence level studies for the present research question and did not claim an added benefit for SOF/VEL. It justified this with the good efficacy and tolerability of the defined ACT options, compared to which no significant advantage of SOF/VEL was to be expected.

Overall, the company did not present any data for adolescents aged 12 to < 18 years to derive an added benefit in comparison with the ACT.

2.4.2 Results on added benefit

The company presented no data for the assessment of the added benefit of SOF/VEL in comparison with the ACT in adolescents aged 12 to < 18 years with CHC. This resulted in no hint of an added benefit of SOF/VEL in comparison with the ACT; an added benefit is not proven.

2.4.3 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of SOF/VEL in comparison with the ACT in adolescents aged 12 to < 18 years with CHC, an added benefit of SOF/VEL in comparison with the ACT is not proven for these patients.

This concurs with the assessment of the company, which claimed no added benefit in the present therapeutic indication.

2.5 Probability and extent of added benefit – summary

Table 13 shows a summary of the probability and extent of the added benefit of SOF/VEL in children and adolescents aged 6 to < 18 years with CHC.

Table 13: SOF/VEL – probability and extent of added benefit

Research questions	Subindication	ACT[a]	Probability and extent of added benefit
1	Children aged 6 to < 12 years with CHC		
	▪ Genotype 1 or 3[b]	Watchful waiting	Hint of non-quantifiable added benefit
	▪ Genotype 2, 4, 5 or 6[c]	Watchful waiting	Added benefit not proven
2	Adolescents aged 12 to < 18 years with CHC		
2a	▪ Genotype 1, 4, 5 or 6	Ledipasvir/sofosbuvir or glecaprevir/pibrentasvir	Added benefit not proven
2b	▪ Genotype 2 or 3	Sofosbuvir + ribavirin or glecaprevir/pibrentasvir	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Study 1143 included no children with confirmed cirrhosis and no children with HIV, HAV or HBV coinfection. Hence, no conclusions on the added benefit can be drawn for these populations.
c. Study 1143 included only 2 children with genotype 2, 4 children with genotype 4 and no children with genotype 5 or 6. Therefore, no conclusions on the added benefit can be drawn for CHC infections with these genotypes.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HAV: hepatitis A virus; HBV: hepatitis B virus; HIV: human immunodeficiency virus; SOF: sofosbuvir; VEL: velpatasvir

The approach for the derivation of 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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