IQWiG Reports – Commission No. A20-64

Sofosbuvir (chronic hepatitis C in children) –

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 (chronische Hepatitis C bei Kindern) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 October 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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Table of contents

List of tables[2]

Page

[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)
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
PT	Preferred Term
RBV	ribavirin
RCT	randomized controlled trial
RKI	Robert Koch Institute
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOF	sofosbuvir
SPC	Summary of Product Characteristics
SVR	sustained virologic response
SVR 12	sustained virologic response12 weeks after the end of treatment
SVR 24	sustained virologic response 24 weeks after the end of treatment

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug sofosbuvir (SOF, in combination with ribavirin [RBV]). 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 24 July 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of SOF (+ RBV) in comparison with the appropriate comparator therapy (ACT) in children aged 3 to < 12 years with genotype 2 or 3 chronic hepatitis C (CHC).

For the benefit assessment of SOF (+ RBV), the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of SOF (+ RBV)

Research question	Therapeutic indication	ACT[a]
1	Children aged 3 to < 12 years with GT 2 or 3 CHC	Watchful waiting
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; GT: genotype; RBV: ribavirin, SOF: sofosbuvir		

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

For children, SOF is only approved in combination with other drugs. The Summary of Product Characteristics (SPC) of SOF recommends treatment regimens and durations only for the combination with RBV. All conclusions on the assessment of the added benefit therefore refer to the combination of SOF (+ RBV).

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

Results

Study pool and patient population

The single-arm, open-label study G334-1112 (hereinafter referred to as "study 1112") was used for the benefit assessment. This study investigated the administration of SOF + RBV in children and adolescents aged 3 to < 18 years with genotype 2 or 3 CHC. The study included different age cohorts. The cohort of 3 to < 6-year-olds relevant for the present assessment comprised 13 children, and the cohort of 6 to < 12-year-olds 41 children.

In compliance with the approval, SOF was administered in combination with RBV in study 1112. The treatment of the children deviated in part from the requirements of the SPC of SOF. However, in the present data constellation, these deviations do not call into question the consideration of the results for included outcomes. Children with genotype 2 CHC were treated for 12 weeks and children with genotype 3 CHC for 24 weeks.

Assessment of the study results

Since one single-arm study was used for the present assessment, the aspects of bias were not assessed for the study included or for any of the outcomes included.

On the basis of the limited evidence, at most hints of an added benefit can be determined.

Results from the single-arm study 1112 were available for the assessment of the added benefit of SOF (+ RBV) in children. The company presented no data on the comparison of SOF (+ RBV) with the ACT. Due to the specific data situation, it was still possible to draw conclusions on the added benefit on the basis of the available evidence.

Nearly all patients included (53 of 54 [98.1%]) achieved sustained virologic response (SVR) 12 weeks (SVR 12) or 24 weeks after the end of therapy (SVR 24) under SOF + RBV. Under watchful waiting, virus elimination (e.g. by spontaneous virus elimination) is unlikely. Hence, even without the presence of studies of direct comparisons, an advantage of SOF (+ RBV) for SVR can be derived.

For the outcome "health-related quality of life", the company presented data for the Pediatric Quality of Life Inventory Version 4.0 Short Form 15 (PedsQL 4.0 SF15). For the patients, there was a change by 0.4 (standard deviation: 14.2) points in the total score at follow-up week 24 compared with baseline.

The company also did not provide any data for a comparison with the ACT watchful waiting to assess the risk of harm of SOF (+ RBV). However, there were no deaths, a serious adverse event (SAE) in only one child (1.9%), and a discontinuation due to adverse events (AEs) in one child (1.9%) observed under SOF + RBV.

Overall, in this specific data constellation (achievement of SVR in 98.1%, no deaths, and occurrence of SAEs or discontinuations due to AEs in 1.9% of the patient population), a

derivation of the added benefit of SOF (+ RBV) is possible. With great certainty, the results regarding SVR cannot be achieved with the ACT watchful waiting. The risk of harm under SOF (+ RBV) observed in study 1112 also 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 (+ RBV) in children with genotype 2 or 3 CHC.

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

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 and because SVR was only 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 (+ RBV) in children with genotype 2 or 3 CHC.

This conclusion on the added benefit refers only to children without cirrhosis. Patients with decompensated cirrhosis were excluded from study 1112.

Table 3 shows a summary of probability and extent of the added benefit of SOF (+ RBV).

Table 3: SOF (+ RBV) – probability and extent of the added benefit for children aged 3 to < 12 years with genotype 2 or 3 CHC

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Children aged 3 to < 12 years with GT 2 or 3 CHC[b]	Watchful waiting	Hint of non-quantifiable added benefit[c]

a. Presentation of the respective ACT specified by the G-BA.
b. The children in study 1112 were treatment-naive (only one child was pretreated), and only children without cirrhosis and without HIV, HAV or HBV coinfection were included. Hence, conclusions on the added benefit can only be drawn for this population.
c. For children, SOF is only approved in combination with other drugs. The SPC of SOF recommends treatment regimens and durations only for the combination with RBV. Conclusions on the added benefit therefore refer to the combination of SOF + RBV.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; GT: genotype; HAV: hepatitis A virus; HBV: hepatitis B virus; HIV: human immunodeficiency virus; RBV: ribavirin; SOF: sofosbuvir; SPC: Summary of Product Characteristics

[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].

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 the present report is the assessment of the added benefit of SOF (in combination with RBV) in comparison with the ACT in children aged 3 to < 12 years with genotype 2 or 3 CHC.

For the benefit assessment of SOF (+ RBV), the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of SOF (+ RBV)

Research question	Therapeutic indication	ACT[a]
1	Children aged 3 to < 12 years with GT 2 or 3 CHC	Watchful waiting
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; GT: genotype; RBV: ribavirin, SOF: sofosbuvir		

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

For children, SOF is only approved in combination with other drugs. The SPC of SOF recommends treatment regimens and durations only for the combination with RBV [3]. All conclusions on the assessment of the added benefit therefore refer to the combination of SOF (+ RBV).

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 list on SOF + RBV (status: 6 May 2020)
- bibliographical literature search on SOF + RBV (last search on 6 May 2020)
- search in trial registries/trial results databases for studies on SOF + RBV (last search on 6 May 2020)
- search on the G-BA website for SOF + RBV (last search on 6 May 2020)

To check the completeness of the study pool:

- bibliographical literature search on SOF + RBV (last search on 6 August 2020)
- search in trial registries for studies on SOF + RBV (last search on 6 August 2020)

Concurring with the company, the check of the completeness of the study pool for children with CHC aged 3 to < 12 years produced no randomized controlled trials (RCTs) on the direct comparison of SOF (+ RBV) versus the ACT.

The company searched for further investigations on SOF and identified the single-arm study G334-1112 (hereinafter referred to as "study 1112"), which was already assessed in the benefit assessment of SOF in adolescents with CHC [4]. The company conducted no information retrieval for studies for the ACT.

The completeness of the study pool for studies with SOF (+ RBV) was also checked for further investigations. No additional relevant study was identified from this check.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment of SOF (+ RBV) in children with CHC.

Table 5: Study pool – non-RCT, single-arm study: SOF + RBV

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 and other sources[c] (yes/no [citation])
G334-1112 (1112[d])	Yes	Yes	No	No[e]	Yes [5-8]	Yes [4,9]

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. Other sources: documents from the search on the G-BA website.
d. In the following tables, the study is referred to with this abbreviated form.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

G-BA: Federal Joint Committee; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir

The study 1112 presented by the company is a single-arm study with SOF + RBV. Although this is a single-arm study, conclusions on the added benefit of SOF (+ RBV) in children aged 3 to < 12 years with genotype 2 or 3 CHC can still be drawn on the basis of this study due to the special data constellation. Study 1112 was therefore used for the assessment of the added benefit. Section 2.4.2 explains the reasons for this.

2.3.2 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 + RBV

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
1112	Single-arm	Treatment-naive and pretreated children and adolescents (3–< 18 years) with genotype 2 or 3 CHC	Genotype 2: SOF + RBV for 12 weeks (N = 31) Genotype 3: SOF + RBV for 24 weeks (N = 75) Cohorts: ▪ Cohort 1: adolescents aged 12–< 18 years (n = 52)[b] ▪ Cohort 2 (children 6–< 12 years) and cohort 3 (children 3–< 6 years) (N = 54): ▫ genotype 2 (n = 18) ▫ genotype 3 (n = 36)	Screening: ≤ 4 weeks PK lead-in phase: 7 days[c] Treatment: 12 or 24 weeks[d] Follow-up: 24 weeks	37 centres in Australia, Belgium, Germany, Italy, New Zealand, Russia, United Kingdom, USA 7/2014–10/2018	Primary: SVR 12, discontinuation due to AEs Secondary: SVR 24, health-related quality of life, AEs

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. The arm is not relevant for the assessment and is not assessed in the following.
c. The PK lead-in phase comprised only a part of the study population (planned for at least 10 treatment-naive patients of each age cohort).
d. Patients who had already participated in the PK lead-in phase continued treatment only until they reached the total planned treatment duration.

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

Table 7: Characteristics of the interventions – non-RCT, single-arm study: SOF + RBV

Study	Intervention
1112	For 12 weeks (genotype 2) or 24 weeks (genotype 3): sofosbuvir[a] once/day, orally, weight-based: ▪ 200 mg/day: children ≥ 17 kg[b] ▪ 150 mg/day: children < 17 kg + ribavirin twice/day, orally, weight-based: ▪ < 47 kg: 15 mg/kg/day ▪ 47–49 kg: 600 mg/day ▪ 50–65 kg: 800 mg/day ▪ 66–80 kg: 1000 mg/day ▪ 81–105 kg: 1200 mg/day ▪ > 105 kg: 1400 mg/day
	Pretreatment: Permitted pretreatment: ▪ IFN with or without RBV, completed ≥ 8 weeks before study start Non-permitted pretreatment: ▪ regular use of anti-inflammatory drugs ▪ systemic corticosteroids for ≥ 5 days **Concomitant treatment:** Permitted concomitant treatment: ▪ pulmonary or nasal corticosteroids Non-permitted concomitant treatment: ▪ 28 days before study start until end of study ▫ erythropoiesis-stimulating drugs ▫ granulocyte-stimulating factor ▫ systemic immunosuppressants including corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine or monoclonal antibodies (e.g. infliximab) ▪ 21 days before study start until end of study ▫ herbal or natural drugs (St. John's Wort, echinacea, milk thistle, Chinese herbs) ▫ antimycotics (rifampin, rifabutin, rifapentine) ▫ anticonvulsants (phenobarbital, phenytoin, carbamazepine, oxcarbazepine

a. As film-coated tablet or granules.
b. According to the SPC of SOF [3], patients with a body weight ≥ 35 kg receive 400 mg.

IFN: interferon; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; SPC: Summary of Product Characteristics

Study 1112 is a single-arm study investigating SOF + RBV in pretreated or treatment-naive children and adolescents aged 3 to < 18 years with genotype 2 or 3 CHC.

The study included different age cohorts. The cohort of 3 to < 6-year-olds relevant for the present assessment comprised 13 children, and the cohort of 6 to < 12-year-olds 41 children. Children with human immunodeficiency virus, hepatitis A virus or hepatitis B virus

coinfection, or with decompensated liver disease were excluded from the study. Children with genotype 2 CHC were treated for 12 weeks and children with genotype 3 CHC for 24 weeks.

In the beginning of the study, some of the patients of each age cohort participated in a 7-day pharmacokinetics lead-in phase to confirm suitability of the dosing of SOF in combination with RBV for the respective age group. To participate, the patients had to be treatment-naive. Subsequently, the patients continued therapy in the treatment phase without interruption until reaching the total planned treatment duration. After analysis of the data from the lead-in phase, further patients were included directly into the 12-week or 24-week treatment phase.

SOF and RBV were each administered largely in compliance with the SPCs [3,10]. SOF is approved as film-coated tablet or granules. In study 1112, SOF was used in both administration forms. The granules are not available in Germany. In the study, SOF was administered at a dosage of 150 mg SOF daily for children with a body weight < 17 kg. Children with a body weight ≥ 17 kg received 200 mg SOF daily. According to the SPC, children with a body weight ≥ 35 kg should receive a daily dose of 400 mg SOF. The body weight of the children in the cohort of the 3- to < 6-year olds was between 13 kg and 19 kg; hence, these children were treated in compliance with the SPC. For the children in the cohort of 6- to < 12-year-olds, it is unclear what the proportion of children with a body weight ≥ 35 kg was. The median body weight of these children was 30 kg (range 15 kg to 80 kg).

In the present data constellation (see Section 2.4), it is assumed that the partial underdosing in study 1112 did not lead to an underestimation of the result for the morbidity outcomes. For the side effect outcomes, this is not per se apparent on the basis of the data prepared by the company in Module 4 A. However, study 1112 was already assessed in the dossier assessment for Commission A17-55 for adolescents aged 12 to < 18 years. The adolescents included in the study received SOF at a dose of 400 mg once daily (in compliance with the approval). No deaths, SAEs or discontinuations due to AEs occurred under this dosing. As none of these events occurred in adolescents, it is not assumed for 6- to < 12-year-old children with a body weight ≥ 35 kg that the harm in study 1112 was underestimated for the present assessment. Concurring with the company, the data of 6- to < 12-year-olds from study 1112 were therefore used for the present benefit assessment despite the partial underdosing of SOF.

The primary outcomes of the study were SVR 12 and discontinuation due to AEs. Secondary outcomes were SVR 24, health-related quality of life, and AEs. The study was completed in October 2018.

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 + RBV

Study **Outcome category** **Outcome**	**Planned follow-up observation**
1112	
Mortality	
All-cause mortality	24 weeks after end of treatment
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	30 days after end of treatment
SAEs	24 weeks after end of treatment

AE: adverse event; 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; SOF: sofosbuvir; SVR 12/SVR 24: sustained virologic response 12/24 weeks after end of treatment

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 + RBV

Study / **Characteristic** / **Category**	**SOF + ribavirin (RBV)**		
1112	Children with GT 2 CHC N = 18	Children with GT 3 CHC N = 36	Total N = 54
Age [years], median [min; max]	7 [3; 11]	8 [3; 11]	8 [3; 11]
Sex [F/M], %	78/22	72/28	74/26
Family origin, n (%)			
White	12 (66.7)	26 (72.2)	38 (70.4)
Asian	2 (11.1)	7 (19.4)	9 (16.7)
Black or African American	1 (5.6)	0 (0)	1 (1.9)
Other	3 (16.7)	3 (8.3)	6 (11.1)
HCV subgenotype, n (%)			
2[a]	3 (16.7)	0 (0)	3 (5.6)
2b	11 (61.1)	0 (0)	11 (20.4)
2a/c	4 (22.2)	0 (0)	4 (7.4)
3a	0 (0)	36 (100)	36 (66.7)
Compensated cirrhosis, n (%)			
Yes	0 (0)	0 (0)	0 (0)
No	4 (22.2)	3 (8.3)	7 (13)
Unknown	14 (77.8)	33 (91.7)	47 (87)
Baseline HCV RNA viral load [IU/mL], n (%)			
< 800 000	9 (50)	23 (63.9)	32 (59.3)
≥ 800 000	9 (50)	13 (36.1)	22 (40.7)
Pretreatment status, n (%)			
Treatment-naive	18 (100)	35 (97.2)	53 (98.1)
Pretreated	0 (0)	1 (2.8)	1 (1.9)
No response	NA	1 (100)	1 (100)
Relapse	NA	0 (0)	0 (0)
IFN intolerance	NA	0 (0)	0 (0)
Treatment discontinuation, n (%)	1 (5.6[b])	0 (0)	1 (1.9[b])
Study discontinuation, n (%)	1 (5.6[b])	0 (0)	1 (1.9[b])

a. No specific subgenotype.
b. Institute's calculation.

CHC: chronic hepatitis C; F: female; GT: genotype; HCV: hepatitis C virus; IFN: interferon; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of patients included; NA: not applicable; RBV: ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid; SOF: sofosbuvir

The mean age of the children in study 1112 was 8 years. Approximately 3 quarters of the children were female, and also approximately 3 quarters were of white family origin. The majority of the patients included had hepatitis C virus genotype 3 (about 2 thirds). None of the

children included in the study had confirmed compensated cirrhosis, but in the vast majority, the cirrhosis status was unknown. Almost all children included in the study were treatment-naive; only one child with genotype 3 had been pretreated.

Transferability of the study results to the German health care context

The company described that the proportion of male children (26%) in study 1112 was markedly lower than the proportion of female children. It stated that, according to the Robert Koch Institute (RKI) [11], regarding sex-specific differences in the number of reported new infections, there were no differences that remained constant over the years. Rather, there were alternating majorities in the number of female or male children affected.

According to the company, most children in study 1112 (94%) were infected via vertical transmission. From the point of view of the company, this transmission route is consistent with the transmission routes relevant in Germany, since, according to the guideline relevant for Germany [12], the main transmission route in children is vertical transmission.

Concurring with the population shares in Germany, the majority of the children in study 1112 (about 70%) were of white family origin, the company stated.

The company concluded overall that a transferability of the study data of study 1112 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.

2.4 Results on added benefit

2.4.1 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-relevant 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

- if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which presented further outcomes in the category of side effects in Module 4 A.

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

Table 10: Matrix of outcomes – non-RCT, single-arm study: SOF + RBV

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
1112	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; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SOF: sofosbuvir; SVR 12/SVR 24: sustained virologic response 12/24 weeks after end of treatment

Outcome "sustained virologic response (SVR)"

In the present benefit assessment, the SVR for patients without cirrhosis or with compensated cirrhosis 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 [13]. As this assessment is based on data from observational studies, it is subject to increased uncertainty.

Specific adverse events

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 present data situation, results on specific AEs are not included in the present benefit assessment due to the lack of informative data on specific AEs under the ACT.

2.4.2 Results

Since one single-arm study 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 for the study population of children with genotype 2 or 3 CHC from study 1112. Where necessary, calculations conducted by IQWiG 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 + RBV

Study	**SOF + RBV**	
Outcome category **Outcome**	**N**	**Patients with event** **n (%)**
1112		
Mortality		
All-cause mortality	54	0 (0)
Morbidity		
SVR 12[a]	54	53 (98.1)
Genotype 2	18	17 (94.4)
Genotype 3	36	36 (100)
SVR 24[a]	54	53 (98.1[b])
Genotype 2	18	17 (94.4[b])
Genotype 3	36	36 (100[b])
Side effects		
AEs (supplementary information)	54	48 (88.9[b])
Genotype 2	18	14 (77.8)
Genotype 3	36	34 (94.4)
SAEs	54	1 (1.9[b])
Genotype 2	18	0 (0)
Genotype 3	36	1 (2.8)
Discontinuation due to AEs	54	1 (1.9[b])
Genotype 2	18	1 (5.6)
Genotype 3	36	0 (0)

a. Sufficiently valid surrogate for the patient-relevant outcome “hepatocellular carcinoma”.
b. Institute’s calculation.

AE: adverse event; n: number of patients with event; N: number of analysed patients; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SOF: sofosbuvir; SVR 12/SVR 24: sustained virologic response 12/24 weeks after end of treatment

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

Study Outcome category Outcome	SOF + ribavirin (RBV)		
	N[a]	Values at baseline mean (SD)	Change at FU week 24 mean (SD)[b]
1112			
Health-related quality of life			
PedsQL (total score, patient-reported)[c]	46[d]	82.0 (13.16)[d]	0.4 (14.19)[d]
Genotype 2	13	84.2 (10.13)	−2.9 (13.27)
Genotype 3	33	81.1 (14.22)	1.7 (14.53)

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 is imputed.
c. Higher (increasing) values mean better quality of life. The questionnaire was completed only by the parents or legal guardian if the children were between 3 and 4 years of age.
d. Institute's calculation.

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

Results from the single-arm study 1112 were available for the assessment of the added benefit of SOF (+ RBV) in children. Due to the specific data situation, it was possible to draw conclusions on the added benefit of SOF (+ RBV) on the basis of the available evidence. On the basis of the available data, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

In the study, almost all patients included, regardless of genotype 2 or 3, (53 of 54 [98.1%]) achieved SVR 12 or SVR 24 under SOF + RBV. Only one child with genotype 2 did not achieve SVR 12/SVR 24. This child discontinued the study medication on day 3 due to an AE (reason for discontinuation, Preferred Term [PT]: abnormal taste of the medication).

Under the ACT watchful waiting, virus elimination (e.g. by spontaneous virus elimination) is unlikely. Hence, even without the presence of studies of direct comparisons, an advantage of SOF (+ RBV) for SVR can be derived.

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 [14]. For the patients, there was a change by 0.4 (standard deviation: 14.2) points in the total score at follow-up week 24 compared with baseline.

The company also did not provide any data for a comparison with the ACT watchful waiting to assess the risk of harm of SOF (+ RBV). However, no deaths, only one SAE (1.9%) and one discontinuation due to AEs (1.9%) were observed under SOF + RBV.

Overall, in this specific data constellation (achievement of SVR in 98.1%, no deaths, and occurrence of SAEs or discontinuations due to AEs in 1.9% of the patient population), a derivation of the added benefit of SOF (+ RBV) is possible. With great certainty, the results regarding SVR cannot be achieved under the ACT watchful waiting. The risk of harm under SOF (+ RBV) observed in study 1112 also 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 only 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 (+ RBV) in children with genotype 2 or 3 CHC.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of SOF in comparison with the ACT is summarized in Table 13.

Table 13: SOF (+ RBV) – probability and extent of the added benefit for children aged 3 to < 12 years with genotype 2 or 3 CHC

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Children aged 3 to < 12 years with GT 2 or 3 CHC[b]	Watchful waiting	Hint of non-quantifiable added benefit[c]

a. Presentation of the respective ACT specified by the G-BA.
b. The children in study 1112 were treatment-naive (only one child was pretreated), and only children without cirrhosis and without HIV, HAV or HBV coinfection were included. Hence, conclusions on the added benefit can only be drawn for this population.
c. For children, SOF is only approved in combination with other drugs. The SPC of SOF recommends treatment regimens and durations only for the combination with RBV [3]. Conclusions on the added benefit therefore refer to the combination of SOF + RBV.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; GT: genotype; HAV: hepatitis A virus; HBV: hepatitis B virus; HIV: human immunodeficiency virus; RBV: ribavirin; SOF: sofosbuvir; SPC: Summary of Product Characteristics

In summary, there is a hint of a non-quantifiable added benefit of SOF (+ RBV) in comparison with the ACT watchful waiting for children aged 3 to < 12 years with genotype 2 or 3 CHC. This added benefit refers only to children without cirrhosis. Patients with decompensated cirrhosis were excluded from study 1112.

The assessment described above deviates from that of company, which derived a hint of a major added benefit of SOF in comparison with the ACT for children aged 3 to < 12 years with genotype 2 or 3 CHC.

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

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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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