IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Sofosbuvir (chronic hepatitis C in 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 (chronische Hepatitis C bei Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 January 2018). 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
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies)
BSC	best supportive care
CHC	chronic hepatitis C
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
peg-IFN	pegylated interferon
RBV	ribavirin
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
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

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 12 October 2017.

Research question

The aim of the present report was to assess the added benefit of SOF (+ RBV) in comparison with the appropriate comparator therapy (ACT) in adolescents aged 12 to < 18 years with genotype 2 or 3 chronic hepatitis C (CHC).

For the benefit assessment of SOF (+ RBV), the 2 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 (+ RBV)

Research question	Subindication	ACT[a]
1	Pretreated adolescents aged 12 to < 18 years with genotype 2 or 3 CHC	Best supportive care (BSC)[b]
2	Treatment-naive adolescents aged 12 to < 18 years with genotype 2 or 3 CHC	Combination of RBV and peg-IFN alfa[c]

a: Presentation of the respective ACT specified by the G-BA.
b: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c: The information provided in the SPCs of the combination partners of the ACT is to be considered.
ACT: appropriate comparator therapy; BSC: best supportive care; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; peg-IFN: pegylated interferon; RBV: ribavirin; SOF: sofosbuvir; SPC: Summary of Product Characteristics

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

For adolescents, 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 ongoing, 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 pretreated and treatment-naive children and adolescents aged 3 to < 18 years with genotype 2 or 3 CHC.

The study documents showed that the data were to be analysed separately for adolescents aged 12 to < 18 years (group 1) and for children aged 3 to < 12 years (group 2). According to the company, only results for group 1, which is the relevant patient population for the present benefit assessment, are currently available.

For group 1, inclusion of pretreated and treatment-naive adolescents with CHC was planned for genotype 2 and for genotype 3 CHC. For adolescents with genotype 2 CHC, only treatment-naive patients were actually included in study 1112.

All patients in study 1112 received SOF at a dosage of 400 mg once daily in combination with RBV, which was dosed based on body weight. The planned treatment duration differed depending on the genotype: Adolescents with genotype 2 CHC received SOF + RBV for 12 weeks, and adolescents with genotype 3 CHC received the same treatment for 24 weeks. Treatment was in compliance with the recommendations provided in the SPC of SOF.

Risk of bias

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.

Based on the limited evidence, at most hints of an added benefit can be derived.

Assessment of the study results for research question 1: pretreated adolescents with genotype 2 or 3 CHC

Results from the single-arm study 1112 were available for the assessment of the added benefit of SOF (+ RBV) in pretreated adolescents. The company presented no data on the comparison of SOF (+ RBV) with the ACT best supportive care (BSC). 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.

All pretreated patients (genotype 3 CHC) included in study 1112 (9 of 9 [100%]) reached sustained virologic response 12 weeks after the end of treatment (SVR 12) or 24 weeks after the end of treatment (SVR 24) under SOF + RBV.

Pretreated adolescents with genotype 2 CHC were not included in study 1112. Nonetheless, conclusions on SVR can also be drawn for these patients with genotype 2. Considering the SVR rates in adolescents with genotype 3 CHC, these are comparable in treatment-naive and

pretreated adolescents irrespective of the pretreatment (96.4% versus 100%). It is assumed that this comparability of the SVR rates also exists for adolescents with genotype 2. Since all treatment-naive adolescents with genotype 2 in study 1112 reached SVR 12 or SVR 24 (100%), high SVR rates are also assumed for pretreated adolescents with genotype 2. The assumption is supported by study results in adults. Results of adults with genotype 2 CHC showed that there are SVR 24 rates of a relevant magnitude both for treatment-naive and for pretreated patients: treatment-naive adults 97.1% and pretreated adults 86.1%. Besides the SVR 24 rates of 100% observed in pretreated adolescents with genotype 3 CHC in study 1112, SVR rates of a relevant magnitude are therefore also assumed for pretreated adolescents with genotype 2 CHC.

Non-antiviral BSC, however, is unlikely to achieve virus elimination (e.g. by spontaneous virus elimination). Even without studies of direct comparisons, an advantage of SOF (+ RBV) versus BSC for SVR can be derived for pretreated patients.

To assess the risk of harm of SOF (+ RBV), the company presented data for the total population (pretreated and treatment-naive patients), but not separately for pretreated adolescents. However, neither deaths, nor serious adverse events (SAEs) or discontinuations due to adverse events (AEs) under SOF + RBV were observed in the total population of adolescents in study 1112, and thus also in pretreated patients (0% each). It is assumed that the risk of harm of SOF (+ RBV) is comparable in pretreated adolescents with genotype 2 CHC, who were not included in study 1112. The company also presented no data on the comparison of SOF (+ RBV) with the ACT BSC.

The company did not present data on health-related quality of life because the analysis of these data was not planned in the present interim analysis of study 1112.

Overall, in this particular data constellation (achievement of SVR in 100% of the patient population, and occurrence of SAEs or discontinuations due to AEs in 0%), a derivation of the added benefit of SOF (+ RBV) is possible. With great certainty, the results regarding SVR cannot be achieved by the ACT BSC. The risk of harm under SOF + RBV observed in study 1112 also did not raise doubts about the advantage this drug combination has in the SVR rate.

Based on the limited evidence, at most hints of an added benefit can be derived. The extent of the added benefit cannot be quantified because there was no comparative study with the ACT BSC 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 pretreated adolescents with genotype 2 or 3 CHC.

This added benefit refers only to adolescents without cirrhosis. Patients with confirmed cirrhosis were not investigated in the included study 1112.

Assessment of the study results for research question 2: treatment-naive adolescents with genotype 2 or 3 CHC

Results from the single-arm study 1112 were available also for the assessment of the added benefit of SOF (+ RBV) in treatment-naive adolescents. However, the data constellation in treatment-naive adolescents differed from that in pretreated patients.

Almost all treatment-naive adolescents in study 1112 reached SVR 12 or SVR 24 under SOF + RBV (40 of 41 [97.6%]). SVR 12 was rated as not achieved for 1 of the 41 adolescents because this adolescent was described as lost to follow-up after complete treatment.

The company presented no data from a systematic search for the ACT RBV + pegylated interferon (peg-IFN) alfa. However, with reference to the S3 guideline published by the Association of the Scientific Medical Societies (AWMF), it described that adolescents with genotype 2 or 3 CHC reached SVR rates of over 90% under RBV + peg-IFN alfa. In view of the studies referenced in this guideline, this is comprehensible.

Hence it is not implausible that comparable SVR rates can be reached under RBV + peg-IFN alfa as those observed under SOF + RBV in study 1112. Therefore, a relevant advantage of SOF (+ RBV) in comparison with the ACT for SVR cannot be assumed automatically.

The company also presented no suitable data for a comparison of SOF (+ RBV) with the ACT RBV + peg-IFN alfa to assess the risk of harm. However, neither deaths, nor SAEs or discontinuations due to AEs under SOF + RBV occurred in the total population of adolescents in study 1112, and thus also in treatment-naive adolescents (0% each). AEs under SOF + RBV occurred in 80% of the patients (in relation to the total population; there were no data on treatment-naive adolescents). From the company's point of view, there is an added benefit of SOF (+ RBV) for side effects per se because interferon-induced side effects are avoided. It referred to selected sources that were not based on a systematic search, including studies and SPCs.

The derivation of the advantage of SOF (+ RBV) in comparison with RBV + peg-IFN alfa for AEs postulated by the company on the basis of the data selectively presented by the company is inadequate. For instance, also no SAEs or deaths occurred under treatment with RBV + peg-IFN alfa in the largest study cited by the company (Wirth 2010). This study comprised 107 children and adolescents, including 9 (8.4%) adolescents with genotype 2 CHC and 5 (4.6%) adolescents with genotype 3 CHC. Only one patient discontinued study treatment due to AEs. In view of the assessments in the area of CHC in adults already conducted by IQWiG, it can be assumed, however, that the risk of harm from SOF (+ RBV) in adolescents is at least not higher than the risk of harm from RBV + peg-IFN alfa.

The company did not present data on health-related quality of life because the analysis of these data was not planned in the present interim analysis of study 1112.

Overall, no advantage of SOF (+ RBV) in comparison with RBV + peg-IFN alfa is assumed for the SVR rates or for the risk of harm in this data constellation. In the overall assessment, the added benefit of SOF (+ RBV) in treatment-naive adolescents with genotype 2 or 3 CHC in comparison with RBV + peg-IFN alfa is not proven.

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

Based on the limited evidence, at most hints of an added benefit can be derived. 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".

There was a hint of a non-quantifiable added benefit of SOF (+ RBV) versus the ACT BSC for pretreated adolescents with genotype 2 or 3 CHC.

There was no hint of an added benefit of SOF (+ RBV) in comparison with the ACT RBV + peg-IFN alfa for treatment-naive adolescents with genotype 2 or 3 CHC. An added benefit is therefore not proven.

These conclusions on the added benefit for pretreated and treatment-naive adolescents with CHC refer exclusively to adolescents without cirrhosis. Patients with confirmed cirrhosis were not investigated in the included study 1112.

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

[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].

Table 3: SOF (+ RBV) – probability and extent of the added benefit of adolescents aged 12 to < 18 years with genotype 2 or 3 CHC

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit**
1	Pretreated adolescents aged 12 to < 18 years with chronic hepatitis C[b]	Best supportive care (BSC)[c]	Hint of a non-quantifiable added benefit[d]
2	Treatment-naive adolescents aged 12 to < 18 years with chronic hepatitis C[b]	Combination of ribavirin and peg-IFN alfa[c]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: Only adolescents without confirmed cirrhosis and without HIV, HAV or HBV coinfection were included in study 1112. Hence conclusions on the added benefit can only be drawn for this population.
c: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
d: For adolescents, 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.
e: The information provided in the SPCs of the combination partners of the ACT is to be considered.
ACT: appropriate comparator therapy; BSC: best supportive care; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HAV: hepatitis A virus; HBV: hepatitis B virus; HIV: human immunodeficiency virus; peg-IFN: pegylated interferon; RBV: ribavirin; SOF: sofosbuvir; SPC: Summary of Product Characteristics

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 was to assess the added benefit of SOF (in combination with RBV) in comparison with the ACT in adolescents aged 12 to < 18 years with genotype 2 or 3 CHC.

For the benefit assessment of SOF (+ RBV), the 2 research questions presented in Table 4 resulted from the ACT specified by the G-BA.

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

Research question	Subindication	ACT[a]
1	Pretreated adolescents aged 12 to < 18 years with genotype 2 or 3 CHC	Best supportive care (BSC)[b]
2	Treatment-naive adolescents aged 12 to < 18 years with genotype 2 or 3 CHC	Combination of RBV and peg-IFN alfa[c]

a: Presentation of the respective ACT specified by the G-BA.
b: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c: The information provided in the SPCs of the combination partners of the ACT is to be considered.
ACT: appropriate comparator therapy; BSC: best supportive care; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; peg-IFN: pegylated interferon; RBV: ribavirin; SOF: sofosbuvir; SPC: Summary of Product Characteristics

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

For adolescents, 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 lists on SOF + RBV (status: 25 July 2017)
- bibliographical literature search on SOF + RBV (last search on 24 July 2017)
- search in trial registries for studies on SOF + RBV (last search on 25 July 2017)

To check the completeness of the study pool:

- bibliographical literature search on SOF + RBV (last search on 16 November 2017)
- search in trial registries for studies on SOF + RBV (last search on 9 November 2017)

The check identified no additional relevant study.

2.3.1 Studies included

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

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Study G334-1112 (1112[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.
RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir

Study 1112 presented by the company for both research questions (pretreated and treatment-naive adolescents) was a single-arm study with SOF + RBV. Due to the specific data constellation, conclusions on the added benefit of SOF + RBV in adolescents with CHC can still be derived on the basis of this study. Study 1112 was therefore used for the assessment of the added benefit. Section 2.4.2 explains the reasons for this.

Data cut-offs on study 1112 presented by the company

Analyses of different data cut-offs were available for the present assessment:

1) Interim analysis with results on the data cut-off from 12 July 2016 [4]. In this interim analysis, only data of patients who had been included in the study until 7 October 2015 (n = 50) were analysed. At this time point, all patients had completed the 12-week follow-up observation period. The number of patients who had also completed the 24-week follow-up observation period is unclear. Data on SVR 12 and AEs are available.

   Analyses on SVR 24 and health-related quality of life were not included because these had not been planned for the interim analysis.

2) An additional analysis on SVR 12 and SVR 24 at the data cut-off from 10 January 2017 for the same patient population as in the interim analysis at the data cut-off from 12 July 2016 (n = 50). At this time point, the 50 patients considered had been followed-up for 24 weeks.

   Data on AEs or health-related quality of life are not available for this data cut-off.

3) Publication on study 1112 [5] comprising data of 2 further adolescents included after 7 October 2015 (n = 52) on SVR 12 and AEs.

   The publication does not contain analyses on SVR 24 and health-related quality of life.

The results on the outcomes available in the data sources are consistent between all 3 data sources. The most recent analyses were therefore used for the present benefit assessment: the data on the data cut-off from 10 January 2017 for SVR 12 and SVR 24, and the data on the data cut-off from 12 July 2016 for AEs.

Section 2.5 contains a reference list for the studies included.

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	Intervention (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
1112	Non-randomized, open-label	Treatment-naive and pretreated children and adolescents with genotype 2 or 3 CHC	Genotype 2: SOF + RBV for 12 weeks Genotype 3: SOF + RBV for 24 weeks Group 1: adolescents aged 12 to < 18 years (N = 50)[f] Group 2[g]: children aged 3 to < 12 years (N = ND)	Screening: up to 28 days[b] PK lead-in phase: 7 days[d] Treatment phase: 12 or 24 weeks[e] Observation: outcome-specific	28 centres in Australia, Germany, Italy, New Zealand, Russia, United Kingdom, USA 7/2014–ongoing Data cut-off for group 1: 7/2016[h]	Primary: SVR 12, discontinuation due to AEs Secondary[c]: SVR 24, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: Up to 42 days for adolescents who required additional determination of the HCV genotype.
c: Amendment 2 removed the analysis of health-related quality of life as secondary outcome from the interim analysis of study 1112.
d: Only some patients from group 1 participated in the PK lead-in phase (treatment-naive, HCV RNA 1000 ≥ IU/mL, body weight ≥ 45 kg).
e: Patients who had already participated in the PK lead-in phase continued treatment only until they reached the total planned treatment duration.
f: The publication on study 1112 [5] contains data from 2 further adolescents (n = 52; see Section 2.3.1).
g: Group 2 is not relevant for the present assessment and is not shown in the following tables.
h: The company additionally transmitted an analysis for the outcomes "SVR 12" and "SVR 24" at the data cut-off from 10 January 2017.

AE: adverse event; CHC: chronic hepatitis C; HCV: hepatitis C virus; N: number of patients included; ND: no data; PK: pharmacokinetics; RBV: ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid; 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	Sofosbuvir 400 mg; once daily, orally + ribavirin twice daily, orally, depending on body weight: < 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[a] for 12 or 24 weeks Pretreatment and concomitant treatment **Pretreatment:** Permitted pretreatment: ▪ IFN with and without RBV treatment, completed ≥ 8 weeks before start of study Non-permitted pretreatment: ▪ regular use of anti-inflammatory drugs ▪ systemic corticosteroids for ≥ 5 days **Concomitant treatment:** Non-permitted concomitant treatment 28 days before start of study 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) ▪ herbal or natural drugs (St. John's Wort, echinacea, milk thistle, Chinese herbs) ▪ antimycotics (rifampin, rifabutin, rifapentine) ▪ anticonvulsants (phenobarbital, phenytoin, carbamazepine, oxcarbazepine

a: Dose for adolescents with a body weight of > 105 kg does not comply with the approval. No adolescent with a body weight of > 105 kg was included in study 1112, however.

IFN: interferon; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir

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

The study documents showed that the data were to be analysed separately for adolescents aged 12 to < 18 years (group 1) and for children aged 3 to < 12 years (group 2). According to the company, only results for group 1, which is the relevant patient population for the present benefit assessment, are currently available. Patients with human immunodeficiency virus (HIV) or hepatitis A or hepatitis B virus coinfection or with decompensated liver were excluded from the study.

For group 1, inclusion of pretreated and treatment-naive adolescents with CHC was planned for genotype 2 and for genotype 3. For adolescents with genotype 2 CHC, only treatment-naive patients were actually included in study 1112.

All patients in study 1112 received SOF at a dosage of 400 mg once daily in combination with RBV, which was dosed based on body weight. The planned treatment duration differed depending on the genotype: Adolescents with genotype 2 CHC received SOF + RBV for 12 weeks, and adolescents with genotype 3 CHC received the same treatment for 24 weeks. Treatment was in compliance with the recommendations provided in the SPC of SOF [3].

In the beginning of the study, some of the patients participated in a 7-day pharmacokinetics lead-in phase to confirm suitability of the dosing of SOF (400 mg) in combination with RBV for the age group concerned. To participate, the patients had to be treatment-naive and weigh at least 45 kg. 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.

Table 8 shows the planned duration of follow-up 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**
Study 1112	
Mortality	
All-cause mortality	30 days 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 / **Characteristics** / **Category**	**SOF + RBV**		
Study 1112	**Adolescents with GT 2 CHC N = 13**	**Adolescents with GT 3 CHC N = 37**	**Adolescents with GT 2 or 3 CHC N = 50**
Age [years], mean (SD)	15 (1.9)	15 (1.8)	15 (1.9)
Sex [F/M], %	38/62	43/57	42/58
Ethnicity, n (%)			
White	11 (84.6)	34 (91.9)	45 (90)
Black	2 (15.4)	0	2 (4)
Asian	0	1 (2.7)	1 (2)
Other	0	2 (5.4)	2 (4)
HCV subgenotype, n (%)			
2	6 (46.2)	0	6 (12)
2b	5 (38.5)	0	5 (10)
2 a/c	2 (15.4)	0	2 (4)
3	0	1 (2.7)	1 (2)
3a	0	36 (97.3)	36 (72)
Compensated cirrhosis, n (%)			
Yes	0	0	0
No	4 (30.8)	16 (43.2)	20 (40)
Unknown	9 (69.2)	21 (56.8)	30 (60)
Baseline HCV RNA viral load [IU/mL], n (%)			
< 800 000	5 (38.5)	12 (32.4)	17 (34)
≥ 800 000	8 (61.5)	25 (67.6)	33 (66)
Pretreatment status, n (%)			
Treatment-naive	13 (100)	28 (75.7)	41 (82)
IFN-tolerant	12 (92.3)	27 (96.4)	39 (95.1)
IFN-intolerant	1 (7.7)	1 (3.6)	2 (4.9)
Pretreated	0	9 (24.3)	9 (18)
No response	NA	6 (66.7)	6 (66.7)
Relapse	NA	2 (22.2)	2 (22.2)
Intolerance	NA	1 (11.1)	1 (11.1)
Treatment discontinuation, n (%)	0[a]	0[a]	0
Study discontinuation, n (%)	0	1 (2.7)	1 (2)

a: The study documents show that 3 of 37 (8.1%) adolescents with GT 3 CHC did not receive complete SOF treatment over the total planned treatment duration of 24 weeks. All adolescents received RBV over the total planned treatment duration, however.

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

The company presented no separate data on the patient characteristics of pretreated and treatment-naive adolescents, but presented the characteristics separately for genotype 2 and 3 and for the total population of adolescents (group 1) of study 1112.

Group 1 of study 1112 included a total of 50 adolescents, of which 41 patients were treatment-naive, and 9 patients were pretreated. The mean age was 15 years. Most adolescents were male (58%) and white (90%). The majority of the patients included had hepatitis C virus (HCV) genotype 3 (74%). None of the adolescents included had confirmed compensated cirrhosis, with the cirrhosis status being unknown in a total of 60%, however. Presence of decompensated liver disease was defined as an exclusion criterion in the study.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.2.7.2 of the full dossier assessment):

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

The choice of patient-relevant outcomes principally concurred with that of the company. However, the operationalization of specific AEs by the company was inadequate for the benefit assessment (see Section 2.6.2.7.2 of the full dossier assessment).

Table 10 shows for which outcomes data were available in the studies 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	SAEs	Discontinuation due to AEs	Specific AEs
Study 1112	Yes	Yes	Yes	No[a]	Yes[b]	Yes[b]	No[c]

a: The analysis of data on health-related quality of life was not planned for the interim analysis presented by the company; hence no corresponding data are available for the assessment.
b: Data on AEs are only available for the total population and separated by genotype 2 and 3, but not by pretreatment status (pretreated/treatment-naive). Overall, no events occurred in the total population, and hence there were also no events in the subpopulations of pretreated and treatment-naive patients.
c: Due to the data situation, no choice of specific AEs is possible.
AE: adverse event; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SOF: sofosbuvir; SVR: sustained virologic response

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.

Based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes.

2.4.2.1 Research question 1: pretreated adolescents

Table 11 summarizes the results for the subpopulation of pretreated adolescents with genotype 2 or 3 CHC from study 1112.

Table 11: Results (mortality, morbidity, side effects) – non-RCT, single-arm study: pretreated adolescents with genotype 2 or 3 CHC, SOF + RBV

Study **Outcome category** **Outcome**		**SOF + RBV**
	N	**Patients with event n (%)**
1112		
Mortality		
All-cause mortality	9	0 (0)
Morbidity		
SVR 12[a]	9	9 (100)
Genotype 2	–[c]	–[b]
Genotype 3	9	9 (100)
SVR 24[a]		
Genotype 2	–[c]	–[b]
Genotype 3	9	9 (100)
Side effects		
AEs (supplementary information)		ND[c]
SAEs[d]	9	0 (0)
Discontinuation due to AEs	9	0 (0)

a: Sufficiently valid surrogate in adults for the patient-relevant outcome "hepatocellular carcinoma". Data separated by CHC genotype are available. Data on SVR 12 and SVR 24 are from the additional analysis on the data cut-off from 10 January 2017 (see Section 2.3.1), at which all patients had been followed-up for 24 weeks.
b: No pretreated adolescents with genotype 2 were included in study 1112.
c: No data are available for the subpopulation of pretreated adolescents. Results for the total population: 40 of 50 patients (80%) had an AE. Data on common AEs in the total population can be found in Appendix A of the full dossier assessment.
d: The data are from the interim analysis at the data cut-off from 12 July 2016 (see Section 2.3.1). The company presented no information on the number of patients included who reached the planned duration of follow-up observation of 24 weeks at this data cut-off (see Section 2.6.2.7.2 of the full dossier assessment).
AE: adverse event; CHC: chronic hepatitis C; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; 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

Results from the single-arm study 1112 were available for the assessment of the added benefit of SOF (+ RBV) in pretreated adolescents. The company presented no data on the comparison of SOF (+ RBV) with the ACT BSC. 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.

All pretreated patients (genotype 3 CHC) included in study 1112 (9 of 9 [100%]; see Table 11) reached SVR 12 or SVR 24 under SOF + RBV.

Pretreated adolescents with genotype 2 CHC were not included in study 1112. Nonetheless, conclusions on SVR can also be drawn for these patients with genotype 2. Considering the SVR rates in adolescents with genotype 3 CHC, these are comparable in treatment-naive and

pretreated adolescents irrespective of the pretreatment (96.4% versus 100%). It is assumed that this comparability of the SVR rates also exists for adolescents with genotype 2. Since all treatment-naive adolescents with genotype 2 in study 1112 reached SVR 12 or SVR 24 (100%; see Table 12), high SVR rates are also assumed for pretreated adolescents with genotype 2. The assumption is supported by study results in adults. Results of adults with genotype 2 CHC showed that there are SVR 24 rates of a relevant magnitude both for treatment-naive and for pretreated patients: treatment-naive adults 97.1% and pretreated adults 86.1% [6]. Besides the SVR 24 rates of 100% observed in pretreated adolescents with genotype 3 CHC in study 1112, SVR rates of a relevant magnitude are therefore also assumed for pretreated adolescents with genotype 2 CHC.

Non-antiviral BSC, however, is unlikely to achieve virus elimination (e.g. by spontaneous virus elimination). Even without studies of direct comparisons, an advantage of SOF (+ RBV) versus BSC for SVR can be derived for pretreated patients.

To assess the risk of harm of SOF (+ RBV), the company presented data for the total population (pretreated and treatment-naive patients), but not separately for pretreated adolescents. However, neither deaths, nor SAEs or discontinuations due to AEs under SOF + RBV were observed in the total population of adolescents in study 1112, and thus also in pretreated patients (0% each; see Table 11). It is assumed that the risk of harm of SOF (+ RBV) is comparable in pretreated adolescents with genotype 2 CHC, who were not included in study 1112. The company also presented no data on the comparison of SOF (+ RBV) with the ACT BSC.

The company did not present data on health-related quality of life because the analysis of these data was not planned in the present interim analysis of study 1112.

Overall, in this particular data constellation (achievement of SVR in 100% of the patient population, and occurrence of SAEs or discontinuations due to AEs in 0%), a derivation of the added benefit of SOF (+ RBV) is possible. With great certainty, the results regarding SVR cannot be achieved by the ACT BSC. The risk of harm under SOF + RBV observed in study 1112 also did not raise doubts about the advantage this drug combination has in the SVR rate.

Based on the limited evidence, at most hints of an added benefit can be derived. The extent of the added benefit cannot be quantified because there was no comparative study with the ACT BSC 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 pretreated adolescents with genotype 2 or 3 CHC.

These conclusions on the added benefit refer only to adolescents without cirrhosis. Patients with confirmed cirrhosis were not investigated in the included study 1112.

2.4.2.2 Research question 2: treatment-naive adolescents

Table 12 summarizes the results for the subpopulation of treatment-naive adolescents with genotype 2 or 3 CHC from study 1112. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations.

Table 12: Results (mortality, morbidity, side effects) – non-RCT, single-arm study: treatment-naive adolescents with genotype 2 or 3 CHC, SOF + RBV

Study **Outcome category** **Outcome**		**SOF + RBV**
	N	**Patients with event n (%)**
1112		
Mortality		
All-cause mortality	41	0 (0)
Morbidity		
SVR 12[a]	41[b]	40 (97.6)
Genotype 2	13	13 (100)
Genotype 3	28	27 (96.4)
SVR 24[a]	41[b]	40 (97.6)
Genotype 2	13	13 (100)
Genotype 3	28	27 (96.4)
Side effects		
AEs (supplementary information)	41	ND[c]
SAEs[d]	41	0 (0)
Discontinuation due to AEs	41	0 (0)

a: Sufficiently valid surrogate in adults for the patient-relevant outcome "hepatocellular carcinoma". Data separated by CHC genotype are available. Data on SVR 12 and SVR 24 are from the additional analysis on the data cut-off from 10 January 2017 (see Section 2.3.1), at which all patients had been followed-up for 24 weeks.
b: Institute's calculation.
c: No data are available for the subpopulation of pretreated adolescents. Results for the total population: 40 of 50 patients (80%) had an AE. Data on common AEs in the total population can be found in Appendix A of the full dossier assessment.
d: The data are from the interim analysis at the data cut-off from 12 July 2016 (see Section 2.3.1). The company presented no information on the number of patients included who reached the planned duration of follow-up observation of 24 weeks at this data cut-off (see Section 2.6.2.7.2 of the full dossier assessment).
AE: adverse event; CHC: chronic hepatitis C; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; 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

Results from the single-arm study 1112 were available also for the assessment of the added benefit of SOF (+ RBV) in treatment-naive adolescents. However, the data constellation in treatment-naive adolescents differed from that in pretreated patients (see Section 2.4.2.1).

Almost all treatment-naive adolescents in study 1112 reached SVR 12 or SVR 24 under SOF + RBV (40 of 41 [97.6%]; Table 12). SVR 12 was rated as not achieved for 1 of the 41 adolescents because this adolescent was described as lost to follow-up after complete treatment.

The company presented no data from a systematic search for the ACT RBV + peg-IFN alfa. However, with reference to the S3 guideline published by the AWMF [7], it described that adolescents with genotype 2 or 3 CHC reached SVR rates of over 90% under RBV + peg-IFN alfa. In view of the studies referenced in this guideline, this is comprehensible.

Hence it is not implausible that comparable SVR rates can be reached under RBV + peg-IFN alfa as those observed under SOF + RBV in study 1112. Therefore, a relevant advantage of SOF (+ RBV) in comparison with the ACT for SVR cannot be assumed automatically.

The company also presented no suitable data for a comparison of SOF (+ RBV) with the ACT RBV + peg-IFN alfa to assess the risk of harm. As described in Section 2.4.2.1, however, neither deaths, nor SAEs or discontinuations due to AEs occurred in the total population of adolescents in study 1112, and thus also in treatment-naive adolescents (0% each; see Table 12). AEs under SOF + RBV occurred in 80% of the patients (in relation to the total population; there were no data on treatment-naive adolescents). From the company's point of view, there is an added benefit of SOF (+ RBV) for side effects per se because interferon-induced side effects are avoided. It referred to selected sources that were not based on a systematic search, including studies and SPCs [8-22].

The derivation of the advantage of SOF (+ RBV) in comparison with RBV + peg-IFN alfa for AEs postulated by the company on the basis of the data selectively presented by the company is inadequate. For instance, also no SAEs or deaths occurred under treatment with RBV + peg-IFN alfa in the largest study cited by the company (Wirth 2010). This study comprised 107 children and adolescents, including 9 (8.4%) adolescents with genotype 2 CHC and 5 (4.6%) adolescents with genotype 3 CHC. Only one patient discontinued study treatment due to AEs. In view of the assessments in the area of CHC in adults already conducted by IQWiG [6,23-26], it can be assumed, however, that the risk of harm from SOF (+ RBV) in adolescents is at least not higher than the risk of harm from RBV + peg-IFN alfa.

The company did not present data on health-related quality of life because the analysis of these data was not planned in the present interim analysis of study 1112.

Overall, no advantage of SOF (+ RBV) in comparison with RBV + peg-IFN alfa is assumed for the SVR rates or for the risk of harm in this data constellation. In the overall assessment, the added benefit of SOF (+ RBV) in treatment-naive adolescents with genotype 2 or 3 CHC in comparison with RBV + peg-IFN is not proven.

2.4.3 Probability and extent of added benefit – summary

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 of adolescents aged 12 to < 18 years with genotype 2 or 3 CHC

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Pretreated adolescents aged 12 to < 18 years with chronic hepatitis C[b]	Best supportive care (BSC)[c]	Hint of a non-quantifiable added benefit[d]
2	Treatment-naive adolescents aged 12 to < 18 years with chronic hepatitis C[b]	Combination of ribavirin and peg-IFN alfa[c]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: Only adolescents without confirmed cirrhosis and without HIV, HAV or HBV coinfection were included in study 1112. Hence conclusions on the added benefit can only be drawn for this population.
c: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
d: For adolescents, 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.
e: The information provided in the SPCs of the combination partners of the ACT is to be considered.
ACT: appropriate comparator therapy; BSC: best supportive care; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HAV: hepatitis A virus; HBV: hepatitis B virus; HIV: human immunodeficiency virus; peg-IFN: pegylated interferon; RBV: ribavirin; SOF: sofosbuvir; SPC: Summary of Product Characteristics

In summary, there was a hint of a non-quantifiable added benefit of SOF (+ RBV) versus the ACT BSC for pretreated adolescents with genotype 2 or 3 CHC.

There was no hint of an added benefit of SOF (+ RBV) in comparison with the ACT RBV + peg-IFN alfa for treatment-naive adolescents with genotype 2 or 3 CHC. An added benefit is therefore not proven.

These conclusions on the added benefit for pretreated and treatment-naive adolescents with CHC refer exclusively to adolescents without cirrhosis. Patients with confirmed cirrhosis were not investigated in the included study 1112.

The assessment of the added benefit deviates from that of the company, which derived a hint of a major added benefit in comparison with the respective comparator therapy for pretreated and treatment-naive adolescents with genotype 2 or 3 CHC (without 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.

2.5 List of included studies

Gilead Sciences. Safety and efficacy of sofosbuvir + ribavirin in adolescents and children with genotype 2 or 3 chronic HCV infection: full text view [online]. In: ClinicalTrials.gov. 14.06.2017 [Accessed: 23.11.2017]. URL: https://ClinicalTrials.gov/show/NCT02175758.

Gilead Sciences. A phase 2, open-label, multicenter, multi-cohort, single-arm study to investigate the safety and efficacy of sofosbuvir + ribavirin in adolescents and children with genotype 2 or 3 chronic HCV infection [online]. In: EU Clinical Trials Register. [Accessed: 23.11.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-002283-32.

Gilead Sciences. A phase 2, open-label, multicenter, multi-cohort, single-arm study to investigate the safety and efficacy of sofosbuvir + ribavirin in adolescents and children with genotype 2 or 3 chronic HCV infection: study GS-US-334-1112; interim clinical study report [unpublished]. 2016.

Wirth S, Rosenthal P, Gonzalez-Peralta RP, Jonas MM, Balistreri WF, Lin CH et al. Sofosbuvir and ribavirin in adolescents 12-17 years old with hepatitis C virus genotype 2 or 3 infection. Hepatology 2017; 66(4): 1102-1110.

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Please see full dossier assessment for full reference list.

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8. Merck Sharp Dohme. Fachinformation PegIntron 50 µg/80 µg/100 µg/120 µg/150 µg Clearclick Fertigpen (Peginterferon alfa-2b); Stand der Information: Juli. 2015.

9. Roche Pharma. Fachinformation Copegus 200 mg/400 mg Filmtablette (Ribavirin); Stand der Information: Januar. 2015.

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