IQWiG Reports – Commission No. A22-26

Sofosbuvir/velpatasvir (chronic hepatitis C in children 3 to < 6 years of age) –

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, 3 bis < 6 Jahre) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 May 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Sofosbuvir/velpatasvir (chronic hepatitis C in children 3 to < 6 years of age) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
8 February 2022

Internal Commission No.
A22-26

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Keywords: Sofosbuvir, Velpatasvir, Hepatitis C – Chronic, Child – Preschool, Benefit Assessment, NCT03022981

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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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCV	hepatitis C virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PedsQL	Pediatric Quality of Life Inventory
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SVR	sustained virologic response

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. 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 8 February 2022.

Research question

The aim of this report is to assess the added benefit of sofosbuvir/velpatasvir in comparison with the appropriate comparator therapy (ACT) for the treatment of chronic hepatitis C virus (HCV) infection in children ages 3 to < 6 years.

The research questions shown in Table 2 result from the ACT specified by the G-BA.

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

Research question	Therapeutic indication	ACT[a]
1	Chronic HCV infection genotype 1, 4, 5, or 6 in children ages 3 to < 6 years	Ledipasvir/sofosbuvir
2	Chronic HCV infection genotype 2 or 3 in children ages 3 to < 6 years	Sofosbuvir + ribavirin
a. Presented is the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HCV: hepatitis C virus		

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

Results

The company did not find any directly comparative randomized controlled trials (RCTs) with the drug to be assessed in the relevant population (children ages 3 to < 6 years). For this reason, the company has presented the single-arm study GS-US-342-1143 (hereinafter referred to as G342-1143). In cohort 3 of the study, children ages 3 to < 6 years were treated with sofosbuvir/velpatasvir for 12 weeks.

The company did not present any data on the ACT. It did not compare individual arms of different studies because in its opinion, effects relevant for the benefit assessment or statistically significant advantages of sofosbuvir/velpatasvir were not to be expected with regard to clinical outcomes in comparison with the respective ACT in the population of children ages 3 to < 6 years. The company presented the results of the G342-1143 study on the outcome categories

of mortality, morbidity, health-related quality of life, and side effects but claimed no added benefit for sofosbuvir/velpatasvir.

Deriving added benefit on the basis of single-arm studies would be possible in case of very large effects in comparison with the ACT. Due to the high proportion of patients who discontinued treatment (17%) and the associated percentage of imputed values, the available data from the single-arm study G342-1143 allow only a very limited evaluation of the results in comparison with the ACT.

In the G342-1143 study (cohort 3), 29 of 33 (87.9%) 3 to < 6-year old patients with genotype 1 or 4 as well as 5 of 8 patients (62.5%) with genotype 2 or 3 achieved sustained virologic response 12 or 24 weeks after treatment end (SVR_{12}, SVR_{24}) on sofosbuvir/velpatasvir. In total, 1 (2.4%) discontinuation due to adverse events (AEs) was observed. No serious AEs (SAEs), severe AEs, or deaths occurred in the study.

Dossier assessments have already been conducted for the drug combinations ledipasvir/sofosbuvir and sofosbuvir + ribavirin, which are specified as the ACTs for the present therapeutic indication. For each of the drug combinations, both treatment-naive and treatment-experienced children (ages 3 to < 12 years) exhibited SVR_{12} or SVR_{24} rates ≥ 95%. In addition, both under ledipasvir/sofosbuvir and under sofosbuvir + ribavirin, 1 SAE and 1 discontinuation due to AEs were observed. No deaths occurred.

Concurring with the company, no added benefit of sofosbuvir/velpatasvir can be derived from the data of the G342-1143 study. Overall, the company therefore presented no suitable data for deriving an added benefit in comparison with the ACT.

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

Table 3 shows a summary of the probability and extent of added benefit of sofosbuvir/velpatasvir.

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

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Chronic HCV infection genotype 1, 4, 5, or 6 in children ages 3 to < 6 years	Ledipasvir/sofosbuvir	Added benefit not proven
2	Chronic HCV infection genotype 2 or 3 in children ages 3 to < 6 years	Sofosbuvir + ribavirin	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HCV: hepatitis C virus			

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of sofosbuvir/velpatasvir in comparison with the ACT for the treatment of chronic HCV infection in children ages 3 to < 6 years.

The research questions shown in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of sofosbuvir/velpatasvir

Research question	Therapeutic indication	ACT[a]
1	Chronic HCV infection genotype 1, 4, 5, or 6 in children ages 3 to < 6 years	Ledipasvir/sofosbuvir
2	Chronic HCV infection genotype 2 or 3 in children ages 3 to < 6 years	Sofosbuvir + ribavirin
a. Presented is the respective ACT specified by the GBA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HCV: hepatitis C virus		

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

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 sofosbuvir/velpatasvir (status: 17 November 2021)
- bibliographical literature search on sofosbuvir/velpatasvir (last search on 17 November 2021)
- search in trial registries / trial results databases for studies on sofosbuvir/velpatasvir (last search on 17 November 2021)

To check the completeness of the study pool:

- Search in trial registries for sofosbuvir/velpatasvir (last search on 10 March 2022); see Appendix A of the full dossier assessment for search strategies.

Concurring with the company, the check of completeness of the study pool did not reveal any directly comparative RCTs on the drug to be assessed in the relevant population (children ages 3 to < 6 years).

The company reports having foregone information retrieval for nonrandomized studies of a lower evidence level if neither a direct comparison nor adjusted indirect comparisons versus

the ACT is possible. It justifies this approach by stating that effects relevant for the benefit assessment or statistically significant advantages of sofosbuvir/velpatasvir with regard to clinical outcomes in comparison with the respective ACT are not to be expected in the population of children ages 3 to < 6 years.

Overall, the company has not presented any suitable data for deriving an added benefit in comparison with the ACT for children ages 3 to < 6 years with chronic HCV infection.

However, the company asserts that it has presented the available evidence on which the approval for paediatric patients ages 3 to < 6 years with chronic HCV infection is based. The evidence in question is from the single-arm GS-US-342-1143 study on sofosbuvir/velpatasvir (hereinafter referred to as G342-1143) [3-5]. The company has claimed no added benefit of sofosbuvir/velpatasvir.

Description of the G342-1143 study

The G342-1143 study enrolled a total of 216 children and adolescents in 3 cohorts. The company analysed cohort 3, which comprises 41 treatment-naive children ages 3 to < 6 years with chronic HCV infection. Cohorts 1 and 2 of the G342-1143 study comprised older children and adolescents ages 6 to < 18 years; these 2 cohorts differ from the target population of the present benefit assessment and have already been analysed in dossier assessment A20-86 [6].

Cohort 3 was intended to include children with chronic HCV infection of all 6 genotypes. Ultimately, however, this cohort included only children with HCV genotypes 1 through 4 (see Appendix B, Table 9 of the full dossier assessment). The patient population defined in research question 1 therefore comprises only children with genotype 1 (n = 32 [78%]) or genotype 4 (n = 1 [2%]). The patient population defined for research question 2 comprises children with genotype 2 (n = 6 [15%]) or genotype 3 (n = 2 [5%]). Further information on patient characteristics is found in Appendix B of the full dossier assessment.

A portion of the patients in each age cohort participated in a 7-day pharmacokinetic lead-in phase at the start of the study. Afterwards, patients continued therapy without interruption in the treatment phase until the intended total treatment duration of 12 weeks was reached. After analysis of the pharmacokinetic lead-in phase, additional patients were enrolled directly into the treatment phase.

Sofosbuvir/velpatasvir is approved in 2 pharmaceutical forms: as a coated granulate and as a film-coated tablet [7]. The granulate is currently (as of 2 May 2022) unavailable in Germany; according to the company, it is expected to become available by the end of the 2nd quarter 2022. The children in cohort 3 received sofosbuvir/velpatasvir in weight-based dosing in the form of the coated granulate. In accordance with approval, children weighing < 17 kg received a once-daily dose of 150 mg / 37.5 mg (sofosbuvir/velpatasvir), while children with a body weight ≥ 17 kg received 200 mg / 50 mg once daily [7]. The company notes that the latter dosage was also administered to 1 child in cohort 3 with a body weight ≥ 30 kg, despite the approval

specifying a dose of 400 mg / 100 mg starting from this body weight. The company has foregone a separate presentation of the population treated on-label, noting that despite the underdosage, the child achieved sustained virologic response 12 weeks after treatment end (SVR_{12}).

The primary outcome of the G342-1143 study is adverse events (AEs), with special focus being placed on AEs leading to discontinuation of the study drug. Secondary outcomes are sustained virologic response 12 or 24 weeks after treatment end (SVR_{12} and SVR_{24}) and health-related quality of life. For the outcomes on side effects and health-related quality of life, the company has presented results only for the entire cohort 3, rather than separately for the patient populations of the 2 research questions.

No suitable data for assessing added benefit

Concurring with the company's assessment, the single-arm study G342-1143 is deemed unsuitable for deriving any conclusions on the added benefit of sofosbuvir/velpatasvir in children ages 3 to < 6 years in comparison with the ACT.

In the G342-1143 study (cohort 3), 29 of 33 (87.9%) 3 to < 6-year old patients with genotype 1 or 4 as well as 5 of 8 patients (62.5%) with genotype 2 or 3 achieved sustained virologic response 12 or 24 weeks after treatment end (SVR_{12}, SVR_{24}) on sofosbuvir/velpatasvir. In this context, it must be noted that no SVR_{12} value was available for 7 of the 41 children (17%); for these children, the value was imputed, with a missing value at follow-up week 12 being imputed as a responder if the measurements before and after were rated as response. Any other missing values were imputed as nonresponders. Missing values for SVR_{24} were imputed in the same way as SVR_{12} status. The available documents show that at least 6 of the 7 children who discontinued treatment prematurely did not participate in follow-up visits; therefore, no SVR_{12} or SVR_{24} values were available for these children, who were imputed to be nonresponders.

For outcomes on health-related quality of life and side effects, results are available only for the entire cohort 3 – rather than separately for patients with genotype 1 or 4 versus for patients with genotype 2 or 3. To survey health-related quality of life in the G342-1143 study, the company used the instrument Pediatric Quality of Life Inventory (PedsQL). For children in cohort 3, the total score at follow-up week 24 showed a mean change from baseline by 1.9 points (standard deviation [SD]: 14.26; see Appendix B, Table 11 of the full dossier assessment). In total, 1 (2.4%) discontinuation due to AEs was observed. No SAEs, severe AEs, or deaths occurred in the study (see Appendix B, Table 10 of the full dossier assessment).

For the drug combinations of ledipasvir/sofosbuvir and sofosbuvir + ribavirin, which were identified as the ACTs, dossier assessments have already been conducted in the present therapeutic indication [8,9]. These dossier assessments include results on treatment-naive and treatment-experienced children ages 3 to < 12 years with genotypes 1 and 4 (ledipasvir/sofosbuvir [8]) or genotypes 2 and 3 (sofosbuvir + ribavirine [9]) for the outcome categories of mortality, morbidity, health-related quality of life, and side effects. These results

are also from single-arm studies. In summary, results show that SVR_{12} and SVR_{24} rates ≥ 95% were reached on the respective drug combinations by both treatment-naive and pretreated children. In addition, both under ledipasvir/sofosbuvir and under sofosbuvir + ribavirin, 1 SAE and 1 discontinuation due to AEs were observed. No deaths occurred. For health-related quality of life, the PedsQL total score at follow-up week 24 showed a mean change from baseline of 2.0 (SD: 15.7) on ledipasvir/sofosbuvir and of 0.4 (SD: 14.2) on sofosbuvir + ribavirin.

Deriving added benefit on the basis of single-arm studies would require very large effects in comparison with the ACT [1]. Due to the high proportion of patients who discontinued treatment (17%) and the associated percentage of imputed values, the available data from the single-arm study G342-1143 allow only a very limited evaluation of the results in comparison with the ACT.

Concurring with the company, no added benefit of sofosbuvir/velpatasvir can be derived from the data of the G342-1143 study. Overall, the company therefore presented no suitable data for deriving an added benefit in comparison with the ACT.

2.4 Results on added benefit

The company has not submitted any suitable data for assessing the added benefit of sofosbuvir/velpatasvir in comparison with the ACT in children ages 3 to < 6 years with chronic HCV infection. This results in no hint of added benefit of sofosbuvir/velpatasvir in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit – summary

Table 5 summarizes the result of the assessment of added benefit of sofosbuvir/velpatasvir in comparison with the ACT.

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

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Chronic HCV infection genotype 1, 4, 5, or 6 in children ages 3 to < 6 years	Ledipasvir/sofosbuvir	Added benefit not proven
2	Chronic HCV infection genotype 2 or 3 in children ages 3 to < 6 years	Sofosbuvir + ribavirin	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HCV: hepatitis C virus			

The above-described assessment of extent and probability agrees with that of the company.

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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