IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-41

Ledipasvir/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 *Ledipasvir/Sofosbuvir (chronische Hepatitis C bei Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 November 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Ledipasvir/sofosbuvir (chronic hepatitis C in adolescents) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

16 August 2017

Internal Commission No.:

A17-41

Address of publisher:

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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.

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Keywords: ledipasvir, sofosbuvir, hepatitis C – chronic C, adolescent, benefit assessment, NCT02249182

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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
BSC	best supportive care
CHC	chronic hepatitis C
CSR	clinical study report
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)
LDV/SOF	ledipasvir/sofosbuvir
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
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 combination ledipasvir/sofosbuvir (LDV/SOF). 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 16 August 2017.

Research question

The aim of the present report was to assess the added benefit of LDV/SOF compared with the appropriate comparator therapy (ACT) in adolescents aged 12 to < 18 years with chronic hepatitis C (CHC).

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

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

Research question	Subindication	ACT[a]
1	Pretreated adolescents aged 12 to < 18 years with CHC[b]	Best supportive care (BSC)[c]
2	Treatment-naive adolescents aged 12 to < 18 years with CHC[b]	Combination of ribavirin and peginterferon alfa[d]

a: Presentation of the respective ACT specified by the G-BA.
b: Under consideration of the approval status of LDV/SOF for the different CHC genotypes depending on cirrhosis and pretreatment status.
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: 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; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

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

An overview of the data presented by the company is shown in Table 3.

Table 3: Data presented by the company on the research questions

Research question	Subindication	Data presented by the company
1	Pretreated adolescents aged 12 to < 18 years with CHC	
	▪ Genotype 1	Single-arm study G337-1116
	▪ Genotype 3, 4, 5, 6[a]	No data
2	Treatment-naive adolescents aged 12 to < 18 years with CHC	
	▪ Genotype 1	Single-arm study G337-1116
	▪ Genotype 3, 4, 5, 6[a]	No data
a: LDV/SOF is not approved for genotype 2 [3]. CHC: chronic hepatitis C; LDV/SOF: ledipasvir/sofosbuvir		

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 G337-1116 (hereinafter referred to as "study 1116") was used for the benefit assessment. This study investigated the administration of LDV/SOF in pretreated and treatment-naive children and adolescents aged 3 to < 18 years with 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.

Inclusion of patients with CHC genotype 1, 4, 5 or 6 was planned for group 1. However, only adolescents with CHC genotype 1, who were either treatment-naive (N = 80) or pretreated (N = 20), were included.

The treatment-naive adolescents included 1 patient with confirmed diagnosis of compensated cirrhosis; however, the cirrhosis status was unknown for 45% of the pretreated patients and for 60% of the treatment-naive patients. Presence of decompensated liver disease was defined as an exclusion criterion. Patients coinfected with human immunodeficiency virus (HIV), hepatitis A and hepatitis B were also excluded from the study.

Corresponding to the specifications on the treatment regimen, all 100 patients in group 1 received a fixed combination of 90 mg LDV/400 mg SOF once daily over a period of 12 weeks.

Risk of bias

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

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

Assessment of the study results for pretreated adolescents with CHC

Genotype 1

Results of a subpopulation from the single-arm study 1116 were available for the assessment of the added benefit of LDV/SOF in pretreated adolescents with CHC. Due to the specific data situation, however, it was still possible to draw conclusions on the added benefit of LDV/SOF on the basis of the available evidence.

Study 1116 showed that all pretreated patients, without exception (100%), reached sustained virologic response 12 weeks after the end of treatment (SVR 12) or 24 weeks after the end of treatment (SVR 24). Non-antiviral best supportive care (BSC), however, is unlikely to achieve virus elimination (e.g. by spontaneous virus elimination). Hence, even without the presence of studies of direct comparisons, an advantage of LDV/SOF for SVR can be derived.

In addition, neither deaths, nor serious adverse events (SAEs) or discontinuations due to adverse events (AEs) under LDV/SOF were observed in the total group 1 of study 1116, and thus also in pretreated adolescents (0% each).

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 1116.

Overall, in this particular data constellation (achievement of SVR in 100% of the patient population, and occurrence of SAEs in 0%), a derivation of the added benefit of LDV/SOF is possible because, with great certainty, these results regarding the SVR cannot be achieved by the ACT BSC. The risk of harm under LDV/SOF observed in study 1116 also did not raise doubts about 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 LDV/SOF in pretreated adolescents with CHC genotype 1.

This added benefit refers only to adolescents without cirrhosis or with compensated cirrhosis. Patients with decompensated cirrhosis were not investigated in the included study 1116.

Genotypes 3, 4, 5 and 6

The company presented no data for the assessment of the added benefit in pretreated patients with CHC genotype 3, 4, 5 and 6. The added benefit is not proven for these patients.

Treatment-naive adolescents with CHC

Genotype 1

Results of a subpopulation from the single-arm study 1116 were also available for the assessment of the added benefit of LDV/SOF in treatment-naive adolescents. Similar to the pretreated patient population, it is possible to draw conclusions on the added benefit of LDV/SOF also for treatment-naive patients on the basis of the available evidence due to the particular data situation.

SVR12 or SVR24 under LDV/SOF was achieved by 78 of 80 (97.5%) treatment-naive patients in study 1116.

The company described for the ACT ribavirin + peginterferon alfa that fewer than 60% of the adolescents with CHC genotype 1 reached SVR. In view of the assessments in the area of CHC in adults already conducted by IQWiG, it can be assumed that there is currently no evidence showing SVR rates of a similar magnitude for ribavirin + peginterferon alfa as the rates observed under LDV/SOF in study 1116. Hence for SVR, an advantage of LDV/SOF can be assumed in comparison with the ACT ribavirin + peginterferon alfa, the magnitude of which cannot be assessed.

As described for pretreated adolescents with CHC, neither deaths, nor SAEs or discontinuations due to AEs under LDV/SOF occurred in the total group 1 of study 1116, and thus also in treatment-naive adolescents (0% each). From the company's point of view, there is an added benefit of LDV/SOF for side effects per se because interferon-induced side effects are avoided.

The derivation of the advantage of LDV/SOF in comparison with ribavirin + peginterferon alfa for AEs postulated by the company on the basis of the data selectively presented by the company is inadequate. For example, there were also no SAEs or deaths under ribavirin + peginterferon alfa in the largest study cited by the company, which included 107 children and adolescents (Wirth 2010). 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 LDV/SOF is at least not higher than the risk of harm from ribavirin + peginterferon 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 1116.

In the present situation, there is a hint of a non-quantifiable added benefit of LDV/SOF in treatment-naive adolescents with CHC genotype 1 in comparison with ribavirin + peginterferon alfa.

This added benefit refers only to adolescents without cirrhosis or with compensated cirrhosis. Patients with decompensated cirrhosis were not investigated in the included study 1116.

Genotypes 3, 4, 5 and 6

The company presented no data for the assessment of the added benefit in treatment-naive patients with CHC genotype 3, 4, 5 and 6. The added benefit is not proven for these patients.

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 comparison with the respective ACTs.

In the present situation, there is a hint of a non-quantifiable added benefit of LDV/SOF in comparison with the respective ACT for pretreated and treatment-naive adolescents with CHC genotype 1. This added benefit refers only to adolescents without cirrhosis or with compensated cirrhosis. Patients with decompensated cirrhosis were not investigated in the included study 1116.

There was no hint of an added benefit of LDV/SOF in comparison with the ACT for adolescents with CHC genotype 3, 4, 5 and 6; an added benefit is therefore not proven.

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

[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 4: LDV/SOF – Probability and extent of the added benefit of adolescents aged 12 to < 18 years with CHC

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Pretreated adolescents aged 12 to < 18 years with chronic hepatitis C	Best supportive care (BSC)[c]	
	▪ Genotype 1[b]		Hint of a non-quantifiable added benefit
	▪ Genotype 3, 4, 5, 6		Added benefit not proven
2	Treatment-naive adolescents aged 12 to < 18 years with chronic hepatitis C	Combination of ribavirin and peginterferon alfa[d]	
	▪ Genotype 1[b]		Hint of a non-quantifiable added benefit
	▪ Genotype 3, 4, 5, 6		Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: Only adolescents with CHC genotype 1 without cirrhosis or with compensated cirrhosis, and without HIV, HAV or HBV coinfection, were included in study 1116. 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: 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; G-BA: Federal Joint Committee; HAV: hepatitis A virus; HBV: hepatitis B virus; HIV: human immunodeficiency virus; LDV/SOF: ledipasvir/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 this report was to assess the added benefit of LDV/SOF compared with the ACT in adolescents aged 12 to < 18 years with CHC.

For the benefit assessment of LDV/SOF, the 2 research questions presented in Table 5 resulted from the ACT specified by the G-BA.

Table 5: Research questions of the benefit assessment of LDV/SOF

Research question	Subindication	ACT[a]
1	Pretreated adolescents aged 12 to < 18 years with CHC[b]	Best supportive care (BSC)[c]
2	Treatment-naive adolescents aged 12 to < 18 years with CHC[b]	Combination of ribavirin and peginterferon alfa[d]

a: Presentation of the respective ACT specified by the G-BA.
b: Under consideration of the approval status of LDV/SOF for the different CHC genotypes depending on cirrhosis and pretreatment status [3].
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: 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; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

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

An overview of the data presented by the company is shown in Table 6.

Table 6: Data presented by the company on the research questions

Research question	Subindication	Data presented by the company
1	Pretreated adolescents aged 12 to < 18 years with CHC	
	▪ Genotype 1	Single-arm study G337-1116
	▪ Genotype 3, 4, 5, 6[a]	No data
2	Treatment-naive adolescents aged 12 to < 18 years with CHC	
	▪ Genotype 1	Single-arm study G337-1116
	▪ Genotype 3, 4, 5, 6[a]	No data

a: LDV/SOF is not approved for genotype 2 [3].
CHC: chronic hepatitis C; LDV/SOF: ledipasvir/sofosbuvir

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

For both research questions, 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 LDV/SOF (status: 28 June 2017)
- bibliographical literature search on LDV/SOF (last search on 28 June 2017)

- search in trial registries for studies on LDV/SOF (last search on 28 June 2017)

To check the completeness of the study pool:

- bibliographical literature search on LDV/SOF (last search on 27 September 2017)
- search in trial registries for studies on LDV/SOF (last search on 1 September 2017)

Concurring with the company, the check of the completeness of the study pool for pretreated and treatment-naive adolescents produced no randomized controlled trials (RCTs) on the direct comparison of LDV/SOF versus the ACT.

The company therefore searched for further investigations on LDV/SOF. The company's search produced the single-arm study G337-1116 (hereinafter referred to as "study 1116") for both research questions (pretreated and treatment-naive adolescents).

The completeness of the study pool was also checked for further investigations. This check produced no further relevant studies.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment of LDV/SOF in pretreated and treatment-naive adolescents.

Table 7: Study pool – non-RCT, single-arm study: LDV/SOF

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 G337-1116 (1116[b])	Yes	Yes	No

a: Study for which the company was sponsor.
b: Hereinafter, the study is referred to with this abbreviated form.
LDV/SOF: ledipasvir/sofosbuvir; RCT: randomized controlled trial

Study 1116 presented by the company for both research questions (pretreated and treatment-naive adolescents) was a single-arm study with LDV/SOF. Due to the specific data constellation, conclusions on the added benefit of LDV/SOF in adolescents with CHC can still be derived on the basis of this study. Study 1116 was therefore used for the assessment of the added benefit. Section 2.4.2 explains the reasons for this for individual research questions.

Section 2.5 contains a reference list for the study included.

2.3.2 Study characteristics

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

Table 8: Characteristics of the study included – non-RCT, single-arm study: LDV/SOF

Study	Study design	Population	Intervention (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
1116	Non-randomized, open-label	Treatment-naive and pretreated children and adolescents with CHC genotype 1, 3, 4, 5 or 6[b]	Genotype 1, 4, 5 or 6[b]: ledipasvir/sofosbuvir Genotype 3[b]: ledipasvir/sofosbuvir + ribavirin Group 1: adolescents aged 12 to < 18 years (N = 100) Group 2[c]: children aged 3 to < 12 years (N = ND)	Screening: up to 28 days PK lead-in phase: 10 days[d] Treatment phase: 12[e] or 24 weeks Observation: outcome-specific	24 centres in Australia, United Kingdom, United States of America 11/2014–ongoing Data cut-off for group 1: 4/2016[f]	Primary: SVR 12 Secondary: SVR 24, health-related quality of life, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: According to the study protocol and its amendments, it was planned to include adolescents with CHC genotype 1, 3 (United Kingdom only), 4, 5 or 6 into group 1. However, only adolescents with genotype 1 were included.
c: The population is not relevant for the assessment and is not shown in the following tables.
d: Only some patients participated in the PK lead-in phase (treatment-naive, no cirrhosis, minimum weight of 45 kg).
e: Patients who had already participated in the PK lead-in phase continued treatment only until they reached the total treatment duration of 12 weeks.
f: 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; LDV/SOF: ledipasvir/sofosbuvir; N: number of patients included; ND: no data; PK: pharmacokinetics; RCT: randomized controlled trial; SVR: sustained virologic response

Table 9: Characteristics of the intervention – non-RCT, single-arm study: LDV/SOF

Study	Intervention
1116	Adolescents with CHC genotype 1[a]: ledipasvir 90 mg/sofosbuvir 400 mg, once daily, orally for 12 weeks: ▪ treatment-naive adolescents with or without cirrhosis ▪ pretreated adolescents without cirrhosis for 24 weeks: ▪ pretreated adolescents with cirrhosis[b]

a: Inclusion of adolescents with CHC of different genotypes was planned for group 1. However, only adolescents with genotype 1 were included. The information on the intervention is therefore limited to these patients.
b: According to the study documents, none of the pretreated adolescents had confirmed cirrhosis. The cirrhosis status was unknown in 45% of the pretreated adolescents.
CHC: chronic hepatitis C; LDV/SOF: ledipasvir/sofosbuvir; RCT: randomized controlled trial

Study 1116 is an ongoing, single-arm, open-label study investigating LDV/SOF in pretreated and treatment-naive children and adolescents aged 3 to < 18 years with 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 coinfected with HIV, hepatitis A and hepatitis B were excluded from the study.

Inclusion of adolescents with CHC genotype 1, 4, 5 or 6 was planned for group 1; adolescents with CHC genotype 3 were additionally included in the study centre of the United Kingdom. Different treatment regimens were mandated, depending on genotype, pretreatment, cirrhosis status and country. However, only adolescents with CHC genotype 1, who were either treatment-naive (N = 80) or pretreated (N = 20), were included into group 1. Corresponding to the specifications on the treatment regimen, all 100 patients in group 1 therefore received a fixed combination of 90 mg LDV/400 mg SOF once daily over a period of 12 weeks.

In the beginning of the study, some of the patients participated in a 10-day pharmacokinetics lead-in phase to confirm suitability of LDV/SOF dosing (90 mg/400 mg) for the age group concerned. To participate, the patients had to be treatment-naive, have no cirrhosis and weigh at least 45 kg. Subsequently, the patients continued therapy in the treatment phase without interruption until reaching the total treatment duration of 12 weeks mandated. After analysis of the data from the lead-in phase, further patients were also included directly into the 12-week treatment phase.

Table 10 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 10: Planned duration of follow-up – non-RCT, single-arm study: LDV/SOF

Study **Outcome category** **Outcome**	**Planned follow-up**
1116	
Mortality	
All-cause mortality	24 weeks after end of treatment[a]
Morbidity	
SVR 12	12 weeks after end of treatment
SVR 24	24 weeks after end of treatment
Health-related quality of life	24 weeks after end of treatment
Side effects	
AEs	30 days after end of treatment
SAEs	24 weeks after end of treatment
a: Deaths were recorded in the framework of SAEs. AE: adverse event; LDV/SOF: ledipasvir/sofosbuvir; SAE: serious adverse event; SVR: sustained virologic response; RCT: randomized controlled trial	

Table 11 shows the characteristics of the patients in the study included.

Table 11: Characteristics of the study populations – non-RCT, single-arm study: LDV/SOF

Study Characteristics Category	**LDV/SOF**	
1116	**Pretreated patients N = 20**	**Treatment-naive patients N = 80**
Age [years], mean (SD)	15 (1.7)	15 (1.7)
Sex [F/M], %	65.0/35.0	62.5/37.5
Ethnicity, n (%)		
White	19 (95.0)	71 (88.8)
Black	0 (0)	7 (8.8)
Asian	0 (0)	2 (2.5)
Unknown	1 (5)	0 (0)
HCV subgenotype, n (%)		
1a	15 (75.0)	66 (82.5)
1b	5 (25.0)	14 (17.5)
Cirrhosis, n (%)		
Yes	0 (0)	1 (1.3)
No	11 (55.0)	31 (38.8)
Unknown	9 (45.0)	48 (60.0)
Baseline HCV RNA viral load [IU/mL], n (%)		
< 800 000	9 (45.0)	36 (45.0)
≥ 800 000	11 (55.0)	44 (55.0)
Response to prior therapy, n (%)		
No response	13 (65)	NA
Relapse	6 (30)	NA
Intolerance	1 (5)	NA
Treatment discontinuation, n (%)	0 (0)	1 (1.3)[a]
Study discontinuation, n (%)	0 (0)	2 (2.5)[b]

a: There were no data on SVR 4 or SVR 12 for this patient, but there were data on SVR 24.
b: According to the company, 2 patients did not participate in study visits during the follow-up observation period and were therefore recorded as lost to follow-up.

F: female; HCV: hepatitis C virus; LDV/SOF: ledipasvir/sofosbuvir; M: male; n: number of patients in the category; N: number of patients included; NA: not applicable; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation

The mean age of the 20 pretreated adolescents and the 80 treatment-naive adolescents in study 1116 was 15 years. Most adolescents were female (65% and 63%) and white (95% and 89%). All patients included had hepatitis C virus (HCV) genotype 1. One of the treatment-naive adolescents had confirmed diagnosis of compensated cirrhosis, but the cirrhosis status was unknown in many patients in both subpopulations (45% and 60%). 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 deviates from that of the company (see Section 2.6.2.7.2 of the full dossier assessment).

A clinical study report (CSR) from 16 June 2016 [4] with results of an interim analysis for the data cut-off from 28 April 2016 was available for study 1116. This analysis contained no analyses on SVR 24 or on health-related quality of life as these had not been planned for the interim analysis. However, the company transmitted results for the data cut-off from 10 January 2017 for SVR 24.

Table 12 shows for which outcomes data were available in the studies included.

Table 12: Matrix of outcomes – non-RCT, single-arm study: LDV/SOF

Study	Outcomes						
	All-cause mortality	SVR 12	SVR 24	Health-related quality of life	SAEs	Discontinuation due to AEs	Specific AEs
Study 1116	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 are only available for the total population. 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; LDV/SOF: ledipasvir/sofosbuvir; SAE: serious adverse event; SVR: sustained virologic response; RCT: randomized controlled trial

2.4.2 Results

Since one single-arm study without comparative assessment with the ACT was used for the present assessment, the aspects of bias were not assessed for the study included or for all 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 Pretreated adolescents with CHC

Genotype 1

Table 13 summarizes the results for the subpopulation of pretreated adolescents with CHC genotype 1 from the single-arm study 1116.

Table 13: Results (mortality, morbidity, side effects) – non-RCT, single-arm study: pretreated adolescents with CHC genotype 1, LDV/SOF

Study	LDV/SOF	
Outcome category **Outcome**	**N**	**Patients with event** **n (%)**
1116		
Mortality		
All-cause mortality	20	0 (0)
Morbidity		
SVR 12[a]	20	20 (100)
SVR 24[a]	20	20 (100)
Side effects		
AEs (supplementary information)		ND[b]
SAEs	20	0 (0)
Discontinuation due to AEs	20	0 (0)

a: Sufficiently valid surrogate in adults for the patient-relevant outcome "hepatocellular carcinoma"; data are from the analysis on the data cut-off from 10 January 2017 transmitted by the company.
b: No data are available for the subpopulation of pretreated adolescents. Results for the total population: 71 of 100 adolescents (71%) had an AE. Data on individual AEs in the total population can be found in Appendix A of the full dossier assessment.
AE: adverse event; CHC: chronic hepatitis C; LDV/SOF: ledipasvir/sofosbuvir; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; SVR 12/SVR 24: sustained virologic response 12/24 weeks after end of treatment

Results of a subpopulation from the single-arm study 1116 were available for the assessment of the added benefit of LDV/SOF in pretreated adolescents (CHC genotype 1). Due to the specific data situation, however, it was still possible to draw conclusions on the added benefit of LDV/SOF on the basis of the available evidence.

Study 1116 showed that all pretreated patients, without exception (100%, see Table 13), reached SVR 12or SVR 24. Non-antiviral BSC, however, is unlikely to achieve virus elimination (e.g. by spontaneous virus elimination). Hence, even without the presence of studies of direct comparisons, an advantage of LDV/SOF for SVR can be derived.

The company also presented no data for a comparison of LDV/SOF with the ACT BSC to assess the risk of harm. However, neither deaths, nor SAEs or discontinuations due to AEs under LDV/SOF were observed in the total group 1 of study 1116, and thus also in pretreated patients (0% each, see Table 13). The company presented no separate data for the patient population of pretreated adolescents.

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 1116.

Overall, in this particular data constellation (achievement of SVR in 100% of the patient population, and occurrence of SAEs in 0%), a derivation of the added benefit of LDV/SOF is possible. With great certainty, the results regarding the SVR cannot be achieved by the ACT BSC. The risk of harm under LDV/SOF observed in study 1116 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 comparison with the ACT BSC.

In the present situation, there is a hint of a non-quantifiable added benefit of LDV/SOF in pretreated adolescents with CHC genotype 1.

This added benefit refers only to adolescents without cirrhosis or with compensated cirrhosis. Patients with decompensated cirrhosis were not investigated in the included study 1116.

Genotypes 3, 4, 5 and 6

The company presented no data for the assessment of the added benefit in pretreated patients with CHC genotype 3, 4, 5 and 6. The added benefit is not proven for these patients.

2.4.2.2 Treatment-naive adolescents

CHC genotype 1

Table 14 summarizes the results for the subpopulation of treatment-naive adolescents with CHC genotype 1 from study 1116.

Table 14: Results (mortality, morbidity, side effects) – non-RCT, single-arm study: treatment-naive adolescents with CHC genotype 1, LDV/SOF

Study	LDV/SOF	
Outcome category Outcome	N	Patients with event n (%)
1116		
Mortality		
All-cause mortality	80	0 (0)
Morbidity		
SVR 12[a]	80	78 (97.5)
SVR 24[a]	80	78 (97.5)
Side effects		
AEs (supplementary information)		ND[b]
SAEs	80	0 (0)
Discontinuation due to AEs	80	0 (0)

a: Sufficiently valid surrogate in adults for the patient-relevant outcome "hepatocellular carcinoma"; data are from the analysis on the data cut-off from 10 January 2017 company (see Section 2.4.1). The interim analysis from 16 June 2016 reported that 77 of 80 (96.3%) adolescents achieved SVR 12 because data for one patient were missing at this time point. In the analysis from 10 January 2017, however, the SVR 12 was rated as achieved for this patient because SVR was determined both at treatment week 4 and at week 24 after the end of treatment (SVR 24) in this patient.

b: No data are available for the subpopulation of treatment-naive patients. Results for the total population: 71 of 100 adolescents (71%) had an AE. Data on individual AEs in the total population can be found in Appendix A of the full dossier assessment.

AE: adverse event; CHC: chronic hepatitis C; LDV/SOF: ledipasvir/sofosbuvir; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; SVR 12/SVR 24: sustained virologic response 12/24 weeks after end of treatment

Results of a subpopulation from the single-arm study 1116 were available for the assessment of the added benefit of LDV/SOF also in treatment-naive adolescents (CHC genotype 1). Similar to the pretreated patient population, it is possible to draw conclusions on the added benefit of LDV/SOF also for treatment-naive patients on the basis of the available evidence due to the particular data situation.

SVR12 or SVR24 under LDV/SOF was achieved by 78 of 80 (97.5%) treatment-naive patients in study 1116 (Table 14). According to the company, no data on SVR 12 or SVR 24 were available for 2 of 80 (2.5%) patients because they did not participate in study visits during the follow-up observation period and were therefore described in the dossier as lost to follow-up.

The company described for the ACT ribavirin + peginterferon alfa that fewer than 60% of the adolescents with CHC genotype 1 reached SVR. The company referred to chosen studies [5-7]. It is unclear to what extent the SVR rates of < 60% cited by the company can be confirmed by systematically searched evidence. However, in view of the assessments in the area of CHC in adults already conducted by IQWiG [8-12], it can be assumed that there is

currently no evidence showing SVR rates of a similar magnitude for ribavirin + peginterferon alfa as the rates observed under LDV/SOF in study 1116 (see Table 14). Hence for SVR, an advantage of LDV/SOF can be assumed in comparison with the ACT ribavirin + peginterferon alfa, the magnitude of which cannot be assessed.

The company also presented no data for a comparison of LDV/SOF with the ACT ribavirin + peginterferon 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 under LDV/SOF occurred in the total group 1 of study 1116, and thus also in treatment-naive adolescents (0% each; see Table 14). From the company's point of view, there is an added benefit of LDV/SOF for side effects per se because interferon-induced side effects are avoided. The company referred to chosen, not systematic searched studies [5-7,13-19].

The derivation of the advantage of LDV/SOF in comparison with ribavirin + peginterferon alfa for AEs postulated by the company on the basis of the data selectively presented by the company is inadequate. For example, there were also no SAEs or deaths under ribavirin + peginterferon alfa in the largest study cited by the company, which included 107 children and adolescents (Wirth 2010 [6]). 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 [8-12], it can be assumed, however, that the risk of harm from LDV/SOF is at least not higher than the risk of harm from ribavirin + peginterferon 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 1116.

Overall, in this particular data constellation (achievement of SVR in 97.5% of the patient population, and occurrence of SAEs in 0%), a derivation of the added benefit of LDV/SOF is possible. Under consideration of the assessments in the area of CHC in adults already conducted by IQWiG [8-12], it can be assumed that there are no comparable SVR rates under ribavirin + peginterferon alfa as under LDV/SOF. Besides, it can be assumed that the risk of harm from LDV/SOF is at least not higher than the risk of harm from ribavirin + peginterferon alfa.

Based on the available data, at most hints of an added benefit can be derived. The extent of the added benefit cannot be quantified because there was no comparison with the ACT ribavirin + peginterferon alfa.

In the overall consideration of the present situation, there is a hint of a non-quantifiable added benefit of LDV/SOF in treatment-naive adolescents with CHC genotype 1 in comparison with ribavirin + peginterferon alfa.

This added benefit refers only to adolescents without cirrhosis or with compensated cirrhosis. Patients with decompensated cirrhosis were not investigated in the included study 1116.

Genotypes 3, 4, 5 and 6

The company presented no data for the assessment of the added benefit in treatment-naive patients with CHC genotype 3, 4, 5 and 6. The added benefit is not proven for these patients.

2.4.3 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of LDV/SOF in comparison with the ACT is summarized in Table 15.

Table 15: LDV/SOF – Probability and extent of the added benefit of adolescents aged 12 to < 18 years with CHC

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Pretreated adolescents aged 12 to < 18 years with chronic hepatitis C	Best supportive care (BSC)[c]	
	▪ Genotype 1[b]		Hint of a non-quantifiable added benefit
	▪ Genotype 3, 4, 5, 6		Added benefit not proven
2	Treatment-naive adolescents aged 12 to < 18 years with chronic hepatitis C	Combination of ribavirin and peginterferon alfa[d]	
	▪ Genotype 1[b]		Hint of a non-quantifiable added benefit
	▪ Genotype 3, 4, 5, 6		Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: Only adolescents with CHC genotype 1 without cirrhosis or with compensated cirrhosis, and without HIV, HAV or HBV coinfection, were included in study 1116. 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: 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; G-BA: Federal Joint Committee;
HAV: hepatitis A virus; HBV: hepatitis B virus; HIV: human immunodeficiency virus;
LDV/SOF: ledipasvir/sofosbuvir; SPC: Summary of Product Characteristics

In summary, there is a hint of a non-quantifiable added benefit of LDV/SOF in comparison with the respective ACT for pretreated and for treatment-naive adolescents with CHC genotype 1. This added benefit refers only to adolescents without cirrhosis or with compensated cirrhosis. Patients with decompensated cirrhosis were not investigated in the included study 1116.

There was no hint of an added benefit of LDV/SOF in comparison with the ACT for adolescents with CHC genotype 3, 4, 5 and 6; an added benefit is therefore not proven.

Except for the assessment regarding adolescents with CHC genotype 3, this does not concur with the assessment of the company. The company derived a hint of a major added benefit of

LDV/SOF in pretreated and treatment-naive adolescents with CHC genotype 1. For adolescents with genotype 4, 5 and 6, the company claimed a hint of a non-quantifiable added benefit.

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

Balistreri WF, Murray KF, Rosenthal P, Bansal S, Lin CH, Kersey K et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. Hepatology 2017; 66(2): 371-378.

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Gilead Sciences. A phase 2, open-label, multicenter, multi-cohort study to investigate the safety and efficacy of ledipasvir/sofosbuvir fixed dose combination +/- ribavirin in adolescents and children with chronic HCV-Infection: study GS-US-337-1116; interim clinical study report [unpublished]. 2016.

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-41-ledipasvir-sofosbuvir-hepatitis-c-benefit-assessment-according-to-35a-social-code-book-v.7964.html.