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Ledipasvir/sofosbuvir (Addendum to Commission A14-44)[1]

Addendum

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Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV	human immunodeficiency virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PEG	peginterferon
RBV	ribavirin
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
SVR	sustained virologic response

1 Background

On 8 April 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A14-44 (Ledipasvir/sofosbuvir – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

The pharmaceutical company (hereinafter referred to as "the company") submitted documents on 5 studies with ledipasvir/sofosbuvir in the commenting procedure on the early benefit assessment of ledipasvir/sofosbuvir. The G-BA commissioned IQWiG to assess the documents submitted.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The company submitted documents on 5 different studies with ledipasvir/sofosbuvir in the commenting procedure on the early benefit assessment of ledipasvir/sofosbuvir. These 5 studies can be allocated to 4 different research questions according to dossier assessment A14-44 [1]. The 5 studies and their allocation to the research questions of dossier assessment A14-44 are listed in the following Table 1.

Table 1: Studies and research questions assessed in the present addendum

Study	**Research question according to dossier assessment A14-44 on ledipasvir/sofosbuvir**
SIRIUS (GS-US-337-0121) [2]	1c (genotype 1, treatment-experienced patients)
ION-4 (GS-US-337-0115) [3]	1d (genotype 1, patients with HIV coinfection)
SOLAR-1 (GS-US-337-0123) [4]	2 (genotype 1/4, patients with decompensated cirrhosis of the liver)
SYNERGY (CO-US-337-0117) [5] 1119 (GS-US-337-1119) [6]	4 (genotype 4)
HIV: human immunodeficiency virus	

In the following Sections 2.1 to 2.4, the studies are assessed in relation to the research questions. It is indicated for each research question whether this assessment changes the conclusion of dossier assessment A14-44 [1]. The results for the 4 research questions are summarized in Section 2.5.

2.1 Research question 1c (genotype 1, treatment-experienced patients)

For research question 1c (treatment-experienced patients with genotype 1), the company submitted further documents on the SIRIUS study with its comment [2]. The company had already included this study in its historical comparison in the dossier on ledipasvir/sofosbuvir [7]. However, the documents presented at the time were insufficient for assessing the SIRIUS study [1].

No conclusion on the added benefit of ledipasvir/sofosbuvir can be derived from the SIRIUS study alone because there is no comparison with the appropriate comparator therapy (ACT) (triple therapy). However, the SIRIUS study constitutes an important expansion of the historical comparison between ledipasvir/sofosbuvir and triple therapy in treatment-experienced genotype 1 patients from dossier assessment A14-44. For treatment with ledipasvir/sofosbuvir for 24 weeks, only results from one study (ION-2), and only for 109 (total population) and 22 (subgroup of patients with cirrhosis) patients, were available there [1].

Firstly, the design and the results of the SIRIUS study are presented below. Subsequently, the historical comparison on ledipasvir/sofosbuvir expanded with the addition of the SIRIUS study is described and it is investigated whether this expansion changes the conclusions of dossier assessment A14-44.

Characteristics of the SIRIUS study

The following tables Table 2 and Table 3 describe the SIRIUS study.

Table 2: Characteristics of the SIRIUS study (research question 1c: genotype 1, treatment-experienced patients)

Study	Study design	Population	Interventions (number of randomized patients)[a]	Study duration	Location and period of study
SIRIUS	RCT, double-blind, multicentre	Treatment-experienced adults with CHC genotype 1 with cirrhosis who have not responded to previous treatment with PEG + RBV and to previous treatment with triple therapy[b]	Group 1: LDV/SOF (24W) (N = 77) (LDV/SOF (90 mg/400 mg) orally once daily + RBV placebo twice daily)	Screening: 4 weeks Treatment phase: 24 weeks Follow-up: 24 weeks	France 9/2013 – 11/2014

a: Only the arms relevant for the assessment are presented.
b: Stratified by genotype 1a or 1b and by response to pretreatment.
CHC: chronic hepatitis C; LDV/SOF: ledipasvir/sofosbuvir; N: number of randomized patients; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; W: weeks

Table 3: Characteristics of the study population of the SIRIUS study (research question 1c: genotype 1, treatment-experienced patients)

Study	N	Age [years]	Sex [F/M]	Patients with cirrhosis	Genotype [1/unknown or other]	Baseline viral load [< 800 000/ ≥ 800 000 IU/mL]	Ethnicity [white/black/ other]	Treatment discontinuations
		mean (SD)	%	n (%)	%	%	%	n (%)
SIRIUS	78[a]	57 (11)	28/72	78 (100)	100/0	15/85	96/4/0	0 (0)

a: Information for safety population; one patient from Group 2 who had been erroneously treated with LDV/SOF was allocated to Group 1.
F: female; IU: international units; LDV/SOF: ledipasvir/sofosbuvir; M: male; Number of analysed patients; n: number of patients in the category; SD: standard deviation; W: weeks

The SIRIUS study was a randomized, double-blind, placebo-controlled phase 2 study. A total of 155 treatment-experienced genotype 1 patients with pre-existing cirrhosis of the liver were enrolled in the SIRIUS study. All patients had been pretreated both with dual therapy consisting of peginterferon (PEG) and ribavirin (RBV) and with triple therapy consisting of a protease inhibitor plus PEG plus RBV. It was a multicentre study conducted France.

The patients were allocated to the 2 groups ledipasvir/sofosbuvir plus placebo (treatment duration of 24 weeks, Group 1) or ledipasvir/sofosbuvir plus RBV (treatment duration of 12 weeks, Group 2). Only Group 1 received approval-compliant treatment, which is why Group 2 is not relevant for the present assessment.

Results of the SIRIUS study

The following Table 4 shows the results of the SIRIUS study for those outcomes for which a historical comparison in treatment-experienced genotype 1 patients was possible in dossier assessment A14-44 on ledipasvir/sofosbuvir [1]. These were sustained virologic response (SVR), mortality, and results on adverse events (AEs) (serious adverse events [SAEs] and discontinuation due to AEs; supplementary presentation: AEs).

Table 4: Results (SVR 12, mortality, AEs) of the SIRIUS study (research question 1c: genotype 1, treatment-experienced patients)

Study Outcome	**LDV/SOF**	
	N	**Patients with events n (%)**
SIRIUS (LDV/SOF 24W)		
SVR 12	77	75 (97.4)
Mortality	78	0 (0)
AEs	78	68 (87.2)
SAEs	78	8 (10.3)
Discontinuation due to AEs	78	0 (0)

AE: adverse event; LDV/SOF: ledipasvir/sofosbuvir; N: number of analysed patients; n: number of patients with event; SAE: serious adverse event; SVR 12: sustained virologic response 12 weeks after the end of treatment; W: weeks

Historical comparison under inclusion of the SIRIUS study

The following Table 5 shows the results of the historical comparison of ledipasvir/sofosbuvir (treatment duration of 24 weeks) versus triple therapy under inclusion of the SIRIUS study. Patients with and without cirrhosis are not presented separately, because no corresponding data on AEs were available separately, and because no different conclusions for these patient groups were drawn in dossier assessment A14-44 [1].

The results of dossier assessment A14-44 are also presented in Table 5 to allow a comparison with these results.

Table 5: Results (SVR 12 and SVR 24), research question 1c (genotype 1, treatment-experienced patients): historical comparison of ledipasvir/sofosbuvir vs. triple therapy

Comparison	**LDV/SOF**		**PI + PEG + RBV**		**LDV/SOF vs. PI + PEG + RBV**	
	N[a]	**Patients with events[a] n (%) [min-max]**	**N**	**Patients with events n (%) [min-max]**	**RR [95% CI][b]; p-value[c]**	
					Responders	**Non-responders**
LDV/SOF 24W vs. triple therapy	**186**	**183 (98.4) [97.4-99.1]**	**711**	**399 (56.1) [50.0-66.2]**	**1.75 [1.64; 1.88]; < 0.001**	**0.04 [0.01; 0.11]; < 0.001**
LDV/SOF 24W vs. triple therapy without SIRIUS study (from A14-44)	109	108 (99.1) [NA]	711	399 (56.1) [50.0-66.2]	1.77 [1.65; 1.89]; < 0.001	0.02 [0; 0.15]; < 0.001

a: Institute's calculation.
b: Institute's calculation, asymptotic.
c: p-value: Institute's calculation, unconditional exact test (CSZ method according to [8])

CI: confidence interval; CSZ: convexity, symmetry, z score; LDV/SOF: ledipasvir/sofosbuvir; max: maximum across all study arms (%); min: minimum across all study arms (%); N: number of analysed patients across all study arms; n: number of patients with event across all study arms; NA: not applicable because only one study was available; PEG: peginterferon alfa; PI: protease inhibitor; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SVR 12: sustained virologic response 12 weeks after the end of treatment; SVR 24: sustained virologic response 24 weeks after the end of treatment; vs.: versus; W: weeks

Table 6: Results (mortality and AEs), research question 1c (genotype 1, treatment-experienced patients): historical comparison of ledipasvir/sofosbuvir vs. triple therapy

Outcome Comparison	LDV/SOF		PI + PEG + RBV		LDV/SOF vs. PI + PEG + RBV
	N	Patients with events n (%) [min-max]	N[a]	Patients with events[a] n (%) [min-max]	RR [95% CI][b]; p-value[c]
Mortality					
LDV/SOF 24W vs. triple therapy	**187**	**0 (0) [0-0]**	**717**	**4 (0.6) [0-0.8]**	NC
LDV/SOF 24W vs. triple therapy without SIRIUS study (from A14-44)	109	0 (0) [NA]	717	4 (0.6) [0-0.8]	NC
Adverse events					
LDV/SOF 24W vs. triple therapy	**187**	**156 (83.4) [80.7-87.2]**	**689**	**679 (98.5) [98.3-98.9]**	NC
LDV/SOF 24W vs. triple therapy without SIRIUS study (from A14-44)	109	88 (80.7) [NA]	689	679 (98.5) [98.3-98.9]	NC
Serious adverse events					
LDV/SOF 24W vs. triple therapy	**187**	**14 (7.5) [5.5-10.3]**	**689**	**86 (12.5) [8.3-14.1]**	**0.60 [0.35; 1.03]; 0.059**
LDV/SOF 24W vs. triple therapy without SIRIUS study (from A14-44)	109	6 (5.5) [NA]	689	86 (12.5) [8.3-14.1]	0.44 [0.20; 0.98]; 0.036
Discontinuation due to adverse events					
LDV/SOF 24W vs. triple therapy	**187**	**0 (0) [0-0]**	**689**	**45 (6.5) [5.5-9.2]**	**0.04 [0.00; 0.65]; < 0.001**
LDV/SOF 24W vs. triple therapy without SIRIUS study (from A14-44)	109	0 (0) [NA]	689	45 (6.5) [5.5-9.2]	0.07 [0; 1.12]; 0.009[d]

a: Institute's calculation.
b: Institute's calculation (asymptotic).
c: Institute's calculation: unconditional exact test (CSZ method according to [8]).
d: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
AE: adverse event; CI: confidence interval; LDV/SOF: ledipasvir/sofosbuvir; max: maximum across all study arms (%); min: minimum across all study arms (%); N: number of analysed patients across all study arms; n: number of patients with event across all study arms; NA: not applicable because only one study was available; NC: not calculated; PEG: peginterferon alfa; PI: protease inhibitor; RBV: ribavirin; RR: relative risk; SAE: serious adverse event; vs.: versus; W: weeks

Sustained virologic response (SVR 12/SVR 24)

The inclusion of the SIRIUS study resulted in no important change of the result of the historical comparison for the outcome "SVR 12/SVR 24". Hence the conclusion of dossier assessment A14-44 on this outcome is also unchanged: There is a hint of an added benefit of ledipasvir/sofosbuvir versus the ACT.

Mortality and adverse events

The inclusion of the SIRIUS study did not change the result of the historical comparison for the outcome “mortality”.

The historical comparison under inclusion of the SIRIUS study showed no statistically significant difference between ledipasvir/sofosbuvir and the ACT for the outcome “SAEs”. In contrast, the historical comparison without inclusion of the SIRIUS study showed a statistically significant result. As described in dossier assessment A14-44, the results on mortality and on AEs are interpretable only to a limited extent due to different observation periods. Hence in dossier assessment A14-44, no advantage of ledipasvir/sofosbuvir was derived for SAEs because there was no dramatic effect [1]. The conclusion of dossier assessment A14-44 on the outcome “SAEs” was therefore not changed by the inclusion of the SIRIUS study.

For the outcome “discontinuation due to AEs”, no advantage of ledipasvir/sofosbuvir was derived in dossier assessment A14-44 because the operationalization of the outcome was partly unclear in the studies on the comparator therapy (discontinuation of 1, 2 or all drugs) [1]. This was also not changed by the inclusion of the SIRIUS study. So the observed difference can be caused solely or to an important degree by the fact that the operationalization of the outcome differed between the studies with ledipasvir/sofosbuvir on the one hand and the studies on the ACT on the other hand.

In the overall assessment of the results on mortality and AEs, the inclusion of the SIRIUS study did not change the conclusion of dossier assessment A14-44 on mortality and AEs: Overall, there was no sign of greater harm from ledipasvir/sofosbuvir.

Summary

The inclusion of the SIRIUS study did not change the conclusion of dossier assessment A14-44 for research question 1c (genotype 1, treatment-experienced patients): There is a hint of a non-quantifiable added benefit of ledipasvir/sofosbuvir versus the ACT for this patient group.

2.2 Research question 1d (genotype 1, patients with HIV coinfection)

For research question 1d (genotype 1, patients with HIV coinfection), the company submitted documents on the ION-4 study with its comments [3]. However, it did not present a complete historical comparison under consideration of the results of the ION-4 study. As described in dossier assessment A14-44 on ledipasvir/sofosbuvir, the company only searched and presented the results on the ACT as examples [1,7]. However, the company argued in its comment that for ledipasvir/sofosbuvir, the results on SVR between patients with and without HIV coinfection do not differ to an important degree and that therefore a joint conclusion irrespective of the presence of HIV coinfection can be drawn [9].

The design and the results of the ION-4 study on the outcomes "SVR", "mortality" and "AEs" are presented below. For the sake of completeness, this information is also presented for the ERADICATE study, in which the patients were also treated with ledipasvir/sofosbuvir, and which the company had already included in its incomplete historical comparison in the dossier [10,11].

After this presentation it is investigated whether conclusions for patients with HIV coinfection can be derived on the basis of the data on the ION-4 and ERADICATE studies in comparison with the results of the historical comparisons on genotype 1 patients without HIV coinfection.

Characteristics of the ERADICATE and ION-4 studies

The following tables Table 7 and Table 8 describe the ERADICATE and ION-4 studies.

Table 7: Characteristics of the ERADICATE and ION-4 studies (research question 1d: genotype 1, patients with HIV coinfection)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study
ERADICATE	One-arm, open-label, multicentre	Treatment-naive[a] adults with CHC genotype 1 without cirrhosis and HIV coinfection	LDV/SOF 12W (N = 50) (LDV/SOF (90 mg/400 mg) orally once daily)	Screening: ND Treatment phase: 12 weeks Follow-up: 12 weeks	United States 6/2013 – 8/2014[b]
ION-4	One-arm, open-label, multicentre	Treatment-naive[a] and treatment-experienced[a] adults with CHC genotype 1 or 4 with or without cirrhosis, with HIV coinfection[c]	LDV/SOF 12W (N = 335) (LDV/SOF (90 mg/400 mg) orally once daily)	Screening: 28–42 days Treatment phase: 12 weeks Follow-up: 24 weeks	Canada, New Zealand, United States 2/2014 – 1/2015

a: Regarding antiviral therapy of the HCV infection.
b: Data cut-off for primary analysis, planned end of study: 4/2015.
c: Patients had antiretroviral pretreatment (with efavirenz, rilpivirine or raltegravir) and had to continue this treatment during the study.
CHC: chronic hepatitis C; HCV: hepatitis C virus; HIV: human immunodeficiency virus; LDV/SOF: ledipasvir/sofosbuvir; N: number of patients included; n: number of patients in the relevant subpopulation; W: weeks

Table 8: Characteristics of the study populations of the ERADICATE and ION-4 studies (research question 1d: genotype 1, patients with HIV coinfection)

Study	N	Age [years]	Sex [F/M]	Patients with cirrhosis	Genotype [1/unknown or other]	Baseline viral load [< 800 000/ ≥ 800 000 IU/mL]	Ethnicity [white/black/ other]	Treatment discontinuations
		mean (SD)	%	n (%)	%	%	%	n (%)
ERADICATE	50	ND	26[a]/74[a]	0 (0)	98/2	46[a]/54[a]	14[a]/84[a]/2[a]	0 (0)
ION-4	335	52 (8)	18/82	67 (20)	98/2	11/89	61/34/5	9 (2.7)

a: Institute's calculation.
F: female; HIV: human immunodeficiency virus; IU: international units; LDV/SOF: ledipasvir/sofosbuvir; M: male; N: number of patients included; n: number of patients in the category; ND: no data; SD: standard deviation

ERADICATE

The ERADICATE study was an open-label, one-arm, multicentre study. 50 treatment-naive CHC genotype 1 patients (2 patients with unknown genotype) with HIV coinfection were enrolled. Only patients without cirrhosis were enrolled. The patients were treated with ledipasvir/sofosbuvir for 12 weeks.

ION-4

The ION-4 study was an open-label, one-arm, multicentre study. 335 CHC patients with genotype 1 or 4 with HIV coinfection were enrolled. Since only 8 patients (2.4%) with genotype 4 were enrolled, the ION-4 study is only suitable for conclusions in patients with genotype 1. Both treatment-naive (approximately 45%) and treatment-experienced (approximately 55%) patients as well as patients with (20%) and without (80%) cirrhosis were enrolled.

The patients were treated with ledipasvir/sofosbuvir for 12 weeks. According to the Summary of Product Characteristics (SPC), patients with cirrhosis should generally be treated with ledipasvir/sofosbuvir for 24 weeks. Shortened treatment of 12 weeks may be considered only if there is low risk for disease progression [12]. Low risk of disease progression was not an inclusion criterion of the ION-4 study, however. The results for patients with cirrhosis can therefore only be evaluated to a limited extent.

Results of the ERADICATE and ION-4 studies

The following Table 9 shows the results of the ERADICATE and ION-4 studies on the outcomes “SVR 12”, “mortality” and “AEs”. The results on SVR 12 in the subgroups of patients with and without cirrhosis and for treatment-naive and treatment-experienced patients are also presented for the ION-4 studies. The corresponding results were not available for the other outcomes.

Table 9: Results (SVR 12, mortality, AEs) of the ERADICATE and ION-4 studies (research question 1d: genotype 1, patients with HIV coinfection)

Study	**LDV/SOF**	
Outcome Subgroup	**N**	**Patients with events n (%)**
ERADICATE (LDV/SOF 12W)		
SVR 12	50	49 (98.0)
Mortality	50	0 (0)
Adverse events	50	50 (100)
Serious adverse events	50	1 (2)
Discontinuation due to AEs	50	0 (0)
ION-4 (LDV/SOF 12W)		
SVR 12	335	321 (95.8)
Treatment-naive	150	142 (94.7)
without cirrhosis	130	125 (96.2)
with cirrhosis	20	17 (85.0)
Treatment-experienced	185	179 (96.8)
without cirrhosis	138	133 (96.4)
with cirrhosis	47	46 (97.9)
Mortality	335	1 (0.3)
Adverse events	335	257 (76.7)
Serious adverse events	335	8 (2.4)
Discontinuation due to adverse events	335	0 (0)

AE: adverse event; HIV: human immunodeficiency virus; LDV/SOF: ledipasvir/sofosbuvir; N: number of analysed patients; n: number of patients with event; SVR 12: sustained virologic response 12 weeks after the end of treatment; W: weeks

In both of the ERADICATE and ION-4 studies, approximately 95% of treatment-naive and treatment-experienced patients achieved SVR under ledipasvir/sofosbuvir. SAEs occurred in approximately 2% of the patients, discontinuations due to AEs did not occur in either study.

For patients with cirrhosis, the results can be evaluated only to a limited extent for the reasons stated above (treatment duration only 12 weeks without proof for low risk of disease progression). In treatment-naive patients with cirrhosis, the SVR 12 rate was lower (85%) than in the other subgroups, but only 20 treatment-naive patients with cirrhosis were enrolled.

Comparison with the results of the historical comparisons on genotype 1 patients without HIV coinfection

Results on SVR

For most subgroups of genotype 1 patients, the SVR 12 rates observed in patients with HIV coinfection in the ERADICATE and ION-4 studies were within the ranges observed in genotype 1 patients without HIV coinfection under ledipasvir/sofosbuvir [1]. The group of treatment-naive patients with cirrhosis, for which overall only few data were available, is an exception. Moreover, there were no data for the treatment duration of 24 weeks for patients with cirrhosis.

The company did not present the complete evidence on the ACT for genotype 1 patients with HIV coinfection [7]. However, both the studies described by the company in its dossier and the studies additionally cited in dossier assessment A14-44 consistently showed notably lower SVR rates in these patients than the studies considered for genotype 1 patients without HIV coinfection in the historical comparison [1,7]. This applies equally to treatment-naive and treatment-experienced patients and to patients with and without cirrhosis. Hence for the present assessment it can be assumed for patients with HIV coinfection that SVR under the ACT is achieved at most as frequently as in patients without HIV coinfection. Studies in patients with HIV coinfection that were not included in the company's historical comparison are not expected to raise principal doubts about this.

For the outcome "SVR", the results of the historical comparison for genotype 1 patients without HIV coinfection can overall be used for genotype 1 patients with HIV coinfection as a result. This applies to treatment-naive and treatment-experienced patients without cirrhosis.

Results on mortality and adverse events

The results on mortality and AEs of the ERADICATE and ION-4 studies were also within the range of the results observed under ledipasvir/sofosbuvir in patients without HIV coinfection [1]. This only applies to treatment with ledipasvir/sofosbuvir for 12 weeks because no data for treatment of 24 weeks in patients with HIV coinfection was available. These are necessary for the assessment of AEs in patients with cirrhosis, however, because shorter treatment of 12 weeks is only an exceptional option in these patients (see above).

The data on the ACT (submitted incompletely by the company) did not show that considerably fewer AEs occurred in patients with HIV coinfection than in patients with HIV coinfection [1,7]. The data are too uncertain, however, to assume a similar event rate for these 2 patient groups. This is of only minor relevance for the comparison of treatment with ledipasvir/sofosbuvir for 12 weeks because, on the one hand, only few SAEs and practically no discontinuations due to AEs were observed in the studies on the 12-week treatment with ledipasvir/sofosbuvir. On the other, the conclusion "no sign of greater harm of ledipasvir/sofosbuvir" was derived from the historical comparisons in genotype 1 patients without HIV coinfection in dossier assessment A14-44 due to the uncertainty of the data [1].

This conclusion can also be derived for patients with HIV coinfection (only for patients without cirrhosis) from the available data.

Summary

In summary, the conclusions on the added benefit of ledipasvir/sofosbuvir for patients without HIV coinfection can be used for genotype 1 patients with HIV coinfection without cirrhosis. As a result, there is a hint of a non-quantifiable added benefit of ledipasvir/sofosbuvir both for treatment-naive and for treatment-experienced genotype 1 patients with HIV coinfection without cirrhosis.

There are still no sufficient data for genotype 1 patients with HIV coinfection with cirrhosis. The conclusion of dossier assessment A14-44 for this patient group has therefore not changed: The added benefit of ledipasvir/sofosbuvir for this patient group is not proven.

2.3 Research question 2 (genotype 1/4, patients with decompensated cirrhosis of the liver)

For research question 2 (genotype 1/4, patients with decompensated cirrhosis of the liver), the company submitted further documents on the SOLAR-1 study with its comment [4]. The company had already presented this study in the dossier on ledipasvir/sofosbuvir. However, the documents presented at the time were insufficient for assessing the SOLAR-1 study.

No conclusion on the added benefit of ledipasvir/sofosbuvir can be derived from the SOLAR-1 study alone because there is no comparison with the ACT (no antiviral therapy) chosen by the company. As explained in dossier assessment A14-44, such a comparison is necessary also under the assumption that no SVR occurs under the ACT chosen by the company (corresponding to a rate of 0% for the outcome "SVR") [1]. SAEs under ledipasvir/sofosbuvir occurred in approximately 40% of the patients in the SOLAR-1 study (see Table 12). This means that the positive result (SVR rate) is offset by an important negative result (SAE rate). A balancing of these positive and negative results in comparison with the ACT can only be conducted in an adequate way if also the negative result (SAE rate) can be estimated for the comparator therapy. However, the company did not provide such an estimation in the dossier or in its comment and therefore presented no adequate balancing on the added benefit of ledipasvir/sofosbuvir [7,9]. The new documents on the SOLAR-1 did therefore not change the conclusions of dossier assessment A14-44.

Design, population and results of the SOLAR-1 study are presented as supplementary information in the following tables.

Table 10: Characteristics of the SOLAR-1 study (research question 2 genotype 1/4, patients with decompensated cirrhosis of the liver)

Study	Study design	Population	Interventions (number of randomized patients)[a]	Study duration	Location and period of study
SOLAR-1	RCT[b], open-label, parallel, multicentre	Treatment-naive and treatment-experienced adults with CHC genotype 1 and 4[c] with advanced liver disease before and after transplantation	Cohort A (before liver transplantation) Group 1 (CPT class B): LDV/SOF + RBV 24W (N = 29) Group 2 (CPT class C): LDV/SOF + RBV 24W (N = 26) Cohort B (after liver transplantation) Group 5 (CPT class B): LDV/SOF + RBV 24W (N = 26) Group 6 (CPT class C): LDV/SOF + RBV 24W (N = 4) (intervention in each case LDV/SOF (90 mg/400 mg) orally once daily + RBV orally depending on weight 1000–1200 mg/day)[d]	Screening: 28 days Treatment phase: 12 or 24 weeks Follow-up: 24 weeks	United States 5/2013 – 1/2015[e]

a: Only the arms relevant for research question 2 are presented (patients with decompensated cirrhosis and treatment duration of 24 weeks).
b: After inclusion in the study, the patients were divided into 2 cohorts (before and after transplantation). The cohorts were divided into further 7 groups depending on the severity of the disease, which were randomized to treatment of 12 or 24 weeks.
c: Only 1 patient with genotype 4 was included in the relevant arm (in Group 5). The SOLAR-1 study is therefore unsuitable for conclusions in genotype 4 patients.
d: The initial dosage of RBV in Cohort A was 600 mg/day. This dosage could be increased to 1000–1200 mg/day in case of good tolerability and haemoglobin > 10 g/dL.
e: Data cut-off for interim analysis after 12 weeks of follow-up, or liver transplantation; study is ongoing.

CHC: chronic hepatitis C; CPT: Child-Pugh-Turcotte score; LDV/SOF: ledipasvir/sofosbuvir; N: number of randomized patients; RBV: ribavirin; RCT: randomized controlled trial; W: weeks

Table 11: Characteristics of the study population of the SOLAR-1 study (research question 2 genotype 1/4, patients with decompensated cirrhosis of the liver)

Study Study arm	**N**	**Age [years]** **mean (SD)**	**Sex [F/M]** **%**	**Genotype [1/ unknown or other]** **%**	**Baseline viral load [< 800 000/ ≥ 800 000 IU/mL]** **%**	**Ethnicity [white/ black/ other]** **%**	**Treatment discontin-uations** **n (%)**
SOLAR-1							
Group 1 (CPT class B) 24W	29	58 (7)	38/62	100/0	ND	90/10/0	4 (13.8)
Group 2 (CPT class C) 24W	26	59 (5)	31/69	100/0	ND	92/4/4	4 (15.4)
Group 5 (CPT class B) 24 W	26	61 (7)	12/88	96/4	ND	92/8/0	4 (15.4)
Group 6 (CPT class C) 24W	4	61 (2)	0/100	100/0	ND	100/0/0	1 (25.0)

CPT: Child-Pugh-Turcotte Score; F: female; IU: international units; M: male; N: number of randomized patients; n: number of patients in the category; ND: no data; SD: standard deviation; W: weeks

Table 12: Results (SVR 12, mortality, AEs) of the SOLAR-1 study (research question 2: genotype 1/4, patients with decompensated cirrhosis of the liver)

Study	**LDV/SOF + RBV**	
Outcome / **Group**	**N**	**Patients with events n (%)**
SOLAR-1		
SVR 12		
Group 1 (CPT class B) 24W	27[a]	24 (88.9)
Group 2 (CPT class C) 24W	23[a]	20 (87.0)
Group 5 (CPT class B) 24W	26	23 (88.5)
Group 6 (CPT class C) 24W	4	3 (75.0)
Mortality		
Group 1 (CPT class B) 24W	29	2 (6.9)
Group 2 (CPT class C) 24W	26	1 (3.8)
Group 5 (CPT class B) 24W	26	2 (7.7)
Group 6 (CPT class C) 24W	4	0 (0)
Adverse events		
Group 1 (CPT class B) 24W	29	28 (96.6)
Group 2 (CPT class C) 24W	26	26 (100)
Group 5 (CPT class B) 24W	26	26 (100)
Group 6 (CPT class C) 24W	4	4 (100)
Serious adverse events		
Group 1 (CPT class B) 24W	29	10 (34.5)
Group 2 (CPT class C) 24W	26	11 (42.3)
Group 5 (CPT class B) 24W	26	11 (42.3)
Group 6 (CPT class C) 24W	4	3 (75.0)
Discontinuation due to adverse events[a]		
Group 1 (CPT class B) 24W	29	2 (6.9)
Group 2 (CPT class C) 24W	26	2 (7.7)
Group 5 (CPT class B) 24W	26	3 (11.5)
Group 6 (CPT class C) 24W	4	0 (0)

a: 2 patients in Group 1 and 3 patients in Group 3 were not included in the assessment because they had liver transplantation during their LDV/SOF treatment.
b: Discontinuation of treatment with LDV/SOF.

AE: adverse event; CPT: Child-Pugh-Turcotte score; LDV/SOF: ledipasvir/sofosbuvir; N: number of analysed patients; n: number of patients with event; RBV: ribavirin; SVR 12: sustained virologic response 12 weeks after the end of treatment; W: weeks

2.4 Research question 4 (genotype 4)

For research question 4 (genotype 4), the company submitted documents on the studies SYNERGY and 1119 with its comment [5,6]. The company had presented no results on research question 4 in the dossier on ledipasvir/sofosbuvir; both studies, SYNERGY and 1119, had been designated as "ongoing" in the dossier [7].

No conclusion on the added benefit of ledipasvir/sofosbuvir in genotype 4 can be derived from the studies SYNERGY and 1119 alone because there is no comparison with the ACT. Without such a comparison with the ACT, no adequate balancing of benefit and harm for ledipasvir/sofosbuvir can be conducted. The company did not present such a comparison (e.g. as historical comparison) with its comment either.

The documents on the studies SYNERGY and 1119 did therefore not change the conclusions of dossier assessment A14-44. Design, population and results of both studies are presented as supplementary information in the following tables.

Table 13: Characteristics of the studies SYNERGY and 1119 (research question 4: genotype 4)

Study	Study design	Population	Interventions (number of patients included)[a]	Study duration	Location and period of study
SYNERGY	Not randomized, open-label, single-centre	Treatment-naive and treatment-experienced adults with CHC genotype 4	Group E: LDV/SOF 12W (N = 21) (LDV/SOF (90 mg/400 mg) orally once daily)	Screening: ND Treatment phase: 12 weeks Follow-up: ND	United States 9/2013 – 2/2015
1119	Not randomized, open-label, multicentre	Treatment-naive and treatment-experienced adults with CHC genotype 4 and 5[b]	Group 1 (GT 4 TN): LDV/SOF 12W (N = 22) Group 2 (GT 4 TE): LDV/SOF 12W (N = 22) (in each group LDV/SOF (90 mg/400 mg) orally once daily)	Screening: 28–42 days Treatment phase: 12 weeks Follow-up: up to 24 weeks	France 3/2014 – 11/2014[c]

a: Only the arms relevant for research question 4 are presented (patients with CHC genotype 4).
b: Up to 50% of the patients in each group were allowed to have cirrhosis.
c: Data cut-off for interim analysis after 12 weeks of follow-up; study is ongoing.
CHC: chronic hepatitis C; GT: genotype; LDV/SOF: ledipasvir/sofosbuvir; N: number of patients included; TE: treatment-experienced; TN: treatment-naive; W: weeks

Table 14: Characteristics of the study populations of the studies SYNERGY and 1119 (research question 4: genotype 4)

Study	N	Age [years]	Sex [F/M]	Patients with cirrhosis	Genotype [4/unknown or other]	Baseline viral load [< 800 000/ ≥ 800 000 IU/mL]	Ethnicity [white/black/ other]	Treatment discontinuations
		mean (SD)	%	n (%)	%	%	%	n (%)
SYNERGY (LDV/SOF 12W, Group E)	21	55 (10)	33/67	7 (33)	100/0	38/62	52/43/5	1 (4.8)
1119 (LDV/SOF 12W, Group 1 + 2)	44	51 (8.9)	36/64	10 (23)	100/0	30/70	82/18	0 (0)

CHC: chronic hepatitis C; F: female; IU: international units; LDV/SOF: ledipasvir/sofosbuvir; M: male; N: number of patients included; n: number of patients in the category; SD: standard deviation; W: weeks

Table 15: Results (SVR 12, mortality, AEs) of the studies SYNERGY and 1119 (research question 4: genotype 4)

Study **Outcome**	**LDV/SOF**	
	N	**Patients with events n (%)**
SYNERGY (LDV/SOF 12W, Group E)		
SVR 12	21	20 (95)
Patients with cirrhosis	7	ND
Patients without cirrhosis	14	ND
Mortality	21	0 (0)
Adverse events	21	19 (90)
Serious adverse events	21	1 (5)
Discontinuation due to adverse events	21	0 (0)
1119 (LDV/SOF 12W, Group 1 + 2)		
SVR 12	44	41 (93.2)
Patients with cirrhosis	10	10 (100)
Patients without cirrhosis	34	31 (91.2)[a]
Mortality	44	0 (0)
Adverse events	44	31 (70.5)
Serious adverse events	44	0 (0)
Discontinuation due to adverse events	44	0 (0)

a: Institute's calculation.

AE: adverse event; LDV/SOF: ledipasvir/sofosbuvir; N: number of analysed patients; n: number of patients with event; SAE: serious adverse event; SVR 12: sustained virologic response 12 weeks after the end of treatment; W: weeks

2.5 Summary

The documents subsequently submitted by the company in the comments changed the conclusions of dossier assessment A14-44 on ledipasvir/sofosbuvir for research question 1d (genotype 1, patients with HIV coinfection). No changes resulted from the documents subsequently submitted regarding the 3 research questions 1c (genotype 1, treatment-experienced patients), 2 (genotype 1/4, patients with decompensated cirrhosis of the liver) and 4 (genotype 4).

An overview of the results on these 4 research questions is presented in the following Table 16.

Table 16: Ledipasvir/sofosbuvir - extent and probability of the added benefit for the research questions assessed in the present addendum

Research question	**Patient group**	**ACT**[a]	**Extent and probability of added benefit**[c]
1c	Genotype 1, treatment-experienced patients	PEG + RBV or[b] **BOC + PEG + RBV** or **TVR + PEG + RBV**	Hint of non-quantifiable added benefit
1d	Genotype 1, patients with HIV coinfection	PEG + RBV	*Patients without cirrhosis: hint of non-quantifiable added benefit* Patients with cirrhosis: Added benefit not proven
2	Genotype 1/4, patients with decompensated cirrhosis	No separate ACT specified; company's choice: no antiviral therapy	Added benefit not proven
4	Genotype 4	PEG + RBV	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The information provided in the SPCs of the combination partners of the ACTs are to be taken into account, particularly with regard to the approved therapeutic indications, dosages, treatment duration and prognostic factors. The necessity of using triple therapy has to be considered when favourable prognostic factors are present.
c: Italic type: change in comparison with dossier assessment A14-44 [1].
ACT: appropriate comparator therapy; BOC: boceprevir; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus; PEG: peginterferon alfa; RBV: ribavirin; SPC: Summary of Product Characteristics; TVR: telaprevir

3 References

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