IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ledipasvir/sofosbuvir – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.10 of the dossier assessment *Ledipasvir/Sofosbuvir – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 26 February 2015). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BOC	boceprevir
CHC	chronic hepatitis C
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	fixed-dose combination of ledipasvir/sofosbuvir
PEG	peginterferon
PEG2a	peginterferon alfa-2a
PEG2b	peginterferon alfa-2b
PI	protease inhibitor
PR	peginterferon and ribavirin
RBV	ribavirin
RGT	response-guided therapy
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
SVR	sustained virologic response
TVR	telaprevir

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. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 24 November 2014.

Research question

The aim of this report was to assess the added benefit of the fixed-dose combination of ledipasvir/sofosbuvir compared with the appropriate comparator therapy (ACT) in adult patients with chronic hepatitis C (CHC).

The G-BA specified different ACTs for different subindications. These result in different research questions, which are presented in Table 2.

Table 2: Research questions of the benefit assessment of ledipasvir/sofosbuvir and corresponding ACTs by the G-BA

Research question	**Subindication CHC**	**ACT specified by the G-BA**
1	Genotype 1	
1a	Treatment-naive patients without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)[a]
1b	Treatment-naive patients with cirrhosis	Dual therapy (combination of peginterferon and ribavirin)[b]
1c	Treatment-experienced patients	Dual therapy (combination of peginterferon and ribavirin) or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)[a]
1d	Patients with HIV coinfection	Dual therapy (combination of peginterferon and ribavirin)[c]
2	Genotype 1/4	
	Patients with decompensated cirrhosis	No separate ACT specified; company's choice: no antiviral therapy
3	Genotype 3	
3a	Treatment-naive patients with cirrhosis	Dual therapy (combination of peginterferon and ribavirin)
3b	Treatment-experienced patients	Dual therapy (combination of peginterferon and ribavirin)
4	Genotype 4	
4a	Treatment-naive patients	Dual therapy (combination of peginterferon and ribavirin)
4b	Treatment-experienced patients	Dual therapy (combination of peginterferon and ribavirin)

a: 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.
b: Data currently available prove no superiority of triple therapy for treatment-naive patients with cirrhosis. Dual therapy is therefore to be regarded as ACT in these situations.
c: Only very few data for triple therapy are currently available for patients with HIV coinfection. Dual therapy is therefore to be regarded as ACT in these situations.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus; SPC: Summary of Product Characteristics

The company presented data only for part of the research questions. An overview of the data presented by the company is shown in Table 3.

Table 3: Data presented on the research questions

Research question	Subindication CHC	Data presented by the company
1	Genotype 1	
1a	Treatment-naive patients without cirrhosis	Historical comparison
1b	Treatment-naive patients with cirrhosis	Historical comparison
1c	Treatment-experienced patients	Historical comparison
1d	Patients with HIV coinfection treatment-naive treatment-experienced	 Historical comparison with presentation of an example of the evidence on the ACT no data
2	Genotype 1/4	
	Patients with decompensated cirrhosis	Study on LDV/SOF without comparison with the comparator therapy chosen by the company
3	Genotype 3	
3a	Treatment-naive patients with cirrhosis	Study on LDV/SOF not used in compliance with the approval without comparison with the ACT
3b	Treatment-experienced patients	No data
4	Genotype 4	No data
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; HIV: human immunodeficiency virus; LDV/SOF: ledipasvir/sofosbuvir		

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier.

Historical comparisons (unadjusted indirect comparisons) of ledipasvir/sofosbuvir versus the respective ACT were available in the present benefit assessment. The certainty of results of a historical comparison is generally considered to be inadequate and therefore allows no derivation of an added benefit. Dramatic effects are an exception.

The following operationalization serves as an orientation for the classification as a dramatic effect: An observed effect can be regarded as dramatic when it is not explicable solely by the impact of confounding factors, i.e. if it is statistically significant at a level of 1% and, expressed as the estimated relative risk, exceeds the value of 10 (or is 1/10 or lower). A 10-fold increase or decrease in risk usually reflects a (more or less) deterministic course. Moreover, the risk of the examined event should be at least 5% in at least one of the groups compared.

Hence at most hints of an added benefit or greater harm of ledipasvir/sofosbuvir were derived from the results of the available comparisons if dramatic effects were present.

Results

Research question 1a: CHC genotype 1, treatment-naive patients without cirrhosis

For treatment-naive genotype 1 patients without cirrhosis, there was a historical comparison of ledipasvir/sofosbuvir versus the triple therapy with protease inhibitor (PI) (telaprevir [TVR] or boceprevir [BOC]) + peginterferon (PEG) + ribavirin (RBV).

Study pool

On the ledipasvir/sofosbuvir (LDV/SOF) side, the studies ION-1 (study arm LDV/SOF 12 weeks), ION-3 (study arms LDV/SOF 8 weeks and LDV/SOF 12 weeks) and LONESTAR (Group 1 LDV/SOF 8 weeks and Group 2 LDV/SOF 12 weeks of Cohort 1) were included. On the ACT side, the studies ADVANCE (study arm T12PR), ILLUMINATE (study arms T12PR24 [randomly assigned] and T12PR48 [non-randomly assigned]), Marcellin 2011 (all 4 study arms), OPTIMIZE (study arms TVR twice daily and TVR every 8 hours), Manns 2014 (study arm BOC + peginterferon and ribavirin [PR]) and SPRINT-2 (Group 2 BOC + PEG + RBV response-guided therapy [RGT]) were included in the comparison.

Results

Morbidity – sustained virologic response (SVR) as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

The proportion of patients with SVR after 12 weeks of treatment with ledipasvir/sofosbuvir was considerably larger than after 24 to 48-week treatment (RGT regimen) with triple therapy with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin. The proportion of patients with SVR was nearly 100% under treatment with ledipasvir/sofosbuvir. Overall, the effect can be regarded as dramatic and could be observed in comparison with both treatment regimens (triple therapy with TVR or BOC). The tendency to a dramatic effect already occurred in a treatment duration of 8 weeks with ledipasvir/sofosbuvir, but was not as pronounced in this comparison as it was in the comparison of 12 weeks of ledipasvir/ sofosbuvir versus the ACT.

Overall, there was a hint of an added benefit of ledipasvir/sofosbuvir versus the ACT with triple therapy with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin for the outcome "SVR".

Mortality and adverse events

Overall, no conclusive interpretation of the data on mortality and adverse events (AEs) of ledipasvir/sofosbuvir in comparison with the ACT was possible due to the large differences in observation periods. However, the data did not suggest greater harm from ledipasvir/ sofosbuvir.

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life in comparison with the ACT.

Research question 1b: CHC genotype 1, treatment-naive patients with cirrhosis

For treatment-naive genotype 1 patients with cirrhosis, there was a historical comparison of ledipasvir/sofosbuvir versus dual therapy with PEG + RBV.

Study pool

On the ledipasvir/sofosbuvir side, the ION-1 study (study arms LDV/SOF 12 weeks and LDV/SOF 24 weeks) was included. On the ACT side, the studies ADVANCE (study arm PR), Bronowicki 2014 (study arm PBO + pegINFα/RBV), COMMAND-1 (study arm placebo + P/R), JUMP-C (study arm placebo + Peg-INFα-2a/RBV), PROPEL (study arm placebo + Peg-INFα-2a/RBV), QUEST-1 (study arm placebo group), QUEST-2 (study arm placebo group), SPRINT-1 (Part 1, study arm PR48) and SPRINT-2 (study arm Group 1) were included.

Results

Morbidity – SVR as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

The proportion of patients with SVR after 24 weeks of treatment with ledipasvir/sofosbuvir was considerably larger than after 48-week treatment with dual therapy consisting of peginterferon and ribavirin. The proportion of patients with SVR was nearly 100% under treatment with ledipasvir/sofosbuvir. Overall, the effect can be regarded as dramatic. There was a dramatic effect in comparison with the ACT also in a treatment duration of 12 weeks with ledipasvir/sofosbuvir, but the proportion of patients with SVR (94.1%) was not as high in this treatment duration as in a treatment duration of 24 weeks with ledipasvir/sofosbuvir.

Overall, there was a hint of an added benefit of ledipasvir/sofosbuvir versus the ACT with dual therapy consisting of peginterferon and ribavirin for the outcome "SVR".

Mortality and adverse events

No conclusive interpretation of the data on mortality and AEs was possible for research question 1b. There were only data on the total population of the study arms, which could not be used for the assessment of mortality and AEs, however. The overall proportion of the relevant subpopulation (patients with cirrhosis) was below 30%. Moreover, the observation period of 12 to 24 weeks differed considerably from the observation period of 48 weeks for the comparator therapy. Discontinuations due to AEs in the total population occurred less frequently under ledipasvir/sofosbuvir than under the ACT. However, the proportion of events in SAEs was larger under ledipasvir/sofosbuvir than under the ACT, although the different observation periods caused a bias in favour of ledipasvir/sofosbuvir (the observation period of the comparator therapy was considerably longer). Based on the available information, greater harm from ledipasvir/sofosbuvir could not be excluded.

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life in comparison with the ACT.

Research question 1c: CHC genotype 1, treatment-experienced patients

For treatment-experienced genotype 1 patients, there was a historical comparison of ledipasvir/sofosbuvir versus the triple therapy with protease inhibitor (telaprevir or boceprevir) + PEG + RBV.

Study pool

On the ledipasvir/sofosbuvir side, the studies ELECTRON (Part 6, Group 16), LONESTAR (Group 4 LDV/SOF 12 weeks of Cohort 2), ION-2 (study arms LDV/SOF 12W and LDV/SOF 24W) und GS-US-337-0113 (study arm LDV/SOF 12 weeks) were included in the benefit assessment. On the ACT side, the studies ATTAIN (study arm TVR/PR), REALIZE (study arm T12PR48), RESPOND-2 (groups 2 and 3) and Flamm 2013 (study arm BOC/PEG2a/R) were included.

Results

Morbidity – SVR as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

The proportion of patients with SVR after 24 weeks of treatment with ledipasvir/sofosbuvir was considerably larger than after 24 to 48-week treatment (RGT regimen) with triple therapy with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin. The proportion of patients with SVR was nearly 100% under treatment with ledipasvir/sofosbuvir. Overall, the effect can be regarded as dramatic and could be observed in comparison with both treatment regimens (triple therapy with TVR or BOC). There was a dramatic effect in comparison with the ACT also in a treatment duration of 12 weeks with ledipasvir/sofosbuvir, but the proportion of patients with SVR (95.1%) was not as high in this treatment duration as in a treatment duration of 24 weeks with ledipasvir/sofosbuvir.

A comparable effect in SVR could also be observed in the subgroups of patients with or without cirrhosis after 24 weeks of treatment with ledipasvir/sofosbuvir. After 12 weeks of treatment, as in the total population, a dramatic effect was also notable in patients without cirrhosis; the proportion of patients with SVR was not as high, however. In the subgroup of patients with cirrhosis, in contrast, there was no dramatic effect after 12 weeks of treatment.

Overall, there was a hint of an added benefit of ledipasvir/sofosbuvir versus the ACT with triple therapy with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin for the outcome "SVR".

Mortality and adverse events

The certainty of results of the outcomes on mortality and AEs was low. Overall, uncertainties resulted from the differences in treatment durations and hence observation periods. The number of serious AEs (SAEs) under treatment with ledipasvir/sofosbuvir increased with the treatment duration. In a treatment duration with ledipasvir/sofosbuvir of 24 weeks, in SAEs, the difference between the treatments was statistically significant at a level of 5% in favour of ledipasvir/sofosbuvir, but could not be classified as a dramatic effect. For the outcome "discontinuation due to AEs", there was the additional uncertainty that the operationalization of the outcome was partly unclear in the studies on the ACT (discontinuation of 1, 2 or all drugs). In the overall consideration of the results on mortality and AEs, there was no sign of greater harm from ledipasvir/sofosbuvir, however.

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life in comparison with the ACT.

Research question 1d: CHC genotype 1, patients with HIV coinfection

The historical comparison of ledipasvir/sofosbuvir versus the ACT presented by the company for research question 1d (CHC genotype 1, patients with human immunodeficiency virus [HIV] coinfection) was incomplete regarding content and therefore unsuitable for the benefit assessment.

The company itself presented the data on the ACT as an example.

Research question 2: CHC genotype 1/4, patients with decompensated cirrhosis

No comparative data were available for assessing the added benefit of ledipasvir/sofosbuvir for CHC genotype 1 or 4 patients with decompensated cirrhosis. The company only presented non-comparative data from the SOLAR-1 study for research question 2. This information presented by the company was unsuitable for assessing the added benefit of ledipasvir/ sofosbuvir for research question 2.

Research question 3: CHC genotype 3

No comparative data were available for assessing the added benefit of ledipasvir/sofosbuvir for CHC genotype 3 patients. The company only presented non-comparative data from the ELECTRON-2 study for treatment-naive CHC genotype 3 patients with cirrhosis. There was no comparison with the evidence on the ACT and, furthermore, the treatment with ledipasvir/sofosbuvir in the ELECTRON-2 study was not in compliance with the approval.

Research question 4: CHC genotype 4

The company did not investigate research question 4 in its dossier. Hence no comparative data were available for assessing the added benefit of ledipasvir/sofosbuvir for CHC genotype 4 patients.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug ledipasvir/sofosbuvir compared with the ACT is assessed as follows:

Research question 1a: CHC genotype 1, treatment-naive patients without cirrhosis

On the positive side, there is an added benefit with the extent "non-quantifiable" in the category "serious late complications". Overall, no conclusive interpretation of the outcomes on mortality and AEs was possible due to the differences in observation periods. However, the observed events on mortality and AEs provided no sign that treatment with ledipasvir/sofosbuvir leads to greater harm than the comparator therapy.

In summary, there is a hint of a non-quantifiable added benefit of ledipasvir/sofosbuvir versus the ACT with triple therapy with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin for treatment-naive CHC genotype 1 patients without cirrhosis.

Research question 1b: CHC genotype 1, treatment-naive patients with cirrhosis

On the positive side, there is an added benefit with the extent "non-quantifiable" in the category "serious late complications". Overall, no conclusive interpretation of the outcomes on mortality and AEs was possible due to the low proportion of the relevant subpopulation of the total population of the study arms (3.6% to 27.1%) and the differences in observation periods. Greater harm from ledipasvir/sofosbuvir cannot be excluded. This potentially raises doubts about the positive effect of ledipasvir/sofosbuvir in SVR.

In summary, there is no proof of added benefit versus the ACT of dual therapy with peginterferon and ribavirin for treatment-naive CHC genotype 1 patients with cirrhosis.

Research question 1c: CHC genotype 1, treatment-experienced patients

On the positive side, there is an added benefit with the extent "non-quantifiable" in the category "serious late complications". Overall, no conclusive interpretation of the outcomes on mortality and AEs was possible due to the differences in observation periods and to the partially unclear operationalization of the outcome "discontinuation due to AEs". However, the observed events on mortality and AEs provided no sign that treatment with ledipasvir/sofosbuvir leads to greater harm than the comparator therapy.

[4] 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), see [1]. 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, no added benefit, or less benefit), see [2].

In summary, there is a hint of a non-quantifiable added benefit of ledipasvir/sofosbuvir versus the ACT with triple therapy with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin for treatment-experienced CHC genotype 1 patients.

Research question 1d: CHC genotype 1, patients with HIV coinfection

No proof of added benefit of ledipasvir/sofosbuvir versus the ACT specified by the G-BA could be derived for treatment-naive or treatment-experienced CHC genotype 1 patients with HIV coinfection from the available data.

Research question 2: CHC genotype 1/4, patients with decompensated cirrhosis

No proof of added benefit of ledipasvir/sofosbuvir versus the comparator therapy chosen by the company could be derived for CHC genotype 1 or 4 patients with decompensated cirrhosis from the available data.

Research question 3: CHC genotype 3

No proof of added benefit of ledipasvir/sofosbuvir versus the ACT specified by the G-BA could be derived for CHC genotype 3 patients from the available data.

Research question 4: CHC genotype 4

Since no data were available, no proof of added benefit of ledipasvir/sofosbuvir versus the ACT specified by the G-BA could be derived for CHC genotype 4 patients.

Table 4 presents a summary of the extent and probability of the added benefit of ledipasvir/ sofosbuvir in comparison with the ACT.

Table 4: Ledipasvir/sofosbuvir – extent and probability of added benefit

Research question	Patient group with CHC	ACT[a]	Extent and probability of added benefit
1a	Genotype 1, treatment-naive patients without cirrhosis	PEG + RBV or[b] **BOC + PEG + RBV** or **TVR + PEG + RBV**	Hint of non-quantifiable added benefit
1b	Genotype 1, treatment-naive patients with cirrhosis	PEG + RBV	Added benefit not proven
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	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
3	Genotype 3	PEG + RBV	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.

ACT: appropriate comparator therapy; BOC: boceprevir; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus; PEG: peginterferon alfa; RBV: ribavirin; SPC: Summary of Product Characteristics; TVR: telaprevir

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

2.2 Research questions of the dossier assessment

The aim of this report was to assess the added benefit of the fixed-dose combination of ledipasvir/sofosbuvir compared with the ACT in adult patients with CHC.

The G-BA specified different ACTs for different subindications. Table 5 shows the research questions of the benefit assessment and the corresponding ACTs specified by the G-BA.

Table 5: Research questions of the benefit assessment of ledipasvir/sofosbuvir and corresponding ACTs by the G-BA

Research question	Subindication CHC	ACT specified by the G-BA
1	Genotype 1	
1a	Treatment-naive patients without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)[a]
1b	Treatment-naive patients with cirrhosis	Dual therapy (combination of peginterferon and ribavirin)[b]
1c	Treatment-experienced patients	Dual therapy (combination of peginterferon and ribavirin) or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)[a]
1d	Patients with HIV coinfection	Dual therapy (combination of peginterferon and ribavirin)[c]
2	Genotype 1/4	
	Patients with decompensated cirrhosis	No separate ACT specified
3	Genotype 3	
3a	Treatment-naive patients with cirrhosis	Dual therapy (combination of peginterferon and ribavirin)
3b	Treatment-experienced patients	Dual therapy (combination of peginterferon and ribavirin)
4	Genotype 4	
4a	Treatment-naive patients	Dual therapy (combination of peginterferon and ribavirin)
4b	Treatment-experienced patients	Dual therapy (combination of peginterferon and ribavirin)

a: 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.
b: Data currently available prove no superiority of triple therapy for treatment-naive patients with cirrhosis. Dual therapy is therefore to be regarded as ACT in these situations.
c: Only very few data for triple therapy are currently available for patients with HIV coinfection. Dual therapy is therefore to be regarded as ACT in these situations.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus; SPC: Summary of Product Characteristics

The company largely followed the G-BA with regard to the ACT. In cases where the G-BA provided several options to choose from (treatment-naive patients without cirrhosis [research question 1a] and treatment-experienced patients [research question 1c], in each case with genotype 1), the company chose triple therapy as ACT. For genotype 1 or 4 patients with decompensated cirrhosis or before or after liver transplantation and for patients after failure of triple therapy, the company regarded antiviral therapy as inappropriate. This was only accepted for patients with decompensated cirrhosis of the liver (research question 2) because treatment with peginterferon is contraindicated in these patients.

The company presented data only for part of the research questions. An overview of the data presented by the company is shown in Table 6.

Table 6: Data presented on the research questions

Research question	**Subindication CHC**	**Data presented by the company**
1	Genotype 1	
1a	Treatment-naive patients without cirrhosis	Historical comparison
1b	Treatment-naive patients with cirrhosis	Historical comparison
1c	Treatment-experienced patients	Historical comparison
1d	Patients with HIV coinfection treatment-naive treatment-experienced	 Historical comparison with presentation of an example of the evidence on the ACT No data
2	Genotype 1/4	
	Patients with decompensated cirrhosis	Study on LDV/SOF without comparison with the comparator therapy chosen by the company
3	Genotype 3	
3a	Treatment-naive patients with cirrhosis	Study on LDV/SOF not used in compliance with the approval without comparison with the ACT
3b	Treatment-experienced patients	No data
4	Genotype 4	No data
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; HIV: human immunodeficiency virus; LDV/SOF: ledipasvir/sofosbuvir		

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier.

Historical comparisons (unadjusted indirect comparisons) of ledipasvir/sofosbuvir versus the respective ACT were available in the present benefit assessment. The certainty of results of a historical comparison is generally considered to be inadequate and therefore allows no derivation of an added benefit. Dramatic effects are an exception.

The following operationalization serves as an orientation for the classification as a dramatic effect: An observed effect can be regarded as dramatic when it is not explicable solely by the impact of confounding factors, i.e. if it is statistically significant at a level of 1% and, expressed as the estimated relative risk, exceeds the value of 10 (or is 1/10 or lower). A 10-fold increase or decrease in risk usually reflects a (more or less) deterministic course. Moreover, the risk of the examined event should be at least 5% in at least one of the groups compared.

Hence at most hints of an added benefit or greater harm of ledipasvir/sofosbuvir were derived from the results of the available comparisons if dramatic effects were present.

2.3 Research question 1a: CHC genotype 1, treatment-naive patients without cirrhosis

2.3.1 Information retrieval and study pool (research question 1a)

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 ledipasvir/sofosbuvir (studies completed up to 6 November 2014)
- bibliographical literature search on ledipasvir/sofosbuvir (last search on 5 September 2014)
- search in trial registries for studies on ledipasvir/sofosbuvir (last search on 2 October 2014)
- bibliographical literature search on the ACT (last search on 22 September 2014)
- search in trial registries for studies on the ACT (last search on 2 October 2014)

To check the completeness of the study pool:

- bibliographical literature search on ledipasvir/sofosbuvir (last search on 12 December 2014)
- search in trial registries for studies on ledipasvir/sofosbuvir (last search on 12 December 2014)
- search in trial registries for studies on the ACT (last search on 7 January 2015)

From the check of completeness, the GS-US-337-0113 study was additionally identified as potentially relevant study for the historical comparison.

Direct comparison

There were no direct comparative studies on ledipasvir/sofosbuvir versus the ACT for treatment-naive genotype 1 patients without cirrhosis.

Historical comparison

For treatment-naive genotype 1 patients without cirrhosis, the company presented a historical comparison of ledipasvir/sofosbuvir versus the triple therapy with protease inhibitor (TVR or BOC) + PEG + RBV. The historical comparison consisted of individual study arms from 3 studies on ledipasvir/sofosbuvir and 6 studies on the ACT.

The company did not include the GS-US-337-0113 study on the ledipasvir/sofosbuvir side, although the inclusion criteria were fulfilled. Since the results of the study did not raise doubts about the result of the benefit assessment, however, the results of the company's study pool were used for the present benefit assessment. Further explanations can be found in Section 2.11.2.3.2.1 of the full dossier assessment.

2.3.1.1 Studies included

The studies listed in Table 7 were included in the benefit assessment.

Table 7: Study pool – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV

Research question study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Studies with ledipasvir/sofosbuvir			
ION-1	Yes	Yes	No
ION-3	Yes	Yes	No
LONESTAR	Yes	Yes	No
Studies with the ACT PI + PEG + RBV			
Telaprevir + PEG + RBV			
ADVANCE	No	No	Yes
ILLUMINATE	No	No	Yes
Marcellin 2011	No	No	Yes
OPTIMIZE	No	No	Yes
Boceprevir + PEG + RBV			
Manns 2014	No	No	Yes
SPRINT-2	No	No	Yes

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
CHC: chronic hepatitis C; LDV/SOF: ledipasvir/sofosbuvir; PEG: peginterferon alfa; PI: protease inhibitor; RBV: ribavirin; RCT: randomized controlled trial; vs.: versus

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

Table 8 and Table 9 describe the studies used for the benefit assessment. Table 10 shows the patient characteristics of the studies included.

Table 8: Characteristics of the studies included – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study
Studies with ledipasvir/sofosbuvir					
ION-1	RCT, open-label, multicentre	Treatment-naive adults with CHC genotype 1 with or without cirrhosis[a]	Group 1: LDV/SOF (24W) (N = 217) Group 2: LDV/SOF + RBV (24W) (N = 218) Group 3: LDV/SOF (12W) (N = 217) Group 4: LDV/SOF + RBV (12W) (N = 218) Relevant subpopulation thereof[b]: Group 3 (n = 180)	Screening: 4 weeks Treatment phase: 12 or 24 weeks Follow-up: up to 24 weeks	France, Germany, Italy, Spain, United Kingdom, United States 9/2012–4/2014
ION-3	RCT, open-label, multicentre	Treatment-naive adults with CHC genotype 1 without cirrhosis	Group 1: LDV/SOF (12W) (N = 216) Group 2: LDV/SOF + RBV (8W) (N = 216) Group 3: LDV/SOF (8W) (N = 215) Relevant subpopulation thereof[b]: Group 1 (n = 216) Group 3 (n = 215)	Screening: 4 weeks Treatment phase: 8 or 12 weeks Follow-up: up to 24 weeks	United States 5/2013–3/2014
LONESTAR	RCT, open-label, parallel, monocentric	Treatment-naive without cirrhosis and treatment-experienced with[d] or without cirrhosis, adults with CHC genotype 1	Cohort 1 (TN)[c] Group 1: LDV/SOF (8W) (N = 20) Group 2: LDV/SOF + RBV (8W) (N = 21) Group 3: LDV/SOF (12W) (N = 19) Cohort 2 (TE)[e] Group 4: LDV/SOF (12W) (N = 19) Group 5: LDV/SOF + RBV (12W) (N = 21) Relevant subpopulation thereof[b]: Cohort 1 Group 1 (n = 20) Group 3 (n = 19)	Screening: 4 weeks Treatment phase: 8 or 12 weeks Follow-up: up to 24 weeks	United States 10/2012–1/2014

(continued)

Table 8: Characteristics of the studies included – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study
Studies with telaprevir + PEG + RBV					
ADVANCE	RCT, double-blind, parallel, multicentre	Treatment-naive adults with CHC genotype 1 with or without cirrhosis[f]	Group 1 (T12PR): TVR + PEG2a + RBV (RGT) (N = 365) Group 2 (T8PR): TVR + PEG2a + RBV (N = 365) Group 3 (PR): placebo + PEG2a + RBV (N = 365) Relevant subpopulation thereof[b]: Group 1 (n = 342)	Screening: no data Treatment phase: 24 or 48 weeks Follow-up: 24, 48 or 60 weeks	Argentina, Australia, Austria, Canada, France, Germany, Israel, Italy, Poland, Spain, United Kingdom, United States 3/2008–5/2010
ILLUMINATE	RCT, open-label, parallel, multicentre	Treatment-naive adults with CHC genotype 1 with or without cirrhosis	Group 1 (T12PR24 [RA]): TVR + PEG2a + RBV (24W) (N = 162) Group 2 (T12PR48): TVR + PEG2a + RBV (48W) (N = 160) Group 3 (T12PR48 [NRA]): TVR + PEG2a + RBV (48W) (N = 118) Relevant subpopulation thereof[b]: Group 1 (n = 144) Group 3 (n = 106)	Screening: no data Treatment phase: 24 or 48 weeks Follow-up: 24 or 48 weeks	Belgium, Netherlands, United States 10/2008–7/2010
Marcellin 2011	RCT, open-label, parallel, multicentre	Treatment-naive adults with CHC genotype 1 without cirrhosis[g]	Group 1 (q8h alfa-2a): TVR + PEG2a + RBV (RGT) (N = 40) Group 2 (q8h alfa-2b): TVR + PEG2b + RBV (RGT) (N = 42) Group 3 (q12h alfa-2a): TVR + PEG2a + RBV (RGT) (N = 40) Group 4 (q12h alfa-2b): TVR + PEG2b + RBV (RGT) (N = 39) Relevant subpopulation thereof[b]: Group 1 (n = 39) Group 2 (n = 41) Group 3 (n = 40) Group 3 (n = 37)	Screening: no data Treatment phase: 24 or 48 weeks Follow-up: 24 weeks	Austria, Belgium, France, Germany, Italy, Netherlands, Spain 10/2007–8/2009

(continued)

Table 8: Characteristics of the studies included – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study
OPTIMIZE	RCT, open-label, parallel, multicentre	Treatment-naive adults with CHC genotype 1 with or without cirrhosis	Group 1 (bid): TVR + PEG2a + RBV (RGT) (N = 369) Group 2 (q8h): TVR + PEG2a + RBV (RGT) (N = 371) Relevant subpopulation thereof[b]: Group 1 (n = 315) Group 2 (n = 321)	Screening: 4 weeks Treatment phase: 24 or 48 weeks Follow-up: at least 24 weeks	Australia, Austria, Belgium, Brazil, France, Germany, Ireland, Mexico, Poland, Spain, Sweden, United Kingdom, United States 11/2010–11/2012
Studies with boceprevir + PEG + RBV					
Manns 2014	RCT, double-blind, parallel, multicentre	Treatment-naive adults with CHC genotype 1 with[h] or without cirrhosis	Group 1: MK-5172 100 mg + PEG2b + RBV (RGT) (N = 66) Group 2: MK-5172 200 mg + PEG2b + RBV (RGT) (N = 68) Group 3: MK-5172 400 mg + PEG2b + RBV (RGT) (N = 67) Group 4: MK-5172 800 mg + PEG2b + RBV (RGT) (N = 65) Group 5: BOC + PEG2b + RBV (RGT) (N = 66) Relevant subpopulation thereof[b]: Group 5 (n = 66)	Screening: no data Treatment phase: 24, 28 or 48 weeks Follow-up: 24, 44 or 48 weeks	Argentina, Canada, France, Germany, Israel, Italy, United States 9/2011 ongoing planned end 3/2015
SPRINT-2	RCT, double-blind, with open-label administration of PEG2b + RBV, parallel, multicentre	Treatment-naive adults with CHC genotype 1 with or without cirrhosis	Group 1: PEG2b + RBV (48W) (N = 364) Group 2: BOC + PEG2b + RBV (RGT; 28W) (N = 368) Group 3: BOC + PEG2b + RBV (48W) (N = 366) Relevant subpopulation thereof[b]: Group 2 (n = 337)	Screening: no data Treatment phase: 28 or 48 weeks Follow-up: 24 or 44 weeks	Argentina, Belgium, Canada, France, Germany, Italy, Netherlands, Spain, United States 8/2008–5/2010

(continued)

Table 8: Characteristics of the studies included – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV (continued)

a: Up to 20% of the study population included could have confirmed cirrhosis.
b: Genotype 1 patients without cirrhosis.
c: Stratified according to genotype 1a or 1b and without cirrhosis.
d: In Cohort 2, up to 50% of the study population included could have confirmed cirrhosis.
e: Stratified according to genotype 1a or 1b and with or without cirrhosis.
f: Stratified according to genotype 1a or 1b and baseline viral load < 800 000 IU/mL or ≥ 800 000 IU/mL.
g: 4 patients with cirrhosis (2.5%) were included by mistake, but were allowed to continue treatment.
h: Patients with cirrhosis only included in Group 1.

bid: twice daily; BOC: boceprevir; CHC: chronic hepatitis C; IU: international units; LDV/SOF: ledipasvir/sofosbuvir; N: number of randomized patients; n: relevant subpopulation; ND: no data; NRA: non-randomly assigned; PEG2a: peginterferon alfa-2a; PEG2b: peginterferon alfa-2b; PI: protease inhibitor; PR: peginterferon and ribavirin; q8h: every 8 hours; RA: randomly assigned; RBV: ribavirin; RCT: randomized controlled trial; RGT: response-guided therapy; TE: treatment-experienced; TN: treatment-naive; TVR: telaprevir; vs.: versus; W: weeks

Table 9: Characteristics of the interventions – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV

Study	Intervention[a]
Studies with ledipasvir/sofosbuvir	
ION-1	LDV/SOF (90 mg/400 mg) tablet once daily for 12 weeks
ION-3	Group 1: LDV/SOF (90 mg/400 mg) tablet once daily for 12 weeks Group 3: LDV/SOF (90 mg/400 mg) tablet once daily for 8 weeks
LONESTAR	Group 1: LDV/SOF (90 mg/400 mg) tablet once daily for 8 weeks Group 3: LDV/SOF (90 mg/400 mg) tablet once daily for 12 weeks
Studies with the ACT PI	
Telaprevir + PEG + RBV	
ADVANCE	TVR + PEG2a + RBV for 12 weeks, then PEG2a + RBV for 12 weeks (patients with undetectable HCV RNA in week 4 and 12) or 36 weeks (patients with detectable HCV RNA in week 4 or 12): T12PR: TVR 750 mg q8h orally, PEG2a 180 µg once/week SC, RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)
ILLUMINATE	Group 1: T12PR24 (RA): TVR + PEG2a + RBV for 12 weeks, then PEG2a + RBV for 12 weeks (patients with undetectable HCV RNA in week 4 and 12) Group 3: T12PR48 (NRA): TVR + PEG2a + RBV for 12 weeks, then PEG2a + RBV for 36 weeks (patients with detectable HCV RNA in week 4 or 12) In each case TVR 750 mg q8h orally, PEG2a 180 µg once/week SC, RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)
Marcellin 2011	TVR + PEG2a/b + RBV for 12 weeks, then PEG2a/b + RBV for 12 weeks (patients with undetectable HCV RNA in week 4 to 20) or 36 weeks (patients with detectable HCV RNA in week 4 to 20): Group 1: TVR 750 mg q8h orally, PEG2a 180 µg once/week SC, RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg) Group 2: TVR 750 mg q8h orally, PEG2b 1.5 µg/kg/week SC, RBV 800 to 1200 mg/day orally (depending on body weight: < 65 kg = 800 mg; ≥ 65 - ≤ 85 kg = 1000 mg; ≥ 85 kg = 1200 mg) Group 3: TVR 1125 mg q12h orally, PEG2a 180 µg once/week SC, RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg) Group 4: TVR 1125 mg q12h orally, PEG2b 1.5 µg/kg/week SC., RBV 800 to 1200 mg/day orally (depending on body weight: < 65 kg = 800 mg; ≥ 65 - ≤ 85 kg = 1000 mg; ≥ 85 kg = 1200 mg)
OPTIMIZE	TVR + PEG2a + RBV for 12 weeks, then PEG2a + RBV for 24 weeks (patients with undetectable HCV RNA in week 4) or 48 weeks (patients with detectable HCV RNA in week 4): Group 1: TVR 1125 mg q12h orally, PEG2a 180 µg once/week SC, RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg) Group 2: TVR 750 mg q8h orally, PEG2a 180 µg once/week SC, RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)

(continued)

Table 9: Characteristics of the interventions – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV (continued)

Study	Intervention[a]
Boceprevir + PEG + RBV	
Manns 2014	BOC + PEG2b + RBV for 4 weeks, then BOC + PEG2b + RBV for 24 weeks (patients with undetectable HCV RNA in week 8 and 24) or 32 weeks (patients with detectable HCV RNA in week 8 and undetectable HCV RNA in week 24) followed by PEG2b + RBV for 12 weeks: Group 5: BOC 800 mg 3 times daily orally, PEG2b 1.5 µg/kg body weight once/week SC, RBV 600 to 1400 mg/day twice daily depending on body weight
SPRINT-2	PEG2b + RBV for 4 weeks, then BOC + PEG2b + RBV for 24 weeks (patients with undetectable HCV RNA in week 8 to 24 [early responders]) or BOC + PEG2b + RBV for 24 weeks and subsequent PLC + PEG2b + RBV for 20 weeks (patients with detectable HCV RNA in week 8 or later and undetectable HCV RNA in week 24 [late responders]): Group 2: BOC 800 mg 3 times daily orally, PEG2b 1.5 µg/kg/week SC, RBV 600 to 1400 mg/day orally (depending on body weight: 40 to 50 kg = 600 mg/day, > 50 to 65 kg = 800 mg/day, > 65 to 80 kg = 100 mg/day, > 85 to 105 kg = 1200 mg/day, > 105 to 125 kg= 1400 mg/day)

a: Only the arms relevant for the assessment are presented in this table.

BOC: boceprevir; CHC: chronic hepatitis C; HCV RNA: hepatitis C virus ribonucleic acid; LDV/SOF: ledipasvir/sofosbuvir; NRA: non-randomly assigned; PEG: peginterferon; PEG2a: peginterferon alfa-2a; PEG2b: peginterferon alfa-2b; PI: protease inhibitor; PLC: placebo; q8h: every 8 hours; q12h: every 12 hours; RA: randomly assigned; RBV: ribavirin; RCT: randomized controlled trial; SC: subcutaneously; TVR: telaprevir; vs.: versus

Table 10: Characteristics of the study populations – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV

Study **study arm**	**N**	**Age** **[years]** **mean (SD)**	**Sex** **[F/M]** **%**	**Patients with cirrhosis** **n (%)**	**Genotype** **[1/unknown or other]** **%**	**Viral load** **[< 800 000/** **≥ 800 000 IU/mL][a]** **%**	**Ethnicity** **[white/black/other]** **%**	**Treatment discontin-uations** **n (%)**
Studies with ledipasvir/sofosbuvir								
ION-1[b]								
LDV/SOF (12W)	214	52 (11)	41/59	34 (15.9)	99/1	21/79	87/11/1[c]	2 (0.9[c])
ION-3								
LDV/SOF (8W)	215	53 (10)	40/60	0	100/0	16/84	76/21/3[c]	0 (0)
LDV/SOF (12W)	216	53 (11)	41/59	0	100/0	20/80	77/19/3[c]	5 (2.3[c])
LONESTAR (Cohort 1)								
LDV/SOF (8W)	20	48 (11)	30/70	0	100/0	45/55	75/20/5	0 (0)
LDV/SOF (12W)	19	46 (12)	42.1/58	0	100/0	37/63	89/5/5	1 (5.3[c])
Studies with the ACT PI + PEG + RBV								
Telaprevir + PEG + RBV								
ADVANCE[b]								
TVR + PEG2a + RBV (T12PR; 24 or 48W)	363	47 (11)	41/59	21 (5.8)[d]	> 99/< 1	23/77	90/7/3[c]	95 (26.2[c])
ILLUMINATE[b]								
TVR + PEG2a + RBV (T12PR24 [RA]; 24W)	162	49 (9)	36/64	18 (11.1)	99/1	ND/77	83/10/6	1 (0.6[c])
TVR + PEG2a + RBV (T12PR48 [NRA]; 48W)	118	50 (9)	41/53	12 (10.2)	99/1	ND/92	73/17/10	39 (33.1[c])

(continued)

Table 10: Characteristics of the study populations – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV (continued)

Study Study arm	N	Age [years] mean (SD)	Sex [F/M] %	Patients with cirrhosis n (%)	Genotype [1/unknown or other] %	Viral load [< 800 000/ ≥ 800 000 IU/mL][a] %	Ethnicity [white/black/ other] %	Treatment discontin-uations n (%)
Marcellin 2011[b]								
TVR + PEG2a + RBV q8h (q8 alfa-2a)	40	47[e] [23–63[f]]	50/50	1 (2.5)	100/0	25/75	90/5/5[c]	6 (15.0)[c]
TVR + PEG2b + RBV q8h (q8 alfa-2b)	42	46[e] [20–65[f]]	52/48	1 (2.4)	100/0	19/81	90/2/7[c]	8 (19.0)[c]
TVR + PEG2a + RBV bid (q12 alfa-2a)	40	40[e] [22–61[f]]	48/52	0 (0)	100/0	18/82	90/3/8[c]	8 (20.0)[c]
TVR + PEG2b + RBV bid (q12 alfa-2b)	39	49[e] [19–63[f]]	51/49	2 (5.1)	100/0	13/87	92/3/5[c]	11 (28.2)[c]
OPTIMIZE[b]								
TVR + PEG2a + RBV (bid)	369	48 (11)	43[c]/57	54 (14.6[c])	99/1	15/85	90/5/4[c]	ND
TVR + PEG2a + RBV (q8h)	371	48 (11)	37[c]/63	49 (13.2[c])	99/1	15/85	94/4/2[c]	ND
Boceprevir + PEG + RBV								
Manns 2014								
BOC + PEG2b + RBV (RGT)	66	52[e] [20–65[f]]	44[c]/56	0 (0)	100/0	ND/74	79/18/3	ND
SPRINT-2								
BOC + PEG2b + RBV (RGT)	368	50 (9)	38/62	16 (4.3[c])	97/3	ND/85	83/14/3[c]	139 (37.8)[c]

(continued)

Table 10: Characteristics of the study populations – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV (continued)

a: Unless otherwise stated.
b: There were no data for the relevant subpopulation of patients without cirrhosis. Since the proportion of patients with cirrhosis is < 20%, the characteristics of the total population are provided here.
c: Institute's calculation.
d: In Module 4, the company presented deviating percentages: 21 (7.1%). However, these do not comply with the 21 patients with cirrhosis stated.
e: Median.
f: Minimum-maximum.

bid: twice daily; CHC: chronic hepatitis C; F: female; IU: international units; LDV/SOF: ledipasvir/sofosbuvir; M: male; N: number of analysed patients; n: number of patients in the category; ND: no data; NRA: non-randomly assigned; PEG: peginterferon; PEG2a: peginterferon alfa-2a; PI: protease inhibitor; q8h: every 8 hours; RA: randomly assigned; RBV: ribavirin; RCT: randomized controlled trial; RGT: response-guided therapy; SD: standard deviation; TVR: telaprevir; vs.: versus; W: weeks

Studies on ledipasvir/sofosbuvir

The studies ION-1, ION-3 and LONESTAR were included for ledipasvir/sofosbuvir. The studies ION-1 and ION-3 were pivotal, randomized, open-label phase 3 studies for approval of ledipasvir/sofosbuvir. The LONESTAR study was an open-label randomized phase 2 study.

ION-1

Adult CHC genotype 1 patients with (up to 20% of the total population) and without cirrhosis who had not received previous treatment with interferon, ribavirin or other HCV-specific direct acting antivirals were included in the ION-1 study. The patients were treated with LDV/SOF or with LDV/SOF in combination with RBV for 12 or 24 weeks. Group 3, in which the patients were treated with LDV/SOF for 12 weeks, was relevant for research question 1a (treatment-naive CHC genotype 1 patients without cirrhosis). The relevant subpopulation of Group 3 was patients without cirrhosis.

ION-3

Adult CHC genotype 1 patients without cirrhosis who had not received previous treatment with interferon, ribavirin or other treatment for HCV were included in the ION-3 study. The patients were treated with LDV/SOF for 8 or 12 weeks or with LDV/SOF in combination with RBV for 8 weeks. The groups 1 and 3, in which the patients were treated with LDV/SOF for 12 or 8 weeks, were relevant for research question 1a (treatment-naive CHC genotype 1 patients without cirrhosis).

LONESTAR

Both treatment-naive patients (Cohort 1; no previous treatment with interferon, ribavirin or another treatment for chronic hepatitis C virus [HCV] infection) and treatment-experienced patients (Cohort 2; virologic failure on a PI + PEG + RBV regimen) were included in the LONESTAR study. Treatment-naive patients were not allowed to have cirrhosis; approximately half of the treatment-experienced patients were allowed to have cirrhosis. The treatment-naive patients in Cohort 1 were assigned to 8- or 12-week treatment with LDV/SOF or to 8-week treatment with LDV/SOF in combination with RBV. The groups 1 and 3 of Cohort 1 were relevant for research question 1a (treatment-naive CHC genotype 1 patients without cirrhosis).

Studies with the ACT (triple therapy)

ADVANCE

The ADVANCE study was a randomized, double-blind phase 3 study. Adult CHC genotype 1 patients with and without cirrhosis who had not been previously treated for HCV were included in the study. The patients were treated in 3 study arms with 2 different telaprevir regimens or placebo, in each case in combination with peginterferon alfa-2a and ribavirin. The study arm T12PR, in which patients were treated with the approval-compliant RGT regimen of triple therapy with telaprevir (TVR + PEG + RBV), was relevant for research

question 1a (treatment-naive CHC genotype 1 patients without cirrhosis). The relevant subpopulation was patients without cirrhosis.

ILLUMINATE

The ILLUMINATE study was a randomized, open-label phase 3 study, in which adult CHC genotype 1 patients with and without cirrhosis who had not been previously treated for HCV were included. In the study, the approval-compliant RGT regimen of triple therapy with telaprevir (TVR + PEG + RBV) was investigated in the relevant patient population in 3 study arms. The patients were initially not randomized and treated with TVR + PEG + RBV for 12 weeks and with PEG + RBV for another 12 weeks. Patients who responded to the treatment were randomly assigned to 2 treatment arms: end of treatment or PEG + RBV for another 24 weeks. Patients who did not respond to the treatment were not randomized and treated with PEG + RBV for another 24 weeks. The patients were not randomly allocated to this treatment arm, but the allocation was based on treatment results and not on the choice of the physician or the patient. The study arms T12PR24 (randomly assigned) and T12PR48 (non-randomly assigned) were relevant for the present benefit assessment. The relevant subpopulation was patients without cirrhosis.

Marcellin 2001

The Marcellin 2011 study was a randomized, open-label phase 2a study. Treatment-naive adult CHC genotype 1 patients without cirrhosis were included in the study. In 4 study arms, the patients received approval-compliant treatment with telaprevir (twice daily or 3 times daily), in each case in combination with peginterferon alfa-2a or peginterferon alfa-2b and ribavirin. The treatment duration was response-guided. All 4 arms of the study were relevant for the present benefit assessment.

OPTIMIZE

The OPTIMIZE study was a randomized, open-label phase 3 study, in which adult CHC genotype 1 patients with and without cirrhosis who had not been previously treated for HCV were included. The patients were treated in 2 arms with an approval-compliant response-guided treatment regimen of triple therapy with telaprevir (TVR [twice daily or 3 times daily] + PEG + RBV). Both study arms were relevant for the present benefit assessment; the relevant subpopulations were patients without cirrhosis.

Manns 2014

The Manns 2014 study was a randomized, double-blind phase 2 study. Treatment-naive adult CHC genotype 1 patients without cirrhosis were included. The patients were treated in 4 arms with a response-guided treatment regimen of triple therapy with MK-5172 (grazoprevir) + PEG + RBV. The 5fth study arm, in which patients were treated with an approval-compliant response-guided treatment regimen of triple therapy with boceprevir (BOC + PEG + RBV), was relevant for the present benefit assessment.

SPRINT-2

The SPRINT-2 study was a randomized, double-blind phase 3 study. Treatment-naive adult CHC genotype 1 patients with and without cirrhosis were included in the study. In Group 1, the patients were treated with dual therapy (PEG + RBV) for 48 weeks, in Group 2 with an RGT regimen of triple therapy with boceprevir (BOC + PEG + RBV), and in Group 3 with a fixed treatment regimen of triple therapy with boceprevir (BOC + PEG + RBV). Group 2 was relevant for research question 1a; the relevant subpopulation was patients without cirrhosis.

Treatment duration/observation period in the studies

The requirements of the respective Summaries of Product Characteristics (SPCs) resulted in fixed treatment durations for the fixed-dose combination of ledipasvir/sofosbuvir and the triple therapies with telaprevir or boceprevir in combination with PEG + RBV. In the studies on ledipasvir/sofosbuvir, the patients were treated in compliance with the approval for 8 or 12 weeks. In the studies on the ACT, the patients were treated considerably longer: depending on their response to treatment with BOC + PEG + RBV for 28 or 48 weeks or with TVR + PEG + RBV for 24 or 48 weeks. AEs were followed-up in the studies for approximately 30 days. This resulted in markedly different observation periods with a minimum difference of 12 weeks and a maximum difference of 40 weeks. As a result, the effect estimations for AEs and mortality on the basis of naive proportions presented by the company represent no adequate analysis, and overall no conclusive interpretation of the data on these outcome categories could be conducted. Consequently, no effect estimations are presented, and they were also not used for the benefit assessment.

2.3.2 Results on added benefit (research question 1a)

2.3.2.1 Outcomes included

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.11.2.7.3 of the full dossier assessment):

- Mortality
  - deaths
- Morbidity
  - sustained virologic response 12 or 24 weeks after the end of treatment (SVR 12 or SVR 24) as sufficiently valid surrogate for the patient-relevant outcome “HCC”
- Health-related quality of life
- Adverse events
  - overall rate of SAEs
  - discontinuation due to AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.11.2.7.3 of the full dossier assessment).

Table 11 shows for which outcomes data were available in the studies included.

Table 11: Matrix of outcomes – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV

Comparison / study	Outcomes						
	All-cause mortality	SVR 12	SVR 24	Health-related quality of life	AEs	SAEs	Discontinuation due to AEs
Studies with ledipasvir/sofosbuvir							
ION-1	Yes	Yes	No	Yes[a]	Yes	Yes	Yes
ION-3	Yes	No	Yes	Yes[a]	Yes	Yes	Yes
LONESTAR	Yes	Yes	No	No	Yes	Yes	Yes
Studies with the ACT PI + PEG + RBV							
Telaprevir + PEG + RBV							
ADVANCE	Yes	No	Yes	No	Yes	Yes	Yes
ILLUMINATE	Yes	No	Yes	No	Yes	Yes	Yes
Marcellin 2011	Yes	No	Yes	No	Yes	Yes	Yes
OPTIMIZE	Yes	Yes	No	No	Yes	Yes	Yes
Boceprevir + PEG + RBV							
Manns 2014	Yes	No	Yes	No	Yes	Yes	Yes
SPRINT-2	Yes	No	Yes	No	Yes	Yes	Yes

a: Measured with SF-36, CLDQ-HCV and FACIT-F.

AE: adverse event; CHC: chronic hepatitis C; CLDQ-HCV: Chronic Liver Disease Questionnaire-Hepatitis C; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; LDV/SOF: ledipasvir/sofosbuvir; PEG: peginterferon; PI: protease inhibitor; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; 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

2.3.2.2 Results

The following tables (Table 12 and Table 13) summarize the results on the historical comparison of ledipasvir/sofosbuvir versus triple therapy with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin in treatment-naive CHC genotype 1 patients without cirrhosis.

The summarizing analyses in the company's dossier were used for this. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. Further explanations can be found in Section 2.11.2.7.3 of the full dossier assessment.

Table 12: Results for SVR (SVR 12 or SVR 24) – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV

Comparison	**LDV/SOF**		**PI + PEG + RBV**		**LDV/SOF vs. PI + PEG + RBV**	
	N	**Patients with events n (%) [min-max]**	**N**	**Patients with events n (%) [min-max]**	**RR [95% CI]; p-value[a]**	
					Responders	**Non-responders**
LDV/SOF 8W vs. triple therapy	**235**	**221 (94.0) [94.0-95.0]**	**1843**	**1382 (75.0) [60.6-82.6]**	**1.25 [1.2; 1.31]; < 0.001**	**0.24 [0.14; 0.4]; < 0.001**
LDV/SOF 8W vs. **TVR** + PEG + RBV			1440	1120 (77.8) [74.7-82.6]	1.21 [1.16; 1.26]; < 0.001	0.27 [0.16; 0.45]; < 0.001
LDV/SOF 8W vs. **BOC** + PEG + RBV			403	262 (65.0) [60.6-65.9]	1.45 [1.34; 1.56]; < 0.001	0.17 [0.1; 0.29]; < 0.001
LDV/SOF 12W vs. triple therapy	**415**	**405 (97.6) [94.7-99.4]**	**1843**	**1382 (75.0) [60.6-82.6]**	**1.3 [1.26; 1.34]; < 0.001**	**0.1 [0.05; 0.18]; < 0.001**
LDV/SOF 12W vs. **TVR** + PEG + RBV			1440	1120 (77.8) [74.7-82.6]	1.25 [1.22; 1.29]; < 0.001	0.11 [0.06; 0.2]; < 0.001
LDV/SOF 12W vs. **BOC** + PEG + RBV			403	262 (65.0) [60.6-65.9]	1.5 [1.4; 1.62]; < 0.001	0.07 [0.04; 0.13]; < 0.001

a: p-value: Institute's calculation, unconditional exact test (CSZ method according to [3]) or Fisher exact test (from a total sample size of 1000 patients).

BOC: boceprevir; CHC: chronic hepatitis C; 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; 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; TVR: telaprevir; vs.: versus; W: weeks

Table 13: Results for mortality and AEs – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV

Outcome comparison	LDV/SOF		PI + PEG + RBV		LDV/SOF vs. PI + PEG + RBV
	N	Patients with events n (%) [min-max]	N	Patients with events n (%) [min-max]	RR[a] [95% CI]; p-value
Mortality					
LDV/SOF 8W vs. triple therapy	**235**	**0 (0) [0-0]**	**1610**	**3 (0.2)[b] [0-0.6]**	**NC**
LDV/SOF 8W vs. **TVR** + PEG + RBV			1544	3 (0.2) [0-0.6]	
LDV/SOF 8W vs. **BOC** + PEG + RBV			66	0 (0)[b] [NA]	
LDV/SOF 12W vs. triple therapy	**449**	**0 (0) [0-0]**	**1610**	**3 (0.2)[b] [0-0.6]**	**NC**
LDV/SOF 12W vs. **TVR** + PEG + RBV			1544	3 (0.2) [0-0.6]	
LDV/SOF 12W vs. **BOC** + PEG + RBV			66	0 (0)[b] [NA]	
AEs					
LDV/SOF 8W vs. triple therapy	**235**	**156 (66.4) [45.0-68.4]**	**1978**	**1955 (98.8) [97.0-99.4]**	**NC**
LDV/SOF 8W vs. **TVR** + PEG + RBV			1544	1526 (98.8) [98.2-99.4]	
LDV/SOF 8W vs. **BOC** + PEG + RBV			434	429 (98.8) [97.0-99.2]	
LDV/SOF 12W vs. triple therapy	**449**	**331 (73.7) [42.1-80.8]**	**1978**	**1955 (98.8) [97.0-99.4]**	**NC**
LDV/SOF 12W vs. **TVR** + PEG + RBV			1544	1526 (98.8) [98.2-99.4]	
LDV/SOF 12W vs. **BOC** + PEG + RBV			434	429 (98.8) [97.0-99.2]	
SAEs					
LDV/SOF 8W vs. triple therapy	**235**	**4 (1.7) [0-1.9]**	**1978**	**174 (8.8) [3.9-12.4]**	**NC**
LDV/SOF 8W vs. **TVR** + PEG + RBV			1544	127 (8.2) [3.9-12.4]	
LDV/SOF 8W vs. **BOC** + PEG + RBV			434	47 (10.8) [7.6-11.4]	
LDV/SOF 12W vs. triple therapy	**449**	**7 (1.6) [0.5-5.3]**	**1978**	**174 (8.8) [3.9-12.4]**	**NC**
LDV/SOF 12W vs. **TVR** + PEG + RBV			1544	127 (8.2) [3.9-12.4]	
LDV/SOF 12W vs. **BOC** + PEG + RBV			434	47 (10.8) [7.6-11.4]	

(continued)

Table 13: Results for mortality and AEs – RCT, further investigations: treatment-naive CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV (continued)

Outcome comparison	LDV/SOF		PI + PEG + RBV		LDV/SOF vs. PI + PEG + RBV
	N	Patients with events n (%) [min-max]	N	Patients with events n (%) [min-max]	RR[a] [95% CI]; p-value
Discontinuation due to AEs					
LDV/SOF 8W vs. triple therapy	**235**	**0 (0) [0-0]**	**1238[c]**	**116 (9.4)[c] [4.6-13.6]**	**NC**
LDV/SOF 8W vs. **TVR** + PEG + RBV			804[c]	62 (7.7)[c] [4.6-9.9]	
LDV/SOF 8W vs. **BOC** + PEG + RBV			434	54 (12.4) [12.2-13.6]	
LDV/SOF 12W vs. triple therapy	**449**	**2 (0.4) [0-0.9]**	**1238[c]**	**116 (9.4)[c] [4.6-13.6]**	**NC**
LDV/SOF 12W vs. **TVR** + PEG + RBV			804[c]	62 (7.7)[c] [4.6-9.9]	
LDV/SOF 12W vs. **BOC** + PEG + RBV			434	54 (12.4) [12.2-13.6]	

a: Effect estimates not presented because, overall, no conclusive interpretation of the outcome categories was possible due to the differences in observation periods in the 2 groups (more than twice as long in the comparator group).
b: The relevant SPRINT-2 study, in which 1 of 368 patients died, was not considered in the company's results.
c: Institute's calculation (asymptotic) because the company's calculations were based on inadequate data (see also Section 2.11.2.7.3 of the full dossier assessment).

AE: adverse event; BOC: boceprevir; CHC: chronic hepatitis C; 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; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TVR: telaprevir; vs.: versus; W: weeks

Morbidity

SVR as sufficiently valid surrogate for the patient-relevant outcome "HCC"

The proportion of patients with SVR after 12 weeks of treatment with ledipasvir/sofosbuvir was considerably larger than after 24 to 48-week treatment (RGT regimen) with triple therapy with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin. The proportion of patients with SVR was nearly 100% under treatment with ledipasvir/sofosbuvir. Overall, the effect can be regarded as dramatic (see Section 2.11.2.2 of the full dossier assessment) and could be observed in comparison with both treatment regimens (triple therapy with TVR or BOC). The tendency to a dramatic effect already occurred in a treatment duration of 8 weeks with ledipasvir/sofosbuvir, but was not as pronounced in this comparison as it was in the comparison of 12 weeks of ledipasvir/sofosbuvir versus the ACT.

Overall, there was a hint of an added benefit of ledipasvir/sofosbuvir versus the ACT with triple therapy with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin for the outcome "SVR".

This deviates from the company's assessment. The company also derived an added benefit for the outcome "SVR", but the probability was unclear because it derived both a hint and an indication of an added benefit.

Mortality and adverse events

Overall, no conclusive interpretation of the data on mortality and AEs of ledipasvir/sofosbuvir in comparison with the ACT was possible due to the large differences in observation periods. However, the data did not suggest greater harm from ledipasvir/sofosbuvir.

This deviates from the company's assessment, which derived an indication of an added benefit of ledipasvir/sofosbuvir.

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life in comparison with the ACT.

2.3.2.3 Subgroups and other effect modifiers

There were no subgroup analyses on the comparison of ledipasvir/sofosbuvir with the ACT.

2.3.3 Extent and probability of added benefit (research question 1a)

The derivation of extent and probability of added benefit is presented below using the positive and negative effects from the assessment.

The approach for deriving an overall conclusion on added benefit based on the aggregation of the positive and negative effects from the assessment is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.3.1 Overall conclusion on added benefit

Table 14 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of LDV/SOF in comparison with PI + PEG + RBV (treatment-naive CHC genotype 1 patients without cirrhosis)

Positive effects	**Negative effects**
Hint of added benefit – extent: "non-quantifiable" (outcome category: serious late complications: HCC, assessed with the surrogate SVR)	
No conclusive interpretation of the data on AEs and mortality was possible, but there was no sign of greater harm from LDV/SOF.	
AE: adverse event; CHC: chronic hepatitis C; HCC: hepatocellular carcinoma; LDV/SOF: ledipasvir/sofosbuvir; PEG: peginterferon alfa; PI: protease inhibitor; RBV: ribavirin; SVR: sustained virologic response	

On the positive side, there is an added benefit with the extent "non-quantifiable" in the category "serious late complications". Overall, no conclusive interpretation of the outcomes on mortality and AEs was possible due to the differences in observation periods. However, the observed events on mortality and AEs provided no sign that treatment with ledipasvir/sofosbuvir leads to greater harm than the comparator therapy.

In summary, there is a hint of a non-quantifiable added benefit of ledipasvir/sofosbuvir versus the ACT with triple therapy with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin for treatment-naive CHC genotype 1 patients without cirrhosis.

This deviates from the company's approach, which derived an indication of major added benefit.

2.3.4 List of included studies (research question 1a)

ADVANCE

Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH et al. Supplementary appendix to "Telaprevir for previously untreated chronic hepatitis C virus infection (N Engl J Med 2011; 364(25): 2405-2416)" [online]. 2011. URL: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1012912/suppl_file/nejmoa1012912_appendix.pdf.

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Vertex Pharmaceuticals. A phase 3 study of 2 dose regimens of telaprevir in combination with peginterferon alfa-2a (Pegasys) and ribavirin (Copegus) in treatment-naive subjects with genotype 1 chronic hepatitis C [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 6 October 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Vertex Pharmaceuticals. A phase 3 study of telaprevir in combination with Pegasys and Copegus in treatment-naive subjects with genotype 1 hepatitis C virus (HCV): tabular view [online]. In: ClinicalTrials.gov. 16 July 2014 [accessed: 6 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/record/NCT00627926.

Vertex Pharmaceuticals. A phase 3 study of 2 dose regimens of telaprevir in combination with peginterferon alfa-2a (Pegasys) and ribavirin (Copegus) in treatment-naive subjects with genotype 1 chronic hepatitis C [online]. In: EU Clinical Trials Register. [Accessed: 15 February 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-004720-20.

Vertex Pharmaceuticals. A phase 3 study of telaprevir in combination with Pegasys and Copegus in treatment-naive subjects with genotype 1 hepatitis C virus (HCV): study results [online]. In: ClinicalTrials.gov. 16 July 2014 [accessed: 5 February 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00627926.

ILLUMINATE

Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med 2011; 365(11): 1014-1024.

Vertex Pharmaceuticals. A randomized study of stopping treatment at 24 weeks or continuing treatment to 48 weeks in treatment-naïve subjects with genotype 1 chronic hepatitis C who achieve an extended rapid viral response (eRVR) while receiving telaprevir, peginterferon alfa2a (Pegasys) and ribavirin (Copegus) [online]. In: EU Clinical Trials Register. [Accessed: 6 October 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2008-003836-39.

Vertex Pharmaceuticals. A study evaluating 24-week and 48-week telaprevir-based regimen in treatment naïve subjects with genotype 1 chronic hepatitis C who achieve an extended rapid viral response: study results [online]. In: ClinicalTrials.gov. 30 September 2013 [accessed: 5 February 2015]. URL: https://www.clinicaltrials.gov/ct2/show/NCT00758043.

Vertex Pharmaceuticals. A study evaluating 24-week and 48-week telaprevir-based regimen in treatment naïve subjects with genotype 1 chronic hepatitis C who achieve an extended rapid viral response: tabular view [online]. In: ClinicalTrials.gov. 30 September 2013 [accessed: 6 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00758043.

ION-1

Gilead. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-naive subjects with chronic genotype 1 HCV infection: study GS-US-337-0102 (ION-1); final clinical study report [unpublished]. 2014.

Gilead. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection: study GS-US-337-0102; statistical analysis plan [unpublished]. 2013.

Gilead. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection: study GS-US-337-0102; clinical study protocol [unpublished]. 2012.

Gilead Sciences. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 6 October 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Gilead Sciences. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection [online]. In: EU Clinical Trials Register. [Accessed: 6 October 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=GS-US-337-0102.

Gilead Sciences. Safety and efficacy of ledipasvir/sofosbuvir fixed-dose combination (FDC) with and without ribavirin for the treatment of HCV: tabular view [online]. In: ClinicalTrials.gov. 12 May 2014 [accessed: 6 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/NCT01701401.

ION-3

Gilead. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed-dose combination ± ribavirin for 8 weeks and sofosbuvir/ledipasvir fixed-dose combination for 12 weeks in treatment-naive subjects with chronic genotype 1 HCV infection: study GS-US-337-0108 (ION-3); interim clinical study report [unpublished]. 2014.

Gilead. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed-dose combination ± ribavirin for 8 weeks and sofosbuvir/ledipasvir fixed-dose combination for 12 weeks in treatment-naive subjects with chronic genotype 1 HCV infection: study GS-US-337-0108 (ION-3); final synoptic clinical study report [unpublished]. 2014.

Gilead. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed-dose combination ± ribavirin for 8 weeks and sofosbuvir/ledipasvir fixed-dose combination for 12 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection: study GS-US-337-0108 (ION-3); statistical analysis plan [unpublished]. 2013.

Gilead. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/ledipasvir fixed-dose combination ± ribavirin for 8 weeks and sofosbuvir/ledipasvir fixed-dose combination for 12 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection: study GS-US-337-0108; clinical study protocol [unpublished]. 2013.

Gilead Sciences. Safety and efficacy of ledipasvir/sofosbuvir fixed-dose combination ± ribavirin for the treatment of HCV (ION-3): tabular view [online]. In: ClinicalTrials.gov. 10 March 2014 [accessed: 6 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/NCT01851330.

LONESTAR

Gilead. A phase 2, randomized, open-label study of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin in subjects with chronic genotype 1 HCV infection: study GS-US-337-0118 (LONESTAR); clinical study protocol [unpublished]. 2012.

Gilead. A phase 2, randomized, open-label study of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin in subjects with chronic genotype 1 HCV infection: study GS-US-337-0118 (LONESTAR); interim clinical study report [unpublished]. 2013.

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Gilead Sciences. Safety and efficacy of LDV/SOF fixed-dose combination (FDC) ± ribavirin in HCV genotype 1 subjects: tabular view [online]. In: ClinicalTrials.gov. 17 March 2014 [accessed: 6 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/NCT01726517.

Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet 2013; 383(9916): 515-523.

Manns 2014

Manns MP, Vierling JM, Bacon BR, Bruno S, Shibolet O, Baruch Y et al. The combination of MK-5172, peginterferon, and ribavirin is effective in treatment-naive patients with hepatitis C virus genotype 1 infection without cirrhosis. Gastroenterology 2014; 147(2): 366-76.e6.

Merck Sharp & Dohme. MK-5172 administered with peginterferon and ribavirin in treatment-naïve patients with chronic hepatitis C (MK-5172-003): tabular view [online]. In: ClinicalTrials.gov. 5 September 2014 [accessed: 26 September 2014]. URL: http://www.clinicaltrials.gov/ct2/show/NCT01353911.

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Marcellin 2011

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SPRINT-2

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Schering-Plough Research Institute. A phase 3, safety and efficacy study of boceprevir in previously untreated subjects with chronic hepatitis C genotype 1 [online]. In: PharmNet.Bund Klinische Prüfungen. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Merck Sharp & Dohme. Safety and efficacy of boceprevir in previously untreated subjects with chronic hepatitis C genotype 1 (study P05216AM2)(COMPLETED)(SPRINT-2): study results [online]. In: ClinicalTrials.gov. 2 December 2014 [accessed: 5 February 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00705432.

2.4 Research question 1b: CHC genotype 1, treatment-naive patients with cirrhosis

2.4.1 Information retrieval and study pool (research question 1b)

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 ledipasvir/sofosbuvir (studies completed up to 6 November 2014)
- bibliographical literature search on ledipasvir/sofosbuvir (last search on 5 September 2014)
- search in trial registries for studies on ledipasvir/sofosbuvir (last search on 2 October 2014)
- bibliographical literature search on the ACT (last search on 22 September 2014)
- search in trial registries for studies on the ACT (last search on 2 October 2014)

To check the completeness of the study pool:

- bibliographical literature search on ledipasvir/sofosbuvir (last search on 12 December 2014)
- search in trial registries for studies on ledipasvir/sofosbuvir (last search on 12 December 2014)
- search in trial registries for studies on the ACT (last search on 7 January 2015)

No additional relevant study was identified from the check.

Direct comparison

There were no direct comparative studies on ledipasvir/sofosbuvir versus the ACT for treatment-naive genotype 1 patients with cirrhosis.

Historical comparison

The company presented a historical comparison of ledipasvir/sofosbuvir versus dual therapy with PEG + RBV for treatment-naive genotype 1 patients with cirrhosis. The historical comparison consisted of individual study arms from 1 study on ledipasvir/sofosbuvir and 9 studies on the ACT.

2.4.1.1 Studies included

The studies listed in Table 15 were included in the benefit assessment.

Table 15: Study pool – RCT, further investigations: treatment-naive CHC genotype 1 patients with cirrhosis, LDV/SOF vs. PEG + RBV

Research question study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Studies with ledipasvir/sofosbuvir			
ION-1	Yes	Yes	No
Studies with the ACT PEG + RBV			
ADVANCE	No	No	Yes
Bronowicki 2014	No	No	Yes
COMMAND-1	No	No	Yes
JUMP-C	No	No	Yes
PROPEL	No	No	Yes
QUEST-1	No	No	Yes
QUEST-2	No	No	Yes
SPRINT-1	No	No	Yes
SPRINT-2	No	No	Yes

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
CHC: chronic hepatitis C; LDV/SOF: ledipasvir/sofosbuvir; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; vs.: versus

Section 2.4.4 contains a reference list for the studies included.

2.4.1.2 Study characteristics

Table 16 and Table 17 describe the studies used for the benefit assessment. Table 18 shows the patient characteristics of the studies included.

Table 16: Characteristics of the studies included – RCT, further investigations: treatment-naive CHC genotype 1 patients with cirrhosis, LDV/SOF vs. PEG + RBV

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study
Studies with ledipasvir/sofosbuvir					
ION-1	RCT, open-label, multicentre	Treatment-naive adults with CHC genotype 1 with or without cirrhosis[a]	Group 1: LDV/SOF (24W) (N = 217) Group 2: LDV/SOF + RBV (24W) (N = 218) Group 3: LDV/SOF (12W) (N = 217) Group 4: LDV/SOF + RBV (12W) (N = 218) Relevant subpopulation thereof[b]: Group 1 (n = 33) Group 3 (n = 34)	Screening: 4 weeks Treatment phase: 12 or 24 weeks Follow-up: up to 24 weeks	France, Germany, Italy, Spain, United Kingdom, United States 9/2012–4/2014
Studies with the ACT PEG + RBV					
ADVANCE	RCT, double-blind, parallel, multicentre	Treatment-naive adults with CHC genotype 1 with or without cirrhosis[c]	Group 1 (T12PR): TVR + PEG2a + RBV (RGT) (N = 365) Group 2 (T8PR): TVR + PEG2a + RBV (N = 365) Group 3 (PR): placebo + PEG2a + RBV (N = 365) Relevant subpopulation thereof[b]: Group 3 (n = 21)	Screening: no data Treatment phase: 24 or 48 weeks Follow-up: 24, 48 or 60 weeks	Argentina, Australia, Austria, Canada, France, Germany, Israel, Italy, Poland, Spain, United Kingdom, United States 3/2008–5/2010
Bronowicki 2014	RCT, double-blind, placebo-controlled, parallel, multicentre	Treatment-naive adults with CHC genotype 1 or 4 with or without cirrhosis[d]	Group 1: asunaprevir + PEG2a + RBV (N = 177) Group 2: placebo + PEG2a + RBV (N = 61) Relevant subpopulation thereof[b]: Group 2 (n = 9)	Screening: no data Treatment phase: 24 or 48 weeks Follow-up: 24 weeks	Argentina, France, Germany, Ireland, Italy, Spain, United Kingdom, United States 1/2011–10/2012

(continued)

Table 16: Characteristics of the studies included – RCT, further investigations: treatment-naive CHC genotype 1 patients with cirrhosis, LDV/SOF vs. PEG + RBV (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study
COMMAND-1	RCT, double-blind, placebo-controlled, parallel, multicentre	Treatment-naive adults with CHC genotype 1 or 4 with or without cirrhosis[d]	Group 1: daclatasvir + PEG2a + RBV (N = 159) Group 2: daclatasvir + PEG2a + RBV (N = 158) Group 3: placebo + PEG2a + RBV (N = 78) Relevant subpopulation thereof[b]: Group 3 (n = 8)	Screening: no data Treatment: 24 or 48 weeks Follow-up: 24 or 48 weeks	Australia, Canada, Denmark, Egypt, France, Germany, Italy, Mexico, Sweden, United States 7/2010–8/2012
JUMP-C	RCT, double-blind, parallel, multicentre, phase 2b	Treatment-naive adults with CHC genotype 1 or 4 with or without cirrhosis	Group 1 (A): MCB + PEG2a + RBV (RTG, 24 or 48W) (N = 81) Group 2 (B): placebo + PEG2a + RBV (48W) (N = 85)[e] Relevant subpopulation thereof[b]: Group 2 (n = 23)	Screening: no data Treatment phase: 24 or 48 weeks Follow-up: 24 or 48 weeks	Canada, United States 1/2010–10/2011
PROPEL	RCT, double-blind, parallel, multicentre	Treatment-naive adults with CHC genotype 1 or 4 with or without cirrhosis	Group 1 (A): MCB + PEG2a + RBV (N = 85) Group 2 (B): MCB + PEG2a + RBV (N = 84) Group 3 (C): MCB + PEG2a + RBV (N = 85) Group 4 (D): MCB + PEG2a + RBV (N = 85) Group 5 (E): placebo + PEG2a + RBV (N = 85) Relevant subpopulation thereof[b]: Group 5 (n = 19)	Screening: no data Treatment duration: 24 or 48 weeks Follow-up: 24 weeks	Australia, Austria, Canada, France, Germany, Italy, Spain, United Kingdom, United States 3/2009–6/2011
QUEST-1[f]	RCT, double-blind, parallel, placebo-controlled, multicentre	Treatment-naive adults with CHC genotype 1 with or without cirrhosis	Group 1: simeprevir + PEG2a + RBV (RGT, 24 or 48W) (N = 264) Group 2: placebo + PEG2a + RBV (48W) (N = 130) Relevant subpopulation thereof[b]: Group 2 (n = 17)	Screening: up to 6 weeks Treatment duration: 24 or 48 weeks Follow-up: up to 24 weeks	Australia, Canada, Germany, Italy, Mexico, New Zealand, Romania, Russia, Spain, Ukraine, United Kingdom, United States 1/2011–1/2013

(continued)

Table 16: Characteristics of the studies included – RCT, further investigations: treatment-naive CHC genotype 1 patients with cirrhosis, LDV/SOF vs. PEG + RBV (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study
QUEST-2[g]	RCT, double-blind, parallel, placebo-controlled, multicentre	Treatment-naive adults with CHC genotype 1 with or without cirrhosis	Group 1: simeprevir + PEG2a or PEG2b + RBV (RGT, 24 or 48W) (N = 257) Group 2: placebo + PEG2a or PEG2b + RBV (48W) (N = 134) Relevant subpopulation thereof[b]: Group 2 (n = 15)	Screening: up to 6 weeks Treatment duration: 24 or 48 weeks Follow-up: 24 or 48 weeks	Argentina, Austria, Belgium, Brazil, Bulgaria, France, Germany, Netherlands, Poland, Portugal, Slovakia, Spain, Turkey, United States 1/2011–2/2013
SPRINT-1[h]	RCT, open-label, parallel, multicentre	Treatment-naive adults with CHC genotype 1 with or without cirrhosis	Part 1: Group 1 (PR48): PEG2b + RBV (± BOC[i]) (48W) (N = 104) Group 2 (PR4/PRB24): PEG2b + RBV + BOC (24W) (N = 103) Group 3 (PR4/PRB44): PEG2b + RBV + BOC (44W) (N = 103) Group 4 (PRB28): PEG2b + RBV + BOC (28W) (N = 107) Group 5 (PRB48): PEG2b + RBV + BOC (48W) (N = 103) Part 2: Group 6 (PRB48): PEG2b + RBV + BOC (48W) (N = 16) Group 7 (low-dose PRB48): PEG2b + RBV + BOC (48W) (N = 59) Relevant subpopulation thereof[b]: Group 1 (n = 8)	Screening: no data Treatment: 24 or 48 weeks Follow-up: 24 weeks	Canada, Europe, United States 1/2007–8/2008

(continued)

Table 16: Characteristics of the studies included – RCT, further investigations: treatment-naive CHC genotype 1 patients with cirrhosis, LDV/SOF vs. PEG + RBV (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study
SPRINT-2	RCT, double-blind, parallel, multicentre	Treatment-naive adults with CHC genotype 1 with or without cirrhosis	Group 1: PEG2b + RBV (48W) (N = 364) Group 2: BOC + PEG2b + RBV (RGT; 28W) (N = 368) Group 3: BOC + PEG2b + RBV (48W) (N = 366) Relevant subpopulation thereof[b]: Group 1 (n = 13)	Screening: no data Treatment phase: 24 or 48 weeks Follow-up: 24 or 44 weeks	Argentina, Belgium, Canada, France, Germany, Italy, Netherlands, Spain, United States 8/2008-5/2010

a: Up to 20% of the study population included could have confirmed cirrhosis.
b: Treatment-naive genotype 1 patients with cirrhosis.
c: Stratified according to genotype 1a or 1b and baseline viral load < 800 000 IU/mL or ≥ 800 000 IU/mL.
d: The number of patients with genotype 4 and compensated cirrhosis (only genotype 1) was limited to 10%.
e: Only patients with genotype 1 were included.
f: 1 additional patient was randomized without information on the group.
g: 2 additional patients were randomized without information on the group.
h: 3 additional patients were randomized, but not treated. No information on the group.
i: After week 24, 36 patients were treated with the triple therapy of BOC + PEG2b + RBV for another 24 weeks.

BOC: boceprevir; CHC: chronic hepatitis C; IU: international units; LDV/SOF: ledipasvir/sofosbuvir; MCB: mericitabine; N: number of randomized patients; n: relevant subpopulation; ND: no data; PEG: peginterferon alfa; PEG2a: peginterferon alfa-2a; PEG2b: peginterferon alfa-2b; PR: peginterferon and ribavirin; RBV: ribavirin; RCT: randomized controlled trial; RGT: response-guided therapy; TVR: telaprevir; vs.: versus; W: weeks

Table 17: Characteristics of the interventions – RCT, further investigations: treatment-naive CHC genotype 1 patients with cirrhosis, LDV/SOF vs. PEG + RBV

Study	Intervention[a]
Studies with ledipasvir/sofosbuvir	
ION-1	Group 1: LDV/SOF (90 mg/400 mg) tablet once daily for 24 weeks Group 3: LDV/SOF (90 mg/400 mg) tablet once daily for 12 weeks
Studies with the ACT PEG + RBV	
ADVANCE	PEG2a + RBV for 48 weeks (+ placebo in the first 12 weeks): PEG2a 180 µg once/week SC, RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)
Bronowicki 2014	PEG2a + RBV for 24 weeks (+ placebo), then PEG2a + RBV for another 24 weeks: PEG2a 180 µg once/week SC, RBV 1000 to 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)
COMMAND-1	PEG2a + RBV for 24 weeks (+ placebo), then PEG2a + RBV for another 24 weeks: PEG2a 180 µg once/week SC, RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)
JUMP-C	PEG2a + RBV for 48 weeks (+ placebo in the first 24 weeks): PEG2a 180 µg once/week SC, RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)
PROPEL	PEG2a + RBV for 48 weeks (+ placebo in the first 12 weeks): PEG2a 180 µg once/week SC, RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)
QUEST-1	PEG2a + RBV for 12 weeks (+ placebo), then PEG2a + RBV for another 36 weeks: PEG2a 180 µg once/week SC, RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)
QUEST-2	PEG2a + RBV or PEG2b + RBV for 12 weeks (+ placebo); then PEG2a + RBV or PEG2b + RBV for 12 weeks (patients with undetectable HCV RNA in week 12) or 36 weeks (patients with detectable HCV RNA in week 12): PEG2a 180 µg once/week SC RBV 1000 or 1200 mg/day orally (depending on body weight: < 75 kg = 1000 mg, ≥ 75 kg = 1200 mg) or PEG2b 1.5 µg/kg once/week SC, RBV 800 to 1400 mg/day orally (depending on body weight: ≤ 65 kg = 800 mg, 66–80 kg = 1000 mg, 81–105 kg = 1200 mg, > 105 kg = 1400 mg)[b]
SPRINT-1	PEG2b + RBV for 24 weeks, then PEG2b + RBV for 24 weeks (patients with undetectable HCV RNA in week 24) or BOC + PEG2b + RBV for 24 weeks (patients with detectable HCV RNA in week 24)[c]: PEG2b 1.5 µg/kg once/week SC, RBV 800 to 1400 mg/day orally (depending on body weight: ≤ 65 kg = 800 mg, 66−80 kg = 1000 mg, 81−105 kg = 1200 mg, > 105 kg = 1400 mg), BOC 800 mg 3 times daily orally
SPRINT-2	PEG2b + RBV for 4 weeks run-in phase, then PEG2b + RBV (+ placebo) for 44 weeks: PEG2b 1.5 µg/kg once/week SC., RBV 600 to 1400 mg/day orally depending on body weight

a: Only the arms relevant for the assessment are presented in this table.
b: According to the SPC, the dose for 65 kg body weight is 1000 mg.
c: 36 of 104 patients (34.6%) were treated with BOC + PEG2b + RBV.

BOC: boceprevir; CHC: chronic hepatitis C; HCV RNA: hepatitis C virus ribonucleic acid; LDV/SOF: ledipasvir/sofosbuvir; PEG: peginterferon alfa; PEG2a: peginterferon alfa-2a; PEG2b: peginterferon alfa-2b; RBV: ribavirin; RCT: randomized controlled trial; SC: subcutaneously; vs.: versus

Table 18: Characteristics of the study populations – RCT, further investigations: treatment-naive CHC genotype 1 patients with cirrhosis, LDV/SOF vs. PEG + RBV

Study Study arm Population	N	Age [years] mean (SD)	Sex [F/M] %	Patients with cirrhosis n (%)	Genotype [1/unknown or other] %	Viral load [< 800 000/ ≥ 800 000 IU/mL][a] %	Ethnicity [white/black/ other] %	Treatment discontin-uations n (%)
Studies with ledipasvir/sofosbuvir								
ION-1								
LDV/SOF (12W)								
total study arm	214	52 (11)	41/59	34 (15.9)	99/1	21/79	87/11/1[b]	2 (0.9[b])
relevant subpopulation	34	ND	ND	34 (100)	ND	ND	ND	ND
LDV/SOF (24W)								
total study arm	217	53 (10)	36/64	33 (15.2)	99/1	23/77	82/15/4[b]	9 (4.1[b])
relevant subpopulation	33	ND	ND	33 (100)	ND	ND	ND	ND
Studies with the ACT PEG + RBV								
ADVANCE								
PEG2a + RBV (48W)								
total study arm	361	47 (10)	42/58	21 (5.8)	99/1	ND/77	88/8/4[b]	159 (44.0[b])
relevant subpopulation	21	ND	ND	21 (100)	ND	ND	ND	ND
Bronowicki 2014								
PEG2a + RBV (48W)								
total study arm	61	48 (ND)	31[b]/69	9 (14.8)	89/11[c]	ND	77/11/11	20[b] (32.8)
relevant subpopulation	9	ND	ND	9 (100)	ND	ND	ND	ND
COMMAND-1								
PEG2a + RBV (48W)								
total study arm	78	51 [25–66][d]	29[b]/71	8 (10.3)	92/8[c]	ND/78	77/12/12	41 (52.6[b])
relevant subpopulation	8	ND	ND	8 (100)	ND	ND	ND	ND

(continued)

Table 18: Characteristics of the study populations – RCT, further investigations: treatment-naive CHC genotype 1 patients with cirrhosis, LDV/SOF vs. PEG + RBV (continued)

Study Study arm Population	N	Age [years] mean (SD)	Sex [F/M] %	Patients with cirrhosis n (%)	Genotype [1/unknown or other] %	Viral load [< 800 000/ ≥ 800 000 IU/mL][a] %	Ethnicity [white/black/ other] %	Treatment discontin-uations n (%)
JUMP-C								
PEG2a + RBV (48W)								
total study arm	85	48 (10)	21[b]/79	23 (27.1)	100/0	16[b]/84	81/9/9	44 (51.8[b])
relevant subpopulation	23	ND	ND	23 (100)	ND	ND	ND	ND
PROPEL								
PEG2a + RBV (48W)								
total study arm	84	48 [22–65[e]]	39[b]/61	19 (22.6[b])	92[b]/8[c]	21[b]/79	89/4/7	31 (36.9[b])
relevant subpopulation	19	ND	ND	19 (100)	ND	ND	ND	ND
QUEST-1								
PEG2a + RBV (48W)								
total study arm	130	46 (11)	44/56	17 (13.1[b,f])	100/0	26/74	94/3/3	102 (78.5[b])
relevant subpopulation	17	ND	ND	17 (100)	ND	ND	ND	ND
QUEST-2								
PEG2a + RBV (48W)								
total study arm	134	46 (12)	43/57	15 (11.2[b])	98/2	27/73	92/7/1	ND
relevant subpopulation	15	ND	ND	15 (100)	ND	ND	ND	ND

(continued)

Table 18: Characteristics of the study populations – RCT, further investigations: treatment-naive CHC genotype 1 patients with cirrhosis, LDV/SOF vs. PEG + RBV (continued)

Study **Study arm** **Population**	**N**	**Age [years] mean (SD)**	**Sex [F/M] %**	**Patients with cirrhosis n (%)**	**Genotype [1/unknown or other] %**	**Viral load [< 800 000/ ≥ 800 000 IU/mL][a] %**	**Ethnicity [white/black/ other] %**	**Treatment discontin-uations n (%)**
SPRINT-1								
PEG2b + RBV (48W)								
total study arm	104	48 (7)	33/67	8 (7.7[b])	100/0	ND/90[g]	80/15/5[b]	52 (50.0[b])
relevant subpopulation	8	ND	ND	8 (100)	ND	ND	ND	ND
SPRINT-2								
PEG2b + RBV (48W)								
total study arm	363	49 (10)	43[b]/57	13 (3.6[b])	96/4	ND/85	82/14/4[b]	204 (56.2[b])
relevant subpopulation	13	ND	ND	13 (100)	ND	ND	ND	ND

a: Unless otherwise stated.
b: Institute's calculation.
c: Genotype 4 patients.
d: Median (minimum-maximum).
e: Minimum-maximum.
f: Deviating information in dossier assessment A14-18 simeprevir: 12%.
g: < 600 000/≥ 600 000 IU/mL.

CHC: chronic hepatitis C; F: female; IU: international units; LDV/SOF: ledipasvir/sofosbuvir; M: male; N: number of analysed patients; n: number of patients in the category; ND: no data; PEG: peginterferon alfa; PEG2a: peginterferon alfa-2a; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; TVR: telaprevir; vs.: versus

Studies on LDV/SOF

The ION-1 study was included on ledipasvir/sofosbuvir.

ION-1

The ION-1 study was a pivotal, randomized, open-label phase 3 study for approval of ledipasvir/sofosbuvir. Adult CHC genotype 1 patients with (up to 20% of the total population) and without cirrhosis who had not received previous treatment with interferon, ribavirin or other HCV-specific direct acting antivirals were included in the ION-1 study. The patients were allocated to 12- or 24-week treatment with LDV/SOF or with LDV/SOF in combination with RBV. The groups 1 and 3, in which the patients were treated with LDV/SOF for 12 or 24 weeks, were relevant for research question 1b (treatment-naive CHC genotype 1 patients with cirrhosis). The relevant subpopulations were patients without cirrhosis (Group 1: 33 of 217 patients, 15.2%; Group 3: 34 of 214 patients, 15.9%).

Studies with the ACT (dual therapy, PEG + RBV)

ADVANCE

The ADVANCE study was a randomized, double-blind phase 3 study, in which adult CHC genotype 1 patients with and without cirrhosis who had not been previously treated for HCV were included. The patients were treated in 3 study arms with 2 different telaprevir regimens or placebo, in each case in combination with peginterferon alfa-2a and ribavirin. The study arm PR48, in which the patients were treated for 48 weeks with PEG + RBV in addition to placebo, was relevant for research question 1b (treatment-naive CHC genotype 1 patients with cirrhosis). The relevant subpopulation was patients with cirrhosis (21 of 361 patients, 5.8%).

Bronowicki 2014

The Bronowicki 2014 study was a randomized, double-blind, placebo-controlled study. Treatment-naive adult patients with CHC genotype 1 or 4 were included in the study. Up to 10% of the genotype 1 patients could have cirrhosis. The proportion of patients with genotype 4 was also limited to 10%. The patients were treated with asunaprevir or placebo, in each case in combination with peginterferon alfa-2a and ribavirin. The placebo study arm, in which the patients were treated for 48 weeks with PEG + RBV in addition to placebo, was relevant for research question 1b (treatment-naive CHC genotype 1 patients with cirrhosis). The relevant subpopulation was patients with cirrhosis (9 of 61 patients, 14.8%).

COMMAND-1

The COMMAND-1 study was a randomized, double-blind, placebo-controlled phase 2b study. Treatment-naive adult patients with CHC genotype 1 or 4 were included in the study. Up to 10% of the genotype 1 patients could have cirrhosis. The proportion of patients with genotype 4 was also limited to 10%. The patients were treated with daclatasvir (2 dosages) or with placebo, in each case in combination with peginterferon alfa-2a and ribavirin. The placebo study arm, in which the patients were treated for 48 weeks with PEG + RBV in addition to placebo, was relevant for research question 1b (treatment-naive CHC genotype 1

patients with cirrhosis). The relevant subpopulation was patients with cirrhosis (8 of 78 patients, 10.3%).

JUMP-C

The JUMP-C study was a randomized, double-blind phase 2b study. Treatment-naive adult patients with CHC genotype 1 or 4 were included in the study. The patients were treated with mericitabine or placebo, in each case in combination with peginterferon alfa-2a and ribavirin. The placebo study arm, in which the patients were treated for 48 weeks with PEG + RBV in addition to placebo, was relevant for research question 1b (treatment-naive CHC genotype 1 patients with cirrhosis). No genotype 4 patients were in this study arm. The relevant subpopulation was genotype 1 patients with cirrhosis (23 of 85 patients, 27.1%).

PROPEL

The PROPEL study was a randomized, double-blind phase 2b study. Treatment-naive adult patients with CHC genotype 1 or 4 were included in the study. The patients were treated in 4 study arms with different treatment regimens with mericitabine in combination with peginterferon alfa-2a and ribavirin. The 5th study arm, in which the patients were treated for 48 weeks with PEG + RBV in addition to placebo, was relevant for research question 1b (treatment-naive CHC genotype 1 patients with cirrhosis). The proportion of patients in this study arm was 23% (19 of 84 patients). The proportion of patients with genotype 4 from the patients with cirrhosis was unclear. Overall, only 8% of the patients (7 of 84 patients) were infected with genotype 4 in this study arm.

QUEST-1

The QUEST-1 study was a randomized, double-blind, placebo-controlled phase 3 study. Treatment-naive adult CHC genotype 1 patients with and without cirrhosis were included. The patients were allocated to treatment with simeprevir or placebo, in each case in combination with peginterferon alfa-2a and ribavirin. The placebo study arm, in which the patients were treated for 48 weeks with PEG + RBV in addition to placebo, was relevant for research question 1b (treatment-naive CHC genotype 1 patients with cirrhosis). The relevant subpopulation was patients with cirrhosis (17 of 130 patients, 13.1%).

QUEST-2

The QUEST-2 study was a randomized, double-blind, placebo-controlled phase 3 study. Treatment-naive adult CHC genotype 1 patients with and without cirrhosis were included. The patients were allocated to treatment with simeprevir or placebo, in each case in combination with peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin. The placebo study arm, in which the patients were treated for 48 weeks with PEG + RBV in addition to placebo, was relevant for research question 1b (treatment-naive CHC genotype 1 patients with cirrhosis). The relevant subpopulation was patients with cirrhosis (15 of 134 patients, 11.2%).

SPRINT-1

The SPRINT-1 study was a randomized, open-label phase 2 study. Treatment-naive adult CHC genotype 1 patients with and without cirrhosis were included in the study. The study consisted of 2 parts: In the first part, 2 treatment durations (28 or 48 weeks) were investigated, with or without a 4-week run-in phase with peginterferon alfa-2b and ribavirin, followed by 24 or 44 weeks of triple therapy (BOC + PEG2b + RBV). In the second part of the study, the patients were treated for 48 weeks with BOC + PEG2b + RBV, with standard dosing of ribavirin in one arm, and a lower ribavirin dose in the other. The control arm of the first part, in which the patients were treated with dual therapy (PEG + RBV) for 48 weeks, was relevant for research question 1b. The relevant subpopulation was patients with cirrhosis (8 of 104 patients, 7.7%).

SPRINT-2

The SPRINT-2 study was a randomized, double-blind phase 3 study. Treatment-naive adult CHC genotype 1 patients with and without cirrhosis were included in the study. In Group 1, the patients were treated with dual therapy (PEG + RBV) for 48 weeks, in Group 2 with an RGT regimen of triple therapy with boceprevir (BOC + PEG + RBV), and in Group 3 with a fixed treatment regimen of triple therapy with boceprevir (BOC + PEG + RBV). Group 1 was relevant for research question 1b; the relevant subpopulation was patients with cirrhosis (13 of 363 patients, 3.6%).

Treatment duration/observation period in the studies

The requirements of the respective SPCs resulted in fixed treatment durations for the fixed-dose combination of ledipasvir/sofosbuvir and the dual therapy with PEG + RBV. In the studies on ledipasvir/sofosbuvir, the patients were treated in compliance with the approval for 12 or 24 weeks. In the studies on the ACT, the patients were treated for 48 weeks. AEs were followed-up in the studies for approximately 30 days. This resulted in markedly different observation periods with a minimum difference of 24 weeks and a maximum difference of 36 weeks. As a result, effect estimations for AEs and mortality on the basis of naive proportions represent no adequate analysis, and overall no conclusive interpretation of the data on these outcome categories could be conducted. Consequently, no effect estimations were used for the benefit assessment. However, the company also presented no effect estimate for the subpopulation of interest.

2.4.2 Results on added benefit (research question 1b)

2.4.2.1 Outcomes included

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.11.2.7.3 of the full dossier assessment):

- Mortality
  - deaths

- Morbidity
  - sustained virologic response 12 or 24 weeks after the end of treatment (SVR 12 or SVR 24) as sufficiently valid surrogate for the patient-relevant outcome “HCC”
- Health-related quality of life
- Adverse events
  - overall rate of SAEs
  - discontinuation due to AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.11.2.7.3 of the full dossier assessment).

Table 19 shows for which outcomes data were available in the studies included.

Table 19: Matrix of outcomes – RCT, further investigations: treatment-naive CHC genotype 1 patients with cirrhosis, LDV/SOF vs. PEG + RBV

Comparison study	Outcomes						
	All-cause mortality	SVR 12	SVR 24	Health-related quality of life	AEs	SAEs	Discontinuation due to AEs
Studies with ledipasvir/sofosbuvir							
ION-1	Yes	Yes	No	No[a,b]	No	No	No
Studies with the ACT PEG + RBV							
ADVANCE	No[b]	No	Yes	No	No[b]	No[b]	No[b]
Bronowicki 2014	Yes[c]	No	Yes	No	No[b]	No[b]	No[b]
COMMAND-1	Yes[c]	No	Yes	No	No[b]	No[b]	No[b]
JUMP-C	No	No	Yes	No	No[b]	No[b]	No[b]
PROPEL	Yes[c]	No	Yes	No	No[b]	No[b]	No[b]
QUEST-1	Yes[c]	Yes	No	No	No[b]	No[b]	No[b]
QUEST-2	Yes[c]	Yes	No	No	No[b]	No[b]	No[b]
SPRINT-1	No	No	Yes	No	No[b]	No[b]	No[b]
SPRINT-2	No[b]	No	Yes	No	No[b]	No[b]	No[b]

a: Measured with SF-36, CLDQ-HCV and FACIT-F.
b: Analysis only for the total study population.
c: No deaths occurred in the total study arm.
AE: adverse event; CHC: chronic hepatitis C; CLDQ-HCV: Chronic Liver Disease Questionnaire-Hepatitis C; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; LDV/SOF: ledipasvir/sofosbuvir; PEG: peginterferon; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; 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

2.4.2.2 Results

The following tables (Table 20 and Table 21) summarize the results on the historical comparison of ledipasvir/sofosbuvir versus dual therapy with peginterferon and ribavirin in treatment-naive CHC genotype 1 patients with cirrhosis.

The summarizing analyses in the company's dossier were used for this. Since the dossier contained no analyses on mortality and AEs for the relevant subpopulations, the results of the total population of the study arms are only presented as additional information. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. Further explanations can be found in Section 2.11.2.7.3 of the full dossier assessment.

Table 20: Results for SVR (SVR 12 or SVR 24) – RCT, further investigations: treatment-naive CHC genotype 1 patients with cirrhosis, LDV/SOF vs. PEG + RBV

Comparison	LDV/SOF		PEG + RBV		LDV/SOF vs. PEG + RBV	
	N	Patients with events n (%) [min-max]	N	Patients with events n (%) [min-max]	RR [95% CI]; p-value[a]	
					Responders	Non-responders
LDV/SOF 12W vs. PEG + RBV	34	32 (94.1) [NA]	133	46 (34.6) [21.7-47.4]	2.72 [2.12; 3.49]; < 0.001	0.09 [0.02; 0.35]; < 0.001
LDV/SOF 24W vs. PEG + RBV	33	32 (97.0) [NA]	133	46 (34.6) [21.7-47.4]	2.8 [2.2; 3.57]; < 0.001	0.05 [0.01; 0.32]; < 0.001

a: p-value: Institute's calculation, unconditional exact test (CSZ method according to [3])

CHC: chronic hepatitis C; 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; 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 21: Results for mortality and AEs – RCT, further investigations: treatment-naive CHC genotype 1 patients with cirrhosis, LDV/SOF vs. PEG + RBV (data of the company from Module 4 of the dossier)

Outcome comparison	LDV/SOF		PEG + RBV		LDV/SOF vs. PEG + RBV
	N[a]	Patients with events n (%) [min-max]	N[a]	Patients with events n (%) [min-max]	RR [95% CI]; p-value
Mortality[b]					
LDV/SOF 24W vs. PEG + RBV					
total study arm	217	0 (0) [NA]	848	1 (0.1) [0-0.3]	
relevant subpopulation	33	0 (0) [NA]	133	ND	ND
AEs[b]					
LDV/SOF 24W vs. PEG + RBV					
total study arm	217	178 (82.0) [NA]	1237	1210 (97.8) [93.4-100]	
relevant subpopulation	33	ND	133	ND	
SAEs[b]					
LDV/SOF 24W vs. PEG + RBV					
total study arm	217	18 (8.3) [NA]	1400	100 (7.1) [3.5-8.5]	
relevant subpopulation	33	ND	133	ND	ND
Discontinuation due to AEs[b]					
LDV/SOF 24W vs. PEG + RBV					
total study arm	217	4 (1.8) [NA]	1400	126 (9.0) [0.7-15.7]	
relevant subpopulation	33	ND	133	ND	ND
Health-related quality of life	No evaluable data[c]				

a: Data available only for the total population, proportion of patients with cirrhosis in all studies between 3.6% and 27.1% (in total, 33 patients for LDV/SOF and 133 patients for the ACT).
b: Data of the company from Module 4 of the dossier.
c: No evaluable data for the studies with the ACT available.

ACT: appropriate comparator therapy; AE: adverse event; CHC: chronic hepatitis C; 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; ND: no data; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SAE: serious; vs.: versus; W: weeks

Morbidity

SVR as sufficiently valid surrogate for the patient-relevant outcome "HCC"

The proportion of patients with SVR after 24 weeks of treatment with ledipasvir/sofosbuvir was considerably larger than after 48-week treatment with dual therapy consisting of peginterferon and ribavirin. The proportion of patients with SVR was nearly 100% under treatment with ledipasvir/sofosbuvir. Overall, the effect can be regarded as dramatic (see Section 2.11.2.2 of the full dossier assessment). There was a dramatic effect in comparison with the ACT also in a treatment duration of 12 weeks with ledipasvir/sofosbuvir, but the proportion of patients with SVR (94.1%) was not as high in this treatment duration as in a treatment duration of 24 weeks with ledipasvir/sofosbuvir.

Overall, there was a hint of an added benefit of ledipasvir/sofosbuvir versus the ACT with dual therapy consisting of peginterferon and ribavirin for the outcome "SVR".

This deviates from the company's assessment, which derived an indication of added benefit.

Mortality and adverse events

No conclusive interpretation of the data on mortality and AEs was possible for research question 1b. The company presented data of the total population of the study arms for ledipasvir/sofosbuvir and the ACT. However, the proportion of the relevant subpopulation (patients with cirrhosis) was only between 3.6% and 27.1% in the study arms. Hence the total population could not be used for assessing mortality and AEs. The company made no effort to compile data for the relevant subpopulation. Moreover, the observation period of 12 to 24 weeks differed considerably from the observation period of 48 weeks for the ACT. Hence the data on mortality and AEs provided by the company are only presented as additional information in Table 21. Discontinuations due to AEs in the total population occurred less frequently under ledipasvir/sofosbuvir than under the ACT. However, the proportion of events in SAEs was larger under ledipasvir/sofosbuvir than under the ACT, although the different observation periods caused a bias in favour of ledipasvir/sofosbuvir (the observation period of the comparator therapy was considerably longer). Based on the available information, greater harm from ledipasvir/sofosbuvir could not be excluded.

This deviates from the company's assessment, which derived an indication of an added benefit of ledipasvir/sofosbuvir.

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life in comparison with the ACT.

2.4.2.3 Subgroups and other effect modifiers

There were no subgroup analyses on the comparison of ledipasvir/sofosbuvir with the ACT.

2.4.3 Extent and probability of added benefit (research question 1b)

The derivation of extent and probability of added benefit is presented below using the positive and negative effects from the assessment.

The approach for deriving an overall conclusion on added benefit based on the aggregation of the positive and negative effects from the assessment is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Overall conclusion on added benefit

Table 22 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 22: Positive and negative effects from the assessment of LDV/SOF in comparison with PEG + RBV (treatment-naive CHC genotype 1 patients with cirrhosis)

Positive effects	**Negative effects**
Hint of added benefit – extent: "non-quantifiable" (outcome category: serious late complications: HCC, assessed with the surrogate SVR)	
No conclusive interpretation of data on AEs and mortality was possible; harm from LDV/SOF cannot be excluded.	
AE: adverse event; CHC: chronic hepatitis C; HCC: hepatocellular carcinoma; LDV/SOF: ledipasvir/sofosbuvir; PEG: peginterferon alfa; RBV: ribavirin; SVR: sustained virologic response	

On the positive side, there is an added benefit with the extent "non-quantifiable" in the category "serious late complications". Overall, no conclusive interpretation of the outcomes on mortality and AEs was possible due to the low proportion of the relevant subpopulation of the total population of the study arms (3.6% to 27.1%) and the differences in observation periods. Greater harm from ledipasvir/sofosbuvir cannot be excluded. This potentially raises doubts about the positive effect of ledipasvir/sofosbuvir in SVR.

In summary, there is no proof of added benefit versus the ACT of dual therapy with peginterferon and ribavirin for treatment-naive CHC genotype 1 patients with cirrhosis.

This deviates from the company's approach, which overall derived an indication of major added benefit.

2.4.4 List of included studies (research question 1b)

ADVANCE

Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH et al. Supplementary appendix to "Telaprevir for previously untreated chronic hepatitis C virus infection (N Engl J Med 2011; 364(25): 2405-2416)" [online]. 2011. URL: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1012912/suppl_file/nejmoa1012912_appendix.pdf.

Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011; 364(25): 2405-2416.

Vertex Pharmaceuticals. A phase 3 study of 2 dose regimens of telaprevir in combination with peginterferon alfa-2a (Pegasys) and ribavirin (Copegus) in treatment-naive subjects with genotype 1 chronic hepatitis C [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 6 October 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Vertex Pharmaceuticals. A phase 3 study of 2 dose regimens of telaprevir in combination with peginterferon alfa-2a (Pegasys) and ribavirin (Copegus) in treatment-naive subjects with genotype 1 chronic hepatitis C [online]. In: EU Clinical Trials Register. [Accessed: 15 February 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-004720-20.

Vertex Pharmaceuticals. A phase 3 study of telaprevir in combination with Pegasys and Copegus in treatment-naive subjects with genotype 1 hepatitis C virus (HCV): study results [online]. In: ClinicalTrials.gov. 16 July 2014 [accessed: 5 February 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00627926.

Vertex Pharmaceuticals. A phase 3 study of telaprevir in combination with Pegasys and Copegus in treatment-naive subjects with genotype 1 hepatitis C virus (HCV): tabular view [online]. In: ClinicalTrials.gov. 16 July 2014 [accessed: 6 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/record/NCT00627926.

Bronowicki 2014

Bristol-Myers Squibb. A phase 2a/2b study of BMS-650032 in combination with peginterferon alfa-2a (Pegasys) and ribavirin (Copegus) in treatment-naive subjects with genotypes 1 and 4 chronic hepatitis c infection: revised protocol 05, incorporating protocol amendments 03, 05, 06, 07 and 08.+ pharmacogenetics blood sample protocol amendment 01 (v2.0, dated 12-Nov-2009) [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 2 October 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Bristol-Myers Squibb. A phase 2a/2b study of BMS-650032 in combination with peginterferon alfa-2a (Pegasys) and ribavirin (Copegus) in treatment-naive subjects with genotypes 1 and 4 chronic hepatitis C infection [online]. In: EU Clinical Trials Register. [Accessed: 26 September 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2009-013652-69.

Bristol-Myers Squibb. Study of BMS-650032 with peginterferon alfa-2a plus ribavirin: tabular view [online]. In: ClinicalTrials.gov. 20 June 2013 [accessed: 26 September 2014]. URL: https://www.clinicaltrials.gov/ct2/show/record/NCT01030432.

Bronowicki JP, Ratziu V, Gadano A, Thuluvath PJ, Bessone F, Martorell CT et al. Randomized trial of asunaprevir plus peginterferon alfa and ribavirin for previously untreated genotype 1 or 4 chronic hepatitis C. J Hepatol 2014; 61(6): 1220-1227.

COMMAND-1

Bristol-Myers Squibb. A phase 2b study of BMS-790052 in combination with peg-interferon alfa-2a and ribavirin in treatment naive subjects with chronic hepatitis C genotype 1 and 4 infection [online]. In: EU Clinical Trials Register. [Accessed: 26 September 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2010-018295-24.

Bristol-Myers Squibb. A phase 2b study of BMS-790052 in combination with peg-interferonalfa-2a and ribavirin in treatment naive subjects with chronic hepatitis C genotype 1 and 4 infection: revised protocol number 03, incorporating amendments 03, 04 and 05+ pharmacogenetics blood sample amendment number 01; site specific (version 1.0, dated 16-Apr-10) [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 2 October 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Bristol-Myers Squibb. Study of BMS-790052 add-on to standard of care in treatment naive subjects (HEPCAT): tabular view [online]. In: ClinicalTrials.gov. 31 May 2013 [accessed: 26 September 2014]. URL: https://www.clinicaltrials.gov/ct2/show/NCT01125189.

Hezode C, Hirschfield GM, Ghesquiere W, Sievert W, Rodriguez-Torres M, Shafran SD et al. Daclatasvir plus peginterferon alfa and ribavirin for treatment-naive chronic hepatitis C genotype 1 or 4 infection: a randomised study. Gut 30 July 2014 [Epub ahead of print].

ION-1

Gilead. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-naive subjects with chronic genotype 1 HCV infection: study GS-US-337-0102 (ION-1); final clinical study report [unpublished]. 2014.

Gilead. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection: study GS-US-337-0102; statistical analysis plan [unpublished]. 2013.

Gilead. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection: study GS-US-337-0102; clinical study protocol [unpublished]. 2012.

Gilead Sciences. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 6 October 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Gilead Sciences. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection [online]. In: EU Clinical Trials Register. [Accessed: 6 October 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=GS-US-337-0102.

Gilead Sciences. Safety and efficacy of ledipasvir/sofosbuvir fixed-dose combination (FDC) with and without ribavirin for the treatment of HCV: tabular view [online]. In: ClinicalTrials.gov. 12 May 2014 [accessed: 6 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/NCT01701401.

JUMP-C

Hoffmann-La Roche. A study of RO5024048 in combination with Pegasys (peginterferon alfa-2a) and Copegus (ribavirin) in patients with chronic hepatitis C genotype 1 or 4: tabular view [online]. In: ClinicalTrials.gov. 22 September 2014 [accessed: 6 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/NCT01057667.

Pockros PJ, Jensen D, Tsai N, Taylor R, Ramji A, Cooper C et al. JUMP-C: a randomized trial of mericitabine plus pegylated interferon alpha-2a/ribavirin for 24 weeks in treatment-naive HCV genotype 1/4 patients. Hepatology 2013; 58(2): 514-523.

PROPEL

Hoffmann-La Roche. A randomized, double-blinded, multicenter, dose and duration finding study to evaluate the sustained virologic response of the HCV polymerase inhibitor Prodrug (RO5024048) in combination with Pegasys and Copegus versus the currently approved combination of Pegasys and Copegus in treatment-naive patients with chronic hepatitis C genotype 1 or 4 virus infection [online]. In: EU Clinical Trials Register. [Accessed: 6 October 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=NV20536.

Hoffmann-La Roche. A study of RO5024048 in combination with Pegasys and Copegus in treatment-naive patients with chronic hepatitis C, genotype 1 or 4: tabular view [online]. In: ClinicalTrials.gov. 22 September 2014 [accessed: 6 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00869661.

Wedemeyer H, Jensen D, Herring R Jr, Ferenci P, Ma MM, Zeuzem S et al. PROPEL: a randomized trial of mericitabine plus peginterferon alpha-2a/ribavirin therapy in treatment-naive HCV genotype 1/4 patients. Hepatology 2013; 58(2): 524-537.

QUEST-1

Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet 2014; 384(9941): 403-413.

Janssen R&D Ireland. An efficacy, safety, and tolerability study of TMC435 in treatment-naive, genotype 1 hepatitis C-infected patients (QUEST-1): study results [online]. In: ClinicalTrials.gov. 20 May 2014 [accessed: 5 February 2015]. URL: https://www.clinicaltrials.gov/ct2/show/results/NCT01289782.

Janssen R&D Ireland. An efficacy, safety, and tolerability study of TMC435 in treatment-naive, genotype 1 hepatitis C-infected patients (QUEST-1): tabular view [online]. In: ClinicalTrials.gov. 20 May 2014 [accessed: 2 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/record/NCT01289782.

Janssen R&D Ireland. A phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 vs. placebo as part of a treatment regimen including peginterferon alfa-2a and ribavirin in treatment-naïve, genotype 1 hepatitis C-infected subjects [online]. In: EU Clinical Trials Register. [Accessed: 2 October 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2010-020444-36.

Janssen-Cilag International. A phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 vs. placebo as part of a treatment regimen including peginterferon alfa-2a and ribavirin in treatment-naïve, genotype 1 hepatitis C-infected subjects [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 2 October 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

QUEST-2

Janssen R&D Ireland. An efficacy, safety, and tolerability study of TMC435 in treatment-naive, genotype 1 hepatitis C-infected participants (QUEST-2): study results [online]. In: ClinicalTrials.gov. 10 June 2014 [accessed: 5 February 2015]. URL: https://www.clinicaltrials.gov/ct2/show/results/NCT01290679.

Janssen R&D Ireland. An efficacy, safety, and tolerability study of TMC435 in treatment-naive, genotype 1 hepatitis C-infected participants (QUEST-2): tabular view [online]. In: ClinicalTrials.gov. 10 June 2014 [accessed: 2 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/record/NCT01290679.

Janssen R&D Ireland. A phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 versus placebo as part of a treatment regimen including peginterferon alpha-2a (Pegasys) and ribavirin (Copegus) or peginterferon alpha-2b (PegIntron) and ribavirin (Rebetol) in treatment-naïve, genotype 1, hepatitis C-infected subjects [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 2 October 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Manns M, Marcellin P, Poordad F, De Araujo ES, Buti M, Horsmans Y et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2014; 384(9941): 414-426.

Tibotec Pharmaceuticals. A phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 versus placebo as part of a treatment regimen including peginterferon α-2a (Pegasys) and ribavirin (Copegus) or peginterferon α-2b (PegIntron) and ribavirin (Rebetol) in treatment-naïve, genotype 1, hepatitis C-infected subjects [online]. In: EU Clinical Trials Register. [Accessed: 2 October 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2010-021174-11.

SPRINT-1

Kwo PY, Lawitz EJ, McCone J, Schiff ER, Vierling JM, Pound D et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet 2010; 376(9742): 705-716.

Merck Sharp & Dohme. Safety and efficacy of SCH 503034 in previously untreated subjects with chronic hepatitis C infected with genotype 1 (study P03523): full text view [online]. In: ClinicalTrials.gov. 30 October 2014 [accessed: 14 January 2015]. URL: http://ClinicalTrials.gov/show/NCT00423670.

Merck Sharp & Dohme. Safety and efficacy of SCH 503034 in previously untreated subjects with chronic hepatitis C infected with genotype 1 (study P03523): study results [online]. In: ClinicalTrials.gov. 30 October 2014 [accessed: 7 January 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00423670.

Schering Plough Research Institute. A safety and efficacy study of sch 503034 in previously untreated subjects with chronic hepatitis C infected with genotype 1 [online]. In: EU Clinical Trials Register. [Accessed: 7 October 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2006-002543-92.

Schering-Plough Research Institute. A safety and efficacy study of SCH 503034 in previously untreated subjects with chronic hepatitis C infected with genotype 1 [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 7 October 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

SPRINT-2

Bruno S, Vierling JM, Esteban R, Nyberg LM, Tanno H, Goodman Z et al. Efficacy and safety of boceprevir plus peginterferon-ribavirin in patients with HCV G1 infection and advanced fibrosis/cirrhosis. J Hepatol 2012; 58(3): 479-487.

Merck Sharp & Dohme. Safety and efficacy of boceprevir in previously untreated subjects with chronic hepatitis C genotype 1 (study P05216AM2)(COMPLETED)(SPRINT-2): study results [online]. In: ClinicalTrials.gov. 2 December 2014 [accessed: 5 February 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00705432.

Merck Sharp & Dohme. Safety and efficacy of boceprevir in previously untreated subjects with chronic hepatitis C genotype 1 (study P05216AM2)(COMPLETED)(SPRINT-2): tabular view [online]. In: ClinicalTrials.gov. 2 June 2014 [accessed: 7 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00705432.

Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011; 364(13): 1195-1206.

Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS et al. Supplementary appendix to "Boceprevir for untreated chronic HCV genotype 1 infection (N Engl J Med 2011; 364(13): 1195-1206)" [online]. 2011 [accessed: 3 February 2015]. URL: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1010494/suppl_file/nejmoa1010494_appendix.pdf.

Schering Plough Research Institute. A phase 3, safety and efficacy study of boceprevir in previously untreated subjects with chronic hepatitis C genotype 1 [online]. In: EU Clinical Trials Register. [Accessed: 7 October 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2007-005508-42.

Schering-Plough Research Institute. A phase 3, safety and efficacy study of boceprevir in previously untreated subjects with chronic hepatitis C genotype 1 [online]. In: PharmNet.Bund Klinische Prüfungen. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

2.5 Research question 1c: CHC genotype 1, treatment-experienced patients

2.5.1 Information retrieval and study pool (research question 1c)

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 ledipasvir/sofosbuvir (studies completed up to 6 November 2014)
- bibliographical literature search on ledipasvir/sofosbuvir (last search on 5 September 2014)
- search in trial registries for studies on ledipasvir/sofosbuvir (last search on 2 October 2014)
- bibliographical literature search on the ACT (last search on 22 September 2014)
- search in trial registries for studies on the ACT (last search on 2 October 2014)

To check the completeness of the study pool:

- bibliographical literature search on ledipasvir/sofosbuvir (last search on 12 December 2014)
- search in trial registries for studies on ledipasvir/sofosbuvir (last search on 12 December 2014)
- search in trial registries for studies on the ACT (last search on 7 January 2015)

For the historical comparison, there were deviations compared with the study pool of the company, which are named below.

Direct comparison

There were no direct comparative studies on ledipasvir/sofosbuvir versus the ACT for treatment-experienced genotype 1 patients.

Historical comparison

For treatment-experienced genotype 1 patients, the company presented a historical comparison of ledipasvir/sofosbuvir versus the triple therapy with protease inhibitor (telaprevir or boceprevir) + PEG + RBV. The historical comparison consisted of individual study arms from 4 studies on LDV/SOF and 4 studies on the ACT.

The company did not include the GS-US-337-0113 study on the ledipasvir/sofosbuvir side, although the inclusion criteria were fulfilled. The results of the study were used for the present benefit assessment. The company included another potentially relevant study (GS-US-337-0121). However, no final conclusion could be drawn on the relevance of this study from the documents presented by the company, and overall the study was not evaluable because there was neither a clinical study report (CSR) nor a full publication nor a comprehensive

registry report. The study was not used for the present benefit assessment. Further explanations can be found in Section 2.11.2.3.2.1 of the full dossier assessment.

2.5.1.1 Studies included

The studies listed in Table 23 were included in the benefit assessment.

Table 23: Study pool – RCT, further investigations: treatment-experienced CHC genotype 1 patients, LDV/SOF vs. PI + PEG + RBV

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Studies with ledipasvir/sofosbuvir			
ELECTRON (Part 6)	Yes	Yes	No
GS-US-337-0113 (Japan)	Yes	Yes	No
LONESTAR	Yes	Yes	No
ION-2	Yes	Yes	No
Studies with the ACT PI + PEG + RBV			
Telaprevir + PEG + RBV			
ATTAIN	No	No	Yes
REALIZE	No	No	Yes
Boceprevir + PEG + RBV			
RESPOND-2	No	No	Yes
Flamm 2013	No	No	Yes

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; LDV/SOF: ledipasvir/sofosbuvir; PEG: peginterferon alfa; PI: protease inhibitor; RBV: ribavirin; RCT: randomized controlled trial; vs.: versus

Section 2.5.4 contains a reference list for the studies included.

2.5.1.2 Study characteristics

Table 24 and Table 25 describe the studies used for the benefit assessment. Table 26 shows the patient characteristics of the studies included.

Table 24: Characteristics of the studies included – RCT, further investigations: treatment-experienced CHC genotype 1 patients, LDV/SOF vs. PI + PEG + RBV

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study
Studies with ledipasvir/sofosbuvir					
ELECTRON (Part 6)	RCT, open-label, parallel, multicentre	Adults ▪ treatment-experienced with CHC genotype 1 with cirrhosis who have not responded to previous treatment with PEG + RBV (Group 16 and 17) ▪ treatment-naive and -experienced with CHC genotype 2 or 3 (Group 18 and 19) ▪ CHC genotype 1 and haemophilia (Group 20) ▪ treatment-naive with CHC genotype 1 (Group 21 and 22)	Group 16: LDV/SOF (12W) (N = 10) Group 17: LDV/SOF + RBV (12W) (N = 9) Group 18: LDV/SOF (12W, TN) (N = 10) Group 20: LDV/SOF + RBV (12W) (N = 14) Group 21: LDV/SOF + RBV (6W) (N = 25) Relevant subpopulation thereof[a]: Group 16 (n = 10)	Screening: 4 weeks Treatment phase: 6 or 12 weeks Follow-up: up to 48 weeks	New Zealand 11/2010–12/2013
GS-US-337-0113 (Japan)	RCT, open-label, parallel, multicentre	Treatment-naive and treatment-experienced adults with CHC genotype 1 with or without cirrhosis[b]	Group 1[c]: LDV/SOF TN (12 W) (N = 83) Group 2[c]: LDV/SOF + RBV TN (12W) (N = 83) Group 3[d]: LDV/SOF TE (12 W) (N = 88) Group 4[d]: LDV/SOF + RBV TE (12 W) (N = 87) Relevant subpopulation thereof[a]: Group 3 (n = 88)	Screening: 4 weeks Treatment phase: 12 weeks Follow-up: 24 weeks	Japan 10/2013–8/2014

(continued)

Table 24: Characteristics of the studies included – RCT, further investigations: treatment-experienced CHC genotype 1 patients, LDV/SOF vs. PI + PEG + RBV (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study
LONESTAR	RCT, open-label, parallel, monocentric	Treatment-naive without cirrhosis and treatment-experienced with or without cirrhosis[e], adults with CHC genotype 1	Cohort 1 (TN)[f] Group 1: LDV/SOF (8W) (N = 20) Group 2: LDV/SOF + RBV (8W) (N = 21) Group 3: LDV/SOF (12W) (N = 19) Cohort 2 (TE)[g] Group 4: LDV/SOF (12W) (N = 19) Group 5: LDV/SOF + RBV (12W) (N = 21) Relevant subpopulation thereof[a]: Group 4 (n = 19)	Screening: 4 weeks Treatment phase: 8 or 12 weeks Follow-up: 24 weeks	United States 10/2012–1/2014
ION-2	RCT, open-label, parallel, multicentre	treatment-experienced adults with CHC genotype 1 who have not responded to previous treatment with PEG + RBV (non-responders or relapsers), with or without cirrhosis[h]	Group 1: LDV/SOF (24W) (N = 110) Group 2: LDV/SOF + RBV (24W) (N = 111) Group 3: LDV/SOF (12W) (N = 109) Group 4: LDV/SOF + RBV (12W) (N = 111) Relevant subpopulation thereof[a]: Group 1 (n = 110) Group 3 (n = 109)	Screening: 4 weeks Treatment phase: 12 or 24 weeks Follow-up: up to 24 weeks	United States 1/2013-2/2014

(continued)

Table 24: Characteristics of the studies included – RCT, further investigations: treatment-experienced CHC genotype 1 patients, LDV/SOF vs. PI + PEG + RBV (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study
Studies with telaprevir + PEG + RBV					
ATTAIN	RCT, double-blind, parallel, multicentre	Adults with CHC genotype 1, at least 1 previous course of treatment with peginterferon alfa-2a or 2b in combination with RBV for at least 12 (null responders) or 20 (partial responders) consecutive weeks with only partial or no response	Group 1: SIM + PEG + RBV (N = 385) Group 2: TVR + PEG + RBV (N = 386) Relevant subpopulation thereof[a]: Group 2 (n = 386)	Screening: 6 weeks Treatment phase: SIM or TVR: 12 weeks PEG and RBV: 48 weeks Follow-up: up to 24 weeks	Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Norway, Poland, Portugal, Romania, Spain, Sweden, Switzerland, United Kingdom, United States 2/2012-2/2013
REALIZE	RCT, double-blind, parallel, multicentre	Adults, 18–70 years with CHC genotype 1, compensated liver disease (including cirrhosis), unsuccessfully previously treated with PEG + RBV: relapsers or non-responders	Group 1 (T12PR48): TVR + PEG + RBV (N = 266; thereof relapsers with cirrhosis: n = 28; relapsers without cirrhosis: n = 117; non-responders: n = 121) Group 2 (T12DSPR48): TVR + PEG + RBV (N = 264; thereof relapsers: n = 141; non-responders: n = 123) Group 3 (PR48): PEG + RBV (N = 132; thereof relapsers: n = 68; non-responders: n = 64) Relevant subpopulation thereof (null or partial responders and relapsers with cirrhosis): Group 1 (n = 149)	Treatment phase: ▪ Group 1: PEG/RBV for 48 weeks with TVR for 12 weeks (then placebo for 4 weeks) ▪ Group 2: PEG/RBV for 48 weeks with placebo for 4 weeks, then TVR for 12 weeks (delayed start of treatment) ▪ Group 3: PEG/RBV for 48 weeks with placebo for 16 weeks Follow-up: 24 weeks	Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Israel, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, United Kingdom, United States 9/2008–7/2010

(continued)

Table 24: Characteristics of the studies included – RCT, further investigations: treatment-experienced CHC genotype 1 patients, LDV/SOF vs. PI + PEG + RBV (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study
Studies with boceprevir + PEG + RBV					
RESPOND-2	RCT, double-blind, with open-label administration of PEG + RBV, parallel, multicentre	Treatment-experienced adults with CHC genotype 1, unsuccessfully previously treated with PEG + RBV: relapsers or non-responders	Group 1: PEG + RBV standard treatment (N = 80) Group 2: BOC + PEG + RBV (RGT) (N = 162) Group 3: BOC + PEG + RBV fixed duration treatment (N = 162) Relevant subpopulation thereof: Group 2 (n = 132) (subgroup without cirrhosis) Group 3 (n = 22) (subgroup with cirrhosis)	Run-in phase: 4 weeks Treatment phase: 32 or 44 weeks Follow-up: 24 weeks	Belgium, Canada, France, Germany, Italy, Spain, United States 8/2008–4/2010
Flamm 2013	RCT, double-blind, with open-label administration of PEG + RBV, parallel, multicentre	Treatment-experienced patients with CHC genotype 1 with or without cirrhosis, unsuccessfully previously treated with PEG + RBV: relapsers or non-responders	Group 1: PEG + RBV (N = 67) Group 2: BOC + PEG + RBV (N = 134) Relevant subpopulation thereof (subgroup with cirrhosis): Group 2 (n = 24)	Pretreatment with PEG and RBV: 4 weeks Treatment phase: 44 weeks Follow-up: 24 weeks	Belgium, Canada, France, Germany, Italy, United States 2/2009–10/2010

a: Genotype 1 patients with or without cirrhosis, treated in compliance with the approval.
b: Up to 40% of the patients in each treatment group were allowed to have cirrhosis.
c: Stratified by cirrhosis status.
d: Stratified by cirrhosis status and by category of pretreatment (relapse/breakthrough, non-response, interferon intolerant).
e: Approximately 50% of the patients in each treatment group were allowed to have cirrhosis.
f: Stratified by genotype 1a or 1b.
g: Stratified by genotype 1a or 1b and with or without cirrhosis.
h: Approximately 20% of the patients in each treatment group were allowed to have cirrhosis, and approximately 50% had to have unsuccessful previous treatment with PI + PEG + RBV (non-responders or relapsers).

BOC: boceprevir; CHC: chronic hepatitis C; LDV/SOF: ledipasvir/sofosbuvir; N: number of randomized patients; n: relevant subpopulation; PEG: peginterferon alfa; PI: protease inhibitor; RBV: ribavirin; RCT: randomized controlled trial; RGT: response-guided therapy; SIM: simeprevir; TE: treatment-experienced; TN: treatment-naive; TVR: telaprevir; vs.: versus; W: weeks

Table 25: Characteristics of the interventions – RCT, further investigations: treatment-experienced CHC genotype 1 patients, LDV/SOF vs. PI + PEG + RBV

Study	Intervention[a]
Studies with ledipasvir/sofosbuvir	
ELECTRON (Part 6)	12 weeks LDV/SOF (90 mg/400 mg) orally once daily
GS-US-337-0113 (Japan)	12 weeks LDV/SOF (90 mg/400 mg) orally once daily
LONESTAR	12 weeks LDV/SOF (90 mg/400 mg) orally once daily
ION-2	Group 1: 12 weeks LDV/SOF (90 mg/400 mg) orally once daily Group 3: 24 weeks LDV/SOF (90 mg/400 mg) orally once daily
Studies with the ACT PI + PEG + RBV	
Telaprevir + PEG + RBV	
ATTAIN	Week 1–12: TVR 150 mg orally 3 times daily + PEG2a 180 µg SC once weekly + RBV 1000 or 1200 mg orally (depending on body weight: < 75 kg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) daily, divided into 2 doses Week 13–48: PEG2a + RBV, same dosage as week 1–12
REALIZE	Week 1–12: TVR 750 mg orally every 8 hours Week 1–48: PEG2a 180 µg SC once weekly + RBV 1000 or 1200 mg orally (depending on body weight: < 75 kg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) daily, divided into 2 doses
Boceprevir + PEG + RBV	
RESPOND-2	Run-in: 4 weeks PEG2b 1.5 µg/kg/week SC + RBV 600–1400 mg/day orally (twice daily) Treatment: Group 2: BOC 800 mg 3 times daily + PEG2b + RBV for 32 weeks From week 36 depending on the virologic response in TW 8 and in the following period up to TW 12, the patients were divided into the following subarms: ▪ HCV RNA in TW 8 and TW 12 negative: end of treatment in TW 36 ▪ Patients with positive HCV RNA in TW 8 but who become negative for HCV RNA by TW 12 were switched blind in TW 36 from boceprevir to placebo and treated for a further 12 weeks with PEG2b + RBV Group 3: BOC 800 mg 3 times daily + PEG2b + RBV for 44 weeks
Flamm 2013	Run-in: 4 weeks PEG2a 180 µg SC once weekly, RBV orally depending on body weight 1000 or 1200 mg/day twice daily Treatment: 44 weeks BOC 800 mg orally 3 times daily + PEG2a 180 µg SC once weekly, RBV orally depending on body weight 1000 or 1200 mg/day twice daily

a: Only the arms relevant for the assessment are presented in this table.

BOC: boceprevir; CHC: chronic hepatitis C; HCV RNA: hepatitis C virus ribonucleic acid; LDV/SOF: ledipasvir/sofosbuvir; PEG: peginterferon alfa; PEG2a: peginterferon alfa-2a; PEG2b: peginterferon alfa-2b; PI: protease inhibitor; RBV: ribavirin; RCT: randomized controlled trial; SC: subcutaneously; TVR: telaprevir; TW: treatment week; vs.: versus

Table 26: Characteristics of the study populations – RCT, further investigations: treatment-experienced CHC genotype 1 patients, LDV/SOF vs. PI + PEG + RBV

Study study arm population	N	Age [years] mean (SD)	Sex [F/M] %	Patients with cirrhosis n (%)	Genotype [1/unknown or other] %	Proportion non-responders/ relapsers %	Baseline viral load [< 800 000/ ≥ 800 000 IU/mL][a] %	Ethnicity [white/black/ other] %	Treatment discontin-uations n (%)
Studies with ledipasvir/sofosbuvir									
ELECTRON (Part 6)									
LDV/SOF 12W	10	61 (5)	0/100	10 (100)	100/0	100/0	20/80[b]	80/ND/ND	0 (0)
GS-US-337-0113									
LDV/SOF 12W	88	61 (8.5)	59/41	28 (31.8)	100/0	33/50	11/89	0/0/100	0 (0)
LONESTAR									
LDV/SOF 12W (Cohort 2)	19	54 (7)	21/79	11 (57.9)	100/0	63/37[c]	21/79	84/11/5[c]	0 (0)
ION-2									
LDV/SOF 12W	109	56 (7)	32/68	22 (20.2)	100/0	45/55	6/94	77/22/1[c]	0 (0)
LDV/SOF 24W	109	56 (8)	32/68	22 (20.2)	100/0	45/55	15/85	83/16/1[c]	2 (1.8)
Studies with the ACT PI + PEG + RBV									
Telaprevir + PEG + RBV									
ATTAIN									
TVR + PEG + RBV	384	50 (11)	42/58	75 (19.5)	100/0	100/0	13/87	95/4/1	61 (15.9)
REALIZE									
T12PR48[d]	121	50 (ND)	30/70	ND (36)	100/0	100/0	6/94	ND	ND

(continued)

Table 26: Characteristics of the study populations – RCT, further investigations: treatment-experienced CHC genotype 1 patients, LDV/SOF vs. PI + PEG + RBV (continued)

Study population group	N	Age [years] mean (SD)	Sex [F/M] %	Patients with cirrhosis n (%)	Genotype [1/unknown or other] %	Proportion non-responders/ relapsers %	Baseline viral load [< 800 000/ ≥ 800 000 IU/mL][a] %	Ethnicity [white/black/ other] %	Treatment discontin-uations n (%)
Boceprevir + PEG + RBV									
RESPOND-2									
BOC + PEG + RBV RGT[e]	162	53 (7)	40/60	17 (10.5)	100/0	35/65	9[c]/91	88/11/1[c]	52 (32.1)[c]
BOC + PEG + RBV fixed									
total study arm	162	52 (8)	30/70	22 (13.6)[c]	99/1	36/64	12/88	84/12/4[c]	55 (34.0)[c]
relevant subpopulation	22	ND	ND	22 (100)	ND	ND	ND	ND	ND
Flamm 2013									
BOC + PEG + RBV									
total study arm	134	52 (ND)	28/72	24 (18)	100/0	27/73	25/75	89/9/2	55 (41.0)[c]
relevant subpopulation	24	ND	ND	24 (100)	ND	ND	ND	ND	ND

a: Unless otherwise stated.
b: < 6 $\log_{10}$ IU/mL vs. ≥ 6 $\log_{10}$ IU/mL
c: Institute's calculation.
b: There were no data for the relevant subpopulation (null or partial responders + relapsers with cirrhosis, n = 149). Since the proportion of relapsers with cirrhosis (n = 28), for which no data were available, was < 20% of the relevant subpopulation, the characteristics for the null or partial responders are presented here.
e: The relevant subpopulation (patients without cirrhosis, n = 132) was > 80% of the total population; hence the total population is presented here (there was no information for the subpopulation).

BOC: boceprevir; CHC: chronic hepatitis C; F: female; IU: international units; LDV/SOF: ledipasvir/sofosbuvir; M: male; N: number of analysed patients; n: number of patients in the category; ND: no data; PEG: peginterferon alfa; PI: protease inhibitor; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; TVR: telaprevir; vs.: versus

Studies on ledipasvir/sofosbuvir

The studies ELECTRON (Part 6), LONESTAR, ION-2 and GS-US-337-0121 were included for ledipasvir/sofosbuvir. The ION-2 study was a pivotal, randomized, open-label phase 3 study for approval of ledipasvir/sofosbuvir. The studies ELECTRON (Part 6), LONESTAR and GS-US-337-0113 were randomized phase 2 and phase 3 studies.

ELECTRON (Part 6)

The ELECTRON study was a randomized, open-label phase 2a study, in which different treatment regimens with sofosbuvir as monotherapy or in combination with other drugs for the treatment of CHC genotype 1, 2 and 3 were investigated. In Part 6 of the study, sofosbuvir in fixed-dose combination with ledipasvir, with and without ribavirin, was investigated. Group 16, in which treatment-experienced genotype 1 patients were treated with LDV/SOF for 12 weeks, was relevant for research question 1c (treatment-experienced genotype 1 patients). The patients were not allowed to have responded to previous treatment with PI + PEG + RBV (null response) and had to have cirrhosis.

GS-US-337-0113 (Japan)

The GS-US-337-0113 study was a randomized, open-label phase 3b study, which was conducted in Japan. Both treatment-naive patients (groups 1 and 2) and treatment-experienced patients (groups 3 and 4) were included in the study. Approximately 40% of the patients could have cirrhosis. The patients were treated with LDV/SOF for 12 weeks (groups 1 and 3) or with LDV/SOF in combination with RBV (groups 2 and 4). Group 3, in which the patients were treated with LDV/SOF for 12 weeks, was relevant for research question 1c (treatment-experienced CHC genotype 1 patients). In this group, 28 of 88 patients (31.8%) had cirrhosis, 33% of the patients were non-responders, and 50% were relapsers; the remaining 17% were intolerant to interferon.

ION-2

Treatment-experienced adult CHC genotype 1 patients with and without cirrhosis were included in the ION-2 study. Approximately 20% of the patients could have cirrhosis; approximately half of the patients were required to not have responded to triple therapy (PI + PEG + RBV). The patients were treated with LDV/SOF or with LDV/SOF in combination with RBV for 12 or 24 weeks. The groups 1 and 3, in which the patients were treated with LDV/SOF for 12 or 24 weeks, were relevant for research question 1c (treatment-experienced CHC genotype 1 patients). In both groups, 22 of 109 patients (20.2%) had cirrhosis, 45% of the patients were non-responders, and 55% relapsers.

LONESTAR

Both treatment-naive patients (Cohort 1; no previous treatment with interferon, ribavirin or another treatment for chronic HCV infection) and treatment-experienced patients (Cohort 2; virologic failure on a PI + PEG + RBV regimen) were included in the LONESTAR study. Treatment-naive patients were not allowed to have cirrhosis; approximately half of the

treatment-experienced patients were allowed to have cirrhosis. The treatment-experienced patients in Cohort 2 were allocated to 12-week treatment with LDV/SOF or with LDV/SOF in combination with RBV. Group 4 (LDV/SOF 12 weeks) of Cohort 2 (treatment-experienced patients) was relevant for research question 1c (treatment-experienced CHC genotype 1 patients). In this group, 11 of 19 patients (57.9%) had cirrhosis, 63% of the patients were non-responders, and 37% relapsers.

Studies with the ACT (triple therapy)

ATTAIN

The ATTAIN study was a randomized, double-blind phase 3 study, in which treatment-experienced adult genotype 1 patients who had only partially responded or not responded to previous treatment with peginterferon alfa-2a and ribavirin (non-responders) were included. The patients were allocated either to treatment with simeprevir + PEG + RBV or to treatment with telaprevir + PEG + RBV. The study arm in which the patients received the 48-week approval-compliant treatment regimen with telaprevir + PEG + RBV was relevant for research question 1c (treatment-experienced CHC genotype 1 patients). All patients in this study arm were non-responders (of which 146 were partial responders, and 238 were null responders). 75 of 384 patients (19.5%) had cirrhosis.

REALIZE

The REALIZE study was a randomized, double-blind, placebo-controlled phase 3 study, in which treatment-experienced adult genotype 1 patients who had not responded to previous treatment with peginterferon and ribavirin were included. The patients were allocated to 2 different treatment regimens with telaprevir + PEG + RBV or with placebo + PEG + RBV. The study arm in which the patients received the 48-week fixed treatment regimen with telaprevir + PEG + RBV was relevant for research question 1c (treatment-experienced CHC genotype 1 patients). The relevant, approval-compliant subpopulation (n = 149, 56.0%) in this study arm comprised partial responders (n = 49), null responders (n = 72) and relapsed patients with cirrhosis (n = 28). Data on the outcomes were available for non-responders (partial and null responders, 121 patients). 36% of these patients had cirrhosis.

RESPOND-2

The RESPOND-2 study was a randomized, double-blind phase 3 study, in which treatment-experienced adult genotype 1 patients who had not responded to previous treatment with peginterferon alfa-2a or alfa-2b plus ribavirin were included. The patients were allocated to an RGT regimen and to a fixed treatment regimen with boceprevir + PEG + RBV or to 48-week treatment with placebo + PEG + RBV. Study arm 2, in which patients were treated with the approval-compliant RGT regimen of triple therapy with boceprevir + PEG + RBV, was relevant for research question 1c (treatment-experienced CHC genotype 1 patients). The relevant, approval-compliant subpopulation of this study arm was patients without cirrhosis (132 of 162 patients, 81.5%). Study arm 3, in which the patients were treated with a fixed treatment regimen with boceprevir + PEG + RBV, was also relevant. The relevant, approval-

compliant subpopulation of this study arm was patients with cirrhosis (22 of 162 patients, 13.6%).

Flamm 2013

The inclusion criteria of the Flamm 2013 study were identical to the ones of the RESPOND-2 study. The patients were allocated to a fixed treatment regimen with boceprevir + PEG + RBV or to 48-week treatment with placebo + PEG + RBV. The study arm in which the patients were treated with the fixed treatment regimen with boceprevir + PEG + RBV was relevant for research question 1c (treatment-experienced CHC genotype 1 patients). The relevant, approval-compliant subpopulation of this study arm was patients with cirrhosis (24 of 134 patients, 17.9%).

Pretreatment in the studies

The patients in the studies on ledipasvir/sofosbuvir and on the ACT differed regarding their pretreatment. In the studies on LDV/SOF, the majority of the patients were pretreated with triple therapy (PI + PEG + RBV); only in the LONESTAR study, 50% of the patients were allowed to have different pretreatment. The patients in the studies on the ACT, in contrast, had to have pretreatment with dual therapy (PEG + RBV).

Treatment duration/observation period in the studies

The requirements of the respective SPCs resulted in fixed treatment durations for the fixed-dose combination of ledipasvir/sofosbuvir and the triple therapies with telaprevir or boceprevir in combination with PEG + RBV. In the studies on ledipasvir/sofosbuvir, the patients were treated in compliance with the approval for 12 or 24 weeks. In the studies on the ACT, the patients were treated longer: 48 weeks with BOC + PEG + RBV and 24 weeks (early response in relapsed patients) or 48 weeks with TVR + PEG + RBV. AEs were followed-up in the studies for approximately 30 days. This resulted in different observation periods with a minimum difference of 0 weeks and a maximum difference of 36 weeks.

As a result, the effect estimations for AEs and mortality on the basis of naive proportions presented by the company represent no adequate analysis, and overall no conclusive interpretation of the data on these outcome categories could be conducted. This particularly applies to the comparison of 12-week treatment with ledipasvir/sofosbuvir with the ACT. Consequently, no effect estimations are presented for this, and they were also not used for the benefit assessment. Correspondingly, the difference in observation periods was smaller for the comparison of the 24-week treatment with ledipasvir/sofosbuvir with the ACT. The results were used under consideration of the increased uncertainty of the data situation, which was very uncertain anyway, by applying the criteria for a dramatic effect.

2.5.2 Results on added benefit (research question 1c)

2.5.2.1 Outcomes included

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.11.2.7.3 of the full dossier assessment):

- Mortality
  - deaths
- Morbidity
  - sustained virologic response 12 or 24 weeks after the end of treatment (SVR 12 or SVR 24) as sufficiently valid surrogate for the patient-relevant outcome “HCC”
- Health-related quality of life
- Adverse events
  - overall rate of SAEs
  - discontinuation due to AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.11.2.7.3 of the full dossier assessment).

Table 27 shows for which outcomes data were available in the studies included.

Table 27: Matrix of outcomes – RCT, further investigations: treatment-experienced CHC genotype 1 patients, LDV/SOF vs. PI + PEG + RBV

Comparison study	Outcomes						
	All-cause mortality	SVR 12	SVR 24	Health-related quality of life	AEs	SAEs	Discontinuation due to AEs
Studies with ledipasvir/sofosbuvir							
ELECTRON (Part 6)	Yes	Yes	No	No	Yes	Yes	Yes
GS-US-337-0113 (Japan)	Yes	Yes	No	No[a, b]	No[b]	No[b]	Yes
LONESTAR	Yes	Yes	No	No	Yes	Yes	Yes
ION-2	Yes	No	Yes	Yes[c]	Yes	Yes	Yes
Studies with the ACT PI + PEG + RBV							
Telaprevir + PEG + RBV							
ATTAIN	Yes	Yes	No	No[d]	Yes	Yes	Yes
REALIZE	Yes	No	Yes	No[d]	Yes	Yes	Yes
Boceprevir + PEG + RBV							
RESPOND-2	Yes	No	Yes	No[d]	Yes[e]	Yes[e]	Yes[e]
Flamm 2013	No[b]	No	Yes	No	No[b]	No[b]	No[b]

a: Measured with the SF-36.
b: No data for the relevant subpopulation.
c Measured with SF-36, CLDQ-HCV and FACIT-F.
d: No evaluable data.
e: No information for the relevant subpopulation with cirrhosis for Group 3.
AE: adverse event; CHC: chronic hepatitis C; CLDQ-HCV: Chronic Liver Disease Questionnaire-Hepatitis C; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; LDV/SOF: ledipasvir/sofosbuvir; PEG: peginterferon alfa; PI: protease inhibitor; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; 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

2.5.2.2 Results

The following tables (Table 28 and Table 29) summarize the results on the historical comparison of ledipasvir/sofosbuvir and triple therapy with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin in treatment-experienced CHC genotype 1 patients.

Table 30 and Table 31 present the results for the subgroups of treatment-experienced patients with and without cirrhosis as additional information. No evaluable data on mortality, AEs and health-related quality of life were available for these subgroups.

Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. Further explanations can be found in Section 2.11.2.7.3 of the full dossier assessment.

Table 28: Results for SVR (SVR 12 or SVR 24) – RCT, further investigations: treatment-experienced CHC genotype 1 patients, LDV/SOF vs. PI + PEG + RBV

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 12W vs. triple therapy	**226**	**215 (95.1) [70.0-100]**	**711**	**399 (56.1) [50.0-66.2]**	**1.70 [1.58; 1.82]; < 0.001**	**0.11 [0.06; 0.20]; < 0.001**
LDV/SOF 12W vs. **TVR** + RBV + PEG			533	285 (53.5) [50.3-54.7]	1.78 [1.63; 1.94]; < 0.001	0.10 [0.06; 0.19]; < 0.001
LDV/SOF 12W vs. **BOC** + RBV + PEG			178	114 (64.0) [50.0-66.2]	1.49 [1.33; 1.66]; < 0.001	0.14 [0.07; 0.25]; < 0.001
LDV/SOF 24W vs. triple therapy	**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**
LDV/SOF 24W vs. **TVR** + RBV + PEG			533	285 (53.5) [50.3-54.7]	1.85 [1.71; 2.01]; < 0.001	0.02 [0; 0.14]; < 0.001
LDV/SOF 24W vs. **BOC** + RBV + PEG			178	114 (64.0) [50.0-66.2]	1.55 [1.38; 1.73]; < 0.001	0.03 [0; 0.18]; < 0.001

a: Institute's calculation because the company's calculations were based on inadequate data (see also Section 2.11.2.7.3 of the full dossier assessment).
b: Institute's calculation, asymptotic.
c: p-value: Institute's calculation, unconditional exact test (CSZ method according to [3]).

BOC: boceprevir; CHC: chronic hepatitis C; 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; TVR: telaprevir; vs.: versus; W: weeks

Table 29: Results for mortality and AEs – RCT, further investigations: treatment-experienced CHC genotype 1 patients, LDV/SOF vs. PI + PEG + RBV

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 12W vs. triple therapy	**226**	**0 (0)** **[0-0]**	**717**	**4 (0.6)** **[0-0.8]**	NC
LDV/SOF 12W vs. **TVR** + RBV + PEG			533	3 (0.6) [0-0.8]	
LDV/SOF 12W vs. **BOC** + RBV + PEG			184	1 (0.1) [NA]	
LDV/SOF 24W vs. triple therapy	**109**	**0 (0)** **[NA]**	**717**	**4 (0.6)** **[0-0.8]**	NC
LDV/SOF 24W vs. **TVR** + RBV + PEG			533	3 (0.6) [0-0.8]	
LDV/SOF 24W vs. **BOC** + RBV + PEG			184	1 (0.1) [NA]	
AEs					
LDV/SOF 12W vs. triple therapy	**138**	**87 (63.0)** **[36.8-70.0]**	**689**	**679 (98.5)** **[98.3-98.9]**	NC
LDV/SOF 12W vs. **TVR** + RBV + PEG			505	497 (98.4) [98.3-98.4]	
LDV/SOF 12W vs. **BOC** + RBV + PEG			184	182 (98.9) [NA]	
LDV/SOF 24W vs. triple therapy	**109**	**88 (80.7)** **[NA]**	**689**	**679 (98.5)** **[98.3-98.9]**	NC
LDV/SOF 24W vs. **TVR** + RBV + PEG			505	497 (98.4) [98.3-98.4]	
LDV/SOF 24W vs. **BOC** + RBV + PEG			184	182 (98.9) [NA]	
SAEs					
LDV/SOF 12W vs. triple therapy	**138[d]**	**1 (0.7)** **[0-5.3]**	**689**	**86 (12.5)** **[8.3-14.1]**	NC
LDV/SOF 12W vs. **TVR** + RBV + PEG			505	64 (12.7) [8.3-14.1]	
LDV/SOF 12W vs. **BOC** + RBV + PEG			184	22 (12.0) [NA]	
LDV/SOF 24W vs. triple therapy	**109**	**6 (5.5)** **[NA]**	**689**	**86 (12.5)** **[8.3-14.1]**	**0.44 [0.20; 0.98]; 0.036**
LDV/SOF 24W vs. **TVR** + RBV + PEG			505	64 (12.7) [8.3-14.1]	0.43 [0.19; 0.98]; 0.033
LDV/SOF 24W vs. **BOC** + RBV + PEG			184	22 (12.0) [NA]	0.46 [0.19; 1.10]; 0.077

(continued)

Table 29: Results for mortality and AEs – RCT, further investigations: treatment-experienced CHC genotype 1 patients, LDV/SOF vs. PI + PEG + RBV (continued)

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]
Discontinuation due to AEs					
LDV/SOF 12W vs. triple therapy	**226**	**0 (0) [0-0]**	**689**	**45 (6.5) [5.5-9.2]**	NC
LDV/SOF 12W vs. **TVR** + RBV + PEG			505	28 (5.5) [5.5-5.8]	
LDV/SOF 12W vs. **BOC** + RBV + PEG			184	17 (9.2) [NA]	
LDV/SOF 24W vs. triple therapy	**109**	**0 (0) [NA]**	**689**	**45 (6.5) [5.5-9.2]**	**0.07 [0; 1.12]; 0.009[e]**
LDV/SOF 24W vs. **TVR** + RBV + PEG			505	28 (5.5) [5.5-5.8]	0.08 [0; 1.32]; 0.012[e]
LDV/SOF 24W vs. **BOC** + RBV + PEG			184	17 (9.2) [NA]	0.05 [0; 0.79]; 0.001

a: Institute's calculation because the company's calculations were based on inadequate data (see also Section 2.11.2.7.3 of the full dossier assessment).
b: Institute's calculation (asymptotic) because the company's calculations were based on inadequate data (see also Section 2.11.2.7.3 of the full dossier assessment). Effect estimates not presented for the comparison with LDV/SOF 12W because, overall, no conclusive interpretation of the outcome categories was possible due to the differences in observation periods in the 2 groups (more than twice as long in the comparator group).
c: Institute's calculation, unconditional exact test (CSZ method according to [3]).
d: In the GS-US-337-0113 study, no data were available for the relevant population (treatment-experienced patients). However, only 3 events occurred in the total study population so that this does not raise doubts about the overall result.
e: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
AE: adverse event; BOC: boceprevir; CHC: chronic hepatitis C; 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; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TVR: telaprevir; vs.: versus; W: weeks

Table 30: Results for SVR (SVR 12 or SVR 24), mortality, AEs and health-related quality of life – RCT, further investigations: treatment-experienced CHC genotype 1 patients with cirrhosis, LDV/SOF vs. PI + PEG + RBV

Outcome 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
SVR 12 or SVR 24						
LDV/SOF 12W vs. triple therapy	**71**	**64 (90.1) [70.0-100.0]**	**193**	**92 (47.7) [38.7-77.3]**	**1.89 [1.60; 2.23]; < 0.001**	**0.19 [0.09; 0.39]; < 0.001**
LDV/SOF 12W vs. **TVR** + RBV + PEG			147	63 (42.9) [38.7-47.2]	2.10 [1.72; 2.57]; < 0.001	0.17 [0.08; 0.35]; < 0.001
LDV/SOF 12W vs. **BOC** + RBV + PEG			46	29 (63.0) [50.0-77.3]	1.43 [1.13; 1.81]; < 0.001	0.27 [0.12; 0.59]; < 0.001
LDV/SOF 24W vs. triple therapy	**22**	**22 (100.0) [NA]**	**193**	**92 (47.7) [38.7-77.3]**	**2.10 [1.81; 2.43]; < 0.001**	**0.04 [0; 0.66]; < 0.001**
LDV/SOF 24W vs. **TVR** + RBV + PEG			147	63 (42.9) [38.7-47.2]	2.33 [1.94; 2.81]; < 0.001	0.04 [0; 0.60]; < 0.001
LDV/SOF 24W vs. **BOC** + RBV + PEG			46	29 (63.0) [50.0-77.3]	1.59 [1.27; 1.98]; < 0.001	0.06 [0; 0.94]; < 0.001
Mortality	No evaluable data[d]					
Adverse events						
AEs	No evaluable data[d]					
SAEs	No evaluable data[d]					
Discontinuation due to AEs	No evaluable data[d]					
Health-related quality of life	No evaluable data[e]					

a: Institute's calculation because the company's calculations were based on inadequate data (see also Section 2.11.2.7.3 of the full dossier assessment).
b: Institute's calculation, asymptotic.
c: p-value: Institute's calculation, unconditional exact test (CSZ method according to [3])
d: The company presented no separate analyses according to cirrhosis status in its dossier.
e: No evaluable data for the studies with the ACT available.

AE: adverse event; BOC: boceprevir; CHC: chronic hepatitis C; 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; SAE: serious adverse event; SVR 12: sustained virologic response 12 weeks after the end of treatment; SVR 24: sustained virologic response 24 weeks after the end of treatment; TVR: telaprevir; vs.: versus; W: weeks

Table 31: Results for SVR (SVR 12 or SVR 24), mortality, AEs and health-related quality of life – RCT, further investigations: treatment-experienced CHC genotype 1 patients without cirrhosis, LDV/SOF vs. PI + PEG + RBV

Outcome comparison	LDV/SOF		PI + PEG + RBV		LDV/SOF vs. PI + PEG + RBV	
	N	Patients with events n (%) [min-max]	N	Patients with events n (%) [min-max]	RR [95% CI]; p-value[a]	
					Responders	Non-responders
SVR 12 or SVR 24						
LDV/SOF 12W vs. triple therapy	**155**[b]	**151 (97.4)**[b] **[95.4-100]**	**518**	**307 (59.3) [53.2-58.6]**	**1.64 [1.52; 1.77]**[c]**; < 0.001**	**0.06 [0.02; 0.17]**[c]**; < 0.001**
LDV/SOF 12W vs. **TVR** + RBV + PEG			386	222 (57.5) [53.2-58.6]	1.51 [1.33; 1.72][c]; < 0.001	0.07 [0.03; 0.20][c]; < 0.001
LDV/SOF 12W vs. **BOC** + RBV + PEG			132	85 (64.4) [NA]	1.69 [1.55; 1.85][c]; < 0.001	0.06 [0.02; 0.16][c]; < 0.001
LDV/SOF 24W vs. triple therapy	**86**	**85 (98.8) [NA]**	**518**	**307 (59.3) [NA]**	**1.67 [1.55; 1.8]; < 0.001**	**0.03 [ND]; < 0.001**
LDV/SOF 24W vs. **TVR** + RBV + PEG			386	222 (57.5) [NA]	1.72 [1.57; 1.88]; < 0.001	0.03 [ND]; < 0.001
LDV/SOF 24W vs. **BOC** + RBV + PEG			132	85 (64.4) [53.2-58.6]	1.53 [1.35; 1.75]; < 0.001	0.03 [ND]; < 0.001
Mortality	No evaluable data[d]					
Adverse events						
AEs	No evaluable data[d]					
SAEs	No evaluable data[d]					
Discontinuation due to AEs	No evaluable data[d]					
Health-related quality of life	No evaluable data[e]					

a: p-value: Institute's calculation, unconditional exact test (CSZ method according to [3])
b: Institute's calculation because the company's calculations were based on inadequate data (see also Section 2.11.2.7.3 of the full dossier assessment).
c: Institute's calculation, asymptotic.
d: The company presented no separate analyses according to cirrhosis status in its dossier.
e: No evaluable data for the studies with the ACT available.

AE: adverse event; BOC: boceprevir; CHC: chronic hepatitis C; 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; SAE: serious adverse event; SVR 12: sustained virologic response 12 weeks after the end of treatment; SVR 24: sustained virologic response 24 weeks after the end of treatment; TVR: telaprevir; vs.: versus; W: weeks

Morbidity

SVR as sufficiently valid surrogate for the patient-relevant outcome "HCC"

The proportion of patients with SVR after 24 weeks of treatment with ledipasvir/sofosbuvir was considerably larger than after 24 to 48-week treatment (RGT regimen) with triple therapy

with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin. The proportion of patients with SVR was nearly 100% under treatment with ledipasvir/sofosbuvir. Overall, the effect can be regarded as dramatic (see Section 2.11.2.2 of the full dossier assessment) and could be observed in comparison with both treatment regimens (triple therapy with TVR or BOC). There was a dramatic effect in comparison with the ACT also in a treatment duration of 12 weeks with ledipasvir/sofosbuvir, but the proportion of patients with SVR (95.1%) was not as high in this treatment duration as in a treatment duration of 24 weeks with ledipasvir/sofosbuvir.

A comparable effect in SVR could also be observed in the subgroups of patients with or without cirrhosis after 24 weeks of treatment with ledipasvir/sofosbuvir. After 12 weeks of treatment, as in the total population, a dramatic effect was also notable in patients without cirrhosis; the proportion of patients with SVR was not as high, however. In the subgroup of patients with cirrhosis, in contrast, there was no dramatic effect after 12 weeks of treatment.

Overall, there was a hint of an added benefit of ledipasvir/sofosbuvir versus the ACT with triple therapy with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin for the outcome “SVR”.

This deviates from the company’s assessment, which derived an indication of added benefit for the outcome “SVR”.

Mortality and adverse events

Overall, no conclusive interpretation of the data on mortality and AEs of ledipasvir/sofosbuvir after 12 weeks of treatment in comparison with the ACT was possible due to the large differences in observation periods.

For the comparison of ledipasvir/sofosbuvir after 24 weeks of treatment with the ACT, the data for these outcomes could be used under consideration of an increased uncertainty in the presence of dramatic effects. In SAEs, the difference between the treatments was statistically significant at a level of 5% in favour of ledipasvir/sofosbuvir, but could not be classified as a dramatic effect. For the outcome “discontinuation due to AEs”, the operationalization of the outcome was partly unclear in the studies on the ACT (discontinuation of 1, 2 or all drugs). In the overall consideration of the results on mortality and AEs, there was no sign of greater harm from ledipasvir/sofosbuvir, however.

The assessment of the outcomes on mortality and AEs deviates from that of the company, which derived a hint of an added benefit for SAEs and an indication of an added benefit for discontinuations due to AEs.

Health-related quality of life

The company’s dossier contained no evaluable data on health-related quality of life in comparison with the ACT.

2.5.2.3 Subgroups and other effect modifiers

There were no subgroup analyses on the comparison of ledipasvir/sofosbuvir with the ACT.

2.5.3 Extent and probability of added benefit (research question 1c)

The derivation of extent and probability of added benefit is presented below using the positive and negative effects from the assessment.

The approach for deriving an overall conclusion on added benefit based on the aggregation of the positive and negative effects from the assessment is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.3.1 Overall conclusion on added benefit

Table 32 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 32: Positive and negative effects from the assessment of LDV/SOF in comparison with PI + PEG + RBV (treatment-experienced CHC genotype 1 patients)

Positive effects	**Negative effects**
Hint of added benefit – extent: "non-quantifiable" (outcome category: serious late complications: HCC, assessed with the surrogate SVR)	
No conclusive interpretation of the data on AEs and mortality was possible, but there was no sign of greater harm from LDV/SOF.	
AE: adverse event; CHC: chronic hepatitis C; HCC: hepatocellular carcinoma; LDV/SOF: ledipasvir/sofosbuvir; PEG: peginterferon alfa; PI: protease inhibitor; RBV: ribavirin; SVR: sustained virologic response	

On the positive side, there is an added benefit with the extent "non-quantifiable" in the category "serious late complications". Overall, no conclusive interpretation of the outcomes on mortality and AEs was possible due to the differences in observation periods and to the partially unclear operationalization of the outcome "discontinuation due to AEs". However, the observed events on mortality and AEs provided no sign that treatment with ledipasvir/sofosbuvir leads to greater harm than the comparator therapy.

In summary, there is a hint of a non-quantifiable added benefit of ledipasvir/sofosbuvir versus the ACT with triple therapy with a protease inhibitor (boceprevir or telaprevir), peginterferon and ribavirin for treatment-experienced CHC genotype 1 patients.

This deviates from the company's approach, which derived an indication of major added benefit.

2.5.4 List of included studies (research question 1c)

ATTAIN

Janssen R&D Ireland. A phase III, randomized, double-blind trial to evaluate the efficacy, safety and tolerability of TMC435 vs. telaprevir, both in combination with PegIFNalpha-2a and ribavirin, in chronic hepatitis C genotype-1 infected subjects who were null or partial responders to prior PegIFNalpha and ribavirin therapy [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 2 October 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Janssen R&D Ireland. A phase III, randomized, double-blind trial to evaluate the efficacy, safety and tolerability of TMC435 vs. telaprevir, both in combination with PegIFNα-2a and ribavirin, in chronic hepatitis C genotype-1 infected subjects who were null or partial responders to prior PegIFNα and ribavirin therapy [online]. In: EU Clinical Trials Register. [Accessed: 26 September 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=TMC435HPC3001.

Janssen R&D Ireland. TMC435HPC3001: an efficacy, safety and tolerability study for TMC435 vs telaprevir in combination with PegINFα-2a and ribavirin in chronic hepatitis C patients who were null or partial responders to prior PegINFα-2a and ribavirin therapy (ATTAIN); tabular view [online]. In: ClinicalTrials.gov. 12 May 2014 [accessed: 26 September 2014]. URL: https://www.clinicaltrials.gov/ct2/show/NCT01485991.

Reddy KR, Zeuzem S, Zoulim F, Weiland O, Horban A, Stanciu C et al. A phase III randomised, double-blind study to evaluate the efficacy, safety and tolerability of simeprevir vs telaprevir in combination with pegylated interferon and ribavirin in chronic hepatitis C virus genotype 1 treatment-experienced patients: the ATTAIN study [online]. In: 24th Conference of the Asian Pacific Association for the Study of the Liver; 12-15 March 2014; Brisbane, Australien. [Accessed: 30 January 2015]. URL: http://www.natap.org/2014/APASL/APASL_20.htm.

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Simeprevir: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A14-18 [online]. 28 August 2014 [accessed: 17 September 2014]. (IQWiG-Berichte; Volume 239). URL: https://www.iqwig.de/download/A14-18_Simeprevir_Nutzenbewertung-35a-SGB-V.pdf.

ELECTRON

Gilead. A multi-center, open-labeled exploratory study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics following oral administration of PSI-7977 400 mg and ribavirin for 12 weeks with and without pegylated interferon in treatment-naïve patients with chronic HCV infection genotype 2 or genotype 3: study P7977-0523 (ELECTRON); second interim clinical study report [unpublished]. 2013.

Gilead. A multi-center, open-labeled exploratory study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics following oral administration of PSI-7977 400 mg and ribavirin for 12 weeks with and without pegylated interferon in treatment-naïve patients with chronic HCV infection genotype 2 or genotype 3: study P7977-0523 (ELECTRON); final synoptic clinical study report [unpublished]. 2014.

Gilead. A multi-center, open-labeled exploratory study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics following oral administration of PSI-7977 400 mg and ribavirin for 12 weeks with and without pegylated interferon in treatment-naïve patients with chronic HCV infection genotype 2 or genotype 3: study P7977-0523; statistical analysis plan [unpublished]. 2013.

Gilead. A multi-center, open-labeled exploratory study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics following oral administration of PSI-7977 400 mg and ribavirin for 12 weeks with and without pegylated interferon in treatment-naïve patients with chronic HCV infection genotype 2 or genotype 3: study P7977-0523; clinical study protocol [unpublished]. 2012.

Gilead Sciences. Open-labeled study of PSI-7977 and RBV with and without peg-ifn in treatment-naïve patients with HCV GT2 or GT3: tabular view [online]. In: ClinicalTrials.gov. 28 May 2014 [accessed: 6 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/NCT01260350.

Flamm 2013

Flamm SL, Lawitz E, Jacobson I, Bourliere M, Hezode C, Vierling JM et al. Boceprevir with peginterferon alfa-2a-ribavirin is effective for previously treated chronic hepatitis C genotype 1 infection. Clin Gastroenterol Hepatol 2012; 11(1): 81-87.e4.

Merck Sharp & Dohme. Boceprevir in combination with peginterferon alfa-2a and ribavirin in participants with chronic hepatitis C genotype 1 who failed prior treatment with peginterferon/ribavirin (study P05685AM2) (COMPLETED): tabular view [online]. In: ClinicalTrials.gov. 29 April 2014 [accessed: 2 October 2014]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00845065.

Merck Sharp & Dohme. Boceprevir in combination with peginterferon alfa-2a and ribavirin in participants with chronic hepatitis C genotype 1 who failed prior treatment with peginterferon/ribavirin (Study P05685AM2)(COMPLETED): study results [online]. In: ClinicalTrials.gov. 31 October 2014. URL: https://clinicaltrials.gov/ct2/show/results/NCT00845065.

Schering Plough Research Institute. A phase 3 safety and efficacy study of boceprevir in combination with peginterferon alfa-2a and ribavirin in subjects with chronic hepatitis C genotype 1 who failed prior treatment with peginterferon/ribavirin [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 2 October 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Schering Plough Research Institute. A phase 3 safety and efficacy study of boceprevir in combination with peginterferon alfa-2a and ribavirin in subjects with chronic hepatitis C genotype 1 who failed prior treatment with peginterferon/ribavirin [online]. In: EU Clinical Trials Register. [Accessed: 2 October 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=P05685.

Vierling JM, Zeuzem S, Poordad F, Bronowicki JP, Manns MP, Bacon BR et al. Safety and efficacy of boceprevir/peginterferon/ribavirin for HCV G1 compensated cirrhotics: meta-analysis of 5 trials. J Hepatol 2014; 61(2): 200-209.

Vierling JM, Zeuzem S, Poordad F, Bronowicki JP, Manns MP, Bacon BR et al. Supplementary data for "Safety and efficacy of boceprevir/peginterferon/ribavirin for HCV G1 compensated cirrhotics: meta-analysis of 5 trials (J Hepatol 2014; 61(2): 200-209)" [online]. 2014. URL: http://www.journal-of-hepatology.eu/article/S0168-8278(14)00203-7/addons.

GS-US-337-0113 (Japan)

Gilead. A phase 3b, randomized, multicenter, open-label study to investigate the efficacy and safety of ledipasvir/sofosbuvir fixed-dose combination ± ribavirin in treatment-naïve and treatment-experienced Japanese subjects with chronic genotype 1 HCV infection: study GS-US-337-0113; version 2.0; statistical analysis plan [unpublished]. 2014.

Gilead. A phase 3b, randomized, multicenter, open-label study to investigate the efficacy and safety of ledipasvir/sofosbuvir fixed-dose combination ± ribavirin in treatment-naïve and treatment-experienced Japanese subjects with chronic genotype 1 HCV infection. GS-US-337-0113; interim clinical study report [unpublished]. 2014.

Gilead. A phase 3b, randomized, multicenter, open-label study to investigate the efficacy and safety of ledipasvir/sofosbuvir fixed-dose combination ± ribavirin in treatment-naïve and treatment-experienced Japanese subjects with chronic genotype 1 HCV infection: study GS-US-337-0113; clinical study protocol [unpublished]. 2013.

Gilead Sciences. Efficacy and safety of sofosbuvir/ledipasvir ± ribavirin in Japanese participants with chronic genotype 1 HCV infection [online]. In: ClinicalTrials.gov. 16 April 2014 [accessed: 24 September 2014]. URL: http://www.clinicaltrials.gov/ct2/show/study/NCT01975675.

ION-2

Gilead. A phase 3, multicenter, randomized, open-label study to investigate the efficacy and safety of sofosbuvir/gs-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-experienced subjects with chronic genotype 1 HCV infection: study GS-US-337-0109 (ION-2); interim clinical study report [unpublished]. 2014.

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2.6 Research question 1d: CHC genotype 1, patients with HIV coinfection

2.6.1 Information retrieval and study pool (research question 1d)

2.6.1.1 Treatment-naive patients

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 ledipasvir/sofosbuvir (studies completed up to 6 November 2014)
- bibliographical literature search on ledipasvir/sofosbuvir (last search on 5 September 2014)
- search in trial registries for studies on ledipasvir/sofosbuvir (last search on 2 October 2014)
- bibliographical literature search on the ACT (last search on 22 September 2014)
- search in trial registries for studies on the ACT (last search on 2 October 2014)

To check the completeness of the study pool:

- bibliographical literature search on ledipasvir/sofosbuvir (last search on 12 December 2014)
- search in trial registries for studies on ledipasvir/sofosbuvir (last search on 12 December 2014)
- simplified search on whether a relevant amount of data from one-arm studies was not considered by the company in the unadjusted indirect comparisons (last search on 22 January 2015)

Direct comparison

There were no direct comparative studies of ledipasvir/sofosbuvir versus the ACT for treatment-naive CHC genotype 1 patients with HIV coinfection.

Historical comparison

The historical comparison of ledipasvir/sofosbuvir versus the ACT presented by the company was incomplete with regard to content and therefore unsuitable for the benefit assessment (see Section 2.11.2.1 of the full dossier assessment).

The company itself presented the data on the ACT only as an example.

2.6.1.2 Treatment-experienced patients

The company presented no data for treatment-experienced patients with HIV coinfection.

2.6.2 Results on added benefit (research question 1d)

No adequate data were available for assessing the added benefit of ledipasvir/sofosbuvir for CHC genotype 1 patients with HIV coinfection. The added benefit of ledipasvir/sofosbuvir versus the ACT is therefore not proven for CHC genotype 1 patients with HIV coinfection.

2.6.3 Extent and probability of added benefit (research question 1d)

No proof of added benefit of ledipasvir/sofosbuvir versus the ACT specified by the G-BA could be derived for treatment-naive or treatment-experienced CHC genotype 1 patients with HIV coinfection from the available data. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

In contrast, the company derived a hint of major added benefit for treatment-naive CHC genotype 1 patients with HIV coinfection.

2.7 Research question 2: CHC genotype 1/4, patients with decompensated cirrhosis

2.7.1 Information retrieval and study pool (research question 2)

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 ledipasvir/sofosbuvir (studies completed up to 6 November 2014)
- bibliographical literature search on ledipasvir/sofosbuvir (last search on 5 September 2014)
- search in trial registries for studies on ledipasvir/sofosbuvir (last search on 2 October 2014)

To check the completeness of the study pool:

- bibliographical literature search on ledipasvir/sofosbuvir (last search on 12 December 2014)
- search in trial registries for studies on ledipasvir/sofosbuvir (last search on 12 December 2014)

The company identified neither direct comparative studies nor studies for an indirect comparison for research question 2. No relevant direct comparative studies were identified from the check of completeness either.

The company only presented non-comparative data from the SOLAR-1 study [4] for research question 2. The information presented by the company was unsuitable for assessing the added benefit of LDV/SOF for research question 2.

On the one hand, the SOLAR-1 study itself was not evaluable on the basis of the documents presented by the company. The company used 2 presentations on the study results for the reporting of results. These allowed no adequate assessment of the SOLAR-1 study, however. Moreover, the results partly deviated from the draft of a CSR presented in Module 5. This draft, however, also did not contain all information relevant for the assessment; references were leading nowhere (apparently due to the draft status of the CSR).

On the other hand, the company conducted no comparison with the ACT “no antiviral therapy” it had chosen. This was of less relevance for the assessment of the outcome “SVR” because even sporadic spontaneous remissions in patients with decompensated cirrhosis of the liver would probably not raise doubts about the overall result: In an analysis of all missing values as non-responders, the SVR rate in the relevant study arms (patients with decompensated cirrhosis of the liver, Child-Pugh-Turcotte classification B or C) was between approximately 57% (post-transplantation) and approximately 76% (pre-transplantation). However, it is not possible to assess the harm of LDV/SOF without systematically processing

the evidence on the ACT "no antiviral therapy" because not only the AEs of the treatment, but also disease-related complications can be recorded when recording AEs. In the relevant study arms, SAEs occurred in approximately 42% of the patients, which would raise doubts about the potentially positive result of LDV/SOF in SVR in an overall balancing of the benefit and harms.

It should be noted as additional information that almost exclusively genotype 1 patients were included in the SOLAR-1 study. Only 1 patient with genotype 4 was treated in the study arms of interest. Irrespective of the aspects mentioned above, no conclusions on genotype 4 patients can therefore be drawn based on the SOLAR-1 study.

2.7.2 Results on added benefit (research question 2)

No data were available for assessing the added benefit of ledipasvir/sofosbuvir versus the ACT chosen by the company for CHC genotype 1 or 4 patients with decompensated cirrhosis. Hence the added benefit of ledipasvir/sofosbuvir versus the ACT "no antiviral therapy" chosen by the company is not proven for CHC genotype 1 or 4 patients with decompensated cirrhosis.

2.7.3 Extent and probability of added benefit (research question 2)

No proof of added benefit of ledipasvir/sofosbuvir versus the comparator therapy chosen by the company could be derived for CHC genotype 1 or 4 patients with decompensated cirrhosis from the available data. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

In contrast, the company derived an indication of major added benefit for this research question based on the non-comparative data for CHC genotype 1 or 4 patients with decompensated cirrhosis.

2.8 Research question 3: CHC genotype 3

2.8.1 Information retrieval and study pool (research question 3)

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 ledipasvir/sofosbuvir (studies completed up to 6 November 2014)
- bibliographical literature search on ledipasvir/sofosbuvir (last search on 5 September 2014)
- search in trial registries for studies on ledipasvir/sofosbuvir (last search on 2 October 2014)

To check the completeness of the study pool:

- bibliographical literature search on ledipasvir/sofosbuvir (last search on 12 December 2014)
- search in trial registries for studies on ledipasvir/sofosbuvir (last search on 12 December 2014)

The company identified neither direct comparative studies nor studies for an indirect comparison for research question 3. No relevant direct comparative studies were identified from the check of completeness either.

The company only presented non-comparative data from the ELECTRON-2 study [5] for treatment-naive CHC genotype 3 patients with cirrhosis. There was no comparison with the evidence on the ACT and, furthermore, the treatment with LDV/SOF + RBV in the ELECTRON-2 study was not in compliance with the approval.

2.8.2 Results on added benefit (research question 3)

No data were available for assessing the added benefit of ledipasvir/sofosbuvir for CHC genotype 3 patients. The added benefit of ledipasvir/sofosbuvir versus the ACT is therefore not proven for CHC genotype 3 patients.

2.8.3 Extent and probability of added benefit (research question 3)

No proof of added benefit of ledipasvir/sofosbuvir versus the ACT specified by the G-BA could be derived for CHC genotype 3 patients from the available data. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

In contrast, the company assumed a hint of a non-quantifiable added benefit based on the non-comparative data for treatment-naive genotype 3 patients with cirrhosis for this research question.

2.9 Research question 4: CHC genotype 4

The company did not investigate research question 4 on CHC genotype 4 patients.

2.9.1 Results on added benefit (research question 4)

There were no analyses on research question 4. The added benefit of ledipasvir/sofosbuvir versus the ACT is therefore not proven for CHC genotype 4 patients.

2.9.2 Extent and probability of added benefit (research question 4)

Since no data were available, no proof of added benefit of ledipasvir/sofosbuvir versus the ACT specified by the G-BA could be derived for CHC genotype 4 patients. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

The company derived no added benefit for this research question.

2.10 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of ledipasvir/sofosbuvir in comparison with the ACT is summarized in Table 33.

Table 33: Ledipasvir/sofosbuvir – extent and probability of added benefit

Research question	Patient group with CHC	ACT[a]	Extent and probability of added benefit
1a	Genotype 1, treatment-naive patients without cirrhosis	PEG + RBV or[b] **BOC + PEG + RBV** or **TVR + PEG + RBV**	Hint of non-quantifiable added benefit
1b	Genotype 1, treatment-naive patients with cirrhosis	PEG + RBV	Added benefit not proven
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	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
3	Genotype 3	PEG + RBV	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.
ACT: appropriate comparator therapy; BOC: boceprevir; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus; PEG: peginterferon alfa; RBV: ribavirin; SPC: Summary of Product Characteristics; TVR: telaprevir

The G-BA decides on the added benefit.

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