IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A14-18

Simeprevir – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.8 of the dossier assessment *Simeprevir – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 August 2014). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Simeprevir – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
22 May 2014

Internal Commission No.:
A14-18

Address of publisher:
Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Christoph F. Dietrich, Caritas Hospital Bad Mergentheim, Bad Mergentheim, Germany

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

IQWiG employees involved in the dossier assessment[2]:

- Michael Köhler
- Andreas Gerber-Grote
- Wolfram Groß
- Tatjana Hermanns
- Marco Jost
- Michaela Florina Kerekes
- Stefanie Reken
- Christoph Schürmann
- Astrid Seidl
- Beate Wieseler
- Min Zhou

Keywords: simeprevir, hepatitis c, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables[3]

Page

[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AUC	area under the curve
CES-D	Centre for Epidemiologic Studies Depression Scale
CHC	chronic hepatitis C
CI	confidence interval
CSR	clinical study report
EQ-5D	European Quality of Life-5 Dimensions
FSS	Fatigue Severity Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PEG	pegylated interferon alpha (2a or 2b)
PLC	placebo
PT	Preferred Term
RBV	ribavirin
RCT	randomized controlled trial
RNA	ribonucleic acid
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SIM	simeprevir
SOC	System Organ Class
SPC	Summary of Product Characteristics
SVR	sustained virologic response
TVR	telaprevir
VAS	visual analogue scale
WPAI	Work Productivity and Activity Impairment Questionnaire

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 simeprevir. 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 22 May 2014.

Research question

The aim of this report was to assess the added benefit of simeprevir (SIM) in adult patients with chronic hepatitis C (CHC) infection.

The company followed the G-BA's appropriate comparator therapy (ACT), but specified it by stipulating triple therapy consisting of telaprevir, peginterferon alfa and ribavirin (TVR + PEG + RBV) as ACT for previous non-responders with genotype 1. For all other patient groups, the ACT was dual therapy consisting of peginterferon alfa and ribavirin (PEG + RBV).

Table 2 shows the research questions of the present benefit assessment.

Table 2: Research questions of the benefit assessment of simeprevir

Research question	Therapeutic indication CHC	ACT[a]
1a	Genotype 1, treatment-naive	Dual therapy (combination of peginterferon alfa and ribavirin)
1b	Genotype 1, relapsed patients	Dual therapy (combination of peginterferon alfa and ribavirin)
1c	Genotype 1 previous non-responders including partial and null responders	Triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon alfa and ribavirin)
1d	Genotype 1 with HIV coinfection	Dual therapy (combination of peginterferon alfa and ribavirin)
2	Genotype 4	Dual therapy (combination of peginterferon alfa and ribavirin)
a: Designation of the G-BA's ACT or of the option chosen by the company. ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus		

This deviates from the presentation in the dossier, where treatment-naive patients and relapsed patients were summarized in one research question.

Moreover, the company presented a study on the interferon-free simeprevir treatment option as additional information. According to the separate commission from 27 May 2014, the evidence provided for this study was considered and presented.

The assessment was based on patient-relevant outcomes. Direct comparative randomized controlled trials (RCTs) were included in the assessment.

Results

Research question 1a: CHC genotype 1, treatment-naive patients

The studies PILLAR, QUEST-1 and QUEST-2 were included in the assessment of research question 1a.

Study characteristics

The studies PILLAR, QUEST-1 and QUEST-2 were double-blind RCTs and had been completed at the time of the commission. Treatment-naive patients with CHC genotype 1 were included in each of the studies. Only patients without cirrhosis were included in the PILLAR study, whereas the patient population in both QUEST studies comprised patients with or without cirrhosis. The patients of all 3 studies received either simeprevir or placebo in combination with peginterferon alfa and ribavirin. Simeprevir was administered at a dosage of 150 mg/day for 12 weeks. Out of the 4 SIM + PEG + RBV arms in total of the PILLAR study, only the combination with 150 mg simeprevir, administered over a period of 12 weeks, was relevant for the benefit assessment. There were 2 study arms each in the QUEST-1 and QUEST-2 phase 3 studies.

In all 3 studies, a response-guided treatment regimen was planned in the SIM + PEG + RBV arms, i.e. the treatment was to be reduced from principally planned 48 weeks to 24 weeks when prespecified criteria regarding virologic response were met. Except for negligible deviations, this applied to the patients of the SIM + PEG + RBV arms of all 3 studies. A treatment duration of 24 weeks for treatment-naive patients concurs with the approval. In contrast, 48-week treatment for all patients independent from virologic response was planned for the control arms of all 3 studies, which concurs with the approvals for peginterferon alfa and ribavirin.

Moreover, in both treatment groups in all 3 studies, treatment discontinuation was planned in case of inadequate virologic response. In the study protocols, specific threshold values based on the viral load of the patients were defined for several time points in the course of the study. If these were exceeded, treatment was to be discontinued (time-point specific either only simeprevir or placebo or the total study medication). The total observation period in all 3 studies was 72 weeks, independent from the individual treatment period of a patient.

Risk of bias and certainty of conclusions

The risk of bias at study level was rated as low for all 3 studies. However, reduced certainty of conclusions was assumed for individual outcomes because within the studies the frequency

at which dual therapy was discontinued differed considerably in the study arms. These premature treatment discontinuations particularly occurred in the placebo (PLC) + PEG + RBV arms, which resulted in shorter treatment durations in these patients than recommended by the approval. Moreover, in the SIM + PEG + RBV arms of all 3 studies, up to 14% of the patients were treated longer than recommended by the approval, which was caused by criteria for treatment discontinuation that deviated from the information in the Summary of Product Characteristics (SPC) and package information leaflet. The certainty of conclusions is therefore reduced for the following outcomes: sustained virologic response 24 weeks after the end of treatment (SVR 24), fatigue (measured with the Fatigue Severity Scale [FSS]), depression (measured with the Centre for Epidemiologic Studies Depression Scale [CES-D]) and health status (measured with the European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]). As a consequence, no more than "indications" of added benefit can be derived for these outcomes.

As in the PLC + PEG + RBV arms of the studies, treatment was discontinued prematurely in up to 28% of the patients, and particularly considerably more often than in the SIM + PEG + RBV arms (the difference was up to 25 percentage points), this probably affects the effects on adverse events to the disadvantage of SIM + PEG + RBV. A bias caused by the fact that up to 14% of the patients were treated longer in the SIM arms than is recommended by the approval can have an effect in the same direction. Hence in case of lesser harm from SIM + PEG + RBV, the certainty of conclusions of the studies for these outcomes can be regarded as high (including the ones of the highly biased QUEST-2 study). The derivation of proof of lesser harm from SIM + PEG + RBV is possible because of this.

Results

Mortality

As only in the QUEST-2 study 2 deaths occurred at all, an added benefit of SIM + PEG + RBV in comparison with PEG + RBV in treatment-naive patients with CHC genotype 1 is not proven with regard to mortality.

Morbidity – sustained virologic response 24 weeks after the end of treatment

SVR was included as sufficiently valid surrogate for the outcome "hepatocellular carcinoma (HCC)". Because of the heterogeneity of the results it was not reasonable to summarize the data on the outcome "SVR 24" in a meta-analysis. However, all 3 studies included showed statistically significant results for SVR 24 in favour of SIM + PEG + RBV.

In addition, there was proof of an effect modification for the SVR 24 by the characteristic "IL28B genotype" and an indication of an effect modification by the characteristic "Q80K polymorphism". With regard to SVR 24, this results in an indication of an added benefit of SIM + PEG + RBV for patients with IL28B genotypes CT or TT. For patients with the IL28B genotypes CC, an added benefit for SVR 24 is not proven. There is an indication of an added

benefit for SVR 24 for patients without Q80K polymorphism, and a hint of an added benefit for patients with Q80K polymorphism.

Morbidity – depression using the CES-D

The CES-D was not recorded in the PILLAR study. The meta-analysis of the results of QUEST-1 and QUEST-2 resulted in a statistically significant advantage in favour of SIM + PEG + RBV.

There was an indication of an effect modification by the characteristic "genotype (1a or 1b)" and proof of an effect modification by the characteristic "Q80K polymorphism". However, in none of the subgroups, there was a statistically significant and not potentially irrelevant effect. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV is therefore not proven.

Morbidity – fatigue using the FSS

The meta-analysis of all 3 studies on the outcome "fatigue" resulted in a statistically significant advantage in favour of SIM + PEG + RBV.

There were indications of an effect modification by the characteristics "METAVIR fibrosis score" and "Q80K polymorphism" for this outcome. This results in a hint of an added benefit for patients with a METAVIR score F0-F2, and for patients without Q80K polymorphism in a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV with regard to the outcome "fatigue". For the other subgroups, an added benefit is not proven.

Morbidity – health status using the EQ-5D VAS

No effect estimates on health status were available for the PILLAR study. The meta-analysis of the results of QUEST-1 and QUEST-2 resulted in a statistically significant advantage in favour of SIM + PEG + RBV.

For this outcome, there was proof of an effect modification by the characteristics "age", "genotype (1a or 1b)" and "Q80K polymorphism". This results in an indication of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for patients aged 45 years or younger and for patients without Q80K polymorphism. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV is not proven for older patients and for patients with Q80K polymorphism as well as for the subgroups "genotype 1a and 1b".

Health-related quality of life

There were no evaluable data on health-related quality of life.

Adverse events

The results of the outcomes "serious adverse events (SAEs)" and "discontinuation due to adverse events (AEs)" could each be summarized in meta-analyses. There was no statistically significant difference between the treatment arms in any of the 2 outcomes.

There was an indication of an effect modification by the characteristic "METAVIR fibrosis score" for the outcome "SAEs". This results in an indication of lesser harm from SIM + PEG + RBV in comparison with PEG + RBV for patients with a METAVIR score F3 to F4. For patients with a METAVIR score F0-F2, greater or lesser harm from SIM + PEG + RBV is not proven.

There were no 72-week data from the PILLAR study for the outcomes "pruritus" and "rash". Because of the heterogeneity of the results, in both cases, it was not reasonable to calculate a common effect estimate from the studies QUEST-1 and QUEST-2.

The QUEST-1 study showed a statistically significant difference in favour of the comparator therapy PLC + PEG + RBV for the outcome "pruritus". In the QUEST-2 study, there was no statistically significant difference between the treatment groups. As both studies had the same (high) certainty of results with regard to the outcome "pruritus", it is not possible to derive greater or lesser harm from SIM + PEG + RBV. Greater or lesser harm is therefore not proven for the outcome "pruritus".

For the outcome "rash", the results of both studies were not statistically significant. Greater or lesser harm from SIM + PEG + RBV in comparison with PEG + RBV is thus not proven for this outcome.

Research question 1b: CHC genotype 1, relapsed patients after prior treatment response

The PROMISE study was included in the assessment of research question 1b.

Study characteristics

The PROMISE study was a double-blind RCT and had been completed at the time of the commission. Patients with or without cirrhosis were included who initially had undetectable hepatitis C virus (HCV) ribonucleic acid (RNA) after 24 weeks or more of prior interferon-based therapy and in whom HCV RNA was detected again within one year after the last administration of the drug (relapsed patients). The patients received simeprevir or placebo, each in combination with peginterferon alfa and ribavirin, with simeprevir being administered at a dosage of 150 mg/day for 12 weeks.

A response-guided treatment regimen was planned in the SIM + PEG + RBV arm of the study, i.e. the treatment was to be discontinued after treatment success. Treatment of 48 weeks was initially planned for all patients. However, this treatment duration could be reduced to 24 weeks when prespecified criteria regarding virologic response were met. With negligible exceptions, these criteria were met so that > 80% of the patients of the SIM + PEG + RBV arm were treated for 24 weeks. This treatment duration concurs with the approval for relapsed patients. The planned treatment duration in the PLC + PEG + RBV arm of the study was 48 weeks for all patients irrespective of the virologic response, which concurs with the approvals for peginterferon alfa and ribavirin.

Moreover, in both treatment groups, treatment discontinuation was planned in case of inadequate virologic response. In the study protocol, specific threshold values of the viral load of the patients were defined for several time points in the course of the study. If these were exceeded, treatment was to be discontinued (time-point specific either only simeprevir or placebo or the total study medication).

The total observation period of the study was 72 weeks, irrespective of a patient's individual treatment duration.

Risk of bias and certainty of conclusions

The risk of bias at study level was rated as high for the study because the number of patients who discontinued treatment prematurely differed considerably between the 2 treatment arms. The same applies to the number of patients who discontinued the study.

These premature treatment discontinuations particularly occurred in the PLC + PEG + RBV arms, which resulted in shorter treatment durations in these patients than recommended by the approval. Moreover, in the SIM + PEG + RBV arm, approximately 6% of the patients were treated longer than recommended by the approval, which was caused by criteria for treatment discontinuation that deviated from the information in the SPC and package information leaflet.

This resulted in a reduced certainty of conclusions for the following outcomes: SVR 24, fatigue (using the FSS), depression (using the CES-D) and health status (using the EQ-5D VAS). Hence no more than "hints" of an added benefit can be derived for these outcomes.

As in the PLC + PEG + RBV arm of the study, treatment was discontinued prematurely in approximately 10% of the patients, and particularly more often than in the SIM + PEG + RBV arm (the difference was approximately 8 percentage points), whereas on the other hand approximately 6% of the patients in the SIM + PEG + RBV arm were treated longer than recommended by the approval, this probably affects the effects on AEs to the disadvantage of SIM + PEG + RBV. Hence in case of lesser harm from SIM + PEG + RBV, the certainty of conclusions for these outcomes is regarded as high despite the high risk of bias. The derivation of indications of lesser harm from SIM + PEG + RBV is possible because of this.

Results

Mortality

One patient died in each of the 2 treatment groups of the study. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV for relapsed patients with CHC genotype 1 is therefore not proven with regard to mortality.

Morbidity – sustained virologic response 24 weeks after the end of treatment

There was a statistically significant difference in favour of SIM + PEG + RBV for the outcome "SVR 24".

In addition, there was proof of an effect modification by the characteristic "age" for this outcome. There was an indication of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for the outcome "SVR 24" for all 3 age subgroups (≤ 45 years, > 45 to ≤ 65 years and > 65 years).

Morbidity – depression using the CES-D

There was a statistically significant difference in favour of SIM + PEG + RBV for the outcome "depression".

Hedges' g was used to evaluate the relevance of the effect. The 95% confidence interval (CI) did not lie completely below the irrelevance threshold of −0.2. It was therefore possible that the effect was within a range that is irrelevant.

An added benefit of SIM + PEG + RBV in comparison with PEG + RBV for the outcome "depression" is therefore not proven.

Morbidity – fatigue using the FSS

There was a statistically significant difference in favour of SIM + PEG + RBV for the outcome "fatigue".

In addition, there was proof of an effect modification by the characteristic "sex". This results in a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV with regard to the outcome "fatigue" in women. For men, an added benefit is not proven.

Morbidity – health status using the EQ-5D VAS

There was a statistically significant difference in favour of SIM + PEG + RBV for the outcome "health status".

In addition, there was proof of effect modifications with regard to the characteristics "genotype 1a/1b" and "Q80K polymorphism", and an indication of an effect modification with regard to the characteristic "sex". In each case, this results in a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for women, patients with genotype 1b and patients without Q80K polymorphism. For the other subgroups, an added benefit is not proven.

Health-related quality of life

There were no evaluable data on health-related quality of life.

Adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs" in the total population.

In addition, there was proof of an effect modification by the characteristic "sex" and

indications of an effect modification by the characteristics “age” and “METAVIR fibrosis score”. This results in an indication of lesser harm in male patients. For women, greater or lesser harm is not proven. There were no statistically significant effects with regard to the characteristics “age” and “fibrosis score” in the individual subgroups and the total population. Lesser or greater harm for these subgroups is therefore not proven.

There was no statistically significant difference between the treatment groups for the outcome “discontinuation due to AEs”.

For the outcome “fatigue”, there was no statistically significant difference between the treatment groups. Greater or lesser harm from SIM + PEG + RBV in comparison with PEG + RBV is thus not proven.

There was a statistically significant difference in favour of the comparator therapy PLC + PEG + RBV for the outcome “dyspnoea”. The extent of this effect was no more than marginal, however, because the upper limit of the CI, with reversed direction of effect, was larger than the threshold value of 0.90. Greater or lesser harm from SIM + PEG + RBV in comparison with PEG + RBV is thus not proven.

Research question 1c: CHC genotype 1, previous non-responders (including partial and null responders)

The ATTAIN study was included in the assessment of research question 1c.

Study characteristics

The ATTAIN study was a double-blind RCT, in which adults with CHC genotype 1 virus infection were treated. The patients were non-responders, i.e. they had received at least one previous course of peginterferon α-2a or 2b in combination with ribavirin for ≥ 12 weeks (null responders) or ≥ 20 weeks (partial responders). The previous treatment must not have been discontinued due to peginterferon/ribavirin intolerance. Null responders were defined as patients who had a < 2 log10 IU/mL reduction in HCV RNA after 12 weeks of treatment in comparison with baseline, and in whom HCV RNA could be detected at the end of treatment. Partial responders were defined as patients who had a ≥ 2 log10 IU/mL reduction in HCV RNA after 12 weeks of treatment in comparison with baseline, and in whom HCV RNA could be detected at the end of treatment, but not before the end of week 20. In the ATTAIN study, randomization was stratified by response (null response and partial response) to the last peginterferon α/ribavirin treatment and by genotype 1 subtypes (1a and 1b).

The patients were treated with SIM + PEG + RBV in the intervention arm and with TVR + PEG + RBV in the comparator arm for 12 weeks each. In both treatment arms, this was followed by subsequent treatment with PEG + RBV for 36 weeks. The planned follow-up observation period was 12 weeks (e.g. for the primary outcome “SVR 12” at the data cut-off at week 60) and 24 weeks (data cut-off at week 72).

In both treatment groups, treatment discontinuation was planned in case of inadequate

virologic response. In the study protocol, specific threshold values of the viral load of the patients were defined for several time points in the course of the study. If these were exceeded, treatment was to be discontinued.

The ATTAIN study was not yet completed at the time of the benefit assessment. As the results at week 72 were not yet available, the available analyses at the planned data cut-off at week 60 were used.

Risk of bias and certainty of conclusions

The risk of bias at study level was rated as low. However, in the study 11.3% of the patients in the SIM + PEG + RBV arm were treated longer than recommended by the approval, which was caused by criteria for treatment discontinuation that deviated from the information in the SPC and package information leaflet. This caused uncertainty regarding the interpretability of the study results for answering the research question of the benefit assessment. It was therefore assumed that the certainty of conclusions was reduced for the following outcomes: SVR 12, fatigue (using the FSS), depression (using the CES-D) and health status (using the EQ-5D VAS). Hence no more than "hints" of an added benefit can be derived for these outcomes.

For all outcomes on AEs, the fact that the treatment duration in the SIM + PEG + RBV arm was longer than recommended by the approval probably has a disadvantageous effect for SIM + PEG + RBV. Hence in case of lesser harm from SIM + PEG + RBV, the certainty of conclusions of the study for these outcomes can be regarded as high. No more than "indications" of lesser harm can be derived for all outcomes on AEs.

Results

Mortality

There was no statistically significant difference between treatment with SIM + PEG + RBV and TVR + PEG + RBV for mortality. 3 deaths occurred under TVR + PEG + RBV. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV is not proven with regard to the outcome "mortality".

Morbidity – SVR 12 weeks after the end of treatment

There was no statistically significant difference between treatment with SIM + PEG + RBV and TVR + PEG + RBV for SVR 12. In addition, there was an indication of an effect modification by the characteristic "age" for the outcome "SVR 12". In none of the 3 age groups, there was a statistically significant difference between the treatment groups. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV is not proven with regard to the outcome "SVR 12".

Morbidity – depression using the CES-D

There was no statistically significant difference between treatment with SIM + PEG + RBV in

comparison with TVR + PEG + RBV for the outcome "depression" measured with the CES-D. There were indications of an effect modification for this outcome with regard to the characteristics "genotype 1a/1b" and "response to prior therapy". No statistically significant or not potentially irrelevant difference between the treatment groups was observed in any of the subgroups. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV is not proven with regard to the outcome "depression".

Morbidity – fatigue using the FSS

An improvement for the outcome "fatigue" in comparison with the baseline values was observed in both study arms. There was no statistically significant difference between the treatment arms. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV is not proven with regard to the outcome "fatigue".

Morbidity – health status using the EQ-5D VAS

An improvement for the outcome "health status" in comparison with the baseline values was observed in both study arms. There was a statistically significant difference in favour of treatment with SIM + PEG + RBV in comparison with TVR + PEG + RBV. The standardized mean difference (SMD in the form of Hedges' g) was considered to check the relevance of this result. The 95% CI of the SMD did not lie completely above the irrelevance threshold of 0.2. It was therefore possible that the effect was within a range that is irrelevant. In addition, there were indications of an effect modification with regard to the characteristics "METAVIR fibrosis score" and "Q80K polymorphism". No statistically significant or not potentially irrelevant difference between the treatment groups was observed in any of the subgroups. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV is not proven with regard to the outcome "health status".

Health-related quality of life

There were no evaluable data on health-related quality of life.

Adverse events

There was a statistically significant difference in favour of SIM + PEG + RBV in comparison with TVR + PEG + RBV for the outcome "SAEs". In addition, there was an indication of an effect modification by the characteristic "baseline viral load". Both for patients with low and for patients with high viral load, statistically significantly more SAEs occurred under SIM + PEG + RBV than under TVR + PEG + RBV. This results in an indication of lesser harm from SIM + PEG + RBV in comparison with TVR + PEG + RBV.

There was a statistically significant difference in favour of treatment with SIM + PEG + RBV for the outcome "discontinuation due to AEs". This results in an indication of lesser harm from SIM + PEG + RBV in comparison with TVR + PEG + RBV. In addition, there was an indication of an effect modification by the characteristic "age". For patients of the age group from 45 to 65 years, statistically significantly fewer discontinuations due to AEs occurred under SIM + PEG + RBV than under TVR + PEG + RBV. For the age groups under 45 and

over 65 years, there were no statistically significant differences between the treatment groups.

There was a statistically significant difference in favour of treatment with SIM + PEG + RBV for the outcome "skin and subcutaneous tissue disorders". This results in an indication of lesser harm from SIM + PEG + RBV in comparison with TVR + PEG + RBV.

There was a statistically significant difference in favour of treatment with SIM + PEG + RBV for the outcome "gastrointestinal disorders". This results in an indication of lesser harm from SIM + PEG + RBV in comparison with TVR + PEG + RBV with regard to the outcome "gastrointestinal disorders".

There was a statistically significant difference in favour of treatment with SIM + PEG + RBV for the outcome "serious anaemias". This results in an indication of lesser harm from SIM + PEG + RBV in comparison with TVR + PEG + RBV for the outcome "serious anaemias".

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

No evaluable evidence was available in the dossier for research question 1d because the company presented no systematic search and assessment of suitable data on the ACT in the dossier. Hence the completeness of the comparator data presented in Section 4.4.2 of the dossier was unclear. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV for patients with CHC genotype 1 and human immunodeficiency virus (HIV) coinfection is therefore not proven.

Research question 2: patients with CHC genotype 4

No evaluable evidence was available in the dossier for research question 2 because the company presented no systematic search and assessment of suitable data on the ACT in the dossier. Hence the completeness of the comparator data presented in Section 4.4.2 of the dossier was unclear. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV for patients with CHC genotype 4 is therefore not proven.

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 simeprevir (in combination with peginterferon alfa and ribavirin) compared with the ACT is assessed as presented in Table 3.

[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].

Table 3: Simeprevir – extent and probability of added benefit in adult patients with CHC genotype 1 or 4

Research question	**ACT**[a]	**Subgroup**	**Extent and probability of added benefit**
Treatment-naive CHC genotype 1 patients	**Dual therapy (combination of peginterferon and ribavirin)** or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin) treatment-naive patients with cirrhosis: dual therapy	Q80K polymorphism: no	Indication of non-quantifiable added benefit
		Q80K polymorphism: yes	Hint of non-quantifiable added benefit
		IL28B genotype: CT/TT	Indication of non-quantifiable added benefit
		IL28B genotype: CC	Added benefit not proven
Pretreated relapsed patients with CHC genotype 1	**Dual therapy (combination of peginterferon and ribavirin)** or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)	Indication of non-quantifiable added benefit	
Previous non-responders including partial and null responders with CHC genotype 1	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)**	Indication of a major added benefit	
Patients with CHC genotype 1 and HIV coinfection	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven	
Patients with CHC genotype 4	Dual therapy (combination of peginterferon and ribavirin)	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.			

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

Additional presentation of data presented on studies with simeprevir in combination with sofosbuvir as interferon-free treatment option

According to the supplementary commission by the G-BA, studies presented by the company for patients for whom simeprevir in combination with sofosbuvir can be used as interferon-

free treatment option were assessed. The company specified no ACT in its dossier in this treatment situation and presented an RCT in which all treatment arms included simeprevir. In summary, the COSMOS study used by the company is unsuitable to investigate the added benefit of simeprevir in combination with sofosbuvir as interferon-free treatment option for the following reasons:

- Only patients were included who were principally suitable for interferon treatment, in whom no intolerance was detectable, and for whom there was no urgent need for treatment with the interferon-free treatment option with simeprevir.
- The patients did partially not receive approval-compliant treatment.
- There was no adequate comparison to prove the added benefit of simeprevir in combination with sofosbuvir as interferon-free treatment option.

2.2 Research questions

The aim of this report was to assess the added benefit of simeprevir in adult patients with chronic hepatitis C infection.

The company followed the G-BA's ACT, but specified it by stipulating triple therapy consisting of TVR + PEG + RBV as ACT for previous non-responders with genotype 1. For all other patient groups, the ACT was dual therapy consisting of PEG + RBV.

Table 4 shows the research questions of the present benefit assessment.

Table 4: Research questions of the benefit assessment of simeprevir

Research question	Therapeutic indication CHC	ACT[a]
1a	Genotype 1, treatment-naive	Dual therapy (combination of peginterferon alfa and ribavirin)
1b	Genotype 1, relapsed patients	Dual therapy (combination of peginterferon alfa and ribavirin)
1c	Genotype 1 previous non-responders including partial and null responders	Triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon alfa and ribavirin)
1d	Genotype 1 with HIV coinfection	Dual therapy (combination of peginterferon alfa and ribavirin)
2	Genotype 4	Dual therapy (combination of peginterferon alfa and ribavirin)

a: Designation of the G-BA's ACT or of the option chosen by the company (see Section 2.9.1 of the full dossier assessment).
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus

This deviates from the presentation in the dossier, where treatment-naive patients and relapsed patients were summarized in one research question.

Moreover, the company presented a study on the interferon-free simeprevir treatment option as additional information. According to the separate commission from 27 May 2014, the evidence provided for this study was considered and presented (see Appendix A of the full dossier assessment).

The assessment was based on patient-relevant outcomes. Direct comparative RCTs were included in the assessment.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.9.1 and 2.9.2.1 of the full dossier assessment.

2.3 Research question 1a: HCV genotype 1, treatment-naive patients

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on simeprevir (studies completed up to 6 March 2014)
- bibliographical literature search on simeprevir (last search on 5 May 2014)
- search in trial registries for studies on simeprevir (last search on 6 March 2014)

To check the completeness of the study pool:

- bibliographical literature search on simeprevir (last search on 12 June 2014)
- search in trial registries for studies on simeprevir (last search on 12 June 2014)

No additional relevant study was identified from the check.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.9.2.1 and 2.9.2.3 of the full dossier assessment.

2.3.1.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
PILLAR (TMC435TiDP16-C205)	Yes	Yes	No
QUEST-1 (TMC435TiDP16-C208)	Yes	Yes	No
QUEST-2 (TMC435TiDP16-C216)	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. CHC: chronic hepatitis C; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; vs.: versus			

Section 2.3.4 contains a reference list for the studies included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections 2.9.2.3.1 and 2.9.2.3.2 of the full dossier assessment.

2.3.1.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PILLAR	RCT, double-blind, parallel, multicentre	Non-pretreated adults (18-70 years) with chronic HCV genotype 1 infection without cirrhosis	Group 1: SIM (75 mg, 12 weeks) + PEG + RBV (N = 78)[b] group 2: SIM (150 mg, 12 weeks) + PEG + RBV (N = 78) group 3: SIM (75 mg, 24 weeks) + PEG + RBV (N = 75)[b] group 4: SIM (150 mg, 24 weeks) + PEG + RBV (N = 79)[b] group 5: placebo (24 weeks) + PEG + RBV (N = 78)	Treatment duration: group 1 to 4: 24 or 48 weeks[c] (response-guided), of which with SIM: 12 weeks (group 1 and 2) or 24 weeks (group 3 and 4) group 5: 48 weeks follow-up: up to week 72	Australia, Austria, Belgium, Canada, Denmark, France, Germany, New Zealand, Norway, Poland, Russia, Spain, United States[d] 5/2009-4/2011	Primary: proportion of patients with SVR in week 72 secondary: proportion of patients with SVR 24 weeks after the end of treatment (SVR 24), symptoms, adverse events
QUEST-1	RCT, double-blind, parallel, multicentre	Non-pretreated adults (≥ 18 years) with chronic HCV genotype 1 infection with or without cirrhosis	Group 1: SIM + PEG + RBV (N = 264) group 2: placebo + PEG + RBV (N = 130)	Treatment duration: group 1: 24 or 48[c] weeks (response-guided), of which with SIM: 12 weeks group 2: 48 weeks follow-up: up to week 72	Australia, Canada, Germany, Great Britain, Italy, Mexico, New Zealand, Puerto Rico, Romania, Russia, Spain, Ukraine, United States 1/2011-1/2013	Primary: proportion of patients with SVR 12 secondary: proportion of patients with SVR 24, symptoms, adverse events

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients) (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
QUEST-2	RCT, double-blind, parallel, multicentre	Non-pretreated adults (≥ 18 years) with chronic HCV genotype 1 infection with or without cirrhosis	Group 1: SIM + PEG + RBV (N = 257) group 2: placebo + PEG + RBV (N = 134)	Treatment duration: group 1: 24 or 48 weeks[c] (response-guided), of which with SIM: 12 weeks group 2: 48 weeks follow-up: up to week 72	Argentina, Austria, Belgium, Brazil, Bulgaria, France, Germany, Netherlands, Poland, Portugal, Slovakia, Spain, Turkey, United States 1/2011-2/2013	Primary: proportion of patients with SVR 12 secondary: proportion of patients with SVR 24, symptoms, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: Not relevant for the benefit assessment, therefore not presented hereinafter.
c: The approval-compliant treatment duration is 24 weeks; the deviations of the study population from the approval population do not result in the study not being used for the assessment (see Section 2.9.2.4.1 of the full dossier assessment).
d: 14 countries were named in Module 4 of the dossier.

CHC: chronic hepatitis C; HCV: hepatitis C virus; N: number of randomized patients; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; SVR: sustained virologic response; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients)

Study	SIM + PEG + RBV	PLC + PEG +RBV	Concomitant medication
PILLAR	Week 1-12: SIM 150 mg orally once daily + PEG 180 µg subcutaneously, 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 13-24 or 13-48 (response-guided): PEG + RBV, same dosage as week 1-12	Week 1-48: PEG 180 µg subcutaneously, 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 the first 24 weeks thereof in combination with placebo	Prohibited at any time point (including pretreatment): ▪ any other anti-HCV treatments Prohibited from screening until the end of the study: ▪ immunomodulators ▪ investigational vaccines ▪ substances that stimulate blood production ▪ CYP3A4 inducers Prohibited during the first 24 weeks of the study: ▪ CYP3A4 inhibitors ▪ CYP3A4 substrates with small therapeutic indices ▪ CYP2D6 substrates with small therapeutic indices ▪ CYP2C8 substrates with narrow therapeutic indices
QUEST-1	Week 1-12: SIM 150 mg orally once daily + PEG 180 µg subcutaneously, 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 13-24 or 13-48 (response-guided): PEG + RBV, same dosage as week 1-12	Week 1-48: PEG 180 µg subcutaneously, 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 the first 12 weeks thereof in combination with placebo	Prohibited at any time point (including pretreatment): ▪ any other anti-HCV treatments Prohibited from 30 days before screening until the end of the study: ▪ investigational vaccines Prohibited from screening until the end of the study: ▪ immunomodulators ▪ substances that stimulate blood production Prohibited during the first 24 weeks of the study: ▪ CYP3A4 inducers ▪ CYP3A4 inhibitors ▪ CYP3A4 substrates with small therapeutic indices ▪ CYP1A2 substrates ▪ CYP2C8 substrates ▪ statins

(continued)

Table 7: Characteristics of the interventions – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients) (continued)

Study	SIM + PEG + RBV	PLC + PEG +RBV	Concomitant medication
QUEST-2	Week 1-12: SIM 150 mg orally once daily + PegIFNα-2a 180 µg subcutaneously, 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 or PegIFNα-2b pen 1.5 µg/kg/week + RBV 800 to 1400 mg orally (depending on body weight: ≤ 65 kg = 800 mg/day; 66−80 kg = 1000 mg, 81−105 kg = 1200 mg, > 105 kg = 1400 mg/day)[a] daily, divided into 2 doses week 13-24 or 13-48 (response-guided): PEG + RBV, same dosage as week 1-12	Week 1-48: PegIFNα-2a 180 µg subcutaneously, 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 or PegIFNα-2b pen 1.5 µg/kg/week + RBV 800 to 1400 mg orally (depending on body weight: ≤ 65 kg = 800 mg/day; 66-80 kg = 1000 mg, 81−105 kg = 1200 mg, > 105 kg = 1400 mg/day)[a] daily, divided into 2 doses the first 12 weeks thereof in combination with placebo	Prohibited at any time point (including pretreatment): ▪ any other anti-HCV treatments Prohibited from 30 days before screening until the end of the study: ▪ investigational vaccines Prohibited from screening until the end of the study: ▪ immunomodulators ▪ substances that stimulate blood production Prohibited during the first 24 weeks of the study: ▪ CYP3A4 inducers ▪ CYP3A4 inhibitors ▪ CYP3A4 substrates with small therapeutic indices ▪ CYP1A2 substrates ▪ CYP2C8 substrates ▪ statins

a: According to the SPC, the dose for 65 kg body weight is 1000 mg.

CHC: chronic hepatitis C; CYP: cytochrome P450; HCV: hepatitis C virus; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; SPC: Summary of Product Characteristics; vs.: versus

The studies PILLAR, QUEST-1 and QUEST-2 were double-blind RCTs and had been completed at the time of the commission. In the PILLAR study, the patients were randomized in a ratio of 1:1:1:1:1, and in each of the QUEST studies in a ratio of 2:1. Treatment-naive patients with CHC genotype 1 were included in each of the studies. Only patients without cirrhosis were included in the PILLAR study, whereas the patient population in both QUEST studies comprised patients with or without cirrhosis. In the phase 2b study PILLAR, 4 different treatment regimens consisting of SIM + PEG + RBV were compared with a combination of PLC + PEG + RBV. Out of the simeprevir arms of the study, only the combination with 150 mg simeprevir, administered over a period of 12 weeks, was relevant for the benefit assessment. The other 3 simeprevir arms could not be used for the benefit assessment because the dosage or the treatment duration was not compliant with the approval. There were 2 study arms each in the QUEST-1 and QUEST-2 phase 3 studies. The patients received either simeprevir or placebo in combination with peginterferon alfa and ribavirin. Simeprevir was administered at a dosage of 150 mg/day for 12 weeks.

A response-guided treatment regimen was planned in the SIM + PEG + RBV arms of all 3 studies, i.e. treatment was to be discontinued on treatment success. Treatment of 48 weeks was initially planned for all patients. However, this treatment duration could be reduced to 24 weeks when prespecified criteria regarding virologic response were met. Except for marginal deviations, the treatment duration in the SIM + PEG + RBV arms of all 3 studies was 24 weeks. A treatment duration of 24 weeks for treatment-naive patients concurs with the approval [3]. In contrast, 48-week treatment for all patients independent from virologic response was planned for the control arms of all 3 studies, which concurs with the approvals for peginterferon alfa and ribavirin [4-7]. Table 58 of the full dossier assessment provides an overview of the treatment regimens and the criteria for reduction in treatment duration.

Moreover, in both treatment groups in all 3 studies, treatment discontinuation was planned in case of inadequate virologic response. In the study protocols, specific threshold values based on the viral load of the patients were defined for several time points in the course of the study. If these were exceeded, treatment was to be discontinued (time-point specific either only simeprevir or placebo or the total study medication). See Section 2.9.2.4.1 of the full dossier assessment for more details.

Peginterferon alfa-2a was used for the combination with simeprevir and ribavirin in all 3 studies. The QUEST-2 study deviates from this as in some countries peginterferon alfa-2b was used as an alternative to peginterferon alfa-2a. In a second step of randomization, patients in these countries were allocated in a ratio of 1:1 either to peginterferon alfa-2a plus ribavirin or to peginterferon alfa-2b plus ribavirin.

Primary outcome of the PILLAR study was the SVR in week 72 after the start of treatment (SVR W72). In the QUEST studies, the SVR 12 weeks after the end of treatment (SVR 12) was the primary outcome. The SVR 24 weeks after the end of treatment (SVR 24) was secondary outcome in all 3 studies. The total observation period in all 3 studies was 72 weeks, independent from the individual treatment period of a patient.

Table 8 shows the characteristics of the patients in the studies included.

Table 8: Characteristics of the study populations – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients)

Study group	N	Age [years] mean (SD)	Sex [F/M] %	Fibrosis score[a] %	Cirrhosis [with/without] %	Genotype [1a/1b/other] %	Viral load [≤ 800 000/ > 800 000 IU/mL] %	Ethnicity [white/ black/ other] %	Study discontinua-tions n (%)
PILLAR									
SIM + PEG + RBV	77	44 (12)	44/56	F0-F1: 57.2[b] F2: 33.8 F3: 9.1 F4: 0	0/100	48.7/50.0/1.3	10.4/89.6	96.1/3.9/0	7 (9.1)
PLC + PEG + RBV	77	43 (11)	49/51	F0-F1: 57.2[b] F2: 33.8 F3: 9.1 F4: 0	0/100	38.2/61.8/0	18.2/81.8	96.1/2.6/1.3[c]	6 (7.8)
QUEST-1									
SIM + PEG + RBV	264	46 (11)	44/56	F0-F1: 45.7 F2: 24.8 F3: 17.8 F4: 11.6	12/88	55.7/44.3/0	17.4/82.6	86.0/10.2/3.8[d]	25 (9.5)[e]
PLC + PEG + RBV	130	46 (11)	43/57	F0-F1: 38.5 F2: 30.8 F3: 18.5 F4: 12.3	12/88	56.9/43.1/0	26.2/73.8	93.8/3.1/3.1[d]	12 (9.2)[e]

(continued)

Table 8: Characteristics of the study populations – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients) (continued)

Study group	N	Age [years] mean (SD)	Sex [F/M] %	Fibrosis score[a] %	Cirrhosis [with/without] %	Genotype [1a/1b/other] %	Viral load [≤ 800 000/ > 800 000 IU/mL] %	Ethnicity [white/ black/ other] %	Study discontinua-tions n (%)
QUEST-2									
SIM + PEG + RBV	257	45 (12)	46/54	F0-F1: 52.4 F2: 26.2 F3: 14.5 F4: 6.9	7/93	40.9/58.4/0.8	22.6/77.4	92.2/6.2/1.6[d]	16 (6.2)[f]
PLC + PEG + RBV	134	46 (12)	43/57	F0-F1: 44.8 F2: 31.3 F3: 12.7 F4: 11.2	11/89	40.3/57.5/2.2	26.9/73.1	91.8/7.5/0.7[d]	21 (15.7)[f]

a: Information based on METAVIR score: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis.
b: Institute's calculation.
c: Other: Hawaiians or pacific islanders; Institute's calculation.
d: Other: American Indians or native Alaskans, Hawaiians or pacific islanders, Asians, mixed ethnicity; Institute's calculation.
e: Contradictory information in the dossier (in Module 4: SIM + PEG + RBV: 21 discontinuations, PLC + PEG + RBV: 10 discontinuations).
f: Contradictory information in the dossier (in Module 4: SIM + PEG + RBV: 12 discontinuations, PLC + PEG + RBV: 17 discontinuations).
CHC: chronic hepatitis C; F: female; IU: international units; M: male; N: number of randomized (or treated) patients; n: number of patients with event; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; SIM: simeprevir; vs.: versus

The 3 studies included in the benefit assessment for research question 1a had very similar patient populations. The PILLAR study differed from the 2 QUEST studies by the smaller size of the relevant treatment groups (77 patients in each treatment group, compared with the approximately 400 in total of the QUEST studies), and by the exclusion of patients with cirrhosis. These could be included in the QUEST studies if their cirrhosis was compensated.

Regarding the distribution of patients with genotype 1a and 1b, the QUEST-1 study differed from the other studies because the proportion of patients with genotype 1a was 10 percentage points higher than the proportion of patients with genotype 1b. In PILLAR and QUEST-2, more patients with genotype 1b than with genotype 1a were included.

Regarding all other characteristics, there were no important differences between the studies. The differences between the treatment groups were also marginal in all studies. The mean age of the patients was consistently 45 years. Marginally more men than women were enrolled in all 3 studies. Patients without cirrhosis, with 88 to 93%, were the majority in the QUEST-1 and QUEST-2 studies, so that there was comparability with the PILLAR study (100%, see above). Baseline viral load was mostly high (73 to 89%) with the proportion of patients with low baseline viral load being consistently 4 to 9 percentage points higher in the comparator groups than in the SIM + PEG + RBV arms. The proportion of patients with white skin was generally above 90%, only in the SIM + PEG + RBV arm of the QUEST-1 study was the proportion 86% in favour of a 10% proportion of patients with dark skin. The proportion of all other ethnicities together was always below 4%.

In the characteristics of the study populations, the company provided no information on the proportions of patients with liver damage according to the METAVIR score, although it presented comprehensive subgroup analyses on this. Only the proportions of patients with and without cirrhosis were presented. The proportions of patients with METAVIR scores F0-F1, F2, F3 and F4 are therefore additionally presented here. The proportion of patients with increasing liver damage decreased in all 3 studies. Depending on the study, 10 to 30% of the patients had F3 or F4 scores (PILLAR: no patients with F4) with no notable differences between the treatment groups.

In summary, the differences between the patient populations were small. Hence hereinafter the study results are summarized in meta-analyses where possible.

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive genotype 1 patients)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
PILLAR	Yes	Yes	Yes	Yes	Yes	Yes	Low
QUEST-1	Yes	Yes	Yes	Yes	Yes	Yes	Low
QUEST-2	Yes	Yes	Yes	Yes	Yes	No[a]	High

a: High differential proportions of study discontinuations (SIM + PEG + RBV: 6.2% vs. PLC + PEG + RBV: 15.7%).
PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; vs.: versus

The risk of bias at study level was rated as high for the QUEST-2 study because the number of patients who discontinued the study differed between the 2 study arms (SIM + PEG + RBV: 6.2%; PLC + PEG + RBV: 15.7%). This was not the case in the PILLAR and QUEST-1 studies so that their risk of bias at study level was rated as low.

This deviates from the company's assessment, which regarded all 3 studies as having low bias.

Overall assessment of the certainty of conclusions

For the studies PILLAR, QUEST-1 and QUEST-2, 2 reasons led to an uncertainty that influenced the certainty of conclusions for some of the outcomes considered. Within the studies, the frequency with which dual therapy was discontinued differed considerably in the study arms. These premature treatment discontinuations particularly occurred in the PLC + PEG + RBV arms, which resulted in shorter treatment durations in these patients than recommended by the approval. Moreover, in the SIM + PEG + RBV arms of all 3 studies, up to 14% of the patients were treated longer than recommended by the approval, which was caused by criteria for treatment discontinuation that deviated from the information in the SPC and package information leaflet. These reasons caused uncertainty regarding the interpretability of the study results for answering the research question of the benefit assessment. The potential uncertainty of the treatment effect in comparison with approval-compliant treatment is discussed below separately for the outcomes considered.

A sensitivity analysis could show for the outcome "SVR 24" that the effect estimate is still statistically significant if the high and different rates of discontinuation- if these were caused by virologic discontinuation criteria - are adequately considered (see Section 2.3.2.3 and

Section 2.9.2.4.1 of the full dossier assessment). Since only aspects caused by premature discontinuations in the PLC + PEG + RBV group could be considered by the sensitivity analysis for this research question, the certainty of conclusions for the outcome "SVR 24" is reduced despite the low risk of bias of the PILLAR and QUEST-1 studies.

A corresponding sensitivity analysis could not be conducted for the results on the outcomes "fatigue" (recorded using the FSS), "depression" (using the CES-D) and "health status" (using the EQ-5D VAS). The certainty of conclusions is reduced for these outcomes as well.

In summary, no more than "indications" of an added benefit can be derived for the outcomes "SVR 24", "fatigue", "depression" and "health status" due to the reduced certainty of conclusions.

As in the PLC + PEG + RBV arms of the studies, treatment was discontinued prematurely in up to 28% of the patients, and particularly considerably more often than in the SIM + PEG + RBV arms (the difference was up to 25 percentage points), this probably affects the effects on adverse events to the disadvantage of SIM + PEG + RBV. A bias caused by the fact that up to 14% of the patients were treated longer in the SIM arms than is recommended by the approval can have an effect in the same direction. Hence in case of lesser harm from SIM + PEG + RBV, the certainty of conclusions of the studies for these outcomes can be regarded as high (including the ones of the highly biased QUEST-2 study). The derivation of proof of lesser harm from SIM + PEG + RBV is possible because of this.

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and Appendix 4-F of the dossier, and in Sections 2.9.2.4.1 and 2.9.2.4.2 of the full dossier assessment.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.9.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - SVR 24 as sufficiently valid surrogate for the patient-relevant outcome "HCC" (additional presentation: SVR at week 72)
  - fatigue using the FSS
  - depression using the CES-D
  - health status using the EQ-5D VAS

- Adverse events
  - overall rate of SAEs
  - treatment discontinuation due to AEs
  - pruritus (Medical Dictionary for Regulatory Activities [MedDRA] Preferred Term [PT])
  - rash (MedDRA PT)

The choice of patient-relevant outcomes deviated from that of the company.

The company used the instruments FFS and CES-D to describe the treatment-related symptoms (fatigue and depression). However, since it is not possible to differentiate between disease-related and treatment-related symptoms this way, these were here regarded to be outcomes of morbidity. The company's approach was also deviated from insofar as the EQ-5D was not completely included in the benefit assessment, but only the VAS. Moreover, the VAS was regarded to be a measurement of the general health status. The Work Productivity and Activity Impairment Questionnaire (WPAI) was also not considered. See Section 2.9.2.4.3 of the full dossier assessment for more details.

Further outcomes, namely the AEs "pruritus" and "rash", which the company did not consider in the dossier, were additionally included. These were included as AEs of particular interest because there were notable differences between the treatment groups (see Appendix C of the full dossier assessment). The operationalization of the outcomes regarding harm deviates from the one of the company, which only presented the data on the first 12 weeks of treatment and on the total treatment phase. Due to the different treatment durations in the study arms, these are not informative enough, which is why the data at week 72 of the observation were used instead (see Section 2.9.2.4.3 of the full dossier assessment).

Further information on the choice of outcomes can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Section 2.9.2.4.3 of the full dossier assessment.

Table 10 shows for which outcomes data were available in the studies included.

Table 10: Matrix of outcomes – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients)

Study	Outcomes										
	All-cause mortality	Sustained virologic response (SVR 24)	Sustained virologic response (SVR W72)	Depression using the CES-D	Fatigue using the FSS	Health status using the EQ-5D VAS	Health-related quality of life	SAEs	Discontinuation due to AEs	Pruritus	Rash
PILLAR	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No
QUEST-1	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
QUEST-2	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

AE: adverse event; CES-D: Centre for Epidemiologic Studies Depression Scale; CHC: chronic hepatitis C; EQ-5D: European Quality of Life-5 Dimensions; FSS: Fatigue Severity Scale; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SIM: simeprevir; SVR: sustained virologic response; VAS: visual analogue scale; vs.: versus

2.3.2.2 Risk of bias

Table 11 shows the risk of bias for these outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive genotype 1 patients)

Study		Outcomes										
	Study level	All-cause mortality	Sustained virologic response (SVR 24)	Sustained virologic response (SVR W72)	Depression using the CES-D	Fatigue using the FSS	Health status using the EQ-5D VAS	Health-related quality of life	SAEs	Discontinuation due to AEs	Pruritus	Rash
PILLAR	L	L	L	L	-	H[a]	L	-	L	L	L	L
QUEST-1	L	L	L	L	L	L	L	-	L	L	L	L
QUEST-2	H	L	H	H	H	H	H	-	H	H	H	H

a: Unclear why the outcome was only recorded for a subpopulation (approximately 63% of the patients).
AE: adverse event; CES-D: Centre for Epidemiologic Studies Depression Scale; EQ-5D: European Quality of Life-5 Dimensions; FSS: Fatigue Severity Scale; H: high; L: low; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SIM: simeprevir; SVR: sustained virologic response; VAS: visual analogue scale; vs.: versus

The risk of bias for this outcome was generally rated as low because bias from premature treatment discontinuations on the mortality effects was rated as unlikely for the rates considered. The company presented no separate results for the outcome “mortality” and conducted no assessment of the risk of bias.

The company rated the risk of bias as low for the outcomes on SVR 24, on morbidity recorded using the instruments FFS, EQ-5D (VAS) and CES-D, and on AEs. The company’s assessment was only accepted for the PILLAR and the QUEST-1 study, which had low bias. The outcome “fatigue” in the PILLAR study was an exception because, for unknown reasons, the FSS was only recorded for a subset of the study population.

However, the certainty of conclusions of the studies was still considered to be reduced for these outcomes so that no more than “indications” of an added benefit could be derived. This did not apply to outcomes on AEs because the certainty of conclusions was regarded as high, which is why no more than proof of lesser harm is possible. This also applied to the highly-biased QUEST-2 study (see Section 2.3.1.2 and Section 2.9.2.4.2 of the full dossier assessment).

Further information on the risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3, and in Appendix 4-F of the dossier, and in Section 2.9.2.4.2 of the full dossier assessment.

2.3.2.3 Results

Table 12 and Table 13 summarize the results on the comparison of SIM + PEG + RBV and PLC + PEG + RBV in treatment-naive CHC genotype 1 patients. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. The data at the analysis date of 72 weeks were used in the benefit assessment for all outcomes on AEs. The figures of the meta-analyses calculated by the Institute can be found in Appendix B of the full dossier assessment.

To answer research question 1a, the company's RCTs included for this research question could be summarized in meta-analyses if data on the respective outcome were available. The certainty of conclusions of all 3 studies was reduced for the reasons mentioned in Sections 2.3.1.2 and 2.3.2.2.

The number of treatment discontinuations in the respective comparator group was regarded as problematic in the QUEST-1 and QUEST-2 studies. As a consequence of the virologic stopping criteria specified by the study protocols, which were to be applied to both treatment arms (see Section 2.9.2.4.1 of the full dossier assessment), a relevant number of patients, particularly in the comparator arms, were treated for a shorter period of time with PLC + PEG + RBV than recommended by the approval (48 weeks [3]). In the company's clinical study reports (CSRs), treatment discontinuations were analysed as patients with treatment failure. The company did not address this problem in the dossier.

Regarding the SVR 24 data, a sensitivity analysis was therefore conducted, in which it was assumed for these patients that they reach the outcome with the probability with which those patients of the control group reach it who did not discontinue dual therapy and the study. For illustration, the result is also presented in Table 12 showing that the high number of these treatment discontinuations did not present such a highly distorting influence on the treatment effect to fully account for it. Even under the even more conservative assumption that all patients who had discontinued dual therapy prematurely had had treatment success, the effect would still remain (not presented in the table, see Appendix B of the full dossier assessment).

Table 12: Results (dichotomous outcomes) – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients)

Outcome category **outcome** **study**	**SIM + PEG + RBV**		**PLC + PEG + RBV**		**SIM + PEG + RBV vs. PLC + PEG + RBV**
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value**
Mortality					
All-cause mortality					
PILLAR	77	0	77	0	No presentation of effect estimates due to low number of events
QUEST-1	264	0	130	0	
QUEST-2	257	2 (0.8)	134	0	
Morbidity					
SVR 24[a]					
PILLAR	77	62 (80.5)	77	50 (64.9)	1.24 [1.02; 1.51][b]; 0.033[b]
QUEST-1	264	210 (79.5)	130	64 (49.2)	1.62 [1.34; 1.94][b]; < 0.001[b]
QUEST-2	257	207 (80.5)	134	67 (50.0)	1.61 [1.35; 1.93][b]; < 0.001[b]
Total				Heterogeneity:	p = 0.082; I^2 = 60.0%[b]
Sensitivity analysis on SVR 24[d]					1.19 [1.09; 1.31][c]; < 0.001[c]
SVR W72					
PILLAR	77	60 (78.7)	77	50 (63.3)	1.20 [0.98; 1.47][b]
QUEST-1	264	207 (78.4)	130	64 (49.2)	1.59 [1.32; 1.92][b]
QUEST-2	257	202 (78.6)	134	67 (50.0)	1.57 [1.31; 1.88][b]
Total				Heterogeneity:	p = 0.071[c]; I^2 = 62.1
Health-related quality of life			No evaluable data available		
Adverse events (72 week)					
Adverse events					
PILLAR	77	76 (98.7)	77	76 (98.7)	
QUEST-1	264	255 (96.6)	130	125 (96.2)	
QUEST-2	257	249 (96.9)	134	132 (98.5)	
Total					
Serious adverse events					
PILLAR	77	6 (7.8)	77	11 (14.3)	0.55 [0.21; 1.40][b]
QUEST-1	264	19 (7.2)	130	14 (10.8)	0.67 [0.35; 1.29][b]
QUEST-2	257	22 (8.6)	134	15 (11.2)	0.76 [0.41; 1.42][b]
Total					0.68 [0.45; 1.02][c]; p = 0.065[c]

(continued)

Table 12: Results (dichotomous outcomes) – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients) (continued)

Outcome category outcome study	SIM + PEG + RBV		PLC + PEG + RBV		SIM + PEG + RBV vs. PLC + PEG + RBV
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
Discontinuation due to AEs[e]					
PILLAR	77	8 (10.4)	77	10 (13.0)	0.80 [0.33; 1.93][b]
QUEST-1	264	7 (2.7)	130	3 (2.3)	1.15 [0.30; 4.37][b]
QUEST-2	257	2 (0.8)	134	0 (0)	2.62 [0.13; 54.1][b]
Total					0.95 [0.46; 1.93][c]; p = 0.879[c]
Pruritus					
PILLAR	77	ND	77	ND	
QUEST-1	264	69 (26.1)	130	20 (15.4)	1.70 [1.08; 2.67][b]
QUEST-2	257	66 (25.7)	134	34 (25.4)	1.01 [0.71; 1.45][b]
Total				Heterogeneity:	p = 0.076; I^2 = 68.2%[c]
Skin rash					
PILLAR	77	ND	77	ND	
QUEST-1	264	63 (23.9)	130	30 (23.1)	1.03 [0.71; 1.51][b]
QUEST-2	257	47 (18.3)	134	15 (11.2)	1.63 [0.95; 2.81][b]
Total				Heterogeneity:	p = 0.174; I^2 = 46.0%[c]

a: Sufficiently valid surrogate for the patient-relevant outcome “hepatocellular carcinoma”.
b: Institute’s calculation, asymptotic.
c: Institute’s calculation from meta-analysis.
d: Institute’s calculation: For patients who discontinued dual therapy, it was assumed in both treatment arms that they reach the outcome with the probability with which those patients of the control group reach it who did not discontinue dual therapy. The variances were adapted according to the data-set re-sizing approach (approach W3 in [8]). Under the even more conservative assumption that all patients who discontinued dual therapy had reached the outcome, this would result in RR = 1.10 [1.03; 1.18].
e: Patients who discontinued all treatments.

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SIM: simeprevir; SVR 24: sustained virologic response 24 weeks after the end of treatment; SVR W72: sustained virologic response in week 72; vs.: versus

Table 13: Results (continuous outcomes) – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients)

Outcome category outcome study	SIM + PEG + RBV			PLC + PEG + RBV			SIM + PEG + RBV vs. PLC + PEG + RBV
	N[a]	Values at start of study mean (SE)	Change at end of study mean[b] (SE)	N[a]	Values at start of study mean (SE)	Change at end of study mean[b] (SD)	Mean difference of the AUC [95% CI][c]; p-value Hedges' g [95% CI]
Morbidity (week 0-72)							
Depression using the CES-D[d]							
PILLAR	not recorded						
QUEST-1	260	15.2 (0.5)	0.3 (0.5)	130	15.5 (0.6)	0.1 (0.7)	-44.11 [-118.6; 30.4]; p = 0.246
QUEST-2	256	15.2 (0.5)	-1.0 (0.5)	133	14.4 (0.7)	0.8 (0.9)	-68.1 [-142.9; 6.6]; p = 0.074
Total							−56.1 [−108.8; −3.3]; p = 0.04 Hedges' g: −0.16 [−0.31; −0.01]
Fatigue using the FSS[e]							
PILLAR	47	2.9 (0.2)	-0.5 (0.2)	50	3.2 (0.2)	-0.4[f] (0.2)	−38.2 [−61.4; −15.0]; p = 0.001[g] Hedges' g: -0.65 [-1.06; -0.24][g]
QUEST-1	260	3.5 (0.1)	-0.5 (0.1)	130	3.3 (0.1)	-0.2 (0.1)	-23.8 [-38.0; -9.6]; p < 0.001 Hedges' g: -0.35 [-0.56; -0.14]
QUEST-2	256	3.1 (0.1)	-0.6 (0.1)	133	3.1 (0.1)	-0.3 (0.2)	-18.8 [-33.5; -4.2]; p = 0.012 Hedges' g: -0.27 [-0.48; -0.06]
Total							−24.1 [−33.4; −14.8]; p < 0.001 Hedges' g: -0.36 [-0.53; -0.19]

(continued)

Table 13: Results (continuous outcomes) – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients) (continued)

Outcome category outcome study	SIM + PEG + RBV			PLC + PEG + RBV			SIM + PEG + RBV vs. PLC + PEG + RBV
	N[a]	Values at start of study mean (SE)	Change at end of study mean[b] (SE)	N[a]	Values at start of study mean (SE)	Change at end of study mean[b] (SD)	Mean difference of the AUC [95% CI][c]; p-value Hedges' g [95% CI]
Health status using the EQ-5D VAS[h]							
PILLAR	77	84.4 (1.6)	1.3 (1.6)[i]	76	83.5 (1.4)	-1.3 (1.6)[i]	ND
QUEST-1	257	81.6 (1.0)	3.8 (1.0)	130	78.2 (1.4)	4.1 (1.6)	223.2 [75.1; 371.3]; p = 0.003 Hedges' g: 0.32 [0.11; 0.53]
QUEST-2	252	82.8 (1.0)	3.9 (1.0)	131	83.6 (1.2)	-0.3 (1.9)	205.2 [52.5; 357. 9]; p = 0.008 Hedges' g: 0.28 [0.07; 0.50]
Total							214.5 [108.2; 320.8]; p < 0.001 Hedges' g: 0.28 [0.14; 0.41]

a: Number of patients in the AUC analysis; the values at the start of the study (possible changes at the end of the study) may be based on other patient numbers.
b: Information for patients with existing values in week 72.
c: Unless stated otherwise, piecewise linear mixed model without imputation of missing values.
d: Negative changes at the end of the study mean improvement in symptoms; the CES-D scale ranges from 0 to 60 points, high values indicate worse state.
e: Negative changes at the end of the study mean improvement in symptoms; the total FSS scale ranges from 1 to 7 points; high values indicate worse state.
f: Inconsistent information in the dossier.
g: From MMRM analysis.
h: Positive changes at the end of the study mean improvement in symptoms; the VAS scale ranges from 0 to 100 with 0 being the best and 100 being the worst imaginable health status.
i: Changes from LOCF analysis.

AUC: area under the curve; CES-D: Centre for Epidemiologic Studies Depression Scale; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FSS: Fatigue Severity Scale; LOCF: last observation carried forward; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SIM: simeprevir; VAS: visual analogue scale; vs.: versus

Mortality

Deaths only occurred in the QUEST-2 study; both cases were observed in the SIM + PEG + RBV arm. No deaths were recorded in the PILLAR and QUEST-1 studies. The

effect estimates are therefore not presented. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV for mortality is not proven.

Morbidity

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

Because of the heterogeneity of the results it was not reasonable to summarize the data on the outcome "SVR 24" in a meta-analysis. However, all 3 studies included showed statistically significant results for SVR 24 in favour of SIM + PEG + RBV.

The result of the sensitivity analysis also showed a statistically significant advantage in favour of SIM + PEG + RBV; in this case a common effect estimate could be calculated. As the number of treatment discontinuations in the comparator arms therefore did not result in such a great bias of the effect estimates as to challenge the statistical significance of the result, the company's analysis was used for the assessment of the added benefit.

The SVR rates at week 72 are presented as additional information in Table 12. They were not used for the derivation of the added benefit. No common effect estimate was calculated here either because of the heterogeneity of the results. The results confirm the data on SVR 24 because a statistically significant advantage in favour of SIM + PEG + RBV could be determined for the QUEST-1 and QUEST-2 studies. The result of the PILLAR study was not statistically significant. However, the study only contained approximately one third of the patient numbers of each of the 2 QUEST studies; the lower limit of its CI was 0.98, in the same direction of effect as in QUEST-1 and QUEST-2.

In addition, there was proof of an effect modification for the SVR 24 by the characteristic "IL28B genotype" and an indication of an effect modification by the characteristic "Q80K polymorphism". With regard to SVR 24, this results in an indication of an added benefit of SIM + PEG + RBV for patients with IL28B genotypes CT or TT. For patients with the IL28B genotypes CC, an added benefit for SVR 24 is not proven. There is an indication of an added benefit for SVR 24 for patients without Q80K polymorphism, and a hint of an added benefit for patients with Q80K polymorphism (see Section 2.3.2.4 for details).

On the basis of the SVR 24, the company also described an added benefit of SIM + PEG + RBV, but differentiated the result exclusively by Q80K polymorphism.

Depression using the CES-D

The outcome "depression" was not recorded in the PILLAR study. The meta-analysis of the results of QUEST-1 and QUEST-2 resulted in a statistically significant advantage in favour of SIM + PEG + RBV. It is to be noted that higher values indicate worsening or increase of depression symptoms, i.e. a negative value of the difference of the areas under the curves (AUCs) indicates less worsening or increased improvement in the SIM + PEG + RBV arm in comparison with the PLC + PEG + RBV arm.

Hedges' g was used to evaluate the relevance of the effect. The 95% CI did not lie completely below the irrelevance threshold of −0.2. It was therefore possible that the effect was within a range that is irrelevant. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV is therefore not proven.

There was an indication of an effect modification by the characteristic "genotype (1a or 1b)" and proof of an effect modification by the characteristic "Q80K polymorphism". However, in none of the subgroups, there was a statistically significant and not potentially irrelevant effect.

The assessment deviates from that of the company, which claimed proof of an added benefit regarding treatment-related symptoms.

Fatigue using the FSS

The meta-analysis of all 3 studies on the outcome "fatigue" resulted in a statistically significant advantage in favour of SIM + PEG + RBV. It is to be noted that higher values indicate an increase in fatigue, i.e. a negative difference of the AUC from the start of treatment until the end of treatment is to be interpreted as increased improvement or less worsening in the SIM + PEG + RBV arm in comparison with the PLC + PEG + RBV arm.

The 95% CI of Hedges' g did not lie completely below the irrelevance threshold of −0.2. It was therefore possible that the effect was within a range that is irrelevant.

There were indications of an effect modification by the characteristics "METAVIR fibrosis score" and "Q80K polymorphism" for this outcome. This results in a hint of an added benefit for patients with a METAVIR score F0-F2, and for patients without Q80K polymorphism in a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV with regard to the outcome "fatigue". For the other subgroups, an added benefit is not proven (see Section 2.3.2.4).

This deviates from the company's assessment, which also described an added benefit exclusively in the subgroups of patients with METAVIR score F0-F2 or without Q80K polymorphism, but claimed the probability "proof" for this added benefit.

Health status using the EQ-5D VAS

No effect estimates on the VAS of the EQ-5D were available for the PILLAR study. The meta-analysis of the results of QUEST-1 and QUEST-2 resulted in a statistically significant advantage in favour of SIM + PEG + RBV. It is to be noted that higher values indicate an improvement in general health status, i.e. that higher values of the AUC difference indicate a positive change in health status in the SIM + PEG + RBV arm in comparison with the PLC + PEG + RBV arm.

The 95% CI of Hedges' g did not lie completely above the irrelevance threshold of 0.2. It was therefore possible that the effect was within a range that is irrelevant.

For this outcome, there was proof of an effect modification by the characteristics "age", "genotype (1a or 1b)" and "Q80K polymorphism". This results in an indication of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for patients aged 45 years or younger and for patients without Q80K polymorphism. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV is not proven for older patients and for patients with Q80K polymorphism as well as for the subgroups "genotype 1a and 1b" (see Section 2.3.2.4).

This deviates from the company's assessment, which claimed proof of added benefit in the total population with regard to health-related quality of life based on the VAS of the EQ-5D among other things.

Health-related quality of life

There were no evaluable data on health-related quality of life. This deviates from the company's approach, which included the EQ-5D (utility and VAS on health status) as well as the WPAI for this purpose. See Section 2.9.2.4.3 of the full dossier assessment for the question of how these outcomes were considered in the benefit assessment.

Adverse events

The results of the outcomes "SAEs" and "discontinuation due to AEs" could each be summarized in meta-analyses. There was no statistically significant difference between the treatment arms in any of the 2 outcomes.

There was an indication of an effect modification by the characteristic "METAVIR fibrosis score" for the outcome "SAEs". This results in an indication of lesser harm from SIM + PEG + RBV in comparison with PEG + RBV for patients with a METAVIR score F3 to F4. For patients with a METAVIR score F0-F2, greater or lesser harm from SIM + PEG + RBV is not proven.

Lesser harm from SAEs in the SIM + PEG + RBV arm despite the use of triple therapy might be explained by the shorter duration of exposition: Treatment with PEG + RBV in the PLC + PEG + RBV arm was planned for 48 weeks, whereas triple therapy was planned for approximately half that time according to the approval.

There were no 72-week data from the PILLAR study for the outcomes "pruritus" and "rash". Because of the heterogeneity of the results, in both cases, it was not reasonable to calculate a common effect estimate from the studies QUEST-1 and QUEST-2.

The QUEST-1 study showed a statistically significant difference in favour of the comparator therapy PLC + PEG + RBV for the outcome "pruritus". In the QUEST-2 study, there was no statistically significant difference between the treatment groups. As both studies had high certainty of results with regard to the outcome "pruritus", it is not possible to derive greater or

lesser harm from SIM + PEG + RBV. Greater or lesser harm is therefore not proven for the outcome “pruritus”.

For the outcome “rash”, the results of both studies were not statistically significant. Greater or lesser harm from SIM + PEG + RBV in comparison with PEG + RBV is thus not proven for this outcome.

The result partly deviates from the company’s assessment, which claimed proof of added benefit based on the reduced study discontinuations due to AEs. However, the company’s assessment was based on an operationalization of this outcome which is regarded to be unsuitable for the benefit assessment (see Section 2.3.2.1 and Section 2.9.2.4.3 of the full dossier assessment).

Pruritus and skin rash were not included in this operationalization by the company in the benefit assessment.

Further information on the outcome results can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Section 2.9.2.4.3 of the full dossier assessment.

2.3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment:

- age (≤ 45 years versus > 45 years to ≤ 65 years versus > 65 years)
- sex
- baseline viral load (< 800 000 IU/mL versus ≥ 800 000 IU/mL)
- presence of cirrhosis of the liver using the stages of the METAVIR score (F0-F3 versus F4); if no separate data are available for the F4 stage (cirrhosis of the liver), the stages “no fibrosis + portal fibrosis” versus “bridges of connective tissues + cirrhosis” (F0-F2 versus F3-F4) are differentiated.
- HCV genotype (1a versus 1b)
- presence of Q80K polymorphism (yes versus no)
- IL28B genotype (CC versus CT versus TT)

This approach partially deviated from that of the company, which did not use the IL28B genotype and additionally analysed subgroups by countries in which the studies were conducted.

Below, only the results on subgroups and outcomes are presented in which there were at least indications of an interaction between treatment effect and subgroup characteristic. The prerequisite for proof of different subgroup effects is a statistically significant interaction ($p < 0.05$). A p-value ≥ 0.05 and < 0.20 provides an indication of an effect modification.

There were no subgroup analyses for the outcome “mortality”. Overall, no suitable data were available for health-related quality of life; therefore no subgroup results can be shown here either.

Table 14 to Table 18 summarize the results on the comparison of SIM + PEG + RBV and PLC + PEG + RBV in treatment-naive CHC genotype 1 patients. Where necessary, the data from the company’s dossier were supplemented by the Institute’s calculations.

Table 14: Subgroups (dichotomous outcomes): SVR 24 – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients)

Characteristic study subgroup	SIM + PEG + RBV		PLC + PEG + RBV		SIM + PEG + RBV vs. PLC + PEG + RBV	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]	p-value
Q80K polymorphism						
PILLAR						
Yes	6	5 (83.3)	7	4 (57.1)	1.46 [0.70; 3.04][a]	
No	71	57 (80.3)	69	45 (65.2)	1.23 [1.00; 1.51][a]	
QUEST-1						
Yes	61	32 (52.5)	30	16 (53.3)	0.98 [0.65; 1.48][a]	
No	201	176 (87.6)	99	47 (47.5)	1.84 [1.49; 2.28][a]	
QUEST-2						
Yes	26	18 (69.2)	14	7 (50.0)	1.38 [0.77; 2.48][a]	
No	229	187 (81.7)	116	57 (49.1)	1.66 [1.37; 2.02][a]	
Total					Interaction:	p = 0.134
Yes					1.16 [0.85; 1.57][b]	p = 0.351[b]
No				Heterogeneity:	p = 0.017; I^2 = 75.6%[b]	
IL28B (CC, CT, TT)						
PILLAR						
CC	22	21 (95.5)	12	12 (100)	0.97 [0.83; 1.13][a]	
CT/TT	33	24 (72.7)	34	17 (50)	1.45 [0.98; 2.16][a]	
QUEST-1						
CC	77	72 (93.5)	37	29 (78.4)	1.19 [1.00; 1.43][a]	
CT/TT	187	138 (73.8)	93	35 (37.6)	1.96 [1.49; 2.58][a]	
QUEST-2						
CC	75	70 (93.3)	42	34 (81.0)	1.15 [0.98; 1.35][a]	
CT/TT	182	132 (72.5)	92	33 (35.9)	2.02 [1.52; 2.70][a]	
Total					Interaction:	p < 0.001[b]
CC					1.10 [0.95; 1.26][b]	p = 0.195[b]
CT/TT					1.87 [1.56; 2.23][b]	p < 0.001[b]

a: Institute's calculation.
b: Institute's calculation from meta-analysis.

CHC: chronic hepatitis C; CI: confidence interval; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SIM: simeprevir; SVR 24: sustained virologic response 24 weeks after the end of treatment; vs.: versus

Table 15: Subgroups (continuous outcomes): fatigue – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients)

Characteristic study subgroup	SIM + PEG + RBV		PLC + PEG + RBV		SIM + PEG + RBV vs. PLC + PEG + RBV	
	N	AUC after 72 weeks mean (SE)	N	AUC after 72 weeks mean (SE)	Mean difference of the AUC [95% CI];	p-value
METAVIR score						
PILLAR						
F0-F2	42	244.1 (9.3)	45	284.2 (9.3)	-40.1 [-64.7; -15.6]	
F3	5	259.5 (30.2)	5	277.1 (29.0)	-58.0 [-127.9; 12.0]	
F4	0	–	0	–		
QUEST-1						
F0-F2	181	240.1 (6.5)	90	276.9 (8.1)	-36.8 [-53.7; -19.9]	
F3	46	272.3 (13.0)	24	263.3 (16.7)	8.9 [-26.4; 44.2]	
F4	30	271.4 (16.3)	16	270.3 (20.2)	1.1 [-39.5; 41.7]	
QUEST-2						
F0-F2	194	229.8 (6.1)	100	257.7 (7.8)	-27.8 [-44.6; -11.1]	
F3	35	273.5 (14.0)	17	244.0 (18.4)	29.5 [-10.7; 69.7]	
F4	17	286.0 (22.5)	15	307.0 (23.5)	-21.1 [-71.0; 28.8]	
Total					Interaction:	p = 0.086[a]
F0-F2					−33.8 [−44.7; −23.0] Hedges' g: −0.50 [−0.66; −0.34][a]	p < 0.001
F3				Heterogeneity	p = 0.104[a]	
F4					-7.74 [-39.2; 23.8][a]	p = 0.630[a]

(continued)

Table 15: Subgroups (continuous outcomes): fatigue – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients) (continued)

Characteristic study subgroup	SIM + PEG + RBV		PLC + PEG + RBV		SIM + PEG + RBV vs. PLC + PEG + RBV	
	N	AUC after 72 weeks mean (SE)	N	AUC after 72 weeks mean (SE)	Mean difference of the AUC [95% CI];	p-value
Q80K polymorphism						
PILLAR						
Yes	3	221.3 (32.3)	6	259.8 (31.3)	-38.5 [-126.3; 49.4]	
No	44	249.3 (9.3)	43	286.4 (9.4)	-37.1 [-61.7; -12.5]	
QUEST-1						
Yes	60	278.6 (11.9)	30	280.6 (14.8)	-2.1 [-33.0; 28.9]	
No	201	242.4 (6.1)	99	271.7 (7.8)	-29.3 [-45.3; -13.2]	
QUEST-2						
Yes	26	265.1 (19.4)	14	273.5 (23.39)	-8.5 [-56.2; 39.3]	
No	227	238.6 (5.6)	114	258.8 (7.3)	-20.2 [-35.9; -4.6]	
Total					Interaction:	p = 0.14
Yes					-6.8 [-31.5; 17.9]	p = 0.59
No					-26.8 [-37.0; -16.6] Hedges' g: -0.40 [-0.55; -0.25]	p < 0.001

a: Institute's calculation from meta-analysis.

AUC: area under the curve; CI: confidence interval; CHC: chronic hepatitis C; N: number of analysed patients; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SE: standard error; SIM: simeprevir; vs.: versus

Table 16: Subgroups (continuous outcomes): depression – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients)

Characteristic study subgroup	SIM + PEG + RBV		PLC + PEG + RBV		SIM + PEG + RBV vs. PLC + PEG + RBV	
	N	AUC after 72 weeks mean (SE)	N	AUC after 72 weeks mean (SE)	Mean difference of the AUC [95% CI];	p-value
Genotype						
PILLAR		Not recorded				
QUEST-1						
1a/other	146	1416.7 (37.9)	74	1389.4 (47.9)	27.3 [-75.3; 129.9]	
1b	115	989.0 (35.0)	56	1114.0 (46.9)	-125.1 [-225.5; -24.7]	
QUEST-2						
1a/other	105	1282.5 (38.6)	57	1352.2 (49.9)	-69.7 [-182.3; 42.8]	
1b	149	1155.8 (34.4)	75	1225.3 (45.3)	-69.6 [-168.8; 29.7]	
Total					Interaction:	p = 0.19
1a/other					-18.4 [-113.3; 76.5]	p = 0.70
1b					-97.1 [-167.6; -26.6] Hedges' g: -0.28 [-0.49; -0.07][a]	p = 0.007
Q80K polymorphism						
PILLAR		Not recorded				
QUEST-1						
Yes	60	1441.7 (56.8)	30	1363.8 (73.0)	77.8 [-83.5; 239.2]	
No	199	1160.6 (31.2)	99	1239.4 (40.0)	-78.8 [-162.3; 4.7]	
QUEST-2						
Yes	26	1393.0 (79.1)	14	1331.9 (98.9)	61.1 [-159.5; 281.8]	
No	226	1190.6 (27.6)	114	1274.3 (36.5)	-83.7 [-164.2; -3.2]	
Total					Interaction:	p = 0.03
Yes					71.9 [-57.5; 201.4]	p = 0.28
No					-81.3 [-139.2; -23.4] Hedges' g: -0.23 [-0.40; -0.07][a]	p = 0.006

a: Institute's calculation from meta-analysis.

AUC: area under the curve; CI: confidence interval; CHC: chronic hepatitis C; N: number of analysed patients; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SE: standard error; SIM: simeprevir; vs.: versus

Table 17: Subgroups (continuous outcomes): health status – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients)

Characteristic study subgroup	SIM + PEG + RBV		PLC + PEG + RBV		SIM + PEG + RBV vs. PLC + PEG + RBV	
	N	AUC after 72 weeks mean (SE)	N	AUC after 72 weeks mean (SE)	Mean difference of the AUC [95% CI];	p-value
Age						
PILLAR		No AUC analysis				
QUEST-1						
≤ 45	111	5938.3 (84.4)	53	5580.9 (110.0)	357.5 [126.2; 588.7]	
> 45 and ≤ 65	140	5552.3 (66.1)	76	5415.4 (86.0)	137.0 [-55.4; 329.4]	
> 65	6	6283.5 (198.2)	1	–	–	
QUEST-2						
≤ 45	121	5998.4 (74.0)	57	5690.7 (100.1)	307.7 [88.3; 527.1]	
> 45 and ≤ 65	126	5593.7 (77.2)	70	5515.1 (97.2)	78.6 [-137.6; 294.7]	
> 65	5	5714.1 (350.1)	4	5000.8 (383.4)	713.3 [-193.8; 1620.3]	
Total					Interaction:	p = 0.007
≤ 45					331.3 [172.4; 490.1] Hedges' g: 0.47 [0.24; 0.70][a]	p < 0.001
> 45 and ≤ 65					111.2 [-32.3; 254.7]	p = 0.13
> 65					713.3 [-149.5; 1576.1]	p = 0.11
Genotype						
PILLAR		No AUC analysis				
QUEST-1						
1a/other	143	5525.7 (75.9)	74	5549.7 (97.1)	-24.0 [-235.9; 187.8]	
1b	114	5974.6 (67.0)	56	5432.1 (91.4)	542.5 [342.4; 742.5]	
QUEST-2						
1a/other	103	5642.2 (90.6)	57	5550.4 (115.1)	91.8 [-162.5; 346.1]	
1b	149	5885.7 (65.9)	74	5602.6 (86.3)	283.2 [93.8; 472.5]	
Total					Interaction:	p = 0.01
1a/other					23.5 [-138.9; 185.9]	p = 0.78
1b					410.8 [156.7; 664.9] Hedges' g: 0.34 [0.13; 0.55][a]	p = 0.002

(continued)

Table 17: Subgroups (continuous outcomes): health status – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients) (continued)

Characteristic study subgroup	SIM + PEG + RBV		PLC + PEG + RBV		SIM + PEG + RBV vs. PLC + PEG + RBV	
	N	AUC after 72 weeks mean (SE)	N	AUC after 72 weeks mean (SE)	Mean difference of the AUC [95% CI];	p-value
Q80K polymorphism						
PILLAR		No AUC analysis				
QUEST-1						
Yes	58	5601.6 (116.1)	30	5686.9 (149.4)	-85.3 [-415.6; 244.9]	
No	197	5761.2 (58.8)	99	5451.0 (77.2)	310.2 [143.7; 476.6]	
QUEST-2						
Yes	25	5619.3 (184.7)	14	5822.2 (234.7)	-202.8 [-741.4; 335.7]	
No	225	5804.6 (56.7)	113	5566.3 (73.9)	238.4 [77.1; 399.7]	
Total					Interaction:	p = 0.01
Yes					-117.7 [-397.6; 162.1]	p = 0.41
No					273.2 [157.5; 388.9]	p < 0.001
					Hedges' g: 0.39 [0.22; 0.56][a]	

a: Institute's calculation from meta-analysis.

AUC: area under the curve; CI: confidence interval; CHC: chronic hepatitis C; N: number of analysed patients; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SE: standard error; SIM: simeprevir; vs.: versus

Table 18: Subgroups (dichotomous outcomes): serious adverse events (72 weeks), RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients)

Characteristic study subgroup	SIM + PEG + RBV		PLC + PEG + RBV		SIM + PEG + RBV vs. PLC + PEG + RBV	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]	p-value
METAVIR score						
PILLAR						
F0-F2	70	6 (8.6)	70	10 (14.3)	0.60 [0.23; 1.56][a]	
F3-F4	7	0 (0)	7	1 (14.3)	0.33 [0.02; 7.02][a]	
QUEST-1						
F0-F2	182	13 (7.1)	90	6 (6.7)	1.07 [0.42; 2.73][a]	
F3-F4	76	6 (7.9)	40	8 (20.0)	0.39 [0.15; 1.06][a]	
QUEST-2						
F0-F2	195	12 (6.2)	102	8 (7.8)	0.78 [0.33; 1.86][a]	
F3-F4	53	6 (11.3)	32	7 (21.9)	0.52 [0.19; 1.40][a]	
Total					Interaction:	p = 0.184[b,c]
F0-F2					0.80 [0.47; 1.35][b]	p = 0,404[b]
F3-F4					0.44 [0.22; 0.88][b]	p = 0,020[b]

a: Institute's calculation.
b: Institute's calculation from meta-analysis.
c: Without consideration of patients with the status "other" (10 patients in QUEST-1, 2 patients in QUEST-2).
CHC: chronic hepatitis C; CI: confidence interval; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SIM: simeprevir; vs.: versus

Morbidity

There were indications or proof of an effect modification for the outcomes "SVR 24", "fatigue", "depression" and "health status".

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

For the surrogate outcome "SVR 24", there was proof of an effect modification by IL28B genotype. The genotypes CT and TT were considered jointly because there was no indication of an effect modification between them. A meta-analysis of the 3 studies included showed a statistically significant advantage in favour of SIM + PEG + RBV for patients with the genotypes CT and TT. This results in an indication of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV.

For patients with the CC genotype, treatment with SIM + PEG + RBV did not result in a statistically significant difference between the treatment groups. It should be noted that in this subgroup, response rates of at least 78% were already achieved in the PEG + RBV group. An

added benefit of SIM + PEG + RBV in comparison with PEG + RBV for this patient group is therefore not proven regarding the SVR 24.

Moreover, there was an indication of an effect modification by the presence of Q80K polymorphism. Because of the heterogeneity of the results it was not reasonable to present a common effect estimate for patients without Q80K polymorphism. However, as all 3 studies showed statistically significant differences in favour of simeprevir, there was an indication of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV (see Figure 9 in Appendix B of the full dossier assessment).

For patients with Q80K polymorphism, the meta-analysis of all 3 studies showed no statistically significant difference between the treatment groups. As the result for the total population was statistically significant and there was only an indication of an effect modification, it cannot be assumed that there is no effect for this subgroup. The certainty of results for this is to be assumed to be lower, however. This results in a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for patients with Q80K polymorphism with regard to SVR 24.

Fatigue using the FSS

There were indications of an effect modification by the characteristics “METAVIR fibrosis score” and “presence of Q80K polymorphism” for the outcome “fatigue”.

With regard to their fibrosis score, it could be differentiated between patients with no or moderate fibrosis (METAVIR score F0-F2), fibrosis with numerous septa (F3) and cirrhosis (F4). For patients with a METAVIR score of F0-F2, the meta-analysis showed a statistically significant difference in favour of simeprevir. The 95% CI of Hedges’ g was completely below the irrelevance threshold of −0.2. This results in a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for this patient group.

Because of the heterogeneity of the results it was not reasonable to present a common effect estimate for patients with a METAVIR score of F3. However, as none of the 3 studies included showed a statistically significant difference between the treatment groups, an added benefit of SIM + PEG + RBV for patients with a METAVIR score of F3 is not proven with regard to fatigue (see Figure 11, Appendix B of the full dossier assessment).

For patients with cirrhosis, the meta-analysis of all 3 studies showed no statistically significant difference between the treatment groups. Hence an added benefit of SIM + PEG + RBV in comparison with PEG + RBV is not proven for patients with cirrhosis with regard to the outcome “fatigue”.

There was no statistically significant difference between the treatment groups for patients with Q80K polymorphism. Hence an added benefit of SIM + PEG + RBV in comparison with PEG + RBV is not proven for these patients with regard to the outcome “fatigue”.

There was a statistically significant difference in favour of SIM + PEG + RBV for patients without Q80K polymorphism. The 95% CI of Hedges' g was completely below the irrelevance threshold of −0.2. This results in a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for this patient group.

Depression using the CES-D

There was proof of an effect modification by the characteristic "Q80K polymorphism" for the outcome "depression". The meta-analysis showed a statistically significant difference in favour of SIM + PEG + RBV for patients without Q80K polymorphism. The 95% CI of Hedges' g did not lie completely below the irrelevance threshold of −0.2. It was therefore possible that the effect was within a range that is irrelevant. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV for patients without Q80K polymorphism with regard to the outcome "depression" is therefore not proven.

For patients with Q80K polymorphism, the meta-analysis of all 3 studies showed no statistically significant difference between the treatment groups. An added benefit of SIM + PEG + RBV for patients with Q80K polymorphism is therefore not proven.

In addition, there was an indication of an effect modification by the characteristic "genotype 1a or 1b". The meta-analysis showed no statistically significant difference between the treatment groups for patients with genotype 1a. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV for patients with genotype 1a is therefore not proven.

The meta-analysis showed a statistically significant difference in favour of SIM + PEG + RBV for patients with genotype 1b. However, the 95% CI of Hedges' g was not completely below the irrelevance threshold of −0.2. Hence an added benefit of SIM + PEG + RBV is not proven for patients with genotype 1b with regard to the outcome "depression".

Overall, as in the total population, there was no proof of added benefit of SIM + PEG + RBV in comparison with PEG + RBV in the patient subgroups for the outcome "depression".

Health status using the EQ-5D VAS

There was proof of an effect modification for each of the characteristics "age", "genotype" and "Q80K polymorphism" for the outcome "health status".

The meta-analysis showed a statistically significant difference in favour of SIM + PEG + RBV for patients aged 45 years or younger. The 95% CI of Hedges' g was completely above the irrelevance threshold of 0.2. This results in an indication of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for patients aged 45 years or younger with regard to health status.

For patients from the age of 45 to 65 years and for patients aged older than 65 years, the meta-analysis showed no statistically significant difference between the treatment groups. An added

benefit of SIM + PEG + RBV in comparison with PEG + RBV for these age groups is therefore not proven.

The meta-analysis showed no statistically significant difference between the treatment groups for patients with genotype 1a.

The meta-analysis showed a statistically significant difference in favour of SIM + PEG + RBV for patients with genotype 1b. The 95% CI of Hedges' g did not lie completely above the irrelevance threshold of 0.2. It was therefore possible that the effect was within a range that is irrelevant. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV regarding health status is therefore not proven for patients of both genotypes.

The meta-analysis showed a statistically significant difference in favour of SIM + PEG + RBV for patients without Q80K polymorphism. The 95% CI of Hedges' g was completely above the irrelevance threshold of 0.2. This results in an indication of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV with regard to health status for patients without Q80K polymorphism.

For patients with Q80K polymorphism, the meta-analysis showed no statistically significant difference between the treatment groups. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV regarding health status is therefore not proven for patients with Q80K polymorphism.

Adverse events

Indications of an effect modification were only available for the outcome "SAEs".

Serious adverse events

There was an indication of an effect modification by the characteristic "fibrosis score" for the outcome "SAEs". No separate data for individual METAVIR scores were available in the studies so that a differentiation from patients with cirrhosis was not possible. Instead, the subgroups of patients with no to moderate fibrosis (F0 to F2) and fibrosis with numerous septa to cirrhosis (F3 to F4) can be presented.

There was no statistically significant difference between the treatment groups for patients with a METAVIR score of F0 to F2. Lesser harm from SIM + PEG + RBV in comparison with PEG + RBV for these patients is therefore not proven.

There was a statistically significant difference in favour of SIM + PEG + RBV for patients with a METAVIR score of F3 to F4. As there was no statistically significant difference in the total population, there is higher uncertainty for such a subgroup result. This results in an indication of lesser harm from SIM + PEG + RBV in comparison with PEG + RBV with regard to SAEs for patients with a METAVIR score of F3 to F4.

Further information on the subgroup results can be found in Module 4, Section 4.3.1.3.2 of the dossier, and in Section 2.9.2.4.3 of the full dossier assessment.

2.3.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit for each subpopulation is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.3.2 resulted in indications or hints of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for the outcomes “HCC” (assessed with the SVR 24 surrogate), “fatigue” and “health status”. Regarding the outcomes on harm, lesser harm was observed for SAEs. The extent of the respective added benefit at outcome level was estimated from these results (see Table 19).

Effect modifications resulted from the characteristics “age”, “genotype” (1a versus 1b or IL28B), “Q80K polymorphism” and “degree of liver damage”. Regarding the latter characteristic, patients with cirrhosis (METAVIR score F4) could not be differentiated from patients without cirrhosis for all outcomes due to the available data. The subgroups F0-F2 and F3-F4 could be used instead to differentiate patients with no to moderate fibrosis from patients with severe fibrosis or cirrhosis.

Table 19: Extent of added benefit at outcome level: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients)

Outcome category **outcome**		**SIM + PEG + RBV vs. PLC + PEG + RBV** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality			
All-cause mortality		Calculation of common estimate not reasonable due to the low number of event	Lesser benefit/added benefit not proven
Morbidity			
HCC, assessed with the SVR 24 surrogate[c]		Heterogeneous results[d,e] There was a statistically significant effect in favour of simeprevir in all 3 studies included in the meta-analysis.	
Q80K polymorphism	yes	52.5% to 83.3% (heterogeneous proportions) vs. 52.9%[f] RR: 1.16 [0.85; 1.57] p = 0.351 probability: "hint"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"
	no	Heterogeneous results[d,e] There was a statistically significant effect in favour of simeprevir in all 3 studies included in the meta-analysis. probability: "indication"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"
IL28B	CC	93.6% vs. 80.8%[f] RR: 1.10 [0.95; 1.26] p = 0.195	Lesser benefit/added benefit not proven
	CT+TT	73.1% vs. 38.7%[f] RR: 1.87 [1.56; 2.23] p < 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"
Fatigue using the FSS		Mean difference of the AUC: -24.1 [-33.4; -14.8] p < 0.001 Hedges' g: -0.36 [-0.53; -0.19][g]	

(continued)

Table 19: Extent of added benefit at outcome level: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients) (continued)

Outcome category outcome		SIM + PEG + RBV vs. PLC + PEG + RBV proportion of events effect estimate [95% CI] p-value probability[a]	Derivation of extent[b]
METAVIR score	F0-F2	Mean difference of the AUC: -33.8 [-44.7; -23.0] p < 0.001 Hedges' g: -0.50 [-0.66; -0.34][g] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
	F3	Heterogeneous results There was no statistically significant effect in any of the 3 studies included in the meta-analysis[h].	Lesser benefit/added benefit not proven
	F4	Mean difference of the AUC: -7.74 [-39.2; 23.8] p = 0.630	Lesser benefit/added benefit not proven
Q80K polymorphism	yes	Mean difference of the AUC: -6.8 [-31.5; 17.9] p = 0.59	Lesser benefit/added benefit not proven
	no	Mean difference of the AUC: -26.8 [-37.0; -16.6] p < 0.001 Hedges' g: -0.40 [-0.55; -0.25][g] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Depression using the CES-D		Mean difference of the AUC: -56.1 [-108.8; -3.3] p = 0.04 Hedges' g: -0.16 [-0.31; -0.01][g]	Lesser benefit/added benefit not proven
Health status using the EQ-5D VAS		Mean difference of the AUC: 214.5 [108.2; 320.8] p < 0.001 Hedges' g: 0.28 [0.14; 0.41][g]	

(continued)

Table 19: Extent of added benefit at outcome level: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients) (continued)

Outcome category outcome		SIM + PEG + RBV vs. PLC + PEG + RBV proportion of events effect estimate [95% CI] p-value probability[a]	Derivation of extent[b]
Age	≤ 45	Mean difference of the AUC: 331.3 [172.4; 490.1] p < 0.001 Hedges' g: 0.47 [0.24; 0.70][g] probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
	> 45 - ≤ 65	Mean difference of the AUC: 111.2 [-32.3; 254.7] p = 0.13	Lesser benefit/added benefit not proven
	> 65	Mean difference of the AUC: 713.3 [-149.5; 1576.1] p = 0.11	Lesser benefit/added benefit not proven
Q80K polymorphism	yes	Mean difference of the AUC: -117.7 [-397.6; 162.1] p = 0.41	Lesser benefit/added benefit not proven
	no	Mean difference of the AUC: 273.2 [157.5; 388.9] p < 0.001 Hedges' g: 0.39 [0.22; 0.56][g] probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Health-related quality of life			
No evaluable data			
Adverse events			
SAEs		7.9% vs. 11.8%[f] RR: 0.68 [0.45; 1.02][d] p = 0.065[d]	
METAVIR score	F0-F2	7.0% vs. 9.4%[f] RR: 0.80 [0.47; 1.35] p = 0.404	Greater/lesser harm not proven
	F3-F4	9.3% vs. 20.3%[f] RR: 0.44 [0.22; 0.88] p = 0.020 probability: "indication"	Outcome category: serious/severe AEs CI_u < 0.90 lesser harm, extent: "non-quantifiable", not more than "considerable"

(continued)

Table 19: Extent of added benefit at outcome level: SIM + PEG + RBV vs. PLC + PEG + RBV (treatment-naive CHC genotype 1 patients) (continued)

Outcome category outcome	**SIM + PEG + RBV vs. PLC + PEG + RBV proportion of events effect estimate [95% CI] p-value probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs	RR: 0.95 [0.46; 1.93][d] 0.8% to 10.4% (heterogeneous proportions) vs. 0% to 13.0% (heterogeneous proportions)[f] p = 0.879[d]	Greater/lesser harm not proven
Pruritus	Heterogeneous results[i] 25.9% vs. 15.4% to 25.4% (heterogeneous proportions)[f]	Greater/lesser harm not proven
Skin rash	Heterogeneous results[h] There was no statistically significant effect in any of the 2 studies included in the meta-analysis.	Greater/lesser harm not proven

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: SVR was used as surrogate for a patient-relevant outcome (HCC). It was regarded as sufficiently valid to be considered in the benefit assessment (see Section 2.9.2.4.2 of the full dossier assessment).
d: Institute's calculation.
e: No effect estimate can be provided because of the heterogeneous data; however, an added benefit can be derived because all 3 studies included showed a statistically significant advantage of simeprevir.
f: Pooled proportion from meta-analysis, Institute's calculation.
g: Added benefit assumed with upper and lower CI limits < -0.2 and > 0.2.
h: No effect estimate can be provided because of the heterogeneous data; none of the studies included showed a significant effect.
AE: adverse event; AUC: area under the curve; CI: confidence interval; CI_u: upper limit of the CI; HCC: hepatocellular carcinoma; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RR; relative risk; SAE: serious adverse event; SIM: simeprevir; SVR 24: sustained virologic response 24 weeks after the end of treatment; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 20 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 20: Positive and negative effects from the assessment of SIM + PEG + RBV in comparison with PEG + RBV (treatment-naive CHC genotype 1 patients)

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ HCC, assessed with the SVR 24 surrogate: ▫ Q80K polymorphism – yes: hint of an added benefit, extent: “non-quantifiable” ▫ Q80K polymorphism – no: indication of an added benefit, extent: “non-quantifiable” ▫ IL28B – CC: lesser benefit/added benefit not proven ▫ IL28B – CT+TT: indication of an added benefit, extent: “non-quantifiable”	-
Non-serious/non-severe symptoms ▪ Fatigue using the FSS: ▫ METAVIR score F0-F2: hint of an added benefit – extent: “non-quantifiable” ▫ METAVIR score F3: lesser benefit/added benefit not proven ▫ METAVIR score F4: lesser benefit/added benefit not proven ▫ Q80K polymorphism – yes: lesser benefit/added benefit not proven ▫ Q80K polymorphism – no: hint of an added benefit – extent: “non-quantifiable”	-
Non-serious/non-severe symptoms ▪ Health status using the EQ-5D VAS: ▫ age ≤ 45 years: indication of an added benefit – extent: “non-quantifiable” ▫ age > 45 to ≤ 65 years: lesser benefit/added benefit not proven ▫ age > 65 years: lesser benefit/added benefit not proven ▫ Q80K polymorphism – yes: lesser benefit/added benefit not proven ▫ Q80K polymorphism – no: indication of an added benefit – extent: “non-quantifiable”	-
Serious/severe adverse events ▪ SAEs: ▫ METAVIR score F0-F2: greater/lesser harm not proven ▫ METAVIR score F3-F4: indication of lesser harm – extent: “non-quantifiable”, no more than “considerable”	-
CHC: chronic hepatitis C; EQ-5D: European Quality of Life-5 Dimensions; FSS: Fatigue Severity Scale; HCC: hepatocellular carcinoma; PEG: peginterferon alfa; RBV: ribavirin; SAE: serious adverse event; SIM: simeprevir; SVR 24: sustained virologic response 24 weeks after the end of treatment; VAS: visual analogue scale; vs.: versus	

Overall, only positive effects remain in the outcome categories “serious/severe symptoms”, “non-serious/non-severe symptoms” and “serious/severe AEs”. Due to the surrogate character of the SVR 24, the extent of added benefit for this outcome cannot be quantified. The extent of added benefit for the continuous outcomes “fatigue”, “depression” and “health status” can also not be quantified.

Due to the high risk of bias of the studies, in general, no more than "indications" of an added benefit could be derived. However, a high certainty of results resulted from the bias to the disadvantage of SIM + PEG + RBV for the outcomes on AEs so that no more than proof of an added benefit could be derived for these outcomes.

The outcome "HCC" has to be considered to be a serious late complication of CHC, whereas the other outcomes on morbidity are considered to be non-serious symptoms. Hence the estimation of the added benefit of SIM + PEG + RBV is largely based on HCC or its SVR 24 surrogate. There were effect modifications so that the results of the individual subgroups have to be considered. When considering the subgroup-specific effects it is notable that the characteristic "Q80K polymorphism" is an effect modifier in each outcome regarding benefit. In all cases with proof or indication of an effect modification there was an indication of added benefit only for patients without Q80K polymorphism. Moreover, proof of an effect modification by the characteristic "IL28B" results in a differentiated added benefit in patient groups with different dimensions of this characteristic.

Regarding the fibrosis score of the patients, there were indications of an effect modification for the outcomes "fatigue" and "SAEs". There was a hint or an indication of an advantage of SIM + PEG + RBV both for patients with a METAVIR score of F0-F2 (regarding improvement of fatigue-related symptoms) and for patients with a score of F3-F4 (regarding the reduction of serious AEs).

Overall, this results in an indication of a non-quantifiable added benefit of SIM + PEG + RBV in comparison with PEG + RBV for patients without Q80K polymorphism and for patients with IL28B genotype CT or TT. For patients with Q80K polymorphism, there is a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV.

For patients with IL28B CC genotype, an added benefit of SIM + PEG + RBV is not proven regarding the outcome "SVR 24". Since no subgroup analyses for this characteristic were available for other outcomes and, moreover, the results were subject to greater uncertainty, no conclusion can be drawn on whether an added benefit can be derived from other outcomes for this patient group. Hence an added benefit of SIM + PEG + RBV in comparison with PEG + RBV is not proven for patients with IL28B CC genotype.

The result of the assessment of the added benefit of simeprevir in comparison with the ACT is summarized in Table 21.

Table 21: Simeprevir – extent and probability of added benefit

Research question	ACT[a]	Subgroup	Extent and probability of added benefit
Treatment-naive CHC genotype 1 patients	**Dual therapy (combination of peginterferon and ribavirin)** or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin) treatment-naive patients with cirrhosis: dual therapy	Q80K polymorphism: no	Indication of non-quantifiable added benefit
		Q80K polymorphism: yes	Hint of non-quantifiable added benefit
		IL28B genotype: CT/TT	Indication of non-quantifiable added benefit
		IL28B genotype: CC	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.			

This deviates from the company's approach, which claimed proof of major added benefit for treatment-naive CHC genotype 1 patients without Q80K polymorphism and proof of considerable added benefit for treatment-naive CHC genotype 1 patients with Q80K polymorphism.

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

2.3.4 List of included studies

PILLAR

Fried MW, Buti M, Dore GJ, Flisiak R, Ferenci P, Jacobson I et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: the randomized PILLAR study. Hepatology 2013; 58(6): 1918-1929.

Janssen Research & Development. A phase IIb, randomized, double-blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 as part of a treatment regimen including peginterferon alfa 2a and ribavirin in treatment-naïve genotype 1 hepatitis C infected subjects: study TMC435-TiDP16-C205 (PILLAR); clinical study report [unpublished]. 2012.

Tibotec Pharmaceuticals. A phase IIb, randomized, double-blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 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: 29 April 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-007147-13.

Tibotec Pharmaceuticals. A phase IIb, randomized, double-blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 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: 8 May 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Tibotec Pharmaceuticals. TMC435-TiDP16-C205: a phase II study of TMC435 in combination with pegylated interferon alpha-2a and ribavirin in patients infected with genotype 1 hepatitis C virus who never received treatment (PILLAR); full text view [online]. In: Clinicaltrials.gov. 28 June 2012 [accessed: 29 April 2014]. URL: http://ClinicalTrials.gov/show/NCT00882908.

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 08.06.2014 [Epub ahead of print].

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: 29 April 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-020444-36.

Janssen R&D Ireland. TMC435-TiDP16-C208: phase III trial of TMC435 in treatment-naive, genotype 1 hepatitis C-infected patients (QUEST-1); full text view [online]. In: Clinicaltrials.gov. 9 July 2013 [accessed: 29 April 2014]. URL: http://ClinicalTrials.gov/show/NCT01289782.

Janssen Research & Development. A phase 3, 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 α-2a and ribavirin in treatment-naïve, genotype 1 hepatitis C infected subjects: study TMC435-TiDP16-C208 (QUEST-1); clinical study report; final analysis [unpublished]. 2013.

Tibotec Pharmaceuticals. 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: 6 March 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

QUEST-2

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: 8 May 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Janssen R&D Ireland. TMC435-TiDP16-C216: phase III trial of TMC435 in treatment-naive, genotype 1 hepatitis C-infected patients (QUEST-2); full text view [online]. In: Clinicaltrials.gov. 26 February 2013 [accessed: 29 April 2014]. URL: http://ClinicalTrials.gov/show/NCT01290679.

Janssen Research & Development. A phase 3, 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: study TMC435-TiDP16-C216 (QUEST-2); clinical study report; final analysis [unpublished]. 2013.

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 8 June 2014 [Epub ahead of print].

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: 29 April 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-021174-11.

2.4 Research question 1b: CHC genotype 1, relapsed patients after prior treatment response

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on simeprevir (studies completed up to 6 March 2014)
- bibliographical literature search on simeprevir (last search on 5 May 2014)
- search in trial registries for studies on simeprevir (last search on 6 March 2014)

To check the completeness of the study pool:

- bibliographical literature search on simeprevir (last search on 12 June 2014)
- search in trial registries for studies on simeprevir (last search on 12 June 2014)

No additional relevant study was identified from the check.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.9.2.1 and 2.9.2.3 of the full dossier assessment.

2.4.1.1 Studies included

The study included in the benefit assessment is listed in the following table.

Table 22: Study pool – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
PROMISE (TMC435HPC3007)	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. CHC: chronic hepatitis C; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; vs.: versus			

2.4.1.2 Study characteristics

Table 23 and Table 24 describe the studies used for the benefit assessment.

Table 23: Characteristics of the studies included – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PROMISE	RCT, double-blind, parallel, multicentre	Adults (≥ 18 years) with confirmed chronic HCV infection (genotype 1) plasma HCV RNA > 10 000 IU/mL at screening relapse after prior interferon-based therapy	Group 1: SIM + PEG + RBV (N = 261) group 2: PLC + PEG + RBV (N = 133)	Treatment duration: simeprevir: 24 or 48 weeks[b] (response-guided) placebo: 48 weeks follow-up: up to 24 weeks	Australia, Austria, Belgium, Canada, France, Germany, Great Britain, Italy, New Zealand, Poland, Puerto Rico, Russia, Spain, United States 1/2011-2/2013	Primary: proportion of patients with SVR 12 in each treatment group Secondary: patients with SVR 24, patients with SVR W72, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: The approval-compliant treatment duration is 24 weeks; the deviations of the study population from the approval population are negligible.
CHC: chronic hepatitis C; HCV: hepatitis C virus; N: number of randomized patients; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid; SIM: simeprevir; SVR: sustained virologic response; SVR W72: sustained virologic response in week 72; vs.: versus

Table 24: Characteristics of the interventions – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study	SIM + PEG + RBV	PLC + PEG +RBV	Concomitant medication
PROMISE	Week 1-12: SIM 150 mg orally once daily + PEG 180 µg subcutaneously 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 13-24 or 13-48 (response-guided): PEG + RBV, same dosage as week 1-12	Week 1-12: placebo orally once daily + PEG 180 µg subcutaneously 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 13-24 or 13-48 (response-guided): PEG + RBV, same dosage as week 1-12	Prohibited at any time point (including pretreatment): ▪ any other anti-HCV treatments Prohibited from 30 days before screening until the end of the study: ▪ investigational vaccines Prohibited from screening until the end of the study: ▪ immunomodulators ▪ substances that stimulate blood production Prohibited during the first 24 weeks of the study: ▪ CYP3A4 inducers ▪ CYP3A4 inhibitors ▪ CYP3A4 substrates with small therapeutic indices ▪ CYP1A2 substrates ▪ CYP2C8 substrates ▪ statins

CHC: chronic hepatitis C; CYP: cytochrome P450; HCV: hepatitis C virus; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; vs.: versus

The PROMISE study was a double-blind RCT and had been completed at the time of the commission. The patients were randomly assigned in a ratio of 2:1. Patients with or without cirrhosis were included who initially had undetectable HCV RNA after 24 weeks or more of prior interferon-based therapy and in whom HCV RNA was detected again within one year after the last administration of the drug (relapsed patients). The patients received simeprevir or placebo, each in combination with peginterferon alfa and ribavirin, with simeprevir being administered at a dosage of 150 mg/day for 12 weeks. Dosage and treatment duration of the comparator therapy with PLC + PEG + RBV were in compliance with the approval.

A response-guided treatment regimen was planned in the SIM + PEG + RBV arm of the study, i.e. the treatment was to be discontinued after treatment success. Treatment of 48 weeks was initially planned for all patients. However, this treatment duration could be reduced to 24 weeks when prespecified criteria regarding virologic response were met. With negligible exceptions, these criteria were met so that > 80% of the patients of the SIM + PEG + RBV arm were treated for 24 weeks. This treatment duration concurs with the approval for relapsed patients [3]. The planned treatment duration in the PLC + PEG + RBV arm of the study was 48 weeks for all patients irrespective of the virologic response, which concurs with the approvals for peginterferon alfa and ribavirin [4,5]. Table 58 of the full

dossier assessment provides an overview of the treatment regimens and the criteria for reduction in treatment duration.

Moreover, in both treatment groups, treatment discontinuation was planned in case of inadequate virologic response. In the study protocol, specific threshold values of the viral load of the patients were defined for several time points in the course of the study. If these were exceeded, treatment was to be discontinued (time-point specific either only simeprevir or placebo or the total study medication). See Section 2.9.2.4.1 of the full dossier assessment for more details.

Primary outcome of the study was the SVR 12; the SVR 24 was recorded as secondary outcome. The total observation period of the study was 72 weeks, irrespective of a patient's individual treatment duration.

Table 25 shows the characteristics of the patients in the studies included.

Table 25: Characteristics of the study populations – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study group	N	Age [years] mean (SD)	Sex [F/M] %	Fibrosis score[a] %	Cirrhosis [with/without] %	Genotype [1a/1b/other] %	Viral load [≤ 800 000/ > 800 000 IU/mL] %	Ethnicity [white/ black/ other] %	Study discontinua-tions n (%)
PROMISE									
SIM + PEG + RBV	260	50 (10)	31/69	F0-F1: 35.2 F2: 31.6 F3: 17.6 F4: 15.6	15.6/84.4[b]	42.3/57.3/0.4	15.8[d]/84.2	93.5/2.7/3.8[e]	10 (3.8)
PLC + PEG + RBV	133	50 (11)	41/59	F0-F1: 36.4 F2: 37.9 F3: 11.4 F4: 14.4	14.4/85.6[c]	40.6/59.4/0	17.3[d]/82.7	96.2/3.0/0.8[f]	14 (10.5)

a: Information based on METAVIR score: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis.
b: Institute's calculation; METAVIR fibrosis score F4 = cirrhosis; N (SIM) = 250.
c: Institute's calculation; METAVIR fibrosis score F4 = cirrhosis; N (PLC) = 132.
d: Institute's calculation.
e: Institute's calculation; Hawaiians or pacific islanders = 0.4%, Asians = 3.1%, and mixed ethnicity = 0.4%.
f: Asians.

CHC: chronic hepatitis C; F: female; IU: international units; M: male; N: number of randomized patients who received at least one dose of their allocated study medication; n: number of patients with event; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; SIM: simeprevir; vs.: versus

The PROMISE study comprised 260 patients in the SIM + PEG + RBV arm and 133 patients in the PLC + PEG + RBV arm. The average age of 50 years was identical in both treatment groups. More men than women were treated in both treatment groups. Patients without cirrhosis were the majority (84 and 85% respectively). In both treatment arms, baseline viral load was high in approximately 85% of the patients. More than 90% of the patients were white. The rate of study discontinuations was low (2% and 4% respectively). In both treatment groups, approximately 15 to 20% more patients with genotype 1b than with genotype 1a were included. In summary, there were no important differences between the treatment groups.

In the characteristics of the study population, the company provided no information on the proportions of patients with liver damage according to the METAVIR score, although it presented comprehensive subgroup analyses on this. Only the proportions of patients with and without cirrhosis were presented. The proportions of patients with METAVIR scores F0-F1, F2, F3 and F4 are therefore additionally presented here. The proportion of patients with increasing degree of liver damage decreased in both treatment groups. Patients with a METAVIR score of F3 or F4 together comprised approximately 25 to 30% of the population.

Table 26 shows the risk of bias at study level.

Table 26: Risk of bias at study level – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
PROMISE	Yes	Yes	Yes	Yes	Yes	No[a]	High

a: High differential proportions of study discontinuations (SIM + PEG + RBV: 3.8% vs. PLC + PEG + RBV: 10.5%).

CHC: chronic hepatitis C; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; vs.: versus

The risk of bias at study level was rated as high for the study because the number of patients who discontinued treatment prematurely due to non-response differed considerably between the 2 treatment arms. The same applies to the number of patients who discontinued the study. This deviates from the company's assessment, which regarded the study as having low bias.

Overall assessment of the certainty of conclusions

The use of the study medication, which was partially not in compliance with the approval, resulted in situations that influenced the informative value of the results for the PROMISE

study. Within the studies, the frequency with which dual therapy was discontinued differed considerably in the study arms. These premature treatment discontinuations particularly occurred in the PLC + PEG + RBV arms, which resulted in shorter treatment durations in these patients than recommended by the approval. Moreover, in the SIM + PEG + RBV arm, approximately 6% of the patients were treated longer than recommended by the approval, which was caused by criteria for treatment discontinuation that deviated from the information in the SPC and package information leaflet. These reasons caused uncertainty regarding the interpretability of the study results for answering the research question of the benefit assessment. The potential uncertainty of the treatment effect in comparison with approval-compliant treatment is discussed below separately for the outcomes considered.

A sensitivity analysis could show for the outcome "SVR 24" that the effect estimate is still statistically significant if the rates of discontinuation - if these were caused by virologic discontinuation criteria - and the patients who discontinued the study, and treatment in the SIM + PEG + RBV arm, which was longer than approved, are considered adequately. Despite the high risk of bias (see Section 2.3.2.3 and Section 2.9.2.4.1 of the full dossier assessment), the certainty of conclusions for the outcome "SVR 24" was rated as high. Hence no more than an "indication" of added benefit can be derived for this outcome.

A corresponding sensitivity analysis could not be conducted for the results on the outcomes "fatigue" (using the FSS), "depression" (using the CES-D) and "health status" (using the EQ-5D VAS) so that their certainty of conclusions is regarded to be reduced. Hence no more than "hints" of an added benefit can be derived for these outcomes.

As in the PLC + PEG + RBV arm of the study, treatment was discontinued prematurely in approximately 10% of the patients, and particularly more often than in the SIM + PEG + RBV arm (the difference was approximately 8 percentage points), whereas on the other hand approximately 6% of the patients in the SIM + PEG + RBV arm were treated longer than recommended by the approval, this probably affects the effects on AEs to the disadvantage of SIM + PEG + RBV. Hence in case of lesser harm from SIM + PEG + RBV, the certainty of conclusions for these outcomes is regarded as high despite the high risk of bias. The derivation of indications of lesser harm from SIM + PEG + RBV is possible because of this.

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and Appendix 4-F of the dossier, and in Sections 2.9.2.4.1 and 2.9.2.4.2 of the full dossier assessment.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.9.2.4.3 of the full dossier assessment):

- Mortality

- overall survival

- Morbidity
  - SVR 24 as sufficiently valid surrogate for the patient-relevant outcome “HCC” (additional presentation: SVR at week 72)
  - fatigue using the FSS
  - depression using the CES-D
  - health status using the EQ-5D VAS

- Adverse events
  - overall rate of SAEs
  - treatment discontinuation due to AEs
  - fatigue (PT)
  - flu-like illness (PT)
  - dyspnoea (PT)
  - eye disorders (System Organ Class [SOC])

The choice of patient-relevant outcomes deviated from that of the company.

The company used the instruments FFS and CES-D to describe the treatment-related symptoms. However, since it is not possible to differentiate between disease-related and treatment-related symptoms this way, these were here regarded to be outcomes of morbidity. The company’s approach was also deviated from insofar as the EQ-5D was not completely included in the benefit assessment, but only the VAS. Moreover, the VAS was regarded to be a measurement of the general health status. The WPAI was also not considered. See Section 2.9.2.4.3 of the full dossier assessment for more details.

Further outcomes, namely the AEs “pruritus” and “rash”, which the company did not consider in the dossier, were additionally included. These were included as AEs of particular interest because there were notable differences between the treatment groups (see Appendix C of the full dossier assessment). The operationalization of the outcomes regarding harm deviates from the one of the company, which only presented the data on the first 12 weeks of treatment and on the total treatment phase. Due to the different treatment durations in the study arms, these are not informative enough, which is why the data at week 72 of the observation were used instead (see Section 2.9.2.4.3 of the full dossier assessment).

Further information on the choice of outcomes can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Section 2.9.2.4.3 of the full dossier assessment.

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

Table 27: Matrix of outcomes – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study	Outcomes												
	All-cause mortality	Sustained virologic response (SVR 24)	Sustained virologic response (SVR W72)	Depression using the CES-D	Fatigue using the FSS	Health status using the EQ-5D VAS	Health-related quality of life	SAEs	Discontinuation due to AEs	Fatigue	Flu-like illness	Dyspnoea	Eye disorders
PROMISE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AE: adverse event; CES-D: Centre for Epidemiologic Studies Depression Scale; CHC: chronic hepatitis C; EQ-5D: European Quality of Life-5 Dimensions; FSS: Fatigue Severity Scale; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SIM: simeprevir; SVR: sustained virologic response; VAS: visual analogue scale; vs.: versus

2.4.2.2 Risk of bias

Table 40 shows the risk of bias for these outcomes.

Table 28: Risk of bias at study and outcome level – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study		Outcomes												
	Study level	All-cause mortality	Sustained virologic response (SVR 24)	Sustained virologic response (SVR W72)	Depression using the CES-D	Fatigue using the FSS	Health status using the EQ-5D VAS	Health-related quality of life	SAEs	Discontinuation due to AEs	Fatigue	Flu-like illness	Dyspnoea	Eye disorders
PROMISE	H	L	H	H	H	H	H	–	H	H	H	H	H	H

AE: adverse event; CES-D: Centre for Epidemiologic Studies Depression Scale; CHC: chronic hepatitis C; EQ-5D: European Quality of Life-5 Dimensions; FSS: Fatigue Severity Scale; H: high; L: low; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SIM: simeprevir; SVR: sustained virologic response; VAS: visual analogue scale; vs.: versus

The risk of bias for this outcome was generally rated as low because bias from premature treatment discontinuations on the mortality effects was rated as unlikely for the rates considered. The company presented no separate results for the outcome "mortality" and conducted no assessment of the risk of bias.

The company assessed the risk of bias as low for all other outcomes considered. The company's assessment was not accepted. The reasons responsible for a high risk of bias at study level also lead to a high risk of bias for these outcomes. Nonetheless, the certainty of conclusions for the outcome "SVR 24" and all outcomes on AEs was rated as high (see Section 2.4.1.2). Hence no more than "indications" of an added benefit can be derived for these outcomes; and no more than "hints" of an added benefit can be derived for the outcomes "fatigue", "depression" and "health status".

Further information on the risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3, and in Appendix 4-F of the dossier, and in Section 2.9.2.4.2 of the full dossier assessment.

2.4.2.3 Results

Table 39 and Table 30 summarize the results on the comparison of SIM + PEG + RBV and PLC + PEG + RBV in relapsed CHC genotype 1 patients. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. The data at the analysis date of 72 weeks were used for all data on AEs. The figures of the meta-analyses calculated by the Institute can be found in Appendix B of the full dossier assessment.

As a consequence of the virologic stopping criteria specified by the study protocols, which were to be applied to both treatment groups (see Section 2.9.2.4.1 of the full dossier assessment), a relevant number of patients in the comparator arms were treated for a shorter period of time with PLC + PEG + RBV than recommended by the approval (48 weeks [3]). In the company's CSRs, treatment discontinuations were analysed as patients with treatment failure. The company did not address this problem in the dossier. Regarding the SVR 24 data, a sensitivity analysis was therefore conducted, in which it was assumed for these patients that they reach the outcome with the probability with which those patients of the control group reach it who did not discontinue dual therapy and the study. For illustration, the result is also presented in Table 29 showing that the high number of treatment discontinuations did not have a relevantly distorting influence on the treatment effect with regard to statistical significance.

Table 29: Results (dichotomous outcomes) – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study outcome category outcome	SIM + PEG + RBV		PLC + PEG +RBV		SIM + PEG + RBV vs. PLC + PEG + RBV
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
PROMISE					
Mortality					
All-cause mortality	260	1 (0.4)	133	1 (0.8)	0.49 [0.03; 9.11][a]; 0.698[c]
Morbidity					
SVR 24[b]	260	201 (77.3)	133	45 (33.8)	2.28 [1.79; 2.92][d]; < 0.001[c]
Additionally: sensitivity analysis for the surrogate outcome "SVR 24"					
					1.82 [1.45; 2.30][e]
SVR W72	260	199 (76.5)	133	45 (33.8)	2.26 [1.77; 2.90][d]; < 0.001[c]
Health-related quality of life	No evaluable data available				
Adverse events[f]					
AEs	260	255 (98.1)	133	126 (94.7)	
SAEs	260	23 (8.8)	133	14 (10.5)	0.84 [0.45; 1.58][d]; 0.608[c]
Discontinuation due to AEs	260	1 (0.4)	133	0 (0)	1.54 [0.06; 37.6][d]; 0.487[c]
Fatigue	260	89 (34.2)	133	59 (44.4)	0.77 [0.60; 0.99][g]; 0.051[c]
Flu-like illness	260	78 (30.0)	133	27 (20.3)	1.48 [1.01; 2.17][d]; 0.041[c]
Dyspnoea	260	27 (10.4)	133	5 (3.8)	2.76 [1.09; 7.01][d]; 0.023[c]
Eye disorders	260	28 (10.8)	133	29 (21.8)	0.49 [0.31; 0.79][d]; 0.003[c]

(continued)

Table 29: Results (dichotomous outcomes) – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients) (continued)

a: Peto odds ratio, Institute's calculation, asymptotic.
b: Sufficiently valid surrogate for the patient-relevant outcome "HCC".
c: Institute's calculation, unconditional exact test (CSZ method according to [9]).
d: Institute's calculation, asymptotic.
e: Institute's calculation: For patients who discontinued dual therapy and for patients who discontinued the study, it was assumed in both treatment arms that they reach the outcome with the probability with which those patients of the control group reach it who did not discontinue dual therapy and the study. It was assumed that the patients who discontinued the study did not also belong to the group of patients who discontinued dual therapy. The variances were adapted according to the data-set re-sizing approach a (approach W3 in [8]). Under the even more conservative assumption that all patients who discontinued dual therapy or the study had reached the outcome, this would result in RR = 1.53 [1.30; 1.81].
f: Data analysed up to week 72.
g: Institute's calculation, asymptotic. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SIM: simeprevir; SVR: sustained virologic response; SVR W72: sustained virologic response in week 72; vs.: versus

Table 30: Results (continuous outcomes) – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study outcome category outcome	SIM + PEG + RBV			PLC + PEG +RBV			SIM + PEG + RBV vs. PLC + PEG + RBV
	N[a]	Values at start of study mean (SE)	Change at end of study mean[b] (SD)	N[a]	Values at start of study mean (SD)	Change at end of study mean[b] (SD)	Mean difference of the AUC[b] [95% CI]; p-value Hedges' g [95% CI]
PROMISE							
Morbidity (week 0-72)							
Depression using the CES-D[c]	238	14.41 (0.42)	0.25 (0.55)	111	13.17 (0.58)	0.34 (0.64)	-98.3 [-165.7; -30.9]; 0.004 -0.31 [-0.52; -0.1]
Fatigue using the FSS[d]	238	3.59 (0.10)	-0.49 (0.11)	114	3.26 (0.12)	-0.20 (0.13)	-29.4 [-43.8; -15.1]; < 0.001 -0.43 [-0.64; -0.22]
Health status using the EQ-5D VAS[e]	235	78.89 (1.01)	3.28 (1.15)	112	81.16 (1.31)	0.57 (1.51)	352.0 [193.4; 510.6]; < 0.001 0.47 [0.25; 0.68]

a: Number of patients in the AUC analysis; the values at the start of the study may be based on other patient numbers.
b: Piecewise linear mixed model without imputation of missing values.
c: Negative changes at the end of the study mean improvement in symptoms; the CES-D scale ranges from 0 to 60 points, high values indicate worse state.
d: Negative changes at the end of the study mean improvement in symptoms; the total FSS scale ranges from 1 to 7 points; high values indicate worse state.
e: Positive changes at the end of the study mean improvement in symptoms; the VAS scale ranges from 0 to 100 with 0 being the best and 100 being the worst imaginable health status.
AUC: area under the curve; CES-D: Centre for Epidemiologic Studies Depression Scale; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FSS: Fatigue Severity Scale; N: number of analysed patients; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SIM: simeprevir; VAS: visual analogue scale; vs.: versus

Mortality

One patient died in each of the 2 treatment groups of the study. There was no statistically significant difference between the treatment groups. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV for mortality is not proven.

Morbidity

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

There was a statistically significant difference in favour of SIM + PEG + RBV for the outcome "SVR 24". This was confirmed by the sensitivity analysis, which is why the analysis conducted by the company was used for the assessment of the added benefit.

The SVR rates at week 72 are presented as additional information in Table 29. They were not used for the derivation of the added benefit. The results confirm the data on SVR 24 because a statistically significant advantage in favour of SIM + PEG + RBV could be determined here as well.

In addition, there was proof of an effect modification by the characteristic "age" for this outcome. There was an indication of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for the outcome "SVR 24" for all 3 age subgroups (≤ 45 years, > 45 to ≤ 65 years and > 65 years) (see Section 2.4.2.4).

This concurs with the company's assessment, which differentiated between patients with and without Q80K polymorphism however.

Depression using the CES-D

There was a statistically significant difference in favour of SIM + PEG + RBV for the outcome "depression". It is to be noted that higher values indicate worsening or increase of depression symptoms, i.e. a negative difference of the AUCs indicates less worsening or increased improvement in the SIM + PEG + RBV arm in comparison with the PLC + PEG + RBV arm.

Hedges' g was used to evaluate the relevance of the effect. The 95% CI did not lie completely below the irrelevance threshold of −0.2. It was therefore possible that the effect was within a range that is irrelevant.

An added benefit of SIM + PEG + RBV in comparison with PEG + RBV for the outcome "depression" is therefore not proven.

This deviates from the company's assessment, which claimed an indication of added benefit for relapsed patients for this outcome.

Fatigue using the FSS

There was a statistically significant difference in favour of SIM + PEG + RBV for the outcome "fatigue". It is to be noted that higher values indicate worsening or increase of depression symptoms, i.e. a negative difference of the AUCs indicates less worsening or increased improvement in the SIM + PEG + RBV arm in comparison with the PLC + PEG + RBV arm.

Hedges' g was used to evaluate the relevance of the effect. The 95% CI was completely below the irrelevance threshold of −0.2. In addition, there was proof of an effect modification by the characteristic "sex". This results in a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV with regard to the outcome "fatigue" in women. For men, an added benefit is not proven (see Section 2.4.2.4).

This deviates from the company's assessment, which claimed an indication of added benefit for all relapsed patients.

Health status using the EQ-5D VAS

There was a statistically significant difference in favour of SIM + PEG + RBV for the outcome "health status". It is to be noted that higher values indicate an improvement in general health status, i.e. that a positive effect indicates an increased improvement or less worsening in the SIM + PEG + RBV than in the PLC + PEG + RBV arm.

Hedges' g was used to evaluate the relevance of the effect. The 95% CI was completely above the irrelevance threshold of 0.2. In addition, there was proof of effect modifications with regard to the characteristics "genotype 1a/1b" and "Q80K polymorphism", and an indication of an effect modification with regard to the characteristic "sex". In each case, this results in a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for women, patients with genotype 1b and patients without Q80K polymorphism. For the other subgroups, an added benefit is not proven (see Section 2.4.2.4).

This deviates from the company's assessment, which claimed an indication of added benefit for relapsed patients without Q80K polymorphism.

Health-related quality of life

There were no evaluable data on health-related quality of life. This deviates from the company's approach, which included the EQ-5D (utility and VAS on health status) as well as the WPAI for this purpose. See Section 2.9.2.4.3 of the full dossier assessment for the question of the consideration of these outcomes in the benefit assessment.

Adverse events

Serious adverse events

In the total population, there was no statistically significant difference between the treatment groups for the outcome "SAEs".

In addition, there was proof of an effect modification by the characteristic "sex" and indications of an effect modification by the characteristics "age" and "METAVIR fibrosis score". This results in an indication of lesser harm in male patients. For women, greater or lesser harm is not proven. There were no statistically significant effects with regard to the characteristics "age" and "fibrosis score" in the individual subgroups and the total population. Lesser or greater harm for these subgroups is therefore not proven (see Section 2.4.2.4).

This deviates from the company's assessment, which mentioned no relevant effect modifications for SAEs.

Treatment discontinuations due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". There was an indication of an effect modification by the characteristic "baseline viral load". However, greater or lesser harm is not proven for patients with low or high viral load because the extent of the observed effects was no more than marginal.

This concurs with the company's assessment.

Fatigue

There was no statistically significant difference between the treatment groups for the outcome "fatigue". There were no results on subgroups. Greater or lesser harm from SIM + PEG + RBV in comparison with PEG + RBV is thus not proven.

The company did not consider this outcome in Module 4 of the dossier.

Flu-like illness

There was a statistically significant difference in favour of the comparator therapy PLC + PEG + RBV for the outcome "flu-like illness". The extent of this effect was no more than marginal, however, because the upper limit of the CI, with reversed direction of effect, was larger than the threshold value of 0.90 (see also the *General Methods* of the Institute [1]). There were no results on subgroups. Greater or lesser harm from SIM + PEG + RBV in comparison with PEG + RBV is thus not proven.

The company did not consider this outcome in Module 4 of the dossier.

Dyspnoea

There was a statistically significant difference in favour of the comparator therapy PLC + PEG + RBV for the outcome "dyspnoea". The extent of this effect was no more than marginal, however, because the upper limit of the CI, with reversed direction of effect, was larger than the threshold value of 0.90 (see also the *General Methods* of the Institute [1]). There were no results on subgroups. Greater or lesser harm from SIM + PEG + RBV in comparison with PEG + RBV is thus not proven.

The company did not consider this outcome in Module 4 of the dossier. There were no results on subgroups.

Eye disorders

There was a statistically significant difference in favour of SIM + PEG + RBV for the outcome "eye disorders". There were no results on subgroups. This results in an indication of lesser harm from SIM + PEG + RBV in comparison with PEG + RBV for eye disorders.

The company did not consider this outcome in Module 4 of the dossier.

Further information on the outcome results can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Section 2.9.2.4.3 of the full dossier assessment.

2.4.2.4 Subgroups and other effect modifiers

See Section 2.3.2.4 for a list of the relevant subgroups and comparison with the company's approach.

Below, only the results on subgroups and outcomes are presented in which there were at least indications of an interaction between treatment effect and subgroup characteristic. The prerequisite for proof of different subgroup effects is a statistically significant interaction ($p < 0.05$). A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. There were no subgroup analyses for the outcome "mortality". Overall, no suitable data were available for health-related quality of life; therefore no subgroup results can be shown here either.

Table 31 to Table 35 summarize the results on the comparison of SIM + PEG + RBV and PEG + RBV in CHC patients. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 31: Subgroups (dichotomous outcomes): SVR 24 – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study characteristic subgroup	**SIM + PEG + RBV**		**PLC + PEG +RBV**		**SIM + PEG + RBV vs. PLC + PEG + RBV**	
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI][a]**	**p-value[b]**
PROMISE						
Age						
≤ 45 years	78	63 (80.8)	35	19 (54.3)	1.49 [1.08; 2.05]	0.004
> 45 – 65 years	172	130 (75.6)	95	26 (27.4)	2.76 [1.97; 3.87]	< 0.001
> 65 years	10	8 (80.0)	3	0 (0)	6.18 [0.45; 84.3][c]	0.016
					Interaction:	0.016[c]

a: Institute's calculation, asymptotic.
b: Institute's calculation, unconditional exact test (CSZ method according to [9]).
c: Institute's calculation, asymptotic. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SIM: simeprevir; SVR: sustained virologic response; vs.: versus

Table 32: Subgroups (continuous outcomes): Fatigue – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study characteristic subgroup	SIM + PEG + RBV		PLC + PEG +RBV		SIM + PEG + RBV vs. PLC + PEG + RBV	
	N	AUC at week 72 mean (SE)	N	AUC at week 72 mean (SE)	Mean difference [95% CI]	p-value[a]
PROMISE						
Sex						
men	174	255.3 (6.2)	77	265.0 (8.5)	-9.7 [-27.4; 8.0]	0.285
women	76	280.5 (9.4)	54	333.4 (11.0)	-52.9 [-77.3; -28.5] Hedges' g: -0.75 [-1.11; -0.39]	< 0.001
					Interaction:	0.005[b]

a: Institute's calculation.
b: Institute's calculation from meta-analysis.
AUC: area under the curve; CHC: chronic hepatitis C; CI: confidence interval; N: number of analysed patients; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; vs.: versus

Table 33: Subgroups (dichotomous outcomes): Health status – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study characteristic subgroup	SIM + PEG + RBV		PLC + PEG +RBV		SIM + PEG + RBV vs. PLC + PEG + RBV	
	N	AUC at week 72 mean (SE)	N	AUC at week 72 mean (SE)	Mean difference [95% CI]	p-value[a]
PROMISE						
Sex						
men	174	5594.1 (67.3)	77	5338.7 (91.7)	255.4 [63.7; 447.1] Hedges' g: 0.36 [0.09; 0.63]	0.009
women	75	5437.7 (100.6)	52	4953.9 (119.4)	483.8 [205.7; 761.8] Hedges' g: 0.61 [0.25; 0.97]	< 0.001
					Interaction:	0.185[b]
Genotype						
1a	108	5410.6 (93.9)	50	5328.7 (126.1)	81.8 [-188.4; 352.0]	0.533
1b	141	5633.3 (68.8)	79	5108.9 (88.2)	524.5 [331.0; 717.9] Hedges' g: 0.74 [0.46; 1.03]	< 0.001
					Interaction:	0.009[b]
Q80K polymorphism						
yes	29	5489.1 (187.1)	18	5589.1 (227.6)	-100.1 [-569.0; 368.9]	0.676
no	217	5539.8 (58.9)	111	5135.6 (77.3)	404.3 [235.5; 573.1] Hedges' g: 0.55 [0.31; 0.78]	< 0.001
					Interaction:	0.047[b]

a: Institute's calculation.
b: Institute's calculation from meta-analysis.
AUC: area under the curve; CHC: chronic hepatitis C; CI: confidence interval; N: number of analysed patients; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; vs.: versus

Table 34: Subgroups (dichotomous outcomes): SAEs – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study characteristic subgroup	SIM + PEG + RBV		PLC + PEG +RBV		SIM + PEG + RBV vs. PLC + PEG + RBV	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI][a]	p-value[b]
PROMISE						
Age						
≤ 45 years	78	8 (10.3)	35	0 (0)	7.75 [0.46; 130.6]	0.052
> 45 – 65 years	172	13 (7.6)	95	14 (14.7)	0.51 [0.25; 1.05]	0.064
> 65 years	10	2 (20.0)	3	0 (0)	1.82 [0.11; 30.3]	0.433
					Interaction:	0.111[c]
Sex						
men	179	9 (5.0)	79	10 (12.7)	0.40 [0.17; 0.94]	0.032
women	81	14 (17.3)	54	4 (7.4)	2.33 [0.81; 6.71]	0.116
					Interaction:	0.010[c]
METAVIR score						
F0 – F2	167	16 (9.6)	98	8 (8.2)	1.17 [0.52; 2.64]	0.718
F3 – F4	83	6 (7.2)	34	6 (17.6)	0.41 [0.14; 1.18]	0.098
					Interaction:	0.121[c]

a: Institute's calculation, asymptotic.
b: Institute's calculation, unconditional exact test (CSZ method according to [9]).
c: Institute's calculation from meta-analysis.

CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SIM: simeprevir; vs.: versus

Table 35: Subgroups (dichotomous outcomes): Discontinuation due to AEs – RCT, direct comparison: SIM + PEG + RBV vs. PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Study characteristic subgroup	SIM + PEG + RBV		PLC + PEG +RBV		SIM + PEG + RBV vs. PLC + PEG + RBV	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI][a]	p-value[b]
PROMISE						
Baseline viral load						
≤ 800 000 IU/mL	41	0 (0)	23	3 (13.0)	0.08 [0.00; 1.51][c]	0.019
> 800 000 IU/mL	219	6 (2.7)	110	4 (3.6)	0.75 [0.22; 2.61]	0.715
					Interaction:	0,160[d]

a: Institute's calculation, asymptotic.
b: Institute's calculation, unconditional exact test (CSZ method according to [9]).
c: Institute's calculation, asymptotic. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
d: Institute's calculation from meta-analysis.
AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; IU: international units; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SIM: simeprevir; vs.: versus

Morbidity

There were indications or proof of an effect modification for the outcomes "SVR 24", "fatigue" and "health status".

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

There was proof of an effect modification with regard to the patients' age for the outcome "SVR 24". Nevertheless, the differences between the treatment groups were statistically significant in favour of SIM + PEG + RBV in all 3 age groups. This results in an indication of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for all age groups.

Fatigue using the FSS

There was proof of an effect modification by the patients' sex for the outcome "fatigue". There was a statistically significant difference in favour of SIM + PEG + RBV for the subgroup of women. The 95% CI of Hedges' g was completely below the irrelevance threshold of −0.2. This results in a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for women.

There was no statistically significant difference between the treatment groups in the subgroup of men. An added benefit of SIM + PEG + RBV in comparison with PEG + RBV for men is therefore not proven.

Health status using the EQ-5D VAS

For the outcome "health status", there was proof of an effect modification for the characteristics "genotype 1a/1b" and "Q80K polymorphism", and an indication of an effect modification by the characteristic "sex".

There was no statistically significant difference between the treatment groups for patients with genotype 1a. Hence an added benefit of SIM + PEG + RBV in comparison with PEG + RBV with regard to health status is not proven for patients with genotype 1a.

There was a statistically significant difference in favour of SIM + PEG + RBV for patients with genotype 1b. The 95% CI of Hedges' g was completely above the irrelevance threshold of 0.20. This results in a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for patients with genotype 1b with regard to health status.

There was a statistically significant difference in favour of SIM + PEG + RBV for patients without Q80K polymorphism. The 95% CI of Hedges' g was completely above the irrelevance threshold of 0.2. This results in a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for patients without Q80K polymorphism with regard to health status.

There was no statistically significant difference between the treatment groups for patients with Q80K polymorphism. Hence an added benefit of SIM + PEG + RBV in comparison with PEG + RBV regarding health status is not proven for patients with Q80K polymorphism.

There was a statistically significant difference in favour of SIM + PEG + RBV for women. The 95% CI of Hedges' g was completely above the irrelevance threshold of 0.2. This results in a hint of an added benefit of SIM + PEG + RBV in comparison with PEG + RBV for women with regard to health status.

There was a statistically significant difference in favour of SIM + PEG + RBV for men. The 95% CI of Hedges' g was not completely above the irrelevance threshold of 0.2. Hence an added benefit of SIM + PEG + RBV in comparison with PEG + RBV with regard to health status is not proven for men.

Adverse events

There were indications or proof of effect modifications for the outcomes "SAEs" and "treatment discontinuations due to AEs".

Serious adverse events

There was proof of an effect modification by the characteristic "sex" for the outcome "SAEs". There was a statistically significant difference in favour of SIM + PEG + RBV for men. This results in an indication of lesser harm from SIM + PEG + RBV in comparison with PEG + RBV for men with regard to SAEs.

For women, there was no statistically significant difference between the treatment groups. Greater or lesser harm from SIM + PEG + RBV in comparison with PEG + RBV for women is thus not proven.

There was an indication of an effect modification for the characteristics "age" and "fibrosis score". Only data on the subgroups F0-F2 and F3-F4, but not separately for patients with cirrhosis (F4), were available for fibrosis score. However, there was no statistically significant difference between the treatment groups in any subgroup. Hence an added benefit of SIM + PEG + RBV in comparison with PEG + RBV with regard to SAEs is not proven for any age group or fibrosis score.

Treatment discontinuations due to adverse events

There was an indication of an effect modification by the characteristic "baseline viral load" for the outcome "treatment discontinuations due to AEs". There was a statistically significant difference in favour of SIM + PEG + RBV for patients with low viral load. The extent of this effect was no more than marginal, however, because the upper limit of the CI, with reversed direction of effect, was larger than the threshold value of 0.90.

There was no statistically significant difference between the treatment groups for patients with high viral load. Hence an added benefit of SIM + PEG + RBV in comparison with PEG + RBV with regard to discontinuations due to AEs is not proven for patients with low or high viral load.

Further information on the subgroup results can be found in Module 4, Section 4.3.1.3.2 of the dossier, and in Section 2.9.2.4.3 of the full dossier assessment.

2.4.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit for each subpopulation is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.4.2 resulted in indications or hints of an added benefit of simeprevir in comparison with peginterferon alfa and ribavirin for the outcomes "HCC" (assessed with the SVR 24 surrogate), "fatigue" and "health status". Regarding the outcomes on harm, lesser harm was observed for SAEs. The extent of the respective added benefit at outcome level was estimated from these results (see Table 36).

Effect modifications resulted from the characteristics “age”, “sex”, “genotype (1a/1b)”, “Q80K polymorphism” and “METAVIR fibrosis score”. For the outcome “SAEs”, for which an indication of effect modification by fibrosis score was present, patients with cirrhosis (F4) could not be differentiated from patients without cirrhosis (F0-F3) because only data on the subgroups F0-F2 and F3-F4 were available.

Table 36: Extent of added benefit at outcome level: SIM + PEG + RBV vs. PEG + RBV (relapsed CHC genotype 1 patients)

Outcome category **outcome**	**SIM + PEG + RBV vs. PEG + RBV** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0.4% vs. 0.8% Peto-OR: 0.49 [0.03; 9.11][c] p = 0.698[d]	Lesser benefit/added benefit not proven
Morbidity		
HCC, assessed with the SVR 24 surrogate[e]	77.3% vs. 33.8% RR: 2.28 [1.79; 2.92][g] p < 0.001[d]	
Age ≤ 45	80.8% vs. 54.3% RR: 1.49 [1.08; 2.05][g] p = 0.004[d] probability: “indication”	Outcome category: serious/severe symptoms/late complications added benefit, extent: “non-quantifiable”
> 45 – ≤ 65	75.6% vs. 27.4% RR: 2.76 [1.97; 3.87][g] p < 0.001[d] probability: “indication”	Outcome category: serious/severe symptoms/late complications added benefit, extent: “non-quantifiable”
> 65	80.0% vs. 0% RR: 6.18 [0.45; 84.3][g] p = 0.016[d,h] probability: “indication”	Outcome category: serious/severe symptoms/late complications added benefit, extent: “non-quantifiable”
Depression using the CES-D	Mean difference of the AUC: -98.3 [-165.7; -30.9] p = 0.004 Hedges’ g: -0.31 [-0.52; -0.1][f]	Lesser benefit/added benefit not proven
Health status using the EQ-5D VAS	Mean difference of the AUC: 352.0 [193.4; 510.6] p < 0.001 Hedges’ g: 0.47 [0.25; 0.68][f]	
Sex men	Mean difference of the AUC: 255.4 [63.7; 447.1] p = 0.009 Hedges’ g: 0.36 [0.09; 0.63][f]	Lesser benefit/added benefit not proven

(continued)

Table 36: Extent of added benefit at outcome level: SIM + PEG + RBV vs. PEG + RBV (relapsed CHC genotype 1 patients) (continued)

Outcome category outcome		**SIM + PEG + RBV vs. PEG + RBV proportion of events effect estimate [95% CI] p-value probability**[a]	**Derivation of extent**[b]
	women	Mean difference of the AUC: 483.8 [205.7; 761.8] p < 0.001 Hedges' g: 0.61 [0.25; 0.97] probability: "hint"	Outcome category: non-serious/non-severe symptoms added benefit, extent: "non-quantifiable"
Genotype	1a	Mean difference of the AUC: 81.8 [-188.4; 352.0] p = 0.533	Lesser benefit/added benefit not proven
	1b	Mean difference of the AUC: 524.5 [331.0; 717.9] p < 0.001 Hedges' g: 0.74 [0.46; 1.03] probability: "hint"	Outcome category: non-serious/non-severe symptoms added benefit, extent: "non-quantifiable"
Q80K polymorphism	yes	Mean difference of the AUC: -100.1 [-569.0; 368.9] p = 0.676	Lesser benefit/added benefit not proven
	no	Mean difference of the AUC: 404.3 [235.5; 573.1] p < 0.001 Hedges' g: 0.55 [0.31; 0.78] probability: "hint"	Outcome category: non-serious/non-severe symptoms added benefit, extent: "non-quantifiable"
Fatigue using the FSS		Mean difference of the AUC: -29.4 [-43.8; -15.1] p < 0.001 Hedges' g: -0.43 [-0.64; -0.22][f]	
Sex	men	Mean difference of the AUC: -9.7 [-27.4; 8.0] p = 0.285	Lesser benefit/added benefit not proven

(continued)

Table 36: Extent of added benefit at outcome level: SIM + PEG + RBV vs. PEG + RBV (relapsed CHC genotype 1 patients) (continued)

Outcome category **outcome**		**SIM + PEG + RBV vs. PEG + RBV** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
	women	Mean difference of the AUC: -52.9 [-77.3; -28.5] p < 0.001 Hedges' g: -0.75 [-1.11; -0.39][f] probability: "hint"	Outcome category: non-serious/non-severe symptoms added benefit, extent: "non-quantifiable"
Health-related quality of life		No evaluable data available	
Adverse events			
SAEs		8.8% vs. 10.5% RR: 0.84 [0.45; 1.58][g] p = 0.608[d]	
Sex	men	5.0% vs. 12.7% RR: 0.40 [0.17; 0.94][g] p = 0.032[d] probability: "indication"	Outcome category: serious/severe AEs CI_u < 1.00 lesser harm, extent: "minor"
	women	17.3% vs. 7.4% RR: 2.33 [0.81; 6.71][g] p = 0.116[d]	Greater/lesser harm not proven
Discontinuation due to AEs		0.4% vs. 0% RR: 1.54 [0.06; 37.6][g] p = 0.487[d]	Greater/lesser harm not proven
Baseline viral load	≤ 800 000 IU/mL	0% vs. 13.0% RR: 0.08 [0.00; 1.51] p = 0.019[d,h]	Outcome category: non-serious/non-severe adverse events 0.90 < CI_u greater/lesser harm not proven
	> 800 000 IU/mL	2.7% vs. 3.6% RR: 0.75 [0.22; 2.61] p = 0.715[d]	Greater/lesser harm not proven
Fatigue		34.2% vs. 44.4% RR: 0.77 [0.60; 0.99][f] p = 0.051[d,h]	Greater/lesser harm not proven

(continued)

Table 36: Extent of added benefit at outcome level: SIM + PEG + RBV vs. PEG + RBV (relapsed CHC genotype 1 patients) (continued)

Outcome category **outcome**	**SIM + PEG + RBV vs. PEG + RBV** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Flu-like illness	30.0% vs. 20.3% RR: 1.48 [1.01; 2.17][g] 0.68 [0.46; 0.99][i] p = 0.041[f]	Outcome category: non-serious/non-severe adverse events $0.90 < CI_u$ greater/lesser harm not proven
Dyspnoea	10.4% vs. 3.8% RR: 2.76 [1.09; 7.01][g] 0.36 [0.14; 0.92][i] p = 0.023[d]	Outcome category: non-serious/non-severe adverse events $0.90 < CI_u$ greater/lesser harm not proven
Eye disorders	10.8% vs. 21.8% RR: 0.49 [0.31; 0.79][f] p = 0.003[d] probability: "indication"	Outcome category: non-serious/non-severe adverse events $CI_u < 0.80$ lesser harm, extent: "considerable"

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Peto odds ratio, Institute's calculation, asymptotic.
d: Institute's calculation, unconditional exact test (CSZ method according to [9]).
e: SVR was used as surrogate for a patient-relevant outcome (HCC). It is regarded as sufficiently valid to be considered in the benefit assessment (see Section 2.9.2.4 of the full dossier assessment).
f: Added benefit assumed with upper and lower CI limit of < -0.20 and > 0.20.
g: Institute's calculation, asymptotic.
h: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
i: Proportion of events SIM + PEG + RBV vs. PEG + RBV (reversed direction of effect to enable direct use of limits to derive the extent of added benefit).
AE: adverse event; AUC: area under the curve; CES-D: Centre for Epidemiologic Studies Depression Scale; CHC: chronic hepatitis C; CI: confidence interval; CI_u: upper limit of the CI; CSZ: convexity, symmetry, z score; EQ-5D: European Quality of Life-5 Dimensions; FSS: Fatigue Severity Scale; HCC: hepatocellular carcinoma; PEG: peginterferon alfa; RBV: ribavirin; RR; relative risk; SAE: serious adverse event; SIM: simeprevir; SVR 24: sustained virologic response 24 weeks after the end of treatment; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 37 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 37: Positive and negative effects from the assessment of SIM + PEG + RBV in comparison with PLC + PEG + RBV (relapsed CHC genotype 1 patients)

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ HCC, assessed with the SVR 24 surrogate: indication of added benefit – extent: non-quantifiable	-
Non-serious/non-severe symptoms ▪ Fatigue using the FSS: ▫ sex: women: hint of an added benefit – extent: "non-quantifiable" ▫ sex: men: lesser benefit/added benefit not proven	-
Non-serious/non-severe symptoms ▪ Health status using the EQ-5D VAS: ▫ sex: women: hint of an added benefit – extent: "non-quantifiable" ▫ sex: men: lesser benefit/added benefit not proven ▫ genotype 1a: lesser benefit/added benefit not proven ▫ genotype 1b: hint of an added benefit – extent: "non-quantifiable" ▫ Q80K polymorphism: yes: lesser benefit/added benefit not proven ▫ Q80K polymorphism: no: hint of an added benefit – extent: "non-quantifiable"	-
Serious/severe adverse events ▪ SAEs: ▫ sex: women: greater/lesser harm not proven ▫ sex: men: indication of lesser harm – extent: "minor"	-
Non-serious/non-severe adverse events ▪ eye disorders: indication of lesser harm – extent: "considerable"	-
CHC: chronic hepatitis C; EQ-5D: European Quality of Life-5 Dimensions; FSS: Fatigue Severity Scale; HCC: hepatocellular carcinoma; PEG: peginterferon alfa; PLC: placebo; RBV: ribavirin; SAE: serious adverse event; SIM: simeprevir; SVR 24: sustained virologic response 24 weeks after the end of treatment; VAS: visual analogue scale; vs.: versus	

Overall, only positive effects remain in the outcome categories "serious/severe symptoms", "non-serious/non-severe symptoms", "serious/severe AEs" and non-serious/non-severe AEs". Due to the surrogate character of the SVR 24, the extent of added benefit for this outcome cannot be quantified. The extent of added benefit for the continuous outcomes "fatigue", "depression" and "health status" can also not be quantified.

Whereas an indication of a non-quantifiable added benefit can be derived for the outcome "HCC", only hints can be derived for all other outcomes regarding benefit due to the high risk of bias of the study. There was an indication of lesser harm for each of the outcomes "SAEs" (men) and "eye disorders". Hence, summarizing the results for relapsed CHC genotype 1 patients, there is an indication of a non-quantifiable added benefit.

The result of the assessment of the added benefit of simeprevir in comparison with the ACT is summarized in Table 38.

Table 38: Simeprevir – extent and probability of added benefit

Research question	ACT[a]	Extent and probability of added benefit
Pretreated relapsed patients with CHC genotype 1	**Dual therapy (combination of peginterferon and ribavirin)** or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)	Indication of non-quantifiable added benefit
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. ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee		

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.4 List of included studies

PROMISE

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 hepatitis C, genotype 1 infected subjects who relapsed after previous interferon-based therapy [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 6 March 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Janssen R&D Ireland. TMC435HPC3007: phase III trial of TMC435 in genotype 1 hepatitis C-infected patients who relapsed after previous therapy; full text view [online]. In: Clinicaltrials.gov. 26 March 2014 [accessed: 29 April 2014]. URL: http://ClinicalTrials.gov/show/NCT01281839.

Janssen Research & Development. 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 α-2a and ribavirin in hepatitis C, genotype 1 infected subjects who relapsed after previous interferon-based therapy: study TMC435HPC3007 (PROMISE); clinical study report; final analysis [unpublished]. 2013.

Tibotec Pharmaceuticals. 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 hepatitis C, genotype 1 infected subjects who relapsed after previous interferon-based therapy [online]. In: EU Clinical Trials Register. [Accessed: 29 April 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-021113-23.

2.5 Research question 1c: CHC genotype 1, previous non-responders (including partial and null responders)

2.5.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on simeprevir (studies completed up to 6 March 2014)
- bibliographical literature search on simeprevir (last search on 5 May 2014)
- search in trial registries for studies on simeprevir (last search on 6 March 2014)

To check the completeness of the study pool:

- bibliographical literature search on simeprevir (last search on 12 June 2014)
- search in trial registries for studies on simeprevir (last search on 12 June 2014)

No additional relevant study was identified from the check.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.9.2.1 and 2.9.2.3 of the full dossier assessment.

2.5.1.1 Studies included

The study listed in the following table was included in the benefit assessment of simeprevir in pretreated genotype 1 patients who have not adequately responded to prior therapy (previous non-responders, including partial and null responders).

Table 39: Study pool – RCT, direct comparison: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
ATTAIN (TMC435HPC3001)	No	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. CHC: chronic hepatitis C; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; TVR: telaprevir; vs.: versus			

The study pool concurred with the study pool of the company.

Section 2.5.4 contains a reference list for the study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections 2.9.2.3.1 and 2.9.2.3.2 of the full dossier assessment.

2.5.1.2 Study characteristics

Table 40 and Table 41 describe the study used for the benefit assessment; Table 42 shows the characteristics of the patients of the ATTAIN study.

Table 40: Characteristics of the studies included – RCT, direct comparison: SIM + PEG + RBV vs. TIR + PEG + RBV (previous non-responders with CHC genotype 1)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ATTAIN	RCT, double-blind, parallel, multicentre	Adults (≥ 18 years) with confirmed chronic HCV infection (genotype 1) plasma HCV RNA > 10 000 IU/mL at screening at least 1 previous course of treatment with PEG alfa-2a or 2b in combination with RBV for at least 12 (null responders[b]) or 20 (partial responders[c]) consecutive weeks with only partial or no response[d]	Group 1: SIM + PEG + RBV (N = 385) group 2: TVR + PEG + RBV (N = 386) only PEG and RBV administered in week 13-48	Screening phase: 6 weeks treatment duration: SIM or TVR: 12 weeks PEG and RBV: up to week 48 follow-up duration: 12 and 24 weeks total study duration: 72 weeks from the start of treatment	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 start: 2/2012 available data cut-off: 2/2014[e]	Primary: proportion of patients with SVR 12 in each treatment group secondary: patients with SVR 24, symptoms, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: Null responders: patients who had a < 2 log10 IU/mL reduction in HCV RNA after 12 weeks of treatment in comparison with baseline, and in whom HCV RNA could be detected at the end of treatment.
c: Partial responders: patients who had a ≥ 2 log10 IU/mL reduction in HCV RNA after 12 weeks of treatment in comparison with baseline, and in whom HCV RNA could be detected at the end of treatment, but not before the end of week 20.
d: Patients were not allowed to have discontinued prior therapy due to intolerance.
e: The ATTAIN study was not yet completed at the time of the benefit assessment. The available analyses at the data cut-off of 60 weeks were used for the benefit assessment. This data cut-off was planned a priori for the analysis of the primary outcome (SVR 12).

CHC: chronic hepatitis C; HCV: hepatitis C virus; IU: international units; N: number of randomized patients; PEG: peginterferon alfa; RBV: ribavirin; RNA: ribonucleic acid; RCT: randomized controlled trial; SIM: simeprevir; SVR: sustained virologic response; TVR: telaprevir; vs.: versus

Table 41: Characteristics of the interventions – RCT, direct comparison: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1)

Study	SIM + PEG + RBV	TVR + PEG + RBV	Concomitant medication
ATTAIN	Week 1-12: SIM 150 mg orally once daily + PEG 180 µg subcutaneously 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: PEG + RBV, same dosage as week 1-12	Week 1-12: TVR 750 mg orally once daily + PEG 180 µg subcutaneously 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: PEG + RBV, same dosage as week 1-12	Prohibited medication (during the study): ▪ anti-HCV medications (except study medication) ▪ any investigational medications and vaccines ▪ immunomodulators except PEG ▪ certain CYP3A4 inducers, inhibitors and substrates, including ▫ antiepileptics (including carbamazepine and phenytoin) ▫ antiarrhythmics (including amiodarone, flecainide and propafenone) ▫ corticosteroids (prednisone and methylprednisone) ▪ CYP1A2 substrates (amitriptyline, theophylline) ▪ CYP2AC8 substrates (repaglinide, torasemide) ▪ certain statins (atorvastatin, lovastatin and simvastatin) Some medications required the sponsor's approval, including: warfarin, certain antidepressants, calcium channel antagonists and certain statins (pravastatin, rosuvastatin and fluvastatin).
CHC: chronic hepatitis C; CYP: cytochrome P450; HCV: hepatitis C virus; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; TVR: telaprevir; vs.: versus			

Table 42: Characteristics of the study populations – RCT, direct comparison: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non responders with CHC genotype 1)

Study group subgroup	N	Null responders/ partial responders n (%)	Age [years] mean (SD)	Sex [F/M] %	Fibrosis score[a] %	Cirrhosis [with/ without][e] %	Genotype [1a/1b/ other] %	Viral load [≤ 800 000/ > 800 000 IU/mL] %	Ethnicity [white/ black/ other] %	Study discontinua-tions n (%)
ATTAIN										
SIM + PEG + RBV	379	234 (62) 145 (38)	49 (10)	36/64	F0-F1: 29.3 F2: 26.4 F3: 26.0 F4: 18.3	23.2/76.8	43/56.7/0.3	11.6[b]/88.4	94.2/5.6/0.5[c]	21 (5.5)
TVR + PEG + RBV	384	238 (62) 146 (38)	50 (11)	42/58	F0-F1: 27.4 F2: 28.0 F3: 29.2 F4: 15.4	19.5/80.5	42.2/57.3/0.6	13.0[b]/87.0	94.5/4.4/1.0[d]	29 (7.6)

a: Information based on METAVIR score: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis.
b: Institute's calculation.
c: Institute's calculation; Native Americans or Alaskans = 0.3% and unknown (inquiry not allowed due to local regulations) = 0.3%.
e: Institute's calculation; Native Americans or Alaskans = 0.5%, Asians = 0.3%, and mixed ethnicity = 0.3%.
e: Determined using invasive and non-invasive techniques.

CHC: chronic hepatitis C; F: female; IU: international units; M: male; N: number of randomized patients who received at least one dose of their allocated study medication; n: number of patients with event; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; SIM: simeprevir; TVR: telaprevir; vs.: versus

The ATTAIN study was a double-blind RCT, in which adults with CHC genotype 1 virus infection were treated. The patients were non-responders, i.e. they had received at least one previous course of peginterferon α-2a or 2b in combination with ribavirin for ≥ 12 weeks (null responders) or ≥ 20 weeks (partial responders). The previous treatment must not have been discontinued due to peginterferon/ribavirin intolerance. Null responders were defined as patients who had a < 2 log10 IU/mL reduction in HCV RNA after 12 weeks of treatment in comparison with baseline, and in whom HCV RNA could be detected at the end of treatment. Partial responders were defined as patients who had a ≥ 2 log10 IU/mL reduction in HCV RNA after 12 weeks of treatment in comparison with baseline, and in whom HCV RNA could be detected at the end of treatment, but not before the end of week 20. In the ATTAIN study, randomization was stratified by response (null response and partial response) to the last peginterferon α/ribavirin treatment and by genotype 1 subtypes (1a and 1b).

The patients were treated with SIM + PEG + RBV in the intervention arm and with TVR + PEG + RBV in the comparator arm for 12 weeks each. In both treatment arms, this was followed by subsequent treatment with PEG + RBV for 36 weeks. The planned follow-up observation period was 12 weeks (e.g. for the primary outcome "SVR 12" at the data cut-off at week 60) and 24 weeks (data cut-off at week 72).

The treatment groups were comparable with regard to the characteristics described in Table 42. The proportion of patients with cirrhosis (determined with invasive and non-invasive techniques) in the SIM + PEG + RBV arm and in the TVR + PEG + RBV arm was approximately 23% and 20% respectively. Based on the METAVIR score, almost half of the patients had advanced liver damage (fibrosis score F3-F4). The majority of patients had a high viral load, the virus genotype 1b was somewhat more common than genotype 1a.

Data availability at the data cut-offs at week 60 and week 72

The ATTAIN study was not yet completed at the time of the benefit assessment. As the results at week 72 were not yet available, the available analyses at the planned data cut-off at week 60 were used for the benefit assessment.

Criteria for discontinuation of the ATTAIN study

In both arms of the ATTAIN study, in case of treatment failure, criteria for discontinuation were applied that did not fully concur with the specifications of the SPCs for the discontinuation of treatment in case of inadequate virologic response (see Section 2.9.2.4.1 of the full dossier assessment). The deviations from the approval particularly applied to the SIM + PEG + RBV arm. Contrary to the approval, only in case of higher virus concentration than stipulated in the SPC (>1000 IU/mL instead of ≥ 25 IU/mL) treatment was discontinued in week 4 and 12 in this study arm. Hence patients with a viral load of ≥ 25 IU/mL and ≤ 1000 IU/mL were treated up to 20 weeks longer in the ATTAIN study.

The criteria for discontinuation mentioned were also applied in the TVR + PEG + RBV arm. However, for TVR + PEG + RBV, this approach complies with the specifications of the SPC on telaprevir (see Table 60 of the full dossier assessment).

The proportion of patients affected did not exceed a threshold of 20%. Hence the results of the study are generally evaluable and interpretable.

Table 43 shows the risk of bias at study level. Concurring with the company's assessment, this is rated as low for the ATTAIN study.

Table 43: Risk of bias at study level – RCT, direct comparison: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
ATTAIN	Yes	Yes	Yes	Yes	Yes	Yes	Low

CHC: chronic hepatitis C; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; TVR: telaprevir; vs.: versus

Overall assessment of the certainty of conclusions

According to the company, in the ATTAIN study 11.3% of the patients in the SIM + PEG + RBV arm were treated longer than recommended by the approval, which was caused by criteria for treatment discontinuation that deviated from the information in the SPC and package information leaflet. This caused uncertainty regarding the interpretability of the study results for answering the research question of the benefit assessment. It was therefore assumed that the certainty of conclusions was reduced for the following outcomes: SVR 12, fatigue (using the FSS), depression (using the CES-D) and health status (EQ-5D VAS). Hence no more than "hints" of an added benefit can be derived for these outcomes.

For all outcomes on AEs, the fact that the treatment duration in the SIM + PEG + RBV arm was longer than recommended by the approval probably has a disadvantageous effect for SIM + PEG + RBV. Hence in case of lesser harm from SIM + PEG + RBV, the certainty of conclusions of the study for these outcomes can be regarded as high. No more than "indications" of lesser harm can be derived for all outcomes on AEs.

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4, Sections 4.3.1.2.1 and 4.3.1.2.2, and Appendix 4-F of the dossier and in Sections 2.9.2.4.1 and 2.9.2.4.2 of the full dossier assessment.

2.5.2 Results on added benefit

2.5.2.1 Outcomes included

The following patient-relevant outcomes and surrogates were considered in this assessment (for reasons, see Section 2.9.2.4.3 of the full dossier assessment):

- Mortality (all-cause mortality)
- Morbidity
  - SVR 12 weeks after the end of treatment (SVR 12) as sufficiently valid surrogate for the patient-relevant outcome "HCC"
  - fatigue using the FSS
  - depression using the CES-D
  - health status using the EQ-5D VAS
- Health-related quality of life
- Adverse events
  - SAEs
  - treatment discontinuation due to AEs
  - skin and subcutaneous tissue disorders (SOC)
  - gastrointestinal disorders (SOC)
  - serious anaemias (PT)

Results on the SVR 12 were available on the data cut-off at week 60. These were used for the benefit assessment instead of the SVR 24. Regarding AEs, skin and subcutaneous tissue disorders and gastrointestinal disorders were additionally considered. There were no evaluable data on health-related quality of life.

The choice of patient-relevant outcomes deviates from that of the company, which, on the one hand, used further outcomes for the assessment of the added benefit in the dossier (Module 4) (see Section 2.9.2.4.3 or the full dossier assessment), and, on the other, did not regard outcomes as outcome (mortality) or allocated outcomes to different outcome categories (EQ-5D VAS to health-related quality of life). Contrary to the dossier, mortality was assessed to be an independent outcome in the present benefit assessment. The EQ-5D VAS was regarded to be a measurement of health status.

Further outcomes, namely the AEs "skin and subcutaneous tissue disorders (SOC)", "gastrointestinal disorders (SOC)" and "serious anaemias (PT)", which the company did not consider in the dossier, were additionally included. These were included as AEs of particular interest because there were notable differences between the treatment groups (see Appendix C of the full dossier assessment). For the consideration of anaemias, the company did not use

serious events, which were recorded using the PT "anaemias", but a different analysis, which was rated as inadequate (see Section 2.9.2.4.3 of the full dossier assessment).

Further information on the choice of outcomes can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Section 2.9.2.4.3 of the full dossier assessment.

Table 44 shows for which of the included outcomes of the ATTAIN study data were available.

Table 44: Matrix of outcomes – RCT, direct comparison: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1)

Study	Outcomes										
	All-cause mortality	**Sustained virologic response (SVR 12)**	**Fatigue using the FSS**	**Depression using the CES-D**	**Health status using the EQ-5D VAS**	**Health-related quality of life**	**Serious adverse events**	**Discontinuation due to adverse events**	**Skin and subcutaneous tissue disorders**	**Gastrointestinal disorders**	**Serious anaemias**
ATTAIN	Yes	Yes	Yes	Yes	Yes	–[a]	Yes	Yes	Yes	Yes	Yes

a: No evaluable data, see Section 2.9.2.4.3 of the full dossier assessment.

CES-D: Centre for Epidemiologic Studies Depression Scale; CHC: chronic hepatitis C; EQ-5D: European Quality of Life-5 Dimensions; FSS: Fatigue Severity Scale; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; SVR: sustained virologic response; VAS: visual analogue scale; vs.: versus

2.5.2.2 Risk of bias

Table 45 shows the risk of bias for these outcomes.

Table 45: Risk of bias at study and outcome level – RCT, direct comparison: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1)

Study		Outcomes									
	Study level	All-cause mortality	Sustained virologic response (SVR 12)	Fatigue using the FSS	Depression using the CES-D	Health status using the EQ-5D VAS	Serious adverse events	Discontinuation due to adverse events	Skin and subcutaneous tissue disorders	Gastrointestinal disorders	Serious anaemias
ATTAIN	L	L	L	L	L	L	L	L	L	L	L

CES-D: Centre for Epidemiologic Studies Depression Scale; CHC: chronic hepatitis C; EQ-5D: European Quality of Life-5 Dimensions; FSS: Fatigue Severity Scale; L: low; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; SVR: sustained virologic response; VAS: visual analogue scale; vs.: versus

The company presented no separate results for the outcome "mortality" and conducted no assessment of the risk of bias. Due to the low risk of bias at study level, a low risk of bias is also assumed for this outcome.

The company rated the risk of bias as low for the outcomes "SVR 12", "fatigue", "depression" and "health status" as well as for AEs. The company's assessment was accepted.

Since reduced certainty of conclusions was assumed for the outcomes "SVR 12", "fatigue", "depression" and "health status" (see Section 2.5.1.2), no more than "hints" of an added benefit can be derived. No more than "indications" of lesser harm were derived for all outcomes on AEs.

Further information on the risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3, and in Appendix 4-F of the dossier and in Section 2.9.2.4.2 of the full dossier assessment.

2.5.2.3 Results

Table 46 and Table 47 summarize the results on the comparison of SIM + PEG + RBV and TVR + PEG + RBV in previous non-responders (including partial and null responders) with genotype 1. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. Only the ATTAIN study was available for the assessment of simeprevir in pretreated genotype 1 patients with no or partial response.

Table 46: Results (dichotomous outcomes) – RCT, direct comparison: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1)

Study outcome category outcome	SIM + PEG + RBV		TVR + PEG + RBV		SIM + PEG + RBV vs. TVR + PEG + RBV
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
ATTAIN					
Mortality					
All-cause mortality	379	0 (0)	384	3 (0.8)	0.14 [0.01; 2.79][b] 0.086[c]
Morbidity					
SVR 12	379	203 (53.6)	384	210 (54.7)	0.98 [0.86; 1.12]; 0.755
Health-related quality of life	No evaluable data available				
Adverse events[a]					
AEs	379	359 (94.7)	384	378 (98.4)	
SAEs	379	22 (5.8)	384	54 (14.1)	0,41 [0.26; 0.66]; < 0.001
Discontinuation due to AEs	379	5 (1.3)	384	21 (5.5)	0.24 [0.09; 0.63][b]; 0.002[c]
Skin and subcutaneous tissue disorders	379	206 (54.4)	384	272 (70.8)	0.77 [0.69; 0.86][b]; < 0.001[c]
Gastrointestinal disorders	379	184 (48.5)	384	246 (64.1)	0.76 [0.67; 0.86][b]; < 0.001[c]
Serious anaemias	379	2 (0.5)	384	16 (4.2)	0.13 [0.03; 0.55][b]; 0.001[c]

a: Data analysed until the end of the treatment phase.
b: Institute's calculation, asymptotic.
c: Institute's calculation, unconditional exact test (CSZ method according to [9]).
d: Peto odds ratio, Institute's calculation, asymptotic.

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SIM: simeprevir; SVR: sustained virologic response; TVR: telaprevir; vs.: versus

Table 47: Results (continuous outcomes) – RCT, direct comparison: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1)

Study outcome category outcome	SIM + PEG + RBV			TVR + PEG + RBV			SIM + PEG + RBV vs. TVR + PEG + RBV
	N[a]	Values at start of study mean (SE)	Change at end of study mean[b] (SD)	N[a]	Values at start of study mean (SD)	Change at end of study mean[b] (SD)	Mean difference of the AUC [95% CI]; p-value
ATTAIN							
Morbidity (week 0-72)							
Fatigue using the FSS[c]	378	3.1 (0.08)	-0.20 (0.08)	381	3.1 (0.08)	-0.25 (0.08)	-8.8 [-20.7; 3.1]; 0.146
Depression using the CES-D[d]	378	13.50 (0.39)	1.02 (0.49)	380	13.43 (0.36)	1.94 (0.45)	-33.7 [-90.0; 22.5]; 0.241
Health status using the EQ-5D VAS[e]	378	79.8 (0.92)	2.0 (0.92)	380	78.7 (0.83)	1.2 (1.00)	141.1 [13.5; 268.7]; 0.03 Hedges' g: 0.15 [0.01; 0.30]

a: Number of patients in the AUC analysis; the values at the start of the study may be based on other patient numbers.
b: Unless stated otherwise, LOCF analysis of the ITT population.
c: Negative changes at the end of the study mean improvement in symptoms; the total FSS scale ranges from 1 to 7 points; high values indicate worse state.
d: Negative changes at the end of the study mean improvement in symptoms; the CES-D scale ranges from 0 to 60 points, high values indicate worse state.
e: Positive changes at the end of the study mean improvement in symptoms; the VAS scale ranges from 0 to 100 with 0 being the best and 100 being the worst imaginable health status.
AUC: area under the curve; CES-D: Centre for Epidemiologic Studies Depression Scale; CHC: chronic hepatitis C; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FSS: Fatigue Severity Scale; ITT: intention to treat; LOCF: last observation carried forward; N: number of analysed patients; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SIM: simeprevir; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

Mortality (all-cause mortality)

There was no statistically significant difference between treatment with SIM + PEG + RBV and TVR + PEG + RBV for mortality. 3 deaths occurred under TVR + PEG + RBV. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV is not proven with regard to the outcome "mortality".

The assessment deviates from that of the company, which conducted no separate assessment for the outcome "mortality".

Morbidity

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

There was no statistically significant difference between treatment with SIM + PEG + RBV and TVR + PEG + RBV for SVR 12. In addition, there was an indication of an effect modification by the characteristic "age" for the outcome "SVR 12". In none of the 3 age groups, there was a statistically significant difference between the treatment groups. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV is not proven with regard to the outcome "SVR 12". The assessment concurs with that of the company.

Fatigue using the FSS

An improvement for the outcome "fatigue" measured with the FSS in comparison with the baseline values was observed in both study arms. There was no statistically significant difference between the treatment arms. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV is not proven with regard to the outcome "fatigue". This concurs with the company's assessment.

Depression using the CES-D

There was no statistically significant difference between treatment with SIM + PEG + RBV in comparison with TVR + PEG + RBV for the outcome "depression" measured with the CES-D. In addition, there were indications of an effect modification for this outcome with regard to the characteristics "genotype 1a/1b" and "response to prior therapy". No statistically significant or not potentially irrelevant difference between the treatment groups was observed in any of the subgroups. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV is not proven with regard to the outcome "depression". This concurs with the company's assessment.

Health status using the EQ-5D VAS

An improvement for the outcome "health status" in comparison with the baseline values was observed in both study arms. There was a statistically significant difference in favour of treatment with SIM + PEG + RBV in comparison with TVR + PEG + RBV. The SMD (in the form of Hedges' g) was considered to check the relevance of this result. The 95% CI of the SMD did not lie completely above the irrelevance threshold of 0.2. It was therefore possible that the effect was within a range that is irrelevant. In addition, there were indications of an effect modification with regard to the characteristics "METAVIR fibrosis score" and "Q80K polymorphism". No statistically significant or not potentially irrelevant difference between the treatment groups was observed in any of the subgroups. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV is not proven with regard to the outcome "health status".

This result deviates from that of the company, which categorized data of the EQ-5D VAS as health-related quality of life and derived an indication of an added benefit of simeprevir.

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life for non-responders with CHC genotype 1. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV is not proven with regard to health-related quality of life.

This assessment deviates from that of the company, which conducted an assessment for the outcome "health-related quality of life" using the EQ-5D VAS, and derived an indication of an added benefit of simeprevir (see Section on morbidity).

Adverse events

The events recorded until the end of the treatment phase were considered for the assessment of AEs.

SAEs

There was a statistically significant difference in favour of SIM + PEG + RBV in comparison with TVR + PEG + RBV for the outcome "SAEs". In addition, there was an indication of an effect modification by the characteristic "baseline viral load". Both for patients with low and for patients with high viral load, statistically significantly fewer SAEs occurred under SIM + PEG + RBV than under TVR + PEG + RBV.

This results in an indication of lesser harm from SIM + PEG + RBV in comparison with TVR + PEG + RBV. The assessment concurs with that of the company.

Discontinuation due to AEs

Different operationalizations were available for the outcome "discontinuation due to AEs". In contrast to the company, which used the operationalization "stopping of at least one medication", data on the operationalization "stopping of all medications" were used for the benefit assessment. There was a statistically significant difference in favour of treatment with "SIM + PEG + RBV". This results in an indication of lesser harm from SIM + PEG + RBV in comparison with TVR + PEG + RBV. The assessment concurs with that of the company, although different operationalizations were used.

In addition, there was an indication of an effect modification by the characteristic "age". For patients of the age group from 45 to 65 years, statistically significantly fewer discontinuations due to AEs occurred under SIM + PEG + RBV than under TVR + PEG + RBV. For the age groups under 45 and over 65 years, there were no statistically significant differences between the treatment groups.

Skin and subcutaneous tissue disorders

In contrast to the company, which analysed cutaneous reactions in the dossier, the SOC "skin and subcutaneous tissue disorders" was used for the benefit assessment. There was a statistically significant difference in favour of treatment with "SIM + PEG + RBV". This

results in an indication of lesser harm from SIM + PEG + RBV in comparison with TVR + PEG + RBV with regard to the outcome "skin and subcutaneous tissue disorders". This assessment concurs with that of the company in that the company determined an indication of a reduction in the occurrence of cutaneous reactions for treatment with SIM + PEG + RBV for the outcome "cutaneous reactions".

Gastrointestinal disorders

There was a statistically significant difference in favour of treatment with SIM + PEG + RBV for the outcome "gastrointestinal disorders". This results in an indication of lesser harm from SIM + PEG + RBV in comparison with TVR + PEG + RBV with regard to the outcome "gastrointestinal disorders". The company presented no separate analysis for these AEs.

Serious anaemias

There was a statistically significant difference in favour of treatment with SIM + PEG + RBV for the outcome "serious anaemias". This results in an indication of lesser harm from SIM + PEG + RBV in comparison with TVR + PEG + RBV for the outcome "serious anaemias". The company also assessed the outcome "anaemias". However, this assessment was based on AEs and additional MedDRA PTs. The result concurs with that of the company, which derived an indication of reduced occurrence of anaemia under simeprevir treatment.

Further information on the outcome results can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Section 2.9.2.4.3 of the full dossier assessment.

2.5.2.4 Subgroups and other effect modifiers

Selected subgroups were investigated for the presence of heterogeneous treatment effects in order to identify possible effect modifications. The company presented the corresponding analyses for the outcomes it rated as relevant.

Hence there were no subgroup analyses for the outcomes "skin and subcutaneous tissue disorders", "gastrointestinal disorders" and "serious anaemias", which were additionally rated as relevant, and they could also not be subsequently calculated from the available documents. Subgroup analyses for the outcome "mortality" were not conducted because of the low event rates.

Subgroup analyses for the following characteristics were considered:

- age (≤ 45 years, > 45 years to ≤ 65 years, > 65 years)
- sex
- baseline viral load (≤ 800 000 IU/mL, > 800 000 IU/mL)
- genotype (1a, 1b)
- Q80K polymorphism

- METAVIR score (F0-F2, F3, F4)
- response to prior therapy (null responders, partial responders)

Except for age, the subgroup characteristics presented by the company and the cut-off values were specified a priori in the studies. Below, only the results on subgroups and outcomes are presented in which there were at least indications of an interaction between treatment effect and subgroup characteristic. The prerequisite for proof of different subgroup effects is a statistically significant interaction ($p < 0.05$). A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification.

There were no subgroup analyses for the outcome "mortality". Overall, no suitable data were available for health-related quality of life; therefore no subgroup results can be shown here either.

Table 48 to Table 51 show the results regarding the subgroup analyses.

Table 48: Subgroups (dichotomous outcomes): outcome "SVR 12" by age, RCT, direct comparison: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1)

Study characteristic subgroup	SIM + PEG + RBV		TVR + PEG + RBV		SIM + PEG + RBV vs. TVR + PEG + RBV	
	N	Patients with events n (%)	N	Patients with events n (%)	RR[a] [95% CI]	p-value
ATTAIN						
Age						
≤ 45 years	119	66 (55.5)	114	77 (67.5)	0.82 [0.67; 1.01]	0.061[b]
> 45 - ≤ 65 years	252	131 (52.0)	255	125 (49.0)	1.06 [0.89; 1.26]	0.521[b]
> 65 years	8	6 (75.0)	15	8 (53.3)	1.41 [0.76; 2.61]	0.398[b]
					Interaction:	0.084[c]

a: Institute's calculation, asymptotic.
b: Institute's calculation, unconditional exact test (CSZ method according to [9]).
c: Institute's calculation from meta-analysis.
CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SIM: simeprevir; SVR: sustained virologic response; TVR: telaprevir; vs.: versus

Table 49: Subgroups (continuous outcomes): outcome "depression" by genotype and response to prior therapy, RCT, direct comparison: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1)

Study characteristic subgroup	SIM + PEG + RBV		TVR + PEG + RBV		SIM + PEG + RBV vs. TVR + PEG + RBV	
	N	AUC at week 60 mean (SE)	N	AUC at week 60 mean (SE)	Mean difference [95% CI]	p-value
ATTAIN						
Genotype						
1a	162	1114.9 (31.3)	163	1089.9 (31.7)	25.0 [-62.6; 112.5]	
1b	213	892.3 (25.7)	219	972.3 (25.4)	-80.0 [-151.1; -9.0] Hedges' g: -0.21 [-0.40; -0.02]	
					Interaction:	0.07
Response to prior therapy						
null responders	ND	963.6 (24.6)		1032.9 (24.6)	-69.3 [-137.7; -1.0] Hedges' g: -0.18 [0.36; -0.00][a]	0.047
partial responders	ND	1027.6 (35.2)		1004.4 (35.1)	23.1 [-74.8; 121.1]	0.642
					Interaction:	0.129[b]

a: Institute's calculation under the assumption that 234 vs. 238 patients were observed. This corresponds to the number of null responders and partial responders in the study. The actual number of patients is unknown and presumably lower.
b: Institute's calculation from meta-analysis.
AUC: area under the curve; CHC: chronic hepatitis C; CI: confidence interval; N: number of analysed patients; ND: no data; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; SIM: simeprevir; TVR: telaprevir; vs.: versus

Table 50: Subgroups (continuous outcomes): outcome "health status" by METAVIR score and Q80K polymorphism, RCT, direct comparison: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1)

Study characteristic subgroup	SIM + PEG + RBV		TVR + PEG + RBV		SIM + PEG + RBV vs. TVR + PEG + RBV	
	N	AUC at week 60 mean (SE)	N	AUC at week 60 mean (SE)	Mean difference [95% CI]	p-value
ATTAIN						
METAVIR score[a]						
F0 – F2	ND	4584.2 (65.6)	ND	4412.1 (64.1)	172.1 [-8.1; 352.3]	0.061
F3	ND	4162.0 (105.2)	ND	4382.3 (96.7)	-220.4 [-502.4; 61.6]	0.125
F4	ND	4298.0 (118.2)	ND	4178.3 (125.5)	119.6 [-222.0; 461.3]	0.489
					Interaction:	0.068[b]
Q80K polymorphism						
yes	37	4457.6 (166.8)	28	3877.6 (191.6)	580.0 [73.2; 1086.7] Hedges' g: 0.56 [0.05; 1.06]	0.030
no	332	4444.0 (48.2)	348	4350.6 (47.5)	93.4 [-39.5; 226.3]	
					Interaction:	0.06

a: Information based on METAVIR score: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis.
b: Institute's calculation. Interaction of the groups F0-F2, F3 and F4.

AUC: area under the curve; CHC: chronic hepatitis C; CI: confidence interval; N: number of analysed patients; ND: no data; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SIM: simeprevir; TVR: telaprevir; vs.: versus

Table 51: Subgroups (dichotomous outcomes): outcome "SAEs" by baseline viral load, RCT, direct comparison: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1)

Study characteristic subgroup	SIM + PEG + RBV		TVR + PEG + RBV		SIM + PEG + RBV vs. TVR + PEG + RBV	
	N	Patients with events n (%)	N	Patients with events n (%)	RR[a] [95% CI]	p-value
ATTAIN						
Baseline viral load[b]						
≤ 800 000 IU/mL	44	1 (2.3)	50	10 (20.0)	0.11 [0.02; 0.85]	0.008[c]
> 800 000 IU/mL	335	21 (6.3)	334	44 (13.2)	0.48 [0.29; 0.78]	0.003[c]
					Interaction:	0,169[d]

a: Institute's calculation, asymptotic.
b: Data analysed until the end of the treatment phase.
c: Institute's calculation, unconditional exact test (CSZ method according to [9]).
d: Institute's calculation from meta-analysis.
CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SIM: simeprevir; TVR: telaprevir; vs.: versus

Table 52: Subgroups (dichotomous outcomes): outcome "discontinuation due to AEs" by age, RCT, direct comparison: SIM + PEG + RBV vs. TVR + PEG + RBV

Study characteristic subgroup	SIM + PEG + RBV		TVR + PEG + RBV		SIM + PEG + RBV vs. TVR + PEG + RBV	
	N	Patients with events n (%)	N	Patients with events n (%)	RR[a] [95% CI]	p-value
ATTAIN						
Age[b]						
≤ 45 years	119	5 (4.2)	114	9 (7.9)	0.53 [0.18; 1.54]	0.256[c]
> 45 - ≤ 65 years	252	12 (4.8)	255	36 (14.1)	0.34 [0.18; 0.63]	< 0.001[c]
> 65 years	8	2 (25.0)	15	2 (13.3)	1.88 [0.32; 10.92]	0.600[c]
					Interaction:	0,181[d]

a: Institute's calculation, asymptotic.
b: Data analysed until the end of the treatment phase.
c: Institute's calculation, unconditional exact test (CSZ method according to [9]).
d: Institute's calculation from meta-analysis.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; PEG: peginterferon alfa; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SIM: simeprevir; TVR: telaprevir; vs.: versus

Morbidity

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

There was an indication of an effect modification by the characteristic "age" for the outcome "SVR 12". The result showed no statistically significant advantage for any of the age groups for one of the treatment arms. Hence for all age groups, there is no proof of added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV.

Depression using the CES-D

There were indications of an effect modification by the characteristics "genotype" and "response to prior therapy" for the outcome "depression". There was a statistically significant difference in favour of SIM + PEG + RBV in comparison with TVR + PEG + RB in genotype 1b patients and patients who were null responders in prior therapy. The SMD (in the form of Hedges' g) was considered to check the relevance of this result. In both cases, the 95% CI of the SMD did not lie completely below the irrelevance threshold of -0.2. It was therefore possible that the effect was within a range that is irrelevant. No statistically significant differences between the treatment groups were observed in the subgroups of genotype 1a patients or of patients with partial response to prior therapy. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV with regard to the outcome "depression" is not proven in any of the subgroups.

Health status using the EQ-5D VAS

There was an indication of an effect modification by the characteristic "METAVIR fibrosis score" and "Q80K polymorphism" for the outcome "health status".

There was no statistically significant advantage in any of the subgroups by fibrosis score for one of the treatment arms.

For the characteristic "Q80K polymorphism", there was a statistically significant difference in favour of SIM + PEG + RBV in comparison with TVR + PEG + RB in patients with Q80K polymorphism for the outcome "health status". The SMD (in the form of Hedges' g) was considered to check the relevance of this result. The 95% CI of the SMD did not lie completely above the irrelevance threshold of 0.2. It was therefore possible that the effect was within a range that is irrelevant. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV with regard to health status is not proven in patients with Q80K polymorphism.

Adverse events

SAEs

There was an indication of an effect modification by the characteristic "baseline viral load" for the outcome "SAEs". There was a statistically significant difference in favour of SIM + PEG + RBV in comparison with TVR + PEG + RBV in a baseline viral load of ≤ 800 000 IU/mL and of > 800 000 IU/mL. For both groups, there is an indication of lesser

harm from SIM + PEG + RBV in comparison with TVR + PEG + RBV. Based on the available data, the result of the total population was eventually used instead of the result of the individual subgroups (see Section 2.5.3.2).

Discontinuation due to AEs

There was an indication of an effect modification by the characteristic "age" for the outcome "discontinuation due to AEs". There was a statistically significant difference in favour of SIM + PEG + RBV for the age group of patients from 45 to 65 years. For this age group, there was an indication of lesser harm from SIM + PEG + RBV in comparison with TVR + PEG + RBV.

There was no statistically significant difference between the treatment groups for the age groups of patients up to 45 years and over 65 years. Hence an added benefit of SIM + PEG + RBV in comparison with TVR + PEG + RBV is not proven for these age groups with regard to discontinuations due to AEs.

Further information on the subgroup results can be found in Module 4, Section 4.3.1.3.2 of the dossier, and in Section 2.9.2.4.3 of the full dossier assessment.

2.5.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit at outcome level for pretreated genotype 1 patients who have not adequately responded to prior therapy (previous non-responders, including partial and null responders) is presented below, taking into account the various outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of the Institute [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.3.1 Assessment of added benefit at outcome level

The available data presented in Section 2.5.2 resulted in indications of lesser harm from SIM + PEG + RBV in comparison with TVR + PEG + RBV for the outcomes "SAEs", "discontinuation due to AEs", "skin and subcutaneous tissue disorders (SOC)", "gastrointestinal disorders (SOC)" and "serious anaemias (PT)".

The extent of the respective added benefit at outcome level was estimated from these results (see Table 53).

Table 53: Extent of added benefit at outcome level: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1)

Outcome category **outcome**	**SIM + PEG + RBV vs. TVR + PEG + RBV** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0.8% RR: 0.14 [0.01; 2.79][c] p = 0.086[d]	Added benefit not proven
Morbidity		
HCC, assessed with the SVR surrogate[e]	53.6% vs. 54.7% RR: 0.98 [0.86; 1.12] p = 0.755	Added benefit not proven
Fatigue using the FSS	Mean difference/AUC: -8.8 [-20.7; 3.1] p = 0.146	Added benefit not proven
Health status using the EQ-5D VAS	Mean difference/AUC: 141.1 [13.5; 268.7] p = 0.03 Hedges' g: 0.15 [0.01; 0.30]	Added benefit not proven
Depression using the CES-D	Mean difference/AUC: -33.7 [-90.0; 22.5] p = 0.241	Added benefit not proven
Health-related quality of life	No evaluable data	
Adverse events		
SAEs	5.8% vs. 14.1% RR: 0.41 [0.26; 0.66] p < 0.001	
baseline viral load ≤ 800 000 IU/mL	2.3 % vs. 20.0 % RR: 0.11 [0.02; 0.85] p = 0.008 probability: "indication"	Outcome category: serious/severe AEs CI_u < 0.90 lesser harm extent: "major"[f]

(continued)

Table 53: Extent of added benefit at outcome level: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1) (continued)

Outcome category **outcome**	**SIM + PEG + RBV vs. TVR + PEG + RBV** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
> 800 000 IU/mL	6.3% vs. 13.2% RR: 0.48 [0.29; 0.78] p = 0.003 probability: "indication"	Outcome category: serious/severe AEs CI_u < 0.80 lesser harm extent: "major"[g]
Discontinuation due to AEs	1.3% vs. 5.5% RR: 0.24 [0.09; 0.63][c] p = 0.002[d]	
age ≤ 45	4.2% vs. 7.9% RR: 0.53 [0.18; 1.54][c] p = 0.256[d]	Greater/lesser harm not proven
> 45 – ≤ 65	4.8% vs. 14.1% RR: 0.34 [0.18; 0.63][c] p < 0.001[d] probability: "indication"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 lesser harm extent: "considerable"
> 65	25.0% vs. 13.3% RR: 1.88 [0.32; 10.92][c] p = 0.600[d]	Greater/lesser harm not proven
Skin and subcutaneous tissue disorders	54.4% vs. 70.8% RR: 0.77 [0.69; 0.86][c] p < 0.001[d] probability: "indication"	Outcome category: non-serious/non-severe AEs CI_u < 0.90 lesser harm extent: "minor"
Gastrointestinal disorders	48.5% vs. 64.1% RR: 0.76 [0.67; 0.86][c] p < 0.001[d] probability: "indication"	Outcome category: non-serious/non-severe AEs CI_u < 0.90 lesser harm extent: "minor"
Serious anaemias	0.5% vs. 4.2% RR: 0.13 [0.03; 0.55][c] p = 0.001[d] probability: "indication"	Outcome category: serious/severe AEs CI_u < 0.75, risk < 5% lesser harm extent: "considerable"

(continued)

Table 53: Extent of added benefit at outcome level: SIM + PEG + RBV vs. TVR + PEG + RBV (previous non-responders with CHC genotype 1) (continued)

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation, asymptotic.
d: Institute's calculation, unconditional exact test (CSZ method according to [9]).
e: SVR was used as surrogate for a patient-relevant outcome (HCC). It is regarded as sufficiently valid to be considered in the benefit assessment.
f: Lesser harm of major extent for the total population. Due to the small sample size and an even greater effect estimate than in the total population, the extent for the subgroup did not change.
g: Lesser harm of major extent for the total population. Due to the comparable position of the effect estimate in the subgroup and the total population and of the upper limit of the CI for the subgroup near the limit of 0.75, a major extent is assumed.

AE: adverse event; AUC: area under the curve; CES-D: Centre for Epidemiologic Studies Depression Scale; CHC: chronic hepatitis C; CI: confidence interval; CI_u: upper limit of the CI; CSZ: convexity, symmetry, z score; EQ-5D: European Quality of Life-5 Dimensions; HCC: hepatocellular carcinoma; PEG: peginterferon alfa; RBV: ribavirin; RR; relative risk; SAE: serious adverse event; SIM: simeprevir; SVR: sustained virologic response; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

2.5.3.2 Overall conclusion on added benefit

Table 54 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 54: Positive and negative effects from the assessment of SIM + PEG + RBV in comparison with TVR + PEG + RBV (previous non-responders with CHC genotype 1)

Positive effects	**Negative effects**
Serious/severe adverse events ▪ SAEs: indication of lesser harm – extent: "major"	-
Serious/severe adverse events ▪ serious anaemias: indication of lesser harm – extent: "considerable"	-
Non-serious/non-severe adverse events ▪ discontinuation due to AEs: ▫ age < 45 years: greater/lesser harm not proven ▫ age 45-65 years: indication of lesser harm – extent: "considerable" ▫ age > 65 years: greater/lesser harm not proven	-
Non-serious/non-severe adverse events ▪ skin and subcutaneous tissue disorders: indication of lesser harm – extent: "minor"	-
Non-serious/non-severe adverse events ▪ gastrointestinal disorders: indication of lesser harm – extent: "minor"	-
AE: adverse event; CHC: chronic hepatitis C; PEG: peginterferon alfa; RBV: ribavirin; SAE: serious adverse event; SIM: simeprevir; TVR: telaprevir	

Overall, only positive effects remain in the outcome categories “non-serious/non-severe AEs” (extent: “considerable” and “minor”) and “serious/severe AEs” (extent: “major” and “considerable”).

There was an indication of effect modification by baseline viral load for the outcome “SAEs”. Nonetheless, lesser harm with the extent “major” was derived for both subgroups: The extent of lesser harm was determined by the subgroup with high viral load (> 800 000 IU/mL) because this subgroup comprised considerably more patients than the subgroup of patients with low viral load. As this was only an indication of an effect modification, the result of the total population (extent: “major”) was considered in the interpretation of the results. The effect estimate in the subgroup with high viral load was comparable with the one of the total population; and additionally the upper limit of the CI was near the limit of 0.75 indicating a major extent.

There was an indication of lesser harm with the extent “considerable” for the subgroups of patients aged 45 to 65 years of age for the outcome “discontinuation due to AEs”.

It is to be noted that positive effects only occurred in the area of AEs. However, it cannot be derived from the results on all-cause mortality and morbidity (SVR 12, fatigue and depression) that SIM + PEG + RBV achieves considerably worse results in comparison with TVR + PEG + RBV with regard to these outcomes.

Overall, there is an indication of added benefit of SIM + PEG + RBV in comparison with the ACT TVR + PEG + RBV with the extent “major” for pretreated CHC genotype 1 patients who have not adequately responded to prior therapy (previous non-responders, including partial and null responders).

The result of the assessment of the added benefit of simeprevir in comparison with the ACT is summarized in Table 55.

Table 55: Simeprevir – extent and probability of added benefit

Research question	**ACT**[a]	**Extent and probability of added benefit**
Previous non-responders including partial and null responders with CHC genotype 1	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)**	Indication of a major added benefit
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. ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee		

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

2.5.4 List of included studies

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 infectedsubjects who were null or partial responders to prior PegIFNalpha and ribavirin therapy [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 6 March 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. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-001180-53.

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); full text view [online]. In: Clinicaltrials.gov. 17 March 2014 [accessed: 29 April 2014]. URL: http://ClinicalTrials.gov/show/NCT01485991.

Janssen Research & Development. 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: study TMC435HPC3001 (ATTAIN); topline results; week 60 interim analysis [unpublished]. 2014.

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

2.6.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on simeprevir (studies completed up to 6 March 2014)
- bibliographical literature search on simeprevir (last search on 5 May 2014)
- search in trial registries for studies on simeprevir (last search on 6 March 2014)

To check the completeness of the study pool:

- bibliographical literature search on simeprevir (last search on 12 June 2014)
- search in trial registries for studies on simeprevir (last search on 12 June 2014)

No additional relevant study was identified from the check.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.9.2.1 and 2.9.2.3 of the full dossier assessment.

2.6.2 Study pool

The company included the one-arm TMC435-TiDP16-C212 study in the benefit assessment. The company's search for adequate data on the ACT in the dossier was not documented. Hence the completeness of the comparator data presented in Section 4.4.2 of the dossier was unclear. The data of the study were therefore not relevant for the benefit assessment.

Hence no relevant study could be included for research question 1d.

2.6.3 Results and added benefit

The results of the TMC435-TiDP16-C212 study are not presented because the company presented no data on the ACT that were systematically searched for and assessed. An added benefit of SIM + PEG + RBV versus PEG + RBV for patients with CHC genotype 1 and HIV coinfection is therefore not proven.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Section 4.3.2.3.1 of the dossier and in Sections 2.9.2.3.1 and 2.9.2.3.2 of the full dossier assessment.

2.6.4 List of included studies

Not applicable as the company did not present any study in the dossier from which an added benefit of SIM + PEG + RBV versus the ACT PEG + RBV specified by the G-BA could be derived.

2.7 Research question 2: patients with CHC genotype 4

2.7.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on simeprevir (studies completed up to 6 March 2014)
- bibliographical literature search on simeprevir (last search on 5 May 2014)
- search in trial registries for studies on simeprevir (last search on 6 March 2014)

To check the completeness of the study pool:

- bibliographical literature search on simeprevir (last search on 12 June 2014)
- search in trial registries for studies on simeprevir (last search on 12 June 2014)

No additional relevant study was identified from the check.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.9.2.1 and 2.9.2.3 of the full dossier assessment.

2.7.2 Study pool

The company included the one-arm RESTORE study in the benefit assessment. The company's search for adequate data on the ACT in the dossier was not documented. Hence the completeness of the comparator data presented in Section 4.4.2 of the dossier was unclear. The data of the study were therefore not relevant for the benefit assessment.

Hence no relevant study could be included for research question 2.

2.7.3 Results and added benefit

The results of the RESTORE study are not presented because the company presented no data on the ACT that were systematically searched for and assessed. An added benefit of SIM + PEG + RBV versus PEG + RBV for patients with CHC genotype 4 is therefore not proven.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Section 4.3.2.3.1 of the dossier and in Sections 2.9.2.3.1 and 2.9.2.3.2 of the full dossier assessment.

2.7.4 List of included studies

Not applicable as the company did not present any study in the dossier from which an added benefit of SIM + PEG + RBV versus the ACT PEG + RBV specified by the G-BA could be derived.

2.8 Extent and probability of added benefit – summary

Table 56 summarizes the extent and probability of the added benefit of simeprevir for all 5 research questions.

Table 56: Simeprevir – extent and probability of added benefit in adult patients with CHC genotype 1 or 4

Research question	ACT[a]	Subgroup	Extent and probability of added benefit
Treatment-naive CHC genotype 1 patients	**Dual therapy (combination of peginterferon and ribavirin)** or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin) treatment-naive patients with cirrhosis: dual therapy	Q80K polymorphism: no	Indication of non-quantifiable added benefit
		Q80K polymorphism: yes	Hint of non-quantifiable added benefit
		IL28B genotype: CT/TT	Indication of non-quantifiable added benefit
		IL28B genotype: CC	Added benefit not proven
Pretreated relapsed patients with CHC genotype 1	**Dual therapy (combination of peginterferon and ribavirin)** or triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)	Indication of non-quantifiable added benefit	
Previous non-responders including partial and null responders with CHC genotype 1	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [boceprevir or telaprevir], peginterferon and ribavirin)**	Indication of a major added benefit	
Patients with CHC genotype 1 and HIV coinfection	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven	
Patients with CHC genotype 4	Dual therapy (combination of peginterferon and ribavirin)	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.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HIV: human immunodeficiency virus

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

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.9.2.8 of the full dossier assessment.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.1 [online]. 28 November 2013 [accessed: 7 February 2014]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Janssen. OLYSIO 150 mg Hartkapseln: Fachinformation [online]. June 2014 [accessed: 16 July 2014]. URL: http://www.fachinfo.de.

4. Roche. Pegasys 90/135/180 Mikrogramm: Fachinformation [online]. April 2014 [accessed: 11 April 2014]. URL: http://www.fachinfo.de.

5. Roche. Copegus: Fachinformation [online]. April 2014 [accessed: 11 July 2014]. URL: http://www.fachinfo.de.

6. MSD. PegIntron Clearclick Fertigpen: Fachinformation [online]. November 2013 [accessed: 12 May 2014]. URL: http://www.fachinfo.de.

7. MSD. Rebetol 200 mg Hartkapseln: Fachinformation [online]. April 2014 [accessed: 11 July 2014]. URL: http://www.fachinfo.de.

8. Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. Clin Trials 2008; 5(3): 225-239.

9. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-18-simeprevir-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6157.html.