IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ombitasvir/paritaprevir/ ritonavir – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.8 of the dossier assessment *Ombitasvir/Paritaprevir/Ritonavir – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 April 2015). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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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
- Carmen Bartel
- Katharina Biester
- Gertrud Egger
- Andreas Gerber-Grote
- Corinna Kiefer
- Ulrike Lampert
- Anke Schulz
- Anja Schwalm
- Beate Wieseler
- Min Zhou

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CHC	chronic hepatitis C
CI	confidence interval
DSV	dasabuvir
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D VAS	visual analogue scale of the European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCV	hepatitis C virus
HCV-PRO	HCV patient-reported outcomes
HCVTSat	Hepatitis C Virus Treatment Satisfaction
HR	hazard ratio
IDR	incidence density ratio
IU	international units
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MID	minimally important difference
OBV	ombitasvir
PEG	pegylated interferon
PTV	paritaprevir
R	ritonavir
RBV	ribavirin
RCT	randomized controlled trial
RNA	ribonucleic acid
RR	relative risk
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SPC	Summary of Product Characteristics
SVR	sustained virologic response
SVR 12	sustained virologic response 12 weeks after the end of treatment
TVR	telaprevir
WPAI	Work Productivity and Activity Impairment

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 fixed-dose combination ombitasvir/paritaprevir/ritonavir (OBV/PTV/R). 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 21 January 2015.

Research question

The aim of the present report is to assess the added benefit of the fixed-dose combination OBV/PTV/R in comparison with dual therapy of peginterferon and ribavirin (PEG + RBV) or triple therapy of telaprevir, peginterferon and ribavirin (TVR + PEG + RBV) as appropriate comparator therapy (ACT) in patients with chronic hepatitis C (CHC) genotype 1 and 4.

The fixed-dose combination OBV/PTV/R is only approved in combination with other drugs. Depending on the patient group, it is administered together with dasabuvir (DSV) and/or ribavirin. The ribavirin-free combination is only approved in patients with CHC genotype 1b without cirrhosis.

The company followed the G-BA's ACT, and specified it by stipulating triple therapy consisting of TVR + PEG + RBV as ACT for treatment-naive patients with CHC genotype 1 without cirrhosis and for treatment-experienced patients with CHC genotype 1 without or with compensated cirrhosis. For all other patient groups, the ACT was dual therapy consisting of PEG + RBV.

Partly different treatment regimens for certain patient groups resulted from the Summaries of Product Characteristics (SPCs) of OBV/PTV/R, DSV, TVR and PEG or RBV. Further differentiations resulted from the specification of the G-BA's ACT. This led to a total of 16 research questions for the benefit assessment. The research questions are shown in Table 2. For reasons of clarity of the present dossier assessment, the order of the research questions deviates from that of the company.

Table 2: Research questions for the benefit assessment of ombitasvir/paritaprevir/ritonavir

Research question no. in the present assessment[a] (research question no. of the company)	**Population**	**Intervention**	**Appropriate comparator therapy**
	Genotype 1, treatment-naive patients without cirrhosis		
1 (3)	Treatment-naive patients with CHC genotype 1a without cirrhosis	OBV/PTV/R + DSV + RBV	TVR + PEG + RBV
2 (1)	Treatment-naive patients with CHC genotype 1b without cirrhosis	OBV/PTV/R + DSV	TVR + PEG + RBV
	Genotype 1, treatment-experienced patients without cirrhosis		
3 (4)	Treatment-experienced patients with CHC genotype 1a without cirrhosis	OBV/PTV/R + DSV + RBV	TVR + PEG + RBV
4 (2)	Treatment-experienced patients with CHC genotype 1b without cirrhosis	OBV/PTV/R + DSV	TVR + PEG + RBV
	Genotype 1, treatment-naive patients with compensated cirrhosis		
5 (7)	Treatment-naive patients with CHC genotype 1a with compensated cirrhosis	OBV/PTV/R + DSV + RBV	PEG + RBV
6 (5)	Treatment-naive patients with CHC genotype 1b with compensated cirrhosis	OBV/PTV/R + DSV + RBV	PEG + RBV
	Genotype 1, treatment-experienced patients with compensated cirrhosis		
7 (8)	Treatment-experienced patients with CHC genotype 1a with compensated cirrhosis	OBV/PTV/R + DSV + RBV	TVR + PEG + RBV
8 (6)	Treatment-experienced patients with CHC genotype 1b with compensated cirrhosis	OBV/PTV/R + DSV + RBV	TVR + PEG + RBV
	Genotype 1, specific patient populations		
9 (13)	Patients with CHC genotype 1 after liver transplantation	OBV/PTV/R + DSV + RBV	PEG + RBV
10 (15)	Patients with CHC genotype 1 with HIV coinfection	OBV/PTV/R + DSV + RBV	PEG + RBV

(continued)

Table 2: Research questions for the benefit assessment of ombitasvir/paritaprevir/ritonavir (continued)

Research question no. in the present assessment[a] (research question no. of the company)	Population	Intervention	Appropriate comparator therapy
	Genotype 4, specific patient populations		
11 (9)	Treatment-naive patients with CHC genotype 4 without cirrhosis	OBV/PTV/R + RBV	PEG + RBV
12 (10)	Treatment-experienced patients with CHC genotype 4 without cirrhosis	OBV/PTV/R + RBV	PEG + RBV
13 (11)	Treatment-naive patients with CHC genotype 4 with compensated cirrhosis	OBV/PTV/R + RBV	PEG + RBV
14 (12)	Treatment-experienced patients with CV genotype 4 with compensated cirrhosis	OBV/PTV/R + RBV	PEG + RBV
15 (14)	Patients with CHC genotype 4 after liver transplantation	OBV/PTV/R + RBV	PEG + RBV
16 (16)	Patients with CHC genotype 4 with HIV coinfection	OBV/PTV/R + RBV	PEG + RBV

a: The numbering of the research questions corresponds to the presentation in the present benefit assessment; the order deviates from the one of the company in Module 4 A of the dossier.
CHC: chronic hepatitis C; DSV: dasabuvir; OBV: ombitasvir; PEG: peginterferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; TVR: telaprevir

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

Results

Study pool

Suitable data for the benefit assessment were available only for research questions 1 to 3. The randomized controlled trial (RCT) MALACHITE-I was included in the benefit assessment for research question 1 (treatment-naive patients with CHC genotype 1a without cirrhosis) and research question 2 (treatment-naive patients with genotype 1b without cirrhosis); and the RCT MALACHITE-II was included for research question 3 (treatment-experienced patients with CHC genotype 1a without cirrhosis).

Study characteristics

Research questions 1 (treatment-naive patients with CHC genotype 1a without cirrhosis) and 2 (treatment-naive patients with CHC genotype 1b without cirrhosis)

The MALACHITE-I study was an unblinded RCT with 5 treatment arms (A to E). Treatment-naive patients with CHC genotype 1a without cirrhosis were investigated in the treatment arms A and B; and treatment-naive patients with CHC genotype 1b were investigated in the arms D and E. In intervention arm C, also patients with genotype 1b were investigated, but the drug combination of OBV/PTV/R + DSV + RBV administered in this arm did not comply with the approval for these patients. Hence the comparison of treatment arms A and B, and D and E was relevant for the benefit assessment.

Treatment-naive adult patients with CHC genotype 1a without cirrhosis were included in the treatment arms A and B, which are relevant for research question 1. A total of 103 patients were randomly assigned to this comparison (intervention arm A: N = 69, comparator arm B: N = 34).

Treatment-naive adult patients with CHC genotype 1b without cirrhosis were included in the treatment arms D and E, which are relevant for research question 2. A total of 124 patients were randomly assigned to this comparison (intervention arm D: N = 83, comparator arm E: N = 41).

In intervention arm A, the patients received OBV/PTV/R in combination with DSV and RBV over a period of 12 weeks. In intervention arm D, the patients received OBV/PTV/R in combination with DSV over a period of 12 weeks.

In the comparator arms B and E, the patients received triple therapy with TVR + PEG + RBV. The treatment duration with TVR in combination with PEG + RBV was 12 weeks; depending on the response to treatment, treatment was continued with PEG + RBV for further 12 or 36 weeks. Hence the maximum treatment duration was 24 or 48 weeks. The treatment regimens used and the dosages of the drugs complied with the approval for patients with CHC genotype 1a or 1b without cirrhosis.

Research question 3 (treatment-experienced patients with CHC genotype 1a without cirrhosis)

MALACHITE-II was an unblinded RCT with 2 treatment arms. CHC patients with CHC genotype 1 without cirrhosis who had been treated with PEG + RBV at an earlier time point were included in the study. A total of 154 patients were randomly assigned to this comparison (intervention arm A: N = 103, comparator arm B: N = 51).

In arm A, the patients received OBV/PTV/R in combination with DSV and RBV. The combination with ribavirin in this drug combination is not approved for patients with hepatitis C virus (HCV) infection of genotype 1b without cirrhosis. For this reason, only the subpopulation of patients with CHC genotype 1a, which comprised 26 patients (intervention

arm A: N = 19, comparator arm B: N = 7) was relevant for the present benefit assessment. The patients with CHC genotype 1b are not considered further.

The treatment regimen of the intervention OBV/PTV/R + DSV + RBV (treatment arm A) with a treatment duration of 12 weeks and the dosage used complied with the approval for treatment-experienced patients with CHC genotype 1a without cirrhosis. In comparator arm B, the patients were treated with triple therapy of TVR + PEG + RBV. The dosages complied with the approval in each case. The treatment duration with TVR in combination with PEG + RBV was 12 weeks; depending on their response to treatment, the patients continued treatment with PEG + RBV for further 12 or 36 weeks. Hence the maximum treatment duration was 24 or 48 weeks.

Concomitant medications contraindicated according to the approval were not allowed in the studies MALACHITE-I and MALACHITE II. The planned follow-up duration in both studies was 48 weeks after the end of treatment for all patients. Adverse events (AEs) were followed-up in the studies for 30 days after the end of treatment.

Treatment duration/observation period in the studies MALACHITE-I and MALACHITE-II

The requirements of the respective SPCs resulted in fixed treatment durations for the combination therapy OBV/PTV/R + DSV (+ RBV) and the triple therapy with TVR + PEG + RBV. The patients in the OBV/PTV/R + DSV (+ RBV) arm were treated for 12 weeks; the patients in the TVR + PEG + RBV arm were treated for 24 or 48 weeks, depending on their response to treatment. AEs were followed-up in the studies for 30 days after the end of treatment. This resulted in markedly different observation periods with a minimum difference of 12 weeks and a maximum difference of 36 weeks. As a consequence, the effect estimations for AEs and mortality based on naive proportions do not represent an adequate analysis, and analyses on the basis of incidence density ratios (IDRs) need to fulfil certain requirements for them to be acceptable as valid estimates for the hazard ratio (HR). Overall, no conclusive interpretation of the data on the outcome categories on AEs was possible. As a result, no final quantitative conclusion on the harm of OBV/PTV/R was drawn in the overall consideration of AEs.

Risk of bias and certainty of conclusions

The assessment of the risk of bias for the studies MALACHITE-I and MALACHITE-II was identical both at study level and at outcome level.

The risk of bias for the outcome “sustained virologic response 12 weeks after the end of treatment (SVR 12)”, like the risk of bias of the studies overall, was considered to be low. Due to the study design, all patient-reported outcomes (visual analogue scale of the European Quality of Life-5 Dimensions [EQ-5D VAS], Short Form (36) Health Survey [SF-36], HCV patient-reported outcomes [HCV-PRO]) were considered to have a high risk of bias because subjective outcomes in open-label studies generally are to be rated as having a high risk of bias. The risk of bias for the outcomes “mortality” and “overall rates of serious AEs (SAEs)”

was considered to be high because the observation periods between the treatment groups differed notably. In contrast, the risk of bias for the outcome "treatment discontinuation due to AEs" was considered to be low because the different observation periods resulted from the planned limitation of the treatment duration. Due to the markedly different observation periods in the intervention and comparator arm (in the MALACHITE-II study additionally due to the low number of patients in the relevant subpopulation), the data on AEs were largely not interpretable in a meaningful way. Except for treatment discontinuation due to AEs, the results on AEs were therefore not conclusively interpretable in quantitative terms.

In summary, at most indications of an added benefit could be derived for outcomes on the SVR 12 and for treatment discontinuation due to AEs as a consequence; at most hints of an added benefit could be derived for the potentially highly biased outcomes on mortality, on patient-reported outcomes and on AEs for which an analysis was meaningful.

Results for research question 1 (treatment-naive patients with CHC genotype 1a without cirrhosis)

Mortality

In the patient population considered, one death occurred in the OBV/PTV/R + DSV + RBV arm; no patient died in the TVR + PEG + RBV arm. Hence there is no hint of an added benefit of OBV/PTV/R + DSV + RBV versus TVR + PEG + RBV. An added benefit for the outcome "mortality" is therefore not proven.

Morbidity – SVR 12 as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

SVR was included as sufficiently valid surrogate for the outcome "hepatocellular carcinoma". There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the SVR 12. This resulted in an indication of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for the outcome "hepatocellular carcinoma (assessed with the SVR 12)".

Morbidity – health status using the EQ-5D VAS (under treatment)

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the outcome "health status". The standardized mean difference (SMD) in the form of Hedges' g was considered to check the relevance of this result. The 95% confidence interval (CI) of the SMD did not lie fully above the irrelevance threshold of 0.2. It was therefore possible that the effect was within a range that is certainly irrelevant. Hence there is no hint of an added benefit; an added benefit is therefore not proven.

Health-related quality of life – SF-36 (under treatment)

The physical and mental sum score was considered for the SF-36. The mean differences and the prespecified responder analysis of the company were included in each case; patients in

whom the sum score decreased by fewer than 5 points in comparison with baseline were considered as responders.

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the physical sum score in the consideration of the mean differences. The SMD in the form of Hedges' g was considered to check the relevance of this result. The 95% CI of the SMD was fully above the irrelevance threshold of 0.2. It can therefore be assumed that the effect was not within a range that is certainly irrelevant.

Moreover, there was an indication of an effect modification by the characteristic "viral load (HCV ribonucleic acid [RNA] at baseline)". This resulted in a hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for patients with HCV RNA of < 800 000 IU/mL. There was no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for patients with HCV RNA of ≥ 800 000 IU/mL. An added benefit for the outcome "SF-36 (physical sum score)" is therefore not proven for this subgroup.

In the responder analysis, there was no statistically significant difference between the treatment groups for the physical sum score in the total population for research question 1. However, the rate of patients with response in the OBV/PTV/R + DSV + RBV arm was higher than in the TVR + PEG + RBV arm so that this result does not raise doubts about the result of the analysis of the mean differences. There were no subgroup analyses for the responder analysis.

Overall, there is a hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for the physical sum score of the SF-36 for patients with HCV RNA of < 800 000 IU/mL.

There was no statistically significant difference between the treatment groups for the mental sum score of the SF-36 in the consideration of the mean differences.

There was an indication of an effect modification by the characteristic "fibrosis stage", which was recorded with the METAVIR score. However, no separate conclusions for the subgroups resulted from this. Overall, there is no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit for the outcome "SF-36 (mental sum score)" is not proven.

There was no statistically significant difference between the treatment groups for the mental sum score of the SF-36 in the responder analysis. Hence for the mental sum score, the results based on the mean differences were consistent with the responder analysis for the total population.

Health-related quality of life – HCV-PRO (under treatment)

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the outcome "HCV-PRO". 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 fully above the irrelevance threshold of 0.2. It was therefore possible that the effect was within a range that is certainly irrelevant. This resulted in no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit for the outcome "HCV-PRO" is therefore not proven.

Adverse events

No SAEs have occurred in the OBV/PTV/R + DSV + RBV arm in the course of the study so far. In the TVR + PEG + RBV arm, 3 patients (8.8%) had at least one SAE. No IDR was calculated because no event was observed in one arm. The analysis showed no statistically significant difference between the treatment groups for the outcome "treatment discontinuation due to AEs". There was no hint of greater or lesser harm of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for the outcome "treatment discontinuation due to AEs"; greater or lesser harm for this outcome is therefore not proven.

Due to the available data, no valid choice of AEs of particular interest was possible. However, no signs of greater harm of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV resulted from the consideration of the available data.

Results for research question 2 (treatment-naive patients with CHC genotype 1b without cirrhosis)

Mortality

In the patient population considered, no patient has died in the course of the study so far. Hence there is no hint of an added benefit of OBV/PTV/R + DSV + RBV versus TVR + PEG + RBV. An added benefit for the outcome "mortality" is therefore not proven.

Morbidity – SVR 12 as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

SVR was included as sufficiently valid surrogate for the outcome "hepatocellular carcinoma". There was a statistically significant difference in favour of OBV/PTV/R + DSV for the SVR 12. This resulted in an indication of an added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV for the outcome "hepatocellular carcinoma (assessed with the SVR 12)".

Morbidity – EQ-5D VAS (under treatment)

There was a statistically significant difference in favour of OBV/PTV/R + DSV 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 was fully above the irrelevance threshold of

0.2. It can therefore be assumed that the effect was not within a range that is certainly irrelevant.

There was proof of an effect modification for the characteristic "fibrosis stage" expressed with the METAVIR score. This resulted in no hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for patients with a METAVIR score of F0-F1; an added benefit for this subgroup is therefore not proven.

There was a hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for patients with a METAVIR score of ≥ F2.

Health-related quality of life – SF-36 (under treatment)

The physical and mental sum score was considered for the SF-36. The mean differences and the prespecified responder analysis of the company were included in each case; patients in whom the sum score decreased by fewer than 5 points in comparison with baseline were considered as responders.

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the physical sum score in the consideration of the mean differences.

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the physical sum score also in the responder analysis.

Overall, there was a hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for the physical sum score of the SF-36.

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the mental sum score in the consideration of the mean differences. The SMD in the form of Hedges' g was considered to check the relevance of this result. The 95% CI of the SMD was fully above the irrelevance threshold of 0.2. It can therefore be assumed that the effect was not within a range that is certainly irrelevant.

There was an indication of an effect modification by the characteristic "fibrosis stage" expressed with the METAVIR score. There was no hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for patients with a METAVIR score of F0-F1. An added benefit for this subgroup is not proven. There was a hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV in patients with a METAVIR score of ≥ F2.

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the mental sum score in the responder analysis. Both analyses on the mental sum score of the SF-36, both on the basis of the mean differences and the responder analysis, were therefore consistent for the total population of research question 2.

Health-related quality of life – HCV-PRO (under treatment)

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the outcome "HCV-PRO". The SMD in the form of Hedges' g was considered to check the relevance of this result. The 95% CI of the SMD was fully above the irrelevance threshold of 0.2. It can therefore be assumed that the effect was not within a range that is certainly irrelevant.

There were several indications of an effect modification, of which only the characteristic "HCV RNA at baseline" was relevant for the interpretation of the result. For the characteristic "HCV RNA at baseline", there was no hint of an added benefit for patients with < 800 000 IU/mL, so that an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for this subgroup is not proven. In contrast, there was a hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for patients with HCV RNA of ≥ 800 000 IU/mL.

Adverse events

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the outcome "SAEs". Four of the 6 SAEs in the comparator arm had occurred already by week 12 after the start of treatment so that a statistically significant effect was also shown here (Institute's calculation: RR: 0.06 [0.00; 1.01]; p = 0.004). Hence the statistically significant difference from the analysis relevant for the benefit assessment was not only due to the different observation periods of the treatment arms. There was a hint of lesser harm from OBV/PTV/R + DSV in comparison with TVR + PEG + RBV.

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the outcome "treatment discontinuation due to AEs". This resulted in an indication of lesser harm from OBV/PTV/R + DSV in comparison with TVR + PEG + RBV for this outcome.

Due to the available data, no valid choice of AEs of particular interest was possible. However, no signs of greater harm of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV resulted from the consideration of the available data.

Results for research question 3 (treatment-experienced patients with CHC genotype 1a without cirrhosis)

Mortality

In the MALACHITE-II study, no patient has died in the relevant subpopulation in the course of the study so far. Hence there is no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit for the outcome "mortality" is therefore not proven.

Morbidity – SVR 12 as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

SVR was included as sufficiently valid surrogate for the outcome "hepatocellular carcinoma". There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the SVR 12. This resulted in an indication of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for the outcome "hepatocellular carcinoma (assessed with the SVR 12)".

Morbidity – EQ-5D VAS (under treatment)

There was no statistically significant difference between the treatment groups for the outcome "health status". Hence there is no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit regarding the outcome "health status" is therefore not proven.

Health-related quality of life – SF-36 (under treatment)

The physical and mental sum score was considered for the SF-36. The mean differences and the prespecified responder analysis of the company were included in each case; patients in whom the sum score decreased by fewer than 5 points in comparison with baseline were considered as responders.

For the physical sum score, there was no statistically significant difference between the treatment groups for the mean differences or for the responder analysis. This resulted in no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit regarding the outcome "SF-36 (physical sum score)" is therefore not proven.

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the SF-36 mental sum score in the consideration of the mean differences. 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 fully above the irrelevance threshold of 0.2. It was therefore possible that the effect was within a range that is certainly irrelevant. This resulted in no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit for the outcome "SF-36 (mental sum score)" is therefore not proven.

There was no statistically significant difference between the treatment groups for the mental sum score of the SF-36 in the responder analysis. Hence the results of the 2 analyses on the SF-36 are consistent.

Health-related quality of life – HCV-PRO (under treatment)

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the outcome "HCV-PRO". 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 fully above the irrelevance threshold of 0.2. It was therefore possible that the effect was within a range that is certainly

irrelevant. This resulted in no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit for the outcome "HCV-PRO" is therefore not proven.

Adverse events

No SAEs have occurred in the relevant subpopulation of the MALACHITE-II study in the course of the study so far.

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the outcome "treatment discontinuation due to AEs". This resulted in an indication of lesser harm from OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for this outcome. However, this result was based on only 0 versus 2 patients with events.

Due to the available data, no valid choice of AEs of particular interest was possible. Due to the low number of patients in the relevant subpopulation of the study, individual AEs were not considered.

Results for research questions 4 to 16

No direct comparative RCTs on the comparison of OBV/PTV/R with the ACT were available for further patient groups with CHC genotype 1 or 4. Research questions 4 to 10 represent the patient groups with CHC genotype 1. They comprise treatment-experienced patients with CHC genotype 1b without cirrhosis, treatment-naive and treatment-experienced patients with compensated cirrhosis, patients after liver transplantation and patients with HIV coinfection. Research questions 11 to 16 represent the patient groups with CHC genotype 4. They comprise treatment-naive and treatment-experienced patients without cirrhosis and with compensated cirrhosis, patients after liver transplantation and patients with HIV coinfection. For these patient groups, the company included further investigations with the drug under assessment in the patient groups mentioned in the benefit assessment. The investigations presented were mainly RCTs, from each of which the company considered the intervention arm, where, according to the company, OBV/PTV/R was administered in compliance with the approval. No systematic comparison with data on the ACT was conducted. There was no systematic search for comparator data with the ACT. The completeness of the comparator data presented is therefore unclear. Hence the data of the further investigations presented by the company were unsuitable for the benefit assessment.

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 fixed-dose combination ombitasvir/paritaprevir/ritonavir compared with the ACT is assessed as follows:

Table 3 presents a summary of the extent and probability of the added benefit of ombitasvir/paritaprevir/ritonavir.

Table 3: Ombitasvir/paritaprevir/ritonavir – extent and probability of added benefit

Therapeutic indication	**ACT[a]**	**Extent and probability of added benefit**
Treatment-naive patients with CHC genotype 1a without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], peginterferon and ribavirin)**	Indication of non-quantifiable added benefit
Treatment-naive patients with CHC genotype 1b without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], peginterferon and ribavirin)**	Indication of non-quantifiable added benefit
Treatment-experienced patients with CHC genotype 1a without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], peginterferon and ribavirin)**	Indication of non-quantifiable added benefit
Treatment-experienced patients with CHC genotype 1b without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], peginterferon and ribavirin)**	Added benefit not proven
Treatment-naive patients with CHC genotype 1a with compensated cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Treatment-naive patients with CHC genotype 1b with compensated cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven

(continued)

[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). 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). For further details see [1,2].

Table 3: Ombitasvir/paritaprevir/ritonavir – extent and probability of added benefit (continued)

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment-experienced patients with CHC genotype 1a with compensated cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], peginterferon and ribavirin)**	Added benefit not proven
Treatment-experienced patients with CHC genotype 1b with compensated cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], peginterferon and ribavirin)**	Added benefit not proven
Patients with CHC genotype 1 after liver transplantation	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Patients with CHC genotype 1 with HIV coinfection	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Treatment-naive patients with CHC genotype 4 without cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Treatment-experienced patients with CHC genotype 4 without cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Treatment-naive patients with CHC genotype 4 with compensated cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Treatment-experienced patients with CHC genotype 4 with compensated cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Patients with CHC genotype 4 after liver transplantation	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Patients with CHC genotype 4 with HIV coinfection	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.

2.2 Research questions

The aim of the present report is to assess the added benefit of the fixed-dose combination OBV/PTV/R in comparison with dual therapy of PEG + RBV or triple therapy of TVR + PEG + RBV as ACT in patients with CHC genotype 1 and 4.

The fixed-dose combination OBV/PTV/R is only approved in combination with other drugs. Depending on the patient group, it is administered together with DSV and/or ribavirin. The ribavirin-free combination is only approved in patients with CHC genotype 1b without cirrhosis.

The company followed the G-BA's ACT, and specified it by stipulating triple therapy consisting of TVR + PEG + RBV as ACT for treatment-naive patients with CHC genotype 1 without cirrhosis and for treatment-experienced patients with CHC genotype 1 without or with compensated cirrhosis. For all other patient groups, the ACT was dual therapy consisting of PEG + RBV.

Partly different treatment regimens for certain patient groups resulted from the SPCs of OBV/PTV/R, DSV, TVR and PEG or RBV [3-7]. Further differentiations resulted from the specification of the G-BA's ACT. This led to a total of 16 research questions for the benefit assessment (see Section 2.9.2.1 of the full dossier assessment). This concurs with the company's approach.

Table 4 shows the different research questions of the present benefit assessment. For reasons of clarity of the present dossier assessment, the order of the research questions deviates from that of the company.

Table 4: Research questions for the benefit assessment of ombitasvir/paritaprevir/ritonavir

Research question no. in the present assessment[a] (research question no. of the company)	**Population**	**Intervention**	**Appropriate comparator therapy**
	Genotype 1, treatment-naive patients without cirrhosis		
1 (3)	Treatment-naive patients with CHC genotype 1a without cirrhosis	OBV/PTV/R + DSV + RBV	TVR + PEG + RBV
2 (1)	Treatment-naive patients with CHC genotype 1b without cirrhosis	OBV/PTV/R + DSV	TVR + PEG + RBV
	Genotype 1, treatment-experienced patients without cirrhosis		
3 (4)	Treatment-experienced patients with CHC genotype 1a without cirrhosis	OBV/PTV/R + DSV + RBV	TVR + PEG + RBV
4 (2)	Treatment-experienced patients with CHC genotype 1b without cirrhosis	OBV/PTV/R + DSV	TVR + PEG + RBV
	Genotype 1, treatment-naive patients with compensated cirrhosis		
5 (7)	Treatment-naive patients with CHC genotype 1a with compensated cirrhosis	OBV/PTV/R + DSV + RBV	PEG + RBV
6 (5)	Treatment-naive patients with CHC genotype 1b with compensated cirrhosis	OBV/PTV/R + DSV + RBV	PEG + RBV
	Genotype 1, treatment-experienced patients with compensated cirrhosis		
7 (8)	Treatment-experienced patients with CHC genotype 1a with compensated cirrhosis	OBV/PTV/R + DSV + RBV	TVR + PEG + RBV
8 (6)	Treatment-experienced patients with CHC genotype 1b with compensated cirrhosis	OBV/PTV/R + DSV + RBV	TVR + PEG + RBV
	Genotype 1, specific patient populations		
9 (13)	Patients with CHC genotype 1 after liver transplantation	OBV/PTV/R + DSV + RBV	PEG + RBV
10 (15)	Patients with CHC genotype 1 with HIV coinfection	OBV/PTV/R + DSV + RBV	PEG + RBV

(continued)

Table 4: Research questions for the benefit assessment of ombitasvir/paritaprevir/ritonavir (continued)

Research question no. in the present assessment[a] (research question no. of the company)	**Population**	**Intervention**	**Appropriate comparator therapy**
	Genotype 4, specific patient populations		
11 (9)	Treatment-naive patients with CHC genotype 4 without cirrhosis	OBV/PTV/R + RBV	PEG + RBV
12 (10)	Treatment-experienced patients with CHC genotype 4 without cirrhosis	OBV/PTV/R + RBV	PEG + RBV
13 (11)	Treatment-naive patients with CHC genotype 4 with compensated cirrhosis	OBV/PTV/R + RBV	PEG + RBV
14 (12)	Treatment-experienced patients with CV genotype 4 with compensated cirrhosis	OBV/PTV/R + RBV	PEG + RBV
15 (14)	Patients with CHC genotype 4 after liver transplantation	OBV/PTV/R + RBV	PEG + RBV
16 (16)	Patients with CHC genotype 4 with HIV coinfection	OBV/PTV/R + RBV	PEG + RBV

a: The numbering of the research questions corresponds to the presentation in the present benefit assessment; the order deviates from the one of the company in Module 4 A of the dossier.

CHC: chronic hepatitis C; DSV: dasabuvir; OBV: ombitasvir; PEG: peginterferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; TVR: telaprevir

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

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

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 lists on ombitasvir/paritaprevir/ritonavir (studies completed up to 4 November 2014)
- bibliographical literature search on ombitasvir/paritaprevir/ritonavir (last search on 4 November 2014)
- search in trial registries for studies on ombitasvir/paritaprevir/ritonavir (last search on 3 November 2014)

To check the completeness of the study pool:

- search in trial registries for studies on ombitasvir/paritaprevir/ritonavir (last search on 9 February 2015)

No additional relevant study was identified from the check.

2.3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: treatment-naive patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
MALACHITE-I (M13-774)	No	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. CHC: chronic hepatitis C; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; TVR: telaprevir; vs.: versus			

Section 2.3.4 contains a reference list for the studies included.

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: treatment-naive patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[c]
MALACHITE-I	RCT, open-label, parallel	Treatment-naive adults (≥ 18–65 years) with chronic hepatitis C of GT 1a and 1b without cirrhosis	Patients with GT 1a: arm A: OBV/PTV/R + DSV + RBV (N = 69) arm B: TVR + PEG + RBV (N = 34) Patients with GT 1b[a]: arm C: OBV/PTV/R + DSV + RBV (N = 84) arm D: OBV/PTV/R + DSV (N = 83) arm E: TVR + PEG + RBV (N = 41)	Screening: up to 5 weeks Treatment phase: arm A, C and D: 12 weeks arm B and E: 24 or 48 weeks (response-guided) Follow-up: 48 weeks; AEs were followed-up until 30 days after the end of treatment Data cut-off for primary analysis: 11/2014	43 centres[b] in Argentina, Australia, Canada, Chile, Finland, Hungary, Norway, Poland, Romania, Slovak Republic 3/2013 – 6/2015	Primary: proportion of patients with SVR 12 Secondary: proportion of patients with SVR 24[d], health-related quality of life, AEs

a: These arms are not relevant for research question 1 and they will not be presented in the following tables on research question 1.
b: 44 investigation sites according to Module 4.
c: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
d: Data on SVR 24 were not available at the time of submission of the dossier.

AE: adverse event; CHC: chronic hepatitis C; GT: genotype; N: number of randomized patients; n: relevant subpopulation; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SVR: sustained virologic response; TVR: telaprevir; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: treatment-naive patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study	Intervention	Comparison	Concomitant medication
MALACHITE-I	Week 1-12: OBV/PTV/R (25 mg/150 mg/100 mg) once daily orally + DSV 250 mg twice daily orally + RBV 1000 or 1200 mg twice daily orally (depending on weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)	Week 1-12: TVR 750 mg orally every 8 hours + PEG 180 µg once weekly subcutaneously + RBV 1000 or 1200 mg twice daily orally (depending on weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg) Week 13-24 or 13-48 (response-guided): PEG + RBV, same dosage as in week 1-12	Prohibited at start of study: ▪ anti-HCV drugs including TVR, boceprevir, PEG and RBV Prohibited for 2 weeks before the start of the study medication until 2 weeks after the end of the study: ▪ strong or moderate CYP3A substrates, inhibitors and inducers: alfuzosin, amiodarone, astemizole, atorvastatin, carbamazepine, quinidine, cisapride, clarithromycin, conivaptan, dronedarone, efavirenz, eletriptan, eplerenone, everolimus, fusidic acid, itraconazole, St. John's Wort, ketoconazole, lovastatin, midazolam (orally), nefazodone, phenobarbital, phenytoin, pimozide, rifampin, salmeterol, sildenafil, simvastatin, telithromycin, triazolam, voriconazole ▪ CYP2C8 inhibitors: gemfibrozil, trimethoprim ▪ Other prohibited drugs: bepridil, bosentan, buprenorphine, domperidone, ergot derivatives, St. John's Wort, methadone, mifepristone, modafinil, montelukast, ergot alkaloids, pioglitazone, propafenone, quercetin, quinidine, rifabutin, tadalafil, troglitazone, troleandomycin ▪ hormonal contraceptives[a] Prohibited for 2 weeks before the start of the study medication: ▪ antiarrhythmics (class Ia and III), herbal drugs, any drug contraindicated for RBV, TVR or PEG IFN

a: Unless allowed by the investigator.

CHC: chronic hepatitis C; DSV: dasabuvir; HCV: hepatitis C virus; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; TVR: telaprevir; vs.: versus

The MALACHITE-I study was an RCT with 5 treatment arms, of which only the arms A and B are relevant for the research question 1 considered here. Only these arms included patients with genotype 1a. The arms C, D and E investigated only patients with genotype 1b and are therefore not considered further for research question 1.

Treatment-naive adult patients with CHC genotype 1a without cirrhosis were included in the treatment arms A and B, which are relevant for research question 1. A total of 103 patients were randomly assigned to this comparison (intervention arm A: N = 69, comparator arm B: N = 34).

In intervention arm A, the patients received OBV/PTV/R in combination with DSV and RBV over a period of 12 weeks. In comparator arm B, the patients received triple therapy of TVR + PEG + RBV. The treatment duration with TVR in combination with PEG + RBV was 12 weeks; depending on their response to treatment, treatment was continued with PEG + RBV for further 12 or 36 weeks. Hence the maximum treatment duration was 24 or 48 weeks. The treatment regimens used and the dosages of the drugs complied with the approval for patients with CHC genotype 1a without cirrhosis.

Drugs contraindicated according to the SPC were not allowed to be used as concomitant medication in the study.

The planned follow-up duration was 48 weeks after the end of treatment for all patients. AEs were followed-up in the study for 30 days after the end of treatment.

Treatment duration/observation period in the study

The requirements of the respective SPCs resulted in fixed treatment durations for the combination therapy OBV/PTV/R + DSV + RBV and the triple therapy with TVR + PEG + RBV. The patients in the OBV/PTV/R + DSV + RBV arm were treated for 12 weeks; the patients in the TVR + PEG + RBV arm were treated for 24 or 48 weeks, depending on their response to treatment. AEs were followed-up in the study for 30 days after the end of treatment. This resulted in markedly different observation periods with a minimum difference of 12 weeks and a maximum difference of 36 weeks. As a consequence, the effect estimations for AEs and mortality based on naive proportions do not represent an adequate analysis, and analyses on the basis of IDRs need to fulfil certain requirements for them to be acceptable as valid estimates for the HR (see Section 2.9.2.4.2 of the full dossier assessment). Overall, no conclusive interpretation of the data on AEs was possible. As a result, no final quantitative conclusion on the harm of OBV/PTV/R was drawn in the overall consideration of AEs.

Table 8 shows the characteristics of the patients with CHC genotype 1 in the relevant arms of the MALACHITE-I study.

Table 8: Characteristics of the study populations – RCT, direct comparison: treatment-naive patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study Group	**N**	**Age [years] mean (SD)**	**Sex [F/M] %**	**Fibrosis stage [F0-F1/F2/≥ F3] %**	**Viral load [< 800 000/ ≥ 800 000 IU/mL] %**	**Ethnicity [white/black/ Asian/other] %**	**IL28B genotype CC/CT/TT %**	**Study discontinuations n (%)**
MALACHITE-I								
OBV/PTV/R + DSV + RBV	69	46 (12)	30/70	72.1/17.6/10.3	29.0/71.0	89.9/1.4/4.3/4.3[a]	28/58/14	3 (4.3[a])
TVR + PEG + RBV	34	45 (14)	50/50	70.6/20.6/8.8	23.5/76.5	88.2/0/8.8/2.9	32/53/15	3 (8.8[a])

a: Institute's calculation.

CHC: chronic hepatitis C; DSV: dasabuvir; F: female; IU: international units; M: male; N: number of patients included; n: number of patients with event; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; TVR: telaprevir; vs.: versus

The sex ratio in the OBV/PTV/R + DSV + RBV arm was 30% women and 70% men, whereas it was balanced in the comparator arm.

Over 70% of the patients in both treatment arms had no or mild liver damage expressed with a METAVIR score of F0 or F1. Severe fibrosis occurred in a maximum of 10% of the patients. Baseline viral load was high (≥ 800 000 IU/mL) in over 70% of the patients. Almost 90% of the patients were white; fewer than 10% of the patients were Asian, and there were almost no black patients. Just over half of the patients had IL28B genotype CT, another 15% had genotype TT, and approximately 30% of the patients had genotype CC.

Fewer than 10% of the patients in both treatment groups discontinued the study.

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: treatment-naive patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

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			
MALACHITE-I	Yes	Yes	No	No	Yes	Yes	Low

CHC: chronic hepatitis C; DSV: dasabuvir; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; TVR: telaprevir; vs.: versus

The risk of bias at study level was rated as low. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.3.2.2 with the outcome-specific risk of bias.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - SVR 12 as sufficiently valid surrogate for the patient-relevant outcome “hepatocellular carcinoma”
  - health status using the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS)
- Health-related quality of life
  - Short Form (36) Health Survey (SF-36)
  - HCV-PRO
- Adverse events
  - overall rate of SAEs
  - treatment discontinuation due to AEs
  - specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

The company used a total of 5 instruments to measure health-related quality of life. Besides the questionnaires SF-36 and HCV-PRO mentioned above, these were the EQ-5D, the Hepatitis C Virus Treatment Satisfaction (HCVTSat), and the Work Productivity and Activity Impairment (WPAI) questionnaire. The EQ-5D was not included completely in the benefit assessment, but only the VAS. The VAS was also considered to be a measurement of the general health status, i.e. as morbidity outcome. The questionnaires HCVTSat and WPAI were not included in the benefit assessment because they are not considered to be instruments to measure health-related quality of life. See Section 2.9.2.4.3 of the full dossier assessment for more details.

Furthermore, all outcomes called AEs of specific interest by the company and included in its benefit assessment were not included because the operationalizations were not patient-relevant or their patient relevance remained unclear or the available data were unsuitable to produce a valid recording of treatment effects. A detailed justification can be found in Section 2.3.2.2 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: treatment-naive patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study	Outcomes							
	All-cause mortality	Sustained virologic response (SVR 12)	Health status using the EQ-5D VAS	Health-related quality of life using the SF-36	Health-related quality of life using the HCV-PRO	SAEs	Treatment discontinuation due to AEs	Specific AEs
MALACHITE-I	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AE: adverse event; CHC: chronic hepatitis C; DSV: dasabuvir; EQ-5D: European Quality of Life-5 Dimensions; HCV-PRO: hepatitis C virus patient-reported outcomes; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SVR: sustained virologic response; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

2.3.2.2 Risk of bias

Table 11 shows the risk of bias for the relevant outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: treatment-naive patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study	Study level	Outcomes							
		All-cause mortality	Sustained virologic response (SVR 12)	Health status using the EQ-5D VAS	Health-related quality of life using the SF-36	Health-related quality of life using the HCV-PRO	SAEs	Treatment discontinuation due to AEs	Specific AEs
MALACHITE-I	L	H[a]	L	H[b]	H[b]	H[b]	H[c]	N	-[d]

a: Marked difference in observation periods between the treatment arms.
b: Open-label study design; in addition, for the EQ-5D VAS and the SF-36, the proportion of patients from the ITT population not included in the assessment differed by more than 5 percentage points between the treatment arms.
c: Marked difference in observation period between the treatment arms; IDR no suitable approximation of the HR, or IDR not calculated because of zero cell; RR only interpretable in qualitative terms.
d: No comprehensive choice of specific AEs possible because of the notably different observation periods in the individual treatment arms and the resulting uncertainty in the calculation of effect estimates; therefore no quantitative conclusion on harm from OBV/PTV/R + DSV + RBV possible.

AE: adverse event; CHC: chronic hepatitis C; DSV: dasabuvir; EQ-5D: European Quality of Life-5 Dimensions; H: high; HCV-PRO: hepatitis C virus patient-reported outcomes; HR: hazard ratio; IDR: incidence density ratio; L: low; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SVR: sustained virologic response; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome "SVR 12", like the risk of bias of the total study, was considered to be low. Due to the study design, all patient-reported outcomes (EQ-5D VAS, SF-36, HCV-PRO) were considered to have a high risk of bias because subjective outcomes in open-label studies generally are to be rated as having a high risk of bias. The assessments of the risk of bias at outcome level regarding the outcomes mentioned above concur with the company's assessments.

The risk of bias for the outcomes "mortality" and "overall rate of SAEs" was also considered to be high because the observation periods between the treatment groups differed notably. The assessment of the risk of bias concurs with the company's assessment. In contrast, the risk of bias for the outcome "treatment discontinuation due to AEs" was considered to be low because the different observation periods resulted from the planned limitation of the treatment duration. This assessment deviates from that of the company, which sees a high risk of bias also for this outcome.

Since no comprehensive choice of AEs of specific interest was possible, the risk of bias was not assessed. This approach deviates that of the company.

Due to the markedly different observation period in the intervention and comparator arm of the MALACHITE-I study, the data on AEs were largely not interpretable in a meaningful way (see Section 2.9.2.4.3 of the full dossier assessment). Except for treatment discontinuation due to AEs, the results on AEs were therefore not conclusively interpretable in quantitative terms.

In summary, at most indications of an added benefit could be derived for the outcome "SVR 12" and for treatment discontinuation due to AEs as a consequence; at most hints of an added benefit could be derived for the potentially highly biased outcomes on mortality, on patient-reported outcomes and on AEs for which an analysis was meaningful.

2.3.2.3 Results

Table 12 and Table 13 summarize the results on the comparison of OBV/PTV/R + DSV + RBV with TVR + PEG + RBV in treatment-naive patients with CHC infection of genotype 1a without cirrhosis. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

For the benefit assessment, no analysis with time periods comparable for both treatment groups was available for the results on health-related quality of life and health status (EQ-5D VAS). The time from the start of the study until the end of treatment was therefore considered in each case. Hence the corresponding results describe only health-related quality of life and health status under treatment.

Besides the mean differences, responder analyses for the mental and physical SF-36 sum score were additionally included for the SF-36 questionnaire. Responders are patients who improved in the course of the study or who only worsened by fewer than 5 points on the respective scale. This is not a minimally important difference (MID). The responder analysis was still included because it investigated an additional question (see Section 2.9.2.4.3 of the full dossier assessment).

Table 12: Results (dichotomous outcomes) – RCT, direct comparison: treatment-naive patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study **Outcome category** **Outcome**	**OBV/PTV/R + DSV + RBV**		**TVR + PEG + RBV**		**OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV**
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value**
MALACHITE-I					
Mortality					
All-cause mortality	69	1 (1.4)	34	0 (0)	NC
Morbidity					
SVR 12[a]	69	67 (97.1)	34	28 (82.4)	1.18 [1.00; 1.38]; 0.009[b]
Health-related quality of life (under treatment)					
SF-36 responders[c]					
physical sum score	69	53 (76.8)	32	19 (59.4)	1.29 [0.94; 1.77]; 0.075
mental sum score	69	44 (63.8)	32	15 (46.9)	1.36 [0.90; 2.05]; 0.117
Adverse events					
AEs	69	61 (88.4)	34	34 (100)	
SAEs	69	0 (0)	34	3 (8.8)	NC
Treatment discontinuation due to AEs[d]	69	1 (1.4)	34	2 (5.9)	0.25 [0.02; 2.62]; 0.229[e]

a: Sufficiently valid surrogate for the patient-relevant outcome “hepatocellular carcinoma”.
b: Institute’s calculation, unconditional exact test (CSZ method according to [8]). Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods. The company classified patients who discontinued treatment as non-responders. From the available individual patient data, it was verified for all patients except one that the patients actually were non-responders (see Section 2.9.2.2 of the full dossier assessment). A sensitivity analysis conducted by the Institute, in which this patient was categorized as responder, had a similar result, however: RR = 1.14 [0.98; 1.32]; p = 0.026.
c: Patients who improved on the respective scale in the observation period or who worsened by fewer than 5 points are considered responders.
d: Patients who discontinued all treatments.
e: Institute‘s calculation: RR and 95% CI, unconditional exact test (CSZ method according to [8]).
CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; DSV: dasabuvir; N: number of analysed patients; n: number of patients with event; NC: not calculated; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SF-36: Short Form (36) Health Survey; SVR 12: sustained virologic response 12 weeks after the end of treatment; TVR: telaprevir; vs.: versus

Table 13: Results (continuous outcomes) – RCT, direct comparison: treatment-naive patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV (start of study until end of treatment)

Study **Outcome category** **Instrument** **Subscale**	**OBV/PTV/R + DSV + RBV**			**TVR + PEG + RBV**			**OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV**
	N	**Baseline values mean (SD)**	**Change at end of treatment mean (SD)**	**N**	**Baseline values mean (SD)**	**Change at end of treatment mean (SD)**	**Mean difference [95% CI]; p-value[a]**
MALACHITE-I							
Morbidity (under treatment)							
EQ-5D VAS	69	80.4 (ND)	2.1 (15.6)	32	80.3 (ND)	-4.4 (16.2)	6.54 [0.37; 12.71]; 0.038 Hedges' g: 0.41 [−0.01; 0.83]
Health-related quality of life (under treatment)							
SF-36							
physical sum score	69	49.0 (ND)	0.5 (8.6)	32	49.6 (ND)	-5.5 (8.3)	6.08 [2.72; 9.44]; < 0.001 Hedges' g: 0.70 [0.27; 1.13][c]
mental sum score	69	51.5 (ND)	-4.2 (10.6)	32	50.2 (ND)	-5.8 (12.2)	2.13 [-2.39; 6.65] 0.351
HCV-PRO total score	68	78.4 (ND)	-2.4 (18.4)	32	77.3 (ND)	-12.3 (16.1)	10.15 [2.75; 17.55]; 0.008 Hedges' g: 0.55 [0.13; 0.98][c]

a: Unless stated otherwise: mean difference, CI and p-value calculated using an ANCOVA model on the difference of the changes to baseline between the arms, with baseline value and region as covariables and the treatment arm as factor.
b: Calculation by the company; values concur with calculation from data on change at the end of treatment.
c: Hedges' g, Institute's calculation from data on the change at the end of treatment.
CHC: chronic hepatitis C; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HCV-PRO: hepatitis C virus patient-reported outcomes; N: number of analysed patients; ND: no data; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form (36) Health Survey; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

Mortality

In the patient population considered, one death occurred in the OBV/PTV/R + DSV + RBV arm; no patient died in the TVR + PEG + RBV arm. Hence there is no hint of an added benefit of OBV/PTV/R + DSV + RBV versus TVR + PEG + RBV. An added benefit for the outcome "mortality" is therefore not proven. This concurs with the company's assessment.

Morbidity

SVR 12 as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the SVR 12. This resulted in an indication of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for the outcome "hepatocellular carcinoma (assessed with the SVR 12)".

This deviates from the company only in so far as the company made no outcome-specific conclusion on probability.

Health status using the EQ-5D VAS (under treatment)

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the outcome "health status". Higher scores on the EQ-5D VAS indicate better health status. The SMD in the form of Hedges' g was considered to check the relevance of this result. The 95% confidence interval (CI) of the SMD did not lie fully above the irrelevance threshold of 0.2. It was therefore possible that the effect was within a range that is certainly irrelevant. Hence there is no hint of an added benefit; an added benefit is therefore not proven.

The assessment regarding the EQ-5D VAS deviates from the company, which allocated this outcome to health-related quality of life, additionally considered one further period of analysis, and made no outcome-specific conclusion on probability.

Health-related quality of life (under treatment)

SF-36

The physical and mental sum score was considered for the SF-36.

Physical sum score

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the physical sum score in the consideration of the mean differences. The SMD in the form of Hedges' g was considered to check the relevance of this result. The 95% CI of the SMD was fully above the irrelevance threshold of 0.2. It can therefore be assumed that the effect was not within a range that is certainly irrelevant.

Moreover, there was an indication of an effect modification by the characteristic "viral load (HCV RNA at baseline)". This resulted in a hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for patients with HCV RNA of < 800 000 IU/mL. There was no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for patients with HCV RNA of ≥ 800 000 IU/mL. An added benefit for the outcome "SF-36 (physical sum score)" is therefore not proven for this subgroup.

In the responder analysis, there was no statistically significant difference between the treatment groups for the physical sum score in the total population for research question 1. However, the rate of patients with response in the OBV/PTV/R + DSV + RBV arm was numerically higher than in the TVR + PEG + RBV arm. This result does not raise doubts about the result of the analysis of the mean differences. There were no subgroup analyses for the responder analysis.

Overall, there is a hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for the physical sum score of the SF-36 for patients with HCV RNA of < 800 000 IU/mL.

Mental sum score

There was no statistically significant difference between the treatment groups for the mental sum score of the SF-36 in the consideration of the mean differences.

There was an indication of an effect modification by the characteristic "fibrosis stage", which was recorded with the METAVIR score. However, no separate conclusions for the subgroups resulted from this. Overall, there is no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit for the outcome "SF-36 (mental sum score)" is not proven.

There was no statistically significant difference between the treatment groups for the mental sum score of the SF-36 in the responder analysis. Hence for the mental sum score, the results based on the mean differences were consistent with the responder analysis for the total population.

In summary, the assessments regarding the SF-36 partly deviate from the company's assessments. The company considered additional periods of analysis and did not address the outcome-specific probability of the added benefit. Moreover, the company did not derive any consequences for the benefit assessment from subgroup analyses.

HCV-PRO

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the outcome "HCV-PRO". 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 fully above the irrelevance threshold of 0.2. It was therefore possible that the effect was within a range that is certainly irrelevant. This resulted in no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit for the outcome "HCV-PRO" is therefore not proven.

This deviates from the company's assessment, which additionally used a responder analysis on 2 periods of analysis, each of which with a statistically significant result, but derived no conclusion on the outcome-specific probability of the added benefit.

Adverse events

As described in Section 2.4.2.2, the data on AEs were largely not evaluable in a meaningful way. Hereinafter, except for treatment discontinuation due to AEs, only qualitative conclusions are therefore drawn on the comparison of OBV/PTV/R + DSV + RBV with TVR + PEG + RBV.

Overall rate of SAEs and treatment discontinuation due to AEs

No SAEs have occurred in the OBV/PTV/R + DSV + RBV arm in the course of the study so far. In the TVR + PEG + RBV arm, 3 patients (8.8%) had at least one SAE. No IDR was calculated because no event was observed in one arm.

The analysis showed no statistically significant difference between the treatment groups for the outcome "treatment discontinuation due to AEs".

There was no hint of greater or lesser harm of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for the outcome "treatment discontinuation due to AEs", greater or lesser harm for these outcomes is therefore not proven.

Adverse events of particular interest

Due to the available data, no comprehensive choice of AEs of particular interest was possible. However, no signs of greater harm of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV resulted from the consideration of the available data.

Summary

Overall, AEs are not evaluable. Quantitative conclusions are only possible regarding treatment discontinuations due to AEs.

The assessment deviates from that of the company, which, on the basis of the overall rates and some specific AEs of interest, derived quantitative conclusions on the added benefit.

2.3.2.4 Subgroups and other effect modifiers

See Section 2.9.2.4.3 of the full dossier assessment for a list of the relevant effect modifiers.

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. In addition, there had to be a statistically significant effect in at least one of the subgroups. Subgroup results for which no valid conclusion was possible due to missing values in the analysis (e.g. difference of ≥ 15 percentage points between the 2 treatment groups) are not presented. In effect modifiers with more than 2 categories, such as the METAVIR score, the categories of neighbouring effect estimates were summarized if the heterogeneity test provided a p-value of ≥ 0.2.

The prerequisite for proof of an effect modification was a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provided an indication of an effect modification.

Due to the data availability for AEs, which can only be interpreted in qualitative terms, the subgroup results for SAEs were not considered. No subgroup analyses were available for the outcome "treatment discontinuation due to AEs" (in the operationalization considered in the present benefit assessment).

Table 14 summarizes the subgroup results on the comparison of OBV/PTV/R + DSV + RBV with TVR + PEG + RBV in treatment-naive patients with CHC genotype 1a without cirrhosis. Where necessary, the data from the dossier were supplemented by the Institute's calculations.

Table 14: Subgroups (continuous outcomes): outcome "health-related quality of life" by characteristic "HCV RNA" and "METAVIR score", RCT, direct comparison: treatment-naive patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV (start of the study until end of treatment)

Study **Instrument** **Characteristic** **Subgroup**	**OBV/PTV/R + DSV + RBV**			**TVR + PEG + RBV**			**OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV**
	N	**Baseline values mean (SD)**	**Change at end of treatment mean (SD)**	**N**	**Baseline values mean (SD)**	**Change at end of treatment mean (SD)**	**Mean difference [95% CI]; p-value[a]**
MALACHITE-I							
SF-36 (under treatment)							
physical sum score							
HCV RNA							
< 800 000 IU/mL	20	48.6 (ND)	2.5 (7.0)	7	52.5 (ND)	-9.0 (9.9)	10.31 [3.42; 17.19]; 0.005 Hedges' g 1.43 [0.48; 2.38][b]
≥ 800 000 IU/mL	49	49.1 (ND)	-0.3 (9.2)	25	48.8 (ND)	-4.6 (7.7)	4.40 [0.28; 8.51]; 0.037 Hedges' g 0.49 [0.00; 0.98][b]
						Interaction:	p-value = 0.149[c]
mental sum score							
METAVIR score							
F0-F2							-0.61 [-5.43; 4.12]; 0.801[d]
F0-F1	*49*	*51.1 (ND)*	*-4.6 (11.1)*	*22*	*51.8 (ND)*	*−5.1 (12.9)*	*0.18 [-5.22; 5.57]; 0.948*
F2	*12*	*54.0 (ND)*	*-6.4 (9.5)*	*7*	*46.4 (ND)*	*-4.1 (11.0)*	*-3.74 [-15.14; 7.66]; 0.497*
≥ F3	7	50.4 (ND)	1.3 (8.6)	3	47.3 (ND)	-14.4 (8.7)	16.77 [2.94; 30.60]; 0.024 Hedges' g for ≥ F3 1.65 [0.01; 3.29][b]
						Interaction:	p-value = 0.097[c]

a: Unless stated otherwise: mean difference, CI and p-value calculated using an ANCOVA model on the difference of the changes to baseline between the arms, with baseline value between the arms, with baseline value as covariable and treatment arm as factor.
b: Institute's calculation from data on the change at the end of treatment.
c: Calculated using an ANCOVA model with the covariables baseline value, treatment arm, subgroup, and the interaction term treatment arm*subgroup.
d: Mean difference, 95% CI and p-value from the Institute's meta-analysis using the mean differences of the subgroups from ANCOVA with baseline value as covariable and treatment arm as factor.

CHC: chronic hepatitis C; CI: confidence interval; DSV: dasabuvir; HCV RNA: hepatitis C virus ribonucleic acid; IU: international units; N: number of analysed patients; ND: no data; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SF-36: Short Form (36) Health Survey; TVR: telaprevir; vs.: versus

Health-related quality of life (under treatment)

SF-36

There were indications of effect modification for the physical and for the mental sum score of the SF-36 (continuous analysis).

Physical sum score

There was an indication of effect modification by the characteristic "HCV RNA at baseline" for the physical sum score. There was a statistically significant effect in favour of OBV/PTV/R + DSV + RBV both for patients with an HCV RNA concentration of < 800 000 IU/mL and for patients with ≥ 800 000 IU/mL. The SMD in the form of Hedges' g was considered to check the relevance of these results. The 95% CI of the SMD in patients with a viral load of < 800 000 IU/mL was fully above the irrelevance threshold of 0.2. It can therefore be assumed for this subgroup that the effect was not within a range that is certainly irrelevant. There was a hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for patients with a viral load of < 800 000 IU/mL.

For patients with HCV RNA of ≥ 800 000 IU/mL, the 95% CI of the SMD did not lie fully above the irrelevance threshold of 0.2. It is therefore possible that the effect was within a range that is certainly irrelevant. Since only a hint of an added benefit could have been derived already for the total population, there was no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for the subgroup with HCV RNA of ≥ 800 000 IU/mL. An added benefit for the outcome "SF-36 (physical sum score)" is therefore not proven for this subgroup.

This deviates from the company's assessment, which derived no consequences from the subgroup analysis for the benefit assessment.

Mental sum score

For the mental sum score of the SF-36, there was an indication of effect modification by the factor "fibrosis stage" expressed with the METAVIR score. There was no important heterogeneity for the 2 categories F0-F1 and F2 with neighbouring effect estimates (interaction test $p \geq 0.2$). These 2 categories were therefore summarized as category F0-F2.

There was no statistically significant difference between the treatment groups for patients with a METAVIR score of F0-F2. This resulted in no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for this subgroup. An added benefit for the subgroup with a METAVIR score of F0-F2 for the outcome "SF-36 (mental sum score)" is therefore not proven.

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for patients with a METAVIR score of ≥ F3. The SMD in the form of Hedges' g was considered to check the relevance of these results. The 95% CI of the SMD did not lie fully above the irrelevance threshold of 0.2. It is therefore possible that the effect was within a range that is

certainly irrelevant. This resulted in no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for this subgroup. An added benefit for the subgroup with a METAVIR score of ≥ F3 for the outcome "SF-36 (mental sum score)" is therefore not proven.

This deviates from the company's assessment, which derived no consequences from the subgroup analysis for the benefit assessment.

2.3.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit 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 OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for the outcomes "hepatocellular carcinoma (assessed with the surrogate SVR 12)" and "health-related quality of life (under treatment)". The extent of the respective added benefit at outcome level was estimated from these results (see Table 15).

Table 15: Extent of added benefit at outcome level: treatment-naive patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV

Outcome category **Outcome**	**OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	1.4% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Hepatocellular carcinoma, assessed with the surrogate SVR 12	97.1% vs. 82.4% RR: 1.18 [1.00; 1.38] p = 0.009[c] probability: "indication"	Outcome category: serious /severe symptoms/late complications added benefit, extent: "non-quantifiable"
Health status using the EQ-5D VAS (under treatment)	MD: 6.54 [0.37; 12.71] p = 0.038 Hedges' g: 0.41 [-0.01; 0.83]	Lesser benefit/added benefit not proven
Health-related quality of life (under treatment)		
SF-36		
Physical sum score	MD: 6.08 [2.72; 9.44] p < 0.001 Hedges' g: 0.70 [0.27; 1.13]	
HCV RNA < 800 000 IU/mL	MD: 10.31 [3.42; 17.19] p = 0.005 Hedges' g: 1.43 [0.48; 2.83] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
HCV RNA ≥ 800 000 IU/mL	MD: 4.40 [0.28; 8.51] p = 0.037 Hedges' g: 0.49 [0.00; 0.98]	Lesser benefit/added benefit not proven
Mental sum score	Responder analysis: RR: 1.36 [0.90; 2.05] p = 0.117	Lesser benefit/added benefit not proven
HCV-PRO	MD: 10.15 [2.75; 17.55] p = 0.008 Hedges' g: 0.55 [0.13; 0.98]	Lesser benefit/added benefit not proven
Adverse events		
SAEs	0% vs. 8.8%	Greater/lesser harm not proven
Treatment discontinuation due to AEs	1.4% vs. 5.9% RR: 0.25 [0.02; 2.62] p = 0.229	Greater/lesser harm not proven
AEs of particular interest	Choice and quantitative assessment not possible	Greater/lesser harm not proven

(continued)

Table 15: Extent of added benefit at outcome level: treatment-naive patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV (continued)

a: Probability provided if statistically significant differences were present. Decision based on the lower 95% CI limit of Hedges' g in continuous outcomes.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation, unconditional exact test (CSZ method according to [8]).
d: Institute's calculation: including RR and 95% CI, unconditional exact test (CSZ method according to [8]).
AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; DSV: dasabuvir; EQ-5D: European Quality of Life-5 Dimensions; HCV-PRO: hepatitis C virus patient-reported outcomes; HCV RNA: hepatitis C virus ribonucleic acid; MD: mean difference; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SVR 12: sustained virologic response 12 weeks after the end of treatment; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 16 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV (treatment-naive CHC genotype 1a patients without cirrhosis)

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ hepatocellular carcinoma, assessed with the surrogate SVR 12: indication of an added benefit – extent: non-quantifiable	-
Health-related quality of life: ▪ SF-36, physical sum score ▫ HCV RNA < 800 000 IU/mL: hint of an added benefit, extent: "non-quantifiable"	-
CHC: chronic hepatitis C; DSV: dasabuvir; HCV: hepatitis C virus; IU: international units; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RNA: ribonucleic acid; SF-36: Short Form (36) Health Survey; SVR 12: sustained virologic response 12 weeks after the end of treatment; TVR: telaprevir	

Overall, only positive effects remained in the outcome categories "serious/severe symptoms or late complications" and "health-related quality of life". There was an indication of an added benefit for the outcome "hepatocellular carcinoma". The extent of this added benefit could not be quantified, however, because the outcome was only assessed with the surrogate SVR 12. Furthermore, there was a hint of an added benefit for the outcome "health-related quality of life", recorded using the SF-36 instrument, but only for the physical sum score and for the subgroup of patients with low HCV RNA at baseline (extent: non-quantifiable).

Since there was an indication of an added benefit for all patients already from the outcome "hepatocellular carcinoma", the results of the subgroup analysis did not raise doubts about the presence of an added benefit for all treatment-naive patients with genotype 1a without cirrhosis.

Regarding harm from OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV, a quantitative conclusion was only possible for the outcome "treatment discontinuation due to AEs". Greater or lesser harm from OBV/PTV/R + DSV + RBV is not proven for this outcome. The available data allowed no quantitative conclusions for SAEs and specific AEs; however, there was also no sign of greater harm from OBV/PTV/R + DSV + RBV for these outcomes. A weakening of the added benefit of OBV/PTV/R + DSV + RBV did therefore not seem justified.

In summary, there is an indication of a non-quantifiable added benefit of OBV/PTV/R + DSV + RBV versus the ACT TVR + PEG + RBV for treatment-naive patients with CHC genotype 1a without cirrhosis.

The result of the assessment of the added benefit of OBV/PTV/R in comparison with the ACT is summarized in Table 17.

Table 17: Ombitasvir/paritaprevir/ritonavir – extent and probability of the added benefit for treatment-naive patients with CHC genotype 1a without cirrhosis

Therapeutic indication	**ACT[a]**	**Extent and probability of added benefit**
Treatment-naive patients with CHC genotype 1a without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], 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		

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

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

MALACHITE-I

AbbVie. A randomized, open-label study to evaluate the efficacy and safety of ABT-450/ritonavir/ABT-267 and ABT-333 co-administered with and without ribavirin compared to telaprevir co-administered with pegylated interferon α-2a and ribavirin in treatment-naïve adults with chronic hepatitis C genotype 1 virus infection (MALACHITE I): study M13-774; clinical study report (primary analysis) [unpublished]. 2015.

AbbVie. A study to evaluate the efficacy and safety of three experimental drugs compared with Telaprevir (a licensed product) in people with hepatitis C virus infection who have not had treatment before (MALACHITE 1): full text view [online]. In: ClinicalTrials.gov. 26 January 2015 [accessed: 18 February 2015]. URL: http://ClinicalTrials.gov/show/NCT01854697.

AbbVie Deutschland. A randomized, open-label study to evaluate the efficacy and safety of ABT-450/ritonavir/ABT-267 and ABT-333 co-administered with and without ribavirin compared to telaprevir co-administered with pegylated interferon α-2a and ribavirin in treatment-naïve adults with chronic hepatitis C genotype 1 virus infection (MALACHITE I) [online]. In: EU Clinical Trials Register. [Accessed: 18 February 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-003754-84.

2.4 Research question 2: treatment-naive patients with CHC genotype 1b without cirrhosis

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 lists on ombitasvir/paritaprevir/ritonavir (studies completed up to 4 November 2014)
- bibliographical literature search on ombitasvir/paritaprevir/ritonavir (last search on 4 November 2014)
- search in trial registries for studies on ombitasvir/paritaprevir/ritonavir (last search on 3 November 2014)

To check the completeness of the study pool:

- search in trial registries for studies on ombitasvir/paritaprevir/ritonavir (last search on 9 February 2015)

No additional relevant study was identified from the check.

2.4.1.1 Studies included

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

Table 18: Study pool – RCT, direct comparison: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
MALACHITE-I (M13-774)	No	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. CHC: chronic hepatitis C; DSV: dasabuvir; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; TVR: telaprevir; vs.: versus			

Section 2.4.4 contains a reference list for the studies included.

2.4.1.2 Study characteristics

Table 19 and Table 20 describe the studies used for the benefit assessment.

Table 19: Characteristics of the studies included – RCT, direct comparison: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[c]
MALACHITE-I	RCT, open-label, parallel	Treatment-naive adults (≥ 18-65 years) with chronic hepatitis C of GT 1a and 1b without cirrhosis	Patients with GT 1a[a]: arm A: OBV/PTV/R + DSV + RBV (N = 69) arm B: TVR + PEG + RBV (N = 34) Patients with GT 1b: arm C[a]: OBV/PTV/R + DSV + RBV (N = 84) arm D: OBV/PTV/R + DSV (N = 83) arm E: TVR + PEG + RBV (N = 41)	Screening: up to 5 weeks Treatment phase: arm A, C and D: 12 weeks arm B and E: 24 or 48 weeks (response-guided) Follow-up: 48 weeks; AEs were followed-up until 30 days after the end of treatment Data cut-off for primary analysis: 11/2014	43 centres[b] in Argentina, Australia, Canada, Chile, Finland, Hungary, Norway, Poland, Romania, Slovak Republic 3/2013 – 6/2015	Primary: proportion of patients with SVR 12 Secondary: proportion of patients with SVR 24[d], health-related quality of life, AEs

a: These arms are not relevant for research question 2 and they will not be presented in the following tables on research question 2.
b: 44 investigation sites according to Module 4 A.
c: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
d: Data on SVR 24 were not available at the time of submission of the dossier.

AE: adverse event; CHC: chronic hepatitis C; DSV: dasabuvir; GT: genotype; N: number of randomized patients; n: relevant subpopulation; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SVR: sustained virologic response; TVR: telaprevir; vs.: versus

Table 20: Characteristics of the interventions – RCT, direct comparison: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV

Study	Intervention	Comparison	Concomitant medication
MALACHITE-I	Week 1-12: OBV/PTV/R (25 mg/150 mg/100 mg) once daily orally + DSV 250 mg twice daily orally	Week 1-12: TVR 750 mg orally every 8 hours + PEG 180 µg once weekly subcutaneously + RBV 1000 or 1200 mg twice daily orally (depending on weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg) Week 13-24 or 13-48 (response-guided): PEG + RBV, same dosage as in week 1-12	Prohibited at start of study: ▪ anti-HCV drugs including TVR, boceprevir, PEG and RBV Prohibited for 2 weeks before the start of the study medication until 2 weeks after the end of the study: ▪ strong or moderate CYP3A substrates, inhibitors and inducers: alfuzosin, amiodarone, astemizole, atorvastatin, carbamazepine, quinidine, cisapride, clarithromycin, conivaptan, dronedarone, efavirenz, eletriptan, eplerenone, everolimus, fusidic acid, itraconazole, St. John's Wort, ketoconazole, lovastatin, midazolam (orally), nefazodone, phenobarbital, phenytoin, pimozide, rifampin, salmeterol, sildenafil, simvastatin, telithromycin, triazolam, voriconazole ▪ CYP2C8 inhibitors: gemfibrozil, trimethoprim ▪ Other prohibited drugs: bepridil, bosentan, buprenorphine, domperidone, ergot derivatives, St. John's Wort, methadone, mifepristone, modafinil, montelukast, ergot alkaloids, pioglitazone, propafenone, quercetin, quinidine, rifabutin, tadalafil, troglitazone, troleandomycin ▪ hormonal contraceptives[a] Prohibited for 2 weeks before the start of the study medication: ▪ antiarrhythmics (class Ia and III), herbal drugs, any drug contraindicated for RBV, TVR or PEG IFN

a: Unless allowed by the investigator.

CHC: chronic hepatitis C; DSV: dasabuvir; HCV: hepatitis C virus; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; TVR: telaprevir; vs.: versus

The MALACHITE-I study was an RCT with 5 treatment arms, of which only the arms D and E were relevant for the research question 2 considered here. Only these arms included patients with CHC genotype 1b. Exclusively patients with CHC genotype 1a were included in the study arms A and B (see research question 1 of the present benefit assessment). Arm C contained exclusively patients with CHC genotype 1b, but here OBV/PTV/R + DBV was administered in combination with RBV – the combination with ribavirin does not comply with the approval for patients with CHC genotype 1b without cirrhosis. The arms A, B and C were therefore not considered further for research question 2.

Treatment-naive adult patients with CHC genotype 1b without cirrhosis were included in the treatment arms D and E, which are relevant for research question 2. A total of 124 patients were randomly assigned to this comparison (intervention arm D: N = 83, comparator arm E: N = 41).

In intervention arm D, the patients received OBV/PTV/R in combination with DSV over a period of 12 weeks. In comparator arm E, the patients received triple therapy of TVR + PEG + RBV. The treatment duration with TVR was 12 weeks; depending on the response to treatment, treatment was continued with PEG + RBV for further 12 or 36 weeks. Hence the maximum treatment duration was 24 or 48 weeks. The treatment regimens used and the dosages of the drugs complied with the approval for patients with CHC genotype 1b without cirrhosis.

Concomitant medication contraindicated according to the approval was not allowed to be used in the study.

The planned follow-up duration was 48 weeks after the end of treatment for all patients. AEs were followed-up in the study up to 30 days after the end of treatment.

Treatment duration/observation period in the study

The treatment durations (and therefore observation periods in the study arms) differed notably for the treatments relevant for research question 2 because of the recommendations in the respective SPCs. The resulting consequences concur with those described for research question 1 in Section 2.3.1.2.

Table 21 shows the characteristics of the patients with CHC genotype 1b in the relevant arms of the MALACHITE-I study.

Table 21: Characteristics of the study populations – RCT, direct comparison: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV

Study Group	N	Age [years] mean (SD)	Sex [F/M] %	Fibrosis stage [F0-F1/F2/≥ F3] %	Viral load [< 800 000/ ≥ 800 000 IU/mL] %	Ethnicity [white/black/ Asian/other] %	IL28B genotype CC/CT/TT %	Study discontinuations n (%)
MALACHITE-I								
OBV/PTV/R + DSV	83	47 (11)	52/48	72.3/13.3/14.5	18.1/81.9	98.8/0/1.2/0	17/69/14	2 (2.4[a])
TVR + PEG + RBV	41	46 (11)	59/41	75.6/9.8/14.6	22.0/78.0	92.7/0/7.3/0	17/68/15	2 (4.9[a])

a: Institute's calculation.

CHC: chronic hepatitis C; DSV: dasabuvir; F: female; IU: international units; M: male; N: number of patients included; n: number of patients with event; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; TVR: telaprevir; vs.: versus

Approximately 72% and 76% of the patients had no or mild liver damage expressed with a METAVIR score of F0 or F1. Severe fibrosis occurred in approximately 15% of the patients. Baseline viral load was high (≥ 800 000 IU/mL) in approximately 80% of the patients. Over 90% of the patients were white; approximately 1% and 7% of the patients were Asian, and there were no black patients at all. Just under 70% of the patients had IL28B genotype CT, another 15% had genotype TT, and 17% of the patients had genotype CC.

Fewer than 5% of the patients in both treatment groups discontinued the study.

Table 22 shows the risk of bias at study level.

Table 22: Risk of bias at study level – RCT, direct comparison: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV

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			
MALACHITE-I	Yes	Yes	No	No	Yes	Yes	Low

CHC: chronic hepatitis C; DSV: dasabuvir; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; TVR: telaprevir; vs.: versus

The risk of bias at the study level was rated as low for the study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.4.2.2 with the outcome-specific risk of bias.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - SVR 12 as sufficiently valid surrogate for the patient-relevant outcome “hepatocellular carcinoma”
  - health status using the EQ-5D VAS
- Health-related quality of life
  - SF-36
  - HCV-PRO
- Adverse events
  - overall rate of SAEs
  - treatment discontinuation due to AEs
  - specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

The company used a total of 5 instruments to measure health-related quality of life. Besides the questionnaires SF-36 and HCV-PRO mentioned above, these were the EQ-5D, the HCVTSat, and the WPAI. The EQ-5D was not included completely in the benefit assessment, but only the VAS. In addition, the VAS was not considered to be a measurement of health-related quality of life, but for the general health status, i.e. as morbidity outcome. The questionnaires HCVTSat and WPAI were not included in the benefit assessment because they are not considered to be instruments to measure health-related quality of life. See Section 2.9.2.4.3 of the full dossier assessment for more details.

Furthermore, all outcomes called AEs of specific interest by the company and included in its benefit assessment were not included because the operationalizations were not patient-relevant or their patient relevance remained unclear or the available data were unsuitable to produce a valid recording of treatment effects. A detailed justification can be found in Section 2.4.2.2 and in Section 2.9.2.4.3 of the full dossier assessment.

Table 23 shows for which outcomes data were available in the studies included.

Table 23: Matrix of outcomes – RCT, direct comparison: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV

Study	Outcomes							
	All-cause mortality	Sustained virologic response (SVR 12)	Health status using the EQ-5D VAS	Health-related quality of life using the SF-36	Health-related quality of life using the HCV-PRO	SAEs	Treatment discontinuation due to AEs	Specific AEs
MALACHITE-I	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AE: adverse event; CHC: chronic hepatitis C; DSV: dasabuvir; EQ-5D: European Quality of Life-5 Dimensions; HCV-PRO: hepatitis C virus patient-reported outcomes; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SVR: sustained virologic response; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

2.4.2.2 Risk of bias

Table 24 shows the risk of bias for the relevant outcomes.

Table 24: Risk of bias at study and outcome level – RCT, direct comparison: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV

Study		Outcomes							
	Study level	All-cause mortality	Sustained virologic response (SVR 12)	Health status using the EQ-5D VAS	Health-related quality of life using the SF-36	Health-related quality of life using the HCV-PRO	SAEs	Treatment discontinuation due to AEs	Specific AEs
MALACHITE-I	L	H[a]	L	H[b]	H[b]	H[b]	H[c]	L	-[d]

a: Marked difference in observation periods between the treatment arms.
b: Open-label study design.
c: Marked difference in observation period between the treatment arms; IDR no suitable approximation of the HR, or IDR not calculated because of zero cell; RR only interpretable in qualitative terms.
d: No comprehensive choice of specific AEs possible because of the notably different observation periods in the individual treatment arms and the resulting uncertainty in the calculation of effect estimates; therefore no quantitative conclusion on harm from OBV/PTV/R + DSV + RBV possible.

AE: adverse event; CHC: chronic hepatitis C; DSV: dasabuvir; EQ-5D: European Quality of Life-5 Dimensions; H: high; HCV-PRO: hepatitis C virus patient-reported outcomes; HR: hazard ratio; IDR: incidence density ratio; L: low; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SVR: sustained virologic response; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome “SVR 12”, like the risk of bias of the total study, was considered to be low. Due to the study design, all patient-reported outcomes (EQ-5D VAS, SF-36, HCV-PRO) were considered to have a high risk of bias because subjective outcomes in open-label studies generally are to be rated as having a high risk of bias. The assessments of the risk of bias at outcome level regarding the outcomes mentioned above concur with the company’s assessments.

The risk of bias for the outcomes “mortality” and “overall rates of SAEs” was considered to be high because the observation periods between the treatment groups differed notably. The assessment of the risk of bias concurs with the company’s assessment. In contrast, the risk of bias for the outcome “treatment discontinuation due to AEs” was considered to be low because the different observation periods resulted from the planned limitation of the treatment duration. This assessment deviates from that of the company, which sees a high risk of bias also for this outcome.

Since no comprehensive choice of AEs of specific interest was possible, the risk of bias was not assessed. This approach deviates that of the company.

Due to the very different observation period in the intervention and comparator arm of the MALACHITE-I study, the data on AEs were largely not interpretable in a meaningful way (see Section 2.9.2.4.3 of the full dossier assessment). Except for treatment discontinuation due to AEs, the results on AEs were therefore not conclusively interpretable in quantitative terms.

In summary, at most indications of an added benefit could be derived for the outcome "SVR 12" and for treatment discontinuation due to AEs as a consequence; at most hints of an added benefit could be derived for the potentially highly biased outcomes on mortality, on patient-reported outcomes and on AEs for which an analysis was meaningful.

2.4.2.3 Results

Table 25 and Table 26 summarize the results on the comparison of OBV/PTV/R + DSV with TVR + PEG + RBV in treatment-naive patients with CHC infection of genotype 1b without cirrhosis. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

For the benefit assessment, no analysis for comparable time periods was available for the results on health-related quality of life and health status (EQ-5D VAS). The time from the start of the study until the end of treatment was therefore considered in each case. Hence all conclusions on these outcomes describe only health-related quality of life and health status under treatment.

Besides the mean differences, responder analyses for the mental and physical SF-36 sum score were additionally included for the SF-36 questionnaire. Responders were patients who improved in the course of the study or who worsened by fewer than 5 points on the respective scale (a higher score on the SF-36 scales reflects higher quality of life). This is not an MID. The responder analysis was still included because it investigated an additional question (see Section 2.9.2.4.3 of the full dossier assessment).

Table 25: Results (dichotomous outcomes) – RCT, direct comparison: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV

Study Outcome category Outcome	OBV/PTV/R + DSV		TVR + PEG + RBV		OBV/PTV/R + DSV vs. TVR + PEG + RBV
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
MALACHITE-I					
Mortality					
All-cause mortality	83	0 (0)	41	0 (0)	NC
Morbidity					
SVR 12[a]	83	81 (97.6)	41	32 (78.0)	1.25 [1.06; 1.48]; < 0.001[b, c]
Health-related quality of life (under treatment)					
SF-36 responders[d]					
Physical sum score	83	79 (95.2)	40	18 (45.0)	2.12 [1.50; 2.99]; < 0.001
Mental sum score	83	67 (80.7)	40	17 (42.5)	1.90 [1.30; 2.76]; < 0.001
Adverse events					
AEs	83	41 (49.4)	41	40 (97.6)	
SAEs	83	0 (0)	41	6 (14.6)	0.04 [0.00; 0.67]; < 0.001[b]
Treatment discontinuation due to AEs[e]	83	0 (0)	41	4 (9.8)	0.06 [0.00; 1.01]; 0.004[f]

a: Sufficiently valid surrogate for the patient-relevant outcome “hepatocellular carcinoma”.
b: Institute’s calculation, unconditional exact test (CSZ method according to [8]).
c: The company classified patients who discontinued treatment as non-responders. From the available individual patient data, it was verified that the patients actually were non-responders (see Section 2.9.2.2 of the full dossier assessment). A sensitivity analysis conducted by the Institute, in which these patients were categorized as responders, therefore had the same results as the primary analysis of the company.
d: Patients who improved on the respective scale in the observation period or who worsened by fewer than 5 points are considered responders.
e: Patients who discontinued all treatments.
f: Institute‘s calculation: RR and 95% CI (with 0 events in one arm with continuity correction), unconditional exact test (CSZ method according to [8]). 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; DSV: dasabuvir; N: number of analysed patients; n: number of patients with event; NC: not calculated; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SVR 12: sustained virologic response 12 weeks after the end of treatment; TVR: telaprevir; vs.: versus

Table 26: Results (continuous outcomes) – RCT, direct comparison: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV (start of the study until end of treatment)

Study Outcome category Instrument Subscale	OBV/PTV/R + DSV			TVR + PEG + RBV			OBV/PTV/R + DSV vs. TVR + PEG + RBV
	N	Baseline values mean (SD)	Change at end of treatment mean (SD)	N	Baseline values mean (SD)	Change at end of treatment mean (SD)	Mean difference [95% CI]; p-value[a]
MALACHITE-I							
Morbidity (under treatment)							
EQ-5D VAS	83	83.9 (ND)	2.5 (11.4)	40	87.2 (ND)	-7.6 (17.9)	8.31 [3.29; 13.33]; 0.001 Hedges' g: 0.73 [0.34; 1.11][b]
Health-related quality of life (under treatment)							
SF-36							
Physical sum score	83	50.5 (ND)	2.2 (4.3)	40	51.3 (ND)	-5.5 (11.5)	6.86 [4.36; 9.37]; < 0.001 Hedges' g: 1.03 [0.63; 1.43][c]
Mental sum score	83	51.2 (ND)	-0.1 (7.7)	40	52.6 (ND)	-6.4 (11.8)	5.28 [2.01; 8.54]; 0.002 Hedges' g: 0.68 [0.29; 1.07][c]
HCV-PRO total score	83	80.6 (ND)	3.1 (8.9)	40	81.7 (ND)	-12.4 (20.1)	15.04 [10.02; 20.06]; < 0.001 Hedges' g: 1.14 [0.73; 1.54][c]

a: Unless stated otherwise: mean difference, CI and p-value calculated using an ANCOVA model on the difference of the changes to baseline between the arms, with baseline value and region as covariables and the treatment arm as factor.
b: Calculation by the company; values concur with calculation from data on change at the end of treatment.
c: Hedges' g, Institute's calculation from data on the change at the end of treatment.

CHC: chronic hepatitis C; CI: confidence interval; DSV: dasabuvir; EQ-5D: European Quality of Life-5 Dimensions; HCV-PRO: hepatitis C virus patient-reported outcomes; N: number of analysed patients; ND: no data; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form (36) Health Survey; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

Mortality

In the patient population considered, no patient has died in the course of the study so far. Hence there is no hint of an added benefit of OBV/PTV/R + DSV + RBV versus TVR + PEG + RBV. An added benefit for the outcome "mortality" is therefore not proven. This concurs with the company's assessment.

Morbidity

SVR 12 as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the SVR 12. This resulted in an indication of an added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV for the outcome "hepatocellular carcinoma (assessed with the SVR 12)".

This deviates from the company's assessment only in so far as the company made no outcome-specific conclusion on probability.

Health status using the EQ-5D VAS (under treatment)

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the outcome "health status". Higher scores on the EQ-5D VAS indicate better 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 was fully above the irrelevance threshold of 0.2. It can therefore be assumed that the effect was not within a range that is certainly irrelevant.

There was proof of an effect modification for the characteristic "fibrosis stage" expressed with the METAVIR score. This resulted in no hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for patients with a METAVIR score of F0-F1; an added benefit for this subgroup is therefore not proven.

There was a hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for patients with a METAVIR score of ≥ F2.

The assessment regarding the EQ-5D VAS partly deviates from the company's assessment, which allocated this outcome to health-related quality of life, additionally considered one further period of analysis, and made no outcome-specific conclusion on probability. Moreover, the company did not derive any consequences for the benefit assessment from subgroup analyses.

Health-related quality of life (under treatment)

SF-36

The physical and mental sum score was considered for the SF-36.

Physical sum score

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the physical sum score in the consideration of the mean differences. There was a statistically significant difference in favour of OBV/PTV/R + DSV for the physical sum score also in the responder analysis.

Overall, there was a hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for the physical sum score of the SF-36.

Mental sum score

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the mental sum score in the consideration of the mean differences. The SMD in the form of Hedges' g was considered to check the relevance of this result. The 95% CI of the SMD was fully above the irrelevance threshold of 0.2. It can therefore be assumed that the effect was not within a range that is certainly irrelevant.

There was an indication of an effect modification by the characteristic "fibrosis stage" expressed with the METAVIR score. There was no hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for patients with a METAVIR score of F0-F1. An added benefit for this subgroup is not proven. There was a hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV in patients with a METAVIR score of ≥ F2.

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the mental sum score in the responder analysis. Both analyses on the mental sum score of the SF-36, both on the basis of the mean differences and the responder analysis, were therefore consistent for the total population of research question 2. There were no subgroup analyses for the responder analysis.

In summary, the assessments regarding the SF-36 deviate from the company's assessments. The company considered additional periods of analysis and did not address the outcome-specific probability of the added benefit. Moreover, the company did not derive any consequences for the benefit assessment from subgroup analyses.

HCV-PRO

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the outcome "HCV-PRO". The SMD in the form of Hedges' g was considered to check the relevance of this result. The 95% CI of the SMD was fully above the irrelevance threshold of 0.2. It can therefore be assumed that the effect was not within a range that is certainly irrelevant.

There were several indications of an effect modification, of which only the characteristic "HCV RNA at baseline" was relevant for the interpretation of the result. For the characteristic "HCV RNA at baseline", there was no hint of an added benefit for patients with < 800 000 IU/mL, so that an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for this subgroup is not proven. In contrast, there was a hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for patients with HCV RNA of ≥ 800 000 IU/mL.

This deviates from the company's assessment, which for the total population additionally used a responder analysis on 2 periods of analysis, each of which with a statistically significant result, but derived no conclusion on the outcome-specific probability of the added benefit. Moreover, the company did not derive any consequences for the benefit assessment from subgroup analyses.

Adverse events

As described in Section 2.4.2.1, the data on AEs were not completely evaluable in a meaningful way. Based on the concrete data availability, conclusions on SAEs and on treatment discontinuation due to AEs could be drawn for the present research question.

Overall rate of serious adverse events

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the outcome "SAEs". Four of the 6 SAEs in the comparator arm had occurred already by week 12 after the start of treatment so that a statistically significant effect was also shown here (RR: 0.06 [0.00; 1.01]; p = 0.004, Institute's calculation [8]). Hence the statistically significant difference from the analysis relevant for the benefit assessment was not only due to the different observation periods of the treatment arms. There was a hint of lesser harm from OBV/PTV/R + DSV in comparison with TVR + PEG + RBV.

The assessment deviates from the company's assessment only in so far as the company derived no outcome-specific conclusion on probability.

Treatment discontinuation due to adverse events

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the outcome "treatment discontinuation due to AEs". This resulted in an indication of lesser harm from OBV/PTV/R + DSV in comparison with TVR + PEG + RBV for this outcome.

The assessment deviates from the company's assessment only in so far as the company derived no outcome-specific conclusion on probability.

Adverse events of particular interest

Due to the available data, no comprehensive choice of AEs of particular interest was possible. However, no signs of greater harm of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV resulted from the consideration of the available data.

The assessment deviates from that of the company, which chose AEs of particular interest and derived conclusions on the added benefit.

2.4.2.4 Subgroups and other effect modifiers

See Section 2.9.2.4.3 of the full dossier assessment for a list of the relevant effect modifiers.

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. In addition, there must be a statistically significant effect in at least one of the subgroups. Subgroup results for which no valid conclusion is possible due to missing values in the analysis (e.g. difference of ≥ 15 percentage points between the 2 treatment groups) are not presented. In effect modifiers with more than 2 categories, such as the METAVIR score, the categories of neighbouring effect estimates were summarized if the heterogeneity test provided a p-value of ≥ 0.2.

The prerequisite for proof of an effect modification was a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provided an indication of an effect modification.

Due to the data availability for AEs, which can only be interpreted in qualitative terms, the subgroup results for SAEs were not considered. No subgroup analyses were available for the outcome “treatment discontinuation due to AEs” (in the operationalization considered for the present benefit assessment).

Table 27 summarizes the subgroup results on the comparison of OBV/PTV/R + DSV with TVR + PEG + RBV in treatment-naive patients with CHC genotype 1b without cirrhosis. Where necessary, the data from the dossier were supplemented by the Institute’s calculations.

Table 27: Subgroups (continuous outcomes): outcome "morbidity" and "health-related quality of life" by characteristic "sex", "HCV RNA" and "METAVIR score", RCT, direct comparison: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV (start of study until end of treatment)

Study **Instrument** **Characteristic** **Subgroup**	**OBV/PTV/R + DSV**			**TVR + PEG + RBV**			**OBV/PTV/R + DSV vs. TVR + PEG + RBV**
	N	**Baseline values mean (SD)**	**Change at end of treatment mean (SD)**	**N**	**Baseline values mean (SD)**	**Change at end of treatment mean (SD)**	**Mean difference [95% CI]; p-value[a]**
MALACHITE-I							
EQ-5D VAS (under treatment)							
METAVIR score							
F0-F1	60	83.8 (ND)	2.2 (13.0)	30	89.4 (ND)	-5.1 (13.9)	4.91 [-0.47; 10.28]; 0.073
≥ F2							17.21 [9.15; 25.28]; < 0.001[b] Hedges' g: 1.32 [0.49; 2.16][c]
F2	*11*	*87.7 (ND)*	*1.8 (5.1)*	*4*	*86.3 (ND)*	*-13.8 (13.8)*	*15.84 [5.82; 25.86]; 0.005*
≥ F3	*12*	*80.9 (ND)*	*4.8 (5.9)*	*6*	*76.7 (ND)*	*-16.0 (33.4)*	*22.72 [3.08; 42.35]; 0.026*
						Interaction:	p-value = 0.027[d]
SF-36, mental sum score (under treatment)							
METAVIR score							
F0-F1	60	50.3 (ND)	0.1 (8.2)	30	53.4 (ND)	-5.3 (11.9)	4.07 [0.15; 8.00]; 0.042 Hedges' g: 0.56 [0.12; 1.01][c]
≥ F2							12.22 [5.80; 18.63]; < 0.001[b] Hedges' g: 1.02 [0.22; 1.82][c]
F2	*11*	*57.5 (ND)*	*-2.0 (5.0)*	*4*	*50.5 (ND)*	*-7.3 (12.5)*	*11.64 [1.49; 21.79]; 0.028*
≥ F3	*12*	*49.8 (ND)*	*1.2 (7.8)*	*6*	*49.7 (ND)*	*-11.5 (11.5)*	*12.78 [2.97; 22.59]; 0.014*
						Interaction:	p-value = 0.168[d]

(continued)

Table 27: Subgroups (continuous outcomes): outcome "morbidity" and "health-related quality of life" by characteristic "sex", "HCV RNA" and "METAVIR score", RCT, direct comparison: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV (start of study until end of treatment) (continued)

Study Instrument Characteristic Subgroup	OBV/PTV/R + DSV			TVR + PEG + RBV			OBV/PTV/R + DSV vs. TVR + PEG + RBV
	N	Baseline values mean (SD)	Change at end of treatment mean (SD)	N	Baseline values mean (SD)	Change at end of treatment mean (SD)	Mean difference [95% CI]; p-value[a]
HCV-PRO (under treatment)							
Sex							
Women	43	76.9 (ND)	3.9 (8.6)	23	78.2 (ND)	-7.9 (21.8)	11.45 [4.26; 18.65]; 0.002 Hedges' g: 0.80 [0.28; 1.33][c]
Men	40	84.5 (ND)	2.3 (9.3)	17	86.3 (ND)	-18.4 (16.2)	20.36 [13.76; 26.95]; < 0.001 Hedges' g: 1.74 [1.09; 2.40][c]
						Interaction:	p-value = 0.077[d]
HCV RNA							
< 800 000 IU/mL	15	74.2 (ND)	3.1 (9.8)	9	81.9 (ND)	-6.3 (21.7)	7.78 [-5.7; 21.27]; 0.243
≥ 800 000 IU/mL	68	82.0 (ND)	3.1 (8.8)	31	81.6 (ND)	-14.1 (19.6)	17.37 [12.05; 22.68]; < 0.001 Hedges' g: 1.30 [0.84; 1.77][c]
						Interaction:	p-value = 0.107[d]
METAVIR score							
F0-F1	60	79.5 (ND)	3.6 (9.5)	30	82.7 (ND)	-9.8 (18.7)	12.59 [7.05; 18.13]; < 0.001
F2	11	87.9 (ND)	2.4 (7.1)	4	86.3 (ND)	-23.0 (25.7)	26.08 [8.81; 43.35]; 0.006
≥ F3	12	79.3 (ND)	1.3 (7.2)	6	73.6 (ND)	-17.9 (23.5)	20.02 [4.40; 35.64]; 0.015
						Interaction:	p-value = 0.175[d]
				Interaction F0-F1 vs. F3:			p-value = 0.343[e]
				Interaction F2 vs. F3:			p-value = 0.575[e]

(continued)

Table 27: Subgroups (continuous outcomes): outcome "morbidity" and "health-related quality of life" by characteristic "sex", "HCV RNA" and "METAVIR score", RCT, direct comparison: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV (start of study until end of treatment) (continued)

a: Unless stated otherwise: mean difference, CI and p-value calculated using an ANCOVA model on the difference of the changes to baseline between the arms, with baseline value as covariables and the treatment arm as factor.
b: Mean difference, 95% CI and p-value from the Institute's meta-analysis using the mean differences of the subgroups from ANCOVA with baseline value as covariable and treatment arm as factor.
c: Institute's calculation from data on the change at the end of treatment.
d: Calculated using an ANCOVA model with the covariables baseline value, treatment arm, subgroup, and the interaction term treatment arm*subgroup.
e: Institute's calculation, Cochran's Q test. Based on the mean differences from ANCOVA with HCV-PRO value at baseline as covariable and treatment arm as factor.
CHC: chronic hepatitis C; CI: confidence interval; DSV: dasabuvir; EQ-5D: European Quality of Life-5 Dimensions; HCV-PRO: hepatitis C virus patient-reported outcomes; HCV RNA: hepatitis C virus ribonucleic acid; IU: international units; N: number of analysed patients; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

Morbidity

Health status using the EQ-5D VAS (under treatment)

There was proof of an effect modification by the characteristic "fibrosis stage", expressed with the METAVIR score, for the outcome "health status". There was no important heterogeneity for the 2 categories F2 and ≥ F3 with neighbouring effect estimates (interaction test $p \geq 0.2$). These 2 categories were therefore summarized as category ≥ F2.

There was no statistically significant difference between the treatment groups for the subgroup of patients with a METAVIR score of F0-F1. Hence there was no hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for the subgroup with a METAVIR score of F0-F1. An added benefit for this subgroup is therefore not proven.

There was a statistically significant difference in favour of OBV/PTV/R + DBV for patients with a METAVIR score of ≥ F2. The SMD in the form of Hedges' g was considered to check the relevance of this result. The 95% CI of the SMD was fully above the irrelevance threshold of 0.2. It can therefore be assumed that the effect was not within a range that is certainly irrelevant. This resulted in a hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV in patients with a METAVIR score of ≥ F2.

This deviates from the company's assessment, which derived no consequences from the subgroup analysis for the benefit assessment.

Health-related quality of life (under treatment)

SF-36, mental sum score

For the mental sum score of the SF-36 (mean difference), there was an indication of an effect modification by the characteristic "fibrosis stage" expressed with the METAVIR score. There was no important heterogeneity for the 2 categories F2 and ≥ F3 with neighbouring effect estimates (interaction test p ≥ 0.2). These 2 categories were therefore summarized as category ≥ F2.

There was a statistically significant effect in favour of OBV/PTV/R + DBV both for patients with a METAVIR score of F0-F1 and for patients with a score of ≥ F2. The SMD in the form of Hedges' g was considered to check the relevance of these results. The 95% CI of the SMD was above the relevance threshold of 0.2 only for patients with a METAVIR score of ≥ F2. Only for these patients it can therefore be assumed that the effect was not within a range that is certainly irrelevant.

Since only a hint of an added benefit could have been derived already for the total population, there was no hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for patients with a score of F0-F1. An added benefit for this subgroup is not proven.

There was a hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV in patients with a score of ≥ F2.

This deviates from the company's assessment, which derived no consequences from the results of the subgroup analysis for the benefit assessment.

HCV-PRO

There were indications of an effect modification by each of the characteristics "sex", "HCV RNA at baseline" and "fibrosis stage (expressed with the METAVIR score)", for the outcome "HCV-PRO".

Sex

There was a statistically significant difference in favour of OBV/PTV/R + DBV for the characteristic "sex" both for men and for women. The SMD in the form of Hedges' g was considered to check the relevance of these results. In both subgroups, the 95% CI of the SMD was above the relevance threshold of 0.2. It can therefore be assumed that the effect in both subgroups was not within a range that is certainly irrelevant. Hence there was a hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV both for women and for men. Since this was a continuous outcome and the assessment of relevance was based on the SMD in the form of Hedges' g, the extent of added benefit would also be identical for both subgroups and would concur with the result of the total population of research question 2. Hence the subgroup results on the characteristic "sex" on the outcome "HCV-PRO" were not considered further for the present benefit assessment.

This concurs with the company's assessment.

HCV RNA at baseline

There was no statistically significant difference between the treatment groups for patients with an HCV RNA concentration of < 800 000 IU/mL for the characteristic "HCV RNA". Since only a hint of an added benefit could have been derived already for the total population, there was no hint of an added benefit of OBV/PTV/R + DBV in comparison with TVR + PEG + RBV for patients with HCV RNA of < 800 000 IU/mL. An added benefit for this subgroup is therefore not proven.

There was a statistically significant effect in favour of OBV/PTV/R + DBV for patients with an HCV RNA of ≥ 800 000 IU/mL. The SMD in the form of Hedges' g was considered to check the relevance of these results. The 95% CI of the SMD was above the relevance threshold of 0.2. It can therefore be assumed that the effect was not within a range that is certainly irrelevant. Hence there was a hint of an added benefit for patients with HCV RNA of ≥ 800 000 IU/mL.

This deviates from the company's assessment, which derived no consequences for the conclusion of benefit from the subgroup analyses for this outcome.

Fibrosis stage

There was a statistically significant difference in favour of OBV/PTV/R + DBV for the characteristic "fibrosis stage expressed with the METAVIR score" for all subgroups (F0-01, F2 and ≥ F3). None of the categories was considered separately because there was no important heterogeneity between the categories F0-F1 and ≥ F3, or F2 and ≥ F3 (interaction tests p = 0.343 or p = 0.575). Hence it was assumed for the benefit assessment that there was in fact no effect modification for the characteristic "fibrosis stage".

This deviates from the company's assessment only in so far as the company also derived no consequences for the conclusion of benefit from the subgroup analyses for this outcome, but with a different justification.

2.4.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit 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 OBV/PTV/R + DSV in comparison with TVR + PEG + RBV for the outcomes "hepatocellular carcinoma (assessed with the surrogate SVR 12)", "health status" "health-related quality of life", "SAEs" and "treatment discontinuation due to AEs". The extent of the respective added benefit at outcome level was estimated from these results (see Table 28).

Table 28: Extent of added benefit at outcome level: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV in comparison with TVR + PEG + RBV

Outcome category **Outcome**	**OBV/PTV/R + DSV 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%	Lesser benefit/added benefit not proven
Morbidity		
Hepatocellular carcinoma, assessed with the surrogate SVR 12	97.6% vs. 78.0% RR: 1.25 [1.06; 1.48] p < 0.001[c] probability: "indication"	Outcome category: severe/serious symptoms/late complications added benefit, extent: "non-quantifiable"
Health status using the EQ-5D VAS		
METAVIR F0-F1	MD: 4.91 [-0.47; 10.28] p = 0.073	Lesser benefit/added benefit not proven
METAVIR ≥ F2	MD: 17.21 [9.15; 25.28] p < 0.001[d] Hedges' g: 1.32 [0.49; 2.16][e] probability: "hint"	Outcome category: non-severe/non-serious symptoms/late complications added benefit, extent: "non-quantifiable"
Health-related quality of life		
SF-36		
Physical sum score	Responder analysis: RR: 2.12 [1.50; 2.99] RR[f]: 0.47 [0.33; 0.67] p = < 0.001[c] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "major"
Mental sum score	MD: 5.28 [2.01; 8.54] p = 0.002 Hedges' g: 0.68 [0.29; 1.07][e]	
METAVIR F0-F1	MD: 4.07 [0.15; 8.00] p = 0.042 Hedges' g: 0.56 [0.12; 1.01][e]	Lesser benefit/added benefit not proven
METAVIR ≥ F2	MD: 12.22 [5.08; 18.63] p < 0.001[d] Hedges' g: 1.02 [0.22; 1.82][e] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"

(continued)

Table 28: Extent of added benefit at outcome level: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV in comparison with TVR + PEG + RBV (continued)

Outcome category **Outcome**	**OBV/PTV/R + DSV vs. TVR + PEG + RBV** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
HCV-PRO	MD: 15.04 [10.02; 20.06] p < 0.001 Hedges' g: 1.14 [0.73; 1.54][e]	
HCV RNA < 800 000 IU/mL	MD: 7.78 [-5.7; 21.27] p = 0.243	Lesser benefit/added benefit not proven
HCV RNA ≥ 800 000 IU/mL	MD: 17.73 [12.05; 22.68] p < 0.001 Hedges' g: 1.30 [0.84; 1.77][e] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
Adverse events		
SAEs	0% vs. 14.6% RR: 0.04 [0.00; 0.67] p < 0.001[c] probability: "hint"	Outcome category: severe/serious AEs lesser harm, extent: "non-quantifiable"[g]
Treatment discontinuation due to AEs	0% vs. 9.8% RR: 0.06 [0.00; 1.01] p = 0.004[h] probability: "indication"	Outcome category: non-severe/non-serious AEs lesser harm, extent: "non-quantifiable"[i]
AEs of particular interest	Choice and quantitative assessment not possible	Greater/lesser harm not proven

(continued)

Table 28: Extent of added benefit at outcome level: treatment-naive patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV in comparison with TVR + PEG + RBV (continued)

a: Probability provided if statistically significant differences were present. Decision based on the lower 95% CI limit of Hedges' g in continuous outcomes.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation, unconditional exact test (CSZ method according to [8]). Possible discrepancies between p-value (exact) and CI (asymptotic) due to different calculation methods.
d: Mean difference, 95% CI and p-value from the Institute's meta-analysis using the mean differences of the subgroups from ANCOVA with baseline value as covariable and treatment arm as factor.
e: Institute's calculation from data on the change at the end of treatment.
f: Reversed direction of effect to enable direct use of limits based on the upper limits to derive the extent of the added benefit.
g: No valid estimation of the HR using other measures possible because of different observation periods; CI of the RR unreliable for the derivation of the extent; but effect not explicable solely by bias due to the effect size.
h: Institute's calculation: RR and 95% CI (with 0 events in one arm with continuity correction), unconditional exact test (CSZ method according to [8]). Possible discrepancies between p-value (exact) and CI (asymptotic) due to different calculation methods.
i: Since in this case the CI is not regarded to be sufficiently reliable for the determination of the extent because of the asymptotic calculation, the extent of lesser harm cannot be quantified.
AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CI_u: upper limit of CI; CSZ: convexity, symmetry, z score; DSV: dasabuvir; EQ-5D: European Quality of Life-5 Dimensions; HCV RNA: hepatitis C virus ribonucleic acid; HCV-PRO: hepatitis C virus patient-reported outcomes; HR: hazard ratio; IU: international units; MD: mean difference; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 29 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 29: Positive and negative effects from the assessment of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV (treatment-naive CHC genotype 1b patients without cirrhosis)

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ hepatocellular carcinoma, assessed with the surrogate SVR 12: indication of an added benefit – extent: non-quantifiable	-
Non-serious/non-severe symptoms: ▪ Health status using the EQ-5D VAS ▫ METAVIR score ≥ F2: hint of an added benefit, extent: “non-quantifiable”	-
Health-related quality of life: ▪ SF-36 ▫ physical sum score: hint of an added benefit, extent: “major” ▫ mental sum score: METAVIR score ≥ F2: hint of an added benefit, extent: “non-quantifiable” ▪ HCV-PRO: ▫ HCV RNA ≥ 800 000 IU/mL: hint of an added benefit, extent: “non-quantifiable”	-
Severe/serious adverse events ▪ SAEs: hint of lesser harm, extent: “non-quantifiable”	-
Non-severe/non-serious adverse events ▪ treatment discontinuations due to AEs: hint of lesser harm, extent: “non-quantifiable”	-
CHC: chronic hepatitis C; DSV: dasabuvir; HCV: hepatitis C virus; IU: international units; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RNA: ribonucleic acid; SVR 12: sustained virologic response 12 weeks after the end of treatment; TVR: telaprevir	

Overall, only positive effects remained in the outcome categories “severe/serious symptoms or late complications”, “non-severe/non-serious symptoms”, “health-related quality of life”, “severe/serious AEs” and “non-severe/non-serious AEs”. There was an indication of an added benefit for the outcome “hepatocellular carcinoma”. The extent of this added benefit could not be quantified, however, because the outcome was assessed with the surrogate SVR 12.

There was a hint of a non-quantifiable added benefit for patients with a METAVIR score of ≥ F2 for the outcome “health status”.

There were also hints of an added benefit for health-related quality of life, for the physical sum score of the SF-36 for the total population (extent: “major”), for the mental sum score of the SF-36 for patients with a METAVIR score of ≥ F2 and for the HCV-PRO for patients with an HCV RNA concentration of ≥ 800 000 IU/mL (in each case with the extent “non-quantifiable”).

Partly no conclusive quantification could be conducted regarding harm from OBV/PTV/R + DSV in comparison with TVR + PEG + RBV. There was a hint of lesser harm from OBV/PTV/R + DSV, the extent of which was non-quantifiable, for the overall rate of SAEs, and an indication of lesser harm for treatment discontinuation due to AEs. The available data allowed no conclusion for specific AEs; however, there was also no sign of greater harm from OBV/PTV/R + DSV. A weakening of the added benefit of OBV/PTV/R + DSV did therefore not seem justified.

In summary, there is an indication of a non-quantifiable added benefit of OBV/PTV/R versus the ACT for treatment-naive patients with CHC genotype 1b without cirrhosis.

Table 30: Ombitasvir/paritaprevir/ritonavir – extent and probability of the added benefit for treatment-naive patients with CHC genotype 1b without cirrhosis

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment-naive patients with CHC genotype 1b without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], 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		

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

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

2.4.4 List of included studies

MALACHITE-I

AbbVie. A randomized, open-label study to evaluate the efficacy and safety of ABT-450/ritonavir/ABT-267 and ABT-333 co-administered with and without ribavirin compared to telaprevir co-administered with pegylated interferon α-2a and ribavirin in treatment-naïve adults with chronic hepatitis C genotype 1 virus infection (MALACHITE I): study M13-774; clinical study report (primary analysis) [unpublished]. 2015.

AbbVie. A study to evaluate the efficacy and safety of three experimental drugs compared with Telaprevir (a licensed product) in people with hepatitis C virus infection who have not had treatment before (MALACHITE 1): full text view [online]. In: ClinicalTrials.gov. 26 January 2015 [accessed: 18 February 2015]. URL: http://ClinicalTrials.gov/show/NCT01854697.

AbbVie Deutschland. A randomized, open-label study to evaluate the efficacy and safety of ABT-450/ritonavir/ABT-267 and ABT-333 co-administered with and without ribavirin compared to telaprevir co-administered with pegylated interferon α-2a and ribavirin in treatment-naïve adults with chronic hepatitis C genotype 1 virus infection (MALACHITE I) [online]. In: EU Clinical Trials Register. [Accessed: 18 February 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-003754-84.

2.5 Research question 3: treatment-experienced patients with CHC genotype 1a without cirrhosis

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 lists on ombitasvir/paritaprevir/ritonavir (studies completed up to 4 November 2014)
- bibliographical literature search on ombitasvir/paritaprevir/ritonavir (last search on 4 November 2014)
- search in trial registries for studies on ombitasvir/paritaprevir/ritonavir (last search on 3 November 2014)

To check the completeness of the study pool:

- search in trial registries for studies on ombitasvir/paritaprevir/ritonavir (last search on 9 February 2015)

No additional relevant study was identified from the check.

2.5.1.1 Studies included

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

Table 31: Study pool – RCT, direct comparison: treatment-experienced patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
MALACHITE-II (M13-862)	No	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. CHC: chronic hepatitis C; DSV: dasabuvir; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; TVR: telaprevir; vs.: versus			

Section 2.5.4 contains a reference list for the studies included.

2.5.1.2 Study characteristics

Table 32 and Table 33 describe the studies used for the benefit assessment.

Table 32: Characteristics of the studies included – RCT, direct comparison: treatment-experienced patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[c]
MALACHITE-II	RCT, open-label, parallel	Treatment-experienced adults (≥ 18-65 years) with chronic hepatitis C of GT 1a and 1b without cirrhosis[a]	arm A: OBV/PTV/R + DSV + RBV (N = 103) arm B: TVR + PEG + RBV (N = 51) Relevant subpopulation with genotype 1a: arm A (n = 19) arm B (n = 7)	Screening: up to 5 weeks Treatment phase: arm A: 12 weeks arm B: 24 or 48 weeks (response-guided) Follow-up: 48 weeks; AEs were followed-up until 30 days after the end of treatment Data cut-off for primary analysis: 11/2014	27 centres[b] in Argentina, Australia, Chile, Finland, Hungary, Poland, Romania, Slovak Republic 6/2013 – 6/2015	Primary: proportion of patients with SVR 12 Secondary: proportion of patients with SVR 24[d], health-related quality of life, AEs

a: Stratified by hepatitis C subtype 1a or non-1a and response to pretreatment with PEG + RBV (null responders, partial responders, relapsers).
b: 35 investigation sites according to Module 4 A; 27 according to the CSR.
c: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
d: Data for SVR 24 were not yet available at the time of submission of the dossier.

AE: adverse event; CHC: chronic hepatitis C; CSR: clinical study report; DSV: dasabuvir; GT: genotype; N: number of randomized patients; n: relevant subpopulation; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SVR: sustained virologic response; TVR: telaprevir; vs.: versus

Table 33: Characteristics of the interventions – RCT, direct comparison: treatment-experienced patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study	Intervention	Comparison	Concomitant medication
MALACHITE-II	Week 1-12: OBV/PTV/R (25 mg/150 mg/100 mg) once daily orally + DSV 250 mg twice daily orally + RBV 1000 or 1200 mg twice daily orally (depending on weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg)	Week 1-12: TVR 750 mg orally every 8 hours + PEG 180 µg once weekly subcutaneously + RBV 1000 or 1200 mg twice daily orally (depending on weight: < 75 kg = 1000 mg; ≥ 75 kg = 1200 mg) Week 13-24 or 13-48 (response-guided): PEG + RBV, same dosage as in week 1-12	Prohibited at start of study: ▪ anti-HCV drugs including TVR, boceprevir, except PEG and RBV Prohibited for 2 weeks before the start of the study medication until 2 weeks after the end of the study: ▪ strong or moderate CYP3A substrates, inhibitors and inducers: alfuzosin, amiodarone, astemizole, atorvastatin, carbamazepine, quinidine, cisapride, clarithromycin, conivaptan, dronedarone, efavirenz, eletriptan, eplerenone, everolimus, fusidic acid, itraconazole, St. John's Wort, ketoconazole, lovastatin, midazolam (orally), nefazodone, phenobarbital, phenytoin, pimozide, rifampin, salmeterol, sildenafil, simvastatin, telithromycin, triazolam, voriconazole ▪ CYP2C8 inhibitors: gemfibrozil, trimethoprim ▪ Prohibited drugs: bepridil, bosentan, buprenorphine, domperidone, ergot derivatives, St. John's Wort, methadone, mifepristone, modafinil, montelukast, ergot alkaloids, pioglitazone, propafenone, quercetin, quinidine, rifabutin, tadalafil, troglitazone, troleandomycin ▪ hormonal contraceptives[a] ▪ antiarrhythmics (class Ia and III) Prohibited for 2 weeks before the start of the study medication: ▪ herbal drugs (including milk thistle), any medication contraindicated for RBV, TVR or PEG alfa 2a

a: Unless allowed by the investigator.
CHC: chronic hepatitis C; DSV: dasabuvir; HCV: hepatitis C virus; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; TVR: telaprevir; vs.: versus

The MALACHITE-II study was an RCT. CHC patients with CHC genotype 1 without cirrhosis who had been treated with PEG + RBV at an earlier time point were included in the study. The patients were stratified by genotype 1a and 1b and by response to their pretreatment. A total of 154 patients were randomly assigned to this comparison (intervention arm A: N = 103, comparator arm B: N = 51).

In arm A, the patients received OBV/PTV/R in combination with DSV and RBV. The combination with ribavirin in this drug combination is not approved for patients with HCV infection of genotype 1b without cirrhosis. For this reason, only the subpopulation of patients with CHC genotype 1a, which comprised 26 patients (intervention arm A: N = 19, comparator arm B: N = 7) was relevant for the present benefit assessment. The patients with CHC genotype 1b are not considered further.

The treatment regimen of the intervention OBV/PTV/R + DSV + RBV (treatment arm A) with a 12-week treatment duration and the dosage used complied with the approval for treatment-experienced patients with CHC genotype 1a without cirrhosis. In comparator arm B, the patients were treated with triple therapy of TVR + PEG + RBV. The dosages complied with the approval in each case. The treatment duration with TVR in combination with PEG + RBV was 12 weeks; depending on their response to treatment, the patients continued treatment with PEG + RBV for further 12 or 36 weeks. Hence the maximum treatment duration was 24 or 48 weeks.

Concomitant medication contraindicated according to the approval was not allowed to be used in the study.

The planned follow-up duration was 48 weeks after the end of treatment for all patients. AEs were followed-up in the study up to 30 days after the end of treatment.

Treatment duration/observation period in the study

The treatment durations (and therefore observation periods) differed notably for the treatments relevant for research question 3 because of the recommendations in the respective SPCs. The resulting consequences concur with those described for research question 1 in Section 2.3.1.2.

Table 34 shows the characteristics of the patients in the relevant subpopulation of the MALACHITE-II study.

Table 34: Characteristics of the study populations – RCT, direct comparison: treatment-experienced patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study Group	N	Age [years] mean (SD)	Sex [F/M] %	Fibrosis stage [F0-F1/F2/≥ F3] %	Viral load [< 800 000/ ≥ 800 000 IU/mL] %	Ethnicity [white/black/ Asian/other] %	Response to pretreatment [null response/ partial response/ relapse] %	IL28B genotype CC/CT/TT %	Study discon-tinuations n (%)
MALACHITE-II									
OBV/PTV/R + DSV + RBV	19	43 (12)	32/68	84.2/10.5/5.3	21.1/78.9	100/0/0/0	36.8/21.1/42.1	16/68/16	0 (0)
TVR + PEG + RBV	7	46 (10)	43/57	57.1/28.6/14.3	0/100	100/0/0/0	28.6/28.6/42.9	43/14/43	2 (28.6)[a]

a: Institute's calculation; 2 patients who discontinued the study identified with certainty from individual patient data; unclear for 3 further patients whether they discontinued the study; in case of study discontinuation this would have occurred after recording of all outcomes included, however.

CHC: chronic hepatitis C; DSV: dasabuvir; F: female; IU: international units; M: male; N: number of patients included; n: number of patients with event; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; TVR: telaprevir; vs.: versus

The percentage of patients with severe or moderate fibrosis was slightly larger in the comparator arm than in the OBV/PTV/R + DSV + RBV arm (5% and 11% in the OBV/PTV/R + DSV + RBV arm versus approximately 14% and 29% in the TVR + PEG + RBV arm). Furthermore, approximately 79% of the patients in the intervention arm had a baseline viral load of ≥ 800 000 IU/mL, whereas this was the case in all patients in the comparator arm. The majority of patients in the intervention arm had genotype CT (68%), whereas in the comparator arm, the percentage of genotype CC or TT was 43% each.

Regarding response to prior therapy, there were patients with null response (approximately 37% versus 29%), partial response (approximately 21% versus 29%) and relapse (approximately 42% versus 43%) in the population considered.

The number of patients who discontinued the study in the relevant subpopulation was 0 versus 2 patients, which is equivalent to a difference of approximately 29 percentage points.

Table 35 shows the risk of bias at study level.

Table 35: Risk of bias at study level – RCT, direct comparison: treatment-experienced patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

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			
MALACHITE-II	Yes	Yes	No	No	Yes	Yes	Low

CHC: chronic hepatitis C; DSV: dasabuvir; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; TVR: telaprevir; vs.: versus

The risk of bias at the study level was rated as low for the study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.5.2.2 with the outcome-specific risk of bias.

2.5.2 Results on added benefit

2.5.2.1 Outcomes included

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

- Mortality
  - All-cause mortality
- Morbidity
  - SVR 12 as sufficiently valid surrogate for the patient-relevant outcome “hepatocellular carcinoma”
  - health status using the EQ-5D VAS
- Health-related quality of life
  - SF-36
  - HCV-PRO
- Adverse events
  - overall rate of SAEs
  - treatment discontinuation due to AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

The company used a total of 5 instruments to measure health-related quality of life. Besides the questionnaires SF-36 and HCV-PRO mentioned above, these were the EQ-5D, the HCVTSat, and the WPAI. The EQ-5D was not included completely in the benefit assessment, but only the VAS. In addition, the VAS is not considered to be a measurement of health-related quality of life, but for the general health status, i.e. as morbidity outcome. The questionnaires HCVTSat and WPAI were not included in the benefit assessment because they are not considered to be instruments to measure health-related quality of life. See Section 2.9.2.4.3 of the full dossier assessment for more details.

Furthermore, all outcomes called AEs of specific interest by the company and included in its benefit assessment were not included because the operationalizations were not patient-relevant or their patient relevance remained unclear or the available data is unsuitable to produce a valid recording of treatment effects. AEs of specific interest were not considered for the present research question. A detailed justification can be found in Section 2.5.2.2 and in Section 2.9.2.4.3 of the full dossier assessment.

Table 36 shows for which outcomes data were available in the studies included.

Table 36: Matrix of outcomes – RCT, direct comparison: treatment-experienced patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study	Outcomes						
	All-cause mortality	Sustained virologic response (SVR 12)	Health status using the EQ-5D VAS	Health-related quality of life using the SF-36	Health-related quality of life using the HCV-PRO	SAEs	Treatment discontinuation due to AEs
MALACHITE-II	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AE: adverse event; CHC: chronic hepatitis C; DSV: dasabuvir; EQ-5D: European Quality of Life-5 Dimensions; HCV-PRO: hepatitis C virus patient-reported outcomes; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SVR: sustained virologic response; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

2.5.2.2 Risk of bias

Table 37 shows the risk of bias for the relevant outcomes.

Table 37: Risk of bias at study and outcome level – RCT, direct comparison: treatment-experienced patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study	Study level	Outcomes						
		All-cause mortality	Sustained virologic response (SVR 12)	Health status using the EQ-5D VAS	Health-related quality of life using the SF-36	Health-related quality of life using the HCV-PRO	SAEs	Treatment discontinuation due to AEs
MALACHITE-II	L	H[a]	L	H[b]	H[b]	H[b]	H[a]	L

a: Marked difference in observation periods between the treatment arms.
b: Open-label study design; in addition, for all outcomes, the proportion of patients from the ITT not included in the assessment differed by more than 5 percentage points between the treatment arms.

AE: adverse event; CHC: chronic hepatitis C; DSV: dasabuvir; EQ-5D: European Quality of Life-5 Dimensions; H: high; HCV-PRO: hepatitis C virus patient-reported outcomes; HR: hazard ratio; IDR: incidence density ratio; L: low; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SVR: sustained virologic response; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome "SVR 12", like the risk of bias of the total study, was considered to be low. Due to the study design, all patient-reported outcomes (EQ-5D VAS, SF-36, HCV-PRO) were considered to have a high risk of bias because subjective outcomes in open-label studies generally are to be rated as having a high risk of bias. The assessments of the risk of bias at outcome level regarding the outcomes mentioned above concur with the company's assessments.

The risk of bias for the outcomes "mortality" and "overall rates of SAEs" was considered to be high because the observation periods between the treatment groups differed notably. The assessment of the risk of bias concurs with the company's assessment. In contrast, the risk of bias for the outcome "treatment discontinuation due to AEs" was considered to be low because the different observation periods resulted from the planned limitation of the treatment duration. This assessment deviates from that of the company, which sees a high risk of bias also for this outcome.

Due to the notably different observation period in the intervention and comparator arm in conjunction with the low number of patients in the relevant subpopulation of the MALACHITE-II study, the data on AEs were largely not interpretable in a meaningful way (see Section 2.9.2.4.3 of the full dossier assessment). Except for treatment discontinuation due to AEs, the results on AEs were therefore not conclusively interpretable in quantitative terms.

In summary, at most indications of an added benefit can be derived for the outcome "SVR 12" and for treatment discontinuation due to AEs as a consequence; at most hints of an added benefit can be derived for the potentially highly biased outcomes on mortality, on patient-reported outcomes and on AEs for which an analysis is meaningful.

2.5.2.3 Results

Table 38 and Table 39 summarize the results on the comparison of OBV/PTV/R + DSV + RBV with TVR + PEG + RBV in treatment-experienced patients with CHC infection of genotype 1a without cirrhosis. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

For the benefit assessment, no analysis with time periods comparable for both treatment groups was available for the results on health-related quality of life and health status (EQ-5D VAS). The time from the start of the study until the end of treatment was therefore considered in each case. Hence the corresponding results describe only health-related quality of life and health status under treatment.

Besides the mean differences, responder analyses for the mental and physical SF-36 sum score were additionally included for the SF-36 questionnaire. Responders are patients who improved in the course of the study or who only worsened by fewer than 5 points on the respective scale. This is not an MID. The responder analysis was still included because it investigated an additional question (see Section 2.9.2.4.3 of the full dossier assessment).

Table 38: Results (dichotomous outcomes) – RCT, direct comparison: treatment-experienced patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV

Study Outcome category Outcome	OBV/PTV/R + DSV + RBV		TVR + PEG + RBV		OBV/PTV/R + RBV vs. TVR + PEG + RBV
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
MALACHITE-II					
Mortality					
All-cause mortality	19	0 (0)	7	0 (0)	NC
Morbidity					
SVR 12[a]	19	19 (100)	7	4 (57.1)	1.73 [0.94; 3.21]; 0.002[b]
Health-related quality of life (under treatment)					
SF-36 responders[c]					
Physical sum score	19	16 (84.2)	6	3 (50.0)	1.68 [0.74; 3.84]; 0.114
Mental sum score	19	10 (52.6)	6	2 (33.3)	1.58 [0.47; 5.29]; 0.570
Adverse events					
AEs	19	16 (84.2)	7	7 (100)	
SAEs	19	0 (0)	7	0 (0)	NC
Treatment discontinuation due to AEs[d]	19	0 (0)	7	2 (28.6)	0.08 [0.00; 1.49]; 0.018[e]

a: Sufficiently valid surrogate for the patient-relevant outcome “hepatocellular carcinoma”.
b: Institute’s calculation: unconditional exact test (CSZ method according to [8]); discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods; the company classified patients who discontinued treatment as non-responders; from the available individual patient data, it was verified that the patients actually were non-responders (see Section 2.9.2.2 of the full dossier assessment). A sensitivity analysis conducted by the Institute, in which this patient was categorized as responder, therefore had the same results as the primary analysis of the company.
c: Patients who improved on the respective scale in the observation period or who worsened by fewer than 5 points are considered responders.
d: Patients who discontinued all treatments.
e: Institute‘s calculation: RR and 95% CI (with 0 events in one arm with continuity correction), unconditional exact test (CSZ method according to [8]); 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; DSV: dasabuvir; N: number of analysed patients; n: number of patients with event; NC: not calculated; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SVR 12: sustained virologic response 12 weeks after the end of treatment; TVR: telaprevir; vs.: versus

Table 39: Results (continuous outcomes) – RCT, direct comparison: treatment-experienced patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV (start of study until end of treatment)

Study Outcome category Instrument Subscale	OBV/PTV/R + DSV + RBV			TVR + PEG + RBV			OBV/PTV/R + DSV + RBV vs. TVR + PEG + RBV
	N	Baseline values mean (SD)	Change at end of treatment mean (SD)	N	Baseline values mean (SD)	Change at end of treatment mean (SD)	Mean difference [95% CI]; p-value[a]
MALACHITE-II							
Morbidity (under treatment)							
EQ-5D VAS	18	81.5 (ND)	-0.7 (11.7)	6	70.0 (ND)	-6.3 (12.6)	7.91 [-4.43; 20.26]; 0.197
Health-related quality of life (under treatment)							
SF-36							
Physical sum score	19	52.2 (ND)	-0.7 (7.6)	6	52.8 (ND)	-5.7 (5.4)	4.86 [-2.07; 11.79]; 0.160
Mental sum score	19	54.6 (ND)	-3.6 (9.9)	6	49.5 (ND)	-15.6 (16.1)	15.29 [3.91; 26.67]; 0.011 Hedges' g: 1.01 [0.04; 1.98][b]
HCV-PRO total score	18	84.6 (ND)	-1.6 (19.8)	6	77.1 (ND)	-23.4 (18.8)	26.42 [8.69; 44.16]; 0.005 Hedges' g: 1.07 [0.09; 2.06][b]

a: Unless stated otherwise: mean difference, CI and p-value calculated using an ANCOVA model on the difference of the changes to baseline between the arms, with baseline value and region as covariables and the treatment arm as factor.
b: Institute's calculation from data on the change at the end of treatment.

CHC: chronic hepatitis C; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HCV-PRO: hepatitis C virus patient-reported outcomes; N: number of analysed patients; ND: no data; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; SF-36: Short Form (36) Health Survey; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

Mortality

In the MALACHITE-II study, no patient has died in the relevant subpopulation in the course of the study so far. Hence there is no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit for the outcome "mortality" is therefore not proven. This concurs with the company's assessment.

Morbidity

SVR 12 as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma"

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the SVR 12. This resulted in an indication of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for the outcome "hepatocellular carcinoma (assessed with the SVR 12)".

This deviates from the company's assessment only in so far as the company made no outcome-specific conclusion on probability.

Health status using the EQ-5D VAS (under treatment)

There was no statistically significant difference between the treatment groups for the outcome "health status". Hence there is no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit regarding the outcome "health status" is therefore not proven.

This assessment deviates from the company's assessment only in so far as the company considered one further period of analysis and made no outcome-specific conclusion on probability.

Health-related quality of life (under treatment)

SF-36

The physical and mental sum score was considered for the SF-36.

Physical sum score

For the physical sum score, there was no statistically significant difference between the treatment groups for the mean differences or for the responder analysis. This resulted in no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit regarding the outcome "SF-36 (physical sum score)" is therefore not proven.

Mental sum score

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the SF-36 mental sum score in the consideration of the mean differences. 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 fully above the irrelevance threshold of 0.2. It was therefore possible that the effect was within a range that is certainly irrelevant. This resulted in no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit for the outcome "SF-36 (mental sum score)" is therefore not proven.

There was no statistically significant difference between the treatment groups for the mental sum score of the SF-36 in the responder analysis. Hence the results of the 2 analyses on the SF-36 are consistent.

In summary, the assessments regarding the SF-36 partly deviate from the company's assessments. The company considered additional periods of analysis. In addition, the company did not address the outcome-specific probability of the added benefit.

HCV-PRO

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the outcome "HCV-PRO". 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 fully above the irrelevance threshold of 0.2. It was therefore possible that the effect was within a range that is certainly irrelevant. This resulted in no hint of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV; an added benefit for the outcome "HCV-PRO" is therefore not proven.

This assessment deviates from the company's assessment in so far as the company additionally considered responder analyses and further periods of analysis.

Adverse events

As described in Section 2.5.2.2, the data on AEs were largely not evaluable in a meaningful way. Hereinafter, except for treatment discontinuations due to AEs, only qualitative conclusions are therefore drawn on the comparison of OBV/PTV/R + DSV + RBV with TVR + PEG + RBV.

Overall rate of SAEs and treatment discontinuation due to AEs

No SAEs have occurred in the relevant subpopulation of the MALACHITE-II study in the course of the study so far.

There was a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for the outcome "treatment discontinuation due to AEs". This resulted in an indication of lesser harm from OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for this outcome. However, this result was based on only 0 versus 2 patients with events.

AEs of particular interest

Due to the available data, no comprehensive choice of AEs of particular interest was possible. Due to the low number of patients in the relevant subpopulation of the study, individual AEs were not considered.

The assessment deviates from that of the company, which, on the basis of the overall rates and some specific AEs of interest, derived quantitative conclusions on the added benefit.

2.5.2.4 Subgroups and other effect modifiers

See Section 2.9.2.4.3 of the full dossier assessment for a list of the relevant effect modifiers.

Only the results on subgroups and outcomes were to be presented in which there were at least indications of an interaction between treatment effect and subgroup characteristic (see Section 2.3.2.4 for further prerequisites). The prerequisite for proof of an effect modification was a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provided an indication of an effect modification.

For the relevant subpopulation of the MALACHITE-II study, there was only a subgroup analysis on response to prior therapy. No indication of an effect modification was shown here.

No consideration of results on relevant effect modifications was possible for further relevant effect modifiers.

2.5.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit 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.

2.5.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.5.1 resulted in indications of an added benefit of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV for the outcomes “hepatocellular carcinoma (assessed with the surrogate SVR 12)” and “treatment discontinuation due to AEs”. The extent of the respective added benefit at outcome level was estimated from these results (see Table 40).

Table 40: Extent of added benefit at outcome level: treatment-experienced patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV

Outcome category **Outcome**	**OBV/PTV/R + DSV + 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%	Lesser benefit/added benefit not proven
Morbidity		
Hepatocellular carcinoma, assessed with the surrogate SVR 12	100% vs. 57.1% RR: 1.73 [0.94; 3.21] p = 0.002[c] probability: "indication"	Outcome category: severe/serious symptoms/late complications added benefit, extent: "non-quantifiable"
Health status using the EQ-5D VAS	MD: 7.91 [-4.43; 20.26] p = 0.197	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36		
Physical sum score	Responder analysis: RR: 1.68 [0.74; 3.84] p = 0.114[c]	Lesser benefit/added benefit not proven
Mental sum score	Responder analysis: RR: 1.58 [0.47; 5.29] p = 0.570[c]	Lesser benefit/added benefit not proven
HCV-PRO	MD: 26.42 [8.69; 44.16] p = 0.005 Hedges' g: 1.07 [0.09; 2.06]	Lesser benefit/added benefit not proven
Adverse events		
SAEs	0% vs. 0% RR: NC	Greater/lesser harm not proven
Treatment discontinuation due to AEs	0% vs. 28.6% RR: 0.08 [0.00; 1.49] p = 0.018[d] probability: "indication"	Outcome category: non-severe/non-serious AEs lesser harm, extent: "non-quantifiable"[e]

(continued)

Table 40: Extent of added benefit at outcome level: treatment-experienced patients with CHC genotype 1a without cirrhosis, OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV (continued)

a: Probability provided if statistically significant differences were present. Decision based on the lower 95% CI limit of Hedges' g in continuous outcomes.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation, unconditional exact test (CSZ method according to [8]).
d: Institute's calculation: RR and 95% CI (with 0 events in one arm with continuity correction), unconditional exact test (CSZ method according to [8]). Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
e: Since in this case the CI is not regarded to be sufficiently reliable for the determination of the extent because of the asymptotic calculation, the extent of lesser harm cannot be quantified.
AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CI_u: upper limit of CI; CSZ: convexity, symmetry, z score; DSV: dasabuvir; EQ-5D: European Quality of Life-5 Dimensions; HCV-PRO: hepatitis C virus patient-reported outcomes; MD: mean difference; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RR: relative risk; SAE: serious adverse event; SVR 12: sustained virologic response 12 weeks after the end of treatment; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

2.5.3.2 Overall conclusion on added benefit

Table 41 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 41: Positive and negative effects from the assessment of OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV (treatment-experienced CHC genotype 1a patients without cirrhosis)

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ hepatocellular carcinoma, assessed with the surrogate SVR 12: indication of an added benefit – extent: non-quantifiable	-
Non-severe/non-serious adverse events ▪ treatment discontinuations due to AEs: indication of lesser harm, extent: "non-quantifiable"	-
AE: adverse event; CHC: chronic hepatitis C; DSV: dasabuvir; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; SVR 12: sustained virologic response 12 weeks after the end of treatment; TVR: telaprevir	

Overall, only positive effects remained in the outcome categories "serious/severe symptoms or late complications" and "non-severe/non-serious AEs". There was an indication of an added benefit for the outcome "hepatocellular carcinoma". The extent of this added benefit could not be quantified, however, because the outcome was assessed with the surrogate SVR 12.

Regarding harm from OBV/PTV/R + DSV + RBV in comparison with TVR + PEG + RBV, there was an indication of lesser harm from OBV/PTV/R + DSV + RBV, the extent of which is non-quantifiable, for the outcome "treatment discontinuation due to AEs". The available data allowed no quantitative conclusions for SAEs and specific AEs; however, there was also no sign of greater harm from OBV/PTV/R + DSV + RBV. A weakening of the added benefit of OBV/PTV/R + DSV + RBV did therefore not seem justified.

In summary, there was an indication of a non-quantifiable added benefit of OBV/PTV/R + DSV + RBV versus the ACT TVR + PEG + RBV for treatment-experienced patients with CHC genotype 1a without cirrhosis.

The result of the assessment of the added benefit of OBV/PTV/R in comparison with the ACT is summarized in Table 42.

Table 42: Ombitasvir/paritaprevir/ritonavir – extent and probability of the added benefit for treatment-experienced patients with CHC genotype 1a without cirrhosis

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment-experienced patients with CHC genotype 1a without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], 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		

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

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

MALACHITE-II

AbbVie. A randomized, open-labeled study to evaluate the efficacy and safety of ABT-450/ritonavir/ABT-267 and ABT-333 co-administered with ribavirin compared to telaprevir co-administered with pegylated interferon α-2a and ribavirin in treatment-experienced adults with chronic hepatitis C genotype 1 virus infection (MALACHITE-II): study M13-862; clinical study report (primary analysis) [unpublished]. 2015.

AbbVie. A study to evaluate the efficacy and safety of three experimental drugs compared with Telaprevir (a licensed product) for treatment of chronic hepatitis C infection in treatment-experienced adults: full text view [online]. In: ClinicalTrials.gov. 26 January 2015 [accessed: 17 February 2015]. URL: http://ClinicalTrials.gov/show/NCT01854528.

AbbVie Deutschland. A randomized, open-labeled study to evaluate the efficacy and safety of ABT-450/ritonavir/ABT-267 and ABT-333 co-administered with ribavirin compared to telaprevir co-administered with pegylated interferon α-2a and ribavirin in treatment-experienced adults with chronic hepatitis C genotype 1 virus infection (MALACHITE II) [online]. In: EU Clinical Trials Register. [Accessed: 18 February 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-003738-18.

2.6 Research questions 4 to 10: other patient groups with CHC genotype 1

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 lists on ombitasvir/paritaprevir/ritonavir (studies completed up to 4 November 2014)
- bibliographical literature search on ombitasvir/paritaprevir/ritonavir (last search on 4 November 2014)
- search in trial registries for studies on ombitasvir/paritaprevir/ritonavir (last search on 3 November 2014)

To check the completeness of the study pool:

- search in trial registries for studies on ombitasvir/paritaprevir/ritonavir (last search on 9 February 2015)

No additional relevant study was identified from the check.

Study pool

No direct comparative RCTs on the comparison of OBV/PTV/R with the ACT were available for further patient groups with CHC genotype 1. Research questions 4 to 10 (see Table 4) represent these patient groups with CHC genotype 1. They comprise treatment-experienced patients with CHC genotype 1b without cirrhosis, treatment-naive and treatment-experienced patients with compensated cirrhosis, patients after liver transplantation and patients with HIV coinfection. In Section 4.3.2.3 of the dossier, the company included further investigations with the drug under assessment in the patient groups mentioned in the benefit assessment. The investigations presented were mainly RCTs, from each of which the company considered the intervention arm, where, according to the company, OBV/PTV/R was administered in compliance with the approval. No systematic comparison with data on the ACT was conducted. There was no systematic search for comparator data with the ACT. The completeness of the comparator data presented is therefore unclear. Hence the data of the further investigations presented by the company were unsuitable for the benefit assessment.

No relevant study could be included for research questions 4 to 10.

2.6.2 Results and added benefit

The company presented no suitable data for the assessment of the added benefit of OBV/PTV/R for research questions 4 to 10. Hence an added benefit of OBV/PTV/R versus the ACT is not proven for patients from research questions 4 to 10.

2.6.3 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.7 Research questions 11 to 16: patient groups 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 lists on ombitasvir/paritaprevir/ritonavir (studies completed up to 4 November 2014)
- bibliographical literature search on ombitasvir/paritaprevir/ritonavir (last search on 4 November 2014)
- search in trial registries for studies on ombitasvir/paritaprevir/ritonavir (last search on 3 November 2014)

To check the completeness of the study pool:

- search in trial registries for studies on ombitasvir/paritaprevir/ritonavir (last search on 9 February 2015)

No additional relevant study was identified from the check.

Study pool

No direct comparative RCTs on the comparison of OBV/PTV/R with the ACT were available for patients with CHC genotype 4. Research questions 11 to 16 (see Table 4) represent these patient groups with CHC genotype 4. They comprise treatment-naive and treatment-experienced patients without cirrhosis and with compensated cirrhosis, patients after liver transplantation and patients with HIV coinfection. In Section 4.3.2.3 of the dossier, the company included further investigations with the drug under assessment in the patient groups mentioned in the benefit assessment. The investigations presented were mainly RCTs, from each of which the company considered the intervention arm, where, according to the company, OBV/PTV/R was administered in compliance with the approval. No systematic comparison with data on the ACT was conducted. There was no systematic search for comparator data with the ACT. The completeness of the comparator data presented is therefore unclear. Hence the data of the further investigations presented by the company were unsuitable for the benefit assessment.

No relevant study could be included for research questions 11 to 16.

2.7.2 Results and added benefit

The company presented no suitable data for the assessment of the added benefit of OBV/PTV/R for research questions 11 to 16. Hence an added benefit of OBV/PTV/R versus the ACT is not proven for patients with CHC genotype 4.

2.7.3 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.8 Extent and probability of added benefit – summary

Table 43 summarizes the extent and probability of the added benefit of OBV/PTV/R for all research questions.

Table 43: Ombitasvir/paritaprevir/ritonavir – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment-naive patients with CHC genotype 1a without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], peginterferon and ribavirin)**	Indication of non-quantifiable added benefit
Treatment-naive patients with CHC genotype 1b without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], peginterferon and ribavirin)**	Indication of non-quantifiable added benefit
Treatment-experienced patients with CHC genotype 1a without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], peginterferon and ribavirin)**	Indication of non-quantifiable added benefit
Treatment-experienced patients with CHC genotype 1b without cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], peginterferon and ribavirin)**	Added benefit not proven
Treatment-naive patients with CHC genotype 1a with compensated cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Treatment-naive patients with CHC genotype 1b with compensated cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven

(continued)

Table 43: Ombitasvir/paritaprevir/ritonavir – extent and probability of added benefit (continued)

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment-experienced patients with CHC genotype 1a with compensated cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], peginterferon and ribavirin)**	Added benefit not proven
Treatment-experienced patients with CHC genotype 1b with compensated cirrhosis	Dual therapy (combination of peginterferon and ribavirin) or **triple therapy (combination of a protease inhibitor [telaprevir or boceprevir], peginterferon and ribavirin)**	Added benefit not proven
Patients with CHC genotype 1 after liver transplantation	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Patients with CHC genotype 1 with HIV coinfection	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Treatment-naive patients with CHC genotype 4 without cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Treatment-experienced patients with CHC genotype 4 without cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Treatment-naive patients with CHC genotype 4 with compensated cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Treatment-experienced patients with CHC genotype 4 with compensated cirrhosis	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Patients with CHC genotype 4 after liver transplantation	Dual therapy (combination of peginterferon and ribavirin)	Added benefit not proven
Patients with CHC genotype 4 with HIV coinfection	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

In summary, there was an indication of a non-quantifiable added benefit of OBV/PTV/R for treatment-naive patients with genotype 1a and 1b and for treatment-experienced patients with CHC genotype 1a (in each case without cirrhosis). For all other patient groups in the approved therapeutic indication, an added benefit was not proven.

The assessment deviates from the company's assessment, which derived an indication of a major added benefit for treatment-naive patients with genotype 1a and 1b and for treatment-experienced patients with CHC genotype 1a (in each case without cirrhosis). The company derived a hint of a major added benefit for treatment-experienced patients with CHC genotype 1b, and a hint of a considerable added benefit for all other patient groups.

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

References for English extract

Please see full dossier assessment for full reference list.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden: Version 4.2. Köln: IQWiG; 2015. URL: https://www.iqwig.de/download/IQWiG_Methoden_Version_4-2.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2 July 2015 [Epub ahead of print].

3. AbbVie. Viekirax 12,5 mg/75 mg/50 mg Filmtabletten: Fachinformation [online]. January 2015 [accessed: 7 April 2015]. URL: http://www.fachinfo.de.

4. AbbVie. Exviera 250 mg Filmtabletten: Fachinformation [online]. January 2015 [accessed: 7 April 2015]. URL: http://www.fachinfo.de.

5. Janssen. Incivo 375 mg Filmtabletten: Fachinformation [online]. July 2014 [accessed: 7 April 2015]. URL: http://www.fachinfo.de.

6. Roche. Copegus: Fachinformation [online]. April 2014 [accessed: 13 November 2014]. URL: http://www.fachinfo.de.

7. Roche. Pegasys 90/135/180 Mikrogramm: Fachinformation [online]. October 2014 [accessed: 7 April 2015]. URL: http://www.fachinfo.de.

8. 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/a15-04-ombitasvir/paritaprevir/ritonavir-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6601.html.