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Dasabuvir ombitasvir/paritaprevir/ritonavir (Addendum to Commissions A15-03 and A15-04)[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CHC	chronic hepatitis C
CI	confidence interval
CSR	clinical study report
DSV	dasabuvir
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D VAS	European Quality of Life-5 Dimensions visual analogue scale
HCV-PRO	hepatitis C virus patient-reported outcomes
HCVTSat	Hepatitis C Virus Treatment Satisfaction
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IDR	incidence density ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
OBV	ombitasvir
PEG	pegylated interferon
PT	Preferred Term
PTV	paritaprevir
R	ritonavir
RBV	ribavirin
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SMD	standardized mean difference
SVR 12	sustained virologic response 12 weeks after the end of treatment
TVR	telaprevir
WPAI	Work Productivity and Activity Impairment

1 Background

On 11 June 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for the commissions A15-03 (Dasabuvir – Benefit assessment according to §35a Social Code Book V [1]) and A15-04 (Ombitasvir/paritaprevir/ritonavir – Benefit assessment according to §35a Social Code Book V [2]).

With its comment, the pharmaceutical company (hereinafter referred to as "the company") presented further information on results of an adjusted indirect comparison of ombitasvir/paritaprevir/ritonavir in combination with dasabuvir (OBV/PTV/R + DSV) versus triple therapy of telaprevir, peginterferon and ribavirin (TVR + PEG + RBV) in treatment-experienced patients with chronic hepatitis C (CHC) genotype 1b without cirrhosis (research question 4 of the dossier assessment [3,4]). The G-BA commissioned IQWiG to assess the information on this indirect comparison (including information on survival time analyses for adverse events [AEs]).

Moreover, the company presented further information on survival time analyses for AEs for the following patient groups and comparisons [3,4]:

- Research question 1 of the dossier assessment: treatment-naive patients with CHC genotype 1a without cirrhosis (OBV/PTV/R + DSV + RBV versus TVR + PEG + RBV)
- Research question 2 of the dossier assessment: treatment-naive patients with CHC genotype 1b without cirrhosis (OBV/PTV/R + DSV versus TVR + PEG + RBV)
- Research question 3 of the dossier assessment: treatment-experienced patients with CHC genotype 1a without cirrhosis (OBV/PTV/R + DSV + RBV versus TVR + PEG + RBV)

The G-BA commissioned IQWiG to assess this information on these survival time analyses for AEs.

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

2 Assessment

With its comment on the benefit assessment of dasabuvir and ombitasvir/paritaprevir/ritonavir, the company presented an adjusted indirect comparison for research question 4 of the dossier assessment and survival time analyses for AEs for research questions 1 to 3 of the dossier assessment [3,4].

Section 2.1 contains the assessment of the adjusted indirect comparison of OBV/PTV/R + DSV versus TVR + PEG + RBV in treatment-experienced patients with CHC genotype 1b without cirrhosis.

The information on survival time analyses for AEs for research questions 1 to 3 of the dossier assessment is assessed in Section 2.2.

Section 2.3 summarizes whether, and, if any, which conclusions of the original dossier assessments A15-03 and 15-04 were changed by this assessment.

2.1 Research question 4 of the dossier assessment: treatment-experienced patients with CHC genotype 1b without cirrhosis

2.1.1 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 Appendix A of the comment:

- study list on OBV/PTV/R + DSV (studies completed up to 2 April 2015)
- bibliographical literature search on OBV/PTV/R + DSV (last search on 10 April 2015)
- search in trial registries for studies on OBV/PTV/R + DSV (last search on 25 March 2015)
- bibliographical literature search on the appropriate comparator therapy (ACT) TVR + PEG + RBV (last search on 10 April 2015)
- search in trial registries for studies on the ACT TVR + PEG + RBV (last search on 25 March 2015)

To check the completeness of the study pool:

- search in trial registries for studies on OBV/PTV/R + DSV (last search on 29 May 2015)
- search in trial registries for studies on the ACT TVR + PEG + RBV using the common comparator OBV/PTV/R + DSV + RBV (last search on 29 May 2015)

No additional study was identified from the check.

2.1.1.1 Studies included

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

Table 1: Study pool – RCT, indirect comparison: treatment-experienced 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)
PEARL-II	Yes	Yes	No
MALACHITE-II	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

2.1.1.2 Study characteristics

Table 2 and Table 3 describe the studies used for the benefit assessment.

Table 2: Characteristics of the studies included – RCT, indirect comparison: treatment-experienced 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]
Study with OBV/PTV/R + DSV						
PEARL-II	RCT, open-label, parallel	Treatment-experienced adults (≥ 18-70 years) with chronic hepatitis C of GT 1b without cirrhosis Pretreatment with pegIFN in combination with RBV	OBV/PTV/R + DSV + RBV (N = 92) OBV/PTV/R + DSV (N = 95)	Screening: 35 days maximum Treatment phase: 12 weeks Follow-up: 48 weeks Data cut-off for primary analysis: 1/2014	43 centres in Austria, Belgium, Italy, Netherlands, Portugal, Puerto Rico, Sweden, Switzerland, Turkey, United States 8/2012 – ongoing	Primary: proportion of patients with SVR 12 Secondary: health-related quality of life, AEs
Study with TVR + PEG + RBV						
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) Thereof patients with GT 1b: Arm A (n = 84) Arm B (n = 42)	Screening: up to 5 weeks Treatment phase: arm A: 12 weeks arm B: 24 or 48 weeks (response-guided) Follow-up: 48 weeks Data cut-off for primary analysis: 11/2014	27 centres[b] in Argentina, Australia, Chile, Finland, Hungary, Poland, Romania, Slovak Republic 6/2013 – ongoing	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: 34 investigation sites according to the comment.
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 12 or 24: sustained virologic response 12 or 24 weeks after the end of treatment; TVR: telaprevir; vs.: versus

Table 3: Characteristics of the interventions – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV

Study	Intervention	Comparison	Concomitant medication
Study with OBV/PTV/R + DSV			
PEARL-II	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)	OBV/PTV/R (25 mg/150 mg/100 mg) once daily, orally + DSV 250 mg twice daily, orally	Prohibited at start of study: ▪ any previous use of anti-HCV drugs including TVR, boceprevir, DSV and PTV/R except PEG and RBV For 2 weeks before the start of the study medication or 10 half-lives: ▪ strong or moderate CYP3A substrates, inhibitors and inducers: alfuzosin, amiodarone, astemizole, carbamazepine, quinidine, cisapride, clarithromycin, conivaptan, dronedarone, efavirenz, eletriptan, eplerenone, everolimus, fusidic acid, itraconazole, ketoconazole, lovastatin, midazolam (orally), nefazodone, phenobarbital, phenytoin, pimozide, rifampin, salmeterol, simvastatin, telithromycin, triazolam, voriconazole ▪ CYP2C8 inhibitors: gemfibrozil, trimethoprim ▪ Other prohibited drugs: bepridil, bosentan, buprenorphine, St. John's Wort, methadone, mifepristone, modafinil, montelukast, ergot alkaloids, pioglitazone, propafenone, quercetin, quinidine, rifabutin, rosiglitazone, terfenadine, troglitazone, troleandomycin ▪ hormonal contraceptives[a] ▪ herbal agents (including milk thistle) ▪ any medication contraindicated for RBV or TVR

(continued)

Table 3: Characteristics of the interventions – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV (continued)

Study	Intervention	Comparison	Concomitant medication
Study with TVR + PEG + RBV			
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 SC once weekly + 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: ▪ any previous use of 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, 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, 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 agents (including milk thistle) ▪ any medication contraindicated for RBV, TVR or PEG alfa 2a

a: Unless allowed by the investigator.

CHC: chronic hepatitis C; CYP: cytochrome P450, 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

Study with OBV/PTV/R + DSV (PEARL-II)

PEARL-II was a randomized controlled trial (RCT) with 2 treatment arms. Patients with CHC genotype 1b without cirrhosis who had been pretreated with PEG + RBV were included in the study. A total of 187 patients were randomized.

Two drug combinations with OBV/PTV/R + DSV were compared. Ribavirin was administered in addition to this combination in one of both study arms. The combination with ribavirin in this drug combination is not approved for patients with CHC infection of genotype 1b without cirrhosis. In the present comparison, it served as common comparator in an indirect comparison with the ACT TVR + PEG + RBV.

The treatment duration in the OBV/PTV/R + DSV arm was 12 weeks. The treatment regimen used and the dosages of the drugs in this study arm 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.

Primary outcome of the study was sustained virologic response 12 weeks after the end of treatment (SVR 12).

Study with TVR + PEG + RBV (MALACHITE-II)

MALACHITE-II was an 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. 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). Only the subpopulation of patients with CHC genotype 1b, which comprised 126 patients (arm A: 84 patients, arm B: 42 patients) was relevant in the research question considered here. The patients with CHC genotype 1a are not considered further.

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. This study arm served as common comparator for the indirect comparison of OBV/PTV/R + DSV with TVR + PEG + RBV.

In arm B, the patients were treated with 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, the patients continued treatment with PEG + RBV for further 12 or 36 weeks. Hence the maximum treatment duration was 24 or 48 weeks. This treatment was in compliance with the approval.

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.

Primary outcome of the study was sustained virologic response 12 weeks after the end of treatment.

Evaluation of the assumptions of an adjusted indirect comparison (similarity, homogeneity, consistency)

Similarity of the studies PEARL-II and MALACHITE-II

Study populations

Table 4 shows the characteristics of the patients in the studies included.

Table 4: Characteristics of the study populations – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV

Study Group	N[a]	Age [years] mean (SD)	Sex [F/M] %	Fibrosis stage [F0-F1/F2/≥ F3] %	Viral load [< 800 000/ ≥ 800 000 I U/mL] %	Ethnicity [white/black/ Asian/other] %	Response to pretreatment [null response/ partial response/ relapse] %	IL28B genotype CC/CT/TT %	Study discontin-uations, n (%)
PEARL-II									
OBV/PTV/R + DSV	95	54 (11)	40/60	64.2/22.1/13.7	9.5/90.5	90.5/6.3/2.1/1.1	34.7/28.4/36.8	7.4/70.5/22.1	0 (0)[b]
OBV/PTV/R + DSV + RBV	91	54 (11)	51/49	70.3/14.3/15.4	14.3/85.7	92.3/3.3/1.1/3.3	35.2/28.6/36.3	11.0/64.8/24.2	2 (2.2)[b]
MALACHITE-II									
TVR + PEG + RBV	40	45 (10)	40/60	70.0/22.5/7.5	15.0/85.0	100/0/0/0	52.5/25.0/22.5	7.5/70.0/22.5	3 (7.1) – 6 (14.3)[c]
OBV/PTV/R + DSV + RBV	82	48 (12)	49/51	76.8/18.3/4.9	22.0/78.0	100/0/0/0	51.2/25.6/23.2	6.1/62.2/31.7	4 (4.8)[c]

a: Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b: Referring to 95 and 92 randomized patients.
c: Referring to 42 and 84 randomized patients. Institute's calculation from the difference of the number of study discontinuations for the total study and the number of study discontinuations with CHC genotype 1a [1,2], including those patients who had been randomized, but received no study medication. It was uncertain for 3 patients with CHC genotype 1a whether they actually discontinued the study.

CHC: chronic hepatitis C; DSV: dasabuvir; F: female; IU: international units; M: male; N: number of patients analysed; n: number of patients in the category; OBV: ombitasvir; 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 balanced both in the PEARL-II study and in the relevant subpopulation of the MALACHITE-II study, whereas both in the OBV/PTV/R + DSV arm of the PEARL-II study and in the TVR + PEG + RBV arm of the MALACHITE-II study, 60% men were included. Regarding fibrosis stage, patients in both studies mainly had a METAVIR score of F0-F1 (64% to 77%). In both studies, viral load was high in 78% to 91% of the patients. Only white patients were included in the MALACHITE-II study, and over 90% of the patients were white in the PEARL-II study.

Patients with null response, partial response and relapse after previous PEG + RBV treatment were included in both studies. The proportion of patients with null response was approximately 35% in the PEARL-II study and approximately 52% in the MALACHITE-II study. The proportion of patients with partial response to prior therapy was 25% to 29% in both studies; correspondingly, the proportion of patients with relapse was somewhat higher in the PEARL-II study than in the MALACHITE-II study (37% versus 23%). The distribution of IL28B genotypes was similar in both studies, with the genotype CT being the most frequent (62% to 71%), followed by TT (22% to 32%) and CC (6% to 11%).

The rate of patients who discontinued the study was higher in the MALACHITE-II study than in the PEARL-II study, where only 2 patients in total in one treatment arm discontinued the study. It is unclear in the MALACHITE-II study how large the number of patients who discontinued the study actually was in the TVR + PEG + RBV arm because the company only presented the rates of patients who discontinued treatment in Appendix A of the comment (although these were designated as patients who discontinued the study) and the rates of discontinuations for the relevant subpopulation were not clear from the clinical study report (CSR).

No decisive differences between the studies PEARL-II and MALACHITE-II regarding the study populations can be derived from the available data so that both studies were considered to be sufficiently similar for an adjusted indirect comparison in this respect.

Common comparator

The comparability of the use of the common comparator (OBV/PTV/R + DSV + RBV) in the studies included is also relevant for an adjusted indirect comparison. This was considered to be sufficient for the available studies. Dosage and duration of administration was identical in both studies (OBV/PTV/R: 25 mg/150 mg/100 mg once daily, orally; DSV: 250 mg twice daily, orally; RBV: depending on body weight 1000 or 1200 mg distributed to 2 dosages daily, orally: duration of use: 12 weeks).

Consequences for study inclusion and assessment

No important differences between the studies considered could be inferred from the available data. Overall, the 2 studies PEARL-II and MALACHITE-II were considered to be sufficiently similar so that the assumption of similarity for an adjusted indirect comparison was not rejected.

Evaluation of homogeneity and consistency

The indirect comparison considered was an adjusted indirect comparison according to Bucher with only one study in each pairwise comparison. Moreover, there was no direct comparison. An evaluation of homogeneity and consistency is therefore not possible. Hence at most hints of added benefit or harm were derived from the available data.

Table 5 shows the risk of bias at study level.

Table 5: Risk of bias at study level – RCT, indirect comparison: treatment-experienced 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			
Study with OBV/PTV/R + DSV							
PEARL-II	Yes	Yes	No	No	Yes	Yes	Low
Study with TVR + PEG + RBV							
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 study level was rated as low for both studies. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.1.2.2 with the outcome-specific risk of bias.

2.1.2 Results on added benefit

2.1.2.1 Outcomes included

The following patient-relevant outcomes were considered in the 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
  - SF-36
  - hepatitis C virus patient-reported outcomes (HCV-PRO)
- Adverse events
  - overall rate of SAEs
  - treatment discontinuation due to AEs

The choice of outcomes included concurs with that in the dossier assessments on dasabuvir and OBV/PTV/R [1,2]. It deviates from the company's choice, which additionally included further outcomes regarding benefit and harm. In contrast to the original dossiers, the company did not include the outcomes "Work Productivity and Activity Impairment (WPAI)" and "Hepatitis C Virus Treatment Satisfaction (HCVTSat)" in the analyses subsequently submitted in the comment. See Section 2.8.2.4.3 of the full dossier assessments for reasons for the choice of outcomes for the assessment.

In its choice of outcomes on AEs, the company deviated from its approach in the dossiers on dasabuvir and OBV/PTV/R insofar as it only included the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) "rash" and "anaemia" besides the overall rates of AEs, serious AEs (SAEs) and treatment discontinuations due to AEs. These were not included in the present assessment because they present no comprehensive choice of relevant AEs in the treatment situation considered. Hence only SAEs and treatment discontinuations due to AEs were included as outcomes on harm.

Table 6 shows for which outcomes data were available in the studies included.

Table 6: Matrix of outcomes – RCT, direct comparison: treatment-experienced 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 HCV-PRO	Health-related quality of life using the SF-36	SAEs	Treatment discontinuation due to AEs
Study with OBV/PTV/R + DSV							
PEARL-II	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study with TVR + PEG + RBV							
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: hepatitis C virus; 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 12: sustained virologic response 12 weeks after the end of treatment; TVR: telaprevir; VAS: visual analogue scale; vs.: versus

2.1.2.2 Risk of bias

Table 7 shows the risk of bias for the relevant outcomes.

Table 7: Risk of bias at study and outcome level – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV 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
Study with OBV/PTV/R + DSV								
PEARL-II	L	L	L	H[b]	H[b]	H[b]	L	H[b]
Study with TVR + PEG + RBV								
MALACHITE-II	L	H[a]	L	H[b]	H[b]	H[b]	L	H[b]

a: Marked difference in the observation period between the treatment arms.
b: Open-label study design.

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; L: low; 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; vs.: versus

The risk of bias for the outcome "all-cause mortality" was considered to be high in the MALACHITE-II study because the observation periods between the treatment groups differed markedly. The company, however, assumed a low risk of bias regarding this outcome for both studies. The risk of bias for the outcome "SVR 12", like the risk of bias of the total studies, was considered to be low. This concurs with the company's assessment.

Due to the open-label 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 these outcomes concur with the company's assessment.

In the MALACHITE-II study, the observation periods in the individual treatment groups differed considerably for all outcomes on AEs including SAEs. Since the company presented survival time analyses for this outcome, the risk of bias for this outcome can still be considered to be low.

The outcome-specific risk of bias for the outcome "treatment discontinuation due to AEs" was rated as high. Due to the open-label study design, potential bias of the results cannot be

excluded for this subjectively reported outcome unless the events are not to be rated as severe or serious. The company saw a low risk of bias for both outcomes on AEs.

2.1.2.3 Results

Table 8 and Table 9 contain the results on the direct comparison of OBV/PTV/R + DSV with OBV/PTV/R + DSV + RBV and on the direct comparison of TVR + PEG + RBV with OBV/PTV/R + DSV + RBV as well as the results on the adjusted indirect comparisons of OBV/PTV/R + DSV with TVR + PEG + RBV based on these studies. The data from Appendix A of the company's comment were, where necessary, supplemented by the Institute's calculations.

Figure 3 and Figure 4 in Appendix A show the Kaplan-Meier curves for the outcome "SAEs" in the studies PEARL-II and MALACHITE-II.

For the MALACHITE-II study, no analysis on health-related quality of life and health status (EQ-5D VAS) with time periods comparable for both treatment groups was available for the benefit assessment. 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 original dossier assessment [1,2]).

Table 8: Results (dichotomous outcomes) – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV

Outcome category **Outcome** **Comparison** **Study**	**OBV/PTV/R + DSV or TVR + PEG + RBV** **N**	**Patients with event n (%)**	**OBV/PTV/R + DSV + RBV** **N**	**Patients with event n (%)**	**Group difference** **RR [95% CI]; p-value**
Mortality					
All-cause mortality					
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV					
PEARL-II	95	0 (0)	91	0 (0)	NC
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV					
MALACHITE-II	40	0 (0)	82	1 (1.2)	0.67 [0.03; 16.21]; 0.598[a]
Adjusted indirect comparison[b]:					
OBV/PTV/R + DSV vs. TVR + PEG + RBV					NC
Morbidity					
SVR 12[c] responders					
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV					
PEARL-II	91	91 (100)	88	85 (96.6)	1.04 [0.99; 1.08]; 0.078[a]
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV					
MALACHITE-II	40	27 (67.5)	82	81 (98.8)	0.68 [0.55; 0.85]; < 0.001[a]
Adjusted indirect comparison[b]:					
OBV/PTV/R + DSV vs. TVR + PEG + RBV					1.52 [1.21; 1.89]; < 0.001[d]

(continued)

Table 8: Results (dichotomous outcomes) – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV (continued)

Outcome category Outcome Comparison Study	OBV/PTV/R + DSV or TVR + PEG + RBV N	 Patients with event n (%)	OBV/PTV/R + DSV + RBV N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
Health-related quality of life (under treatment)					
SF-36 responders					
Physical sum score					
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV					
PEARL-II	90	76 (84.4)	86	61 (70.9)	1.19 [1.01; 1.40]; 0.031[a]
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV					
MALACHITE-II	39	14 (35.9)	82	69 (84.1)	0.43 [0.28; 0.66]; < 0.001[a]
Adjusted indirect comparison[b]:					
OBV/PTV/R + DSV vs. TVR + PEG + RBV					2.79 [1.76; 4.42]; < 0.001
Mental sum score					
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV					
PEARL-II	90	73 (81.1)	86	60 (69.8)	1.16 [0.98; 1.38]; 0.083[a]
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV					
MALACHITE-II	39	15 (38.5)	82	64 (78.0)	0.49 [0.33; 0.74]; < 0.001[a]
Adjusted indirect comparison[b]:					
OBV/PTV/R + DSV vs. TVR + PEG + RBV					2.36 [1.51; 3.69]; < 0.001
Adverse events					
AEs					
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV					
PEARL-II	95	74 (77.9)	91	72 (79.1)	
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV					
MALACHITE-II	40	36 (90.0)	82	47 (57.3)	

(continued)

Table 8: Results (dichotomous outcomes) – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV (continued)

Outcome category **Outcome**	**OBV/PTV/R + DSV or TVR + PEG + RBV**		**OBV/PTV/R + DSV + RBV**		**Group difference**
Comparison **Study**	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
SAEs					*HR [95% CI]; p-value*[e]
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV					
PEARL-II	95	2 (2.1)	91	2 (2.2)	0.95 [0.13; 6.76]; 0.961
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV					
MALACHITE-II	40	5 (12.5)	82	1 (1.2)	8.94 [1.00; 80.06]; 0.018
Adjusted indirect comparison[b]**:**					
OBV/PTV/R + DSV vs. TVR + PEG + RBV					0.11 [0.01; 2.01]; 0.135
Treatment discontinuation due to AEs[f]					
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV					
PEARL-II	95	0 (0)	91	2 (2.2)	0.19 [0.01; 3.94]; 0.156[a]
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV					
MALACHITE-II	40	3 (7.5)	82	0 (0)	14.17 [0.75; 267.91]; 0.012[a]
Adjusted indirect comparison[b]**:**					
OBV/PTV/R + DSV vs. TVR + PEG + RBV					0.01 [0.00; 0.92]; 0.046

a: Institute's calculation, unconditional exact test (CSZ method according to Andrés [5]).
b: Adjusted indirect comparison according to Bucher [6].
c: Sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma".
d: The company classified patients who discontinued treatment as non-responders. From the available individual patient data, it was verified for all patients except 2 in the MALACHITE-II study that the patients actually were non-responders. A sensitivity analysis conducted by the Institute, in which these 2 patients were categorized as responders, had a similar result, however: RR = 1.41 [1.16; 1.72]; 0.001.
e: Results of a survival time analysis.
f: Patients who discontinued all treatments.

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CSZ: convexity, symmetry, z score; DSV: dasabuvir; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NC: not calculable; 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 9: Results (continuous outcomes) – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV

Outcome category	**OBV/PTV/R + DSV or TVR + PEG + RBV**			**OBV/PTV/R + DSV + RBV**			**Group difference**
Outcome **Study**	**N[a]**	**Baseline values mean (SD)**	**Change at end of treatment mean (SD)**	**N[a]**	**Baseline values mean (SD)**	**Change at end of treatment mean (SD)**	**Mean difference [95% CI]; p-value[b]** ***Hedges' g [95% CI][c]***
Morbidity (under treatment)							
EQ-5D VAS							
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV							
PEARL-II	91	79.1 (ND)	3.4 (12.1)	86	79.4 (ND)	-0.2 (12.3)	3.48 [0.09; 6.87]; 0.044 *0.29 [0.00; 0.59]*
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV							
MALACHITE-II	39	82.4 (ND)	-9.3 (18.6)	82	82.6 (ND)	2.5 (16.0)	-11.88 [-17.87; -5.89]; < 0.001 *-0.70 [-1.09; -0.30]*
Adjusted indirect comparison[d]:							
OBV/PTV/R + DSV vs. TVR + PEG + RBV							15.4 [7.72; 23.08]; < 0.001 *0.99 [0.5; 1.48]*
Health-related quality of life (under treatment)							
SF-36 (physical sum score)							
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV							
PEARL-II	90	51.1 (ND)	-0.5 (5.9)	86	52.2 (ND)	-2.1 (6.1)	1.32 [-0.35; 2.99]; 0.121 *0.26 [-0.03; 0.56]*
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV							
MALACHITE-II	39	51.4 (ND)	-8.0 (8.0)	82	49.8 (ND)	0.6 (7.1)	-8.21 [-10.84; -5.58]; < 0.001 *-1.16 [-1.56; -0.75]*
Adjusted indirect comparison[d]:							
OBV/PTV/R + DSV vs. TVR + PEG + RBV							10.20 [6.75; 13.65]; < 0.001 *1.42 [0.91; 1.92]*

(continued)

Table 9: Results (continuous outcomes) – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, OBV/PTV/R + DSV vs. TVR + PEG + RBV (continued)

Outcome category	OBV/PTV/R + DSV or TVR + PEG + RBV			OBV/PTV/R + DSV + RBV			Group difference
Outcome Study	N[a]	Baseline values mean (SD)	Change at end of treatment mean (SD)	N[a]	Baseline values mean (SD)	Change at end of treatment mean (SD)	Mean difference [95% CI]; p-value[b] *Hedges' g [95% CI][c]*
SF-36 (mental sum score)							
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV							
PEARL-II	90	49.6 (ND)	0.1 (8.5)	86	48.8 (ND)	-2.4 (8.4)	2.81 [0.42; 5.21]; 0.022 *0.29 [0.00; 0.59]*
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV							
MALACHITE-II	39	53.5 (ND)	-8.9 (10.1)	82	51.6 (ND)	-0.7 (7.9)	-8.10 [-11.49; -4.70]; < 0.001 *-0.94 [-1.34, -0.54]*
Adjusted indirect comparison[d]:							
OBV/PTV/R + DSV vs. TVR + PEG + RBV							10.70 [6.33; 15.07]; < 0.001 *1.24 [0.74; 1.74]*
HCV-PRO (total score)							
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV							
PEARL-II	88	77.3 (ND)	1.5 (13.4)	85	77.0 (ND)	-1.6 (14.6)	3.19 [-0.84; 7.21]; 0.120 *0.22 [-0.08; 0.52]*
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV							
MALACHITE-II	39	83.6 (ND)	-18.6 (18.2)	82	81.6 (ND)	-0.8 (15.2)	-17.69 [-23.88; -11.50]; < 0.001 *-1.09 [-1.50; -0.68]*
Adjusted indirect comparison[d]:							
OBV/PTV/R + DSV vs. TVR + PEG + RBV							20.9 [13.09; 28.71]; < 0.001 *1.31 [0.81; 1.81]*

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: 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 covariable and the treatment arm as factor.
c: Calculation using data that were not adjusted with the baseline value.
d: Adjusted indirect comparison according to Bucher [6].

ANCOVA: analysis of covariance; 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; ITT: intention to treat; 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

No patients died in the PEARL-II study in the observation period. In the relevant subpopulation in the MALACHITE-II study, only one patient died in the OBV/PTV/R + DSV + RBV arm. It was therefore not possible to conduct an indirect comparison. Hence there is no hint of an added benefit of OBV/PTV/R + DSV 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"

The indirect comparison showed a statistically significant difference in favour of OBV/PTV/R + DSV for the SVR 12. This resulted in a hint 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, which claimed an indication of added benefit for this outcome.

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

The indirect comparison showed a statistically significant difference in favour of OBV/PTV/R + DSV for the outcome "health status". The company calculated the standardized mean difference (SMD) in the form of Hedges' g to check the relevance of this effect. The 95% confidence interval (CI) was 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 for the characteristic "IL28B genotype". This resulted in no hint of an added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV for patients with an IL28B genotype of CC or TT. An added benefit for these patients is therefore not proven.

There was a hint of an added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV for patients with the IL28B genotype CT.

The company drew no conclusion on the EQ-5D VAS in its consideration of the added benefit.

Health-related quality of life (under treatment)

SF-36

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

Physical sum score

In the indirect comparison, 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. The company calculated the SMD in the form of Hedges' g to check the relevance of this effect. The 95% CI 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". This resulted in a hint of an added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV in patients with a METAVIR score of F0 – F2.

There was no hint of an added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV for patients with a METAVIR score of ≥ F3. An added benefit for these patients is therefore not proven.

In the indirect comparison, there was a statistically significant difference in favour of OBV/PTV/R + DSV in the responder analysis. The results of both analyses on the physical 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. There were no subgroup analyses for the responder analysis.

Mental sum score

In the indirect comparison, 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 company calculated the SMD in the form of Hedges' g to check the relevance of this effect. The 95% CI was 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 added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV.

In the indirect comparison, there was a statistically significant difference in favour of OBV/PTV/R + DSV in the responder analysis. This resulted in a hint of added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV. The results of 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 the research question.

HCV-PRO

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the HCV-PRO. The company calculated the SMD in the form of Hedges' g to check the relevance of this effect. The 95% CI was 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 by the characteristic “fibrosis stage”. This resulted in a hint of an added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV in patients with a METAVIR score of F0 – F2.

There was no hint of an added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV for patients with a METAVIR score of ≥ F3. An added benefit for these patients is therefore not proven.

Assessment of the company on the added benefit regarding health-related quality of life

The assessments on the added benefit regarding health-related quality of life deviate from that of the company. The company based its derivation of the added benefit on the results for the post-treatment week 12 and derived no added benefit because of the lack of relevance of the observed effects.

Adverse events

Overall rate of serious adverse events

The survival time analysis conducted by the company showed no statistically significant difference between the treatments for the outcome “SAEs” in the indirect comparison. Hence there was no hint of an added benefit of OBV/PTV/R + DSV versus TVR + PEG + RBV. An added benefit for this outcome is therefore not proven.

For the overall rate of SAEs, the company claimed that there is no statistically significant difference, but provided no further information on added benefit.

Treatment discontinuation due to AEs

The indirect comparison showed a statistically significant difference in favour of OBV/PTV/R + DSV for the outcome “treatment discontinuation due to AEs”. Due to the marginal effect size, there was no hint of an added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV for this outcome. An added benefit for this outcome is therefore not proven.

The company saw an added benefit here, but provided no information on probability.

2.1.2.4 Subgroups and other 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. In effect modifiers with more than 2 categories, such as fibrosis stage and IL28B genotype, 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.

Table 10 and Table 11 summarize the subgroup results on the indirect comparison of OBV/PTV/R + DSV with TVR + PEG + RBV in treatment-experienced patients with CHC of genotype 1b without cirrhosis. Where necessary, the data from the dossier were supplemented by the Institute's calculations. Indications of an effect modification were also shown for all 3 categories of fibrosis stage for the mental sum score of the SF-36 as well as for the characteristic "IL28B genotype" for the HCV-PRO and the physical sum score of the SF-36. However, all heterogeneity tests provided a p-value of ≥ 0.2 in the pairwise consideration of heterogeneity between the categories of neighbouring effect estimates. These subgroup results are therefore not presented further.

Table 10: Subgroups (continuous outcomes): METAVIR score – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, TVR + PEG + RBV or OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV

Characteristic Outcome Study Subgroup	TVR + PEG + RBV or OBV/PTV/R + DSV			OBV/PTV/R + DSV + RBV			Group difference
	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	Mean difference [95% CI]; p-value[b]
METAVIR score							
HCV-PRO (total score)							
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV							
PEARL-II							
F0 – F1	58	75.7 (ND)	3.1 (14.2)	61	79.0 (ND)	-0.2 (13.9)	2.31 [-2.38; 7.00]; 0.331
F2	19	78.5 (ND)	-1.2 (13.4)	13	71.1 (ND)	-6.4 (16.4)	6.81 [-3.96; 17.58]; 0.206
≥ F3	11	83.2 (ND)	-2.5 (7.4)	11	73.0 (ND)	-4.2 (16.4)	0.94 [-10.98; 12.86]; 0.870
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV							
MALACHITE-II							
F0 – F1	27	82.6 (ND)	-20.3 (19.9)	63	82.8 (ND)	0.8 (13)	-21.17 [-28.02; -14.33]; < 0.001
F2	9	87.2 (ND)	-19.4 (12.8)	15	76.0 (ND)	-3.2 (20.7)	-14.64 [-32.08; 2.81]; 0.096
≥ F3	3	81.8 (ND)	-1.0 (2.4)	4	84.0 (ND)	-18.0 (16.7)	15.50 [-6.35; 37.35]; 0.120
Adjusted indirect comparison[c]							
OBV/PTV/R + DSV vs. TVR + PEG + RBV							Interaction: p-value = 0.002
F0 – F2							23.69 [15.32; 32.06]; < 0.001[d] Hedges' g: 1.50 [0.96; 2.04][d]
F0 – F1							24.4 [14.82; 33.98]; < 0.001
F2							21.4 [4.21; 38.59]; 0.015
≥ F3							-15.3 [-34.99; 4.39]; 0.128

(continued)

Table 10: Subgroups (continuous outcomes): METAVIR score – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, TVR + PEG + RBV or OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV (continued)

Characteristic Outcome Study Subgroup	TVR + PEG + RBV or OBV/PTV/R + DSV			OBV/PTV/R + DSV + RBV			Group difference
	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	N[a]	Baseline values mean (SD)	Change at end of study mean (SD)	Mean difference [95% CI]; p-value[b]
SF-36 physical sum score							
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV							
PEARL-II							
F0 – F1	59	51.1 (ND)	-0.9 (6.6)	61	52.4 (ND)	-1.7 (5.6)	0.51 [-1.57; 2.58]; 0.629
F2	19	50.2 (ND)	0.5 (4.9)	13	52.6 (ND)	-4.1 (7.3)	3.70 [-0.13; 7.53]; 0.058
≥ F3	12	52.6 (ND)	-0.4 (3.9)	12	50.7 (ND)	-2.0 (7.3)	1.93 [-3.01; 6.87]; 0.426
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV							
MALACHITE-II							
F0 – F1	27	51.6 (ND)	-8.3 (8.7)	63	50.5 (ND)	1.0 (6.8)	-8.73 [-11.81; -5.66]; < 0.001
F2	9	51.2 (ND)	-9.4 (6.2)	15	47.3 (ND)	0.3 (8.0)	-8.56 [-15.13; -2.00]; 0.013
≥ F3	3	50.0 (ND)	-1.5 (3.5)	4	48.8 (ND)	-3.4 (8.5)	2.60 [-9.73; 14.93]; 0.590
Adjusted indirect comparison[c]:							
OBV/PTV/R + DSV vs. TVR + PEG + RBV							Interaction: p-value = 0.077
F0 – F2							11.17 [7.47; 14.87]; < 0.001[d] Hedges' g: 1.60 [0.87; 2.33][d]
F0 – F1							10.1 [5.81; 14.39]; < 0.001
F2							14.3 [6.97; 21.63]; < 0.001
≥ F3							-0.3 [-10.66; 10.06]; 0.955

(continued)

Table 10: Subgroups (continuous outcomes): METAVIR score – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, TVR + PEG + RBV or OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV (continued)

a: Number of patients in the ITT population for whom values at the beginning and the end of the study were available.
b: 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 covariable and the treatment arm as factor.
c: Adjusted indirect comparison according to Bucher [6], based on the mean differences of the individual studies that were not adjusted with the baseline value.
d: Institute's calculation.

CHC: chronic hepatitis C; CI: confidence interval; DSV: dasabuvir; HCV-PRO: hepatitis C virus patient-reported outcomes; ITT: intention to treat; 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; vs.: versus

Table 11: Subgroups (continuous outcomes): IL28B genotype – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, TVR + PEG + RBV or OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV

Characteristic **Outcome** **Study** **Subgroup**	**TVR + PEG + RBV or OBV/PTV/R + DSV**			**OBV/PTV/R + DSV + RBV**			**Group difference**
	N[a]	**Baseline values mean (SD)**	**Change at end of study mean (SD)**	**N[a]**	**Baseline values mean (SD)**	**Change at end of study mean (SD)**	**Mean difference [95% CI]; p-value[b]**
IL28B genotype							
EQ-5D VAS							
OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV							
PEARL-II							
CC	7	71.4 (ND)	3.6 (8.0)	10	80.1 (ND)	-2.6 (9.3)	4.46 [-5.53; 14.46]; 0.354
CT	64	79.2 (ND)	3.9 (13.3)	54	78.8 (ND)	-0.1 (13.3)	4.13 [-0.38; 8.64]; 0.073
TT	20	81.5 (ND)	1.7 (9.3)	22	80.3 (ND)	0.8 (11.3)	1.11 [-5.13; 7.36]; 0.720
TVR + PEG + RBV vs. OBV/PTV/R + DSV + RBV							
MALACHITE-II							
CC	3	76.7 (ND)	3.3 (2.9)	5	86.0 (ND)	0.0 (7.1)	1.59 [-8.08; 11.27]; 0.690
CT	27	84.3 (ND)	-11.7 (19.9)	51	83.7 (ND)	3.8 (16.4)	-15.12 [-22.13; -8.11]; < 0.001
TT	9	78.9 (ND)	-6.2 (16.3)	26	79.7 (ND)	0.3 (16.5)	-6.63 [-19.74; 6.47]; 0.310
Adjusted indirect comparison[c]:							
OBV/PTV/R + DSV vs. TVR + PEG + RBV							Interaction: p-value = 0.075
CC and TT							4.61 [-3.93; 13.15]; 0.290
CC							2.9 [-7.95; 13.75]; 0.600
TT							7.4 [-6.46; 21.26]; 0.296
CT							19.5 [9.53; 29.47]; < 0.001 Hedges' g[d]: 1.17 [0.56; 1.78]

(continued)

Table 11: Subgroups (continuous outcomes): IL28B genotype – RCT, indirect comparison: treatment-experienced patients with CHC genotype 1b without cirrhosis, TVR + PEG + RBV or OBV/PTV/R + DSV vs. OBV/PTV/R + DSV + RBV (continued)

a: Number of patients in the ITT population for whom values at the beginning and the end of the study were available.
b: 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 covariable and the treatment arm as factor.
c: Adjusted indirect comparison according to Bucher [6], based on the mean differences of the individual studies that were not adjusted with the baseline value.
d: Institute's calculation.

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; ITT: intention to treat; 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

Morbidity

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

The indirect comparison showed an indication of an effect modification by the characteristic "IL28B genotype" for the outcome "health status". There was no important heterogeneity for the 2 genotypes CC and TT (interaction test $p \geq 0.2$). Both genotypes were therefore considered as one subgroup.

The indirect comparison showed no statistically significant difference between the treatments for the subgroup of patients with IL28B genotype CC or TT. 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 in comparison with TVR + PEG + RBV for patients with the genotypes CC or TT. An added benefit of OBV/PTV/R + DSV is therefore not proven for this subgroup.

There was a statistically significant difference in favour of OBV/PTV/R + DSV for the subgroup of patients with IL28B genotype CT. The SMD in the form of Hedges' g was calculated to check the relevance of this effect. The 95% CI was 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 added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV in the subgroup of patients with IL28B genotype CT.

Health-related quality of life (under treatment)

SF-36, physical sum score

The indirect comparison showed an indication of an effect modification by the characteristic "fibrosis stage" expressed with the METAVIR score for the physical sum score of the SF-36. There was no important heterogeneity for patients with the scores F0-F1 and F2 (interaction test $p \geq 0.2$). These patients were therefore considered as one subgroup.

There was a statistically significant difference in favour of OBV/PTV/R + DSV for patients with a score of F0-F2. The SMD in the form of Hedges' g was calculated to check the relevance of this effect. The 95% CI was 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 added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV in patients with a METAVIR score of F0-F2.

There was no statistically significant difference between the treatments for patients with a METAVIR score of ≥ F3. Since only a hint of an added benefit could have been derived already in the total population, there is no hint of an added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV. An added benefit of OBV/PTV/R + DSV is therefore not proven for these patients.

HCV-PRO

The indirect comparison showed proof of an effect modification by the characteristic "fibrosis stage" expressed with the METAVIR score for the HCV-PRO. There was no important heterogeneity for patients with the scores F0-F1 and F2 (interaction test $p \geq 0.2$). These patients were therefore considered as one subgroup.

There was a statistically significant difference in favour of OBV/PTV/R + DSV for patients with a METAVIR score of F0-F2. The SMD in the form of Hedges' g was calculated to check the relevance of this effect. The 95% CI was 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 added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV in patients with a METAVIR score of F0-F2.

There was no statistically significant difference between the treatments for patients with a METAVIR score of ≥ F3. This resulted in no hint of added benefit of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV. An added benefit of OBV/PTV/R + DSV is therefore not proven for these patients.

Adverse events

There were no subgroup analyses on the survival time analyses for the outcome "SAEs". For the outcome "treatment discontinuation due to AEs", the company presented the result of an interaction test only for the characteristic "sex".

2.1.3 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 [7].

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.

2.1.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.1.2 resulted in 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 (under treatment)” 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 12).

Table 12: Extent of added benefit at outcome level: treatment-experienced 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** **Effect estimate [95% CI][a]** **p-value[a]** **probability[b]**	**Derivation of extent[c]**
Mortality			
All-cause mortality		NC[d]	Lesser benefit/added benefit not proven
Morbidity			
Hepatocellular carcinoma, assessed with the surrogate SVR 12		RR: 1.52 [1.21; 1.89] p < 0.001 probability: "hint"	Outcome category: severe/serious symptoms/late complications added benefit, extent: "non-quantifiable"
Health status using the EQ-5D VAS		MD: 15.4 [7.72; 23.08] p < 0.001 Hedges' g: 0.99 [0.5; 1.48]	
IL28B genotype	CC/TT	MD: 4.61 [-3.93; 13.15] p = 0.290	Lesser benefit/added benefit not proven
	CT	MD: 19.5 [9.53; 29.47] p < 0.001 Hedges' g: 1.17 [0.56; 1.78] 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		MD: 10.20 [6.75; 13.65] p < 0.001 Hedges' g: 1.42 [0.91; 1.92]	
Fibrosis stage	METAVIR F0-F2	MD: 11.17 [7.47; 14.87] p < 0.001 Hedges' g: 1.60 [0.87; 2.33] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
	METAVIR ≥ F3	MD: -0.3 [-10.66; 10.06] p = 0.955	Lesser benefit/added benefit not proven
Mental sum score		Responder analysis: RR: 2.36 [1.51; 3.69] RR[e]: 0.42 [0.27; 0.66] p < 0.001 probability: "hint"	Outcome category: health-related quality of life CI_u < 0.75 added benefit, extent: "major"

(continued)

Table 12: Extent of added benefit at outcome level: treatment-experienced 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** **Effect estimate [95% CI][a]** **p-value[a]** **probability[b]**	**Derivation of extent[c]**
HCV-PRO			
Fibrosis stage	METAVIR F0-F2	MD: 23.69 [15.32; 32.06] p < 0.001 Hedges' g: 1.50 [0.96; 2.04] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
	METAVIR ≥ F3	MD: -15.3 [-34.99; 4.39] p = 0.128	Lesser benefit/added benefit not proven
Adverse events			
SAEs		HR: 0.11 [0.01; 2.01] p = 0.135	Greater/lesser harm not proven
Treatment discontinuation due to AEs		RR: 0.01 [0.00; 0.92] p = 0.046	Outcome category: non-serious/non-severe AEs $0.90 < CI_u < 1.00$ Greater/lesser harm not proven

a: Adjusted indirect comparison according to Bucher [6].
b: Probability given if statistically significant differences are present. Decision based on the lower 95% CI limit of Hedges' g in continuous outcomes.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: No death occurred in the OBV/PTV/R + DSV arm of the PEARL-II study or in the TVR + PEG + RBV arm of the MALACHITE-II study.
e: Institute's calculation: reversed direction of effect to enable direct use of limits to derive extent of added benefit.

AE: adverse event; CHC: chronic hepatitis C; CI: confidence interval; CI_u: upper limit of confidence interval; DSV: dasabuvir; EQ-5D: European Quality of Life-5 Dimensions; HCV-PRO: hepatitis C virus patient-reported outcomes; MD: mean difference; NC: not calculable; 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

2.1.3.2 Overall conclusion on added benefit

Table 13 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 13: Positive and negative effects from the assessment of OBV/PTV/R + DSV in comparison with TVR + PEG + RBV (treatment-experienced CHC genotype 1b patients without cirrhosis)

Positive effects	**Negative effects**
Serious/severe symptoms/late complications: ▪ hepatocellular carcinoma, assessed with the surrogate SVR 12: hint of an added benefit – extent: non-quantifiable	–
non-serious/non-severe symptoms/late complications: ▪ Health status using the EQ-5D VAS ▫ IL28B genotype CT: hint of an added benefit, extent: “non-quantifiable”	
Health-related quality of life: ▪ SF-36 ▫ physical sum score: METAVIR score F0-F2: hint of an added benefit, extent: “non-quantifiable” ▫ mental sum score: hint of an added benefit, extent: “major” ▪ HCV-PRO: ▫ METAVIR score F0-F2: hint of an added benefit, extent: “non-quantifiable”	
CHC: chronic hepatitis C; DSV: dasabuvir; EQ-5D: European Quality of Life-5 Dimensions; HCV: hepatitis C virus; 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; VAS: visual analogue scale	

Overall, only positive effects remain in the outcome categories “serious/severe symptoms or late complications”, “non-serious/non-severe symptoms or late complications” and “health-related quality of life”. In each case, there were hints of an added benefit or lesser harm. The extent was non-quantifiable in nearly all cases with the exception of the outcome “SF-36 (mental sum score)”, where a hint of major added benefit was shown. It should be noted that both the PEARL-II study and the MALACHITE-II study were unblinded, which led to a high risk of bias for subjectively patient-reported outcomes (see Section 2.1.2.2). This resulted in an increased uncertainty regarding extent and probability of the added benefit for these outcomes.

All outcomes considered in this research question were assessed using indirect comparisons without the possibility to check the assumptions of homogeneity and consistency. For this reason alone no more than hints of an added benefit can be derived. In the overall consideration of the added benefit it therefore seems inappropriate to derive a hint of major added benefit only based on an outcome that is subject to high uncertainty such as the SF-36.

In summary, there is a hint of a non-quantifiable added benefit of ombitasvir/paritaprevir/ritonavir and dasabuvir versus the ACT for treatment-experienced patients with CHC genotype 1b without cirrhosis.

Table 14: Ombitasvir/paritaprevir/ritonavir and dasabuvir – extent and probability of the added benefit for treatment-experienced patients with CHC genotype 1b without cirrhosis

Therapeutic indication	**ACT**[a]	**Extent and probability of 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)**	Hint 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.

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

2.1.4 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. 21 April 2015 [accessed: 21 May 2015]. URL: http://clinicaltrials.gov/ct2/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): trial protocol (Hungary) [online]. In: EU Clinical Trial Register. [Accessed: 21 May 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-003738-18/HU.

PEARL-II

AbbVie. A study to evaluate the safety and effect of the experimental drugs ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 in people with chronic hepatitis C (PEARL-II): study results [online]. In: ClinicalTrials.gov. 23 December 2014 [accessed: 22 June 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01674725.

AbbVie. A randomized, open-label, multicenter study to evaluate the safety and antiviral activity of the combination of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 with and without ribavirin in treatment-experienced subjects with genotype 1b chronic hepatitis C virus (HCV) infection (PEARL–II): study M13-389; clinical study report (primary analysis) [unpublished]. 2014.

AbbVie. A study to evaluate the safety and effect of the experimental drugs ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 in people with chronic hepatitis C (PEARL-II): full text view [online]. In: ClinicalTrials.gov. 23 December 2014 [accessed: 20 May 2015]. URL: http://clinicaltrials.gov/ct2/show/NCT01674725.

AbbVie Deutschland. A randomized, open-label, multicenter study to evaluate the safety and antiviral activity of the combination of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 with and without ribavirin in treatment-experienced subjects with genotype 1b chronic hepatitis C virus (HCV) infection (PEARL–II): trial protocol (Sweden) [online]. In: EU Clinical Trial Register. [accessed: 21 May 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-005740-95/SE.

2.2 Research questions 1 to 3 of the dossier assessment: Assessment of the survival time analyses for AEs

In its comment, the company subsequently submitted survival time analyses for several outcomes of the category "AEs" for research questions 1 to 3 of the dossier assessment on dasabuvir and OBV/PTV/R [3,4]. This was a reaction to the statement in the dossier assessment that consideration of the naive rates and the incidence density ratios (IDRs) is inadequate, or only adequate under certain preconditions, because of the markedly different observation periods for AEs. Survival time analyses can be considered to be more informative in case of different observation periods. The company provided survival time analyses for the following outcomes:

- overall rate AEs
- overall rate of SAEs
- anaemia (MedDRA PT)
- rash (PT)

The company's choice was not accepted. The overall rate of AEs was not included because events that are not patient-relevant are also shown in the operationalization of the AEs. Furthermore, the company included the PTs "anaemia" and "rash" because it considered them to be characteristic for telaprevir-containing triple therapy and because the SPC of telaprevir contains special warnings for them. Since it is unclear whether these 2 PTs represent a comprehensive choice of relevant AEs in the research questions investigated, they were not included in the assessment.

Hence only the overall rates of SAEs for all research questions considered were included in the present assessment.

The risk of bias was rated as low both at study level and at outcome level. However, since there was only one relevant study for each of the 3 research questions, no more than indications of an added benefit can be derived for each of the research questions considered.

Table 15 summarizes the results of the survival time analyses conducted by the company on the outcome "SAEs". The corresponding Kaplan-Meier curves for treatment-naive patients with CHC genotype 1a and 1b without cirrhosis are presented in Figure 1 and Figure 2. No figure was available for treatment-experienced patients with genotype 1a without cirrhosis from the MALACHITE-II study because no events occurred in this study population.

Table 15: Results (SAEs) – RCT, direct comparison: treatment-naive patients with CHC genotype 1a and 1b and 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)[a]**		**TVR + PEG + RBV**		**OBV/PTV/R + DSV (+ RBV)[a] vs. TVR + PEG + RBV**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**HR [95% CI]; p-value[b]**
Treatment-naive patients with CHC genotype 1a without cirrhosis					
MALACHITE-I					
Adverse events					
SAEs	69	0 (0)	34	3 (8.8)	NC[c] 0.011
Treatment-naive patients with CHC genotype 1b without cirrhosis					
MALACHITE-I					
Adverse events					
SAEs	83	0 (0)	41	6 (14.6)	NC[c] 0.003
Treatment-experienced patients with CHC genotype 1a without cirrhosis					
MALACHITE-II					
Adverse events					
SAEs	19	0 (0)	7	0 (0)	NC[c]

a: In compliance with the approval, ribavirin is only administered in patients with CHC genotype 1a.
b: Log-rank test.
c: Hazard ratio not calculable because of at least one cell with 0 events.

CHC: chronic hepatitis C; CI: confidence interval; DSV: dasabuvir; HR: hazard ratio; N: number of patients analysed; n: number of patients with event; NC: not calculable; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; TVR: telaprevir; vs.: versus

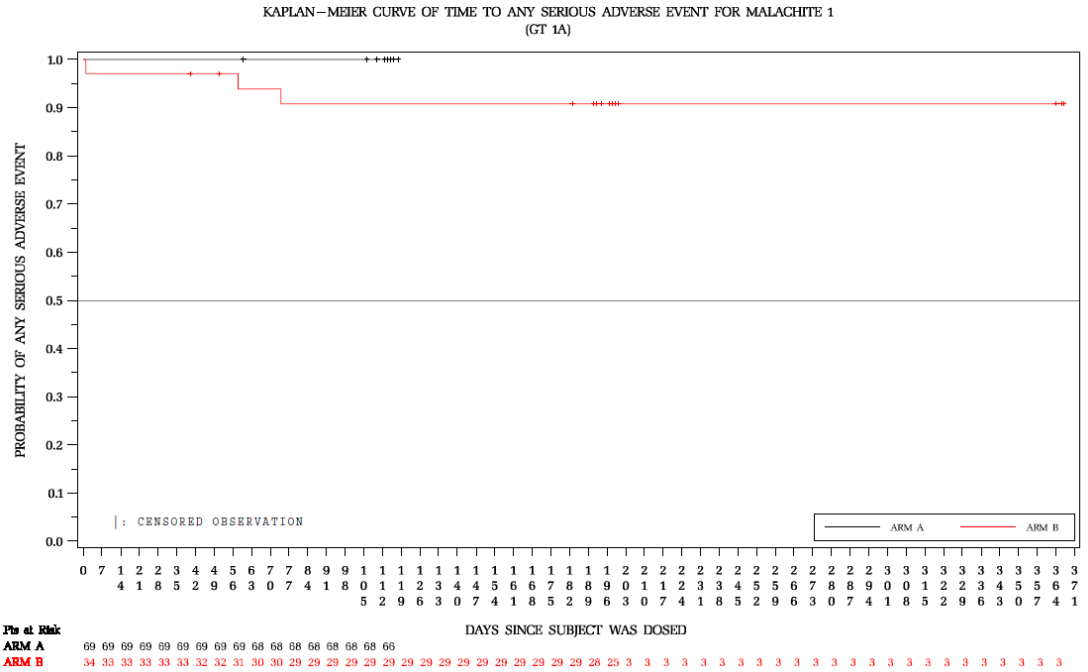

Figure 1: Kaplan-Meier curve for the overall rate of SAEs in treatment-naive patients with CHC genotype 1a without cirrhosis from the MALACHITE-I study (arm A: OBV/PTV/R + DSV + RBV, arm B: TVR + PEG + RBV)

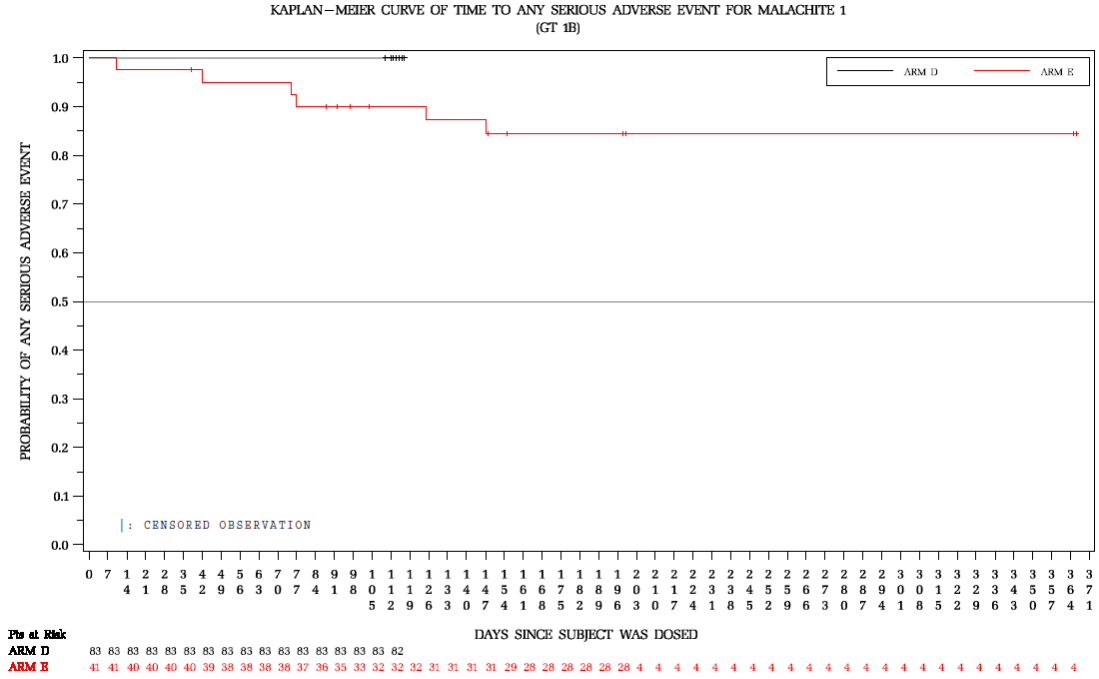

Figure 2: Kaplan-Meier curve for the overall rate of SAEs in treatment-naive patients with CHC genotype 1b without cirrhosis from the MALACHITE-I study (arm D: OBV/PTV/R + DSV, arm E: TVR + PEG + RBV)

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

The survival time analysis showed a statistically significant difference in favour of OBV/PTV/R + DSV + RBV for treatment-naive patients with CHC genotype 1a without cirrhosis. This resulted in an indication of an added benefit of OBV/PTV/R + DSV + RBV versus the ACT TVR + PEG + RBV for the outcome "SAEs".

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

The survival time analysis showed a statistically significant difference in favour of OBV/PTV/R + DSV for treatment-naive patients with CHC genotype 1b without cirrhosis. This resulted in an indication of an added benefit of OBV/PTV/R + DSV versus the ACT TVR + PEG + RBV for the outcome "SAEs".

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

In the MALACHITE-II study, no SAEs occurred in the relevant subpopulation of patients with CHC genotype 1a. Hence there was no hint of an added benefit of OBV/PTV/R + DSV + RBV. An added benefit of OBV/PTV/R+ DSV + RBV versus the ACT TVR + PEG + RBV is therefore not proven for the outcome "SAEs".

Assessment of the added benefit under consideration of the data subsequently submitted

Table 16 presents the extent of added benefit for the outcome "SAEs" under consideration of the survival time analyses subsequently submitted in the company's comment.

Table 16: Extent of added benefit at outcome level for the outcome "SAEs": treatment-naive patients with CHC genotype 1a or 1b without cirrhosis and 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]
Adverse events		
Treatment-naive patients with CHC genotype 1a without cirrhosis		
SAEs	0% vs. 8.8% HR: NC[c] p = 0.011[d] probability: "indication"	Outcome category: severe/serious AEs lesser harm, extent: "non-quantifiable"[e]
Treatment-naive patients with CHC genotype 1b without cirrhosis		
SAEs	0% vs. 14.6% HR: NC[c] p = 0.003[d] probability: "indication"	Outcome category: severe/serious AEs lesser harm, extent: "non-quantifiable"[e]
Treatment-experienced patients with CHC genotype 1a without cirrhosis		
SAEs	0% vs. 0% HR: NC[c]	Lesser benefit/added benefit not proven

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Hazard ratio not calculable because of at least one cell with 0 events.
d: Log-rank test.
e: Extent non-quantifiable because effect size not calculable (see footnote c).
CHC: chronic hepatitis C; CI: confidence interval; CI_u: upper limit of confidence interval; DSV: dasabuvir; HR: hazard ratio; NC: not calculable; OBV: ombitasvir; PEG: pegylated interferon; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; SAE: serious adverse event; TVR: telaprevir; vs.: versus

2.3 Changes versus the dossier assessment and consequences for the assessment of the added benefit

Changes from adjusted indirect comparison on treatment-experienced patients with CHC genotype 1b without cirrhosis

In the original dossier assessments on OBV/PTV/R and dasabuvir no added benefit had been derived for treatment-experienced patients with CHC genotype 1b without cirrhosis [1,2].

Subsequent submission of the adjusted indirect comparison now resulted in a hint of a non-quantifiable added benefit for this research question.

Changes from survival time analyses on adverse events for research questions 1 to 3 of the dossier assessment

For the outcome "SAEs", a hint of lesser harm had been derived only in research question 2 (treatment-naive patients with CHC genotype 1b without cirrhosis) in the dossier assessments on dasabuvir and OBV/PTV/R [1,2]. This analysis of the naive rates was considered to have a high risk of bias due to the different observation periods in the study arms. The survival time analyses of the company now provide an analysis on SAEs with a low risk of bias.

As shown in Table 16, there was an indication of lesser harm of OBV/PTV/R and dasabuvir for the patient groups of treatment-naive patients with CHC genotype 1a or 1b without cirrhosis, the extent of which was non-quantifiable because no hazard ratio including 95% CI could be calculated in either case. Hence in summary, the positive and negative effects for the 3 research questions have changed as follows:

- Research question 1, treatment-naive patients with CHC genotype 1a without cirrhosis: additionally, an indication of lesser harm for the outcome "SAEs", extent non-quantifiable
- Research question 2, treatment-naive patients with CHC genotype 1b without cirrhosis: an indication instead of a hint of lesser harm for the outcome "SAEs", extent non-quantifiable
- Research question 3, treatment-experienced patients with CHC genotype 1a without cirrhosis: no change in comparison with the original dossier assessment

In the original dossier assessment, the overall assessment of the effects resulted in an indication of a non-quantifiable added benefit in all 3 research questions. The assessment of the data subsequently submitted by the company resulted also in indications of a non-quantifiable added benefit for 2 of the 3 research questions. No new statistically significant effects were shown for the third research question. Hence overall, an indication of a non-quantifiable added benefit remains for each of the research questions 1 to 3 of the dossier assessment.

Table 17 shows the result of the assessment for the research questions investigated in the present addendum under consideration of the data subsequently submitted by the company in the comment.

Table 17: Ombitasvir/paritaprevir/ritonavir and dasabuvir – 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)**	Hint of non-quantifiable added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee

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

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dasabuvir: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-03 [online]. 29 April 2015 [accessed: 16 June 2015]. (IQWiG-Berichte; Volume 296). URL: https://www.iqwig.de/download/A15-03_Dasabuvir_Nutzenbewertung-35a-SGB-V.pdf.

2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ombitasvir/Praitaprevir/Ritonavir: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-04 [online]. 29 April 2015 [accessed: 16 June 2015]. (IQWiG-Berichte; Volume 297). URL: https://www.iqwig.de/download/A15-04_Ombitasvir-Paritaprevir-Ritonavir_Nutzenbewertung-35a-SGB-V.pdf.

3. AbbVie Deutschland. Stellungnahme zum IQWiG-Bericht Nr. 296: Dasabuvir; Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-03 [online]. URL: [Soon available under https://www.g-ba.de/informationen/nutzenbewertung/159/#tab/stellungnahmeverfahren in the document "Zusammenfassende Dokumentation"].

4. AbbVie Deutschland. Stellungnahme zum IQWiG-Bericht Nr. 296: Ombitasvir/Pritaprevir/Ritonavir; Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-03 [online]. URL: [Soon available under https://www.g-ba.de/informationen/nutzenbewertung/159/#tab/stellungnahmeverfahren in the document "Zusammenfassende Dokumentation"].

5. 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.

6. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997; 50(6): 683-691.

7. 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.

Appendix A – Kaplan-Meier curves for the overall rate of SAEs in the indirect comparison of OBV/PTV/R + DSV with TVR + PEG + RBV

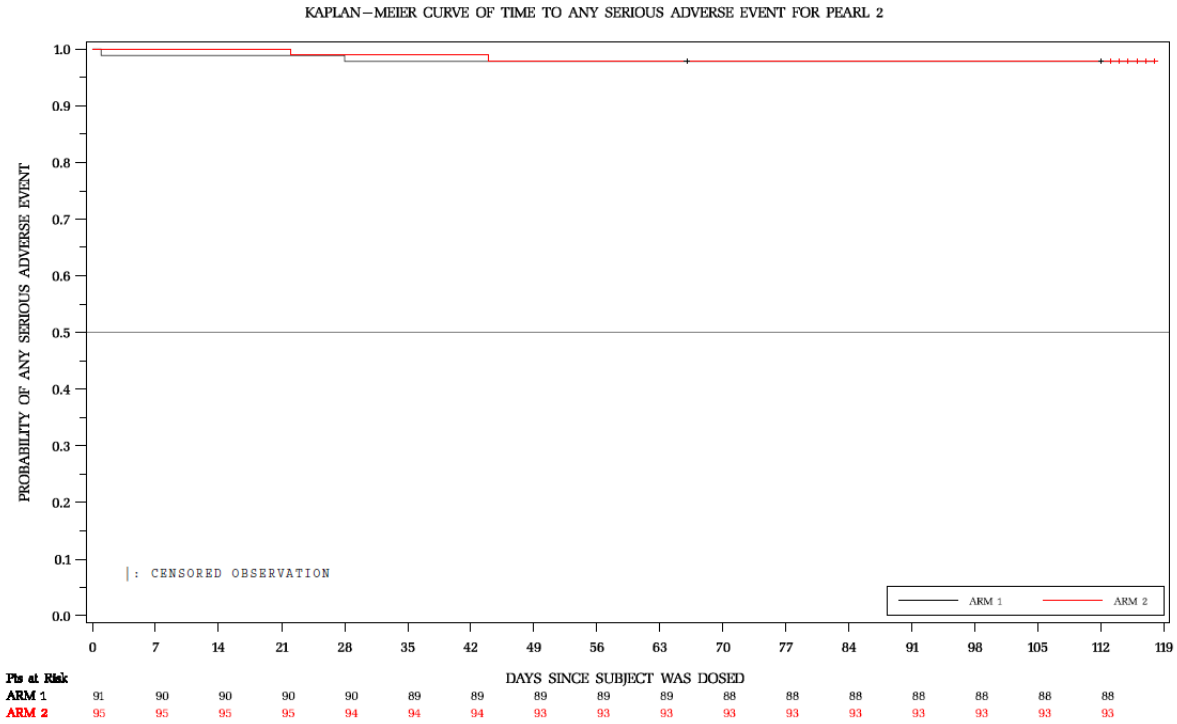

Figure 3: Kaplan-Meier curve for the overall rate of SAEs in treatment-experienced patients with CHC genotype 1b without cirrhosis from the PEARL-II study (arm 1: OBV/PTV/R + DSV + RBV; arm 2: OBV/PTV/R + DSV)

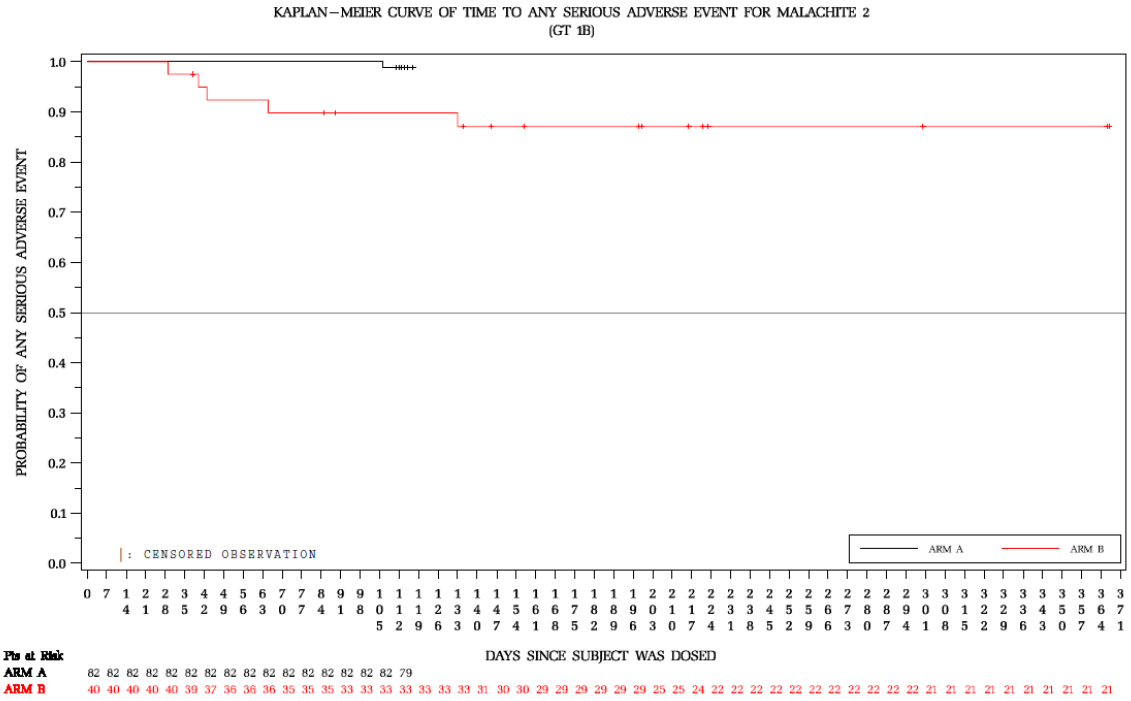

Figure 4: Kaplan-Meier curve for the overall rate of SAEs in treatment-experienced patients with CHC genotype 1b without cirrhosis from the MALACHITE-II study (arm A: OBV/PTV/R + DSV, arm B: TVR + PEG + RBV)