IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A11-17

Boceprevir –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Boceprevir – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status:29.11.2011). In the present extract, references to Sections 2.7 onwards relate to the full version of the assessment report (hereinafter called the "full dossier assessment"). 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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Institute for Quality and Efficiency in Health Care
Dillenburger Str. 27
51105 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:

- Henning Schulze-Bergkamen, National Centre for Tumour Diseases (NCT), Heidelberg University Hospital

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. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect the advisor's opinion.

IQWiG employees involved in the dossier assessment:[2]

- Stefanie Reken
- Gertrud Egger
- Elke Hausner
- Thomas Kaiser
- Stefan K. Lhachimi
- Yvonne-Beatrice Schüler
- Anja Schwalm
- Guido Skipka
- Volker Vervölgyi

Keywords: boceprevir, hepatitis C viral infection, benefit assessment

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

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Abbreviation	Meaning
AE	adverse event
BOC	boceprevir
cHCV	chronic hepatitis C virus
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
IFN	interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PegIFN	pegylated (peg-)interferon-alfa
RBV	ribavirin
RCT	randomized controlled trial
RGT	response-guided therapy
RNA	ribonucleic acid
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SVR	sustained virological response
TW	treatment week

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In its letter of 02.09.2011, the Federal Joint Committee (G-BA) commissioned IQWiG to perform a benefit assessment of the drug boceprevir in accordance with § 35a Social Code Book (SGB) V. This assessment was performed on the basis of a dossier of the pharmaceutical company.

Research question

The benefit assessment of boceprevir was in accordance with the approved therapeutic indications and with the following research questions:

1) In combination with peginterferon + ribavirin in the response-guided therapy (RGT) regimen versus
   - Peginterferon + ribavirin in treatment-naïve patients with chronic hepatitis C virus (cHCV) infection (genotype 1) without cirrhosis and
   - Peginterferon + ribavirin in treatment-experienced patients with cHCV infection (genotype 1) without cirrhosis.
2) In combination with peginterferon + ribavirin in the 48-week fixed duration treatment regimen (48TW) versus
   - Peginterferon + ribavirin in patients with cHCV infection (genotype 1) with cirrhosis and
   - Peginterferon + ribavirin in patients with cHCV infection (genotype 1) with null response to prior interferon- (IFN)-based therapy.

Results

There was a total of 2 relevant double-blind, randomized and active-controlled studies - SPRINT-2 and RESPOND-2. In the SPRINT-2 study, treatment with boceprevir + peginterferon + ribavirin was compared with treatment with peginterferon + ribavirin in treatment-naïve patients. In the RESPOND-2 study, boceprevir + peginterferon + ribavirin was compared with peginterferon + ribavirin in treatment-experienced patients. On the basis of these studies (direct comparison), data were available for 2 of the 4 subindications (hereinafter referred to as subpopulations) given above (treatment-naïve / without cirrhosis; treatment-experienced / without cirrhosis). No adequate data were presented for the subpopulations “patients with cirrhosis” and “patients with null response to prior IFN-based therapy”.

Both studies were approval studies for boceprevir. In so far as the data were available, the present assessment employed analyses which were predominantly restricted to patients treated in accordance with the current approval status of the drug.

The following results were found for the 4 subpopulations named above:

Subpopulation "treatment-naïve / without cirrhosis"

The SPRINT-2 study was the only study available for the assessment of the subpopulation "treatment-naïve / without cirrhosis". The risk of bias was low – both at study level and for individual outcomes. On the basis of the available evidence (one study), indications could be deduced from the data, e.g. for added benefit, .in so far as the informative value was not impaired by outcome-specific aspects.

Mortality

The result for all-cause mortality was not statistically significant. Thus, added benefit for this outcome has not been proven. However, the limited length of the study and the low rate of events are limitations which must be considered when interpreting this result.

Health-related quality of life

The dossier of the pharmaceutical company contained no evaluable data on health-related quality of life. Thus, added benefit for this outcome has not been proven.

Morbidity

Sustained virological response as a surrogate outcome for liver-related late complications

The outcome sustained virological response (SVR) was regarded as sufficiently valid to be regarded as a surrogate for the purpose of this benefit assessment for hepatocellular carcinoma [HCC], a patient-relevant outcome that was, however, not considered in the study included. There was a statistically significant difference in SVR, which was in favour of boceprevir. At outcome level, it must nevertheless be considered that SVR has not been formally validated as a surrogate and that the evaluation of "sufficient validity" is solely based on data from observational studies. However, this increased uncertainty is already reflected in the classification of the extent of added benefit (unquantifiable). Overall there is an indication of added benefit of boceprevir.

Adverse effects

The results for adverse events, serious adverse events, discontinuations due to adverse events, psychiatric events and infections were all not statistically significant. Greater harm for these outcomes is not proven. There was a statistically significant difference for the outcome anaemia, which was to the detriment of boceprevir. Thus, there is an indication of greater harm for the outcome anaemia; these events were almost exclusively non-serious.

Subpopulation "treatment-experienced / without cirrhosis"

The REPOND-2 study was the only study available for the assessment of the subpopulation "treatment-experienced / without cirrhosis". The risk of bias was low – both at study level and for individual outcomes. On the basis of the available evidence (one study), indications could

be deduced from the data, e.g. for added benefit, in so far as the informative value was not weakened by outcome-specific aspects.

Mortality

The result for all-cause mortality was not statistically significant. Thus, added benefit for this outcome has not been proven. However, the limited length of the study and the low rate of events are limitations which must be considered when interpreting this result.

Health-related quality of life

The dossier of the pharmaceutical company contained no evaluable data on health-related quality of life. Thus, added benefit for this outcome has not been proven.

Morbidity

Sustained virological response as a surrogate outcome for liver-related late complications

For the subpopulation "treatment-experienced / without cirrhosis" too, for the purpose of this benefit assessment the outcome SVR was regarded as sufficiently valid to be regarded as a surrogate for a patient-relevant outcome (HCC), which was, however, not considered in the study included. There was a statistically significant difference in SVR, which was in favour of boceprevir. At outcome level, it must nevertheless once again be considered that SVR has not been formally validated and that the evaluation of "sufficient validity" is solely based on data from observational studies. However, this increased uncertainty is already reflected in the classification of the extent of added benefit (unquantifiable). Overall there is an indication of added benefit of boceprevir.

Adverse effects

The results for adverse events, serious adverse events, discontinuations due to adverse events, psychiatric events, infections and anaemia were all not statistically significant. Greater harm for these outcomes has not been proven.

Subpopulation "with cirrhosis"

The pharmaceutical company presented no results for the subpopulation "patients with cirrhosis". Although the studies SPRINT-2 and RESPOND-2 also examined patients who exhibited cirrhosis at the start of the study, no separate results on cirrhosis were presented for any of the relevant outcomes. Moreover, the study SPRINT-2 found that for patients with cirrhosis, the observed effect estimate for SVR was to the detriment of boceprevir, necessitating separate consideration of this group of patients. In addition, the study pool was incomplete. There were no evaluable data. Added benefit has not been proven.

Subpopulation "with null response to prior IFN-based therapy"

The pharmaceutical company presented no data for the subpopulation "patients with null response to prior interferon-based therapy". Added benefit has not been proven.

Probability and extent of added benefit, patient groups with therapeutically-relevant added benefit

On the basis of the above results and bearing in mind the outcome categories and effect sizes, the probability and extent of added benefit of boceprevir is assessed as follows:

For treatment-naïve patients without cirrhosis, there is an indication of added benefit (extent unquantifiable) of boceprevir + peginterferon + ribavirin in comparison with peginterferon + ribavirin. There are both positive and negative results of the same certainty (indication of added benefit); the extent of added benefit was "unquantifiable" and the extent of greater harm was "considerable". As the extent of added benefit is unquantifiable, no final conclusion can be reached as to whether it might be meaningful to downgrade the extent of the added benefit. It nevertheless seems inappropriate to call the indication of added benefit with respect to a serious late complication (HCC) totally into doubt on the basis of the greater harm from non-serious adverse events (anaemia).

For therapy-experienced patients without cirrhosis, there is an indication of added benefit (extent unquantifiable) of boceprevir + peginterferon + ribavirin in comparison with peginterferon + ribavirin. This overall conclusion on the extent of the added benefit is based on the aggregation of the extents of added benefit at outcome level.

For patients with cirrhosis, added benefit of boceprevir + peginterferon + ribavirin in comparison with peginterferon + ribavirin has not been proven.

For patients with null response to prior therapy, added benefit of boceprevir + peginterferon + ribavirin in comparison with peginterferon + ribavirin has not been proven.

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The pharmaceutical company specifies peginterferon + ribavirin as the appropriate comparator therapy for boceprevir for the whole therapeutic indication "chronic hepatitis C, genotype 1". Thus, it follows the specification of the G-BA. For this reason, the appropriate comparator therapy for the benefit assessment of boceprevir was as specified by both the G-BA and the pharmaceutical company.

With respect to the splitting of the overall therapeutic indication "chronic hepatitis C, genotype 1" by cirrhosis status and null response to prior therapy (performed in addition to splitting by treatment-experienced / treatment-naïve patients), the assessment differs considerably from the approach used (i.e. patient groups defined) by the pharmaceutical company. This is justified by the approval status of boceprevir. According to the approval status of boceprevir, the overall therapeutic indication was split into 4 subindications ("subpopulations"), which were then assessed separately (see Table 1).

Table 1: Subpopulations, treatment regimens and appropriate comparator therapy

	Therapeutic indication of boceprevir (in combination with PegIFN/RBV), split into disease entities / subpopulations	**Approved treatment regimen[a]**	**Appropriate comparator therapy**
1	Chronic HCV infection, genotype 1, treatment-naïve patients without cirrhosis	Response-guided therapy regimen	PegIFN in combination with RBV
2	Chronic HCV infection, genotype 1, treatment-experienced patients without cirrhosis	Response-guided therapy regimen	PegIFN in combination with RBV
3	Chronic HCV infection genotype 1, patients with cirrhosis	Fixed duration treatment regimen	PegIFN in combination with RBV
4	Chronic HCV infection genotype 1, patients with null response to prior interferon-based therapy	Fixed duration treatment regimen	PegIFN in combination with RBV
a: Information according to the approval text in accordance with the summary of product characteristics; for information on the treatment regimens in the approval studies, see Section 2.7.2.4.1 of the full dossier assessment. HCV: hepatitis C virus, PegIFN: pegylated (peg-)interferon-alfa, RBV: ribavirin.			

The assessment was based on patient-relevant outcomes. However, one surrogate outcome was used for the assessment of liver-related late complications. The assessment solely included randomized controlled trials (RCTs) with a direct comparator.

Further information on the research question can be found in Module 3, Section 3.1 and Module 4 Section 4.2.1 of the dossier, as well as in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool for the assessment was compiled using the following information and in the following steps:

- Studies performed by the pharmaceutical company on boceprevir in cHCV infection, genotype 1, which had been completed by 01 June 2011;
- Results of a search for studies on boceprevir in trial registries, performed by the pharmaceutical company on 14 July 2011;
- Own searches performed by the Institute and a secondary selection of the information retrieved, using inclusion criteria which deviated considerably from those of the pharmaceutical company with respect to the test intervention. The result of this inspection showed deviations from the study pool in the dossier of the pharmaceutical company for 1 of the 4 subpopulations (one additional study, P05685, was identified for patients with cirrhosis). However, this subpopulation was not presented separately in the dossier, so that

it cannot be considered separately below. Thus, the deviation identified by the Institute with regard to the study pool was not relevant for the further assessment.

Thus, the resulting study pool used for the assessment corresponded to that of the pharmaceutical company. Nevertheless, the individual studies were not used for all subpopulations, as is explained in more detail in Section 2.3.1 below.

Further information on the inclusion criteria for studies in the present benefit assessment and on the method of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, as well as in Sections 2.7.2.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.1 Studies included

With respect to the splitting of the overall therapeutic indication "cHCV, genotype 1" by cirrhosis status and null response to prior therapy (performed in addition to splitting by treatment-experienced / treatment-naïve patients), the assessment differs considerably from the approach used by the pharmaceutical company. This is justified by the fact that the approval regulations recommend different treatment regimens for specific patient groups (see Section 2.2 for an overview of the subpopulations and 2.7.2.1 of the full dossier assessment for a detailed justification of the separate assessment of the given subpopulations). Thus, data were available for only some of the research questions. The available studies did not always investigate the required treatment regimens and separate data were not always available for each subpopulation.

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

Table 2: Study pool

Subpopulation Study	Study Category		
	Study for the approval of the assessed drug (yes/no)	Sponsored Study[a] (yes/no)	Third Party Study (yes/no)
Treatment-naïve patients without cirrhosis			
SPRINT-2 (P05216)	yes	yes	no
Treatment-experienced patients without cirrhosis			
RESPOND-2 (P05101)	yes	yes	no
Patients with cirrhosis			
	No adequate data submitted		
Patients with null response to prior interferon-based therapy			
	No study submitted		
a: Study for which the pharmaceutical company was the sponsor, or in which the company was otherwise financially involved.			

For the assessment of boceprevir (BOC) in combination with peginterferon and ribavirin (PegIFN/RBV) in treatment-naïve patients with cHCV (genotype 1) and without cirrhosis,

one RCT (SPRINT-2) was submitted with the drug to be assessed, in a direct comparison with peginterferon alfa + ribavirin.

For the assessment of BOC in combination with PegIFN/RBV in treatment-experienced patients with cHCV (genotype 1) and without cirrhosis, one RCT (RESPOND-2) was submitted with the drug to be assessed, in a direct comparison with PegIFN/RBV.

For the assessment of BOC in combination with PegIFN/RBV in patients with cHCV (genotype 1) and with cirrhosis, and with a direct comparison between PegIFN/RBV and the drug to be assessed, no adequate data were presented; there were no separate analyses for this subpopulation and the study pool was incomplete.

For the assessment of BOC in combination with PegIFN/RBV in patients with cHCV (genotype 1) with null response to prior interferon-based therapy, and with a direct comparison to PegIFN/RBV, no studies were submitted.

Section 2.6 contains a list of data sources specified by the pharmaceutical company for the included studies.

Further information on the result of the information retrieval and the consequent study pool can be found in Module 4 Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Section 2.7.2.3.1 of the full dossier assessment.

2.3.2 Study characteristics

Table 3 and Table 4 describe the studies for the benefit assessment. Both studies are approval studies for boceprevir.

As already described in Section 2.3.1 on the study pool, the pharmaceutical company submitted data for 2 relevant subpopulations: treatment-naïve patients without cirrhosis (SPRINT-2) and treatment-experienced patients without cirrhosis (RESPOND-2).

In accordance with the approval status, the following therapy regimens should be employed for boceprevir for these subpopulations without cirrhosis:

For **treatment-naïve patients without cirrhosis,** a treatment regimen is intended that was examined in the 3-arm approval study SPRINT-2 as response-guided therapy (RGT). On the basis of the serum concentrations of HCV RNA, the patients were split into early responders and late responders. For early responders, the overall treatment duration was shortened. It was assumed that the influence of the differences in treatment duration between the RGT regimen that is in accordance with the approval status and the regimen applied in SPRINT-2 in late responders were negligible, so that data from the RGT arm were used for the present assessment.

According to the approval text, an RGT regimen is intended for **treatment-experienced patients without cirrhosis**. Here too, differences between the treatment regimen that is in

accordance with the approval status and the regimen applied in the approval study must be considered. In contrast to the RGT arm of RESPOND-2, the approval text does not specify that the treatment of early responders should be shortened. Nevertheless, this appears to be the more appropriate comparison for the study arm with a fixed duration treatment regimen. (In the "fixed dose" treatment regimen, boceprevir was administered to all patients for 12 weeks longer than specified in the approval status. As a consequence shortening the treatment duration in early responders, the administration of boceprevir in accordance with approval was 8 weeks shorter than in the approval study for a fraction of the patients). In this case, the potential influence of the shorter administration of boceprevir (with the same overall duration of therapy as in the approval) on the transferability of results is regarded as being acceptable and the RGT arm of RESPOND-2 was used for this assessment.

Please refer to Section 2.7.2.4.1 of the full dossier assessment for a detailed justification of the use of each study arm in the benefit assessment performed by the Institute.

Table 3 shows the study characteristics including the treatment regimens that lie outside the approval for the subpopulations with usable data and were not considered. Table 4 shows the characteristics of the interventions for the treatment regimens that were in accordance with the approval.

Table 3: Characterization of the studies included

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Site and period of the study	Primary outcome; secondary outcomes*
Treatment-naïve patients without cirrhosis						
SPRINT-2 (P05216)	RCT, double blind, with double blind administration of boceprevir (BOC) or placebo (PLC) in combination with open-label administration of PegIFN and RBV	Treatment-naïve adult patients (≥ 18) with chronic hepatitis C, genotype 1; without PegIFN-based prior treatment	**Arm 1** PegIFN/RBV standard therapy (n = 364) **Arm 2**[b] BOC + PegIFN/RBVBOC response-guided therapy (RGT) (n = 368) **Arm 3**[c] BOC + PegIFN/RBV fixed duration treatment regimen (n = 367)	Treatment: 28 or 48 weeks Follow-up: 24 weeks	Argentina, Belgium, Germany, France, Italy, Canada, Netherlands, Puerto Rico, Spain, USA. August 2008 –May 2010	Primary: Sustained virological response (SVR), defined as no detectable HCV-RNA in the blood 24 weeks after the end of therapy. Secondary: all-cause mortality, health-related quality of life, adverse events, serious adverse events, discontinuation due to adverse events, adverse events related to anaemia, adverse events related to psychiatric side effects, adverse events related to infections.
Treatment-experienced patients without cirrhosis						
RESPOND-2 (P05101)	RCT, double blind, parallel, with double blind administration of BOC or PLC in combination with open-label administration of PegIFN and RBV	Adult patients (>18 years) with chronic hepatitis C, genotype 1; population given pretreatment for 12 months with PegIFN/RB, with either no response (non-responder) or relapse (relapser).	**Arm 1** PegIFN/RBV standard therapy (n = 80) **Arm 2**[b] BOC + PegIFN/RBV response-guided therapy (RGT) (n = 162) **Arm 3**[c] BOC + PegIFN/RBV Fixed duration treatment regimen (n = 162)	Treatment: 36 or 48 weeks Follow-up: 24 weeks	Belgium, Germany, France, Italy, Canada, Puerto Rico, Spain, USA. August 2008 –April 2010	Primary: Sustained virological response (SVR), defined as no detectable HCV-RNA in the blood 24 weeks after the end of therapy. Secondary: all-cause mortality, health related quality of life, adverse events, serious adverse events, discontinuation due to adverse events, adverse events related to anaemia, adverse events related to psychiatric side effects, adverse events related to infections.

(continued)

Table 3: Characterization of the included studies (continued)

a: Extracted primary outcomes include information without consideration of the relevance to the benefit assessment. Extracted secondary outcomes exclusively contain data on available outcomes relevant to this benefit assessment.

b: Population relevant to the assessment

c: Arm not relevant for this assessment and is not presented in the following tables.

BOC: boceprevir; HCV-RNA: hepatitis C virus ribonucleic acid; PegIFN: pegylated (peg-)interferon-alfa; RBV: ribavirin; RCT: randomized controlled trial; RGT: response-guided therapy; SVR: sustained virological response

Table 4: Characterization of the interventions

Study	PegIFN/RBV (control)	BOC + PegIFN/RBV (RGT)
Treatment-naïve patients without cirrhosis		
SPRINT-2 (P05216)	Lead-in: PegIFN 1.5 µg/kg/week sc + RBV 600–1400 mg/day po for 4 weeks Treatment: PLC + PegIFN 1.5 µg/kg/week sc + RBV 600–1400 mg/day for 44 weeks	Lead-in: PegIFN 1.5 µg/kg/week sc + RBV 600–1400 mg/day for 4 weeks Treatment: 2400 mg/day BOC plus PegIFN/RBV for 24 weeks From week 24 – depending on the virological response in TW8 and the following period up to TW24 -, the patients are divided into the following subarns: ▪ **HCV-RNA in TW8 negative**: Patients with negative HCV-RNA in TW8 and TW24 completed the therapy in TW 28 and started follow-up for 44 weeks[a]. ▪ **HCV-RNA in TW8 positive:** Patients with positive HCV RNA in TW8 but who become negative for HCV RNA by TW 24 were switched blind in TW28 from BOC to PLC and treated for a further 20 weeks with PEG2b 1.5 µg/kg/week sc + RBV 600–1400 mg/day. The patients then started follow-up for 24 weeks.
Treatment-experienced patients without cirrhosis		
RESPOND-2 (P05101)	Lead-in: PegIFN 1.5 µg/kg/week sc + RBV 600–1400 mg/day po for 4 weeks Treatment: PLC + PegIFN 1.5 µg/kg/week sc + RBV 600–1400 mg/day po for 44 weeks	Lead-in: PegIFN 1.5 µg/kg/week sc + RBV 600–1400 mg/day for 4 weeks Treatment: 2400 mg/day BOC plus PegIFN/RBV for 32 weeks. From week 36 – depending on the virological response in TW 8 and in the following period up to TW 12, the patients were divided into the following subarms: ▪ **HCV RNA in TW 8 negative:** Patients with negative HCV RNA in TW8 and TW12 ended therapy in TW36 and started follow-up for 36 weeks[b].
RESPOND-2 (P05101) (cont.)		▪ **HCV-RNA in TW 8 positive:** Patients with positive HCV RNA in TW8 but who become negative for HCV RNA by TW 12 were switched blind in TW36 from BOC to PLC and treated for a further 12 weeks with PEG2b 1.5 µg/kg/week sc + RBV 600–1400 mg/day. The patients then started follow-up for 24 weeks.

a: Patients and study sites were blinded up to TW28.
b: Patients and study sites were blinded up to TW36.

BOC: boceprevir; HCV RNA: hepatitis C virus ribonucleic acid; PegIFN: pegylated (peg-)interferon-alfa; po: per os (oral); RBV: ribavirin; RGT: response-guided therapy; sc: subcutaneous; TW: treatment week;

The benefit assessment in this report is based on the 2 studies SPRINT-2 and RESPOND-2. SPRINT-2 is used to assess BOC + PegIFN/RBV (RGT) in a direct comparison with PegIFN/RBV in treatment-naïve patients without cirrhosis. The assessment of BOC + PegIFN/RBV (RGT) in direct comparison with PegIFN/RBV in treatment-experienced patients without cirrhosis is based on the RESPOND-2 study.

Both studies were randomized, active controlled, double blind and included adult patients with cHCV infection of genotype 1. SPRINT-2 only considered treatment-naïve patients and RESPOND-2 only treatment-experienced patients, who had not adequately responded to prior therapy, or who had suffered a relapse. The duration of treatment was between 28 and 48 weeks (SPRINT-2) or between 36 and 48 weeks (RESPOND-2). Of the total of 1099 randomized patients in the SPRINT-2 study, 364 were assigned to the control arm (PR48) and 368 to the RGT arm. Of the 404 randomized patients in the RESPOND-2 study, 80 were assigned to the control arm (PR48) and 162 to the RGT arm. The pharmaceutical company bases its evaluation on the number of patients who took at least one dose of study medication, which reduces the number of patients in the control arm of the SPRINT-2 study by one patient (n = 363). Thus, the relevant study populations included a total of 731 treatment-naïve and 242 treatment-experienced patients. The proportion of patients without cirrhosis in the overall population was a clear majority, with more than 90% in SPRINT-2 (acc. to Module 5 of the dossier) and more than 80% in RESPOND-2. The primary and secondary outcomes in both studies were similar and concentrated on SVR.

All arms of both studies included a 4-week lead-in phase, in which double combinations of PegIFN/RBV were given. In the control arm, the double combination was continued for a further 44 weeks with addition of placebo. In the RGT arm in the SPRINT-2 study, the treatment after the lead-in treatment with the double combination was continued by adding boceprevir for 24 weeks, after which the treatment was either ended (if there was an early response in TW8), or continued with PegIFN/RBV with additional placebo (in patients with a late response). In the RGT arm of the RESPOND-2 study, the treatment after the lead-in treatment with the double combination was continued by adding boceprevir for 32 weeks, after which the treatment was either ended (if there was an early response in TW8), or continued with PegIFN/RBV with additional placebo (in patients with a late response). In both studies, rules were applied for therapy discontinuation, although the time point differed. Treatment of patients was discontinued at once if HCV RNA was detected in the blood at week 12 (RESPOND-2) or at week 24 (SPRINT-2).

Table 5 shows the characteristics of the patients in the studies included.

Table 5: Characterization of the study populations

Study Group	N[a]	Age (years)	Gender f /m (%)	Ethnicity Caucasian and other[b] / Afroamerican (%)	Liver histology cirrhosis / no cirrhosis[c] (%)	Metavir fibrosis score F0-2/ F3-4[c] (%)
Treatment-naïve patients without cirrhosis						
SPRINT-2 (P05216)						
PegIFN/RBV	363	48.6	43 / 57	86 / 14	4 / 93	90 / 7
BOC + PegIFN/RBV (RDT arm)	368	49.8	38 / 62	86 / 14	4 / 92	87 / 9
Treatment-experienced patients without cirrhosis						
RESPOND-2 (P05101)						
PegIFN/RBV	80	52.9	28 / 73	85 / 15	13 / 83	76 / 19[d]
BOC + PegIFN/RBV (RGT arm)	162	52.9	40 / 60	89 / 11	10 / 81	73 / 19[d]

a: FAS evaluation: all randomized persons who received at least one dose of a study medication
b: Ethnicity: Caucasian and other includes American Indians / Alaskans, Asians, Hawaiians, natives of other Pacific islands and multiethnic subjects.
c: There was no information for the remaining patients.
d: Percentages: our calculation
BOC: boceprevir; FAS: full analysis set; PegIFN: pegylated (peg-)interferon-alfa; RBV: ribavirin; RGT: response-guided therapy

There were no relevant differences between difference groups within the individual studies with regard to age, gender, ethnicity, cirrhosis status or fibrosis score. The mean age of the patients was between 49 and 53 years and the mean age of the treatment-experienced patients was somewhat greater than that of the treatment-naïve patients. In both studies, there were far more patients who were not Afroamerican (86-89%). Patients without cirrhosis were clearly in the majority; there were fewer patients with cirrhosis in SPRINT-2 (4%) than in RESPOND-2 (10-13%). Much the same applies to the fibrosis score; severe fibrosis was rarer in SPRINT-2 (7-9%) than in RESPOND-2 (19%).

Thus, the submitted data for the whole study population can be used for the assessment of the subpopulations without cirrhosis. (The proportion of patients without cirrhosis in the two studies was above 80%, so that the risk of potential limitations to the transferability of the results is regarded as acceptable.) Please refer to Section 2.7.2.4.2 of the full dossier assessment for an assessment of the risk of bias at study and outcome level.

Table 6 shows the risk of bias at study level.

Table 6: Risk of bias at study level

Study	Adequate Creation of the Randomization Sequence	Concealment of Group Allocation	Blinding		Evidence for Selective Outcome Reporting	Other Points Influencing Risk of Bias	Risk of Bias at the Study Level
			Patient	Treating staff			
Treatment-naïve patients without cirrhosis							
SPRINT-2 (P05216)	yes	yes	yes	yes	no	no	low
Treatment-experienced patients without cirrhosis							
RESPOND-2 (P05101)	yes	yes	yes	yes	no	no	low

The risk of bias at study level was assessed as low for both studies. This is in accordance with the assessment of the pharmaceutical company.

Further information on the study design and study populations, as well as the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1 and 4.3.1.2.2 of the dossier and in Sections 2.7.2.2, 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

The present assessment incorporates the following patient-relevant outcomes (this procedure is justified in more detail in Section 2.7.2.4.3 of the full dossier assessment):

- Mortality (all-cause mortality)
- Health-related quality of life
- Adverse effects
  - Total rate of adverse events (AEs)
  - Total rate of serious adverse events (SAEs)
  - Total rate of adverse events leading to study discontinuation (discontinuations due to AEs)
  - Total rate of specific adverse events, anaemia
  - Total rate of specific adverse events, psychiatric events
  - Total rate of specific adverse events, infections

In addition, the following outcome is considered as a surrogate. (For a detailed description, please refer to Section 2.4.1 as well as to Section 2.7.2.9.4 of the full dossier assessment):

- Sustained virological response (SVR)

The pharmaceutical company included the outcomes of health-related quality of life, AEs, SAEs, discontinuations due to AEs and SVR in the assessment in the dossier. The other outcomes were additionally included by the Institute, in order to allow optimal assessment of added benefit. Please also refer to Section 2.7.2.4.3 of the full dossier assessment.

Table 7 shows the outcomes for which data were available in the included studies. Table 8 shows the risk of bias for these outcomes.

Table 7: Matrix of the outcomes and data availability

Study	All-cause mortality	SVR	Health-related quality of life	Adverse events	Serious adverse events	Discontinuations due to adverse events	Specific adverse events: anaemia	Specific adverse events: psychiatric events	Specific adverse events: infections
Treatment-naïve patients without cirrhosis									
SPRINT-2 (P05216)	yes	yes	no[a]	yes	yes	yes	yes	yes	yes
Treatment-experienced patients without cirrhosis									
RESPOND-2 (P05101)	yes	yes	no[a]	yes	yes	yes	yes	yes	yes

a: Although the data were available in principle, the outcome could not be used for the dossier assessment, as the proportion of patients in the analysis was under 70%.
SVR: sustained virological response

Table 8: Risk of bias at study level and outcome level

Outcome / Study	Study level	All-cause mortality[a]	SVR	Health-related quality of life	Adverse events	Serious adverse events	Discontinuation due to adverse events	Specific adverse events: anaemia[a]	Specific adverse events: psychiatric events[a]	Specific adverse events: infections[a]
Treatment-naïve patients										
SPRINT-2 (P05216)	low	low	low	-[b]	low	low	low	low	low	low
Treatment-experienced patients										
RESPOND-2 (P05101)	low	low	low	-[b]	low	low	low	low	low	low

a: The assessment of the risk of bias was performed by the Institute, as the outcome was considered in addition to the outcomes considered by the pharmaceutical company.

b: The outcome was not recorded or (adequately) reported. For the justification, please refer to Table 7 or Section 2.7.2.4.2 of the full dossier assessment.

SVR: sustained virological response

Aside from the data on health-related quality of life, which were not used, the availability of outcome data for the direct comparison of BOC + PegIFN/RBV and PegIFN/RBV in treatment-naïve patients without cirrhosis, as well as treatment-experienced patients without cirrhosis (see Table 7) was considered adequate. The outcome selected for the present assessment is in accordance with that of the pharmaceutical company in Module 4, in so far that the outcomes described by the pharmaceutical company in Module 4 are considered. However, for the present assessment additional outcomes were included, which required the use of data from Module 5.

For all outcomes with evaluable data included by the pharmaceutical company, the risk of bias was low. This is in accordance with the assessment of the pharmaceutical company. The Institute also classified the risk of bias as low for the outcomes additionally included in this assessment.

Further information on the selection of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.2, 2.7.2.4.2, 2.7.2.4.3, 2.7.2.8 and 2.7.2.9.4 of the full dossier assessment.

2.4.1 Results on the subpopulations “treatment-naïve patients without cirrhosis” and “treatment-experienced patients without cirrhosis”

Table 9 summarizes the results for the comparison of boceprevir (BOC) + PegIFN/RBV and PegIFN/RBV in treatment-naïve and treatment-experienced patients without cirrhosis. The subpopulations are presented together in this section, to facilitate rapid comparison between the study results. The data shown comprise data presented by the pharmaceutical company for the outcomes considered in Module 4, as well as the outcomes added by the Institute, for which data was taken from Module 5. Moreover, the figures in the dossier were complemented by our own calculation of the relative risks, where these values were not given in the dossier (marked with footnotes).

Table 9: Results of the comparison between BOC + PegIFN/RBV (RGT regimen) vs. PegIFN/RBV, with treatment-naïve (SPRINT-2) and treatment-experienced (RESPOND-2) patients without cirrhosis

Outcome[a] **Study**	**PegIFN/RBV (Control Arm)**		**Boceprevir + PegIFN/RBV (RGT Regimen)**		**Boceprevir + PegIFN/RBV (RGT Regimen) vs. PegIFN/RBV**	
	Total N	**Events N (%)**	**Total N**	**Events N (%)**	**RR [95% CI][b]**	**p-Value**
Sustained virological response after end of therapy[c]						
SPRINT-2	363	137 (37.7)[d]	368	233 (63.3)[d]	1.68 [1.44; 1.96]	< 0.001[e]
RESPOND-2	80	17 (21.3)[d]	162	95 (58.6)[d]	2.76 [1.78; 4.29]	< 0.001[e]
Health-related quality of life	No evaluable data available					
All-cause mortality						
SPRINT-2	363	4 (1)	368	1 (< 1)	0.25 [0.03; 2.20]	0.195[e]
RESPOND-2	80	0	162	1 (1)	not calculable	0.595[e]
Adverse events (AEs)						
SPRINT-2	363	356 (98)	368	365 (99)	1.01 [0.99; 1.03]	0.22[f]
RESPOND-2	80	77 (96)	162	160 (99)	1.03 [0.98; 1.08]	0.34[f]
Serious adverse events (SAEs)						
SPRINT-2	363	31 (9)	368	42 (11)	1.34 [0.86; 2.08]	0.22[f]
RESPOND-2	80	4 (5)	162	16 (10)	1.98 [0.68; 5.72]	0.23[f]
Therapy discontinuations due to adverse events						
SPRINT-2	363	57 (16)	368	45 (12)	0.78 [0.54; 1.12]	0.20[f]
RESPOND-2	80	2 (3)	162	13 (8)	3.21 [0.74; 13.88]	0.15[f]
Specific adverse events: anaemia						
SPRINT-2	363	107 (29)	368	182 (49)	1.68 [1.39; 2.03]	<0.001[e]
RESPOND-2	80	59 (74)	162	131 (81)	1.10 [0.94; 1.27]	0.219[e]
Specific adverse events: psychiatric events						
SPRINT-2	363	214 (59)	368	203 (55)	0.94 [0.83; 1.06]	0.312[e]
RESPOND-2	80	35 (44)	162	77 (48)	1.09 [0.81; 1.46]	0.623[e]
Specific adverse events: infections						
SPRINT-2	363	183 (50)	368	187 (51)	1.01 [0.87; 1.16]	0.934[e]
RESPOND-2	80	45 (56)	162	81 (50)	0.89 [0.69; 1.14]	0.402[e]

The data correspond to the total population, but are applied to the subpopulations without cirrhosis.

a: FAS evaluation: all randomized patients who received at least one dose of study medication
b: Our own calculation, RR BOC + PegIFN/RBV (RGT regimen) vs. PegIFN/RBV.
c: Test: COBAS TaqMan HCV/HPS v2.0 assay with a limit of quantification of 25 IU/ml and a limit of detection of 9.3 IU/ml.
d: EOF: Primary outcome (SVR), the last available value from the period within and after FUW 24. If this is not available, the value from FUW 12 is taken.
e: Our own calculation, unconditional exact test (CSZ method according to [1]).
f: Fisher's exact test.
AE: adverse event; CSZ = convexity, symmetry, z-score; EOF: end of follow-up; FAS: full analysis set; FUW: follow-up week; CI: confidence interval; PegIFN: pegylated (peg-)interferon-alfa; RBV: ribavirin; RGT: response-guided therapy; RR: relative risk; SAE: serious adverse events; SVR: sustained virological response

The presented data were based on the total population in the approval studies, but were used to assess the subpopulations without cirrhosis, as the proportion of patients without cirrhosis in the 2 studies was more than 80% and the risk of potential restriction to transferability was regarded as being acceptable. For an assessment of the risk bias at the study and outcome level, please refer to Section 2.7.2.4.2 of the full dossier assessment.

Moreover, the duration of treatment with boceprevir in the RGT regimen was not in accordance with the duration of treatment in the approval recommendation. A detailed description can be found in Sections 2.3.2 as well as in Section 2.7.2.4.1 of the full dossier assessment. In general, the consequent uncertainty is accepted and the study results are used for the assessment of the corresponding subpopulations.

Nevertheless, the aspects reported in the above sections supported the evaluation that the specific demands for the derivation of proof of benefit from an individual study are fulfilled by neither SPRINT-2 nor RESPOND-2. Thus at most indications, for example, of an added benefit could be derived from the data, unless the informative value was not further weakened by outcome-specific aspects (see too Section 2.7.2.8.1 of the full dossier assessment). Any possible weakening of the results by outcome-specific aspects will be noted separately for individual outcomes in the following presentation of the results. This evaluation differs from that of the pharmaceutical company, which derived proof (not indications) of added benefit from the data.

Mortality

There was no relevant difference in the proportion of patients who died under therapy with BOC + PegIFN/RBV and PegIFN/RBV. Nevertheless, the interpretation of these results is restricted by the limited duration of the studies and the low rate of events. The results were not statistically significant and added benefit for this outcome has not been proven.

Morbidity

Sustained virological response (SVR)

The outcome SVR is not in itself a patient-relevant outcome and there are no available studies on the validation of SVR as a surrogate outcome. There are however results which can be used from observational studies, in which the occurrence of late complications was compared between patients who achieved SVR and those who did not (Section 2.7.2.9.4 of the full dossier assessment). Firstly, these results show that the risk of occurrence of hepatocellular carcinoma (HCC) in patients with SVR is similarly low to that of a comparable population without HCV infection. Secondly, the risks for patients with SVR are clearly lower than for patients without SVR and the underlying biological model appeared to be plausible. Therefore SVR is a sufficiently valid surrogate outcome for the incidence of hepatic cellular carcinoma. It is thus acceptable in principle to consider SVR in this dossier assessment and in the derivation of conclusions about added benefit.

The proportion of patients who achieved SVR was higher under BOC + PegIFN/RBV (RGT) than under PegIFN/RBV. For both subpopulations – treatment-naïve without cirrhosis and treatment-experienced without cirrhosis –, there was a statistically significant difference in favour of boceprevir. The estimated effect was greater in treatment-experienced patients than in treatment-naïve patients.

At outcome level, it must nevertheless be considered that the SVR has not been formally validated as a surrogate and that the evaluation of "sufficient validity" is exclusively based on data from observational studies (see Section 2.7.2.9.4 of the full dossier assessment). This increased uncertainty is already reflected in the classification of the extent of added benefit as unquantifiable.

In summary, there is an indication of added benefit for treatment-naïve patients without cirrhosis and treatment-experienced patients without cirrhosis. This evaluation deviates from that of the pharmaceutical company, which claimed proof of added benefit.

Health-related quality of life

No evaluable data on health-related quality of life is provided in the pharmaceutical company's dossier. Added benefit for health-related quality of life has not been proven.

Adverse effects

There were no relevant differences in the proportions of patients with adverse events, discontinuations due to adverse events, serious adverse events, psychiatric events and infections for BOC + PegIFN/RBV and PegIFN/RBV. The corresponding result was not statistically significant and greater harm has not been proven for these outcomes. This evaluation largely corresponds to that of the pharmaceutical company, which made no summary statement on adverse events. The evaluation of the adverse events of specific interest (psychiatric events, infections) deviates from that of the pharmaceutical company, as these outcomes were not considered in the dossier.

Anaemia occurred more frequently in treatment-naïve patients treated with BOC + PegIFN/RBV than in those patients treated with PegIFN/RBV. For treatment-naïve patients, there was a statistically significant difference to the detriment of boceprevir (SPRINT-2 study). Almost without exception, the events occurring in this context were not serious. There were almost no cases of serious anaemia. As a consequence, there is an indication of greater harm from boceprevir for this outcome in treatment-naïve patients without cirrhosis. There was no relevant difference between BOC + PegIFN/RBV and PegIFN/RBV with respect to the proportion of treatment-experienced patients with anaemia. The result was not statistically significant and greater harm has not been proven for this outcome for treatment-experienced patients without cirrhosis (RESPOND-2 study). The evaluation of this adverse effect of specific interest (anaemia) deviates from the evaluation of the pharmaceutical company, as this outcome was not considered in the dossier.

Further information on the results on the outcome for the subpopulation "treatment-naïve without cirrhosis" and the subpopulation "treatment-experienced without cirrhosis" can be found in Module 4, Sections 4.3.1.3.1, 4.3.1.3.2, and 4.4 of the dossier, as well as in Section 2.7.2.4.3 of the full dossier assessment.

2.4.2 Results for the subpopulation "patients with cirrhosis"

It may have been possible to use studies SPRINT-2 and RESPOND-2 for this comparison. However, the pharmaceutical company would then have had to present separate results for patients with cirrhosis, which was not done. Overall, no separate consideration of patients with cirrhosis was performed in the dossier. The dossier only includes interaction tests, which, in the SPRINT-2 study, found a statistically significant difference between patients with and without cirrhosis with respect to attaining SVR. In patients with cirrhosis the observed effect was even to the detriment of boceprevir. The assessment of added benefit and extent of added benefit in this subpopulation generally requires the critical appraisal of separate data. However, there were no adequate data in the dossier on patients with cirrhosis in the studies included by the pharmaceutical company. The studies were not explicitly evaluated by the pharmaceutical company for this subpopulation. Moreover, Module 5 did not present the corresponding data for all outcomes. In addition, the study pool compiled by the pharmaceutical company was incomplete, as an additional study (P05685) would have been relevant for the treatment regimen that was compliant with the approval.

Added benefit of boceprevir for the subpopulation "patients with cirrhosis" has not been proven. This evaluation deviates substantially from that of the pharmaceutical company, which derived added benefit for the whole therapeutic indication – and thus explicitly also for the subpopulation "patients with cirrhosis".

Further information on results on outcomes for the subpopulation "patients with cirrhosis" can be found in Module 4, Sections 4.3.1.3.1, 4.3.1.3.2 and 4.4 of the dossier and in Sections 2.7.2.4.3 and 2.7.2.8 of the full dossier assessment.

2.4.3 Results for the subpopulation "patients with null response to prior interferon-based therapy"

"Null response" was an exclusion criterion in the studies SPRINT-2 and RESPOND-2. No other study was presented by the pharmaceutical company. Thus, added benefit of boceprevir for this subpopulation has not been proven. This evaluation deviates substantially from that of the pharmaceutical company, which derived an added benefit for the whole therapeutic indication – and thus explicitly also for the subpopulation "patients with null response to prior IFN-based therapy".

Further information on results on outcomes for the subpopulation "patients with null response to prior therapy" can be found in Module 4, Sections 4.3.1.3.1, 4.3.1.3.2 and 4.4 of the dossier and in Sections 2.7.2.1, 2.7.2.4.3 and 2.7.2.8 of the full dossier assessment.

2.5 Extent and probability of the added benefit

The derivation of the extent and probability of the added benefit for each subpopulation at outcome level will be presented in the following text. This considers outcome categories and effect sizes. The method used is explained in Appendix A of benefit assessment A11-02 [2]. The subpopulations of treatment-experienced and treatment-naïve patients without cirrhosis are considered separately in this section.

The approach for the derivation of an overall conclusion on added benefit on the basis of an aggregation of the conclusions derived at outcome level is a suggestion from IQWiG. The G-BA decides on added benefit.

2.5.1 Treatment-naïve patients without cirrhosis

2.5.1.1 Evaluation of the added benefit at outcome level

The data presented in Section 2.4.1 provide an indication of added benefit and an indication of greater harm from boceprevir relative to peginterferon + ribavirin in a direct comparison for the subpopulation "treatment-naïve patients without cirrhosis". The extent of the added benefit was then evaluated at outcome level, as presented in Table 10.

Table 10: Treatment-naïve patients without cirrhosis: BOC + PegIFN/RBV (RGT) vs. PegIFN/RBV – Extent of added benefit at outcome level

	Effect estimate [95% CI] / Proportion of events BOC + PegIFN/RBV vs. PegIFN/RBV / p values / probability[a]	**Derivation of extent[b]**
Mortality		
All-cause mortality	RR 0.25 [0.03; 2.20] <1% vs. 1% p = 0.195	Added benefit / greater harm not proven
Morbidity		
HCC, assessed with the surrogate SVR[c]	Unquantifiable Probability: "indication"	Outcome category: serious / severe Symptoms / late complications Added benefit, extent: "unquantifiable"
Health-related quality of life		
	No evaluable data available	Added benefit not proven

(continued)

Table 10: Treatment-naïve patients without cirrhosis: BOC+PegIFN/RBV (RGT) vs. PegIFN/RBV - extent of added benefit at outcome level (continued)

	Effect estimate [95% CI] / Proportion of events BOC + PegIFN/RBV vs. PegIFN/RBV / p values / probability[a]	**Derivation of extent[b]**
Adverse effects		
Anaemia	RR 1.68 [1.39; 2.03] 49% vs. 29% p < 0.001 Probability: "indication"	Outcome category: non-serious / non-severe adverse effects CI_0 < 0.8 Greater harm, extent: "considerable"[d]
Psychiatric events	RR 0.94 [0.83; 1.06] 55% vs. 59% p = 0.312	Greater or lesser harm not proven
Infections	RR 1.01 [0.87; 1.16] 51% vs. 50% p = 0.934	Greater or lesser harm not proven
AE	RR 1.01 [0.99; 1.03] 99% vs. 98% p = 0.22	Greater or lesser harm not proven
SAE	RR 1.34 [0.86; 2.08] 11% vs. 9% p = 0.22	Greater or lesser harm not proven
Discontinuation due to AE	RR 0.78 [0.54; 1.12] 12% vs. 16% p = 0.20	Greater or lesser harm not proven

a: Probability, given when differences are statistically significant.

b: Depending on the outcome category, the effect size is evaluated with different limits, using the upper limit of the confidence interval (CI_0); see too Appendix A in the report on Project A11-02 [2].

c: SVR is used as surrogate for a patient-relevant outcome (hepatocellular carcinoma). It is regarded as sufficiently valid to be considered in the benefit assessment (for a detailed justification see Section 2.7.2.9.4 of the full dossier assessment).

d: For the derivation of the extent of the added benefit, the direction of the effect was inverted: RR 0.60 [0.49; 0.72] (proportion of events control / boceprevir, CI_o< 0,8).

AE: adverse event; BOC: boceprevir; CI: confidence interval; CI_o: upper limit of the confidence interval; HCC: hepatocellular carcinoma; PegIFN: pegylated (peg-)interferon-alfa; RBV: ribavirin; RGT: response-guided therapy; RR: relative risk, SAE: serious adverse event; SVR; sustained virological response; vs.: versus.

On the basis of the data submitted in the dossier, the extent of the added benefit as measured by HCC (based on SVR, a sufficiently valid but formally unvalidated surrogate) cannot be quantified. Thus it cannot be classified into one of the categories of extent of added benefit. In other words, it is unclear whether the existing added benefit is minor, considerable or major. In situations in which there is uncertainty about the classification of the extent of added

benefit on the basis of the available scientific data, the legislator intends that the evaluation category of “unquantifiable” should be used (see too SGB V § 5 Section 7).

2.5.1.2 Overall conclusion on the added benefit

The summary of the results determining the overall conclusion on added benefit (of major, considerable, minor or unquantifiable extent) is shown in Table 11.

Table 11: Treatment-naïve patients without cirrhosis: results influencing the overall conclusion on added benefit

Positive Effects	**Negative Effects**
Indication of added benefit – extent: unquantifiable (serious late complications: HCC, assessed with the surrogate SVR).	Indication of greater harm – extent: considerable (non-serious adverse events: anaemia)
HCC: hepatocellular carcinoma; SVR: sustained virological response	

The overall summary (Table 11) contains positive and negative results of the same degree of certainty (indication of added benefit). On the basis of the available data, the extent of the added benefit is “unquantifiable” and the extent of the greater harm is “considerable”. As the added benefit is unquantifiable, no final conclusion can be reached as to whether it might be meaningful to downgrade the extent of the added benefit. It nevertheless seems inappropriate to call the indication of added benefit with respect to a serious late complication (HCC) totally into doubt on the basis of the greater harm from non-serious adverse events (anaemia).

In summary, there is an indication of added benefit of unquantifiable extent from BOC + PegIFN/RBV in comparison with the appropriate comparator therapy PegIFN/RBV for treatment-naïve patients without cirrhosis.

2.5.2 Treatment-experienced patients without cirrhosis

2.5.2.1 Assessment of added benefit at outcome level

The data presented in Section 2.4.1 provide an indication of an added benefit of boceprevir in a direct comparison with peginterferon + ribavirin for the subpopulation “treatment-experienced patients without cirrhosis”. An assessment was then performed of the extent of the added benefit in each case at outcome level, as shown in Table 12.

Table 12. Treatment-experienced patients without cirrhosis: BOC + PegIFN/RBV (RGT) vs. PegIFN/RBV – extent of added benefit at outcome level

	Effect estimate [95% CI] / Proportion of events BOC + PegIFN/RBV vs. PegIFN/RBV / p values / probability[a]	**Derivation of extent[b]**
Mortality		
All-cause mortality	Not calculable 0.6% vs. 0% p = 0.595	Added benefit / greater harm not proven
Morbidity		
HCC, assessed with the surrogate SVR[c]	Unquantifiable Probability: indication	Outcome category: serious / severe Symptoms / late complications Added benefit, extent: unquantifiable
Health-related quality of life		
	No evaluable data available	Added benefit not proven
Adverse effects		
Anaemia	RR 1.10 [0.94; 1.27] 81% vs. 74% p = 0.219	Greater or lesser harm not proven
Psychiatric events	RR 1.09 [0.81; 1.46] 48% vs.44% p = 0.623	Greater or lesser harm not proven
Infections	RR 0.89 [0.69; 1.14] 50% vs. 56% p = 0.402	Greater or lesser harm not proven
AE	RR 1.03 [0.98; 1.08] 99% vs. 96% p = 0.34	Greater or lesser harm not proven
SAE	RR 1.98 [0.68; 5.72] 10% vs. 5% p = 0.23	Greater or lesser harm not proven
Discontinuation due to AE	RR 3.21 [0.74; 13.88] 8% vs. 3% p = 0.15	Greater or lesser harm not proven

a: Probability, given when differences are statistically significant .

b: Depending on the outcome category, the effect size is estimated with different limits, using the upper limit of the confidence interval (CI_0); see too Appendix A in the report on Project A11-02 [2].

c: SVR is used as surrogate for a patient-relevant outcome (hepatocellular carcinoma). It is regarded as sufficiently valid to be considered in the benefit assessment (for a detailed justification see Section 2.7.2.9.4 of the full dossier assessment).

AE: adverse event; BOC: boceprevir; CI: confidence interval; HCC: hepatocellular carcinoma; PegIFN: pegylated (peg-)interferon-alfa; RBV: ribavirin; RGT: response-guided therapy; RR: relative risk, SAE: serious adverse event; SVR; sustained virological response; vs.: versus.

On the basis of the data submitted in the dossier, the extent of the added benefit as measured by HCC (based on SVR, a sufficiently valid but formally unvalidated surrogate) cannot be quantified. Thus it cannot be classified into one of the categories of extent of added benefit. In other words, it is unclear whether the existing added benefit is minor, considerable or major. In situations in which there is uncertainty about the classification of the extent of added benefit on the basis of the available scientific data, the legislator intends that the evaluation category of "unquantifiable" should be used (see too SGB V § 5 Section 7).

2.5.2.2 Overall conclusion on added benefit

The summary of the results determining the overall conclusion on added benefit (of major, considerable, minor or unquantifiable extent) is shown in Table 13.

Table 13. Treatment-experienced patients without cirrhosis: results influencing the overall conclusion on added benefit

Positive Effects	Negative Effects
Indication of added benefit – extent: unquantifiable (serious late complications: HCC, assessed with the surrogate SVR).	No proof of greater harm
HCC: hepatocellular carcinoma; SVR: sustained virological response.	

In summary, there is an indication of added benefit of unquantifiable extent from BOC + PegIFN/RBV in comparison with the appropriate comparator therapy PegIFN/RBV for treatment-experienced patients without cirrhosis.

2.5.3 Patients with cirrhosis

As described in Section 2.4.2, there are no data on this research question that can be used. Thus, no conclusions can be made about added benefit.

The added benefit of boceprevir + PegIFN/RBV in comparison with the appropriate comparator therapy PegIFN/RBV is not proven for the subpopulation of patients with cirrhosis.

2.5.4 Patients with null response to prior interferon-based therapy

As described in Section 2.4.3, there are no data on this research question that can be used. Thus, no conclusion can be drawn about added benefit.

The added benefit of boceprevir + PegIFN/RBV in comparison with the appropriate comparator therapy PegIFN/RBV is not proven for the subpopulation "patients with null response to prior interferon-based therapy".

2.5.5 Extent and probability of added benefit – summary

The following table gives an overview of the extent and probability of added benefit for boceprevir in the different subpopulations in comparison to the appropriate comparator therapy:

Table 14: Boceprevir: extent and probability of added benefit

	Overall therapeutic indication of boceprevir (in combination with PegIFN/RBV), split into disease entities and subpopulations	**Treatment regimens according to approval status**	**Appropriate comparator therapy**	**Extent and probability of added benefit**
1	Chronic HCV infection genotype 1, treatment-naïve patients without cirrhosis	Response-guided therapy (RGT) regimen	PegIFN in combination with RBV.	Indication of added benefit of boceprevir (unquantifiable extent)
2	Chronic HCV infection genotype 1, treatment-experienced patients without cirrhosis	Response-guided therapy (RGT) regimen	PegIFN in combination with RBV.	Indication of added benefit of boceprevir (unquantifiable extent)
3	Chronic HCV infection genotype 1, patients with cirrhosis	Fixed duration treatment regimen of 48 weeks	PegIFN in combination with RBV	Added benefit not proven
4	Chronic HCV infection genotype 1, patients with null response to prior interferon-based therapy	Fixed duration treatment regimen of 48 weeks	PegIFN in combination with RBV.	Added benefit not proven
HCV: Hepatitis C virus, PegIFN: pegylated (peg-)interferon-alfa, RBV: ribavirin.				

This overall assessment differs substantially from that of the pharmaceutical company, which claims that boceprevir has major added benefit for treatment-naïve and treatment-experienced populations with hepatitis C genotype 1. The pharmaceutical company regards the populations with / without cirrhosis as only being subgroups and implicitly derives major added benefit for these too.

Further information on the extent and probability of added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

SPRINT-2

Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S et al. Boceprevir for previously treated chronic HCV genotype 1 infection. The New England journal of medicine 2011; 364(13): 1207-1217.

Schering-Plough Research Institute. A randomized, multi-center study double-blinded for boceprevir or placebo in combination with open-label peginterferon alfa-2b plus ribavirin in previously untreated subjects with chronic hepatitis C (hepatitis C virus genotype 1) [SPRINT-2: A Phase 3, Safety and Efficacy Study of Boceprevir in Previously Untreated Subjects With Chronic Hepatitis C Genotype 1 (Protocol No. P05216)]. clinical study report [unpublished] 2010.

Schering-Plough Research Institute. A phase 3, safety and efficacy study of boceprevir in previously untreated subjects with chronic hepatitis C genotype 1: protocol no. P05216; clinical study report [unpublished]. 2010.

RESPOND-2

Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS et al. Boceprevir for untreated chronic HCV genotype 1 infection. The New England journal of medicine 2011; 364(13): 1195-1206.

Schering-Plough Research Institute. A randomized, multicenter study, double-blinded for boceprevir or placebo in combination with open-label PegIntron and ribavirin (weight-based dosing) in adult subjects with hepatitis C virus genotype 1 infection, who demonstrated interferon responsiveness but failed to achieve sustained virologic response on prior treatment with peginterferon/ribavirin. [RESPOND-2: A Phase 3 Safety and Efficacy Study of Boceprevir (SCH 503034) in Subjects With Chronic Hepatitis C Genotype 1 Who Failed Prior Treatment With Peginterferon/Ribavirin (Protocol No. P05101)]. clinical study report [unpublished] 2010.

Schering-Plough Research Institute. A phase 3 safety and efficacy study of boceprevir (SCH 503034) in subjects with chronic hepatitis C genotype 1 who failed prior treatment with peginterferon/ribavirin: protocol no. P05101; clinical study report [unpublished] 2010.

References for English extract

Please see full dossier assessment for full reference list.

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

2. Institute for Quality and Efficiency in Health Care. Ticagrelor - Benefit assessment according to § 35a Social Code Book V. Dossier assessment (Extract: Sections 2.1 to 2.6 and Appendix A); Commission A11-02 [online]. 29.09.2011 [accessed on: 17.04.2012]. (IQWiG Reports, Volume 96). URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf

The full report (German version) is published under www.iqwig.de.