Title page

CLINICAL STUDY REPORT

NON-INTERVENTIONAL, OBSERVATIONAL STUDY FOR ASSESSMENT OF EFFECTIVENESS OF TREATMENT WITH VICTRELIS® (BOCEPREVIR) IN COMBINATION WITH PEGINTERFERON ALFA AND RIBAVIRIN IN CHRONIC HEPATITIS C GENOTYPE 1 INFECTED PATIENTS IN A GERMAN REAL-LIFE POPULATION

NOVUS 40325 (MK3034-101)

Investigational product:	Victrelis® (Boceprevir)
Clinical development phase:	Post-marketing surveillance
Indication:	Chronic hepatitis C
Sponsor:	MSD SHARP & DOHME GMBH Lindenplatz 1 D-85540 Haar
Date of first patient enrolled:	09-Aug-2011
Date of last patient completed:	08-Jun-2015
Sponsor's signatories:	[redacted]
Prepared by:	[redacted]
Report version and date:	0.1 (26-Nov-2015)

This study was performed in compliance with Good Clinical Practices (GCP) including the archiving of essential documents. This report must be kept strictly confidential. Disclosure of the contents (in whole or part) to third parties is permissible only with written consent of MSD SHARP & DOHME GMBH.

1 Synopsis

Title of the study:
Non-interventional, observational study for the assessment of effectiveness of treatment with Victrelis® (boceprevir) in combination with peginterferon alfa and ribavirin in chronic hepatitis C genotype 1 infected patients in a German real-life population

Investigators and study centers:
96 investigators at 96 centers in Germany.

Publication (reference): Not applicable or reference

Studied period:
09-Aug-2011 (first patient in) to 08-Jun-2015 (last patient last contact)

Clinical phase: Post-marketing surveillance

Objectives:[1]

Primary objectives
The assessment of sustained virologic response (SVR) in patients with chronic hepatitis C virus (HCV) genotype 1-infection after treatment with triple therapy of boceprevir in combination with pegylated interferon alpha and ribavirin (peg-IFN/rbv) in all patients and in the following subgroups:[2] treatment-naïve and pre-treated patients (for all patients and non-cirrhotic patients, and cirrhotic patients.

Secondary objectives
The identification, characterization, and assessment of SVR rates in patients with:

- rapid virologic response (RVR; treatment week [TW] 4);
- early virologic response (EVR; TW 8);
- late virologic response (LVR; TW 24).

Further, the number of patients with the following virologic response:

- non-response (no virologic response);
- relapse (after an initial virologic response, virus particles were detected);
- breakthrough (HCV-ribonucleic acid [RNA] negative during treatment, followed by an increase in HCV-RNA by ≥1 $\log_{10}$ during the course of treatment).

1 As described in the observational plan.
2 The selection of subgroups is taken from the statistical analysis plan (SAP). The analysis of all patients was not performed.

Exploratory objective

Assessment and characterization of the SVR rate in other subgroups of medical interest (e.g. drug consumers on stable substitution) separately for treatment-naïve or pre-treated patients.

Methodology:

This was a multi-center, open-label, observational, non-interventional study in adult patients with HCV genotype 1-infection who were indicated for first-time treatment with boceprevir in combination with peg-IFN/rbv. All patients were treated according to the investigator's discretion following routine practices. Treatment may have occurred depending on the previous treatment (treatment-naïve or pre-treated), disease characteristics (with or without liver cirrhosis), and virologic response for a total of 24, 32, or 48 weeks, after a 4-week lead-in period with only peg-IFN/rbv. During the observational period, data were collected at a baseline visit, up to 6 times during the treatment period, and at a follow-up visit 24 weeks after the end of treatment (EOT; at follow-up Week 24 [FW 24].

Number of patients (total and for each treatment) planned and analyzed:

- Planned: 1,100 patients;
- Analyzed: 535 patients enrolled, 505 patients treated.

Diagnosis and criteria for inclusion:

1. ≥18 years old;
2. Chronic HCV genotype 1-infection with compensated liver disease;
3. Anti-HCV therapy with boceprevir in combination with peg-IFN/rbv planned and indicated;
4. Willingness to participate and signed informed consent form.

Test product, dose, mode of administration, batch no.:

No investigational medicinal product was provided by the sponsor. Boceprevir and peg-IFN/rbv dosing was done according to normal clinical practice following the locally approved product recommendations.

Duration of treatment:

Patients were treated with boceprevir combined with peg-IFN/rbv for a total of 24, 32, or 48 weeks, following a 4-week lead-in period with peg-IFN/rbv only.

Criteria for evaluation:[3]

Primary effectivenessvariable

- SVR 24, defined as undetectable HCV-RNA at EOT and at FW 24(or, if HCV-RNA is missing at FW 24, investigator assessed virologic response = SVR);

[3] As defined in the statistical analysis plan.

Secondary effectiveness variables

- RVR, defined as undetectable HCV-RNA at TW 4;
- EVR/Week 8 response, defined as undetectable HCV-RNA at TW 8;
- LVR, defined as undetectable HCV-RNA at TW 24 for the first time during the treatment period (LVR was analyzed for patients with HCV-RNA detectable at TW 12 only);
- Non-response (no virologic response), defined as HCV-RNA detectable at all time points during treatment period;
- Relapse, defined as undetectable HCV-RNA at EOT but detectable HCV-RNA at FW 24 (or, if HCV-RNA is missing at FW 24, investigator assessed virologic response = relapse or non-response);
- (Virologic) Breakthrough, defined as undetectable HCV-RNA during treatment at any visit and subsequent increase of HCV-RNA $\geq 1 \log_{10}$ (i.e. HCV-RNA ≥100 IU/mL) while on treatment.

  Note: Patients with no undetectable HCV-RNA at all visits during treatment, or with no subsequent increase of HCV-RNA $\geq 1 \log_{10}$ (i.e. HCV-RNA ≥100 IU/mL) while on treatment, were not considered having a breakthrough even if the investigator documented a virologic breakthrough at the end of the study.

Further effectiveness variables

- Week 4 response, defined as HCV-RNA $\log_{10}$ decline from Baseline >1 log at TW 4;
- RVR and Week 4 response categorized as $>1 \log_{10}$ decline and RVR, $>1 \log_{10}$ decline and no RVR, $\leq 1 \log_{10}$ decline and RVR, $\leq 1 \log_{10}$ and no RVR;
- Week 12 response categorized as HCV-RNA value at TW 12 undetectable, detectable with ≤100 IU/mL HCV-RNA, or detectable with >100 IU/mL HCV-RNA;
- Week 24 response, defined as HCV-RNA undetectable at TW 24;
- Week 24 response and LVR categorized as HCV-RNA undetectable at TW 24 and LVR, undetectable and no LVR, and detectable and no LVR (only analyzed for patients with HCV-RNA detectable at TW 12);
- EOT response, defined as HCV-RNA undetectable at EOT.

Safety variables

- Adverse events (AEs);
- Serious adverse events;
- Laboratory parameters (hematology, serum chemistry, and coagulation);
- Vital signs.

Statistical methods:

All variables were summarized descriptively and analyzed separately for treatment-naïve and pre-treated patients, including the stratified effectiveness analyses by virologic response status during treatment and by baseline characteristics. The effectiveness analyses (without further stratification by virologic response status during treatment and baseline characteristics) were additionally performed for cirrhotic patients and a subset of analyses for non-cirrhotic patients stratified by pre-treatment status. Logistic regression analyses were conducted to determine potential predictors for therapy failure or success separately for treatment-naïve and pre-treated patients.

For all tests, a 2-sided significance level of 5% was applied. All analyses of effectiveness parameters were exploratory; no adjustment for multiple testing was done. For all tests 2-sided 95% confidence intervals were calculated.

Statistical analysis sets:

The safety analysis set (SAF) consisted of all patients who received at least one dose of study medication, i.e. any dose of boceprevir, peg-IFN and/or rbv. To differentiate between patients who used any dose of boceprevir and patients who did not use any boceprevir but other medications only (e.g. dual therapy patients with peg-IFN and/or rbv only), the SAF was separated into 'SAF - boceprevir' and 'SAF - no boceprevir'.

The full analysis set (FAS) consisted of all evaluable patients of the SAF - boceprevir. A patient was considered evaluable, if at least study start (Baseline; TW 0), start of treatment and at least 1 post baseline visit (TW 4, TW 8, TW 12, TW 24, TW 28, TW 36, TW 48 and/or FW 24) were documented and at least the baseline and 1 post-baseline HCV-RNA assessment were available.

SUMMARY - CONCLUSIONS

Patient disposition

In total, 535 patients were enrolled at 96 practices and hospitals in Germany, and 505 patients were treated (at 91 practices and hospitals) with peg-IFN, rbv, and/or boceprevir. Patient numbers per center varied between 1 and 23 patients. Of the 505 patients who received any treatment, 456 patients were treated with boceprevir, of which 298 patients completed the treatment and 291 patients completed the follow-up phase.

Demography and baseline characteristics

More male (60%) than female (40%) patients were treated with boceprevir. The majority of patients were Caucasian (91%) with a median age of 46 years for male patients and 51 years for female patients. Generally, slightly more patients were aged 50 or older (55%) than less than 50 years (45%). The body mass index of male and female patients was around 27 kg/m².

Results - effectiveness

Primary variable

The SVR at FW 24 was assessed as primary endpoint. Significantly more treatment-naïve than pre-treated patients had an SVR at FW 24.

Patients with sustained virologic response at FW 24 (FAS, N = 451)

	n	Number (%)[a] of patients	95% CI[b]	p-value[c]
Treatment-naïve	229	177 (77.3)	71.3, 82.6	
Pre-treated	128	78 (60.9)	51.9, 69.4	0.0010

[a] Percentages are based on n.
[b] Clopper-Pearson 2-sided CI for binomial proportions.
[c] Pearson chi²-test for treatment-naïve versus pre-treated patients.
CI = confidence interval, FAS = full analysis set, FW = follow-up week, N = number of patients, n = number of patients with available data.

In addition, non-cirrhotic pre-treated and treatment-naïve patients were analyzed for achieving a SVR. More treatment-naïve (79%) than pre-treated patients (63%) achieved an SVR at FW 24. About half of the patients (54%) with cirrhosis had an SVR at FW 24.

Further effectiveness variables

Independent predictors for higher SVR rates in pre-treated and treatment-naïve patients included a >1 $\log_{10}$ decline in HCV-RNA at TW 4 (Week 4 response), EVR, age ≤50 years, normal gamma-glutamyl transferase levels at TW 0, and HCV-RNA ≤400,000 IU/mL at TW 0.

Additional predictors for higher SVR rates in pre-treated patients included normal alanine aminotransferase levels at TW 0 and platelet counts >150,000/µL at TW 0.

Results - safety

In total, 362 patients (79%) in the SAF - boceprevir reported 2201 AEs, of which 81 AEs reported by 48 patients (11%) were serious;[4] 1219 AEs reported by 292 patients (64%) were possibly or probably related to treatment with boceprevir.

Of the 49 patients in the SAF - no boceprevir, 30 patients reported 168 AEs, of which one was serious (jaundice).

[4] Note that for some AEs (including 7 SAEs) the investigator recorded several symptoms, which were coded as separate AEs in the database.

Summary of adverse events (SAF, N = 505)

	Boceprevir (N = 456)	No boceprevir (N = 49)
Number of AEs	2201[a]	168
Number of SAEs	81[a]	1
Number of AEs related to boceprevir[b]	1219	n/a
Number (%)[c] of patients with AEs	362 (79.4)	30 (61.2)
Number (%)[c] of patients with SAEs	48 (10.5)	1 (2.0)
Number (%)[c] of patients with AEs related to boceprevir[b]	292 (64.0)	n/a

[a] Note that (S)AEs with several symptoms were coded as separate (S)AEs in the database.
[b] Probably or possibly related.
[c] Percentages are based on the total number of patients per analysis set.
AE = adverse event, N = number of patients, n/a = not assessed, SAE = serious adverse event, SAF = safety analysis set.

The majority of AEs were mild or moderate. In total, 2 life-threatening AEs (pancytopenia and ascites) were reported, which occurred in 2 patients in the SAF - boceprevir. The events had a probable (pancytopenia) and possible (ascites) relationship to boceprevir and the treatment was stopped or interrupted in both cases.

Anemia and fatigue were the most commonly reported AEs in both analysis sets (reported by 31% and 27% in the SAF - boceprevir, and by 18% and 16% in the SAF - no boceprevir, respectively). Consistent with the increased incidence of anemia, more patients treated with boceprevir reported post-baseline hemoglobin levels <10 g/dL than patients not receiving boceprevir.

Conclusions:

- A combination therapy with pegylated interferon, ribavirin, and boceprevir in routine clinical practice is effective in achieving a high SVR rate in previously untreated patients without liver cirrhosis;
- In a routine clinical care setting, triple therapy was well tolerated and no new safety issues were identified

Date of report: 26-Nov-2015

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4 Abbreviations and definition of terms

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
(e)CRF	(electronic) case report form
DRM	Data Review Meeting
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
EVR	early virologic response
FAS	full analysis set
FW	follow-up week
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Hb	Hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
LVR	late virologic response
OR	odds ratio
peg-IFN	pegylated interferon alpha
rbv	Ribavirin
RBC	red blood cells
RNA	ribonucleic acid
RVR	rapid virologic response
SAE	serious adverse event
SAF	safety analysis set with (SAF - boceprevir) or without (SAF - no boceprevir) boceprevir
SAP	statistical analysis plan
SD	standard deviation
SmPC	summary of product characteristics
SVR	sustained virologic response
TSH	Thyroid-stimulating hormone

TW	treatment week
WBC	white blood cells
WHO	World Health Organization

VICTRELIS® will be referred to as boceprevir throughout this report. ‘FAS - boceprevir’ as defined in the statistical analysis plan, will be referred to as FAS throughout this report.

5 Ethics

5.1 Independent ethics committee or institutional review board

The observational plan, informed consent documents, and any other appropriate study-related documents were reviewed and approved by the independent ethics committee (IEC) of the Ludwig-Maximilians-University, München.

5.2 Ethical conduct of the study

This study was conducted in compliance with the IEC, informed consent regulations, and local regulatory requirements.

5.3 Patient information and consent

Before entry into the clinical study, the investigator explained to each patient the aims and processes of the study. After these explanations and before entering the study, the patient voluntarily signed an informed consent statement and received a copy of the signed and dated form.

The investigator was to receive written permission from the patient for direct access to patient's data as part of the informed consent procedure. Any party (e.g. domestic and foreign regulatory authorities, monitors and auditors) with direct access took all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of the patient's identities and sponsor's proprietary information.

The data collected in the study were to be transferred to the sponsor only in pseudonymous form.

5.4 Regulatory affairs

Before initiating the study, all documents required by local regulations were submitted to the appropriate regulatory authority for review, acceptance, and/or permission.

6 Investigators and study administrative structure

The study was conducted at 96 practices and hospitals (in the following referred to as centers) in Germany.

The sponsor was responsible for the administration and handling of safety reporting. The contract research organization FGK Clinical Research GmbH, München (in the following referred to as FGK) was responsible for data management, statistical analysis, and report writing.

A complete list of all investigators with their affiliation is available in Appendix 16.1.3.

7 Introduction

For nearly 10 years, the standard treatment for chronic hepatitis C has been the combination therapy of pegylated interferon alpha and ribavarin (peg-IFN/rbv). However, only 40-50% of treatment-naïve (i.e. previously untreated) patients infected with hepatitis C virus (HCV) genotype 1 have achieved a sustained virologic response (SVR), i.e. the permanent elimination of HCV-ribonucleic acid (HCV-RNA) from serum. [1,2]

The remaining 50% of patients were non-responders to the standard treatment or had a relapse, with an expected progression of the liver disease. In addition, the success rates for achieving an SVR in patients with HCV genotype 1 who were previous non-responders to standard therapy and retreated with peg-IFN/rbv are very low (20-30% for patients with previous relapse and 6-11% for previous null-responders). [3,4]

During the last 10 years, researchers focused on the development of new substances with antiviral activity targeting the HCV genotype 1, such as the HCV NS3/4A protease inhibitor boceprevir.

Two phase III studies, SPRINT-2 and RESPOND-2, showed significant increases in SVR rates by a factor of 1.7 in treatment-naïve and by a factor of 3 in pre-treated patients, when patients with HCV genotype 1 were treated with boceprevir in combination with the standard treatment. [5,6]

In 2011, boceprevir was approved by the European Medicines Agency (EMA), and the United States Food and Drug Administration as a combination therapy with peg-IFN/rbv for the treatment of pre-treated and previously untreated (treatment-naïve) patients with HCV genotype 1-infection.

The retrospective analyses of SPRINT-2 and RESPOND-2 conducted by the EMA led to different recommended treatment and stopping rules in the European summary of product

characteristics (SmPC) as originally described in these 2 studies (for details refer to the observational plan [in German], Appendix 16.1.1). Therefore, this non-interventional study aimed to address these discrepancies by analyzing data from pre-treated and treatment-naïve patients with or without liver cirrhosis with the indication for treatment with boceprevir in combination with peg-IFN/rbv.

8 Study objectives[1]

Primary objectives

The assessment of SVR in patients with chronic HCV genotype 1-infection after treatment with triple therapy of boceprevir in combination with peg-IFN/rbv in all patients and in the following subgroups:[2] treatment-naïve and pre-treated patients (for all patients and non-cirrhotic patients, and cirrhotic patients.

Secondary objectives

The identification, characterization, and assessment of SVR rates in patients with:

- rapid virologic response (RVR; treatment week [TW] 4);
- early virologic response (EVR; TW 8);
- late virologic response (LVR; (TW 24).

The number of patients with the following virologic response::

- non-response (no virologic response);
- relapse (after an initial virologic response, virus particles were detected);
- breakthrough (HCV-RNA negative during treatment, followed by an increase in HCV-RNA by ≥1 $\log_{10}$ during the course of treatment).

Exploratory objective

Assessment and characterization of the SVR rate in other subgroups of medical interest (e.g. drug consumers on stable substitution) separately for treatment-naïve or pre-treated patients.

1 As described in the observational plan (in German, Appendix 16.1.1).
2 As detailed in the statistical analysis plan (SAP, Appendix 16.1.4). The analysis of all patients was not done.

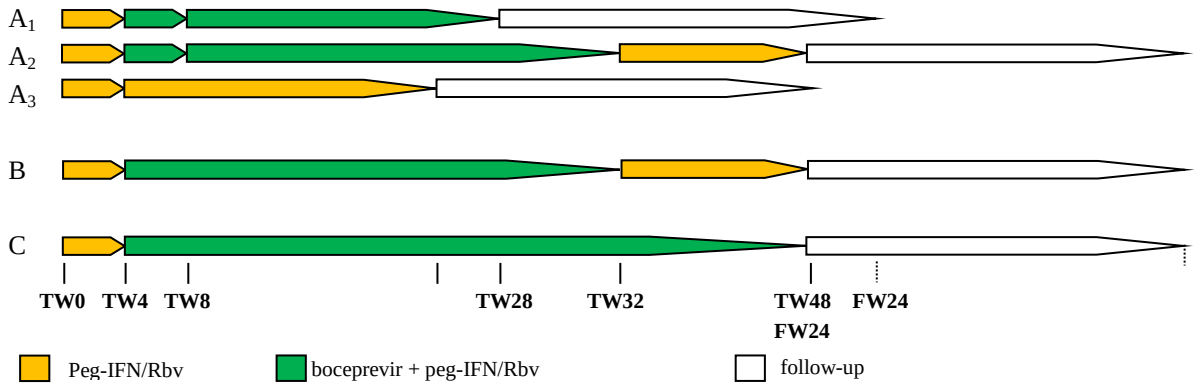
9 Investigational plan

9.1 Overall study design and plan

This was a multi-center, open-label, observational, non-interventional study in adult patients with HCV genotype 1-infection who were indicated for first-time treatment with boceprevir in combination with peg-IFN/rbv. All patients were treated according to the investigator's discretion following routine practices. Treatment may have occurred depending on the previous treatment (treatment-naïve or pre-treated), disease characteristics (with or without liver cirrhosis), and virologic response for a total of 24, 32, or 48 weeks, after a 4-week lead-in period with only peg-IFN/rbv (T-Figure 1). During the observational period, data were collected at a baseline visit, up to 6 times during the treatment period, and at a follow-up visit 24 weeks after the end of treatment (EOT; follow-up week 24 [FW 24].

Data were analyzed continuously at points of interest for publication purposes.

T-Figure 1: Proposed treatment scheme



A_1 = Treatment-naïve patients with neg. HCV-RNA at TW8.
A_2 = Treatment-naïve patients with pos. HCV-RNA at TW8.
A_3 = Treatment-naïve patients with low viral load at TW0 and neg. HCV-RNA at TW4.
B = Pre-treated patients with relapse (i.e. neg. HCV-RNA at end of treatment, but detectable HCV-RNA at follow-up) or partial response (i.e. decline of HCV-RNA by ≥2 $\log_{10}$ at TW 12 compared with Baseline).
C = Previous null-responders (i.e. decline of HCV-RNA by <2 $\log_{10}$ at TW 12 compared with Baseline) and patients with cirrhosis.

HCV-RNA = hepatitis C virus-ribonucleic acid, FW = follow-up week, neg. = negative, peg-IFN/rbv = pegylated interferon alpha and ribavirin (standard therapy), pos. = positive, TW = treatment week.

9.2 Discussion of study design including the choice of control groups

An observational, non-interventional design was chosen to collect data on the effectiveness of the marketed product in a real-life setting.

No procedures were performed other than those of routine clinical practice. All treatments were administered at the discretion of the investigator. Patients were selected according to the boceprevir SmPC.

To close the gap between the data that were used for the product approval in the 2 pivotal studies SPRINT-2 and RESPOND-2 and the treatment recommendations in the European SmPC, real-life data were needed. A detailed list of discrepancies is provided in Table 1 of the observational plan (in German; Appendix 16.1.1).

9.3 Selection of study population

The selection of the study population was based on information in the boceprevir SmPC.

9.3.1 Inclusion criteria

The requirements for inclusion were:

1. ≥18 years old;
2. Chronic HCV genotype 1 infection with compensated liver disease;
3. Anti-HCV therapy with boceprevir in combination with peg-IFN/rbv planned and indicated;
4. Willingness to participate and signed informed consent form.

9.3.2 Exclusion criteria[3]

Patients with any of the following were to be excluded from study participation (based on the boceprevir SmPC):

1. Auto-immune hepatitis;
2. For female patients: known pregnancy or breast-feeding (negative pregnancy test required);
3. Known hypersensitivity to the active substance or any of its excipients;
4. Co-administration with medicines that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events such as orally administered midazolam and triazolam, bepridil, pimozide, lumefantrin and halofantrin, tyrosine-kinase-inhibitors, and ergot derivatives (dihydroergotamine, ergonovine, ergotamine, and methylergonovine).

[3] As detailed in the case report form (CRF).

9.3.3 Removal of patients from therapy or assessment

Every patient had the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The investigator and sponsor had the right to withdraw patients from the study (see below). In case a patient decided to withdraw, all efforts were to be made to complete and report the so far obtained observations as thoroughly as possible.

Patients could be removed from the study if one or more of the following events occurred:[4]

- HCV-RNA levels of ≥1,000 IU/mL at TW 8;
- HCV-RNA levels of ≥100 IU/mL at TW 12;
- Confirmed, detectable HCV-RNA levels at TW 24.

The sponsor could terminate the entire study or the recruitment of further patients by notifying the participating centers 30 days in advance. In that case, all available data were collected, analyzed, and transferred to the sponsor.

9.4 Treatments

9.4.1 Treatments administered

No investigational medicinal product was provided by the sponsor. Patients received the triple therapy according to local clinical practice following the approved product recommendations.

9.4.2 Identity of investigational product

Not applicable.

9.4.3 Method of assigning patients to treatment groups

Not applicable.

9.4.4 Selection of doses in the study

Not applicable.

9.4.5 Selection and timing of dose for each patient

Boceprevir was administered in combination with peg-IFN/rbv for 24, 32, or 44 weeks, depending on previous treatments, the presence or absence of cirrhosis, and the virological response, after a 4-week lead-in period with peg-IFN/rbv standard therapy. For patients with a low virus load at Baseline (<800,000 IU/mL) and a rapid virologic response in TW 4,

[4] Stopping rules taken from the boceprevir SmPC (updated on 5-Mar-2015).

shortening of the standard therapy (peg-IFN/rbv) to 24 weeks was possible without the additional treatment with boceprevir. The recommended dose of boceprevir (according to the European Union-approval) was 800 mg (4 capsules containing 200 mg) 3 times daily orally administered with food (i.e. a total of 12 capsules per day).

9.4.6 Blinding, packaging and labeling

Not applicable.

9.4.7 Prior and concomitant therapy

Boceprevir is a strong inhibitor of CYP3A4/5. Medicines metabolized primarily by CYP3A4/5 may have increased exposure when administered with boceprevir, which could increase or prolong their therapeutic and adverse reactions. Boceprevir does not inhibit or induce the other enzymes of the CYP450.

Further, the combination of boceprevir with rifamipicin or anti-convulsives (such as phenytoin, phenobarbital or carbamazepin) was not recommended. Special caution was to be taken with concomitant treatment with medications that are known to prolong the QT interval, such as amiodaron, chinidin, methadon, pentamidin, and certain neuroleptics.

Refer to the SmPC for more detail.

All prior and concomitant medications taken within 2 weeks before treatment start and during treatment were recorded in the electronic CRF (eCRF).

9.4.8 Treatment compliance

Treatment compliance was assessed by the investigator separately for peg-IFN/rbv at the end of TW 4, and for each of the 3 medications at TWs 8, 12, 24, 28, 36, and 48 as excellent (100% of planned doses), good (≥90% of planned doses), sufficient (≥80% of planned doses), or poor (<80% of planned doses).[5]

9.5 Effectiveness and safety observations

9.5.1 Overview of data collection

A schedule of assessments is provided in T-Table 1.

[5] Based on SAP Appendix (Appendix 16.1.4).

T-Table 1: Schedule of assessments

Data collection	Baseline	Treatment period							Follow-up
	TW0	TW4	TW8	TW12	TW24	TW28[a]	TW36[b]	TW48[b]	FW24
Informed consent	x								
Confirmation of contraception use	x								
Diagnosis and eligibility	x								
Demographic data[c]	x								
Concomitant diseases/medications	x	x	x	x	x	x	x	x	X
Medical history[d]	x								
Physical examination and vital signs	x	x	x	x	x	x	x	x	X
Therapy progression (incl. documentation of termination)		x	x	x	x	x	x	x	X
Laboratory parameters[e]	x	x	x	x	x	x	x	x	X
Compliance		x	x	x	x	x	x	x	
Adverse events	x	x	x	x	x	x	x	x	X

[a] Only in treatment-naïve patients with neg. HCV-RNA at TW8.
[b] For treatment-naïve patients with pos. HCV-RNA at TW8, pre-treated patients with relapse or partial response, null-responders, and patients with cirrhosis.
[c] Was to be assessed at every visit according to the observational plan, but was only assessed at TW0.
[d] Including ultrasound, liver biopsie, and fibroscan, as well as the documentation of consumption of alcohol, drugs, and tobacco. If a liver biopsie was performed, fibrosis was documented following the respective scoring system (METAVIR, ISHAK, or Knodell).
[e] Including HCV-RNA, hematology, coagulation, serum chemistry, and urine drug screen. For the assessment of individual parameters see Section 9.5.3.2.
FW = follow-up week, HCV-RNA = hepatitis C virus-ribonucleic acid, incl. = including, neg. = negative, pos. = positive, TW = treatment week.

9.5.2 Assessment of effectiveness

Virologic response was categorized as SVR, non-response, relapse, and breakthrough and was defined as follows:[6]

- ***SVR***: HCV-RNA undetectable at EOT and at FW 24 (independent of treatment duration);
- ***Non-response***:
  - null-response: decrease in HCV-RNA by <2 $\log_{10}$ in TW 12 compared with Baseline;

[6] As it was assessed by the investigator on the CRF (Appendix 16.1.2).

- partial response: decrease in HCV-RNA by ≥2 $\log_{10}$ in TW 12 compared with Baseline;

- ***Relapse***: HCV-RNA undetectable at EOT, but detectable at FW 24;
- ***Breakthrough***: HCV-RNA undetectable at any visit followed by increase of HCV-RNA by ≥1 $\log_{10}$ while still on treatment.

The definition of virologic response categories as analyzed is detailed in Section 9.5.5.

9.5.3 Assessment of safety

9.5.3.1 Adverse events

An adverse event (AE) was defined as any untoward medical occurrence in a patient administered a pharmaceutical product, biologic (at any dose), whether or not considered related to the use of that product. Adverse events may have included the onset of new illness and the exacerbation of pre-existing conditions as well as pregnancy. Any event that was associated with, or observed in conjunction with, a product overdose whether accidental or intentional, or a product abuse and/or withdrawal, was also considered an AE. All AEs were recorded in the patient's medical records and on the eCRF, including information on the onset and end dates, severity, relationship to study drug, any action taken, and outcome (e.g. hospitalization, discontinuation of therapy). The intensity of the AE was assessed by the investigator. Patients were questioned and/or examined by the principal investigator or a sub-investigator (physician, physician assistant, nurse practitioner). The questioning of patients with regard to the possible occurrence of AEs was generalized such as "How have you been feeling since your last visit?" without suggesting the presence or absence of specific AEs.

AEs with unambiguous relation to the underlying disease of the patient (refer to SmPC) were not recorded in the eCRF.

Intensity and drug relationship

The investigator was to classify the intensity and the drug relationship of an AE according to the following definitions:

Mild:	awareness of sign, symptom, or event, but easily tolerated;
Moderate:	discomfort enough to cause interference with usual activity and may warrant intervention;
Severe:	significantly affects clinical status, incapacitating with inability to do usual activities, and warrants intervention;
Life-threatening:	immediate danger to life.

Not/unlikely related: no temporal association, or the cause of the event had been identified, or the drug, biological, or device could not be implicated;

Possibly related: temporal association, but other etiologies were likely to be the cause; however, involvement of the drug, biological, or device could not be excluded;

Probably related: temporal association, other etiologies were possible but unlikely.

The AE assessment as “expected” or “unexpected” was based on the SmPC.

Serious adverse events

A serious adverse event (SAE) was defined as any experience that suggested a significant hazard to the patient and included any event that

- was fatal;
- was life-threatening (placed the patient at immediate risk of death);
- was permanently disabling;
- required or prolonged hospitalization (hospitalization for routine diagnostic procedures, elective surgery unrelated to the study treatment, or for biopsies are excluded from SAE reporting);
- resulted in a congenital anomaly or birth defect.

Beyond that, an important medical event that, based upon appropriate medical judgment, could jeopardize the patient and required medical or surgical intervention to prevent one of the above listed outcomes was judged as SAE. All changes in laboratory values that were assessed as clinically significant and qualified as SAE were to be reported.

The investigator was to report by fax all SAEs (irrespective of suspected cause), including deaths which occurred while the patient was on study or within 30 days of the last day on which the investigational agent was administered, to the sponsor within one working day after discovery using the SAE form. Initial information by phone was acceptable as long as the SAE form was provided on the same day.

Serious adverse events were to be reported by the sponsor to the ethics committee in accordance with the local law.

9.5.3.2 Safety laboratory assessments

The following parameters were evaluated if they were assessed as part of the investigator's routine practice:[7]

Hematology: *at TW 0, TW 4, TW 8, TW 12, TW 24, TW 28, TW 36, TW 48 and FW 24*: hemoglobin (Hb), hematocrit, erythrocytes, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell (RBC) count, white blood cell count (WBC), neutrophils, monocytes, lymphocytes, CD4+ lymphocytes (only for human immunodeficiency virus [HIV] positive patients), platelets;

Coagulation: *at TW 0, TW 12, TW 24, TW 28, TW 36, TW 48 and FW 24*: quick (prothrombin time), international normalized ratio;

Clinical chemistry: *at TW 0, TW 4, TW 8, TW 12, TW 24, TW 28, TW 36, TW 48 and FW 24*: alanine aminotransferase (AST), aspartate aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, total bilirubin, indirect bilirubin, amylase, lactate dehydrogenase, creatinine, urea, triglyceride, cholesterol, uric acid, glucose, hemoglobin A1c subtype (only for patients with diabetes or elevated glucose values);

at TW 0 only: total protein, albumin, high-density lipoprotein, low-density lipoprotein, insulin, homeostasis model assessment-estimated insulin resistance, iron, ferritin, transferrin, transferrin saturation, alpha fetoprotein, Vitamin D, interleukin-28b (rs12979860) genotype, haptoglobin;

Serology: a*t TW 0, TW 12, TW 24, TW 28, TW 36, TW 48 and FW 24*: Thyroid-stimulating hormone (TSH), triiodothyronine, thyroxine; *at TW 0 and FW 24 (only if elevated at TW 0)*: cryoglobuline;

Urine drug screen: *at TW 0, TW 4, TW 8, TW 12, TW 24, TW 28, TW 36, TW 48 and FW 24:* cocaine, benzodiazepine, barbiturate, amphetamine, cannabinoids, methadone, levo-polamidone, buprenorphine, heroin, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.

[7] Based on the statistical analysis plan (SAP; Appendix 16.1.4).

In addition, the following laboratory and chemistry values were assessed[8]:

- Minimal Hb level categories: ≥10 g/dL, ≥8.5 - <10 g/dL, and <8.5 g/dL;
- Maximal Hb decline from Baseline (g/dL);
- Minimal leukocyte counts according to the World Health Organization (WHO) classification: Grade 0 (>2.0 x 10^3/µL), Grade 1 (2.0 - <3.0 x 10^3/µL), Grade 2 (1.5 - <2.0 x 10^3/µL), Grade 3 (1.0 - <1.5 x 10^3/µL), Grade 4 (<1.0 x 10^3/µL);
- Minimal leukocyte counts according to the WHO classification: Grade 0 (>70 x 10^3/µL), Grade 1 (70 - ≤100 x 10^3/µL), Grade 2 (50 - <70 x 10^3/µL), Grade 3 (25 - <50 x 10^3/µL), Grade 4 (<25 x 10^3/µL);
- Patients who achieved abnormal TSH values at any time point of treatment;
- Patients with estimated glomerular filtration rate (eGFR) declines to <60 at any time point of treatment.[9]

9.5.3.3 Physical examination and vital signs

The physical examination was only performed at Baseline. The complete physical examination included an assessment of the general appearance; head, eyes, ears, nose, and throat; thyroid; lymph nodes; skin; lung; heart; abdomen; extremities; and nervous system. If clinically indicated, assessments of chest, rectum, and genito-pelvic area were documented.

The assessment of vital signs included blood pressure, pulse, body temperature, heart rate, and respiratory rate.

9.5.4 Appropriateness of measurements

All safety assessments are established standard measures.

9.5.5 Effectiveness and safety variables

Effectiveness variables[10]

Primary

- SVR 24, defined as undetectable HCV-RNA at EOT and at FW 24 (or, if HCV-RNA is missing at FW 24, virologic response = SVR);

8 As described in the SAP (Appendix 16.1.9).

9 The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

10 Based on the SAP (Appendix 16.1.4).

Secondary

- RVR, defined as undetectable HCV-RNA at TW 4;
- EVR/Week 8 response, defined as undetectable HCV-RNA at TW 8;
- LVR, defined as undetectable HCV-RNA at TW 24 for the first time during the treatment period (LVR was analyzed for patients with HCV-RNA detectable at TW 12 only);
- Non-response (no virologic response), defined as HCV-RNA detectable at all time points during the treatment period;
- Relapse, defined as undetectable HCV-RNA at EOT but detectable HCV-RNA at FW 24 (or, if HCV-RNA is missing at FW 24, virologic response = relapse or non-response at the end of the study);
- (Virologic) Breakthrough, defined as undetectable HCV-RNA during treatment at any visit and subsequent increase of HCV-RNA ≥1 $\log_{10}$ (i.e. HCV-RNA ≥100 IU/mL) while on treatment.

  Note: Patients with no undetectable HCV-RNA at all visits during treatment, or with no subsequent increase of HCV-RNA ≥1 $\log_{10}$ (i.e. HCV-RNA ≥100 IU/mL) while on treatment, were not considered having a breakthrough even if the investigator documented a virologic breakthrough at the end of the study.

Further effectiveness variables

- Week 4 response, defined as HCV-RNA $\log_{10}$ decline from Baseline >1 $\log_{10}$ at TW 4;
- RVR and Week 4 response categorized as >1 $\log_{10}$ decline and RVR, >1 $\log_{10}$ decline and no RVR, ≤1 $\log_{10}$ decline and RVR, ≤1 $\log_{10}$ and no RVR;
- Week 12 response categorized as HCV-RNA value at TW 12 undetectable, detectable with ≤100 IU/mL HCV-RNA, or detectable with >100 IU/mL HCV-RNA;
- Week 24 response, defined as HCV-RNA undetectable at TW 24;
- Week 24 response and LVR categorized as undetectable at TW 24 and LVR, undetectable and no LVR, and detectable and no LVR (only analyzed for patients with HCV-RNA detectable at TW 12);
- EOT response, defined as HCV-RNA undetectable at EOT;
- Patients were categorized based on their virologic response measured as detectable or undetectable HCV-RNA to:

SVR:	EOT = undetectable, FW 24 = undetectable
Relapse:	EOT = undetectable, FW 24 = detectable
Non-response:	EOT = detectable (detectable at all time points during the treatment period)
Breakthrough:	Breakthrough, but not categorizable to SVR or relapse
Other:	Not categorizable to SVR, relapse, non-response, or breakthrough

Safety variables

- Adverse events;
- serious AEs;
- Laboratory parameters (hematology, serum chemistry, and coagulation);
- Vital signs.

9.6 Data quality assurance

9.6.1 Monitoring

The study was to be monitored regularly according to International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations. All CRFs were to be reviewed against source data for adherence to the observational plan and ICH GCP, as well as for completeness, accuracy and consistency of the data.

9.6.2 Data management procedures

Electronic data capturing was used throughout the study. Investigators were extensively trained on how to use the eCRF system. Data were directly entered into electronic forms and were automatically checked for plausibility and completeness during data entry. Qualified FGK personnel reviewed eCRFs to ensure that they were completed and accurately entered into the database. The monitors also verified that all data entered on the eCRFs were consistent with source documents. The database was further checked for accuracy and consistency by running a series of validated plausibility-check programs at the data management department at FGK. Questions identified were addressed back to the investigator for resolution. Once all questions were resolved the database was locked.

9.6.3 Audits

The clinical study was conducted according to standard operating procedures of MSD SHARP & DOHME GmbH and FGK.

No independent audits were conducted for this study; however, standard routine quality control procedures were employed.

9.7 Financial compensation

As this was an observational, non-interventional study, all costs for routine clinical care including the costs for the study medication were covered by the public health system.

Payments to the investigator for participating in the study were restricted to compensation of time and expenses incurred for additional work (e.g. documentation, patient clarification about the use of the data collected) and were based on the valid statutory scale of medical fees for physicians ("Gebührenverodnung für Ärzte"). Remuneration was calculated such that it did not create incentive to prescribe or recommend the study medication.

9.8 Statistical methods planned in the protocol and determination of sample size

9.8.1 Statistical and analytical plans

Statistical methods are briefly summarized below. A detailed description of statistical methods is provided in the SAP (Appendix 16.1.4).

9.8.1.1 Statistical analysis sets

Safety analysis set

The safety analysis set (SAF) consisted of all patients who received at least one dose of boceprevir, peg-IFN and/or rbv. If the application of any study medication was not certain, the patient was included in the SAF.

To differentiate between patients who used any dose of boceprevir and patients who did not use any boceprevir but other medications only (e.g. dual therapy patients with peg-IFN and/or rbv only), the SAF was separated into 'SAF - boceprevir' and 'SAF - no boceprevir'[11].

All baseline and safety analyses were done on the SAF - boceprevir. For the SAF - no boceprevir, only tables and listings for AEs, drug administration, patient disposition, demographic data, and changes in laboratory values during treatment were generated.

Full analysis set

The full analysis set (FAS) consisted of all evaluable patients of the SAF - boceprevir. A patient was considered evaluable, if at least study start (Baseline; TW 0), start of treatment and at least 1 post baseline visit (TW 4, TW 8, TW 12, TW 24, TW 28, TW 36, TW 48 and/or

[11] Patients initially receiving boceprevir and then changing to treatment with telaprevir were considered as not treated with boceprevir and were included in the SAF - no boceprevir.

FW 24) were documented and at least the baseline and 1 post-baseline HCV-RNA assessment were available.[12]

9.8.1.2 Analysis conventions

Quantitative (continuous) parameters were described by value, standard deviation, minimum, first quartile, median, third quartile, maximum, and 95% confidence interval (CI) by subgroups and overall.

For parameters collected at several visits during the study, the values were analyzed by visit, including absolute values and absolute changes from Baseline (TW 0).

For all tests, a 2-sided significance level of 5% was applied. All analyses of effectiveness parameters were considered exploratory; no adjustment for multiple testing was done. For all tests 2-sided 95% CIs were calculated.

9.8.1.3 Demography and other covariates

All data on demography, epidemiology, antiviral pre-treatment and HCV status, disease characteristics, fertility and contraception, anamnesis (medical history), clinical symptoms and physical examination, clinical anamnesis (including ultrasound, liver biopsy, and fiborscan), HIV and hepatitis B virus (HBV) serology, serum chemistry at Baseline, as well as prior and concomitant medications were summarized descriptively.

All medications were coded using the WHO Drug Dictionary.

9.8.1.4 Effectiveness variables

All effectiveness variables were summarized descriptively and analyzed separately for treatment-naïve and pre-treated patients, including the stratified effectiveness analyses by virologic response status during treatment and by baseline characteristics. The overall effectiveness analyses (without further stratification by virologic response status during treatment and baseline characteristics) were additionally performed for cirrhotic patients and a subset of analyses for non-cirrhotic patients stratified by pre-treatment status (see Section 9.8.1.2 for subgroup analyses). Logistic regression analyses were conducted to determine potential predictors for therapy failure or success.

For the primary endpoint SVR 24, defined as undetectable HCV-RNA at EOT and at FW 24 (or, if HCV-RNA is missing at FW 24, virologic response = SVR at end of study), an exact 2-sided 95% CI for binomial proportions was calculated. To compare relevant subgroups, the

[12] The definition of the FAS was adapted during the data review meeting (DRM; refer to DRM minutes, Appendix 16.1.4).

non-parametric Pearson chi²-test (or Fisher's exact test in case of small samples) for categorical variables was applied.

A logistic regression analysis was carried out to investigate the influence of prognostic factors on SVR 24 and EVR (dependent variables). The following prognostic baseline factors were used as independent variables: pre-treated patients, cirrhosis at Baseline, previous virologic response, drug user under stable substitution, age class at Baseline, baseline laboratory values (GGT, ALT, platelet count, and HCV-RNA), and genotype subtypes 1a/1b. In addition, potential "on-treatment" predictors such as TW 4 response and EVR at TW 8 were evaluated.

For categorical variables using different cut-offs (HCV-RNA) the variable demonstrating the strongest effect in univariate analyses was used for multivariate modeling.

The statistical test of the hypothesis was related to the likelihood ratio chi²-test and model coefficients were tested using Wald tests. Odds ratio estimates with 95% Wald CIs were presented. After the evaluation of the complete model as described above, a backward selection procedure was applied using a significance level of 0.2 for an effect to remain in the model. If the model did not fit for some variables (e.g. convergence criterion not satisfied or variables with many missing values), the affected variables were excluded from the logistic regression analysis model. Additionally, ORs with 95% CIs were calculated using univariate logistic regression models.

A 2-sided Wilcoxon test for paired samples was used to compare the absolute change in HCV-RNA and log-HCV-RNA from Baseline to each post-baseline visit.

9.8.1.5 Safety analysis

Adverse events were coded by using the Medical Dictionary for Regulatory Activities version 15.0 and summarized by system organ class and preferred term, specifying the number of events, and number and rate of patients with events.

For the SAF - boceprevir and the SAF - no boceprevir AEs were summarized without stratification on pre-treatment and cirrhosis status. In addition, AEs were analyzed (overall, serious, and related AEs) for the subgroup of cirrhotic patients in the SAF - boceprevir.

All safety variables were summarized descriptively and no inferential assessments were performed.

9.8.1.6 Subgroup analyses

The following subgroups within the FAS and parameters were analyzed:

- Treatment-naïve patients: demography and all effectiveness analyses;
- Pre-treated patients: demography and all effectiveness analyses;

- Cirrhotic patients: demography, overall effectiveness analyses (without stratification by virologic response status during treatment and baseline characteristics), AE analyses, and changes in laboratory values during treatment;
- Non-cirrhotic patients: demography, overall effectiveness analyses (without stratification by virologic response status during treatment and baseline characteristics), AE analyses, and changes in laboratory values during treatment.[13]

The rates of SVR and other effectiveness variable were investigated in additional subgroups:

- by virologic response status during the treatment (Week 4 response, EVR);
- by baseline characteristics (e.g. drug user under stable substitution, age class [≤50 versus, vs, >50 years], sex, baseline laboratory categories for GGT and ALT [normal vs abnormal], platelet count [≤150,000 vs >150,000], HCV-RNA [≤400,000 vs >400,000 IU/mL and ≤800,00 vs >800,000 IU/mL], and HCV genotype 1 subtypes [1a vs 1b]).

9.8.1.7 Interim analysis

No interim analysis was planned or performed. Data were continuously analyzed at points of interest for publication purposes.

9.8.2 Determination of sample size

The estimates for sample size calculations were based on HCV epidemiologic data in Germany, on data derived from a large observational study of peg-IFN/rbv with over 4,000 participating patients, and on data from the studies IDEAL, SPRINT-2, and RESPOND-2.

A sample size of ≥1,100 patients was required to adequately investigate the objectives of the study. Details on the sample size calculation are provided in Section 10.1 of the observational plan (in German, Appendix 16.1.1).

9.9 Changes in the conduct of the study or planned analyses

There were no amendments to the observational plan.

Physical examinations were only performed at Baseline.

Changes from the observational plan regarding statistical analyses are detailed in the SAP (Appendix 16.1.4) and included:

- No overall analysis of the primary endpoint was conducted;

[13] Based on the SAP Appendix and differing from the SAP, the same subgroup analyses were performed for non-cirrhotic and cirrhotic patients.

- Further effectiveness variables of interest were defined, as Week 4, Week 12, and EOT response, as well as non-response;
- The definition of LVR was used for the newly created endpoint variable Week 24 response (HCV-RNA undetectable at TW 24 yes/no), whereas LVR was defined as undetectable HCV-RNA at TW 24 for the first time during treatment period.
- A patient was presumed to be evaluable, if at least study start (Baseline), start of treatment and at least 1 post-baseline visit (TW 4, TW 8, TW 12, TW 24, TW 28, TW 36, and/or TW 48) were documented.
- The effectiveness outcomes null-response and partial response were not analyzed.

All statistical analyses were based on the SAP Version 2.0. Changes from the SAP Version 1.0 are summarized within SAP Version 2.0 (Appendix 16.1.4).

The sample size of ≥1,100 patients was not achieved. During the course of the study, new medication for the treatment of HCV infections became available, so that fewer patients than anticipated were treated with boceprevir as a routine standard of care procedure.

10 Results - study patients

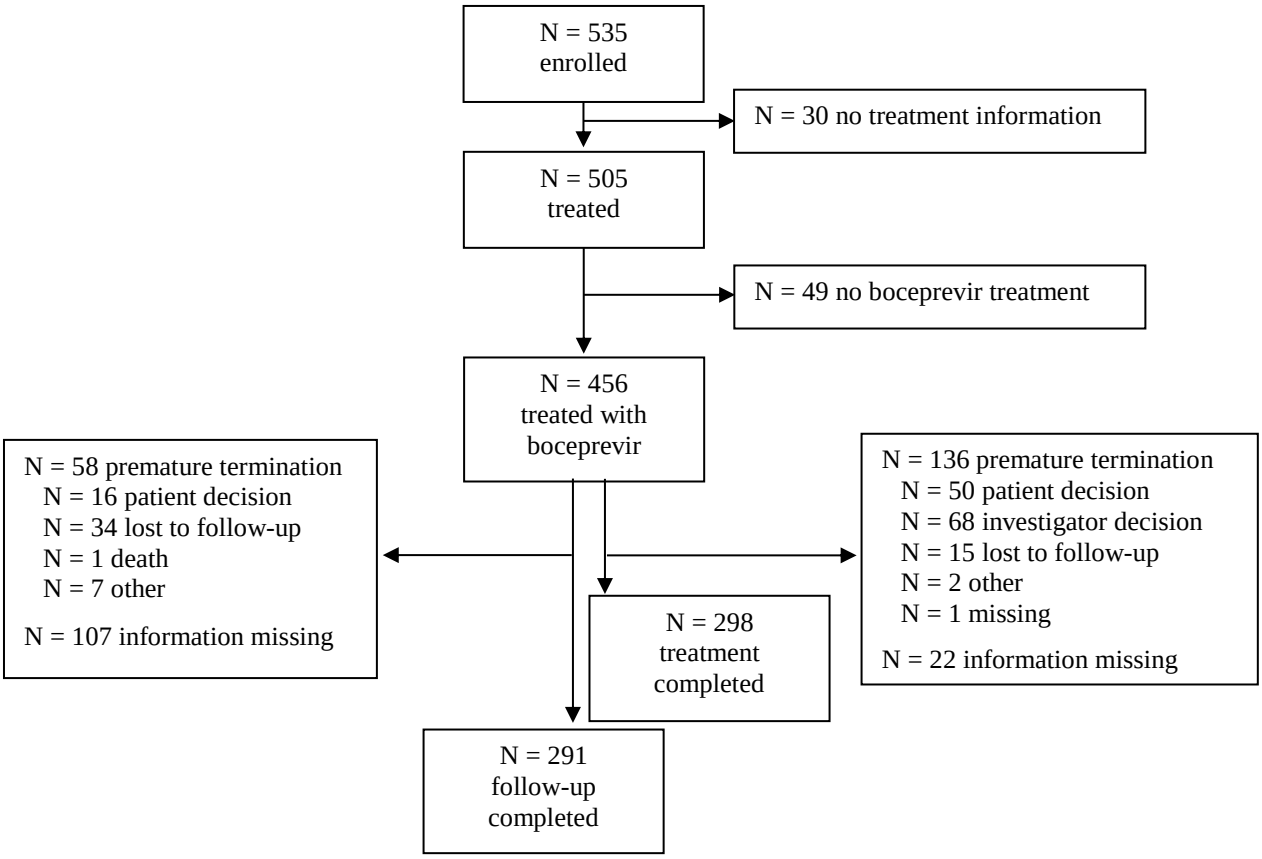
10.1 Disposition of patients and assignment to analysis sets

The disposition of patients is shown in T-Figure 2. In total, 535 patients were enrolled at 96 practices and hospitals in Germany (Listing 1.1.2, Annex 16.3.1) and 505 patients (at 91 practices and hospitals) were treated with pegIFN, rbv, and/or boceprevir. Patient numbers per center varied between 1 and 23 patients (Table 1.1.2, Annex 16.2.1).[14] Of the 505 patients who received any treatment, 456 patients were treated with boceprevir, of which 298 patients completed the treatment and 291 patients completed the follow-up phase.[15]

[14] Only takes into account the 505 patients with treatment information.

[15] Note that patients could have been prematurely terminated during treatment, yet still complete the follow-up phase.

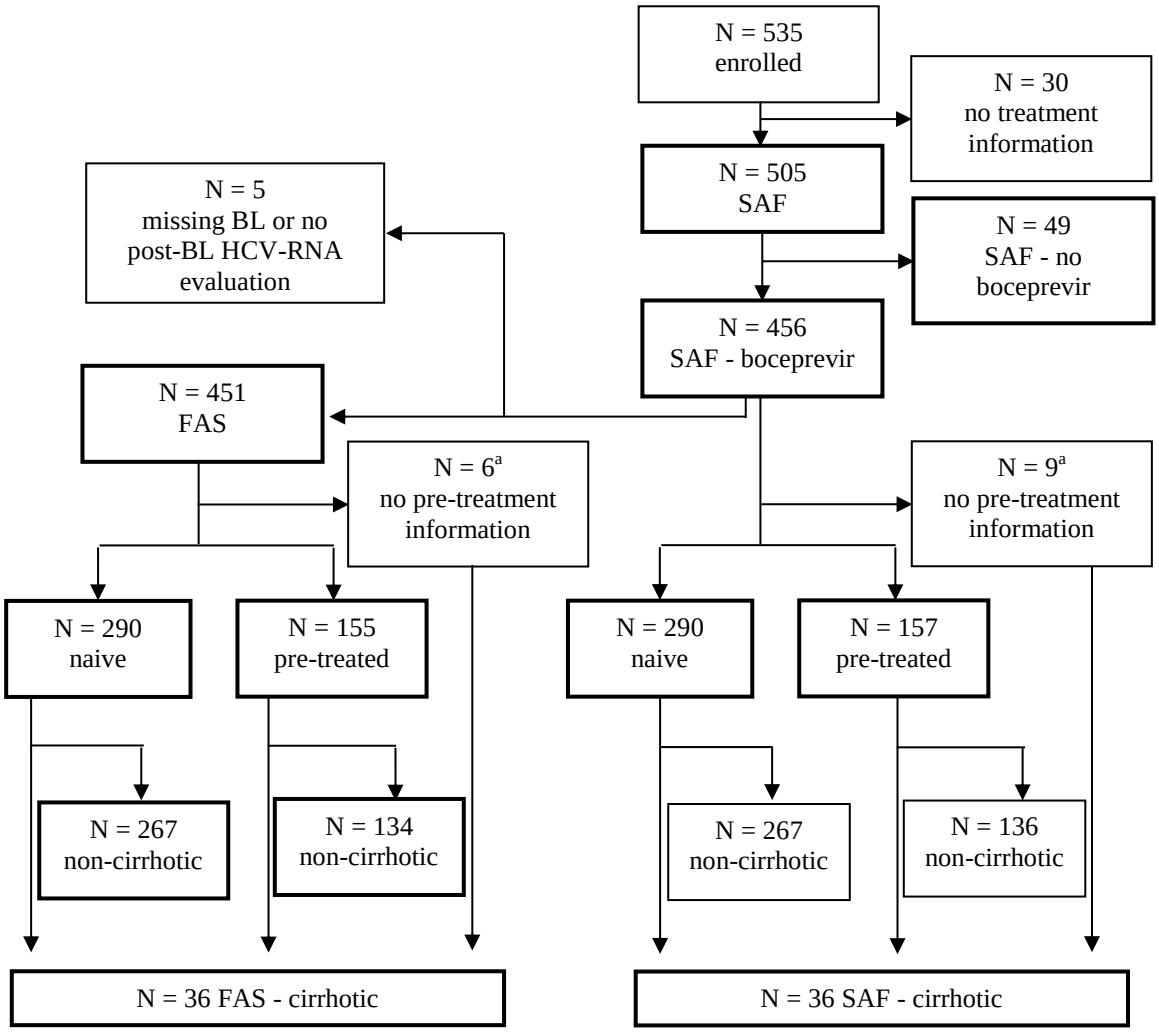
T-Figure 2: Patient disposition



.
N = number of patients.
Data source: Tables 1.1.1, 1.2.1.2 and 1.2.2.2, Appendix 16.2.1; Listing 1.2.1, Appendix 16.3.1.

The assignment of patients to analysis sets is shown in T-Figure 3. All 505 patients who received any treatment were included in the SAF. Patients treated with boceprevir were included in the SAF - boceprevir (N = 456). The FAS only included patients from the SAF - boceprevir, who had at least the baseline and 1 post-baseline HCV-RNA assessment recorded (N = 451). Both, the SAF - boceprevir and FAS, were analyzed in subgroups based on previous treatment and presence or absence of cirrhosis. Analysis sets used for the analysis of study endpoints are highlighted in bold (T-Figure 3).

T-Figure 3: Analysis sets



[a] Calculated by hand.
Analysis sets used for the analysis of endpoints are depicted in bold boxes.
BL = baseline, FAS = full analysis set, N = number of patients, SAF = safety analysis set.
Data source: Table 1.1.1, Appendix 16.2.1; Listing 1.1.1, Appendix 16.3.1.

10.2 Demographics and baseline characteristics

Patient demography at Baseline is summarized in T-Table 2. More male than female patients were treated with boceprevir. Most patients were Caucasian with a median age of 46 years for male patients and 51 years for female patients. Generally, slightly more patients were aged 50 years or older than younger than 50 years. The body mass index of male and female patients was around 27 kg/m².

T-Table 2: Patient demography at Baseline (SAF - boceprevir, N = 456)

Sex[a]		
Male	n (%)[b]	272 (59.9)
Female	n (%)[b]	182 (40.1)
Ethnic origin[c]		
Caucasian	n (%)[b]	413 (91.2)
African, afro-american	n (%)[b]	1 (0.2)
Asian	n (%)[b]	6 (1.3)
other	n (%)[b]	33 (7.3)
Age (years)[a]		
Male (n = 272)	Median (range)	46.0 (18-79)
Female (n = 182)	Median (range)	51.0 (17-77)
≥50 years	n (%)[b]	248 (54.6)
<50 years	n (%)[b]	206 (45.4)
Weight (kg)[d]		
Male (n = 266)	Mean (SD)	84.8 (14.3)
Female (n = 178)	Mean (SD)	72.5 (15.8)
BMI (kg/m^2)[e]		
Male (n = 257)	Mean (SD)	26.7 (4.5)
Female (n = 177)	Mean (SD)	26.6 (5.3)

[a] N = 2 missing. [b] Percentages based on number of patients with available data. [c] N = 3 missing. [d] N = 12 missing. [e] N = 22 missing.
BMI = body mass index, N = number of patients, n = number of patients in category, SAF = safety analysis set, SD = standard deviation.
Data source: Tables 2.1.1.1 and 2.1.2.1, Annex 16.2.2.

Information on weight categories, nationality, German language skills, and insurance and professional status for the SAF - boceprevir is provided in Table 2.1.1.1 and for all other analysis sets in Tables 2.1.1.2 to 2.1.1.7 (Annex 16.2.2). Summary statistics of temperature and years of living in Germany for the SAF - boceprevir are provided Table 2.1.2.1 and for all other analysis sets in Tables 2.1.2.2 to 2.1.2.7 (Annex 16.2.2). By patient data on demographics and baseline characteristics are provided in Listings 2.1.1 and 2.1.2 (Appendix 16.3.2).

About half the female patients (54.9%) were postmenopausal for at least 1 year, and one third (32.9%) were of child-bearing potential (Table 2.4.1, Appendix 16.2.2). Contraceptive methods for female patients of childbearing potential and male patients are summarized in Tables 2.4.1 and 2.4.2, respectively (Appendix 16.2.2). By patient data on fertility and contraception are provided in Listing 2.4 (Appendix 16.3.2).

10.3 Medical history

The medical history is summarized in T-Table 3. The most frequently reported diseases (i.e. in ≥10% of patients) were cardiovascular diseases, psychiatric disorders, and gastrointestinal diseases. All other previous or concomitant diseases were reported by less than 10% of patients.

T-Table 3: Previous or concomitant diseases (SAF - boceprevir, N = 456)

Previous/concomitant disease	Number (%)[a] of patients	
Missing/no disease	4	
Psychiatric disorders	72	(16.0)
Cardiovascular disease	84	(18.6)
Pulmonary diseases	18	(4.0)
Malignant tumor	15	(3.3)
Metabolic disorders/deficiencies	39	(8.6)
Gastrointestinal diseases	56	(12.4)
Bone and joint diseases	32	(7.1)
Kidney diseases	14	(3.1)
Thyroid gland	36	(8.0)
Neurological diseases	14	(3.1)
Eye diseases	8	(1.8)
Infectious diseases	14	(3.1)
Allergies	19	(4.2)
Skin diseases	27	(6.0)
Other diseases	21	(4.7)

[a] Percentages are based on the number of patients with available data (N = 452 for cardiovascular diseases, and N = 451 for all others).
SAF = safety analysis set, N = number of patients.
Data source: Tables 2.5, Annex 16.2.2.

By patient data on medical history are provided in Listing 2.5 (Annex 16.3.2).

10.4 HCV and disease characteristics

10.4.1 Epidemiology, anti-viral treatment, and HCV status

A summary of HCV genotypes and previous therapy is provided in T-Table 4. More patients were infected with HCV genotype 1b than with HCV genotype 1a. The majority of patients with a record of previous treatment received a combination of peg-IFN and rbv. Nearly half the patients with a known response to previous HCV therapy had a relapse, and about a quarter were null-responders. However, for over 60% of patients in the analysis set, information on the last received therapy and the last virologic response are missing.

T-Table 4: HCV characteristics and previous therapy (SAF - boceprevir, N = 456)

	Number (%) of patients	
HCV-RNA genotype		
missing	3	
1a	159	(35.1)
1b	227	(50.1)
1 (no subtype identified)	65	(14.3)
mixed type ½	1	(0.2)
mixed type 1/5	1	(0.2)
overall (non-missing)	453	(100.0)
last HCV therapy		
missing	302	
peg-IFN monotherapy	16	(10.4)
peg-IFN, ribavirin	138	(89.6)
overall (non-missing)	154	(100.0)
last known virologic response		
missing	331	
null-response	30	(24.0)
partial response	23	(18.4)
relapse	57	(45.6)
breakthrough	10	(8.0)
response and re-infection	5	(4.0)
overall (non-missing)	125	(100.0)

HCV = hepatitis C virus, RNA = ribonucleic acid, peg-IFN = pegylated interferon, SAF = safety analysis set, N = number of patients.
Data source: Tables 2.5, Annex 16.2.2.

Data on HCV transmission is summarized in Table 2.2.1 (Appendix 16.2.2). Data on time since infection, diagnosis, last HCV therapy, and RNA concentration at Baseline are summarized in T-Table 5. The median time since HCV infection was about 19 years, and since first HCV diagnosis was about 5 years. The median virus load at Baseline was high with 920,000 IU/mL. All parameters varied greatly between patients.

T-Table 5: HCV status at Baseline (SAF - boceprevir, N = 456)

	n	Median	(Range)
Time since HCV infection [months]	131	228.0	(0-672)
Time since first HCV diagnosis [months]	329	60.0	(0-432)
Time since last therapy [months]	113	50.0	(0-175)
HCV-RNA concentration at BL [IU/mL]	453	$920x10^3$	$(0-140x10^6)$
HCV-RNA concentration (log_{10}) at BL [IU/mL]	453	6.00	(1.0-8.1)

BL = Baseline, HCV = hepatitis C virus, IU = international units, N = number of patients, n = number of patients with available data, SAF = safety analysis set, RNA = ribonucleic acid.
Data source: Table 2.2.2, Annex 16.2.2.

By patient data on epidemiology, anti-viral treatment and HCV status is provided in Listing 2.2 (Appendix 16.3.2).

10.4.2 Disease characteristics

Disease characteristics for the SAF - boceprevir are summarized in Table 2.3.1 (Annex 16.2.2). Assessed characteristics included (but were not limited to) ascites, esophageal varices, hepatic encephalopathy, mixed cryoglobulinemia, vasculitis, membranoproliferative glomerulonephritis, porphyria cutanea tarda, low-grade non-Hodgkin's lymphoma, and HBV and HIV co-infections. The majority of assessed patients (>90%) had negative results for all the above parameters. In 36 patients (of 445 assessed patients; 8.1%), HCV-associated liver cirrhosis was recorded. Data on opiate, alcohol, and nicotine abuse are also summarized in Table 2.3.1 (Annex 16.2.2).

Co-infection with HBV and HIV was reported for 22 (7.7%) and 15 patients (7.1%), respectively (Table 2.8.1, Appendix 16.2.2). A summary of HIV-RNA and HBV-deoxyribonucleic acid quantification at Baseline is provided in Table 2.8.2 (Appendix 16.2.2).

Diagnostic findings including hepatic fibrosis scores (KNODELL, METAVIR, and ISHAK), steatosis, and findings of abdominal ultrasound, as well as serum chemistry for IL-28b at Baseline are provided in Tables 2.7.1 and 2.9.1, respectively (Appendix 16.2.2).

By patient data on disease characteristics, diagnostic findings, HIV and HBV serology, and serum chemistry at Baseline are provided in Listings 2.3.1, 2.3.2, 2.7.1, 2.7.2, 2.8, 2.9.1, and 2.9.2 (Annex 16.2.2).

10.5 Previous and concomitant therapy

Previous concomitant medication and therapy was recorded for 340 patients treated with boceprevir. Frequently recorded medications (i.e. by ≥5% of patients) are summarized in T-Table 6. The most frequently reported medications were for the nervous system (reported by 49% of patients) followed by medications for the alimentary tract and metabolism

(reported by 32% of patients). Citalopram and paracetamol were most commonly taken (by 18% and 17%, respectively).

T-Table 6: Previous and concomitant medication and therapy (SAF - boceprevir, N = 456)

Anatomic group (ATC level 1) WHO-DD preferred term	**Number (%)[a] of patients**
Alimentary tract and metabolism	**147 (32.2)**
Metoclopramide	58 (12.7)
Pantoprazole	46 (10.1)
Anti-infectives for systemic use	**50 (11.0)**
Blood and blood forming organs	**45 (9.9)**
Cardiovascular system	**83 (18.2)**
Rampril	28 (6.1)
Dermatologicals	**64 (14.0)**
Musculo-skeletal system	**54 (11.8)**
Ibuprofen	36 (7.9)
Nervous system	**224 (49.1)**
Paracetamol	77 (16.9)
Citalopram	84 (18.4)
Respiratory system	**45 (9.9)**
Systemic hormonal preparations, excluding sex hormones and insulin	**57 (12.5)**
Levothyroxine	50 (11.0)
Total	**340 (74.6)**

Anatomic group and WHO-DD preferred terms only presented if recorded for ≥5% of patients.

[a] Percentages are based on the number of patients in the analysis set.

ATC = Anatomical therapeutic chemical, N = number of patients, SAF = safety analysis set, WHO-DD = World Health Organization-Drug Dictionary.

Data source: Table 2.10, Appendix 16.2.2.

By patient data on previous and concomitant medication and therapies are provided in Listing 2.10 (Appendix 16.3.2).

10.6 Physical examination and clinical symptoms at Baseline

Physical examination

The physical examination of general condition; abdomen; eyes; skin; lymph nodes; ears, nose, throat; head, neck, thyroid; heart; and lungs showed normal results for ≥80% of patients for all assessed organ systems (Table 2.6.2, Appendix 16.2.2). Except for fatigue, which was reported by 28% of patients, nearly all patients (≥93%) had none of the assessed clinical

symptoms. About 40% of patients reported none of the assessed symptoms at all (Table 2.6.1, Appendix 16.2.2).

By patient data on physical examination results and clinical symptoms are provided in Listing 2.6 (Appendix 16.3.2).

Vital signs

Vital signs at Baseline and post-Baseline are summarized in Table 4.4.1 (Appendix 16.2.4). By patient data is provided in Listing 4.4.1 (Apendix 16.3.4).

10.7 Treatment compliance

Adherence to the treatment regimen was assessed for peg-IFN, rbv, and boceprevir, and is summarized for patients receiving boceprevir separately for treatment-naïve (T-Table 7) and pre-treated patients (T-Table 8). In all treatment weeks, and for all medications, the adherence was excellent for the majority of patients (71-94%) in both analysis sets. Only few patients (<3%) had poor adherence to the planned intake of any of the 3 medications.

T-Table 7: Drug adherence (SAF - boceprevir, treatment-naïve, N = 290)

Medication adherence	**Number (%)[a] of patients**						
	TW4[b] (n = 289)	**TW8 (n = 279)**	**TW12 (n = 266)**	**TW24 (n = 237)**	**TW28 (n = 202)**	**TW36 (n = 85)**	**TW48 (n = 61)**
Peg-IFN							
missing	3 (1.0)	4 (1.4)	5 (1.9)	5 (2.1)	4 (2.0)	4 (4.7)	2 (3.3)
excellent	272 (94.1)	256 (91.8)	236 (88.7)	209 (88.2)	181 (89.6)	73 (85.9)	48 (78.7)
good	14 (4.8)	17 (6.1)	17 (6.4)	21 (8.9)	15 (7.4)	6 (7.1)	11 (18.0)
adequate	-	1 (0.4)	8 (3.0)	1 (0.4)	1 (0.5)	1 (1.2)	-
poor	-	1 (0.4)	-	1 (0.4)	1 (0.5)	1 (1.2)	-
Ribavirin							
missing	6 (2.1)	6 (2.2)	8 (3.0)	8 (3.4)	6 (3.0)	4 (4.7)	2 (3.3)
excellent	252 (87.2)	237 (84.9)	220 (82.7)	182 (76.8)	163 (80.7)	65 (76.5)	50 (82.0)
good	31 (10.7)	33 (11.8)	32 (12.0)	37 (15.6)	30 (14.9)	15 (17.6)	9 (14.8)
adequate	-	3 (1.1)	6 (2.3)	9 (3.8)	2 (1.0)	1 (1.2)	-
poor	-	-	-	1 (0.4)	1 (0.5)	-	-
Boceprevir							
missing	n/a	13 (4.7)	8 (3.0)	8 (3.4)	10 (5.0)	11 (12.9)	11 (18.0)
excellent	n/a	232 (83.2)	223 (83.9)	190 (80.2)	165 (81.7)	63 (74.1)	43 (70.5)
good	n/a	30 (10.8)	27 (10.2)	36 (15.2)	26 (12.9)	10 (11.8)	6 (9.8)
adequate	n/a	1 (0.4)	5 (1.9)	3 (1.3)	-	1 (1.2)	-
poor	n/a	3 (1.1)	3 (1.2)	-	1 (0.5)	-	1 (1.6)

[a] Percentages are based on n. [b] End of the lead-in phase.
N = number of patients in analysis set, n = number of patients with available data, n/a = not applicable, peg-IFN = pegylated interferon, SAF = safety analysis set, TW = treatment week.
Data source: Table 4.3.4.1, Appendix 16.2.2.

T-Table 8: Drug adherence (SAF - boceprevir, pre-treated, N = 157)

Medication adherence	Number (%)[a] of patients						
	TW4[b] (n = 155)	TW8 (n = 149)	TW12 (n = 141)	TW24 (n = 115)	TW28 (n = 97)	TW36 (n = 89)	TW48 (n = 72)
Peg-IFN							
missing	1 (0.6)	3 (2.0)	3 (2.1)	1 (0.9)	2 (2.1)	2 (2.2)	4 (5.6)
excellent	140 (90.3)	134 (89.9)	124 (87.9)	101 (87.8)	85 (87.6)	73 (82.0)	60 (83.3)
good	13 (8.4)	10 (6.7)	14 (9.9)	12 (10.4)	10 (10.3)	13 (14.6)	7 (9.7)
adequate	1 (0.6)	-	-	-	-	1 (1.1)	-
poor	-	2 (1.4)	-	1 (0.9)	-	-	1 (1.4)
Ribavirin							
missing	1 (0.6)	3 (2.0)	3 (2.1)	1 (0.9)	2 (2.1)	2 (2.2)	4 (5.6)
excellent	136 (87.7)	121 (81.2)	112 (79.4)	91 (79.1)	81 (83.5)	70 (78.7)	59 (81.9)
good	18 (11.6)	22 (14.8)	24 (17.0)	22 (19.1)	14 (14.4)	16 (18.0)	8 (11.1)
adequate	-	1 (0.7)	2 (1.4)	-	-	1 (1.1)	-
poor	-	2 (1.4)	-	1 (0.9)	-	-	1 (1.4)
Boceprevir							
missing	n/a	7 (4.7)	3 (2.1)	1 (0.9)	2 (2.1)	3 (3.4)	13 (18.1)
excellent	n/a	119 (79.9)	110 (78.0)	92 (80.0)	81 (83.5)	72 (80.9)	51 (70.8)
good	n/a	18 (12.1)	22 (15.6)	20 (17.4)	13 (13.4)	12 (13.5)	6 (8.3)
adequate	n/a	1 (0.7)	1 (0.7)	-	-	1 (1.1)	1 (1.4)
poor	n/a	4 (2.8)	4 (2.8)	2 (1.8)	1 (1.0)	1 (1.1)	1 (1.4)

[a] Percentages are based on n. [b] End of the lead-in phase.
N = number of patients in analysis set, n = number of patients with available data, n/a = not applicable, peg-IFN = pegylated interferon, SAF = safety analysis set, TW = treatment week.
Data source: Table 4.3.4.2, Appendix 16.2.2.

The adherence of patients not receiving boceprevir is provided in Table 4.3.4.3 (Appendix 16.2.2). By patient data on adherence are provided in Listings 4.3.3.1 and 4.3.3.2 (Appendix 16.3.2).

11 Results - effectiveness

11.1 Primary effectiveness variable

The SVR at FW 24 was assessed as primary endpoint (T-Table 9). Significantly more treatment-naïve than pre-treated patients had achieved an SVR.

T-Table 9: Patients with sustained virologic response at FW 24 (FAS, N = 451)

	n	Number (%)[a] of patients	95% CI[b]	p-value[c]
Treatment-naïve	229	177 (77.3)	71.3, 82.6	
Pre-treated	128	78 (60.9)	51.9, 69.4	0.0010

[a] Percentages are based on n.
[b] Clopper-Pearson 2-sided CI for binomial proportions.
[c] Pearson chi²-test for treatment-naïve versus pre-treated patients.
CI = confidence interval, FAS = full analysis set, FW = follow-up week, N = number of patients, n = number of patients with available data.
Data source: Table 3.2.6.1, Appendix 16.2.3.1.

A set of subgroup analyses was performed for SVR at FW 24, which are presented in the following.

Similarly, the analysis of non-cirrhotic pre-treated and treatment-naïve patients who received boceprevir showed more non-cirrhotic treatment-naïve than pre-treated patients achieving an SVR at FW 24 (T-Table 10). About half of the patients with cirrhosis had an SVR at FW 24.

T-Table 10: Cirrhotic and non-cirrhotic patients with sustained virologic response at FW 24 (FAS, N = 451)

	n	Number (%)[a] of patients	95% CI[b]	p-value[c]
Non-cirrhotic patients				
Treatment-naïve	213	169 (79.3)	73.3, 84.6	
Pre-treated	112	70 (62.5)	52.9, 71.5	0.0011
Cirrhotic patients	26	14 (53.8)	33.4, 73.4	

[a] Percentages are based on n.
[b] Clopper-Pearson 2-sided CI for binomial proportions.
[c] Pearson chi²-test for treatment-naïve versus pre-treated patients.
CI = confidence interval, FAS = full analysis set, FW = follow-up week, N = number of patients, n = number of patients with available data.
Data source: Tables 3.3.6.1 and 3.3.6.2; Appendix 16.2.3.1.

Further subgroup analyses were performed stratified by pre-treatment status (T-Table 11). The frequency of patients with an SVR at FW 24 was compared between the parameter subgroups. For both treatment-naïve and pre-treated patients, patients achieved an SVR at FW 24 more frequently (with $p<0.05$) with a virologic response at Week 4 (versus no response at Week 4), an EVR (versus no EVR), ≤50 years old (versus >50 years old), normal GGT levels (versus elevated levels) at Baseline, or ≤400,000 IU/mL HCV-RNA (versus >400,000 IU/mL) at Baseline.

Pre-treated patients had an SVR at FW 24 more frequently (with $p<0.05$) when they had normal ALT levels (versus elevated levels) at Baseline or a platelet count >150,000/µL (versus ≤150,000/µL) at Baseline. Treatment-naïve patients with HCV-RNA ≤600,000 IU/mL

or ≤800,000 IU/mL more frequently had an SVR at FW 24 than patients with higher HCV-RNA levels.

No difference in SVR achievement was noted between HCV-genotypes, sexes, and drug users on or with no substitution for both pre-treated and treatment-naïve patients (Tables 3.5.6.1, 3.5.6.2, 3.5.6.5, 3.5.6.6, 3.5.6.19, and 3.5.6.20; Appendix 16.2.3.1).

T-Table 11: Subgroup analysis of patients with sustained virologic response at FW 24 (FAS, N = 451)

Parameter	Pre-treated				Treatment-naïve			
Subgroup	n	N (%)[a]	95% CI[b]	p-value[c]	n	N (%)[a]	95% CI[b]	p-value[c]
Week 4 response								
no, ≤1 log_{10}	36	12 (33.3)	18.6, 51.0		45	23 (51.1)	35.8, 66.3	
yes, >1 log_{10}	81	58 (71.6)	60.5, 81.1	**<0.0001**	172	144 (83.7)	77.3, 88.9	**<0.0001**
EVR								
no	46	18 (39.1)	25.1, 54.6		61	32 (52.5)	39.3, 65.4	
yes	67	55 (82.1)	70.8, 90.4	**<0.0001**	153	132 (86.3)	79.8, 91.3	**<0.0001**
Age								
≤50 years	55	40 (72.7)	59.0, 83.9		135	116 (85.9)	78.9, 91.3	
>50 years	73	38 (52.1)	40.0, 63.9	**0.0176**	94	61 (64.9)	54.4, 74.5	**0.0002**
GGT (BL)								
normal	41	31 (75.6)	59.7, 87.6		114	97 (85.1)	77.2, 91.1	
elevated	81	42 (51.9)	40.5, 63.1	**0.0115**	102	69 (67.6)	57.7, 76.6	**0.0024**
ALT (BL)								
normal	26	21 (80.8)	60.6, 93.4		42	35 (83.3)	68.6, 93.0	
elevated	98	55 (56.1)	45.7, 66.1	**0.0218**	181	136 (75.1)	68.2, 81.3	0.2578
Platelet count (BL)								
≤150,000/µL	31	12 (38.7)	21.8, 57.8		36	25 (69.4)	51.9, 83.7	
>150,000/µL	86	57 (66.3)	55.3, 76.1	**0.0075**	175	138 (78.9)	72.1, 84.7	0.2199
HCV-RNA (BL)								
≤400,000 IU/mL	38	28 (73.7)	56.9, 86.6		69	62 (89.9)	80.2, 95.8	
>400,000 IU/mL	89	49 (55.1)	44.1, 65.6	**0.0491**	159	114 (71.7)	64.0, 78.5	**0.0027**
≤600,000 IU/mL	46	33 (71.7)	56.5, 84.0		85	76 (89.4)	80.8, 95.0	
>600,000 IU/mL	81	44 (54.3)	42.9, 65.4	0.0535	143	100 (69.9)	61.7, 77.3	**0.0007**
≤800,000 IU/mL	59	39 (66.1)	52.6, 77.9		98	87 (88.8)	80.8, 94.3	
>800,000 IU/mL	68	38 (55.9)	43.3, 67.9	0.2397	130	89 (68.5)	59.7, 76.3	**0.0003**

Only subgroup analyses with statistically significant differences (p<0.05) in the parameter subgroups are presented. P-values <0.05 are highlighted in **bold**.

[a] Percentages are based on n. [b] Clopper-Pearson 2-sided CI for binomial proportions.

[c] Pearson chi²-test for comparing parameter subgroups.

ALT = alanine aminotransferase, BL = Baseline, CI = confidence interval, EVR = early virologic response, FAS = full analysis set, FW = follow-up week, GGT = gamma glutamyl-transferase, HCV-RNA = hepatitis C virus-ribonucleic acid, IU = international units, N = number of patients, n = number of patients with available data.

Data source: Tables 3.4.6.1 through 3.4.6.4, 3.5.6.3, 3.5.6.4, and 3.5.6.7 through 3.5.6.18; Appendix 16.2.3.1.

The logistic regression analysis is summarized in T-Table 12. Similarly to results presented in T-Table 11, an SVR was more likely achieved in patients ≤50 years, with an EVR at TW 8, HCV-RNA levels ≤400,000 IU/mL at Baseline, platelet counts of >150,000/µL at Baseline, or a Week 4 response. Multiple logistic regression analyses for pre-treated and treatment-naïve

patients, and the subsequent step-wise backward analyses are provided in Tables 3.6.1.2 through 3.6.1.6 (Appendix 16.2.3.1). Univariate logistic regression analyses are provided in Tables 3.6.1.7 through 3.6.1.9 (Appendix 16.2.3.1).

T-Table 12: Logistic regression analysis of sustained virologic response (FAS, N = 451)

Independent variable	Odds ratio	95% CI	p-value
Age (>50 vs ≤50 years)	0.364	0.164, 0.729	0.0053
EVR (yes vs no)	2.529	1.174, 5.447	0.0178
HCV-RNA at BL (≤400,000 vs >400,000 IU/mL)	4.473	1.670, 11.979	0.0029
Platelet count at BL (>150,000 vs ≤150,000/µL)	2.599	1.054, 6.405	0.0380
Week 4 response (>1 log_{10} vs ≤1 log_{10})	3.437	1.526, 7.741	0.0029

Only variables with p-values <0.05 are presented.
BL = Baseline, CI = confidence interval, EVR = early virologic response, FAS = full analysis set, HCV-RNA = hepatitis C virus-ribonucleic acid, IU = international units, N = number of patients, vs = versus.
Data source: Table 3.6.1.1, Appendix 16.2.3.1.

11.2 Further effectiveness variables

HCV-RNA levels

The mean absolute change and log_{10} change in HCV-RNA from Baseline to all post-baseline assessments were significant for treatment-naïve and pre-treated patients (p<0.0001; Wilcoxon-signed rank sum test; Tables 3.1.1.1 and 3.1.1.2, Appendix 16.2.3.2). Results of the HCV-RNA detection are summarized in Table 3.1.2 (Appendix 16.2.3.2).

By patient data on HCV-RNA levels are provided in Listing 3.1.1 (Appendix 16.3.3).

Further effectiveness analyses

All further effectiveness analyses are provided in Appendix 16.2.3.2 in the following tables (as detailed in the SAP Appendix; Appendix 16.1.4):

- Response variables stratified by pre-treatment status:
    - Table 3.2.1.1:Week 4 response/RVR
    - Table 3.2.2.1: Week 8 response/EVR
    - Table 3.2.3.1: Week 12 response
    - Table 3.2.4.1:Week 24 response/LVR
    - Table 3.2.5.1: EOT response
    - Table 3.2.7.1: Relapse
    - Table 3.2.8.1: Non-response

- Table 3.2.9.1: Breakthrough
- Table 3.2.10.1: Response category (SVR/relapse/non-response/breakthrough/ other)

- Subgroups cirrhotic (not stratified) and non-cirrhotic patients (stratified by pre-treatment status):

	Table								
	RVR (W4 response)	EVR (W8 response)	W12 response	LVR (W24 response)	EOT response	Relapse	Non-response	Break-through	Response category
Cirrhotic	3.3.1.1	3.3.2.1	3.3.3.1	3.3.4.1	3.3.5.1	3.3.7.1	3.3.8.1	3.3.9.1	3.3.10.1
Non-cirrhotic	3.3.1.2	3.3.2.2	3.3.3.2	3.3.4.2	3.3.5.2	3.3.7.2	3.3.8.2	3.3.9.2	3.3.10.2

EOT = end of treatment, EVR = early virologic response, LVR = late virologic response, RVR = rapid virologic response, W = week.

- Virologic response or outcome (stratified by pre-treatment status):

		EVR	W12 response	LVR	EOT response	Relapse	Non-response	Break-through	Response category
+ Week 4 response	treatment-naïve	3.4.2.1	3.4.3.1	3.4.4.1	3.4.5.1	3.4.7.1	3.4.8.1	3.4.9.1	3.4.10.1
	pre-treated	3.4.2.2	3.4.3.2	3.4.4.2	3.4.5.2	3.4.7.2	3.4.8.2	3.4.9.2	3.4.10.2
+ EVR	treatment-naïve		3.4.3.3	3.4.4.3	3.4.5.3	3.4.7.3	3.4.8.3	3.4.9.3	3.4.10.3
	pre-treated		3.4.3.4	3.4.4.4	3.4.5.4	3.4.7.4	3.4.8.4	3.4.9.4	3.4.10.4

EOT = end of treatment, EVR = early virologic response, LVR = late virologic response, W = week.

- Virologic response by baseline characteristics (stratified by pre-treatment status):

	RVR (W4 resp.)	EVR (W8 resp.)	W12 resp.	LVR (W24 resp.)	EOT resp.	Relapse	Non-resp.	Break-through	Resp. category
Drug user on substitution	3.5.1.1.-3.5.1.2	3.5.2.1.-3.5.2.2	3.5.3.1.-3.5.3.2	3.5.4.1.-3.5.4.2	3.5.5.1.-3.5.5.2	3.5.7.1.-3.5.7.2	3.5.8.1.-3.5.8.2	3.5.9.1.-3.5.9.2	3.5.10.1.-3.5.10.2
Age	3.5.1.3.-3.5.1.4	3.5.2.3.-3.5.2.4	3.5.3.3.-3.5.3.4	3.5.4.3.-3.5.4.4	3.5.5.3.-3.5.5.4	3.5.7.3.-3.5.7.4	3.5.8.3.-3.5.8.4	3.5.9.3.-3.5.9.4	3.5.10.3.-3.5.10.4
Sex	3.5.1.5.-3.5.1.6	3.5.2.5.-3.5.2.6	3.5.3.5.-3.5.3.6	3.5.4.5.-3.5.4.6	3.5.5.5.-3.5.5.6	3.5.7.5.-3.5.7.6	3.5.8.5.-3.5.8.6	3.5.9.5.-3.5.9.6	3.5.10.5.-3.5.10.6
Baseline lab. values	3.5.1.7-3.5.1.18	3.5.2.7-3.5.2.18	3.5.3.7-3.5.3.18	3.5.4.7-3.5.4.18	3.5.5.7-3.5.5.18	3.5.7.7-3.5.7.18	3.5.8.7-3.5.8.18	3.5.9.7-3.5.9.18	3.5.10.7-3.5.10.18
HCV genotype	3.5.1.19-3.5.1.20	3.5.2.19-3.5.2.20	3.5.3.19-3.5.3.20	3.5.4.19-3.5.4.20	3.5.5.19-3.5.5.20	3.5.7.19-3.5.7.20	3.5.8.19-3.5.8.20	3.5.9.19-3.5.9.20	3.5.10.19-3.5.10.20

EOT = end of treatment, EVR = early virologic response, HCV = hepatitis C virus, lab. = laboratory, LVR = late virologic response, resp. = response, RVR = rapid virologic response, W = week.

By patient data on effectiveness are provided in Listing 3.2.1 (Appendix 16.3.3).

11.3 Effectiveness summary

Overall, significantly more treatment-naïve (77%) than pre-treated patients (61%) had an SVR at FW 24 (T-Table 9). Patients with cirrhosis showed an SVR at FW 24 in 54% of patients (T-Table 10).

Independent predictors for higher SVR rates in pre-treated and treatment-naïve patients included a >1 $\log_{10}$ decline in HCV-RNA at TW 4 (Week 4 response), EVR, age ≤50 years, normal GGT levels at TW 0, and HCV-RNA ≤400,000 IU/mL at TW 0. Additional predictors for higher SVR rates in pre-treated patients included normal ALT levels at TW 0 and platelet counts >150,000/µL at TW 0 (T-Table 11).

12 Results - safety

12.1 Extent of exposure

The treatment duration for the 3 study medications is summarized by analysis set in T-Table 13. The overall median treatment duration was 307 days for pre-treated patients, 197 days for treatment-naïve patients, and 168 days for patients not treated with boceprevir.

T-Table 13: Extent of exposure

	Treatment duration [days]							
	Peg-IFN		Ribavirin		Boceprevir		Total	
	n	median (range)	n	median (range)	n	median (range)	n	median (range)
SAF - boc - pretr. (N = 157)	128	318.5 (40-519)	123	321.0 (36-531)	125	223.0 (15-330)	146	306.5 (42-934)
SAF - boc - naive (N = 290)	253	197.0 (29-396)	252	197.0 (29-396)	247	169.0 (8-368)	282	197.0 (29-414)
SAF - no boc (N = 49)	41	166.0 (1-335)	40	169.0 (3-336)	2[a]	21.0 (14-28)	46	167.5 (1-336)

[a] Two patients received boceprevir treatment for 14 and 28 days, respectively, before changing to treatment with telaprevir.
Boc = boceprevir, N = number of patients in the analysis set, n = number of patients with available data, peg-IFN = pegylated interferon, pretr. = pre-treated, SAF = safety analysis set.
Data source: Tables 4.3.1.1, 4.3.1.2, and 4.3.1.3, Appendix 16.2.4.

By patient data on extent of exposure is provided in Listings 4.3.1.1, 4.3.1.2, 4.3.2.1, and 4.3.2.2 (Appendix 16.3.4).

12.2 Adverse events

12.2.1 Brief summary of adverse events

A brief summary of AEs is shown in T-Table 14. In total, 362 patients in the SAF - boceprevir reported 2201 AEs, of which 81 AEs reported by 48 patients were serious[16] and 1219 AEs reported by 292 patients were possibly or probably related to treatment with boceprevir.

Of the 49 patients in the SAF - no boceprevir, 30 patients reported 168 AEs, of which one was serious.

[16] Note that for some AEs (including 7 SAEs), the investigator recorded several symptoms which were coded as separate AEs in the database.

T-Table 14: Overview of adverse events (SAF, N = 505)

	Boceprevir (N = 456)	No boceprevir (N = 49)
Number of AEs[a]	2201	168
Number of SAEs[a]	81	1
Number of AEs related to boceprevir[b]	1219	n/a
Number (%)[c] of patients with AEs	362 (79.4)	30 (61.2)
Number (%)[c] of patients with SAEs	48 (10.5)	1 (2.0)
Number (%)[c] of patients with AEs related to boceprevir[b]	292 (64.0)	n/a

[a] Note that (S)AEs with several symptoms were coded as separate (S)AEs in the database.
[b] Probably or possibly related.
[c] Percentages are based on the total number of patients per analysis set.
AE = adverse event, N = number of patients, n/a = not applicable, SAE = serious adverse event, SAF = safety analysis set.
Data source: Tables 4.1.1.1, 4.1.1.2, 4.1.2.1, 4.1.2.2, and 4.1.3.1, Appendix 16.2.4.

Of the 36 patients with cirrhosis, 29 (80.6%) reported 157 AEs, of which 13 AEs reported by 8 patients (22.2%) were serious (Tables 4.1.1.3 and 4.1.2.3, Appendix 16.2.4).

Two patients died due to AEs, 1 patient due to confusional state, apathy, and abnormal general physical condition, and another one due to an overdose[17] (Listing 4.1.1.1, Appendix 16.3.4).

By patient data on AEs and SAEs are provided in Listings 4.1.1.1, 4.1.1.2, 4.1.2.1, and 4.1.2.2 (Appendix 16.3.4).

12.2.2 Display of adverse events

An overview of AEs by system organ class is provided in T-Table 15. General disorders and administration site conditions were generally most commonly reported (44% of patients in the SAF - boceprevir and 33% in the SAF - no boceprevir). Blood and lymphatic system disorders and gastrointestinal disorders were frequently reported in patients in the SAF - boceprevir (42% and 37%, respectively), and blood and lymphatic and psychiatric disorders were most frequently reported in patients not receiving boceprevir (both by 29% of patients). Anemia and fatigue were the most commonly reported AEs in both analysis sets (reported by 31% and 27% in the SAF - boceprevir, and by 18% and 16% in the SAF - no boceprevir, respectively).

[17] The AE ‘overdose’ causing the patient’s death was not reported as an AE in the eCRF and is therefore not included in the AE tables and listings.

T-Table 15: Adverse events by system organ class (SAF, N = 505)

System organ class (MedDRA) Preferred term	Number (%)[a] of patients	
	Boceprevir (N = 456)	No boceprevir (N = 49)
Blood and lymphatic system disorders	**193 (42.3)**	**14 (28.6)**
Anemia	141 (30.9)	9 (18.4)
Leucopenia	85 (18.6)	6 (12.2)
Thrombocytopenia	77 (16.9)	5 (10.2)
Gastrointestinal disorders	**169 (37.1)**	**12 (24.5)**
Nausea	91 (20.0)	8 (16.3)
General disorders and administration site conditions	**199 (43.6)**	**16 (32.7)**
Asthenia	31 (6.8)	6 (12.2)
Fatigue	122 (26.8)	8 (16.3)
Influenza like illness	33 (7.2)	5 (10.2)
Infections and infestations	**59 (12.9)**	**6 (12.2)**
Investigations	**68 (14.9)**	**5 (10.2)**
Musculoskeletal and connective tissue disorders	**63 (13.8)**	**7 (14.3)**
Myalgia	22 (4.8)	5 (10.2)
Nervous system disorders	**148 (32.5)**	**11 (22.4)**
Dysgeusia	62 (13.6)	2 (4.1)
Headache	66 (14.5)	6 (12.2)
Psychiatric disorders	**128 (28.1)**	**14 (28.6)**
Depression	34 (7.5)	5 (10.2)
Respiratory, thoracic and mediastinal disorders	**64 (14.0)**	**3 (6.1)**
Skin and subcutaneous disorders	**142 (31.1)**	**9 (18.4)**
Pruritus	56 (12.3)	4 (8.2)
Total	**362 (79.4)**	**30 (61.2)**

Data only presented if reported by ≥10% of patients in any analysis set.

[a] Percentages are based on the total number of patients per analysis set.

MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients, SAF = safety analysis set.

Data source: Tables 4.1.1.1 and 4.1.1.2, Appendix 16.2.4.

Patients with cirrhosis who received boceprevir also most commonly reported anemia and fatigue with a similar frequency (36.1% and 22.2% of patients, respectively; Table 4.1.1.3, Appendix 16.2.4).

12.2.3 Analysis of adverse events

Intensity

In both, the SAF - boceprevir and the SAF - no boceprevir, the majority of AEs were mild or moderate. In total, 2 life-threatening AEs (pancytopenia and ascites) were reported, which occurred in 2 patients in the SAF - boceprevir. The events had a probable (pancytopenia) and possible (ascites) relationship to treatment with boceprevir and the treatment was stopped or interrupted (T-Table 16, Listings 4.1.3 and 4.1.4, Appendix 16.3.4).

T-Table 16: Adverse events by intensity (SAF, N = 505)

Grade	Number (%)[a] of events	
	Boceprevir (N = 456)	No boceprevir (N = 49)
Number of events	2201 (100.0)	168 (100.0)
1 (mild)	1077 (48.9)	116 (69.0)
2 (moderate)	978 (44.4)	49 (29.2)
3 (severe)	135 (6.1)	1 (0.6)
4 (life threatening)	2 (0.1)	-
Grade missing	9 (0.4)	2 (1.2)

[a] Percentages are based on the total number of events per analysis group (calculated by hand). Zero is shown as '-'.
N = number of patients, SAF = safety analysis set.
Data source: Tables 4.1.4.1 and 4.1.4.2, Appendix 16.2.4.

Relation to study medication

In total, 1219 AE reported by 292 patients (64.0%) of the SAF - boceprevir were possibly or probably related to treatment with boceprevir (T-Table 17). The most frequently reported AEs with relation to treatment with boceprevir were anemia, nausea, and dysgeusia (reported by 20%, 15%, and 13% of patients, respectively).

T-Table 17: Adverse events related to boceprevir (SAF - boceprevir, N = 456)

System organ class (MedDRA) Preferred term	Number (%)[a] of patients
Blood and lymphatic system disorders	**131 (28.7)**
Anemia	92 (20.2)
Leukopenia	42 (9.2)
Thrombocytopenia	41 (9.0)
Gastrointestinal disorders	**124 (27.2)**
Nausea	67 (14.7)
General disorders and administration site conditions	**100 (21.9)**
Fatigue	51 (11.2)
Investigations	**43 (9.4)**
Metabolism and nutrition disorders	**28 (6.1)**
Decreased appetite	23 (5.0)
Musculoskeletal and connective tissue disorders	**25 (5.5)**
Nervous system disorders	**95 (20.8)**
Dysgeusia	59 (12.9)
Psychiatric disorders	**70 (15.4)**
Sleep disorder	28 (6.1)
Respiratory, thoracic and mediastinal disorders	**39 (8.6)**
Skin and subcutaneous disorders	**109 (23.9)**
Pruritus	45 (9.9)
Rash	29 (6.4)
Total	**292 (64.0)**

Includes AEs with possible and probable relationship to treatment with boceprevir. Data only presented if reported by ≥5% of patients.

[a] Percentages are based on the total number of patients in the analysis set.

MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients, SAF = safety analysis set.

Data source: Table 4.1.3.1, Appendix 16.2.4.

By patient data on AEs with causal relationship to treatment with boceprevir are provided in Listing 4.1.3 (Appendix 16.3.4).

Outcome

At the end of the study, the majority of AEs had recovered (68% in the SAF - boceprevir and 55% in the SAF - no boceprevir) or the condition remained unchanged (17% in the SAF - boceprevir and 28% in the SAF - no boceprevir). The 3 AEs with the outcome ‘death due to this event’ of 1 patient in the SAF - boceprevir analysis set included confusional state, apathy, and abnormal general physical condition; but, the actual cause of death was stated as decompensated liver cirrhosis (refer to Listing 1.2.1, Appendix 16.3.1).

T-Table 18: Adverse events by outcome (SAF, N = 505)

Outcome	Number (%) of events[a]	
	Boceprevir (N = 456)	No boceprevir (N = 49)
Number of events	2201 (100.0)	168 (100.0)
Death due to other event	1 (0.0)[c]	-
Death due to this event	3 (0.1)	-
Deteriorated	7 (0.3)	-
Improved	124 (5.6)	6 (3.6)
Unknown[b]	182 (8.3)	23 (13.7)
Permanent damage	2 (0.1)	-
Recovered	1497 (68.0)	92 (54.8)
Unchanged	383 (17.4)	47 (28.0)
Missing	2 (0.1)	-

Zero is shown as '-'.
[a] Percentages are based on the total number of events per analysis group (calculated by hand).
[b] Includes unknown, not applicable, not documented, not examined, and not known.
[c] The actual AE causing this patient's death (overdose) was not included in the AE listing.
N = number of patients, SAF = safety analysis set.
Data source: Tables 4.1.1.1 and 4.1.1.2, Appendix 16.2.4; Listing 4.1.1.1, Appendix 16.3.4.

12.2.4 Listing of adverse events by patient

A listing of all AEs by patient is provided in Appendix 16.4.3, Listing 4.1.1.1. By patient data of severe and life-threatening AEs are provided in Listing 4.1.4 and of AEs with missing information about the relationship to boceprevir in Listing 4.1.5 (Appendix 16.3.4).

12.3 Deaths, other serious adverse events, and other significant adverse events

12.3.1 Deaths

Two patients died during the observational study (T-Table 19). Both patients received treatment with boceprevir.

T-Table 19: Deaths (SAF, N = 505)

Patient ID	Date of death	Cause of death	Days since last treatment	Treatment duration			
				Peg-IFN [days]	Rbv [days]	Boc [days]	Overall [weeks]
046-005	20-Oct-2013	Decompensated liver cirrhosis	27	134	140	112	20
134-006	18-Mar-2014	(Self-inflicted) overdose	53	183	190	163	28

Boc = boceprevir, ID = identification, N = number of patients, Peg-IFN = pegylated interferon, Rbv = ribavirin, SAF = safety analysis set.
Data source: Listing 1.2.1, Appendix 16.3.2, Listings 4.1.2.1and 4.3.2.1, Appendix 16.3.4.

12.3.2 Other serious adverse events

In total, 82 SAEs were reported for 49 patients, of which only 1 patient (experiencing 1 SAE) was in the SAF - no boceprevir analysis set (T-Table 20). Generally, blood and lymphatic system disorders and psychiatric disorders were most commonly (i.e. by >2% of patients) reported. The majority of SAEs were single events reported by 1 patient each. SAEs reported by more than 1 patient were anemia, pancytopenia, nausea, and depression.

The only SAE in the SAF - no boceprevir was jaundice.

T-Table 20: Serious adverse events by system organ class (SAF, N = 505)

System organ class (MedDRA) Preferred term	Number (%)[a] of patients	
	Boceprevir (N = 456)	No boceprevir (N = 49)
Blood and lymphatic system disorders	**12 (2.6)**	**-**
Anemia	9 (2.0)	-
Pancytopenia	3 (0.7)	-
Cardiac disorders	**4 (0.9)**	**-**
Eye disorders	**1 (0.2)**	
Gastrointestinal disorders	**6 (1.3)**	**-**
Nausea	3 (0.7)	-
General disorders and administration site conditions	**4 (0.9)**	**-**
Hepatobiliary disorders	**-**	**1 (2.0)**
Infections and infestations	**8 (1.8)**	**-**
Injury, poisoning and procedural complications	**2 (0.4)**	**-**
Investigations	**3 (0.7)**	**-**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**2 (0.4)**	**-**
Nervous system disorders	**7 (1.5)**	**-**
Syncope	2 (0.4)	-
Psychiatric disorders	**10 (2.2)**	**-**
Depression	4 (0.9)	-
Respiratory, thoracic and mediastinal disorders	**3 (0.7)**	
Skin and subcutaneous disorders	**2 (0.4)**	**-**
Surgical and medical procedures	**1 (0.2)**	**-**
Vascular disorders	**3 (0.7)**	**-**
Total	**48 (10.5)**	**1 (2.0)**

Preferred terms only presented if reported by at least 2 patients in any analysis set. N = 0 is shown as '-'.

[a] Percentages are based on the total number of patients per analysis set.
MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients, SAF = safety analysis set.
Data source: Table 4.1.2.1, 4.1.2.2, Appendix 16.2.4.

By patient data on SAEs are provided in Listings 4.1.2.1 and 4.1.2.2 (Appendix 16.3.4).

12.3.3 Other significant adverse events

In the SAF - boceprevir, 68 patients (14.9%) reported AEs of the system organ class 'investigations'. The most commonly reported AEs (i.e. by ≥5 patients, ≥1.1%) were decreased hemoglobin (20 patients, 4.4%), decreased RBC count (6 patients, 1.3%), decreased weight (28 patients, 6.1%), and decreased WBC count (5 patients, 1.1%). All other AEs were reported by ≤3 patients (Table 4.1.1.1, Appendix 16.2.4).

In the SAF - no boceprevir, only 5 patients (10.2%) reported 5 investigations as AEs, including increased body temperature, abnormal laboratory test, increased viral load, and decreased weight (reported by 2 patients; Table 4.1.1.2, Appendix 16.2.4).

12.4 Clinical laboratory evaluation

12.4.1 Laboratory values over time

12.4.1.1 Hematology

Descriptive statistics for all hematology parameters are provided in Table 4.2.2 (Appendix 16.2.4). Shift tables for changes in hematology values for the SAF - boceprevir are provided in Table 4.2.1 (Appendix 16.2.4). Frequent shifts (>10% of patients) from values within the normal range at Baseline to clinically significantly abnormal values at a post-baseline visit were observed in hemoglobin, hematocrit, RBC, WBC, and platelets (Table 4.2.1, Appendix 16.2.4).

The frequency of patients in hematology parameter categories are summarized in T-Table 21. The frequency of patients with hemoglobin values below 10 g/dL was higher in the SAF - boceprevir (39%) than in the SAF - no boceprevir (18%). Similarly, more patients in the SAF - boceprevir (29%) than in the SAF - no boceprevir (14%) had a leukocyte count below 2.0 x 10^3/µl. In both analysis populations >80% of patients had a platelet count of ≥70x10^3/µL (Grade 0 and 1); however, slightly more patients in the SAF - boceprevir had a platelet count of <50x10^3/µl (9%) than in the SAF - no boceprevir (5%).

T-Table 21: Categories for hematology parameters (SAF, N = 505)

Parameter Category	Number (%)[a] of patients Boceprevir (N = 456)	 No boceprevir (N = 49)
Hemoglobin [g/dL]		
missing	8	5
≥10	273 (60.9)	36 (81.8)
≥8.5 - < 10	143 (31.9)	6 (13.6)
<8.5	32 (7.1)	2 (4.5)
Overall (non-missing)	448 (100.0)	44 (100.0)
Leukocyte count [x10³/µL]		
missing	11	6
Grade 0: ≥3.0	116 (26.1)	21 (48.8)
Grade 1: 2.0 - <3.0	202 (45.4)	16 (37.2)
Grade 2: 1.5 - <2.0	94 (21.1)	3 (7.0)
Grade 3: 1.0 - <1.5	32 (7.2)	3 (7.0)
Grade 4: < 1.0	1 (0.2)	-
Overall (non-missing)	445 (100.0)	43 (100.0)
Platelet count [x10³/µL]		
missing	11	5
Grade 0: >100	248 (55.7)	34 (77.3)
Grade 1: 70 - ≤100	120 (27.0)	3 (6.8)
Grade 2: 50-<70	38 (8.5)	5 (11.4)
Grade 3: 25 - <50	35 (7.9)	1 (2.3)
Grade 4: < 25	4 (0.9)	1 (2.3)
Overall (non-missing)	445 (100.0)	44 (100.0)

[a] Percentages are based on the number of overall (non-missing) patients. N = 0 is shown as '-'.
N = number of patients, SAF = safety analysis set.
Data source: Tables 4.2.8.1 and 4.2.8.2, Appendix 16.2.4.

The mean maximal hemoglobin decline from Baseline was 4.2 g/dL (standard deviation [SD]: 1.5 g/dL) in the SAF - boceprevir and 3.2 g/dL (SD: 2.1 g/dL) in the SAF - no boceprevir (Tables 4.2.9.1 and 4.2.9.2, Appendix 16.2.4). Data of patients with cirrhosis are presented in Tables 4.2.8.3 and 4.2.9.3 (Appendix 16.2.4). Hematology values by patient are provided in Listings 4.2.1 (Appendix 16.3.4).

12.4.1.2 Clinical chemistry and coagulation

Descriptive statistics for all coagulation and chemistry parameters are provided in Tables 4.2.4 and 4.2.6, respectively (Appendix 16.2.4). Shift tables for changes in chemistry and coagulation values are provided in Tables 4.2.3 and 4.2.5, respectively (Appendix 16.2.4). No frequent shifts (>5 patients) from values within the normal range at Baseline to clinically

significantly abnormal values at a post-baseline visit were observed for any coagulation or chemistry parameters (Tables 4.2.3 and 4.2.5, respectively, Appendix 16.2.4).

The frequency of patients with abnormal TSH values or an eGFR decline to <60 mL/min/1.73 m² of body surface area during the study is summarized in T-Table 22. In both analysis sets, about 20% of patients had abnormal TSH during the treatment. An eGFR decline was only observed in the SAF - boceprevir.

T-Table 22: Abnormal TSH and eGFR delince during treatment (SAF, N = 505)

	Number (%)[a] of patients	
	Boceprevir (N = 456)	**No boceprevir (N = 49)**
Abnormal TSH during treatment	79 (21.8)[b]	5 (18.5)[d]
eGFR decline to <60 during treatment (mL/min/1.73m² of body surface area)	30 (7.9)[c]	-[e]

N = 0 is shown as '-'.
[a] Percentages are based on the number of overall (non-missing) patients. [b] N = 94 missing.
[c] N = 78 missing. [d] N = 22 missing. [e] N = 11 missing.
eGFR = estimated glomerular firltration rate, N = number of patients, SAF = safety analysis set, TSH = thyroid-stimulating hormone.
Data source: Tables 4.2.8.1 and 4.2.8.2, Appendix 16.2.4.

By patient data of chemistry and coagulation are provided in Listings 4.2.1 (Appendix 16.3.4).

12.4.1.3 Urine drug screen

Results of the urine drug screen are provided in Table 4.2.7 (Appendix 16.2.4) and Listing 4.2.2 (Appenidx 16.3.4).

12.4.2 Individual clinically significant abnormalities

No clinically significant laboratory values were reported as SAEs. Three patients had AEs of the system organ class 'investigations' that were reported as SAEs:

Patient 046-005 experienced an abnormal general physical condition on 08-Aug-2013 (TW 12), about 2 months after the first administration of boceprevir. The event was assessed as probably related to treatment with boceprevir and the treatment was stopped or interrupted. No clinically significant laboratory values were reported in TW 12 (05-Aug-2013). Previously, in TW 4 and TW 8, the patient had clinically significantly low platelets (TW 0: 54x10³/µl, TW 4: 21x10³/µl, TW 8: 17x10³/µl), which were assessed as not clinically significantly abnormal at TW 12 (22x10³/µL; Listing 4.2.1, Appendix 16.3.4). The patient died on 20-Oct-2013 of decompensated liver cirrhosis.

Patient 089-007 experienced a severe abnormal liver function test on 22-Dec-2013 (TW 12) with probable relationship to boceprevir treatment, and the treatment with boceprevir was prematurely discontinued (Listing 4.1.1.1, Appendix 16.3.4;100 days after the first administration of boceprevir). The investigator commented on 07-Feb-2014 that ALT, AST and GGT were extremely increased (Listing 5.1, Appendix 16.3.1). The condition had improved on 08-Mar-2014. The last available laboratory values from TW 12 (23-Dec-2013) were ALT: 93 U/L (TW 0: 597 U/L), AST: 218 U/L (TW 0: 315 U/L), and GGT: 1113 U/L (TW 0: 391 U/L), which were all assessed as not clinically significant by the investigator (Listing 4.2.1, Appendix 16.3.4).

Patient 132-001 experienced 3 incidences of decreased hemoglobin on 08-Feb-2013 (TW 8), 02-Mar-2013 (TW 11), and 19-Jul-2013 (TW 31) with possibly or probably related to treatment with boceprevir, 54 days, 76 days, and 215 days after the first administration of boceprevir. All 3 events were reported as SAEs. At several post-baseline visits, hemoglobin values <8.5 g/dL were recorded (TW 8 and TW 28: 8.2 g/dL, TW 36: 8.1 g/dL), all of which were assessed as not clinically significant by the investigator. On 10-Jul-2013, the following laboratory values were reported as non-serious AEs: hemoglobin 4.53 g/dL, leukocytes 2.6x10³/µL, and thrombocytes 114x10³/µL (Listing 4.1.1.1, Appendix 16.3.4). The patient received transfusions on 18-Jul-2013, and had recovered on the same day.

12.5 Other safety data

12.5.1 Vital signs and BMI

No apparent changes were observed during treatment in any vital sign parameter or the BMI in the SAF- boceprevir (Table 4.4.1, Appendix 16.2.4).

12.5.2 Physical examination

A physical examination was only performed at Screening (see Section 10.6).

12.6 Safety summary

In total, 362 (79.4%) patients in the SAF - boceprevir and 30 (61.2%) patients in the SAF - no boceprevir reported 2201 and 168 AEs, respectively. Anemia and fatigue were the most commonly reported AEs in both analysis populations; however, the frequency for anemia and fatigue was higher in patients treated with boceprevir (reported by 31% and 27% of patients in the SAF - boceprevir, and by 18% and 16% in the SAF - no boceprevir, respectively). The majority of patients had recovered by FW 24.

All but 1 SAE (jaundice) of the 82 reported SAEs were experienced by patients in the SAF - boceprevir. The majority of SAEs were single events reported by 1 patient each. SAEs reported by more than 1 patient were anemia, pancytopenia, nausea, and depression.

The analysis of hematology values over time showed frequent shifts (>10% of patients) from values within the normal range at Baseline to clinically significantly abnormal values at a post-baseline visit in hemoglobin, hematocrit, RBC, WBC, and platelets in the SAF - boceprevir. The frequency of patients with hemoglobin values below 10 g/dL was higher in the SAF - boceprevir (39%) than in the SAF - no boceprevir (18%). Similarly, more patients in the SAF - boceprevir (29%) than in the SAF - no boceprevir (14%) had a leukocyte count below 2.0 x 10^3/µl. Platelet counts were comparable in both analysis populations.

13 Summary and discussion

In recent years, triple therapy with peg-IFN, rbv, and the HCV protease inhibitor boceprevir was widely used as the standard of care for the treatment of patients with chronic HCV genotype 1 infection.

To address discrepancies between the recommended treatment in the European SmPC and the patient population assessed in previously conducted non-interventional studies, this non-interventional study assessed the effectiveness of boceprevir in combination with peg-IFN/rbv in pre-treated and treatment-naïve patients with or without liver cirrhosis.

Data collected in this study showed that high rates of SVR were achieved in non-cirrhotic patients who were previously untreated (79%). Cirrhotic patients had lower SVR rates (54%) than non-cirrhotic patients. The analysis of additional factors favoring high SVR rates, showed that patients with normal ALT or GGT levels at Baseline had higher SVR rates at FW 24, which could partly explain the lower SVR rates observed for cirrhotic patients.

In addition, other factors were identified that favored high SVR rates in all patients, such as age under 50 years, >1 $\log_{10}$ HCV-RNA decline after the lead-in phase, or an EVR (at Week 8).

Anemia was the most commonly reported AE in all patients with a higher rate in patients treated with boceprevir (31% versus 18%). Consistent with the increased incidence of anemia, more patients treated with boceprevir reported hemoglobin levels <10 g/dL than patients not receiving boceprevir.

14 Overall conclusion

- A combination therapy with pegylated interferon, ribavirin, and boceprevir in routine clinical practice is effective in achieving a high SVR rate in previously untreated patients without liver cirrhosis;
- In a routine clinical care setting, triple therapy was well tolerated and no new safety issues were identified.

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16 Appendices

16.1 Study information

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16.1.3 List of investigators

16.1.4 Documentation of statistical methods

16.1.5 Signature of the sponsor

16.2 Tables, figures and graphs referred to but not included in the text

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16.3 Patient data listings

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