Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

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Report date: 31 May 2013	**Trial No. / U No.:** 1220.5 / U12-2567-01	**Date of trial:** 28 Oct 2008 – 28 Nov 2011	**Date of revision:** Not applicable

Title of trial:	Antiviral effect, safety, and pharmacokinetics of BI 201335 NA in hepatitis C virus genotype 1 infected treatment-naïve and treatment-experienced patients for 24 weeks as combination therapy with pegylated interferon α-2a and ribavirin (double blinded, randomised, placebo controlled, Phase II)
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre trial conducted at 100 sites in 15 countries (Argentina, Australia, Austria, Canada, Czech Republic, France, Germany, Great Britain, Korea, Netherlands, Portugal, Romania, Spain, Switzerland, USA)
Publication (reference):	Data from this trial have not been published
Clinical phase:	II
Objectives:	The objective was to investigate the antiviral effect, safety, and pharmacokinetics of BI 201335, given as a soft gelatine capsule, in patients with hepatitis C virus (HCV) genotype 1 infection. Combination therapy of BI 201335 with pegylated interferon α-2a (PegIFN) and ribavirin (RBV), with or without a 3-day lead-in, was assessed in treatment-naïve (TN) and treatment-experienced (TE) patients.

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Methodology:	This was a randomised, placebo-controlled, double-blind, parallel-group trial. Treatment-naïve patients received BI 201335 at doses of 120 mg (once daily) or 240 mg (once daily), or placebo. Treatment-experienced patients received BI 201335 at a dose of 240 mg (once or twice daily) for 24 weeks, in combination with 24 or 48 weeks of PegIFN and RBV. A 3-day lead-in phase with PegIFN and RBV alone preceded therapy with BI 201335 in 2 of the 3 treatment groups with TN and 2 of 3 treatment groups with TE patients. At Week 24, those TN patients receiving BI 201335 at the dose of 240 mg once daily, with or without lead-in, and those TE patients receiving BI 201335 at the dose of 240 mg once daily with lead-in, who had had an HCV viral load below the lower limit of quantification at Week 4 and a viral load below the lower limit of detection up to Week 20 were re-randomised to either continue PegIFN/RBV treatment up to Week 48 or stop all treatment at Week 24.

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No. of subjects:	
planned:	entered: 700
actual:	enrolled: 936 entered: 719 For TN patients 120 mg once daily with lead-in entered: 69 treated: 69 analysed (for primary endpoint): 69 240 mg once daily without lead-in entered: 143 treated: 143 analysed (for primary endpoint): 141 240 mg once daily with lead-in entered: 146 treated: 146 analysed (for primary endpoint): 142 Placebo entered: 71 treated: 71 analysed (for primary endpoint): 71 For TE patients 240 mg once daily with lead-in entered: 143 treated: 142 analysed (for primary endpoint): 142 240 mg once daily without lead-in entered: 76 treated: 76 analysed (for primary endpoint): 76 240 mg twice daily with lead-in entered: 71 treated: 70 analysed (for primary endpoint): 70
Diagnosis and main criteria for inclusion:	Female and male patients, aged 18 to 65 years, with chronic HCV infection with genotype 1 (1a, 1b, or mixed 1a/1b), with an HCV viral load ≥100 000 IU/mL at screening. For TN patients, no prior therapy with interferon, pegylated interferon, or ribavirin was allowed. For TE patients, virological failure with pegylated interferon/ribavirin therapy was to be confirmed. TE patients required histological evidence of chronic necroinflammatory activity or the presence of fibrosis, but no evidence of cirrhosis within 24 months before trial enrolment.

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Test product:	BI 201335 NA, soft gelatine capsule formulation
dose:	120 mg once daily, with 240 mg as loading dose and 3-day placebo lead-in phase 240 mg once daily or twice daily, with 480 mg as loading dose with or without 3-day placebo lead-in phase
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6
Reference therapy:	Placebo (matching BI 201335 NA)
dose:	Not applicable
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6
Reference therapy:	Pegylated interferon α-2a (Pegasys®)
dose:	180 µg once weekly
mode of admin.:	Subcutaneous injection
batch no.:	Refer to Appendix 16.1.6
Reference therapy:	Ribavirin (Copegus®)
dose:	1200 mg per day divided in 2 doses, if ≥75 kg, 1000 mg per day divided in 2 doses, if <75 kg
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6

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Duration of treatment:	24 weeks of combination therapy with BI 201335 and PegIFN/RBV, followed by 24 weeks of PegIFN/RBV treatment alone, dependent on treatment group and re-randomisation. Patients received BI 201335 or placebo and PegIFN/RBV according to their treatment regimen, unless early withdrawal from medication occurred due to a) HCV viral load ≥1000 IU/mL in 2 consecutive visits at least 2 weeks apart, after previous viral load was below lower limit of detection (BLD), b) lack of early virological response, defined as an absence of a viral load reduction by ≥2 $\log_{10}$ from baseline at Week 12, or c) absence of a viral load BLD at Week 24.
Criteria for evaluation:	

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Efficacy:	**Two co-primary endpoints were investigated in this study** • Virological response 4 weeks after the End of Treatment with BI 201335 or placebo ($ETR_{BI\ 201335/placebo\ +\ 4\ weeks}$) • Sustained Virological Response 24 weeks after completion of all therapy (SVR24). **Further important secondary endpoints were** • Early Virological Response (EVR), defined as ≥2 log_{10} reduction in plasma HCV RNA level from baseline at Week 12 • Extended Rapid Virological Response (eRVR), defined as plasma HCV RNA levels below the lower limit of quantification at Week 4 and below the lower limit of detection at Week 12 • End of Treatment Response of BI 201335 or placebo ($ETR_{BI\ 201335/placebo}$), defined as the plasma HCV RNA level below the lower limit of detection at Week 24 • End of Treatment Response (ETR), defined as the plasma HCV RNA level below the lower limit of detection at the end of all therapy (Week 48 or 72) • Time to reach a plasma HCV RNA level BLD • Time to loss of virological response, defined as last value BLD followed by 2 consecutive plasma HCV RNA levels ≥100 IU/mL • Virological rebound, defined as increase of ≥1 log_{10} in plasma HCV RNA level from a quantifiable nadir, or to ≥250 IU/mL after previous nadir <25 IU/mL
Pharmacokinetics:	**For all patients**: Trough plasma concentrations ($C_{min,ss}$) for BI 201335 ZW, ribavirin, and pegylated interferon α-2a **For patients participating in the PK substudy**: PK parameters ($C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $AUC_{\tau,ss}$, and CL/F_{ss}) for steady state levels of BI 201335 ZW and ribavirin
Safety:	Adverse events, tolerability, vital signs and physical examination, laboratory test abnormalities, and laboratory test value changes over time.

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Statistical methods: The proportion of patients who achieved a virological response and the corresponding 95% confidence interval based on the Beta function were calculated in each treatment group for TN and TE patients separately. No formal hypotheses were tested. Statistical tests (2-sided exact Fisher tests for equality of BI 201335 and reference groups) were applied, but were interpreted descriptively only. Descriptive statistics and tabular or graphical displays were used for HCV measurements (absolute and as change from baseline)

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Efficacy

Treatment naïve patients

In TN patients, therapy with BI 201335 as add-on to PegIFN/RBV background medication by randomised treatment showed a high antiviral efficacy in all 3 BI 201335 treatment groups. The highest frequency of SVR24 responders (85.1%) was observed in the BI 201335 240 mg QD - LI group. A lower dose of 120 mg QD BI 201335 led to lower response rates (72.5%) as did a lead-in in the 240 mg QD dose (72.3%). Patients in the placebo group reached a SVR24 responder rate of 56.3%. For all 3 BI 201335 groups clinically meaningful treatment differences compared with placebo were observed. Response rates were higher in patients with genotype 1B compared to genotype 1A in all treatment groups except for the 240 mg QD - LI group.

An end of treatment response 4 weeks after the end of therapy with BI 201335 or placebo was observed in 69.0% of patients in the placebo group, and 74.5 – 86.6% in the BI 201335 treatment groups. These response rates were 2% higher than SVR24 rates in the BI 201335 groups, but 13% higher than SVR24 rates in the placebo group.

The SVR rate of the mRVR patients of the 240 mg QD + LI group was 14.5% lower in patients, who stopped treatment after Week 24 than in patients who continued PegIFN/RBV up to Week 48, which was not statistically significant.

During the first 24 weeks while on treatment with BI 201335 added to PegIFN/RBV the frequency of breakthroughs was low (3.5% – 5.8%) compared to 2.8% during treatment with placebo. During PegIFN/RBV follow-on therapy the frequency of breakthrough was even lower (0% - 2.9%) compared to 4.2% in the placebo group. After the end of treatment, relapse rates between 7.2% in the BI

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201335 120 mg QD + LI group and 10.6% in the BI 201335 240 mg QD + LI were seen. This is lower than the placebo group (15.5%).

Treatment experienced patients

In TE patients rates of SVR24 achievement was 28.2% for BI 201335 240 mg QD + LI, 31.4% for BI 201335 240 mg BID + LI and 40.8% for BI 201335 240 mg QD - LI, which was significantly higher than the SVR rates of the REPEAT trial (8.6%). SVR24 rates were higher in previous partial responders (32.1% – 50.0%) compared to previous null responders (21.1% – 35.0%), which is in line with studies on the recently approved PIs telaprevir and boceprevir. Response rates were higher in patients with genotype 1B compared to genotype 1A in all treatment groups except for the 240 mg BID + LI group.

An undetectable viral load 4 weeks after the end of therapy with BI 201335 was observed in 43.7% of patients in the BI 201335 240 mg QD + LI group and in 50.0% of patients in both the BI 201335 240 mg QD - LI and BI 240 mg BID + LI group. Thus in TE patients, the end of treatment with BI 201335 plus 4 weeks response rates were considerably larger than the observed SVR24 response rates.

SVR24 rates for patients, which were treated with PegIFN/RBV up to Week 48 was highest in the 240 mg QD – LI group (40.8%) followed by the 240 mg QD + LI group (initially re-randomised to continue always; 33.8%). Lowest results were observed in the 240 mg BID + LI group with 31.4%.

After re-randomisation of the BI 201335 240 mg QD + LI group who achieved mRVR, SVR24 rates were higher in patients who continued PegIFN/RBV therapy until Week 48 (72.4%) compared to patients who stopped all treatment after Week 24 (43.3%), indicating that response-guided shortening of therapy is not to be recommended for TE patients.

For TE patients, the frequency of breakthroughs on-treatment with BI 201335 plus PegIFN/RBV (17.1% - 28.9%) were larger than on-treatment with PegIFN/RBV alone (4.9% – 7.1%) and relapse rates (11.8% - 26.8%).

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Pharmacokinetics

BI 201335

240 mg QD showed approximately 50% higher exposure based on AUC and trough concentrations than observed previously in 1220.2 [U10-2363-01]. The might be partially attributed to more Asian patients and female patients participated in this study. Female patients in the higher dose groups (240 mg QD and 240 mg BID) showed approximately 60% higher geometric mean trough concentrations than male patients. Asian patients showed approximately 40% higher geometric mean trough concentrations than white patients, Korean patients showed approximately 46% higher than non-Korean patients.

Ribavirin (RBV)

RBV steady state had been attained at Week 8 regardless of the treatment group. TN and TE patients exhibited similar RBV trough geometric concentrations. In addition, RBV trough concentrations were similar among treatment groups, suggesting there is no or little effect of BI 201335 on the exposure of RBV. On average over the period of Weeks 1 to 24, the geometric mean trough ratios of RBV are mostly within ±10% of the corresponding placebo treatment group.

Pegylated interferon α-2a (PegIFN)

Over the period of Weeks 1 to 24, the geometric mean trough concentrations tend to continue to increase, even after discontinuation after Week 24, i.e. did not seem to have real steady state attained. This is more so for the TE patients.

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Safety results:

Safety

Treatment naïve patients

Overall, BI 201335 demonstrated a favorable safety profile. Frequencies of AEs leading to treatment discontinuation were dose-dependent with lowest values in the placebo group (1.4%) followed by the 120 mg QD + LI group (4.4%). A higher dose of 240 mg QD caused an increase of AEs leading to treatment discontinuation (BI 201335 240 mg QD – LI 5.4%, BI 201335 240 mg QD + LI 10.9%).

Most AEs observed during or up to 30 days after end of treatment were of mild or moderate intensity and those commonly related to PegIFN/RBV therapy (influenza like illness and headache). The main BI 201335-related AEs were gastrointestinal disorders (nausea, diarrhea and vomiting), jaundice, pruritus and rash. For gastrointestinal disorders, AEs of severe intensity were observed for nausea (<3%), and for vomiting (<1%) but not for diarrhea.

Skin rash was managed without treatment interruption in most cases by applying topical treatments and rarely systemic corticosteroids (<5%). The majority of cases were mild with no involvement of other organs. Moderate rash occurred in a higher frequency in both 240 mg QD dose groups (12.3% - 18.1%) compared to the 120 mg QD + LI group (2.9%) and the placebo group (2.8%). Severe rash was reported only in the 240 mg QD dose groups (4%). In 5 patients in each of the 240 mg QD dose groups (3.6 and 3.4% in 240 mg QD + LI and 240 mg QD – LI, respectively) rash led to treatment discontinuation. All cases of severe rash resolved after end of treatment with BI 201335. Photosensitivity mostly manifested as mild erythema limited to sun exposed areas of the body and led to one discontinuation.

At the higher doses of BI 201335 240 mg QD, 20–25% of patients experienced jaundice (usually mild) due to dose-dependent, isolated, indirect hyperbilirubinemia associated with BI 201335. Rates of mild jaundice occurred in the BI 201335 120 mg QD group with a frequency of 6%, compared to 1% in the placebo group. The extent of hyperbilirubinaemia was correlated with UGT1A1 genotype and was highest in patients with homocygous Gilbert´s syndrome. Hyperbilirubinaemia was reversible after end of treatment with BI 201335 and not associated with an increase of liver enzymes, hemolysis or any other clinical

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symptoms. Treatment discontinuation due to jaundice was observed in 1 patient, no treatment discontinuation was reported due to hyperbilirubinaemia.

Changes in safety laboratory values were consistent with those observed with PegIFN/RBV. There was no additional effect of BI 201335 on hemoglobin levels, red blood cells, white blood cells or the occurrence of severe anaemia compared with the placebo group.

Treatment experienced patients

BI 201335 was better tolerated the 240 mg QD dose while the safety profile of the BI 201335 240 mg BID + LI dosing regime was less favourable. AEs leading to treatment discontinuation were lowest in the 240 mg QD –LI group (3.9%), slightly higher in the 240 mg QD + LI group (5.7%) and considerably higher in the 240 mg BID + LI group (23.2%).

In the 240 mg QD dose groups, the main BI 201335-related AEs were mild-to-moderate skin rash, photosensitivity reactions and gastrointestinal events, which tended to occur during the first weeks after BI 201335 initiation up to Week 12.

In the BI 201335 240 mg QD dose groups, only 1 patient discontinued treatment due to rash; however, 10 patients discontinued treatment with the BI 201335 240 mg BID dose because of rash (14.5%).

BI 201335 is associated with incidences of jaundice related to increases in indirect bilirubin, which was most pronounced in the highest dose group. Hyperbilirubinaemia was reversible after cessation of BI 201335 and was not associated with increases in serum ALT, AST, or other markers of liver injury. 2 patients discontinued the trial due to jaundice and hyperbilirubinaemia, and 1 patient due to hyperbilirubinaemia alone. Severe anaemia was observed most frequently in the BI 201335 240 mg BID + LI group with 7.2%.

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Conclusions:

Balance between effect and adverse events

In both patient populations, treatment with BI 201335 once daily or twice daily in doses of 120 mg or 240 mg as add-on to PegIFN/RBV resulted in higher SVR24 response rates compared with PegIFN/RBV plus placebo treatment (TN patients) or response rates seen in a historical control trial with PegIFN/RBV (TE patients). In both the TN and TE patient population BI 201335 up to a dose of 240 mg QD was generally well-tolerated.

In TN patients response to treatment with BI 201335 was different in genotype 1A versus genotype 1B patients. For patients with genotype 1A BI 201335 240 mg QD - LI showed the highest SVR24 response rate with 82.4%, while in patients with genotype 1B the best response was achieved with a lower dose of 120 mg QD + LI (SVR24 86.0%). The frequency of AEs leading to treatment discontinuation were similar for both treatments (5.4% and 4.4%, respectively). The treatment with the least favourable balance between effect and adverse events was BI 201335 240 mg QD + LI with an SVR24 of 72.3% (64.2% for genotype 1A and 79.7% for genotype 1B) and a frequency of AEs leading to treatment discontinuation of 10.9%. The extent of hyperbilirubinaemia was lowest in the BI 201335 120 mg QD + LI group and highest in the BI 201335 240 mg QD + LI group. Occurrence of rash was similar in both groups.

In TE patients, the most favourable results were obtained with BI 201335 240 mg QD – LI treatment, with SVR24 rates of 40.8% and a frequency of AEs leading to treatment discontinuation of 3.9%. SVR24 was 28.2% in the BI 201335 240 mg QD + LI randomized group and 33.8% in the initially re-randomized group to continue treatment to Week 48. The latter value is a more valid comparison to the BI 201335 240 mg QD – LI group, which was not re-randomized. AEs leading to treatment discontinuation were 5.7% in the BI 201335 240 mg QD + LI group compared to 3.9% in the 240 mg QD dose group without lead-in. Also the incidence of rash and the extent of hyperbilirubinaemia was higher in the 240 mg QD + LI group than in the BI 201335 240 mg QD – LI group. The highest investigated dosage of BI 201335 240 mg BID + LI did not show improved SVR24 rates (31.4%), a comparably high rate of treatment discontinuations due to AEs (23.2%) and highest rates of rash and hyperbilirubinaemia. This dosing regime showed the least beneficial outcome with respect to safety and tolerability.

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Response-guided therapy

Response-guided shortening of therapy led to favourable results in TN patients with mRVR of the BI 201335 240 mg QD – LI group. However, in the BI 201335 240 mg QD +LI group SVR24 rates were lower and relapse rates were higher in mRVR patients who stopped all treatment after Week 24, indicating that response-guided shortening of the treatment may not be favourable under this dosing regime.

In TE patients, response-guided shortening of therapy led to a significantly lower rate of SVR24 achievement (43.3% for mRVR patients who stopped treatment after Week 24 versus 72.4% in mRVR patients who continued treatment until Week 48) and is, therefore, not considered a reliable therapy concept in TE patients.

Predictability of treatment success

In TN patients viral load at early time points up to Week 12 showed high positive predictive values. Best positive prediction for BI 201335 treatment success was observed based on BLD Week 4/BLD Week 12 (85 – 93%). The negative predictive values for the active treatments were low for all endpoints that included BLD Week 4, 44 – 86% for endpoints that included BLQ Week 4, and very high for BLD at EoT or later.

In TE patients negative prediction was more reliable based on early time points. Positive predictive values were 42 – 76% for early endpoints that included BLQ at Week 4.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the trial synopsis. They complement disposition results, results for primary and secondary endpoints (EP) of the trial, and safety information. Note that not all secondary endpoints defined in the trial protocol are presented in this synopsis, because their numbers were too large to allow meaningful presentation in this format.

Results for	**presented in**
Patient Disposition in	
Treatment Naïve (TN) Patients	Table 15.1.1.1: 1
Treatment Experienced (TE) Patients	Table 15.1.2.1: 1
End of Treatment Response (ETR) 4 Weeks after End of Treatment (EOT) with BI 201335 or Placebo (Primary EP)	
Treatment Naïve (TN) Patients	Table A1
Treatment Experienced (TE) Patients	Table A1
Sustained Virologic Response (SVR) at 24 Weeks after End of All Therapy (SVR24) (Primary EP)	
Treatment Naïve (TN) Patients	Table 15.2.1.1: 9
Treatment Experienced (TE) Patients	Table 15.2.2.1: 9
Virologic Response (VR) at Week 2 or Week 4 of Treatment (Secondary EP)	
Treatment Naïve (TN) Patients	Table A2
Treatment Experienced (TE) Patients	Table A2
Early Virologic Response (EVR) at Week 12 of Treatment (Secondary EP)	
Treatment Naïve (TN) Patients	Table 15.2.1.4: 1
Treatment Experienced (TE) Patients	Table 15.2.2.4: 2
Extended Rapid Virologic Response (eRVR) at Week 4 and Week 12 of Treatment (Secondary EP)	
Treatment Naïve (TN) Patients	Table 15.2.1.1: 4
Treatment Experienced (TE) Patients	Table 15.2.2.1: 4
Complete Early Virologic Response (cEVR) at Week 12 of Treatment (Secondary EP)	
Treatment Naïve (TN) Patients	Table 15.2.1.1: 2
Treatment Experienced (TE) Patients	Table 15.2.2.1: 2

Continued

Concluded

Results for	**presented in**
End of Treatment Response (ETR) at EOT with BI 201335 or Placebo (Secondary EP)	
Treatment Naïve (TN) Patients	Table 15.2.1.1: 3
Treatment Experienced (TE) Patients	Table 15.2.2.1: 3
End of Treatment Response (ETR) at EOT with All Therapy (Secondary EP)	
Treatment Naïve (TN) Patients	Table 15.2.1.1: 7
Treatment Experienced (TE) Patients	Table 15.2.2.1: 7
Sustained Virologic Response 12 Weeks After End of All Therapy (SVR12) (Secondary EP)	
Treatment Naïve (TN) Patients	Table 15.2.1.1: 7
Treatment Experienced (TE) Patients	Table 15.2.2.1: 7
Virologic Rebound Through Week 24 or 48 (Secondary EP)	
Treatment Naïve (TN) Patients	Table 15.2.1.1: 8
Treatment Experienced (TE) Patients	Table 15.2.2.1: 8
Breakthrough While BI 201335 or Placebo Treatment was Ongoing up to Week 24 (Secondary EP)	
Treatment Naïve (TN) Patients	Table 15.2.1.1: 8
Treatment Experienced (TE) Patients	Table 15.2.2.1: 8
Breakthrough While Receiving SOC (PegIFN/RBV Follow-on Therapy Only) Week 24 Through Week 48 (Secondary EP)	
Treatment Naïve (TN) Patients	Table 15.2.1.1: 8
Treatment Experienced (TE) Patients	Table 15.2.2.1: 8
Relapse at any Time Post-EOT (Secondary EP)	
Treatment Naïve (TN) Patients	Table 15.2.1.1: 8
Treatment Experienced (TE) Patients	Table 15.2.2.1: 8
AE Overall Summary (Secondary EP)	
Treatment Naïve (TN) Patients	Table 15.3.1.2.1: 1
Treatment Experienced (TE) Patients	Table 15.3.2.2.1: 1

Table 15.1.1.1: 1 Patient disposition based on BI201335 treatment by randomised treatment
Screened set

	SOC alone	120 mg QD with lead-in	240 mg QD with lead-in	240 mg QD without lead-in	Total
Enrolled					581
Not entered/randomised					152
Entered/randomised	71	69	143	146	429
Not treated	0	0	0	0	0
Treated	71 (100.0)	69 (100.0)	143 (100.0)	146 (100.0)	429 (100.0)
Not prematurely discontinued from trial med.	57 (80.3)	56 (81.2)	113 (79.0)	129 (88.4)	355 (82.8)
Prematurely discontinued from trial med.	14 (19.7)	13 (18.8)	30 (21.0)	17 (11.6)	74 (17.2)
Adverse Event	1 (1.4)	3 (4.3)	16 (11.2)	8 (5.5)	28 (6.5)
AE study dis. worse	0	0	0	0	0
AE other dis. worse	0	0	1 (0.7)	0	1 (0.2)
AE other	1 (1.4)	3 (4.3)	15 (10.5)	8 (5.5)	27 (6.3)
Lack of efficacy	11 (15.5)	4 (5.8)	5 (3.5)	3 (2.1)	23 (5.4)
Non compl. protocol	0	1 (1.4)	3 (2.1)	1 (0.7)	5 (1.2)
Lost to follow-up	0	1 (1.4)	1 (0.7)	1 (0.7)	3 (0.7)
Refused cont. medic.	1 (1.4)	3 (4.3)	2 (1.4)	2 (1.4)	8 (1.9)
Other	1 (1.4)	1 (1.4)	3 (2.1)	2 (1.4)	7 (1.6)

Note: Percentages are based on the number of patients treated.

Table 15.1.2.1: 1 Patient disposition based on BI201335 treatment by randomised treatment
Screened set

	240 mg QD with lead-in	240 mg QD without lead-in	240 mg BID with lead-in	Total
Enrolled				355
Not entered/randomised				65
Entered/randomised	143	76	71	290
Not treated	1	0	1	2
Treated	142 (100.0)	76 (100.0)	70 (100.0)	288 (100.0)
Not prematurely discontinued from trial med.	97 (68.3)	54 (71.1)	41 (58.6)	192 (66.7)
Prematurely discontinued from trial med.	45 (31.7)	22 (28.9)	29 (41.4)	96 (33.3)
Adverse Event	8 (5.6)	3 (3.9)	16 (22.9)	27 (9.4)
AE study dis. worse	0	0	0	0
AE other dis. worse	0	0	0	0
AE other	8 (5.6)	3 (3.9)	16 (22.9)	27 (9.4)
Lack of efficacy	27 (19.0)	15 (19.7)	9 (12.9)	51 (17.7)
Non compl. protocol	2 (1.4)	1 (1.3)	0	3 (1.0)
Lost to follow-up	0	1 (1.3)	0	1 (0.3)
Refused cont. medic.	6 (4.2)	2 (2.6)	3 (4.3)	11 (3.8)
Other	2 (1.4)	0	1 (1.4)	3 (1.0)

Note: Percentages are based on the number of patients treated.

Table A1. Percentage of Patients with a Virologic Response 4 Weeks after the End of Treatment with BI 201335 or Placebo

Arm	Placebo (TN) N=13	120 mg QD with lead−in (TN) N=14	240 mg QD with lead−in (TN) N=77	240 mg QD without lead−in (TN) N=72	240 mg QD with lead−in (TE) N=88	240 mg QD without lead−in (TE) N=30	240 mg BID with lead−in (TE) N=27
Response (%)	0.0	14.3	59.7	75.0	20.5	3.3	0.0

Abbreviations: BID=twice daily; N=number; QD=once daily; TE=treatment experienced; TN=treatment naïve
Source: Table 15.2.1.1: 3 (TN) and Table 15.2.2.1: 3 (TE)

Table 15.2.1.1: 9 SVR response comparison by randomised treatment
PPS (as observed)

	SOC alone (N = 71)	120 mg QD with lead-in (N = 69)	240 mg QD with lead-in (N = 141)	240 mg QD without lead-in (N = 142)
SVR (1)	40 (56.3)	50 (72.5)	102 (72.3)	119 (83.8)
Percentage, 95% CI (2)	[44.7, 67.3]	[60.9, 81.6]	[64.4, 79.1]	[76.9, 88.9]
Difference, 95% CI (3)		[-0.2, 32.3]	[2.0, 30.1]	[13.0, 41.1]
P-value (4)		0.0537	0.0213	<0.0001

Note: (1) SVR24 result (earliest HCV mRNA result on or after day 155 post end of all treatment) is BLD.
(2) 2-sided 95% confidence interval for the percentage based on the beta function.
(3) 2-sided 95% confidence interval based on the permutation distribution exact.
(4) P-value based on Fisher's exact test (2-sided).
Percentage differences and p-vaues are based on a comparison to the first treatment group.

Table 15.2.2.1: 9 SVR response comparison by randomised treatment
PPS (as observed)

	REPEAT trial (N = 313)	240 mg QD with lead-in (N = 142)	240 mg QD without lead-in (N = 76)	240 mg BID with lead-in (N = 70)
SVR (1)	27 (8.6)	40 (28.2)	31 (40.8)	22 (31.4)
Percentage, 95% CI (2)	[6.0, 12.3]	[21.4, 36.1]	[30.4, 52.1]	[21.8, 43.1]
Difference, 95% CI (3)		[9.7, 29.2]	[19.8, 44.1]	[9.9, 35.3]
P-value (4)		<0.0001	<0.0001	<0.0001

Note: (1) SVR24 result (earliest HCV mRNA result on or after day 155 post end of all treatment) is BLD.
(2) 2-sided 95% confidence interval for the percentage based on the beta function.
(3) 2-sided 95% confidence interval based on the permutation distribution exact.
(4) P-value based on Fisher's exact test (2-sided).
Percentage differences and p-vaues are based on a comparison to the first treatment group.

Table A2. Percentage of Patients with a Virologic Response at Week 2 or Week 4

Arm	Placebo (TN) N=71	120 mg QD with lead−in (TN) N=69	240 mg QD with lead−in (TN) N=141	240 mg QD without lead−in (TN) N=142	240 mg QD with lead−in (TE) N=142	240 mg QD without lead−in (TE) N=76	240 mg BID with lead−in (TE) N=70
Response (%) at Week 2	1.4	69.6	66.7	82.4	27.5	34.2	47.1
Response (%) at Week 4	16.9	89.9	86.5	93.7	63.4	60.5	68.6

Abbreviations: BID=twice daily; N=number; QD=once daily; TE=treatment experienced; TN=treatment naïve
Source: Table 15.2.1.1: 2 (TN) and Table 15.2.2.1: 2 (TE)

Table 15.2.1.4: 1 Frequency of patients with EVR by randomised treatment
PPS (as observed)

EVR achieved	SOC alone (N = 71)	120 mg QD with lead-in (N = 69)	240 mg QD with lead-in (N = 141)	240 mg QD without lead-in (N = 142)	Total (N = 423)
Yes	60 (84.5)	62 (89.9)	125 (88.7)	132 (93.0)	379 (89.6)
No	8 (11.3)	2 (2.9)	3 (2.1)	3 (2.1)	16 (3.8)
Missing	3 (4.2)	5 (7.2)	13 (9.2)	7 (4.9)	28 (6.6)

Note: The Missing category refers to those patients with no post baseline data available.

Table 15.2.2.4: 2 Frequency of patients with EVR by randomised treatment
PPS (as observed)

EVR achieved	240 mg QD with lead-in (N = 142)	240 mg QD without lead-in (N = 76)	240 mg BID with lead-in (N = 70)	Total (N = 288)
Yes	103 (72.5)	58 (76.3)	44 (62.9)	205 (71.2)
No	25 (17.6)	16 (21.1)	9 (12.9)	50 (17.4)
Missing	14 (9.9)	2 (2.6)	17 (24.3)	33 (11.5)

Note: The Missing category refers to those patients with no post baseline data available.

Table 15.2.1.1: 4 Frequency of patients achieving eRVR by randomised treatment
PPS (as observed)

eRVR achieved	SOC alone (N = 71)	120 mg QD with lead-in (N = 69)	240 mg QD with lead-in (N = 141)	240 mg QD without lead-in (N = 142)	Total (N = 423)
Yes	11 (15.5)	59 (85.5)	114 (80.9)	129 (90.8)	313 (74.0)
No	60 (84.5)	10 (14.5)	27 (19.1)	13 (9.2)	110 (26.0)

Table 15.2.2.1: 4 Frequency of patients achieving eRVR by randomised treatment
PPS (as observed)

eRVR achieved	240 mg QD with lead-in (N = 142)	240 mg QD without lead-in (N = 76)	240 mg BID with lead-in (N = 70)	Total (N = 288)
Yes	74 (52.1)	40 (52.6)	36 (51.4)	150 (52.1)
No	68 (47.9)	36 (47.4)	34 (48.6)	138 (47.9)

Table 15.2.1.1: 2 Frequency of patients with viral load BLD and BLQ by visit up to week 24, randomised treatment and discontinuation status. PPS (as observed)

Visit: Week 12

Treatment group / Discontinuation status	n	Virological response			
		BLD	BLQ	>=25	Missing
SOC alone (N = 71)					
No treatments started	0	0	0	0	0
All 3 treatments active	69	30 (42.3)	11 (15.5)	28 (39.4)	0
Only SOC active	0	0	0	0	0
After end of all 3 treatments	1	0	0	1 (1.4)	0
Other	1	0	0	0	1 (1.4)
Total	71	30 (42.3)	11 (15.5)	29 (40.8)	1 (1.4)
120 mg QD with lead-in (N = 69)					
No treatments started	0	0	0	0	0
All 3 treatments active	63	58 (84.1)	2 (2.9)	3 (4.3)	0
Only SOC active	0	0	0	0	0
After end of all 3 treatments	6	2 (2.9)	0	0	4 (5.8)
Other	0	0	0	0	0
Total	69	60 (87.0)	2 (2.9)	3 (4.3)	4 (5.8)
240 mg QD with lead-in (N = 141)					
No treatments started	0	0	0	0	0
All 3 treatments active	124	115 (81.6)	3 (2.1)	6 (4.3)	0
Only SOC active	0	0	0	0	0
After end of all 3 treatments	17	4 (2.8)	0	1 (0.7)	12 (8.5)
Other	0	0	0	0	0
Total	141	119 (84.4)	3 (2.1)	7 (5.0)	12 (8.5)
240 mg QD without lead-in (N = 142)					
No treatments started	0	0	0	0	0
All 3 treatments active	136	129 (90.8)	2 (1.4)	4 (2.8)	1 (0.7)
Only SOC active	1	1 (0.7)	0	0	0
After end of all 3 treatments	5	2 (1.4)	0	0	3 (2.1)
Other	0	0	0	0	0
Total	142	132 (93.0)	2 (1.4)	4 (2.8)	4 (2.8)

Note: BLD = No virus detected, BLQ = Detectable <25 IU/mL

Table 15.2.2.1: 2 Frequency of patients with viral load BLD and BLQ by visit up to week 24, randomised treatment and discontinuation status. PPS (as observed)

Visit: Week 12

Treatment group Discontinuation status	n	Virological response BLD	 BLQ	 >=25	 Missing
240 mg QD with lead-in (N = 142)					
No treatments started	0	0	0	0	0
All 3 treatments active	125	82 (57.7)	14 (9.9)	29 (20.4)	0
Only SOC active	0	0	0	0	0
After end of all 3 treatments	17	1 (0.7)	0	5 (3.5)	11 (7.7)
Other	0	0	0	0	0
Total	142	83 (58.5)	14 (9.9)	34 (23.9)	11 (7.7)
240 mg QD without lead-in (N = 76)					
No treatments started	0	0	0	0	0
All 3 treatments active	71	44 (57.9)	7 (9.2)	20 (26.3)	0
Only SOC active	1	1 (1.3)	0	0	0
After end of all 3 treatments	4	0	0	2 (2.6)	2 (2.6)
Other	0	0	0	0	0
Total	76	45 (59.2)	7 (9.2)	22 (28.9)	2 (2.6)
240 mg BID with lead-in (N = 70)					
No treatments started	0	0	0	0	0
All 3 treatments active	50	34 (48.6)	4 (5.7)	11 (15.7)	1 (1.4)
Only SOC active	5	2 (2.9)	2 (2.9)	1 (1.4)	0
After end of all 3 treatments	15	1 (1.4)	0	1 (1.4)	13 (18.6)
Other	0	0	0	0	0
Total	70	37 (52.9)	6 (8.6)	13 (18.6)	14 (20.0)

Note: BLD = No virus detected, BLQ = Detectable <25 IU/mL

Table 15.2.1.1: 3 Frequency of patients with viral load BLD and BLQ by visit post EOT [BI201335/placebo] by randomised treatment and discontinuation status. PPS (as observed)

Visit: EOT (placebo/BI201335)

Treatment group / Discontinuation status	n	Virological response: BLD	BLQ	>=25	Missing
SOC alone (N = 71)					
No treatments started	1	0	0	1 (1.4)	0
All 3 treatments active	14	8 (11.3)	0	1 (1.4)	5 (7.0)
Only SOC active	50	43 (60.6)	4 (5.6)	3 (4.2)	0
After end of all 3 treatments	6	1 (1.4)	0	5 (7.0)	0
Other	0	0	0	0	0
Total	71	52 (73.2)	4 (5.6)	10 (14.1)	5 (7.0)
120 mg QD with lead-in (N = 69)					
No treatments started	0	0	0	0	0
All 3 treatments active	14	9 (13.0)	0	0	5 (7.2)
Only SOC active	49	44 (63.8)	2 (2.9)	3 (4.3)	0
After end of all 3 treatments	6	4 (5.8)	0	2 (2.9)	0
Other	0	0	0	0	0
Total	69	57 (82.6)	2 (2.9)	5 (7.2)	5 (7.2)
240 mg QD with lead-in (N = 141)					
No treatments started	0	0	0	0	0
All 3 treatments active	21	3 (2.1)	0	1 (0.7)	17 (12.1)
Only SOC active	65	57 (40.4)	3 (2.1)	3 (2.1)	2 (1.4)
After end of all 3 treatments	55	49 (34.8)	1 (0.7)	5 (3.5)	0
Other	0	0	0	0	0
Total	141	109 (77.3)	4 (2.8)	9 (6.4)	19 (13.5)
240 mg QD without lead-in (N = 142)					
No treatments started	0	0	0	0	0
All 3 treatments active	24	12 (8.5)	0	0	12 (8.5)
Only SOC active	63	60 (42.3)	1 (0.7)	2 (1.4)	0
After end of all 3 treatments	55	53 (37.3)	1 (0.7)	1 (0.7)	0
Other	0	0	0	0	0
Total	142	125 (88.0)	2 (1.4)	3 (2.1)	12 (8.5)

Note: BLD = No virus detected, BLQ = Detectable <25 IU/mL

Table 15.2.2.1: 3 Frequency of patients with viral load BLD and BLQ by visit post EOT [BI201335/placebo] by randomised treatment and discontinuation status. PPS (as observed)

Visit: EOT (placebo/BI201335)

Treatment group Discontinuation status	n	Virological response BLD	 BLQ	 >=25	 Missing
240 mg QD with lead-in (N = 142)					
No treatments started	1	0	0	1 (0.7)	0
All 3 treatments active	32	9 (6.3)	1 (0.7)	2 (1.4)	20 (14.1)
Only SOC active	61	43 (30.3)	6 (4.2)	12 (8.5)	0
After end of all 3 treatments	48	31 (21.8)	1 (0.7)	16 (11.3)	0
Other	0	0	0	0	0
Total	142	83 (58.5)	8 (5.6)	31 (21.8)	20 (14.1)
240 mg QD without lead-in (N = 76)					
No treatments started	0	0	0	0	0
All 3 treatments active	18	2 (2.6)	0	4 (5.3)	12 (15.8)
Only SOC active	51	38 (50.0)	4 (5.3)	9 (11.8)	0
After end of all 3 treatments	7	0	0	7 (9.2)	0
Other	0	0	0	0	0
Total	76	40 (52.6)	4 (5.3)	20 (26.3)	12 (15.8)
240 mg BID with lead-in (N = 70)					
No treatments started	0	0	0	0	0
All 3 treatments active	20	5 (7.1)	1 (1.4)	1 (1.4)	13 (18.6)
Only SOC active	38	31 (44.3)	3 (4.3)	3 (4.3)	1 (1.4)
After end of all 3 treatments	12	1 (1.4)	3 (4.3)	8 (11.4)	0
Other	0	0	0	0	0
Total	70	37 (52.9)	7 (10.0)	12 (17.1)	14 (20.0)

Note: BLD = No virus detected, BLQ = Detectable <25 IU/mL

Table 15.2.1.1: 7 Frequency of patients with viral load BLD and BLQ by visit post EOT [all treatment] by randomised treatment and discontinuation status. PPS (as observed)

Visit: EOT

Treatment group / Discontinuation status	n	Virological response: BLD	BLQ	>=25	Missing
SOC alone (N = 71)					
No treatments started	1	0	0	1 (1.4)	0
All 3 treatments active	4	0	0	0	4 (5.6)
Only SOC active	18	11 (15.5)	1 (1.4)	0	6 (8.5)
After end of all 3 treatments	48	38 (53.5)	1 (1.4)	8 (11.3)	1 (1.4)
Other	0	0	0	0	0
Total	71	49 (69.0)	2 (2.8)	9 (12.7)	11 (15.5)
120 mg QD with lead-in (N = 69)					
No treatments started	0	0	0	0	0
All 3 treatments active	6	1 (1.4)	0	0	5 (7.2)
Only SOC active	14	4 (5.8)	0	0	10 (14.5)
After end of all 3 treatments	49	45 (65.2)	0	4 (5.8)	0
Other	0	0	0	0	0
Total	69	50 (72.5)	0	4 (5.8)	15 (21.7)
240 mg QD with lead-in (N = 141)					
No treatments started	0	0	0	0	0
All 3 treatments active	14	2 (1.4)	0	0	12 (8.5)
Only SOC active	16	5 (3.5)	0	2 (1.4)	9 (6.4)
After end of all 3 treatments	111	103 (73.0)	1 (0.7)	7 (5.0)	0
Other	0	0	0	0	0
Total	141	110 (78.0)	1 (0.7)	9 (6.4)	21 (14.9)
240 mg QD without lead-in (N = 142)					
No treatments started	0	0	0	0	0
All 3 treatments active	13	3 (2.1)	0	0	10 (7.0)
Only SOC active	20	9 (6.3)	0	0	11 (7.7)
After end of all 3 treatments	109	104 (73.2)	1 (0.7)	3 (2.1)	1 (0.7)
Other	0	0	0	0	0
Total	142	116 (81.7)	1 (0.7)	3 (2.1)	22 (15.5)

Note: BLD = No virus detected, BLQ = Detectable <25 IU/mL

Table 15.2.2.1: 7 Frequency of patients with viral load BLD and BLQ by visit post EOT [all treatment] by randomised treatment and discontinuation status. PPS (as observed)

Visit: EOT

Treatment group / Discontinuation status	n	Virological response			
		BLD	BLQ	>=25	Missing
240 mg QD with lead-in (N = 142)					
No treatments started	1	0	0	1 (0.7)	0
All 3 treatments active	21	1 (0.7)	1 (0.7)	1 (0.7)	18 (12.7)
Only SOC active	26	5 (3.5)	1 (0.7)	4 (2.8)	16 (11.3)
After end of all 3 treatments	94	63 (44.4)	5 (3.5)	25 (17.6)	1 (0.7)
Other	0	0	0	0	0
Total	142	69 (48.6)	7 (4.9)	31 (21.8)	35 (24.6)
240 mg QD without lead-in (N = 76)					
No treatments started	0	0	0	0	0
All 3 treatments active	12	0	0	3 (3.9)	9 (11.8)
Only SOC active	18	2 (2.6)	0	2 (2.6)	14 (18.4)
After end of all 3 treatments	46	33 (43.4)	1 (1.3)	12 (15.8)	0
Other	0	0	0	0	0
Total	76	35 (46.1)	1 (1.3)	17 (22.4)	23 (30.3)
240 mg BID with lead-in (N = 70)					
No treatments started	0	0	0	0	0
All 3 treatments active	9	0	0	1 (1.4)	8 (11.4)
Only SOC active	20	8 (11.4)	2 (2.9)	3 (4.3)	7 (10.0)
After end of all 3 treatments	41	24 (34.3)	4 (5.7)	12 (17.1)	1 (1.4)
Other	0	0	0	0	0
Total	70	32 (45.7)	6 (8.6)	16 (22.9)	16 (22.9)

Note: BLD = No virus detected, BLQ = Detectable <25 IU/mL

Table 15.2.1.1: 7 Frequency of patients with viral load BLD and BLQ by visit post EOT [all treatment] by randomised treatment and discontinuation status. PPS (as observed)

Visit: SVR 12

Treatment group / Discontinuation status	n	Virological response			
		BLD	BLQ	>=25	Missing
SOC alone (N = 71)					
No treatments started	0	0	0	0	0
All 3 treatments active	0	0	0	0	0
Only SOC active	0	0	0	0	0
After end of all 3 treatments	70	36 (50.7)	0	7 (9.9)	27 (38.0)
Other	1	0	0	0	1 (1.4)
Total	71	36 (50.7)	0	7 (9.9)	28 (39.4)
120 mg QD with lead-in (N = 69)					
No treatments started	0	0	0	0	0
All 3 treatments active	0	0	0	0	0
Only SOC active	0	0	0	0	0
After end of all 3 treatments	69	47 (68.1)	0	4 (5.8)	18 (26.1)
Other	0	0	0	0	0
Total	69	47 (68.1)	0	4 (5.8)	18 (26.1)
240 mg QD with lead-in (N = 141)					
No treatments started	0	0	0	0	0
All 3 treatments active	0	0	0	0	0
Only SOC active	0	0	0	0	0
After end of all 3 treatments	141	92 (65.2)	1 (0.7)	13 (9.2)	35 (24.8)
Other	0	0	0	0	0
Total	141	92 (65.2)	1 (0.7)	13 (9.2)	35 (24.8)
240 mg QD without lead-in (N = 142)					
No treatments started	0	0	0	0	0
All 3 treatments active	0	0	0	0	0
Only SOC active	0	0	0	0	0
After end of all 3 treatments	142	106 (74.6)	0	10 (7.0)	26 (18.3)
Other	0	0	0	0	0
Total	142	106 (74.6)	0	10 (7.0)	26 (18.3)

Note: BLD = No virus detected, BLQ = Detectable <25 IU/mL

Table 15.2.2.1: 7 Frequency of patients with viral load BLD and BLQ by visit post EOT [all treatment] by randomised treatment and discontinuation status. PPS (as observed)

Visit: SVR 12

Treatment group Discontinuation status	n	Virological response BLD	 BLQ	 >=25	 Missing
240 mg QD with lead-in (N = 142)					
No treatments started	0	0	0	0	0
All 3 treatments active	0	0	0	0	0
Only SOC active	0	0	0	0	0
After end of all 3 treatments	142	37 (26.1)	0	36 (25.4)	69 (48.6)
Other	0	0	0	0	0
Total	142	37 (26.1)	0	36 (25.4)	69 (48.6)
240 mg QD without lead-in (N = 76)					
No treatments started	0	0	0	0	0
All 3 treatments active	0	0	0	0	0
Only SOC active	0	0	0	0	0
After end of all 3 treatments	76	27 (35.5)	0	10 (13.2)	39 (51.3)
Other	0	0	0	0	0
Total	76	27 (35.5)	0	10 (13.2)	39 (51.3)
240 mg BID with lead-in (N = 70)					
No treatments started	0	0	0	0	0
All 3 treatments active	0	0	0	0	0
Only SOC active	0	0	0	0	0
After end of all 3 treatments	70	19 (27.1)	0	13 (18.6)	38 (54.3)
Other	0	0	0	0	0
Total	70	19 (27.1)	0	13 (18.6)	38 (54.3)

Note: BLD = No virus detected, BLQ = Detectable <25 IU/mL

Table 15.2.1.1: 8 Final status by randomised treatment
PPS (as observed)

Final status	SOC alone (N = 71)	120 mg QD with lead-in (N = 69)	240 mg QD with lead-in (N = 141)	240 mg QD without lead-in (N = 142)
1 SVR24 BLD	40 (56.3)	50 (72.5)	102 (72.3)	119 (83.8)
2 Breakthrough BI201335	2 (2.8)	4 (5.8)	7 (5.0)	5 (3.5)
3 Breakthrough SOC	3 (4.2)	2 (2.9)	1 (0.7)	0
4 Relapse	11 (15.5)	5 (7.2)	15 (10.6)	11 (7.7)
5 Other rebound	3 (4.2)	1 (1.4)	5 (3.5)	1 (0.7)
6 SVR24 not BLD	7 (9.9)	0	0	0
7 LTFU/SVR24 missing	5 (7.0)	7 (10.1)	11 (7.8)	6 (4.2)

Note: Patients are assigned to categories in descending order of preference.
1 - SVR24 result (earliest HCV mRNA result on or after day 155 post end of all treatment) is BLD.
2 - Confirmed rebound (>=1log10 increase in HCV mRNA) while on BI201335/placebo + 5 days washout.
3 - Confirmed rebound (>=1log10 increase in HCV mRNA) while on SOC only + 5 days washout.
4 - Confirmed rebound (>=1log10 increase in HCV mRNA) post treatment, and BLD at end of all treatment.
5 - Confirmed rebound (>=1log10 increase in HCV mRNA) post treatment, and not BLD at end of all treatment.
6 - SVR24 result (earliest HCV mRNA result on or after day 155 post end of all treatment) is not BLD.
7 - There is no SVR24 result available, i.e. no HCV mRNA samples on or after day 155 post end of all treatment.

Table 15.2.2.1: 8 Final status by randomised treatment
PPS (as observed)

Final status	240 mg QD with lead-in (N = 142)	240 mg QD without lead-in (N = 76)	240 mg BID with lead-in (N = 70)
1 SVR24 BLD	40 (28.2)	31 (40.8)	22 (31.4)
2 Breakthrough BI201335	36 (25.4)	22 (28.9)	12 (17.1)
3 Breakthrough SOC	7 (4.9)	5 (6.6)	5 (7.1)
4 Relapse	38 (26.8)	9 (11.8)	14 (20.0)
5 Other rebound	15 (10.6)	5 (6.6)	11 (15.7)
6 SVR24 not BLD	1 (0.7)	0	1 (1.4)
7 LTFU/SVR24 missing	5 (3.5)	4 (5.3)	5 (7.1)

Note: Patients are assigned to categories in descending order of preference.
1 - SVR24 result (earliest HCV mRNA result on or after day 155 post end of all treatment) is BLD.
2 - Confirmed rebound (>=1log10 increase in HCV mRNA) while on BI201335/placebo + 5 days washout.
3 - Confirmed rebound (>=1log10 increase in HCV mRNA) while on SOC only + 5 days washout.
4 - Confirmed rebound (>=1log10 increase in HCV mRNA) post treatment, and BLD at end of all treatment.
5 - Confirmed rebound (>=1log10 increase in HCV mRNA) post treatment, and not BLD at end of all treatment.
6 - SVR24 result (earliest HCV mRNA result on or after day 155 post end of all treatment) is not BLD.
7 - There is no SVR24 result available, i.e. no HCV mRNA samples on or after day 155 post end of all treatment.

Table 15.3.1.2.1: 1 Adverse event overall summary - treated set

	Lead-in only N (%)	SOC alone N (%)	120 mg QD N (%)	120mg QD w/o N (%)	240 mg QD N (%)	240mg QD w/o N (%)
Number of patients	2 (100.0)	71 (100.0)	68 (100.0)	1 (100.0)	138 (100.0)	149 (100.0)
Patients with any AE	2 (100.0)	67 (94.4)	66 (97.1)	1 (100.0)	136 (98.6)	147 (98.7)
Patients with severe AEs	1 (50.0)	3 (4.2)	8 (11.8)	0 (0.0)	22 (15.9)	19 (12.8)
Patients with investigator defined drug-related AEs	2 (100.0)	63 (88.7)	63 (92.6)	1 (100.0)	134 (97.1)	146 (98.0)
Patients with other significant AEs (according to ICH E3)	1 (50.0)	1 (1.4)	3 (4.4)	0 (0.0)	12 (8.7)	6 (4.0)
Patients with AEs leading to discontinuation of trial drug	1 (50.0)	1 (1.4)	3 (4.4)	0 (0.0)	15 (10.9)	8 (5.4)
Patients with significant AEs (pre-specified events)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with serious AEs	0 (0.0)	2 (2.8)	3 (4.4)	0 (0.0)	18 (13.0)	12 (8.1)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Imm life-threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Disability/incap.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Req.hospitalisation	0 (0.0)	2 (2.8)	3 (4.4)	0 (0.0)	16 (11.6)	8 (5.4)
Prol.hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	5 (3.4)

A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 14.1

Table 15.3.2.2.1: 1 Adverse event overall summary - treated set

	Lead-in only N (%)	240 mg QD N (%)	240mg QD w/o N (%)	240 mg BID N (%)	SOC N (%)
Number of patients	2 (100.0)	141 (100.0)	76 (100.0)	69 (100.0)	164 (100.0)
Patients with any AE	0 (0.0)	137 (97.2)	75 (98.7)	69 (100.0)	71 (43.3)
Patients with severe AEs	0 (0.0)	20 (14.2)	11 (14.5)	19 (27.5)	6 (3.7)
Patients with investigator defined drug-related AEs	0 (0.0)	135 (95.7)	74 (97.4)	69 (100.0)	42 (25.6)
Patients with other significant AEs (according to ICH E3)	0 (0.0)	6 (4.3)	2 (2.6)	15 (21.7)	0 (0.0)
Patients with AEs leading to discontinuation of trial drug	0 (0.0)	8 (5.7)	3 (3.9)	16 (23.2)	0 (0.0)
Patients with significant AEs (pre-specified events)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with serious AEs	0 (0.0)	10 (7.1)	5 (6.6)	13 (18.8)	6 (3.7)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Imm life-threatening	0 (0.0)	2 (1.4)	0 (0.0)	2 (2.9)	0 (0.0)
Disability/incap.	0 (0.0)	1 (0.7)	0 (0.0)	1 (1.4)	0 (0.0)
Req.hospitalisation	0 (0.0)	10 (7.1)	4 (5.3)	12 (17.4)	6 (3.7)
Prol.hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	1 (1.3)	1 (1.4)	0 (0.0)

A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 14.1