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**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-012579-90	
Name of active ingredient: BI 201335 NA		**Page:** 1 of 9	**Synopsis No.:**
Module:		**Volume:**	
Report date: 13 SEP 2012	**Trial No. / U No.:** 1220.40 / U12-2086-02	**Dates of trial:** 21 SEP 2009 – 11 APR 2011	**Date of revision:** 13 JUN 2013

Title of trial:	Antiviral effect and safety of once daily BI 201335 NA in hepatitis C virus genotype 1 infected treatment-naive patients for 12 or 24 weeks as combination therapy with pegylated interferon-α 2a and ribavirin (open-label, randomised, Phase II)
Coordinating Investigator:	[redacted]
Trial sites:	International, multi-centre trial at 27 sites in 6 countries
Publication (reference):	Data from this trial have not been published
Clinical phase:	II
Objectives:	To compare the antiviral efficacy and safety of a 12-week with a 24-week treatment of BI 201335 at a dose of 120 mg once daily, with a 24-week background of pegylated interferon-α 2a (PegIFN) plus ribavirin (RBV), in treatment-naïve patients infected with hepatitis C virus (HCV) genotype 1.
Methodology:	This randomised, open-label, parallel-group trial (SILEN-C3) was part of the SILEN-C series (SILEN-C1 and SILEN-C2 were combined in Trial 1220.5) of the Phase II programme for BI 201335. Treatment-naïve patients received 120 mg of BI 201335 once daily for 12 or 24 weeks, with PegIFN/RBV background medication. Treatment in both the 12-week and the 24-week group began with a 3-day lead-in phase with PegIFN/RBV alone. Subsequently, BI 201335 was administered at a loading dose of 240 mg on Day 1 of BI 201335 treatment, and at doses of 120 mg once daily thereafter. Patients who did not show an extended early virological response (eRVR) continued treatment with PegIFN/RBV alone for a total of 24 to 48 weeks.

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No. of patients:	
planned:	entered: 140 patients
actual:	enrolled: 208 patients randomised: 160 patients BI 201335 120 mg once daily for 12 weeks: entered: 81 treated: 81 analysed (for primary endpoint): 81 BI 201335 120 mg once daily for 24 weeks: entered: 79 treated: 79 analysed (for primary endpoint): 78
Diagnosis and main criteria for inclusion:	Female and male patients, 18 to 70 years of age, with chronic HCV genotype 1 (1a, 1b, or mixed 1a/1b) infection and an HCV viral load ≥100 000 IU/mL at screening. Patients had to be treatment naïve, i.e. have no previous exposure to PegIFN/RBV or a protease inhibitor (PI) for acute or chronic HCV infection.
Test product:	BI 201335 NA, soft gelatine capsule
dose:	120 mg once daily, with a loading dose of 240 mg
mode of admin.:	Oral
batch no.:	B093000182/09JM-068
Reference therapy 1:	Pegylated interferon α-2a (Pegasys®) solution for injection
dose:	180 µg once weekly
mode of admin.:	Subcutaneous injection
batch no.:	B093000537/B1024, B093000902/B1024
Reference therapy 2:	Ribavirin (Copegus®) tablet
dose:	1000 mg per day divided in 2 doses, if body weight <75 kg 1200 mg per day divided in 2 doses, if body weight ≥75 kg
mode of admin.:	Oral
batch no.:	B093000539/104820, B093000538/105919, B093000908/119986, B093000915/118765

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Duration of treatment:	BI 201335 was given over 12 or 24 weeks, in combination with a background of PegIFN/RBV. Patients who did not achieve HCV RNA <25 IU/mL (detected [BLQ] or undetected [BLD)] at Week 4 and HCV RNA <25 IU/mL (BLD) at Weeks 8 and 12 were to continue PegIFN/RBV up to Week 48.
Criteria for evaluation:	
Efficacy:	The primary efficacy endpoint in this study was the frequency of patients with a virological response (HCV RNA below the lower limit of detection) at Week 28 (W28VR). Key secondary and other endpoints were: • The predictive ability of early treatment responses such as the rapid virological response (RVR), eRVR, early treatment success (ETS), and the complete early virological response (cEVR) • Extended rapid virological response (eRVR), defined as a plasma HCV RNA level BLD or BLQ at Week 4, and BLD at Weeks 8 and 12 while on treatment • Sustained virological response 24 weeks after completion of all HCV therapy (SVR) • Sustained virological response 4 weeks after completion of all HCV therapy (SVR4) • Sustained virological response 12 weeks after completion of all HCV therapy (SVR12) • Time to viral load rebound, defined as an increase of HCV RNA by ≥1 $\log_{10}$ or an increase of HCV RNA >25 IU/mL (detected) after initial drop to HCV RNA <25 IU/mL (undetected), or an increase of HCV RNA >25 IU/mL after an initial drop to HCV RNA <25 IU/mL (detected) in 2 consecutive measurements 2 weeks apart • Virological rebound during BI 201335 plus PegIFN/RBV (BI 201335 breakthrough), rebound during PegIFN/RBV alone (PegIFN/RBV breakthrough), or rebound after the end of all HCV therapy (relapse)

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Safety:	Adverse events (AEs), tolerability, vital signs and physical examination, electrocardiogram (ECG), laboratory test abnormalities, and laboratory test value changes over time. The study included the review of data by a DMC external to the sponsor.
Statistical methods:	**Primary endpoint** The rate of patients who achieved a virological response at Week 28 was calculated. The Cochran-Mantel-Haenszel method, stratified by HCV sub-genotype (as identified by NS3-4A sequencing), was used to compare the response rates between patients treated for 12 or 24 weeks with BI 201335. The percent difference and 95% confidence intervals were calculated. **Secondary endpoints** The proportions of patients reaching secondary efficacy endpoints were determined per treatment group. The 95% confidence interval of percent differences was adjusted for HCV sub-genotype. Descriptive statistics, tabular, and graphical displays were used for HCV measurements (absolute and as change from baseline). The time to reach a plasma HCV RNA level BLD was analysed graphically with Kaplan-Meier curves and descriptive statistics.

SUMMARY – CONCLUSIONS:

Efficacy results:	To assess the efficacy and safety of BI 201335, treatment-naïve patients infected with HCV genotype 1 received BI 201335 at a dose of 120 mg once daily for 12 or 24 weeks, in combination with 24 or 48 weeks of PegIFN/RBV background therapy. In all, 160 patients were randomised; all 160 were included in TS and FAS analyses. Due to 1 important protocol violation, 159 patients were included in the PPS analyses. All efficacy analyses were based on the PPS. Differences in demographic and baseline characteristics between the 12-week and 24-week treatment groups were seen regarding sex, baseline viral load, and HCV genotype. The 12-week group included approximately 10% more male patients and more patients with genotype 1a (49.4%) than the 24-week group (36.7%). The 24-week group included about 10% more patients with viral loads <800 000 IU/mL and more patients with genotype 1b (62.0%) than the 12-week group (48.1%).

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Efficacy results (continued):

Concomitant diagnoses were reported more frequently for patients in the 12-week treatment group (76.5%) than for those in the 24-week group (64.6%). While compliance with BI 201335 was high and similar in both treatment arms, for both PegIFN and RBV, compliance rates <80% were reported more frequently for patients in the 12-week group. Thus, the shorter treatment arm included a higher proportion of patients with potential negative baseline predictors of response.

The primary endpoint in this trial was W28VR. In patients receiving BI 201335 at a dose of 120 mg once daily for 12 or 24 weeks, with 24 or 48 weeks of background PegIFN/RBV, W28VR rates were nearly identical in both treatment arms (75.3% in the 12-week and 76.9% in the 24-week group), with a difference in responder rates between the 2 groups of 1.6%, and a genotype-adjusted difference of -1.25% (95% CI -14.3%, 11.8%).

Secondary efficacy endpoints for evaluating early virological response on treatment were RVR, ETS, eRVR, and cEVR.

RVR was achieved by 59.3% of patients in the 12-week group and by 71.8% of those in the 24-week treatment group. This difference in response rates was due to the lower RVR rates of patients with HCV genotype 1a in the 12-week group (42.5%) versus 65.5% in the 24-week group, whereas RVR rates for patients with genotype 1b were similar in both groups (76.9% in the 12-week and 75.0% in the 24-week group). This difference occurred at RVR at Week 4 was carried over into all later efficacy endpoints up to SVR. Importantly, these differences occurred during the first 12 weeks of treatment, when all patients in this trial received identical treatment, and thus cannot be attributed to differences in treatment duration. These differences could be, in part, explained by imbalances in baseline HCV viral loads or HCV 1a and 1b genotypes in the 2 treatment groups, or by other factors such as IL28B genotype, which was not tested in this trial.

The eRVR was the early marker used to steer the response-guided therapy in this trial. Patients who achieved an eRVR stopped all treatment at Week 24; those who did not achieve eRVR, continued with treatment up to Week 48. The eRVR was achieved by 70.4% of patients in the 12-week group and by 83.3% of those in the 24-week group. Thus, over 70% of patients in this trial could stop all HCV therapy after 24 weeks of treatment.

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Efficacy results (continued):

SVR was achieved by 66.7% of patients in the 12-week group and by 74.4% of those in the 24-week group. Of the 10 patients with compensated liver cirrhosis in each of the 2 treatment groups, 3 in the 12-week group and 4 in the 24-week group achieved SVR. Of those beginning the study with viral loads ≥800 000 IU/mL, 63.9% in the 12-week group and 72.1% in the 24-week group achieved SVR.

There was a difference in SVR rates of 7.7% between the 2 treatment groups, which was carried over from the early on-treatment endpoints and was attributable to lower responses of genotype 1a patients in the 12-week group (52.5% versus 72.4% in the 24-week group). In contrast, of the patients with genotype 1b, 82.1% in the 12-week group and 75.0% of those in the 24-week group achieved this response. The genotype-adjusted difference between groups was 4.78% (95% CI -9.0, 18.6).

Nearly all of the patients who achieved SVR reached viral loads BLD prior to completing the 12-week treatment regimen, with 53 of 54 of patients in the 12-week group and 57 of 58 in the 24-week group reaching viral loads BLD on or before Week 8. All patients who reached BLD during these first weeks of identical treatment achieved SVR at similar rates, whether they received 12 or 24 weeks of BI 201335 treatment. The observed differences in response rates seen in the 2 treatment groups were confined to patients who did not achieve BLD during the period of identical treatment, indicating that the observed differences in SVR rates could not be attributed to treatment duration.

The frequency of breakthroughs during BI 201335 (with a background of PegIFN/RBV) treatment was low and similar in both treatment groups; 5 of 81 patients were reported with a breakthrough in the 12-week group and 7 of 78 patients in the 24-week group. Relapse rate and time to relapse were similar in both treatment groups. All but 1 patient relapsed during the first 12 weeks after the end of all therapy. One patient relapsed 12 to 24 weeks after the end of all therapy.

Genotypic and phenotypic resistance analyses will be described in a separate report.

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Safety results:

This open-label study was conducted without placebo control and included 160 treatment-naïve patients with HCV genotype 1 infection who received 120 mg of BI 201335 once daily for 12 or 24 weeks (with a background of PegIFN/RBV for 24 or 48 weeks). Safety analyses included all patients who had received at least 1 dose of study medication during their participation in the study (N=160).

Exposure to all HCV medication included exposure to BI 201335 and to PegIFN/RBV. The mean exposure to all HCV medication was 163.2 days (SD 57.0 days) for patients in the 12-week group and of 164.3 days (SD 39.5 days) in the 24-week group. Exposure to all HCV medications was in accordance with the protocol-defined period of either 24 or 48 weeks.

Adverse events were analysed for 12 weeks or 24 weeks of BI 201335 treatment including the subsequent 30-day washout period after the last dose of BI 201335. For the analyses of laboratory data, a 5-day washout window was applied to the stop date of PegIFN/RBV treatment; for BI 201335 treatments, the wash-out window was 7 days.

Similar frequencies of AEs were reported for both treatments, with rates of 93.8% in the 12-week group and 89.9% in the 24-week group. Over 90% of patients reported AEs of mild or moderate intensity, with similar rates in both groups. AEs of severe intensity were reported by 7.5% and 8.9% of patients in the 12- and 24-week groups, respectively. Three patients (3.8%) in the 12-week group and 5 patients (6.3%) in the 24-week group discontinued treatment prematurely due to AEs. Serious adverse events were reported for 3.8% of patients (N=3) in both treatment groups. No death was reported in this trial.

Overall, 75 patients (93.8%) receiving therapy for 12 weeks and 71 patients (89.9 %) receiving it for 24 weeks reported AEs with onset during BI 201335 treatments. The most frequently reported SOC was skin and subcutaneous tissue disorders, with rates of 55.0% in the 12-week group and of 62.0% in the 24-week group. The most frequently reported PTs (>20%) were pruritus, nausea, rash, headache, asthenia, fatigue, and dry skin.

While receiving BI 201335, 18 patients (22.5%) in the 12-week group and 17 patients (21.5%) in the 24-week group developed rash. One patient in the 24-week group reported a photosensitivity reaction. Most rash events occurred during the first 12 weeks of treatment and were of mild or moderate intensity;

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Safety results (continued):

1 patient reported rash of severe intensity. Two patients discontinued treatment prematurely due to rash. Overall, rash appeared predominantly on the trunk, arms, or legs, and was described as erythema in 87.0% of cases.

In all, 52.5% of patients in the 12-week group and 43.0% in the 24-week group reported GI events with onset during BI 201335 treatments (with a background of PegIFN/RBV), with nausea as the most frequent event. Gastrointestinal events were most frequently of mild or moderate intensity; 3 patients reported severe GI events with onset during BI 201335 treatments. None of the patients in this trial discontinued HCV treatment due to GI events.

Abdominal pain, nausea, vomiting, and diarrhoea were predominantly of mild or moderate intensity; 1 patient reported vomiting of severe intensity. Nausea and vomiting with onset during BI 201335 treatments were more frequently reported in the 12-week group (33.8% versus 21.5% in the 24-week group for nausea, and 13.8% versus 8.9% in the 24-week group for vomiting), whereas diarrhoea was reported more frequently in the 24-week group (19.0% versus 5.0% in the 12-week group). No case of severe diarrhoea was reported during this trial.

The frequencies of jaundice with onset during BI treatments were low and similar in both groups, with rates of 3.7% in the 12-week group and 5.1% in the 24-week group. There were no severe cases and none led to treatment discontinuation.

Laboratory data did not produce unexpected results. There was a similar decrease from baseline to the last value on treatment in mean levels of AST and ALT in both treatment groups; most of these improvements were seen at Week 2, with more gradual improvements throughout the remainder of therapy.

Mean haemoglobin levels decreased from baseline in both BI 201335 treatment groups, in a fashion consistent with PegIFN/RBV treatment. However, most patients (80.5%) in this trial had haemoglobin levels above 10.0 g/dL. One patient with severe anaemia (haemoglobin <8.5 g/dL) was reported in each of the 2 treatment groups; neither of them discontinued treatment. One patient discontinued treatment due to anaemia (haemoglobin 8.5 to ≤10 g/dL). The use of blood cell stimulating factors was low. Four patients in the 12-week group and 9 of those in the 24-week group received erythropoiesis-stimulating agents.

Mean WBC had decreased at similar rates from baseline to the last value on

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Safety results (continued):	treatment in both treatment groups. In both groups, there were minor changes in WBC from baseline at the end of BI 201335 treatments. WBC remained low throughout treatment with PegIFN/RBV alone and recovered, in both groups, after the end of treatment with PegIFN/RBV alone. Similar patterns were seen with platelets, neutrophils, red blood cells, and haemoglobin. Lymphocytes remained largely unchanged in both groups. The isolated indirect hyperbilirubinaemia (direct-to-total-bilirubin ratios ≤0.5) was an expected effect of BI 201335 treatment. Overall during the trial, 4 patients had a direct-to-total-bilirubin ratio >0.5. None of these patients had concomitant ALT or AST elevations >3x ULN.
Conclusions:	High SVR rates were achieved with both 12 and 24 weeks of treatment with BI 201335 at a dose of 120 mg once daily, with a background of PegIFN/RBV, in treatment-naïve patients infected with HCV genotype 1. Response rates were similar in both treatment groups. The minor differences in response occurred early during still identical treatment and were thus not attributable to the different treatment regimens but rather due to random imbalances in baseline factors favouring the 24 weeks group. Over 70% of patients achieved a virological response early in the course of treatment and could end all HCV treatment at Week 24. The 12.5% of patients with compensated liver cirrhosis participating in this trial responded well to BI 201335 treatment. No unexpected safety findings were reported in this trial. The most frequently reported AEs were nausea, pruritus, asthenia, rash, fatigue, headache, and dry skin. Most AEs were of mild or moderate intensity, with similar overall rates in both treatment groups. In the 12-week group, 7.5% of reported AEs of severe intensity; so were 8.9% of AEs in the 24-week group. In 3.8% of patients in the 12-week group and 6.3% of those in the 24-week group, AEs led to discontinuation of treatment. Serious adverse events were reported for 3.8% of patients (N=3) in each treatment group. No fatal cases were reported in this trial. Regarding frequencies and severity, almost all adverse events and laboratory abnormalities were in the ranges reported for treatment with PegIFN/RBV alone. Comparison of both 120-mg-once-daily BI 201335 treatment arms indicated that the treatment duration of 12 weeks achieved similar efficacy as 24 weeks for the treatment-naïve patients infected with HCV genotype 1.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the trial synopsis. They complement patient disposition results and results for secondary endpoints of the trial. Other endpoints defined in the trial protocol are not presented in this synopsis because their numbers were too large to allow meaningful presentation in this format.

Results for	**presented in**
Patient Disposition	Table 15.1.1: 1
Rapid Virological Response (RVR) at Week 4 (Secondary EP)	Table 15.2.2.5: 1
Virological Response at Week 24 (W24VR) (Secondary EP)	Table 15.2.2.2: 1
Virological Response at Week 36 (W36VR) (Secondary EP)	Table 15.2.2.3: 1
End of Treatment Response (ETR) up to 48 Weeks (Secondary EP)	Table 15.2.2.4: 1
Change from Baseline in Viral Load by Visit up to 48 Weeks (Secondary EP)	Table 15.2.2.6: 1
Time to Reach Plasma HCV RNA Level BLD while on Treatment up to 48 Weeks (Secondary EP)	Table 15.2.2.7: 1

Table 15.1.1: 1 Patient disposition based on BI201335 by randomised treatment

	120 MG BI 201335 NA FOR 12 WEEKS	120 MG BI 201335 NA FOR 24 WEEKS	Total
Enrolled			208
Not entered/randomised			48
Entered/randomised	81	79	160
Not treated	0	0	0
Treated	81(100.00)	79(100.00)	160(100.00)
Not prematurely discontinued from trial medication	75(92.59)	67(84.81)	142(88.75)
Prematurely discontinued from trial medication	6(7.41)	12(15.19)	18(11.25)
Adverse event	5(6.17)	5(6.33)	10(6.25)
AE study dis. worse	0(0.00)	0(0.00)	0(0.00)
AE oth. dis. worse	1(1.23)	1(1.27)	2(1.25)
AE other	4(4.94)	4(5.06)	8(5.00)
Non compl. protocol	0(0.00)	0(0.00)	0(0.00)
Lost to follow-up	1(1.23)	1(1.27)	2(1.25)
Refused cont. medication	0(0.00)	2(2.53)	2(1.25)
Other	0(0.00)	4(5.06)	4(2.50)

The information is summarized based on that was collected on the Termination of Trial Medication (TTM) CRF of BI 201335

Table 15.2.2.5: 1 Rapid virological response (RVR) by randomized treatment (PPS)

	120 MG BI 201335 NA FOR 12 WEEKS		120 MG BI 201335 NA FOR 24 WEEKS	
	N(%)	Number of Responders (%)	N(%)	Number of Responders (%)
Number of patients	81(100.0)	48(59.3)	78(100.0)	56(71.8)
Unadjusted difference in %				12.5
Adjusted difference in % #				9.02
95% CI #				(-5.3,23.3)
P-value* #				0.229
Liver Cirrhosis				
No	71	46(64.8)	68	50(73.5)
Yes	10	2(20.0)	10	6(60.0)
Race				
Asian	2	2(100.0)	2	0
Black or African American	2	1(50.0)	1	0
White	77	45(58.4)	75	56(74.7)
Genotype(NS3-4A)				
1A	40	17(42.5)	29	19(65.5)
1B	39	30(76.9)	48	36(75.0)
Other	2	1(50.0)	1	1(100.0)
Baseline VL				
< 800,000 IU/mL	9	8(88.9)	17	14(82.4)
>= 800,000 IU/mL	72	40(55.6)	61	42(68.9)

Cochran-Mantel-Haenszel method adjusted by HCV genotype (1a and 1b only), i.e., 3 patients with subgenotype as other are not included in calculating the adjusted percent difference.
The percent differences and p-values are based on a comparison to the first treatment group.
* p-value is 2-sided.
Randomisation was stratified by presence of cirrhosis and race (black, Asian and others).
RVR responder is defined as patient who achieved HCV plasma viral load below limit of detection at Week 4.

Source data: Appendix 16.2, Listing 4.1, 6.1 ctr\adnstdetsum1v01.sas 03AUG2012

Table 15.2.2.2 1 Virological response at Week 24 (W24VR) by randomized treatment (PPS)

	120 MG BI 201335 NA FOR 12 WEEKS		120 MG BI 201335 NA FOR 24 WEEKS	
	N(%)	Number of Responders (%)	N(%)	Number of Responders (%)
Number of patients	81(100.0)	59(72.8)	78(100.0)	63(80.8)
Unadjusted difference in %				7.9
Adjusted difference in % #				5.48
95% CI #				(-7.3,18.3)
P-value* #				0.417
Liver Cirrhosis				
No	71	54(76.1)	68	56(82.4)
Yes	10	5(50.0)	10	7(70.0)
Race				
Asian	2	2(100.0)	2	1(50.0)
Black or African American	2	1(50.0)	1	1(100.0)
White	77	56(72.7)	75	61(81.3)
Genotype(NS3-4A)				
1A	40	25(62.5)	29	23(79.3)
1B	39	33(84.6)	48	39(81.3)
Other	2	1(50.0)	1	1(100.0)
Baseline VL				
< 800,000 IU/mL	9	8(88.9)	17	15(88.2)
>= 800,000 IU/mL	72	51(70.8)	61	48(78.7)

Cochran-Mantel-Haenszel method adjusted by HCV genotype (1a and 1b only), i.e., 3 patients with subgenotype as other are not included in calculating the adjusted percent difference.
The percent differences and p-values are based on a comparison to the first treatment group.
* p-value is 2-sided.
Randomisation was stratified by presence of cirrhosis and race (black, Asian and others).
W24VR responder is defined as patient who reached HCV plasma viral load below limit of detection at Week 24.

Source data: Appendix 16.2, Listing 4.1, 6.1 ctr\adnstdetsum1v01.sas 03AUG2012

Table 15.2.2.3 1 Virological response at Week 36 (W36VR) by randomized treatment (PPS)

	120 MG BI 201335 NA FOR 12 WEEKS		120 MG BI 201335 NA FOR 24 WEEKS	
	N(%)	Number of Responders (%)	N(%)	Number of Responders (%)
Number of patients	81(100.0)	55(67.9)	78(100.0)	58(74.4)
Unadjusted difference in %				6.5
Adjusted difference in % #				2.99
95% CI #				(-10.6,16.6)
P-value* #				0.676
Liver Cirrhosis				
No	71	51(71.8)	68	53(77.9)
Yes	10	4(40.0)	10	5(50.0)
Race				
Asian	2	2(100.0)	2	2(100.0)
Black or African American	2	1(50.0)	1	1(100.0)
White	77	52(67.5)	75	55(73.3)
Genotype(NS3-4A)				
1A	40	21(52.5)	29	20(69.0)
1B	39	33(84.6)	48	37(77.1)
Other	2	1(50.0)	1	1(100.0)
Baseline VL				
< 800,000 IU/mL	9	8(88.9)	17	14(82.4)
>= 800,000 IU/mL	72	47(65.3)	61	44(72.1)

Cochran-Mantel-Haenszel method adjusted by HCV genotype (1a and 1b only), i.e., 3 patients with subgenotype as other are not included in calculating the adjusted percent difference.
The percent differences and p-values are based on a comparison to the first treatment group.
* p-value is 2-sided.
Randomisation was stratified by presence of cirrhosis and race (black, Asian and others).
W36VR responder is defined as patient who reached HCV plasma viral load below limit of detection at Week 36.

Source data: Appendix 16.2, Listing 4.1, 6.1 ctr\adnstdetsum1v01.sas 03AUG2012

Table 15.2.2.4: 1 End of treatment response (ETR) by randomized treatment (PPS)

	120 MG BI 201335 NA FOR 12 WEEKS		120 MG BI 201335 NA FOR 24 WEEKS	
	N(%)	Number of Responders (%)	N(%)	Number of Responders (%)
Number of patients	81(100.0)	65(80.2)	78(100.0)	67(85.9)
Unadjusted difference in %				5.7
Adjusted difference in % #				3.24
95% CI #				(-8.1,14.6)
P-value* #				0.588
Liver Cirrhosis				
No	71	59(83.1)	68	59(86.8)
Yes	10	6(60.0)	10	8(80.0)
Race				
Asian	2	2(100.0)	2	2(100.0)
Black or African American	2	1(50.0)	1	1(100.0)
White	77	62(80.5)	75	64(85.3)
Genotype(NS3-4A)				
1A	40	29(72.5)	29	24(82.8)
1B	39	35(89.7)	48	42(87.5)
Other	2	1(50.0)	1	1(100.0)
Baseline VL				
< 800,000 IU/mL	9	8(88.9)	17	15(88.2)
>= 800,000 IU/mL	72	57(79.2)	61	52(85.2)

Cochran-Mantel-Haenszel method adjusted by HCV genotype (1a and 1b only), i.e., 3 patients with subgenotype as other are not included in calculating the adjusted percent difference.
The percent differences and p-values are based on a comparison to the first treatment group.
* p-value is 2-sided.
Randomisation was stratified by presence of cirrhosis and race (black, Asian and others).
ETR responder is defined as patient who achieved HCV plasma viral load below limit of detection at end of all HCV therapy.

Source data: Appendix 16.2, Listing 4.1, 6.1 ctr\adnstdetsum1v01.sas 03AUG2012

Table 15.2.2.6: 1 Descriptive statistics of viral load over time (PPS)

	Absolute value						Change from baseline					
Treatment Week	n	Mean	Std	Min	Median	Max	n	Mean	Std	Min	Median	Max
120 MG BI 201335 NA FOR 12 WEEKS												
Baseline	81	6.528	0.4857	5.31	6.575	7.54						
Week 2	76	1.790	0.8917	1.00	1.398	5.48	76	-4.724	0.9059	-6.15	-4.822	-1.51
Week 4	76	1.514	1.1003	1.00	1.000	6.64	76	-4.993	1.1168	-6.37	-5.203	-0.35
Week 8	75	1.378	1.1014	1.00	1.000	6.70	75	-5.128	1.1159	-6.54	-5.364	-0.29
Week 12	76	1.390	1.1251	1.00	1.000	6.10	76	-5.117	1.1495	-6.54	-5.353	-0.95
Week 16	18	1.261	1.1063	1.00	1.000	5.69	18	-5.363	1.2341	-6.37	-5.625	-0.76
Week 20	52	1.364	1.1151	1.00	1.000	5.99	52	-5.056	1.0894	-6.17	-5.282	-0.47
Week 24	12	2.455	1.9992	1.00	1.398	6.44	12	-4.176	2.1635	-6.34	-5.015	-0.03
Week 28	4	1.000	0.0000	1.00	1.000	1.00	4	-5.723	0.6795	-6.34	-5.892	-4.77
Week 36	4	1.099	0.1990	1.00	1.000	1.40	4	-5.624	0.7059	-6.34	-5.693	-4.77
EOT	80	1.610	1.4861	1.00	1.000	6.43	80	-4.910	1.4690	-6.54	-5.353	-0.04
SVR 4*	75	2.213	2.2880	1.00	1.000	7.21	75	-4.296	2.2499	-6.54	-5.217	0.48
SVR 12*	75	2.355	2.3587	1.00	1.000	7.21	75	-4.154	2.3356	-6.54	-5.188	0.48
SVR 24*	73	2.403	2.3982	1.00	1.000	7.21	73	-4.103	2.3673	-6.54	-5.188	0.48
120 MG BI 201335 NA FOR 24 WEEKS												
Baseline	78	6.449	0.6083	4.98	6.567	7.70						
Week 2	78	1.583	0.7773	1.00	1.398	5.19	78	-4.866	0.8664	-6.30	-4.933	-1.55
Week 4	77	1.360	0.9838	1.00	1.000	6.26	77	-5.081	1.1195	-6.70	-5.387	-0.46
Week 8	76	1.359	1.1981	1.00	1.000	6.20	76	-5.088	1.3150	-6.70	-5.427	0.07
Week 12	76	1.340	1.1573	1.00	1.000	6.31	76	-5.107	1.2852	-6.70	-5.427	0.16
Week 16	13	1.085	0.2089	1.00	1.000	1.58	13	-5.262	0.5820	-6.07	-5.299	-4.51
Week 20	57	1.095	0.4028	1.00	1.000	3.37	57	-5.366	0.7319	-6.70	-5.497	-2.97
Week 24	8	1.807	1.5458	1.00	1.199	5.50	8	-4.740	1.6576	-6.09	-5.397	-1.14
Week 28	4	2.233	2.2093	1.00	1.199	5.54	4	-4.369	2.2917	-6.09	-5.138	-1.10
Week 36	2	1.000	0.0000	1.00	1.000	1.00	2	-5.958	0.1909	-6.09	-5.958	-5.82
EOT	78	1.432	1.3306	1.00	1.000	6.59	78	-5.017	1.4434	-6.70	-5.417	0.15
SVR 4*	77	2.078	2.1575	1.00	1.000	7.53	77	-4.367	2.1849	-6.70	-5.228	0.78
SVR 12*	75	2.078	2.1306	1.00	1.000	7.19	75	-4.353	2.1588	-6.70	-5.225	0.42
SVR 24*	75	2.182	2.2375	1.00	1.000	7.19	75	-4.250	2.2439	-6.70	-5.199	0.66

Assuming BLD=10 IU/mL and BLQ=25 IU/mL in the summary
*SVR 4, SVR 12, and SVR 24 represent the follow-up visits 4, 12, and 24 weeks after the end of all medication respectively

Source data: Appendix 16.2, Listing 6.3 ctr\adstddstatv01.sas 03AUG2012

Table 15.2.2.7: 1 Kaplan-Meier estimates of time to below limit of detection by randomised treatment (PPS)

	120 MG BI 201335 NA FOR 12 WEEKS			120 MG BI 201335 NA FOR 24 WEEKS		
Time intervals [Week]	Number at risk*	Event N(%)	Censored N(%)	Number at risk*	Event N(%)	Censored N(%)
(0 – 1]	81	0 (0.0)	1 (1.2)	78	0 (0.0)	0 (0.0)
(1 – 2]	80	1 (1.3)	1 (1.3)	78	2 (2.6)	0 (0.0)
(2 – 4]	78	19 (24.4)	2 (2.6)	76	24 (31.6)	1 (1.3)
(4 – 6]	57	28 (49.1)	0 (0.0)	51	31 (60.8)	0 (0.0)
(6 – 8]	29	3 (10.3)	0 (0.0)	20	1 (5.0)	0 (0.0)
(8 – 12]	26	14 (53.8)	0 (0.0)	19	10 (52.6)	0 (0.0)
(12 – 16]	12	0 (0.0)	4 (33.3)	9	1 (11.1)	1 (11.1)
(16 – 24]	8	0 (0.0)	0 (0.0)	7	2 (28.6)	3 (42.9)
(24 – 28]	8	2 (25.0)	5 (62.5)	2	0 (0.0)	1 (50.0)
>28	1	0 (0.0)	1 (100)	1	0 (0.0)	1 (100)
Median (95% CI)		4.1 (4.1 , 4.6)			4.1 (. , .)	
(Q1 , Q3)		(4 , 8)			(2 , 8)	
Comparison** P-value**					0.1397	

* Number of non-BLD patients on BI201335 medication during the respective time interval.
** Compare 120 MG BI 201335 NA FOR 24 WEEKS over 120 MG BI 201335 NA FOR 12 WEEKS using log-rank test.