804

Virological response and safety of 4 weeks' treatment with the protease inhibitor BI 201335 combined with 48 weeks of peginterferon alfa 2a and ribavirin for treatment of HCV GT-1 patients who failed peginterferon/ribavirin

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ABSTRACT

Background: BI 201335 is a highly potent and specific hepatitis C virus (HCV) NS3/4A protease inhibitor. BI 201335 given at 240 mg once daily (QD) demonstrated a median maximum viral load (VL) reduction by 4.2 $\log_{10}$ (IU/mL) during 14 days of monotherapy in treatment-naïve HCV genotype-1 (GT-1) patients, and by 5.3 $\log_{10}$ in combination with peginterferon (PegIFN) alfa 2a and ribavirin (RBV) for 28 days in treatment-experienced patients. This phase 1 study describes safety and efficacy of BI 201335 in GT-1 patients with virological failure to PegIFN/RBV.

Methods: Patients were randomized to open-label treatment with 240 mg QD (n=15) or twice daily (BID; n=15) in combination with PegIFN (180 mcg/week) and RBV (1,000/1,200 mg/day) for 28 days, followed by PegIFN/RBV until Week 48. Patients with cirrhosis were excluded. All patients received an initial loading dose of 480 mg of BI 201335. Plasma HCV RNA was measured by Roche COBAS TaqMan assay.

Results: Mean age was 50 years, body mass index 26 kg/m^2. Mean VL at baseline was 6.6 $\log_{10}$ (IU/mL). Most patients were null- (40%), or partial- (47%) responders to previous treatment, while 3 patients had breakthroughs and 1 relapsed. During 4 weeks of treatment with BI 201335 and standard-of-care (SOC), all patients showed a rapid VL decline. Mean VL reduction on Day 28 was –5.1 $\log_{10}$ in both groups. All 30 patients continued SOC treatment beyond Day 28. Virological responses until Week 48 are displayed in the table. Sustained virological response rates will be available at the meeting. One virologic breakthrough (≥1 log rebound from VL nadir or VL >100 IU/mL after undetectable VL) was observed during BI 201335 treatment. Treatment was generally safe and well tolerated. Adverse events (AEs) were mainly mild to moderate and typical of PegIFN/RBV. There were no serious AEs. Bilirubin elevations of 2.5–6 x upper limit of normal were observed in 8 and 10 patients at 240 mg QD and BID and were exclusively caused by isolated unconjugated hyperbilirubinemia, likely due to UGT1A1 inhibition. Other lab analyses showed decreases of alanine aminotransferase and blood cell counts typical of PegIFN/RBV.

Conclusions: Four weeks of BI 201335 240 mg once or twice daily combined with PegIFN/RBV exhibited similarly potent on-treatment efficacy in PegIFN/RBV non-responder patients. These data support further studies of both doses in these patients.

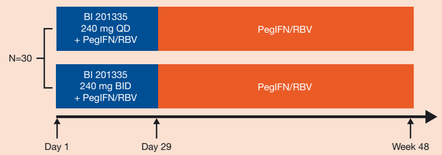
INTRODUCTION

- BI 201335 is a highly potent and specific hepatitis C virus (HCV) NS3/4A protease inhibitor
- Phase 1b clinical investigations demonstrate that BI 201335 once daily (QD) is well tolerated and induces strong antiviral responses in HCV genotype-1 (GT-1) patients[1]
  - during 14 days of monotherapy, a median maximum viral load (VL) reduction of 4.2 $\log_{10}$ IU/mL was observed with 240 mg BI 201335 QD in treatment-naïve patients
  - in treatment-experienced (TE) patients, BI 201335 240 mg QD in combination with peginterferon alfa 2a (PegIFN) and ribavirin (RBV) for 28 days resulted in a median maximum VL reduction of 5.3 $\log_{10}$ IU/mL
- Here we describe a phase 1b study investigating safety and efficacy of 4 weeks of BI 201335 240 mg QD or twice daily (BID) plus PegIFN/RBV in HCV GT-1 patients with previous virological failure to PegIFN/RBV

METHODS

- This trial was an open label, randomized, parallel group comparison of 240 mg BI 201335 QD (n=15) or BID (n=15), given orally for 28 days in combination with PegIFN alfa 2a (180 µg/week subcutaneous) and RBV (weight based: 1,000 or 1,200 mg daily); follow-on treatment with PegIFN/RBV to Week 48 was offered to all patients at the investigator's discretion (**Figure 1**)

FIGURE 1. Trial design



- All patients received a single loading dose of 480 mg BI 201335 as the first dose
- HCV GT-1 patients could be entered if they had never achieved undetectable VL with previous PegIFN/RBV treatment for at least 12 weeks with an approved dose (ie with null or partial response):
  - *null-response* was defined as maximum VL reduction <2 $\log_{10}$ from baseline until Week 12
  - *partial response* was defined as maximum VL reduction by ≥2 $\log_{10}$ from baseline but never achieved undetectable HCV RNA at any time
  - *breakthrough* was defined as achieving undetectable HCV RNA followed by VL rebound at any time during ongoing treatment
  - *relapse* was defined as achieving undetectable HCV RNA during treatment followed by VL rebound after end of treatment
- Exclusion criteria were human immunodeficiency virus or hepatitis B virus coinfection, HCV RNA <100,000 IU/mL, chronic alcohol abuse, liver cirrhosis or history of hepatic decompensation, hyperbilirubinemia >1.5 x upper limit of normal (ULN) (except Gilbert's Disease), alanine aminotransferase (ALT) and aspartate aminotransferase >5 x ULN, INR >1.5 x ULN. Other exclusion criteria were those common for PegIFN/RBV treatment
- Plasma HCV RNA was measured by Roche COBAS TaqMan assay, with a lower limit of quantification of 25 IU/mL and a lower limit of detection of 10 IU/mL
- HCV genotype was determined by Trugene assay at screening. NS3 gene sequencing and phylogenetic analyses were used for definitive subtype assignment

RESULTS

Baseline demographics

- A total of 30 (male and female) HCV GT-1 patients were treated (**Table 1**)
  - the mean age of these 30 patients was 50 ± 10.76 years
  - the mean body mass index (BMI) was 26.3 ± 3.88 kg/m^2
  - at baseline, the mean plasma HCV RNA was 6.66 ± 0.33 $\log_{10}$ IU/mL
- Most patients were null- (70%), or partial- (17%) responders to previous treatment, while 2 patients (6.7%) had breakthroughs and 1 patient (3%) had relapsed

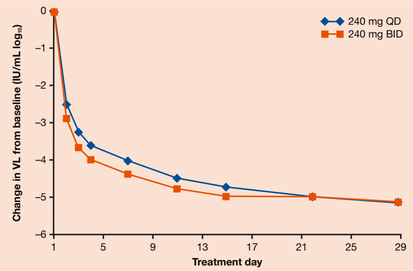
Efficacy

- All 30 randomized patients completed their 4-week course of BI 201335 at the assigned dose

TABLE 1. Baseline demographics

	BI 201335 240 mg QD (n=15)	BI 201335 240 mg BID (n=15)
Gender, n (%)		
Male	10 (66.7)	8 (53.3)
Female	5 (33.3)	7 (46.7)
Race, n (%)		
White	14 (93.3)	15 (100.0)
Black	1 (6.7)	0 (0)
HCV RNA, $\log_{10}$ IU/mL		
Mean	6.71	6.62
Standard deviation	0.25	0.40
GT, n (%)		
1a	9 (60.0)	10 (66.7)
1b	6 (40.0)	5 (33.3)
Age, years		
Mean	51	49
Standard deviation	8.13	13.10
BMI, kg/m^2		
Mean	26.9	25.7
Standard deviation	3.78	4.02
Previous treatment response		
Null responders	11 (73.3)	10 (66.7)
Partial responders	3 (20)	2 (13.3)
Breakthroughs	1 (6.7)	1 (6.7)
Relapsers	0 (0)	1 (6.7)
Unknown	0 (0)	1 (6.7)

FIGURE 2. Mean HCV RNA reductions from baseline (Day 1) over time for the BI 201335 240 mg QD and BID dose groups



- During the first 4 weeks of treatment with BI 201335 and PegIFN/RBV, all patients showed a rapid VL decline (**Figure 2**). Mean VL reduction on Day 29 was –5.1 $\log_{10}$ in both groups
- One virologic rebound (≥1 $\log_{10}$ re-increase from VL nadir) was observed during BI 201335 treatment. This patient was a null-responder to previous PegIFN/RBV
- Rapid virological responses, defined as HCV RNA below the limit of quantification (BLQ) at Day 29, were achieved by 60% and 67% of patients treated with 240 mg QD or BID, respectively
- Follow-on treatment beyond Day 29 was at the discretion of the investigator. All 30 patients continued PegIFN/RBV treatment beyond Day 29 with 6 patients in each group being treated for the full 48 weeks (±2 weeks), and 1 additional QD patient extending PegIFN/RBV to 492 days. The main reason for early PegIFN/RBV discontinuation was virological failure (n=5 at 240 mg QD, n=6 at 240 mg BID)
- Virological response rates up to Week 48, and sustained viral response (SVR) rates, are shown in **Table 2**
- There was no clear association of virological response to current treatment with response to previous PegIFN/RBV therapy (**Table 3**)
- Three patients at one site (2 at 240 mg QD and 1 at BID) with detectable HCV RNA at the end of BI 201335 therapy were treated with an experimental regimen of high-dose silibinin (1,400 mg/day intravenously on 2 consecutive days) between Weeks 5 and 21; 1 patient did not respond, 1 experienced breakthrough and 1 achieved SVR[2]

TABLE 2. Virological response and SVR rates: BI 201335 240 mg QD and BID (missing data are counted as failure)

Virological response	BI 201335 240 mg QD (n=15)	BI 201335 240 mg BID (n=15)
Week 4, n (%)		
BLQ[a]	9/15 (60)	10/15 (67)
BLD[a]	4/15 (27)	4/15 (27)
Week 12, n (%)		
BLD	8/15 (53)	6/15 (40)
ETR[b] n (%)		
BLD	8/15 (53)	6/15 (40)
SVR, n (%)	7/15 (47)	6/15 (40)
Virological failures, n (%)	8/15 (53)	9/15 (60)
Non-response[c]	7	7
Breakthrough on PegIFN/RBV[d]	1	2
Relapse after end of PegIFN/RBV	0	0

[a]BLQ (<25 IU/mL); below lower limit of detection (BLD; <10 IU/mL)
[b]End of treatment response (ETR) indicates the patient was BLD at last visit prior to discontinuation of all study medication
[c]Non-response is defined as never achieving HCV RNA BLD during treatment
[d]Breakthrough is defined as achieving HCV RNA BLD followed by VL rebound during PegIFN/RBV treatment

TABLE 3. Virological response to BI 201335 plus PegIFN/RBV treatment dependent on response to PegIFN/RBV pretreatment

Response to BI 201335 + PegIFN/RBV (n)	Null-responders to PegIFN/RBV (n=21)	Partial responders to PegIFN/RBV (n=5)	Breakthrough to PegIFN/RBV (n=2)	Relapse after PegIFN/RBV (n=1)
SVR	8	3	1	0
Non-response	10	2	1	1
Breakthrough	3	0	0	0
Relapse	0	0	0	0

Safety and tolerability

- Treatment was generally safe and well tolerated in both dose groups
- There were no serious adverse events (AEs) and no early discontinuations of BI 201335, PegIFN or RBV due to AEs
- AEs during the first 4 weeks of treatment with BI 201335 and PegIFN/RBV were mostly mild-to-moderate and typical of PegIFN/RBV. The only dose-dependent AEs were vomiting and jaundice (**Table 4**)

TABLE 4. Most frequent (>10%) AEs during 4 weeks of treatment with BI 201335, PegIFN and RBV

	Most frequent AEs, n (%)	
	BI 201335 240 mg QD (n=15)	BI 201335 240 mg BID (n=15)
Headache	9 (60.0)	10 (66.7)
Nausea	7 (46.7)	8 (53.3)
Diarrhea	8 (53.3)	5 (33.3)
Fatigue	8 (53.3)	2 (13.3)
Vomiting	2 (13.3)	6 (40.0)
Jaundice	1 (6.7)	6 (40.0)
Chills	4 (26.7)	2 (13.3)
Insomnia	4 (26.7)	1 (6.7)
Asthenia	2 (13.3)	3 (20.0)
Myalgia	1 (6.7)	3 (20.0)
Dry skin	0 (0)	3 (20.0)
Cough	2 (13.3)	2 (13.3)
Ocular icterus	1 (6.7)	2 (13.3)
Arthralgia	1 (6.7)	2 (13.3)
Anemia	2 (13.3)	1 (6.7)
Pruritus	2 (13.3)	1 (6.7)
Neutropenia	2 (13.3)	0 (0)
Pain in extremity	2 (13.3)	0 (0)

- Rash was reported in 1 patient (6.7%) treated with BI 201335 at 240 mg QD and BID, respectively, while there were no cases of photosensitivity
- Safety laboratory analyses during triple treatment showed decreases in ALT accompanying the initial VL drops in all patients (**Table 5**). Moreover, blood cell counts dropped in a way typical of PegIFN/RBV. There was no dose-dependent effect of BI 201335 on red or white blood cell counts, platelets or hemoglobin levels
- Maximum total bilirubin elevations of 2.5–6 x ULN were observed in 8 and 10 patients at 240 mg QD and BID, respectively, and were caused by isolated unconjugated hyperbilirubinemia in all cases without signs of liver injury or increased hemolysis. Thus, this event was in accordance with the known inhibitory effect of BI 201335 on UGT1A1. However, jaundice, reported in only 7 patients, was usually of mild intensity and did not lead to dose modifications

TABLE 5. Median (min, max) laboratory changes from baseline to Week 4

Test parameter (normal range)	Laboratory changes from baseline to Week 4, *median (min, max)*	
	BI 201335 240 mg QD (n=15)	BI 201335 240 mg BID (n=15)
ALT (6.0–36.0 U/L)	–26 (–124, 4)	–36 (–70, –2)
Creatinine (31–128 µmol/L)	0 (–0.1, 0.2)	0 (–0.2, 0.3)
Bilirubin, total (0.2–1.2 mg/dL)	2.0 (0.5, 6.0)	2.7 (1.0, 4.0)
Bilirubin, indirect (0–1.2 mg/dL)	1.6 (0.3, 5.8)	2.1 (0.6, 3.3)
Hemoglobin (11.5–18.1 g/dL)	–2.6 (–5.7, 0.4)	–1.9 (–3.7, –0.2)
Platelets (130–400 x 10^9/L)	–40 (–111, –4)	–42 (–98, 92)
White blood cells (3.8–10.7 x 10^9/L)	–2.6 (–4.6, –1.2)	–2.5 (–5.0, 1.3)

CONCLUSIONS

- Four weeks' treatment with 240 mg BI 201335 QD or BID combined with PegIFN/RBV exhibited potent on-treatment activity in patients failing previous PegIFN/RBV, mostly with null-response
- Only one virologic breakthrough was observed during BI 201335 treatment, despite inclusion of mostly PegIFN/RBV non-responders
- Four weeks' treatment with 240 mg BI 201335 QD or BID combined with PegIFN/RBV, and followed by a further 44 weeks of PegIFN/RBV, achieved high sustained antiviral responses
- Both dose groups were similar with regard to on-treatment or sustained virological response
- BI 201335 exhibited a good safety and tolerability profile with no SAEs or early treatment discontinuations in both dose groups
- Rash and photosensitivity, identified in ongoing phase 2 trials at BI 201335 doses of 240 mg QD or higher, were rare during this short-term course of treatment
- However, isolated unconjugated hyperbilirubinemia (likely due to BI 201335 mediated UGT1A1 inhibition), jaundice and vomiting were more common at the 240 mg BID dose level compared to the lower dose group
- Both dosages are currently being tested in the ongoing phase 2 trial, SILEN-C2, in patients with non-response to previous PegIFN/RBV

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