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Safety and antiviral activity of BI 201335, a new HCV NS3 protease inhibitor, in combination therapy with peginterferon alfa-2a (P) and ribavirin (R) for 28 days in P+R treatment-experienced patients with chronic hepatitis C genotype 1 infection

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ABSTRACT

Background: BI 201335 is a HCV NS3 protease inhibitor (EC_{50} of 3-6 nM). A multiple rising dose study evaluated the safety and antiviral activity in P+R treatment-experienced patients (pts) with chronic hepatitis C genotype-1 infection for 28 days as combination therapy with P+R.

Methods: 19 pts (France, Germany, Spain, USA) with a Metavir fibrosis score of 0-3, who experienced previous virologic failure with P+R combination therapy, were assigned to receive BI 201335 once-daily (qd) doses of 48 mg (n=6), 120 mg (n=7), or 240 mg (n=6) in combination with P (180 µg/wk)+R (weight based) for 28 days. All patients were monitored for safety and tolerability of study drugs. The primary endpoint was a ≥2 $\log_{10}$ reduction in HCV viral load (VL) from baseline at any time up to Day 28. Plasma HCV-RNA levels were measured using the Roche COBAS TaqMan assay (LLOQ 25 IU/mL).

Results: 19 pts were white, 11 were male, mean age was 48±9 years, mean body weight was 81±15 kg, and median (range) baseline VL was 6.9 (5.9-7.4) $\log_{10}$. There were no significant demographic differences between dose groups. BI 201335 was well tolerated and no serious or severe adverse events (AEs) were observed among pts in this study. AEs were typical for P+R. One subject discontinued treatment due to an AE (anxiety). A rapid, dose-related decline of VL was observed in all pts. All pts treated with BI 201335 + P+R achieved > 2 $\log_{10}$ VL decline with triple combination therapy. Median (range) maximal decline in VL during 28 day combination therapy for 48 mg, 120 mg, and 240 mg dose cohorts was 4.8 (3.4-5.9), 5.2 (3.9-6.0), and 5.3 (4.8-6.1) $\log_{10}$, respectively. Virologic rebound during treatment was observed during the first 28 days of BI 201335 + P+R dosing in 2/6 pts in the 48 mg and in 1/7 pts in the 120 mg dose groups. In these patients, population sequencing of the NS3/4A protease at baseline and at viral rebound during treatment revealed selection of variants in the NS3 protease domain shown to confer in vitro resistance to BI 201335. No rebound during treatment was seen in the 240 mg qd dose cohort: 5/6 pts had VL < 25 IU/mL at Day 28. The sixth pt had a 4.7 log decline in VL from baseline on Day 28 and VL was < 25 IU/ml at next visit, Day 42.

Conclusion: BI 201335 given once daily in combination therapy with P+R for 28 days was well tolerated, and induced a strong and rapid antiviral response. The results support further study of BI 201335 as a potent protease inhibitor for P+R treatment-experienced HCV patients.

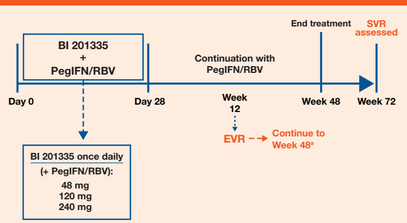
INTRODUCTION

- BI 201335 is a low molecular weight, peptidomimetic serine protease inhibitor (EC_{50} of 3–6 nM) that exhibits potent and specific inhibitory activity against the HCV serine protease (NS3/NS4) required for the maturation of HCV viral polyprotein
  - This mechanism of action suggests that BI 201335 in combination with other HCV therapies, has the potential to be an effective drug for the treatment of chronic HCV infection
- The safety and pharmacokinetics of BI 201335 have been characterized in an escalating single dose study (trial 1220.3) and in a multiple rising dose, 21- to 28-day trial (1220.6) in healthy volunteers
- In Trial 1220.3, treatment with BI 201335 was safe and tolerable in all single dose levels (4 mg to 1200 mg) studied
- In Trial 1220.6, 21 to 28 days of treatment with BI 201335 was safe and generally well tolerated across all dose levels studied (20, 48, 120, and 240 mg once daily). No relevant clinical AEs or laboratory abnormalities were reported for the 20 mg and 48 mg groups
  - At higher doses an increased incidence of headache, gastrointestinal symptoms and unconjugated hyperbilirubinemia was observed
  - The 120 mg dose was associated with slight increases of indirect bilirubin in 3/6 subjects
  - The 240 mg dose was also well tolerated, but all 6 subjects experienced reversible indirect hyperbilirubinemia up to 2.5 x ULN
- Subjects with Gilbert's polymorphism (GP) (UGT1A1*28) were also studied in Trial 1220.6. Of the 9 subjects with GP, all 5 subjects who were homozygous for Gilbert's polymorphisms experienced reversible indirect bilirubin elevations in the serum up to 4.8 x ULN compared to subjects (n=4) with heterozygous polymorphisms who experienced smaller elevations of indirect bilirubin
- These data suggest an association between the UGT1A1 polymorphisms and unconjugated hyperbilirubinemia with high doses of BI 201335
- Steady state pharmacokinetic parameters of BI 201335 from trial 1220.6 indicate that BI 201335 NA has a long half life ($t_{1/2}$, ss = 22.3h–30.9h) that supports once daily dosing

METHODS

- Trial 1220.2 is a phase 1b, multinational study that is evaluating the safety, efficacy, and PK data of multiple rising doses of BI 201335 in HCV genotype 1–infected treatment-naïve (double-blind, placebo-controlled within dose cohorts; Manns MP, et al, AASLD 2008, Abstract 1849) and treatment-experienced (open-label, in combination with pegylated interferon alpha-2a and ribavirin [PegIFN/RBV]) patients
- The current interim analyses review the safety and virologic response of BI 201335 in combination with PegIFN/RBV given for 28 days in treatment-experienced patients
- *Main criteria for eligibility* include: confirmed virologic failure (defined as <2 $\log_{10}$ reduction in VL from baseline) during or after combination treatment with an approved dose of alfa-2a or alfa-2b PegIFN combined with RBV; 18 years or older; HCV genotype 1 (1a, 1b, or mixed 1a/1b) confirmed by genotype analysis at screening; HCV Ab positive or detectable HCV RNA at least 6 months prior to screening; HCV viral load ≥100,000 IU/mL at screening; histologic evidence within 24 months prior to study enrollment of any degree of chronic necroinflammatory activity, or the presence of fibrosis (Ishak grade 1–4 or METAVIR grade 1–3)
- BI 201135 was administered once daily for 28 days in combination with PegIFN/RBV; three once-daily doses of BI 201335 were evaluated: 48 mg, 120 mg, and 240 mg. For each dosage group (n=6 or 7), patients also received combination therapy with standard doses of PegIFN (alfa-2a)/RBV beginning on Day 1 through Day 28 **(Figure 1)**

FIGURE 1. Study design



[a]Treatment with PegIFN/RBV was continued at the discretion of the investigator and patient; PegIFN=pegylated interferon alfa-2a; RBV=ribavirin; SOC=standard of care; SVR=sustained virologic response; EVR=early virologic response

- The effective target dose was selected based on PK models derived from preclinical data and from clinical PK data in trial 1220.6, a 4-week multiple rising dose study of BI 201335 in healthy volunteers, to meet a target median steady state trough plasma level (C_{min}) of ≥17 ng/mL. This target exposure was reached with a single dose of 20mg QD, so that the first dose administered to treatment-experienced patients was the next higher dose (ie, 48 mg QD)
  - A data monitoring committee reviewed safety, efficacy, and PK data to ensure that patients received a safe and virologically relevant dose
- Plasma HCV RNA levels were measured using the Roche COBAS TaqMan® (lower limit of quantitation: 25 IU/mL; lower limit of detection: 10 IU/mL)
- On Day 29, patients ended treatment with BI 201335 and, at the discretion of the investigator and patient, could continue to receive PegIFN [alfa-2a or 2b]/RBV) beyond Day 28
- The *primary efficacy endpoint* was virologic response (VR), defined as a ≥2 $\log_{10}$ reduction in VL from baseline at any time point measured up to Day 28
- Secondary efficacy endpoints include change from baseline in VL on Day 28; rapid virologic response (RVR), defined as undetectable VL (<10 IU/mL) on Day 28; end-of-treatment response (ETR), defined as undetectable (<10 IU/mL) HCV RNA at Week 48; and SVR
- *Primary safety endpoints* include AEs, serious AEs (SAEs), and changes in laboratory abnormalities and test values over time
- Secondary safety endpoints include the occurrence of AEs, by severity and by action taken with regard to test drug, and discontinuations due to AEs
- Patients were monitored frequently for VL, treatment-emergent AEs, and laboratory abnormalities
  - VL was measured on Days 1–4, 6, 10, 14, and 28
    - VL was also measured on Day 21 in those patients with >1 $\log_{10}$ reduction in VL by Day 14
    - For patients continuing with SOC, additional VL measurements were taken after Day 28 to monitor for early virologic response (EVR), end of PegIFN/RBV treatment response and sustained virologic response (SVR)

RESULTS

Baseline demographics

- Nineteen patients who previously experienced virologic failure with PegIFN/RBV therapy were assigned to receive 1 of 3 once-daily doses of BI 201335 in combination with PegIFN/RBV for 28 days. There were no significant differences in patient characteristics between study groups at baseline **(Table 1)**

TABLE 1. Baseline demographics and disease characteristics

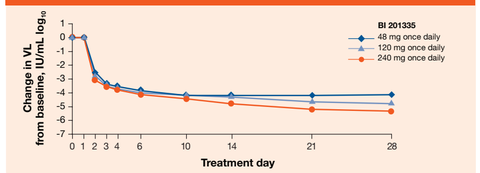
	48 mg BI 201335 + PegIFN/RBV (n=6)	120 mg BI 201335 + PegIFN/RBV (n=7)	240 mg BI 201335 + PegIFN/RBV (n=6)	All patients N=19
Patients, n (%)				
Males	4 (66.7)	4 (57.1)	3 (50.0)	11 (57.9)
Females	2 (33.3)	3 (42.9)	3 (50.0)	8 (42.1)
Ethnicity, n (%)				
White	6 (100)	7 (100)	6 (100)	19 (100)
Age, mean (SD), y	47 (11.8)	47 (4.8)	49 (10.1)	48 (8.8)
HCV VL, median (range), $\log_{10}$ IU/mL	7.1 (5.9–7.3)	7.0 (6.2–7.4)	6.8 (6.3–7.1)	6.9 (5.9–7.4)

PegIFN/RBV=pegylated interferon alfa-2a plus ribavirin; HCV VL=hepatitis C virus viral load

Efficacy

- 100% of patients from all dose groups achieved the primary efficacy endpoint (measured at any point up to Day 28), defined as >2 $\log_{10}$ reduction in VL from baseline, during triple-combination therapy **(Figure 2)**

FIGURE 2. Mean change in VL from baseline to Day 28



VL=viral load

- **Figure 3** shows the VL response from baseline through Day 28 for each patient in the BI 201335 240 mg dose study group
- A rapid, dose-dependent decline in VL was observed in all patients beginning therapy with BI 201335 in combination with PegIFN/RBV **(Table 2)**
- Virologic breakthrough (defined as greater than 0.8 $\log_{10}$ increase in VL from baseline) during treatment was observed over the course of 28 days of therapy in 2/6 patients in the 48 mg dose group and in 1/7 patients in the 120 mg dose group
  - In the 120 mg dose group, 4/7 patients were previously treated null responders (< 0.5 log) and 3/4 of the null responder patients achieved VL less than the lower limit of quantification by Day 28
  - Amplification of the NS3/NS4A protease segment followed by population-based sequencing of baseline and viral rebound samples demonstrated genotypic changes at specific residues within the NS3 protease domain consistent with resistant mutants that were previously characterized in *in vitro* resistance studies
  - Preliminary phenotypic characterization of the mutant NS3 protease domains in the context of the subgenomic replicon demonstrated shifts in the sensitivity to inhibition by BI 201335 consistent with previously characterized point mutants
- No breakthroughs in VL were seen during the first 28 days in the 240 mg dose group
  - At Day 28, VL in 5/6 patients was below the lower limit of quantification (<25 IU/mL); the sixth patient had a 4.7 log decline in VL from baseline on Day 28 and was below the lower level of quantification by the following study visit, Day 42

FIGURE 3. Virologic response from baseline to Day 28 in BI 201335 240 mg dose study group

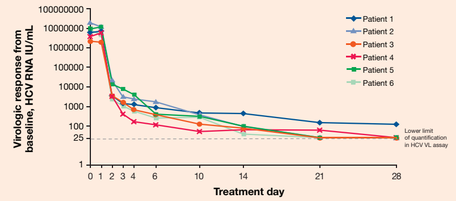


TABLE 2. Maximal virologic response during 28 days of treatment with BI 201335 in combination with PegIFN/RBV, median (min, max), $\log_{10}$ IU/mL

48 mg BI 201335 (n=6)	120 mg BI 201335 (n=7)	240 mg BI 201335 (n=6)
–5.0 (–5.9, –3.4)	–5.2 (–6.0, –3.9)	–5.3 (–6.1, –4.7)

Safety and tolerability

- Reported AEs were judged by the investigators to be unrelated to study drug and were typical of treatment with PegIFN/RBV, including fatigue, nausea, rash, headache, gastrointestinal tract disorders, and anemia
  - During the 28 days of therapy with BI 201335 and PegIFN/RBV, diarrhea was reported in 3 patients in the 48 mg group, 1 patient in the 120 mg group and 2 patients in the 240 mg group. There was no indication of any BI 201335 dose-related gastrointestinal effect
  - During the 28 days of therapy with BI 201335 and PegIFN/RBV, no rash was reported in any study patient. Skin reactions most frequently reported during the first 28 days of study treatment were typical (including local injection site reactions) of those seen with PegIFN/RBV treatment, i.e., dry skin and pruritus. After 30 days following the completion of BI 201335 study treatment, new skin adverse events continued to be reported on PegIFN/RBV follow-on treatment
- No dose-dependent increases in AEs were observed **(Table 3)**
- No SAEs were reported
- One patient (120 mg dose group) discontinued therapy because of anxiety

TABLE 3. Proportion of patients with AEs from baseline through Day 28

Primary system organ class, n (%)	48 mg BI 201335 + PegIFN/RBV (n=6)	120 mg BI 201335 + PegIFN/RBV (n=7)	240 mg BI 201335 + PegIFN/RBV (n=6)	All patients (N=19)
General disorders and administration-site conditions[a]	6 (100.0)	6 (85.7)	4 (66.7)	16 (84.2)
Gastrointestinal tract disorders	4 (66.7)	4 (57.1)	4 (66.7)	12 (63.2)
Nervous system disorders[b]	3 (50.0)	5 (71.4)	4 (66.7)	12 (63.2)
Skin and subcutaneous tissue disorders	5 (83.3)	2 (28.6)	4 (66.7)	11 (57.9)
Musculoskeletal and connective tissue disorders	3 (50.0)	4 (57.1)	1 (16.7)	8 (42.1)
Psychiatric disorders[c]	4 (66.7)	4 (57.1)	1 (16.7)	9 (47.4)
Eye disorders	2 (33.3)	2 (28.6)	1 (16.7)	5 (26.3)
Investigations[d]	0 (0.0)	2 (28.6)	0 (0.0)	2 (10.5)

[a]Fatigue, influenzalike illness, pyrexia and injection site erythema; [b]primarily headache; [c]anxiety, aggression; [d]increase in body temperature (n=2) and weight (n=2)

- Changes in bilirubin were observed with increasing doses of BI 201335 **(Table 4)**
  - At higher doses, an increased incidence of unconjugated hyperbilirubinemia was observed
- No other dose-dependent increase in clinical laboratory parameters was observed

TABLE 4. Median change (min, max) from baseline to Day 28 for selected laboratory parameters

Test parameter (normal range)	48 mg BI 201335 + PegIFN/RBV (n=6)	120 mg BI 201335 + PegIFN/RBV (n=7)	240 mg BI 201335 + PegIFN/RBV (n=6)
Liver function test			
ALT (6.0–36.0 U/L)	–30 (–90, –12)	–48 (–150, –8)	–26 (–152, –13)
AST (9.0–36.0 U/L)	–8 (–29, –2)	–41 (–56, –11)	–13 (–52, –3)
AP (31.0–131.0 U/L)	2 (–18, 15)	–3 (–27, 21)	10 (–6, 28)
Bilirubin, total (0.1–1.6 mg/dL)	0.3 (0.2, 1.6)	0.3 (–0.3, 1.3)	1.0 (0.8, 3.7)
Bilirubin, indirect (0–1.2 mg/dL)	0.2 (0.1, 1.4)	0.2 (0.1, 0.9)	0.7 (0.6, 3.6)
GGT (4.0–60.0 U/L)	–9 (–39, –5)	–24 (–139, 4)	–24 (–92, 6)
Other blood tests			
Hemoglobin (12.7–18.1 g/dL)	–2.4 (–4.9, –0.9)	–2.4 (–4.5, 0.3)	–1.9 (–4.1, –0.5)
Platelets (140–400 x 10^3/uL)	–45 (–73, 36)	–59 (–178, –21)	–19 (–98, 60)
White blood cells (3.8–10.7 x 10^3/uL)	–2.9 (–3.8, –0.7)	–4.1 (–6.7, 1.4)	–3.4 (–6.6, –1.6)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ALP=alkaline phosphatase; GGT=gamma-glutamyl transpeptidase

DISCUSSION AND CONCLUSIONS

- **BI 201335 induced a rapid and steep dose-related virologic response within 2 to 4 days of initiation of combination therapy**
  - **This virologic response was maintained in the majority of patients through Day 28 in the 48 mg and 120 mg dose groups**
  - **Virologic response was maintained in all patients through Day 28 in the 240 mg dose group**
- **BI 201335 given once daily in combination with PegIFN/RBV for 28 days was well tolerated at all dosage levels among treatment-experienced patients**
- **Observed AEs were generally mild to moderate in severity, not considered to be related to study drug but rather typical of PegIFN/RBV**
  - **AEs observed are commonly associated with PegIFN/RBV treatment**
- **No serious AEs were observed among patients in any dosage group studied**
- **The results of this analysis support further study of BI 201335 once daily as part of combination therapy for treatment-experienced patients with chronic HCV infection**

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