LB-7

Strong antiviral activity and safety of IFN-sparing treatment with the protease inhibitor BI 201335, the HCV polymerase inhibitor BI 207127, and ribavirin, in patients with chronic hepatitis C: the SOUND-C1 trial

SOUND-C1

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ABSTRACT

Background: BI 201335 and BI 207127 are potent and specific inhibitors of the hepatitis C virus (HCV) NS3/4A protease and the NS5B RNA-dependent RNA polymerase, respectively. An IFN-free combination of both antivirals with ribavirin (RBV) to eradicate HCV infection would create a major paradigm shift in HCV treatment.

Methods: In this randomized open-label trial, 32 treatment-naïve HCV genotype-1 (GT-1) patients were treated over 4 weeks with 400 or 600 mg three times a day (TID) BI 207127, BI 201335 120 mg once daily (QD) and RBV (1,000/1,200 mg daily in two doses). Plasma HCV RNA virus load (VL) was measured by Roche COBAS TaqMan assay with a lower limit of quantification of 25 IU/mL.

Results: At baseline, mean age was 51 ± 11 years, mean body mass index 23.8 ± 3.4 kg/m², mean VL 6.48 $\log_{10}$. All patients had a rapid and sharp VL decline during the first 2 days, followed by a slower second phase decline in all except 2 patients. One patient experienced VL breakthrough (increase by >1 $\log_{10}$ from nadir during treatment) and 1 other experienced a 0.7 $\log_{10}$ VL increase. Both were in the lower dose group and were GT-1a patients with high baseline VL. On Day 29, all patients were switched per protocol to treatment with BI 201335 and PegIFN/RBV. Virological response rates (VL <25 IU/mL) after 1, 2, 3 and 4 weeks of oral treatment are shown in the table.

TABLE. Proportion of patients with VL <25 IU/mL[a]

	Day 8	Day 15	Day 22	Day 29
400 mg TID BI 207127 + BI 201335 + RBV	4/15	6/15	10/15	11/15
600 mg TID BI 207127 + BI 201335 + RBV	3/17	14/17	17/17	17/17

At the higher dose level, there was no difference between GT-1a and 1b, while GT-1a patients at 400 mg TID had a lower response rate than those with GT-1b. The PegIFN sparing treatment was well tolerated. The most common adverse events (AEs) were mostly mild gastrointestinal effects (diarrhea, nausea, vomiting), rashes or photosensitivity. There were no severe AEs, serious AEs or treatment discontinuations within the 4-week study period. Laboratory parameters did not indicate any relevant changes from baseline, except for a continuous drop in alanine aminotransferase in all patients, a decrease of hemoglobin (median –1.7 and –2.6 g/dL)[a] and increase of unconjugated bilirubin (median +9.8 and +11.5 µmol/L).[a]

Conclusions: PegIFN sparing treatment with the NS3/4A inhibitor BI 201335, NS5B inhibitor BI 207127, and RBV, demonstrated strong early antiviral activity against HCV GT-1 with good safety and tolerability. A phase 2b trial testing different dose regimens of this combination, with longer durations, is planned to evaluate sustained virologic response rates.

[a]Corrected for final data as presented in **Tables 2** and **4.**

INTRODUCTION

- Current standard therapy for hepatitis C virus (HCV) genotype (GT) 1 with peginterferon alfa and ribavirin (PegIFN/RBV) for 48 weeks, has limited efficacy and reduced tolerability, with severe adverse events (AEs) causing treatment discontinuations and contraindications
- New HCV treatments, ie direct-acting antivirals (DAAs), targeting the HCV encoded NS3/4A protease or the NS5B polymerase, with PegIFN/RBV increase sustained virological response (SVR) rates and prevent the rapid selection of resistance mutations seen when DAAs are administered as monotherapy. Thus, problems with interferon tolerability, administration convenience and contraindications remain
- BI 201335 is a potent and specific HCV NS3/4A protease inhibitor with once-daily (QD) dosing.[1] Phase 1b and 2 clinical investigations show that BI 201335 combined with PegIFN/RBV is well tolerated and induces strong antiviral responses in HCV GT-1-infected patients[2,3]
- BI 207127 is a specific and reversible non-nucleoside thumb-pocket 1 HCV NS5B polymerase inhibitor with potent and specific antiviral activity *in vitro*. In clinical phase 1b trials, BI 207127 in combination with PegIFN/RBV demonstrated robust antiviral activity in treatment-naïve (TN) patients[4]
- Drug-resistance studies in cell culture demonstrate that BI 201335 and BI 207127 have different resistance profiles and, in pair-wise combination studies, profoundly reduce the emergence of drug-resistant variants
- This multicenter, open label, phase 1b trial 1241.21 (SOUND-C1) investigates safety, antiviral effect and pharmacokinetics of BI 207127 in combination with BI 201335 and RBV for 4 weeks in TN patients with chronic HCV GT-1 infection

METHODS

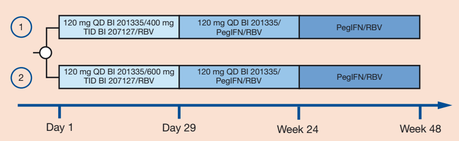
Patients

- Eligible patients were 18 to 75 years of age with chronic HCV GT-1 infection and were therapy-naïve to interferon, PegIFN and RBV, and any DAA for acute or chronic hepatitis C infection, had a HCV viral load (VL) of ≥100,000 IU/mL at screening, and had a liver biopsy within 2 years or fibroscan within 6 months prior to screening that excluded cirrhosis
- Patients with HCV of mixed GT, hepatitis B virus, human immunodeficiency virus, decompensated liver disease, or hyperbilirubinemia (>1.5 x upper limit of normal [ULN]) were excluded (patients with Gilbert's polymorphism were accepted)

Study design

- Multicenter, open-label, randomized phase 1b trial **(Figure 1)**
- Thirty-two TN patients with GT-1 chronic HCV were randomized 1:1 to either 400 mg or 600 mg BI 207127 three times a day (TID), plus 120 mg BI 201335 QD and RBV (weight-based, 1,000 or 1,200 mg/day BID as a divided dose) for 4 weeks
- Randomization was stratified by baseline plasma HCV RNA (<800,000 and ≥800,000 IU/mL) and subgrouped by HCV subtype to enter at least 12 patients with GT-1a and GT-1b, respectively
- A loading dose of 240 mg BI 201335 was given on the first day of administration, followed by 120 mg QD starting on Day 2
- A loading dose of 1,200 mg BI 207127 was given on the first day of administration, followed by two additional doses of 400 or 600 mg on the first day
- The primary efficacy endpoint of this study was rapid virological response (RVR), defined as HCV RNA below the lower limit of quantification (LLOQ) (<25 IU/mL) at Week 4
- Patients with a RVR at Day 29 (ie HCV RNA <25 IU/mL) were switched from their assigned treatment to 120 mg QD BI 201335, PegIFN and RBV until Week 24 or 48, dependent on the achievement of extended rapid virological response (eRVR; defined as HCV RNA ≥25 IU/mL at Week 4 and undetectable from Weeks 8–20)
- Patients with virologic breakthrough before Day 29, defined as HCV RNA rebound ≥1 $\log_{10}$ in plasma HCV RNA from a quantifiable nadir during BI 207127/BI 201335/RBV treatment and confirmed by a second, consecutive plasma HCV RNA measurement, were immediately switched to treatment with PegIFN/RBV alone for 48 weeks

FIGURE 1. Trial schema



- HCV RNA was detected and quantified using the Roche COBAS TaqMan HCV/HPS assay with an LLOQ of 25 IU/mL, as indicated by the manufacturer, whereby results below the quantification limit were reported as either 'detectable' or 'undetectable'
- HCV GT for screening and randomization was determined using the Trugene HCV assay; for the analysis, definitive HCV GTs were based on complete NS5B sequencing and phylogenetic analyses

Genotypic resistance monitoring

- Viral NS3/4A and NS5B genotyping was performed after isolation of viral RNA from plasma using the QiaAmp Viral RNA extraction kit; cDNA was synthesized using Superscript III one-step reverse transcription polymerase chain reaction system platinum Taq DNA polymerase and GT specific primers (limit of detection VL >10^3 IU/mL). The NS3/4A protease and NS5B polymerase nucleotide sequences were obtained by direct DNA sequencing of the respective amplified products using Big Dye Terminator V3.1 and the ABI 3730 Genetic Analyzer (Applied Biosystems) detection system
- Here we report the results of a protocol-specified interim analysis of the 4-week data. Results are compared historically to a recent planned interim analysis of 4 weeks' treatment with 120 mg QD BI 201335 plus PegIFN/RBV

RESULTS

Patient disposition and baseline characteristics

- A total of 32 TN HCV GT-1 patients were randomized. Patients were evenly distributed over both dose groups with regard to baseline VL, race, age, gender, body mass index (BMI) and GT **(Table 1)**

TABLE 1. Summary of baseline characteristics

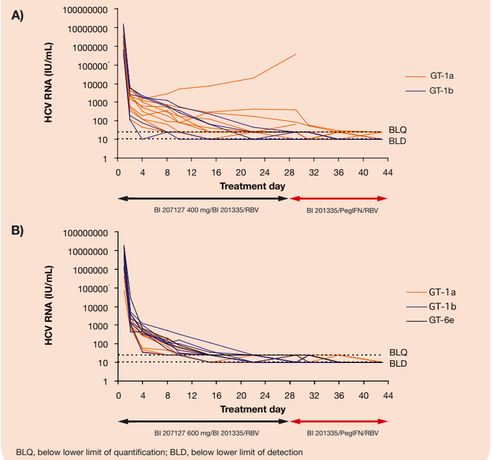
	BI 207127 400 mg + BI 201335 120 mg + RBV (n=15)	BI 207127 600 mg + BI 201335 120 mg + RBV (n=17)
Gender, n (%)		
Male	8 (53.3)	10 (58.8)
Female	7 (46.7)	7 (41.2)
Race, n (%)		
Asian	0 (0)	1 (5.9)
White	15 (100.0)	16 (94.1)
HCV RNA, $\log_{10}$ IU/mL		
Mean	6.45	6.51
Standard deviation	0.51	0.66
GT, n (%)		
1	0 (0)	1[a] (5.9)
1a	10 (66.7)	8 (47.1)
1b	5 (33.3)	8 (47.1)
Age, years		
Mean	51	51
Standard deviation	10.0	11.5
BMI, kg/m²		
Mean	23	24
Standard deviation	2.9	3.8

[a]Retrospective GT analysis based on NS5B sequence identified one GT-1 sample as GT-6e

Antiviral activity

- During the first 2 days of treatment, all patients showed a rapid and steep VL decline, which was followed by a slower second phase decline until Day 29 in all patients in the 600 mg dose group and all but 2 patients in the 400 mg dose group of BI 207127 **(Figure 2)**
- One virologic breakthrough (defined as ≥1 log re-increase from VL nadir) during treatment was observed on Day 10. This patient was switched per protocol to PegIFN/RBV and showed a good virological response 4 weeks later. One other patient showed a VL re-increase from nadir by 0.7 $\log_{10}$ and plateaued at this level. He was switched to BI 201335/PegIFN/RBV treatment at Day 29 and had a VL drop to <100 IU/mL 1 week later. Both were GT-1a patients treated with the lower dose of BI 207127
- Virological response rates (ie HCV RNA <25 IU/mL) at 400 mg TID were 47, 67 and 73% at Day 15, 22 and 29 with higher rates for patients infected with GT-1b than those infected with GT-1a. At 600 mg TID, the corresponding rates were 82, 100 and 100%, without subtype differences. As shown in **Table 2**, most patients in the 600 mg dose group had undetectable VL at Days 21 and 28 (53 and 71%, respectively), while these rates were lower in the 400 mg dose group
- Viral nucleic acid sequencing at baseline, as well as virus isolated from the 1 patient with VL rebound, identified a R155K amino acid change in NS3 and a P495L change in NS5B that represented the selection of double mutant conferring resistance to BI 201335 and BI 207127 in the rebounding patient

FIGURE 2. Course of HCV RNA from baseline to Day 43 for individual patients in A) the BI 207127 400 mg dose group (n=15), and B) the BI 207127 600 mg dose group (n=17)



BLQ, below lower limit of quantification; BLD, below lower limit of detection

TABLE 2. Frequency of patients with HCV RNA below the level of detection (BLD; HCV RNA <10 IU/mL) and below the level of quantification (BLQ, HCV RNA <25 IU/mL) during treatment

	Day 8		Day 15		Day 22		Day 29	
	BLQ	BLD	BLQ	BLD	BLQ	BLD	BLQ	BLD
400 mg TID BI 207127+ BI 201335/RBV (n=15)	4 27% 1a: 2/10 1b: 2/5	0 0% 0/10 0/5	7 47% 1a: 5/10 1b: 2/5	3 20% 1/10 2/5	10 67% 1a: 6/10 1b: 4/5	3 20% 0/10 3/5	11 73% 1a: 6/10 1b: 5/5	3 20% 1/10 2/5
600 mg TID BI 207127+ BI 201335/RBV (n=17)	3 18% 1a: 2/8 1b:1/8 6e: 0/1	0 0% 0/8 0/8 0/1	14 82% 1a: 8/8 1b: 5/8 6e: 1/1	4 25% 3/8 1/8 0/1	17 100% 1a: 8/8 1b: 8/8 6e: 1/1	9 53% 4/8 5/8 0/1	17 100% 1a: 8/8 1b: 8/8 6e: 1/1	12 71% 5/8 7/8 0/1

Safety

- Treatment was generally safe and well tolerated in both dose groups
- There were no severe AEs, no serious AEs and no early discontinuations of BI 207127, BI 201335 or RBV due to AEs
- The most frequent AEs were mild (rarely moderate) gastrointestinal (GI) disorders (nausea, vomiting, and diarrhea) or mild skin reactions (rash and/or photosensitivity) **(Table 3)**

TABLE 3. Most frequent (>20%) AEs

n (%)	BI 207127 400 mg + BI 201335 120 mg + RBV (n=15)	BI 207127 600 mg + BI 201335 120 mg + RBV (n=17)
Headache	5 (33)	2 (12)
Paraesthesia	0 (0)	4 (24)
Nausea	4 (27)	11 (65)
Vomiting	4 (27)	8 (47)
Diarrhoea	4 (27)	3 (18)
Jaundice	4 (27)	3 (18)
Pruritus	3 (20)	6 (35)
Dry skin	4 (27)	1 (6)
Photosensitivity reaction	4 (27)	3 (18)
Rash	3 (20)	7 (41)
Influenza-like illness	4 (27)	10 (59)
Asthenia	6 (40)	5 (29)
Fatigue	3 (20)	4 (24)

- Tolerability compared to standard PegIFN/RBV treatment was uniformly rated as superior by the investigators
- Safety laboratory analyses during treatment showed uniform decreases of alanine aminotransferase (ALT) accompanying the initial VL drops in all patients **(Table 4)**
- White blood cell counts and platelets did not drop in either dose group, as expected from a PegIFN-sparing treatment
- The drop in hemoglobin levels (due to RBV-induced hemolysis) was less than in the historical control of BI 201335 with PegIFN/RBV
- A mild increase in bilirubin was found in 31 patients (6 patients with total bilirubin >3 x ULN), that was exclusively due to isolated unconjugated hyperbilirubinemia. However, only 2 of these 6 patients reported signs of jaundice. There was no association of indirect bilirubin with ALT increases or increased hemolysis. Thus, this event was in accordance with the well-characterized, non-toxic inhibitory effect of BI 201335 on UGT1A1

TABLE 4. Laboratory changes from baseline at Day 29 [median (min, max)] compared to a planned 4-week interim analysis of the phase 2 trial 1220.40 (SILEN-C3), studying BI 201335 plus PegIFN/RBV

Test parameter (normal range)	SOUND-C1 120 mg QD BI 201335 + 400 mg TID BI 207127+ RBV (n=15)	SOUND-C1 120 mg QD BI 201335 + 600 mg TID BI 207127 + RBV (n=17)	For comparison: SILEN-C3 120 mg QD BI 201335 + PegIFN + RBV (n=79)
ALT (0.0–35.0 U/L)	–42 (–236, –6)	–27 (–147, –5)	–29 (–223, 140)
Bilirubin, total (5.1–17 µmol/L)	11.2 (+2.6, +65.5)	17.9 (2.0, 99.2)	8.6 (–2.6, 72.7)
Bilirubin, indirect (3.4–12 µmol/L)	5.3 (1.2, 38.5)	7.8 (1.2, 59.8)	4.1 (–1.0, 44.0)
Hemoglobin (12.0–17.2 g/dL)	–1.7 (–3.5, –0.7)	–2.6 (–4.7, –0.5)	–2.1 (–6.1, 0.8)
Platelets (150–350 x 10^9/L)	67 (2, 103)	89 (21, +144)	–41 (–149, 93)
White blood cells (4.5–11.0 x 10^9/L)	0.3 (–1.6, 2.1)	0.6 (–1.4, 2.4)	–2.8 (–7.2, 6.3)

DISCUSSION

- PegIFN-sparing treatment with the NS3/4A inhibitor BI 201335, the NS5B inhibitor BI 207127, and RBV, demonstrated rapid, strong early antiviral activity against HCV GT-1 with overall good general safety and tolerability
- No virologic breakthrough occurred at the 600 mg dose level and only one virologic breakthrough occurred at the lower dose level, demonstrating that the rapid and uniform selection of resistance mutations associated with protease inhibitor monotherapy is effectively reduced or delayed in this PegIFN-free combination regimen
- The rapid virological response rate in patients of the 600 mg dose group was comparable to that of PegIFN/RBV-based triple combinations with new DAAs (eg BI 201335)
- The safety profile was good with predominance of the expected AEs of mild rashes and GI symptoms, which did not impact treatment continuation
- A phase 2b study is in preparation to evaluate SVR with longer-term PegIFN-sparing treatment

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