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

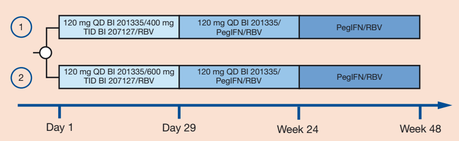
Patients

- 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

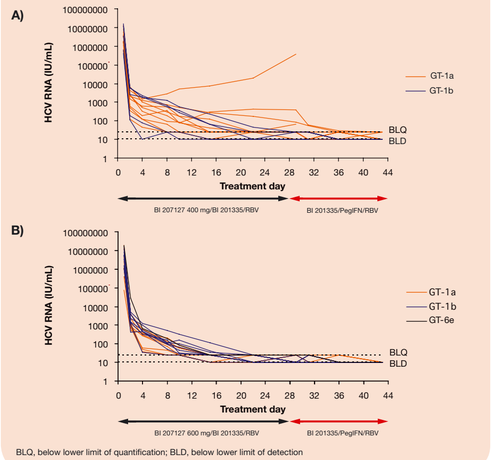
	BI 207127 400 mg + BI 201335 120 mg + RBV (n=15)	BI 207127 600 mg + BI 201335 120 mg + RBV (n=17)
Gender, n (%)		
Male	8 (53.3)	10 (58.8)
Female	7 (46.7)	7 (41.2)
Race, n (%)		
Asian	0 (0)	1 (5.9)
White	15 (100.0)	16 (94.1)
HCV RNA, $\log_{10}$ IU/mL		
Mean	6.45	6.51
Standard deviation	0.51	0.66
GT, 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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LB-8

Combination Therapy With BMS-790052 and BMS-650032 Alone or With Pegylated Interferon and Ribavirin (pegIFN/RBV) Results in Undetectable HCV RNA Through 12 Weeks of Therapy in HCV Genotype 1 Null Responders

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ABSTRACT

Background: BMS-790052 is a potent NS5A inhibitor with broad genotypic coverage while BMS-650032 is a potent hepatitis C virus (HCV) NS3 protease inhibitor with coverage of HCV genotypes (GT) 1a and 1b. Clinical studies combining these compounds alone and with pegylated interferon/ribavirin (pegIFN/RBV) are under way in HCV-infected null responders to determine their safety and efficacy.

Methods: AI447011 is a randomized, open-label, phase 2a study comparing the antiviral activity and safety of BMS-790052 (60 mg QD) and BMS-650032 (600 mg BID) alone (group A) or with pegIFN/RBV (group B) for 24 weeks in HCV GT 1 null responders. The primary aim was to determine the proportion of subjects achieving undetectable HCV RNA levels (<10 IU/mL) at weeks 2 and 4 of therapy and 24 weeks posttreatment. A week 12 interim analysis was performed.

Results: Twenty-one patients (11 group A, 10 group B) were randomized in a sentinel cohort. Median age was 55 years, 13 patients were male, and 16 were white. Virologic responses are presented below:

	Group A BMS-650032 and BMS-790052 (n=11)	Group B BMS-650032, BMS-790052, PegIFN/RBV (n=10)
Genotype 1a n	9	9
Median baseline HCV RNA (IU/mL)	6.9 $\log_{10}$	6.7 $\log_{10}$
Median HCV RNA decline at week 2 (IU/mL)	-5.1 $\log_{10}$	-5.3 $\log_{10}$
RVR[a] n (%)	7 (63.6%)	6 (60%)
eRVR[a] n (%)	4 (36.4%)	6 (60%)
cEVR[a] n (%)	5 (45.5%)	9 (90%)[b]

[a]Intent-to-treat analysis, breakthrough = failure.
[b]One subject with HCV RNA <25 IU/mL at week 12 was undetectable (UD, <10 IU/mL) on retesting.
Rapid virologic response (RVR) = UD by week 4.
Extended rapid virologic response (eRVR) = UD at weeks 4 and 12.
Complete early virologic response (cEVR) = UD by week 12.

Six (54.5%) group A subjects experienced viral breakthrough, while all subjects in group B maintained viral suppression. Viral breakthrough occurred exclusively in individuals infected with GT 1a, occurring as early as week 3 and as late as week 12. The 2 GT 1b subjects in group A remained HCV RNA undetectable. The 6 subjects with viral breakthrough had pegIFN/RBV added to their regimen. HCV RNA levels fell to UD in 2 subjects and to <25 IU/mL in another 2 subjects, while the other 2 subjects had ≥1.5 $\log_{10}$ decreases in HCV RNA levels. No deaths, serious adverse events, or discontinuations due to adverse events were recorded during the analysis period. Diarrhea was the most common adverse event and was mainly mild to moderate in severity.

Conclusions: Treatment with BMS-790052 and BMS-650032 with or without pegIFN/RBV demonstrated similar RVR rates in HCV-infected GT 1 null responders. Six of 11 subjects receiving 2 direct-acting antiviral agents alone experienced viral breakthrough by week 12 while a 4-drug combination maintained viral suppression in all subjects. Should this activity predict SVR, these results will have significant implications for future combination HCV antiviral therapy.

BACKGROUND

- BMS-790052 is a first-in-class, potent, and highly selective inhibitor of hepatitis C virus (HCV) NS5A with in vitro picomolar potency
- BMS-650032 is a highly active HCV NS3 protease inhibitor
- Both BMS-790052 and BMS-650032 have been shown to be generally well-tolerated and to produce robust declines in HCV RNA levels following multiple dosing in subjects chronically infected with HCV genotype 1
- The coadministration of BMS-790052 and BMS-650032 did not result in a clinically meaningful pharmacokinetic interaction in healthy volunteers (AASLD poster 827)
- HCV patients who are null responders to pegylated interferon and ribavirin (pegIFN/RBV) may benefit from combination therapy including 2 direct-acting antiviral agents with or without pegIFN/RBV

OBJECTIVES

- Primary Objective
  - To determine the proportion of subjects with undetectable HCV RNA or a decrease in plasma HCV RNA ≥2 $\log_{10}$ IU/mL at week 2 and the proportion of subjects with undetectable HCV RNA at week 4 (rapid virologic response, RVR)
- Secondary Objectives
  - To assess the safety of coadministration of BMS-790052 and BMS-650032 with and without pegIFN/RBV
  - To assess the pharmacokinetic profiles of subjects treated with BMS-790052 and BMS-650032 with and without pegIFN/RBV
  - To assess the decrease in HCV RNA levels from baseline to days 4, 7, and 14
  - To evaluate the proportion of subjects with RVR
  - To evaluate the proportion of subjects with extended RVR (eRVR), defined as undetectable HCV RNA at both weeks 4 and 12
  - To describe drug-resistant variants associated with virologic failure

METHODS AND METHODS

Study Design

Group A — BMS-790052 + BMS-650032 (n=11)

Group B — BMS-790052 + BMS-650032 + pegIFN/RBV (n=10)

24-week duration of therapy

Follow-up: up to 48 weeks posttreatment

- BMS-790052 (NS5A inhibitor) 60 mg PO QD
- BMS-650032 (NS3 protease inhibitor) 600 mg PO BID
- PegIFNα-2a 180 µg SC once weekly
- RBV 1000-1200 mg daily in 2 divided doses, according to body weight

PO = orally; SC = subcutaneously.

MATERIALS AND METHODS (cont'd)

Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Chronic HCV infection, genotype 1
- Null responders (<2 $\log_{10}$ decline in HCV RNA following 12 weeks of treatment with pegIFN/RBV)
- HCV RNA levels ≥10^5 IU/mL
- FibroTest score of ≤0.72 and APRI ≤2 *or* documented liver biopsy within 12 months showing absence of cirrhosis

Exclusion Criteria

- HCV-infected subjects who are treatment intolerant
- Pregnant or breastfeeding women
- Any of the following laboratory results at screening or prior to dosing:
  - Hemoglobin ≤12 g/dL for women and ≤3 g/dL for men
  - ANC ≤1500/µL
  - Platelet count ≤90,000/µL
  - ALT >5x ULN
  - Direct bilirubin >1.5x ULN
  - Albumin <3.2 g/dL
  - Creatinine clearance <50 mL/min

APRI = Aspartate aminotransferase-to-Platelet Ratio Index; ANC = absolute neutrophil count; ALT = alanine aminotransferase; ULN = upper limit of normal.

Baseline Demographics

	Group A n=11 (%)	Group B n=10 (%)
Median age (y)	54	56.5
Male/Female	9/2	4/6
Race or ethnicity n (%)		
White	9 (82)	7 (70)
African American	2 (18)	3 (30)
Hispanic	4 (46)	2 (20)
Median baseline HCV RNA ($\log_{10}$ IU/mL)	6.9	6.7
HCV Genotype n (%)		
1A	9 (82)	9 (90)
1B	2 (18)	1 (10)
Mean baseline ALT (U/L)	70.5	57.9

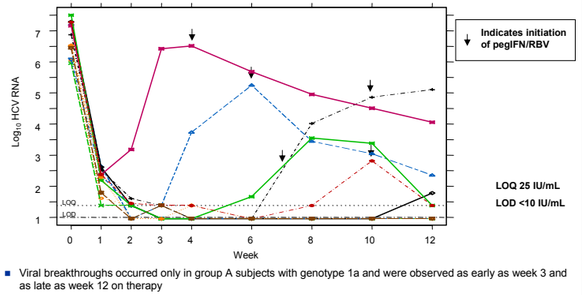
RESULTS

Virologic Response

	Group A n=11 (%)	Group B n=10 (%)
Median HCV RNA decline at week 2 ($\log_{10}$ IU/mL)	-5.1	-5.3
RVR[a] n (%)	7 (64)	6 (60)
eRVR[a] n (%)	4 (36)	6 (60)
cEVR[a,b] n (%)	5 (46)	9 (90)[c]
Viral breakthrough[d]	6/11 (55)	0

[a] Intent-to-treat analysis, breakthrough = failure.
[b] Complete early virologic response (cEVR): undetectable HCV RNA by week 12.
[c] One subject in group B (1/10) did not meet cEVR (week 12 HCV RNA <25 IU/mL); however, on retesting his HCV RNA was undetectable (<10 IU/mL).
[d] Viral breakthrough: a) any increase in HCV RNA ≥1 $\log_{10}$ from nadir, or b) any detectable HCV RNA >25 IU/mL on or after week 4, or c) any detectable HCV RNA <25 IU/mL on or after week 4 confirmed by retesting.

HCV RNA Decline by Subject: Group A

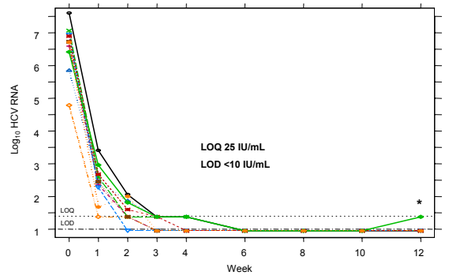


- Viral breakthroughs occurred only in group A subjects with genotype 1a and were observed as early as week 3 and as late as week 12 on therapy
- Viral breakthrough occurred with higher baseline HCV RNA levels
- Subjects with viral breakthrough had pegIFN/RBV added to their treatment
- Preliminary genotypic resistance analysis of subjects demonstrating viral breakthrough indicates detection of drug-resistant variants in both the NS3 protease and NS5A sequences

LOQ = lower limit of quantitation; LOD = limit of detection.

RESULTS (cont'd)

HCV RNA Decline by Subject: Group B



- No viral breakthrough occurred in group B
- 100% of subjects were undetectable by week 6 on therapy
- Virologic control was maintained through week 12 in all subjects
- One subject with HCV RNA <25 IU/mL at week 12 (shown above [*]) was undetectable with immediate retesting

Viral Breakthrough: Rescue With PegIFN/RBV

Subject	Peak HCV RNA Prior to Rescue With PegIFN/RBV	Outcome as of Week 12 Analysis
1	651	UD
2	1356	<25 IU/mL
3	66504	UD
4	73129	321 IU/mL
5	162594	<25 IU/mL
6	3243114	8017 IU/mL

UD = undetectable HCV RNA (<10 IU/mL).

- HCV RNA decreased in all 6 patients after the addition of pegIFN/RBV to the 2 direct-acting antiviral agents; 4 patients had HCV RNA <25 IU/mL as of the week 12 analysis

Steady State Pharmacokinetics

	BMS-650032		BMS-790052	
	Day 14			
PK Parameter	**Group A n=11 (%)**	**Group B n=10 (%)**	**Group A n=11 (%)**	**Group B n=10 (%)**
C_{max} (ng/mL) GM (% CV)	1820 (83.4)	1640 (103)	1020 (31.9)	1430 (28.4)
T_{max} (h) Median (min, max)	2 (2, 4)	2 (1, 4)	2 (1, 24)	1 (1, 4)
AUC_{TAU} (ng/mL*h) - GM (% CV)	6590 (75.8)	6150 (102)	10700 (30.7)	12500 (17.7)
C_{min} (ng/mL) GM (% CV)	86 (87.1)	76.4 (234)	202 (91.2)	255 (65.8)

Preliminary pharmacokinetic (PK) analysis.
C_{max} = maximum observed concentration; T_{max} = time to maximum concentration; AUC = area under the concentration vs time curve; C_{min} = minimum observed concentration; GM = geometric mean; CV = coefficient of variation.

- Exposures largely similar between treatments, suggesting no clinically meaningful effect of pegIFN on either BMS compound
- Exposures also largely consistent with those reported in healthy volunteers (Bifano et al, AASLD poster 827)

Adverse Events

Adverse Events With Frequency >3 Across Both Groups

Preferred Term	Group A n=11 (%)	Group B n=10 (%)	Total N=21 (%)
Diarrhea	8 (73)	7 (70)	15 (71)
Fatigue	6 (55)	7 (70)	13 (62)
Headache	5 (46)	5 (50)	10 (48)
Nausea	2 (18)	5 (50)	7 (33)
Cough	2 (18)	2 (20)	4 (19)
Dizziness	2 (18)	2 (20)	4 (19)
Dyspnea	2 (18)	2 (20)	4 (19)
Insomnia	2 (18)	2 (20)	4 (19)
Pyrexia	3 (27)	1 (10)	4 (19)

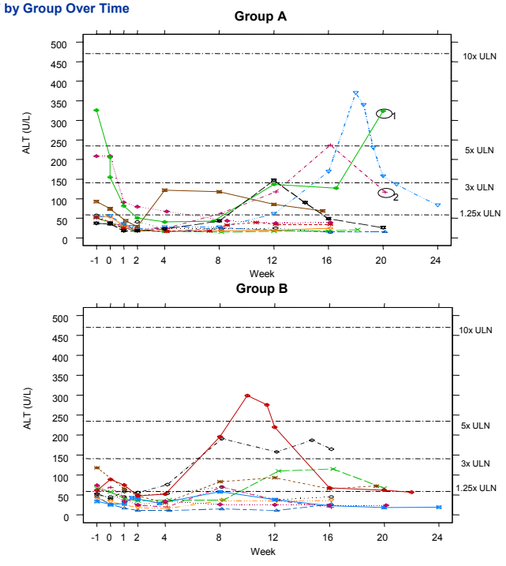
- 100% of subjects completed 12 weeks of therapy
- No serious adverse events or discontinuations of BMS drugs due to adverse events (AEs)
- 20/21 (95%) subjects experienced an AE
- AEs were mainly mild to moderate in severity
- 3 AEs of neutropenia observed in group B only resulted in dose reduction of interferon
- Only 2 "severe" AEs
  - Fatigue in 1 subject in group A
  - Neutropenia in 1 subject in group B

RESULTS (cont'd)

Transient Transaminitis

- 6/21 subjects experienced ALT >3x ULN
  - 2 from group A, 2 from group B, and 2 from group A receiving pegIFN/RBV following viral breakthrough
- Onset was between weeks 6 and 20, and all patients but one were asymptomatic
- Peak ALT elevation was 7.9 x ULN
- Maximum total bilirubin, 1.6 mg/dL (ULN = 1.1 mg/dL)
- Maximum direct bilirubin, 0.6 mg/dL (ULN = 0.2 mg/dL)
- No apparent association with response to therapy or viral breakthrough
- Several subjects were on concomitant medications (acetaminophen [1], pegIFN/RBV [4], both [1])
- Therapy was continued without dose interruption or discontinuation, and all subjects experienced improvement or resolution of condition

ALT by Group Over Time



- Circles indicate the 2 subjects in group A who were also receiving pegIFN/RBV due to viral breakthrough. Both subjects had begun receiving pegIFN/RBV at week 10

Other Safety Findings

- Number of subjects with Grade 3-4 laboratory abnormalities included:
  - 4 Absolute neutrophil counts, all in Group B
  - 2 WBC's, both in Group B
  - 3 ALT, 2 in Group A and 1 in Group B
  - 1 AST in Group A
  - 1 Absolute lymphocyte count in Group B
  - 1 Lipase in Group A
  - 1 Amylase in Group A
- No grade 3-4 laboratory abnormalities for:
  - Hemoglobin
  - Platelets
- No clinically relevant changes in ECGs, vital signs

CONCLUSIONS

- BMS-790052 plus BMS-650032 is generally well-tolerated when coadministered for 12 weeks in HCV-infected patients who were null responders to pegIFN/RBV
- BMS-790052 plus BMS-650032 provided potent early antiviral activity; however, 6/11 cases of viral breakthrough were observed with the 2 drugs when given alone
- BMS-790052 plus BMS-650032 in combination with pegIFN/RBV resulted in undetectable HCV RNA in 9/10 patients by week 12
- Should the antiviral activity demonstrated by 4-drug therapy predict SVR, the results would have significant implications for future therapy
- Study expansion with additional arms is planned based on future data

DISCLOSURES

- A. Lok receives research grant support from GlaxoSmithKline, Bristol-Myers Squibb, Gilead, Roche, and Schering, serves on data safety monitoring boards for Abbott and Bayer; and serves on advisory boards for Gilead, GlaxoSmithKline, and Roche
- R. Reindollar participates in the speaker program for Genentech and participates in clinical research trials with Bristol-Myers Squibb, Merck, and ZymoGenetics.
- R. Ghalib participates in clinical trials and receives funding from Vertex Pharmaceuticals, Merck/Schering Plough, Genetech/Roche, Gilead, Biolex, Bristol Myers Squibb, Achillion, Abbott, and Novartis; and participates in speakers bureaus for Genetech and Three Rivers.
- E. Lawitz receives research and grant support from Abbott Laboratories, Anadys Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, GlobeImmune, Idenix Pharmaceuticals, Idera Pharmaceuticals, Inhibitex, Medarex, Medtronic, Merck & Co., Novartis, Pharmasset, Roche, Schering-Plough, Valeant Pharmaceuticals International, Vertex Pharmaceuticals, ViroChem Pharma, ZymoGenetics.
- G. Everson receives grant support, serves on advisory boards, or participates in speakers bureaus for Roche, Schering, Vertex, Source, GlobeImmune, Pharmasset, HGS/Novartis, GSK, OrthoBiotech, Tibotec, Genentech, Amgen, Medtronic, BMS, Pfizer, Eisai, Abbott, Orphan Therapeutics, Gilead, Conatus, Zymogenetics, Intermune, Three Rivers, HepQuant LLC, PSC Partners Found., STOPSC, and HepC Connection.
- C. Martorell serves as an investigator on clinical studies conducted by Bristol-Myers Squibb, Genetech, Novartis, Gilead, VIIV, and Tibotec, and participates in the speaker bureaus of Bristol-Myers Squibb, Roche (Genentech), Tibotec, and Gilead.
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