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

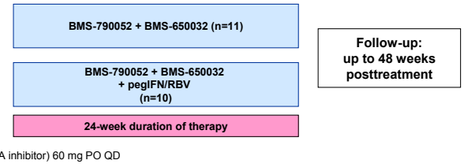
- BMS-790052 is a first-in-class, potent, and highly selective inhibitor of hepatitis C virus (HCV) NS5A with in vitro picomolar potency
- BMS-650032 is a highly active HCV NS3 protease inhibitor
- Both BMS-790052 and BMS-650032 have been shown to be generally well-tolerated and to produce robust declines 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

MATERIALS AND METHODS

Study Design



- 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

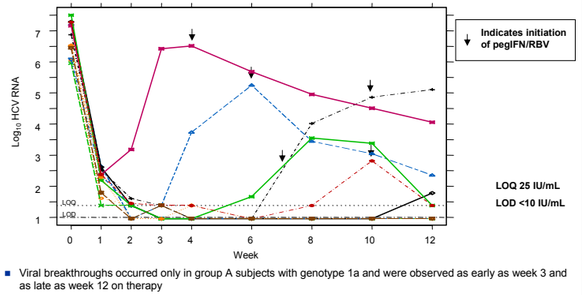
RESULTS

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

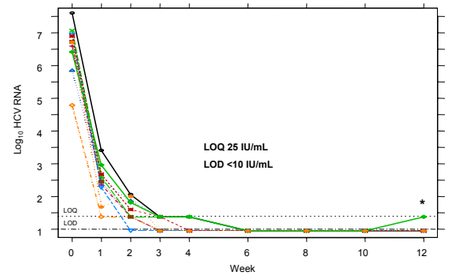


- Viral breakthroughs occurred only in group A subjects with genotype 1a and were observed as early as week 3 and as late as week 12 on therapy
- Viral breakthrough occurred with higher baseline HCV RNA levels
- Subjects with viral breakthrough had pegIFN/RBV added to their treatment
- Preliminary genotypic 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)

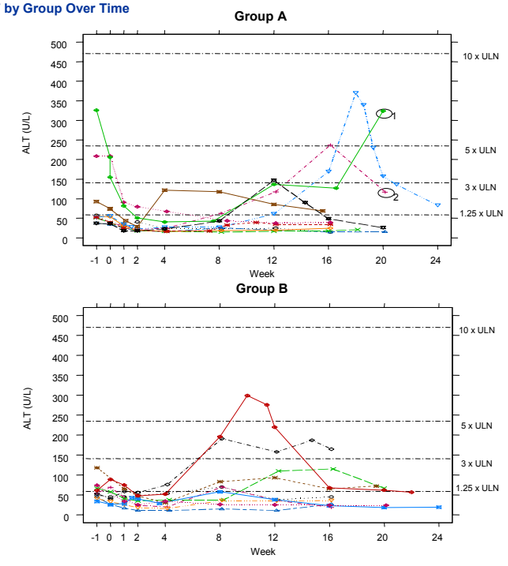
- 100% of subjects completed 12 weeks of therapy
- No serious adverse events or discontinuations of BMS drugs due to adverse events (AEs)
- 20/21 (95%) subjects experienced an AE
- AEs were mainly mild to moderate in severity
- 3 AEs of neutropenia observed in group B only resulted in dose reduction 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, VIV, and Tibotec, and participates in the speaker bureaus of Bristol-Myers Squibb, Roche (Genentech), Tibotec, and Gilead.
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