A CONTINUING MEDICAL EDUCATION ACTIVITY

THE 46TH ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

Online Expert Poster Review and Discussion

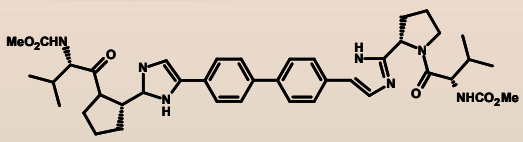
Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

Quadruple Therapy with BMS-790052, BMS-650032 and Peg-IFN/RBV for 24 Weeks Results in 100% SVR_{12} in HCV Genotype 1 Null Responders

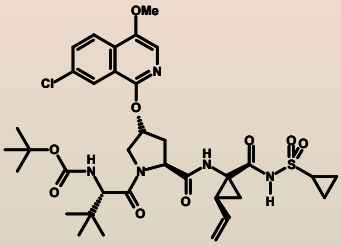
A. Lok, D. Gardiner, E. Lawitz, C. Martorell, G. Everson, R. Ghalib, R. Reindollar, V. Rustgi, F. McPhee, M. Wind-Rotolo, A. Persson, K. Zhu, D. Dimitrova, T. Eley, T. Guo, D. Grasela, C. Pasquinelli

46th EASL Congress, Berlin, Germany
March 30-April 3, 2011
Abstract 1356

Background



BMS-790052(‘052)

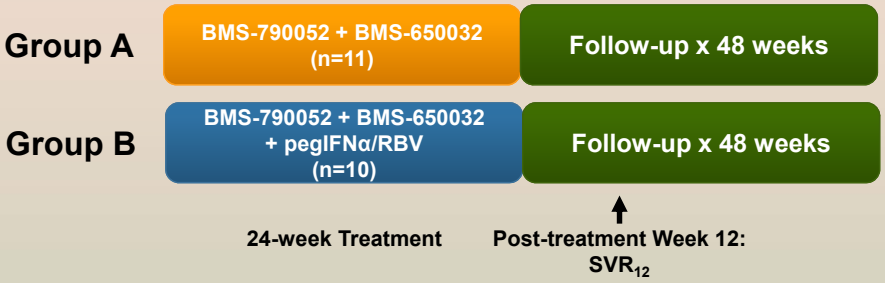


BMS-650032(‘032)

- BMS-790052 is a first-in-class, highly selective HCV NS5A replication complex inhibitor with picomolar in vitro potency and broad genotypic coverage[1]
- BMS-650032 is a potent and selective HCV NS3 protease inhibitor[2]
- Combination of BMS-790052 and BMS-65-0032 yielded additive to synergistic activity in the replicon system
- No clinically important pharmacokinetic interaction[3]

[1]Gao M. Nature 2010;465:96-100.
[2]McPhee F. *J Hepatol* 2010;52(Suppl1):S296. [3]Bifano M. *Hepatology* 2010;52(Suppl1):719A.

Study AI447-011 (Phase IIA, Open Label, Randomized Trial) – Sentinel Cohort



- BMS-790052 (NS5A replication complex 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 according to body weight

Inclusion Criteria

- Chronic genotype 1 HCV infection
- Plasma HCV RNA ≥10^5 IU/mL
- Null responders: <2 $\log_{10}$ IU/mL decline in HCV RNA following previous treatment with ≥12 weeks pegIFNα/RBV
- Absence of cirrhosis
  - By liver biopsy within 12 months of baseline, OR
  - Fibrotest ≤0.72 and APRI ≤2

APRI, Aspartate Aminotransferase-to-Platelet Ratio Index

Methods

- Randomization stratified by HCV subtype (1a vs 1b)
  - Number of 1b patients capped at 2 per treatment group
- HCV RNA levels assayed with Roche COBAS® TaqMan® HCV v2.0
  - LLOQ: 25 IU/mL, LLOD: 10 IU/mL
- IL28B genotype (rs12979860 SNP) assayed using an Applied Biosystems® TaqMan genotyping assay
- Group A patients with viral breakthrough were eligible to have pegIFNα/RBN added to their regimens (rescue) for up to 48 additional weeks

Methods

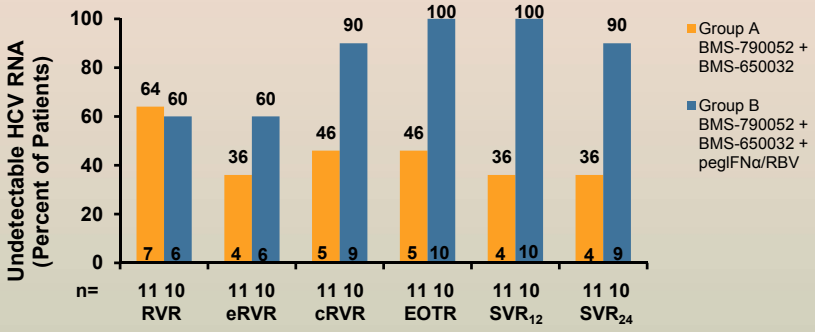
- Endpoints
  - Primary efficacy*SVR_{12}
    - Undetectable HCV RNA at 12 weeks post-treatment.
  - Secondary efficacy*
    - RVR: undetectable HCV RNA at Week 4
    - eRVR: undetectable HCV RNA at Weeks 4 and 12
    - EOTR: undetectable HCV RNA at end of treatment (Week 24)
    - SVR_{24}: undetectable HCV RNA at 24 weeks post-treatment
  - Safety
    - Adverse events (AE), serious AEs, changes in clinical laboratory tests
- Viral breakthrough
  - ≥ 1 log IU/mL increase from nadir in HCV RNA or HCV RNA ≥ LLOQ on or after Week 4
- Viral relapse
  - Confirmed detectable HCV RNA post-treatment after achieving EOTR

*Modified ITT analysis, breakthrough or relapse = failure

Demographics and Baseline Disease Characteristics

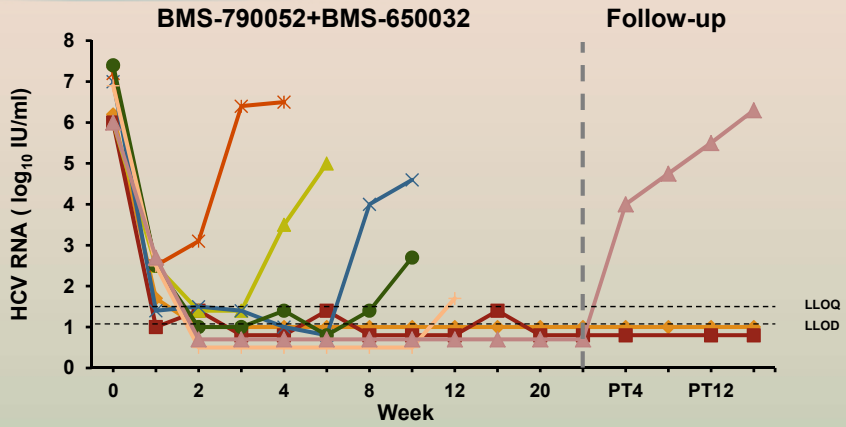
	Group A BMS-790052+ BMS-650032 (n=11)	Group B BMS-790052+ BMS-650032 +pegIFNα/RBV (n=10)
Median age, y	54	56.5
Male, (n%)	9 (82)	4 (40)
Race, (n%) White African American	9 (82) 2 (18)	7 (70) 3 (30)
HCV Genotype, (n%) 1a 1b	9 (82) 2 (18)	9 (90) 1 (10)
IL28B rs12979860 genotype, (n%) CT or TT CC	 10 (91) 1 (9)	 9 (90) 1 (10)
Mean HCV RNA, log_{10} IU/mL (SD)	6.8 (0.57)	6.6 (0.77)
Mean Baseline ALT, U/L	70.5	57.9

Virologic Response During and After Treatment



- Group A: 4 (2/9 GT 1a and 2/2 GT 1b) patients achieved SVR_{12} and SVR_{24}
- Group B: 10/10 achieved SVR_{12} and 9 had SVR_{24}
  - 1 patient had HCV RNA < LLOQ at post-treatment week 24, and undetectable HCV RNA on retesting 35 days later

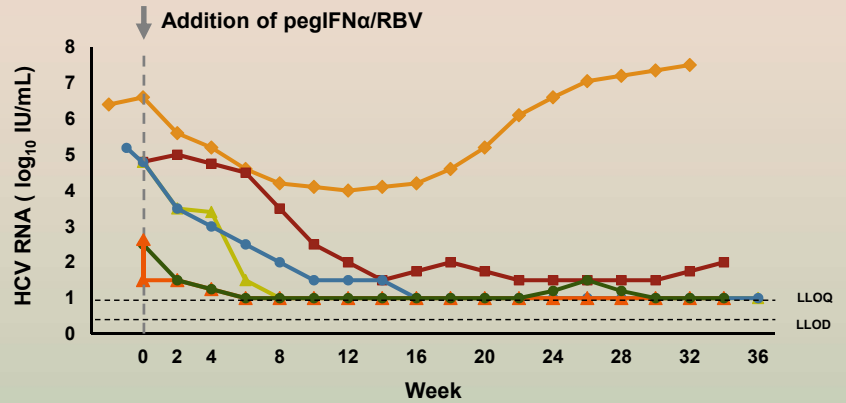
HCV RNA by Patient; Group A



- Six patients (all genotype 1a experienced viral breakthrough on therapy
- One patient with EOTR experienced viral relapse at 4 weeks post-treatment

PT, Post Treatment

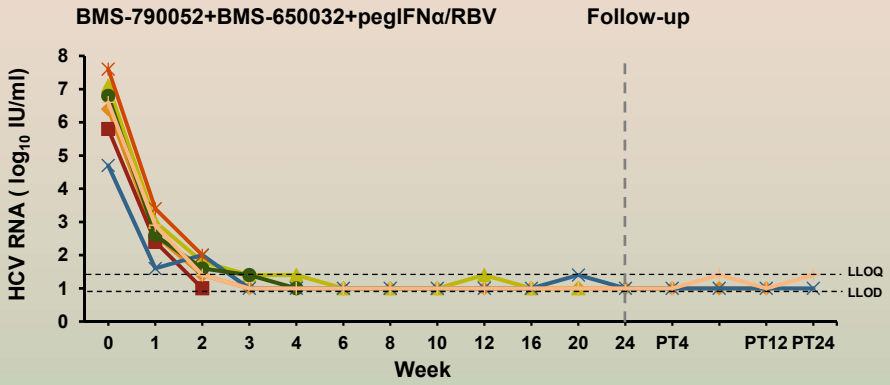
HCV RNA Following Addition of PegIFN/RBV in Patients with Viral Breakthrough



- Addition of pegIFN/RBV suppressed HCV RNA in all 6 patients with viral breakthrough
  - Four patients reached undetectable HCV RNA

*Day 0 is the date on which rescue treatment was initiated.

HCV RNA by Patient: Group B



- 10/10 patients undetectable by week 6 of therapy with no viral breakthrough
- 10/10 patients achieved SVR_{12} and 9/10 achieved SVR_{24}
  - 1 patient <LLOQ at post treatment week 24 and undetectable on retesting 35 days later

PT, Post Treatment

Adverse Events on Treatment in ≥ 4 Patients Across Both Groups

	Group A BMS-790052 + BMS-650032 (n=11)	Group B BMS-790052+BMS-650032 + pegIFNα/RBV (n=10)
Diarrhea	8 (72.7)	7 (70.0)
Fatigue	6 (54.5)	7 (70.0)
Headache	5 (45.5)	5 (50.0)
Nausea	2 (18.2)	5 (50.0)
Cough	3 (27.3)	2 (20.0)
Insomnia	3 (27.3)	3 (30.0)
Pyrexia	3 (27.3)	1 (10.0)
Chills	3 (27.3)	1 (10.0)
Dizziness	2 (18.2)	2 (20.0)
Dyspnea	2 (18.2)	2 (20.0)
Urinary Tract Infection	2 (18.2)	2 (20.0)

Results expressed as n (%); *Includes adverse events in patients who had pegIFNα/RBV added to their regimen

Adverse Events

- Most AEs were mild to moderate in severity
- No serious AEs, or discontinuations due to AEs
- Grade 3 or 4 AEs and clinical labs included fatigue (Group A,1); neutropenia (6, all receiving pegIFNα/RBV); ALT elevations (Group A, 2; Group B, 1)
- No Grade 3 or 4 anemia or thrombocytopenia
- Transient ALT elevation > 3 x ULN in 6 patients
  - 4 from Group A, including 2 receiving pegIFNα/RBV following viral breakthrough; 2 from Group B;
  - Onset between weeks 8 and 20
  - Peak ALT 370 U/L; maximum direct bilirubin 0.6 mg/dL
  - No evidence of association with response to therapy or viral breakthrough
  - ALT stabilized or improved during continued therapy in all patients

Conclusions

In this study of genotype 1 null responders:

- BMS-790052 and BMS-650032 for 24 weeks with and without pegIFNα and RBV were generally well tolerated
- BMS-790052 and BMS-650032 alone
  - 4/11 patients (2/2 G1b and 2/9 G1a) achieved SVR_{12} and SVR_{24}
  - HCV infection can be cured without interferon and ribavirin
- BMS-790052 and BMS-650032 with pegIFNα/RBV for 24-weeks
  - 10/10 patients achieved SVR_{12} and 9/10 achieved SVR_{24}*
  - Quadruple therapy can result in a high rate of cure in this difficult to treat population

*One patient < LLOQ at week 24 post treatment undetectable on retesting 35 days later