**Background**

- **BMS-790052** (‘052)
  - 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\(^3\)

- **BMS-650032** (‘032)

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

Group A
BMS-790052 + BMS-650032 (n=11)  
Follow-up x 48 weeks

Group B
BMS-790052 + BMS-650032 + pegIFNα/RBV (n=10)  
Follow-up x 48 weeks

24-week Treatment  
Post-treatment Week 12: SVR₁₂

- 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 ≥10⁵ IU/mL
- Null responders: <2 log₁₀ 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*SVR12
    • 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)
    • SVR24: 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

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMS-790052+ BMS-650032 (n=11)</td>
<td>BMS-790052+ BMS-650032 + pegIFNα/RBV (n=10)</td>
</tr>
<tr>
<td>Median age, y</td>
<td>54</td>
<td>56.5</td>
</tr>
<tr>
<td>Male, (n%)</td>
<td>9 (82)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Race, (n%)</td>
<td>White</td>
<td>African American</td>
</tr>
<tr>
<td></td>
<td>9 (82)</td>
<td>2 (18)</td>
</tr>
<tr>
<td></td>
<td>2 (18)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>HCV Genotype, (n%)</td>
<td>1a</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td>9 (82)</td>
<td>2 (18)</td>
</tr>
<tr>
<td></td>
<td>7 (70)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>IL28B rs12979860 genotype, (n%)</td>
<td>9 (91)</td>
<td>1 (9)</td>
</tr>
<tr>
<td></td>
<td>CT or TT</td>
<td>CC</td>
</tr>
<tr>
<td></td>
<td>9 (90)</td>
<td>1 (10)</td>
</tr>
<tr>
<td></td>
<td>9 (90)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Mean HCV RNA, log10 IU/mL (SD)</td>
<td>6.8 (0.57)</td>
<td>6.6 (0.77)</td>
</tr>
<tr>
<td>Mean Baseline ALT, U/L</td>
<td>70.5</td>
<td>57.9</td>
</tr>
</tbody>
</table>

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

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.
PT, Post Treatment

HCV RNA by Patient: Group B

- 10/10 patients undetectable by week 6 of therapy with no viral breakthrough
- 10/10 patients achieved SVR12 and 9/10 achieved SVR24
  - 1 patient <LLOQ at post treatment week 24 and undetectable on retesting 35 days later

Adverse Events on Treatment in ≥ 4 Patients Across Both Groups

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

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