Background

- Previous trials in HCV genotype 1 mono-infected patients and in naïve HCV/HIV-co-infected patients have clearly demonstrated that addition of BOC to peg-IFN/RBV significantly increases sustained virological response (SVR).
- We report the SVR12 virological response rate and tolerance data for the HIV/HCV genotype 1 coinfected patients who previously failed peg-IFN/RBV and were enrolled in the ANRS-252HC3 Boceprevir Trial.
- As a significant drug interaction between BOC and ritonavir (rtv) in combination with azatavir (ATV) was reported in healthy volunteers, patients treated with ATV were monitored with a monthly plasma HIV viral load measurement during BOC exposure. ATV trough was also determined at screening, W4, or in case of HCV or HIV breakthrough.
- The PK sub-study performed in this trial pointed out a trend towards a lower ATV PK parameters especially significant for AUC and a substantial variability in RAL PK parameters with a trend towards higher RAL AUC.

Study Design

- Multi-center single arm open label Phase 2 Trial
- Lead-in Phase: 28 days on Peg-IFN/RBV

Main inclusion criteria

- Patients ≥ 18 years, with body weight ≥ 40 Kg and ≤ 125 Kg.
- Chronic HCV genotype 1.
- HIV-1 coinfection.
- Previous virological failure after ≥ 12 weeks Peg-IFN/RBV: 600 mg/day.
- Stable ART for at least 3 months, with at least three molecules among ATV (if boosted or not), RAL, TDF, ABC, FTC, 3TC.
- CD4 ≥ 200 cell/mm3 (p< 15%)
- HIVRNA < 50 cp/ml, ≥ 6 months.
- Liver biopsy ≤ 3 years or cirrhosis on any previous biopsy.

Main exclusion criteria

- HIV coinfected, HIV2 infection.
- Child-B Child cirrhosis, past history of decompensated cirrhosis.
- Previous Null Response with cirrhosis.

SAE (grade 4) according to fibrosis score

<table>
<thead>
<tr>
<th>Number of SAE grade</th>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of SAE (%)</td>
<td>22</td>
<td>6</td>
<td>4</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

Patients' characteristics according to SVR

<table>
<thead>
<tr>
<th>Patient's characteristics</th>
<th>SVR29</th>
<th>ATV27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>4 (13%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (62%)</td>
<td>2 (62%)</td>
</tr>
<tr>
<td>BMI ≥ 25 Kg/m2</td>
<td>18 (58%)</td>
<td>2 (62%)</td>
</tr>
<tr>
<td>CDC stage C</td>
<td>14 (47%)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>CD4 cells/mm3</td>
<td>738 (53-103)</td>
<td>61 (93,1)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml</td>
<td>1 (31%)</td>
<td>1 (31%)</td>
</tr>
<tr>
<td>2 MRT±/ATV</td>
<td>12 (39%)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>2 MRT±/RAL</td>
<td>2 (62%)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Other*</td>
<td>5 (16%)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Results

- Sixty-nine patients were screened and sixty-four were enrolled but only sixty-two patients started boceprevir after the lead-in phase (treatment was stopped for SAE in one case and for patient's decision in the other case).

Patients' status according to previous response

- The W8-RL was < 15 IU/mL in 26 patients, between 15 and 100 IU/mL in 21 and >100 in 17.
- The W12 SVR was achieved in 34/64 patients (53%) including 7 patients who stopped prematurely. HCV treatment for AE or patients' investigator's decision. The W12 SVR seemed to vary according to ART regimen, previous response, HCV subtype but not to fibrosis stage nor IL28 polymorphism.
- During BOc exposure, 6 patients (3 with ATV- and 3 with RAL-CART based regimen) presented one blip of HIV VL. No case of HIV breakthrough or death was observed at this time of analysis.

Virological Response (ITT n=64)

HCV RNA < 15 IU/mL according to cART

- 10 patients stopped HCV treatment for AE: infections in 3/6 patients, general disorders in 4/6 patients, acute pancreatitis in 1, neutropenia in 1 and thrombocytopenia in 1.

Virological Response by characteristics

- Full-length HCV NS3 protease gene was sequenced by Sanger population sequencing from serum samples of 13 patients exhibiting virological failure on BOC-RBV, among whom 11 (85%) were infected with HCV-1a.
- Clinically-relevant BOC-resistance associated amino acid substitutions were detected in serum samples from 7 patients (54%), whereas they were absent at baseline. Six of those 7 patients were infected with HCV of subtype 1a.

Conclusion

- W12 SVR rate was similar to that described in previously treated patients with chronic HCV-1-monoinfection (SVR rate: 59-66%; SVR rate among patients with prior relapse (69% to 75%). Discontinuation for AE was low in this trial.