Pharmacokinetic-pharmacodynamic analyses of TMC435 in patients infected with hepatitis C virus genotypes 2–6

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Disclosure: all authors are employees of Tibotec.

1. Premise
- TMC435-C202 (NCT00812331) was a Phase IIa, open-label trial to assess the antiviral activity, safety, tolerability, and PK of TMC435, administered at 200 mg QD for seven days as monotherapy in treatment-naïve patients infected with HCV GT 2–6.

2. Methods
2.1 Study design
- Eligibility criteria were as follows: adults 18–70 years with documented chronic HCV GT 2–6 infection, with or without cirrhosis (up to Child Pugh A liver disease) and an HCV ribonucleic acid (RNA) level of up to 2 million IU/mL at screening. Patients were randomized to receive either pegylated interferon (PegIFN) alone or PegIFN/RBV combination therapy for 48 weeks.

2.2 Pharmacokinetic assessments and analysis methods
- Safety (including liver enzyme tests) was assessed during 48 weeks of therapy with PegIFN or PegIFN/RBV.

3. Results
3.1 Patients
- 22 patients were evaluated (GT 2: 6, GT 3: 7, GT 4: 8, GT 5: 6, GT 6: 3). The most common adverse events were anemia and increased bilirubin.

3.2 PK data for TMC435 on Day 7 for all patients are shown in Table 2 and Figure 2.

4. Conclusions
- TMC435 demonstrated potent antiviral activity in patients infected with HCV GT 2–6, and activity was observed for all genotypes.

Table 2. Pharmacokinetic profile of TMC435 in patients infected with HCV GT 2–6 following administration of TMC435 200 mg (QD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GT 2</th>
<th>GT 3</th>
<th>GT 4</th>
<th>GT 5</th>
<th>GT 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax(ng/mL)</td>
<td>3315</td>
<td>1110</td>
<td>5450</td>
<td>4230</td>
<td>4960</td>
</tr>
<tr>
<td>Cmin(ng/mL)</td>
<td>170100</td>
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<td>212000</td>
<td>189000</td>
<td>227150</td>
</tr>
<tr>
<td>AUC24h(ng.h/mL)</td>
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<td>6.05</td>
<td>6.05</td>
<td>6.00</td>
<td>6.00</td>
</tr>
<tr>
<td>tmax(h)</td>
<td>4.00</td>
<td>6.05</td>
<td>6.05</td>
<td>6.00</td>
<td>6.00</td>
</tr>
</tbody>
</table>

Figure 2. TMC435 AUC24h on Day 7 following administration of TMC435 200 mg (QD)