ONCE DAILY DUAL-NUCLEOTIDE COMBINATION OF PSI-938 AND PSI-7977 PROVIDES 94% HCV RNA < LOD AT DAY 14: FIRST PURINE/ PYRIMIDINE CLINICAL COMBINATION DATA (THE NUCLEAR STUDY)

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**Abstract #1370**

**Background**

The purine PSI-352938 (PSI-938) was created to be an optimal partner DAA for the pyrimidine PSI-7977. The nucleotides employ different prodrug cleavage pathways, largely independent phosphorylation pathways, competition with separate endogenous nucleotide pools (purine/pyrimidine) and complementary resistance profiles (Sofia J Med Chem 2010, Lam AAC 2010, Reddy Bio Med Chem Lit 2010). This study is the first proof of concept for the combination of 2 nucleotides for the treatment of HCV infection.

**Objectives**

To determine the safety, pharmacokinetic interaction and impact on antiviral activity of PSI-938 and PSI-7977 administered as monotherapy or in combination for 7-14 days.

**Design**

- **400 mg** DAA combination: 8 active and 2 placebo per cohort
- **500 mg** DAA combination: 8 active and 2 placebo per cohort
- **>50,000 IU/mL** of evidence of cirrhosis
- **<15 IU/mL** in as few as 3 days. This correlated with baseline HCV RNA and did not differ by treatment
- **SAFETY**
  - No discontinuations or serious adverse events
  - 28 AEs reported in 16/52 subjects receiving active treatment
  - Five AEs considered possibly related to active study drug
  - Headache (2), fatigue, non cardiac chest pain, dizziness
  - AEs were mild in intensity
  - Two AEs considered possibly related to placebo
  - Increased pruritus and headache.

**Table 1. Subject Demographics and Baseline Characteristics**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n</th>
<th>Median Age (y)</th>
<th>Mean BMI (kg/m(^2))</th>
<th>Median HCV RNA (IU/mL)</th>
<th>HCV 1a/1b n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>23</td>
<td>46.43</td>
<td>41.48</td>
<td>64.64</td>
<td>60</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>17</td>
<td>45.88</td>
<td>42.06</td>
<td>65.66</td>
<td>60</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>17</td>
<td>45.88</td>
<td>42.06</td>
<td>65.66</td>
<td>60</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>17</td>
<td>45.88</td>
<td>42.06</td>
<td>65.66</td>
<td>60</td>
</tr>
</tbody>
</table>

**Table 2. Summary of Antiviral Response by Cohort**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Median (Q1,Q3)</th>
<th>90% SVR</th>
<th>40% SVR</th>
<th>20% SVR</th>
<th>10% SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>-4.8 (-5.5)</td>
<td>938/7977</td>
<td>938/7977</td>
<td>938/7977</td>
<td>938/7977</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>-4.8 (-5.5)</td>
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</tr>
</tbody>
</table>

**Figure 1. PSI-7977 and PSI-938 are Complementary Nucleotides for Combination Therapy**

**Figure 2. Median [O1,Q3] HCV RNA Change from Baseline**

**Figure 3. Comparison of Monotherapy Antiviral Responses with PSI-7851, PSI-7977 and PSI-938 (Median, [O1,Q3])**

**Figure 4. HCV RNA Change from Baseline by Cohort**

**Figure 5. Pharmacokinetic Interaction Data**

**Conclusions**

- PSI-938 and PSI-7977 as monotherapy and in combination were generally safe and well tolerated over 7-14 days.
- Significant antiviral activity was observed with rapid 4-phase reductions followed by continued 4-phase reductions until the end of treatment or assay LOD was reached.
- Of note, PSI-7977 monotherapy produced HCV RNA reductions over 7 days which were similar to PSI-938.
- No viral breakthrough was observed during therapy.
- No significant PK interaction between PSI-938 and PSI-7977 was observed.
- Data support progression to a Phase 2 combination study including PSI-938 and PSI-7977.

**Disclosures**


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