Three-Day, Dose-Ranging Study Of The HCV NS3 Protease Inhibitor GS-9451

E Lawitz1, J Hilli2, T Marbury, M Rodriguez-Torres3, M DeMicco1, J Guesada2, P Shawk, S Gordon, M Shelton, D Coombs,3 J Zong,4 A Bae, K Wong,5 H Mo,4 E Mondou,4 K Hirsch,6 Delaney

1Alamo Medical Research, San Antonio, TX, 2Avail Clinical Research, Deland, FL, 3Orlando Clinical Research Center, Orlando, FL, 4Fondazione De Investigazione De Diego, Santurce, PR, 5Advanced Clinical Research Institute, Anaheim, CA, 6West Coast Clinical Trials, Cypress, CA, 7Charles River, Tampa, WA, 8Henry Ford Health System, Detroit, MI. 9Gilead Sciences, Inc, Foster City, CA.

Introduction

• GS-9451 is a potent and selective, non-communicant HCV NS3 protease inhibitor
• In vitro, EC50 ranging from 7-10 nM in HCV 1a or 1b replicon assays
• In vivo, GS-9451 selected resistance mutations at positions 186 and 195 in NS3 protease
• A single-dose study of GS-9451 in healthy subjects indicated
  - GS-9451 was generally well-tolerated at all tested doses (10 - 1000 mg)
  - Cslope-protein binding-adjusted EC50 at GS-9451 doses >= 300mg.
  - Median terminal half-life ranged from 12-14 hours, supporting QD dosing
  - Food increased GS-9451 exposure ~ 2-fold

Objectives

• To evaluate the safety and tolerability of escalating, multiple, oral doses of GS-9451 in subjects with chronic genotype 1 HCV infection
• To evaluate the antiviral activity of GS-9451 against genotype 1 HCV following administration of multiple oral doses

Secondary:

• To characterize the plasma pharmacokinetics of GS-9451 following administration of escalating, multiple, oral doses in genotype 1 HCV-infected subjects
• To assess the PK/PD relationship between HCV viral load change and GS-9451 plasma concentrations following multiple dose administration
• To compare GS-9451 antiviral activity in genotype 1a versus 1b infections
• To assess genotypic changes from baseline in the NS3A4A coding region of HCV following multiple dose administration of GS-9451 and for up to 48 weeks thereafter

Methods

• Randomized, double-blind, placebo-controlled, dose-escalation study conducted in treatment-naive subjects with genotype 1 chronic HCV infection
• Three days of GS-9451 monotherapy (tablets dosed with food)
• Cohorts:
  - 60 mg GS-9451 or placebo QD (N=10, genotype 1a)
  - 200 mg GS-9451 or placebo QD (N=10, genotype 1a)
  - 200 mg GS-9451 or placebo QD (N=11, genotype 1b)
• Serial PK (Days 1 & 3)
• Resistance testing
  - population sequencing of the entire NS3A4A coding region
  - at Baseline, Day 4 and Day 14 (and Week 12, 24, and 48)

Results

Results - Safety

• All Laboratory abnormalities were all Grade 1/2 except:
  • In vitro
    - EC50 ranging from 7-10 nM in HCV 1a or 1b replicon assays
  • Fold Change in EC50 from WTα
    - Grade 4 total bilirubin in 1 subject (GS-9451 200 mg) – 400 mg QD
    - Grade 3 amylase in 1 subject (GS-9451 200 mg) – 60 mg QD
    - Grade 3 PT in 1 subject (GS-9451 200 mg)  – 35
  • Food increased GS-9451 exposure ~ 2-fold
  • Five subjects with total bilirubin > upper limit of normal (ULN)
    - Telaprevir (PI)
  • No graded ALT values for this subject until the bilirubin resolved on Day 14, when

Results - Pharmacokinetics

Table 4. Mean (CV%) GS-9451 Pharmacokinetic Parameters at Day 1

<table>
<thead>
<tr>
<th>GS-9451 Regimen</th>
<th>Pharmacokinetic Parameter</th>
<th>Placebo</th>
<th>GS-9451 60 mg QD</th>
<th>GS-9451 200 mg QD</th>
<th>GS-9451 400 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Max Cmax (μg/mL)</td>
<td>60 (5)</td>
<td>0.2 (0.1)</td>
<td>0.4 (0.2)</td>
<td>0.4 (0.2)</td>
</tr>
<tr>
<td></td>
<td>AUCtau (μg*hr/mL)</td>
<td>1.5 (1.1)</td>
<td>2 (1.1)</td>
<td>2 (1.1)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td></td>
<td>half-life (h)</td>
<td>9 (7.1)</td>
<td>14 (12.3)</td>
<td>14 (12.3)</td>
<td>14 (12.3)</td>
</tr>
</tbody>
</table>

Results - Antivirals

Conclusions

• GS-9451 is a novel NS3 protease inhibitor with potent (>3 log) antiviral activity in patients
  • Well-tolerated at all tested doses
  • Similar activity in genotype 1a & 1b patients
  • QD dosing (14-17 h Tmax in HCV patients)

Table 5. Median (Range) Maximum Changes from Baseline in HCV RNA (log10 IU/mL)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>GS-9451 60 mg QD</th>
<th>GS-9451 200 mg QD</th>
<th>GS-9451 400 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW (yrs)</td>
<td>56</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/4</td>
<td>5/3</td>
<td>7/2</td>
</tr>
<tr>
<td>Race</td>
<td>1/5/5</td>
<td>1/5/5</td>
<td>1/7/7</td>
</tr>
<tr>
<td>Visibility</td>
<td>1/1/1</td>
<td>1/1/1</td>
<td>1/1/1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>114 (100-120)</td>
<td>112 (100-120)</td>
<td>112 (100-120)</td>
</tr>
</tbody>
</table>

Acknowledgements

Gilead gratefully acknowledges all the patients who participated in this study.

© 2010 Gilead Sciences, Inc All rights reserved