Pharmacokinetics of Filibuvir in Special Populations (Elderly and Hepatically Impaired)

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Disclosures

- Dr. Purohit is an employee of Pfizer, Inc.
- All studies discussed in this presentation were sponsored by Pfizer, Inc.
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  - M Rosario*, M O’Gorman, J Fang, S Srinivasan and J Hammond

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Filibuvir

- A non-nucleoside inhibitor of the HCV polymerase enzyme
- Binds the “Thumb 2” site of the HCV polymerase enzyme
- Demonstrates potent *in vitro* antiviral activity with an overall mean EC$_{50}$ against genotype 1 replicons of 0.059 µM (0.029 µg/mL)
- Equipotent against subtypes 1a and 1b
- Signature resistance mutation is M423T
Filibuvir – Studies in HCV-Infected Patients

- Filibuvir in monotherapy studies in HCV-infected patients demonstrated ~2 log drop in viral load at nadir.

- Filibuvir in combination with pegIFN and ribavirin produced RVR rates of up to 75% and cEVR of up to 88%.

RVR = rapid viral response; BID = twice daily
TID = three times daily

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Filibuvir Clinical Pharmacology

- Rapidly absorbed ($T_{\text{max}}$ 0.5–4 hours)
- Nonlinear pharmacokinetics
  - Exposures increase more than proportional with dose
- ~98% protein bound
- Primarily metabolized by CYP3A
- ~17% of dose eliminated unchanged in urine
- Terminal $T_{1/2}$ of 8–12 hours (biphasic elimination)
Pharmacokinetics, Safety and Tolerance of Multiple Oral Doses of Filibuvir in Elderly Healthy Volunteers

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Rationale and Objective

- Filibuvir is predominantly metabolized by CYP3A
  - Age-dependent decreases in enzymatic activity can reduce clearance of filibuvir in elderly\(^1\)
- As the HCV-infected population ages, a greater proportion of infected patients will fall into the elderly categories
  - An understanding of filibuvir pharmacokinetics in the elderly is important
- The objectives of this study are to investigate the multiple-dose pharmacokinetics, safety and tolerability of 300 mg BID of filibuvir in healthy elderly and young subjects

\(^1\)Michael B. Mayersohn. Special Pharmacokinetic Considerations in the Elderly. Applied Pharmacokinetic Principles of Therapeutic Drug Monitoring. 3rd Ed., 1992., Chapter 9, 1-43
Study Design

- Non-randomized, parallel, three-cohort study
- N=37 subjects
  - 18–55 years (N = 12)
  - 65–74 years (N = 13)
  - 75–85 years (N = 12)
- Regimen – filibuvir 300 mg BID with food for 14 days
- Extensive pharmacokinetic sampling on Day 1 and Day 14
- Safety was assessed throughout the treatment period and follow-up
- One-way analysis of variance (ANOVA) was used to compare the natural log-transformed AUC_{0-12} and C_{max} (Day 14) and the accumulation ratios (AUC_{0-12} and C_{max}) for elderly and very elderly age groups (Test) as compared with the young age group (Reference)
## Demographic Characteristics

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>Young adults (18–55 years)</th>
<th>Elderly (65–74 years)</th>
<th>Very elderly (75–85 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>11/1</td>
<td>7/6</td>
<td>5/7</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.4 (5.7)</td>
<td>78.9 (12.5)</td>
<td>76.9 (10.4)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>69.8–87.5</td>
<td>57.1–98.4</td>
<td>62.1–98.0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.6 (2.5)</td>
<td>30.2 (4.1)</td>
<td>28.8 (3.2)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>20.0–28.9</td>
<td>23.5–34.8</td>
<td>23.6–34.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175.2 (6.0)</td>
<td>161.7 (9.7)</td>
<td>163.3 (6.8)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>167.0–188.0</td>
<td>143.0–173.0</td>
<td>153.0–173.0</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Pharmacokinetic Results – Day 14 Median Concentration Profiles

- Young adults (18–55 years)
- Elderly (65–75 years)
- Very elderly (75–85 years)

Plasma filibuvir concentration (ng/mL) vs. Time (hours)
## Pharmacokinetic Results

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Young adult (18–55)</th>
<th>Elderly (65–74)</th>
<th>Very elderly (75–85)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1 (single dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>$\text{AUC}_{0-12}$ (\text{ng}\cdot\text{hr/mL})</td>
<td>38570 (30)</td>
<td>47720 (24)</td>
<td>43710 (26)</td>
</tr>
<tr>
<td>$\text{C}_{\text{max}}$ (\text{ng/mL})</td>
<td>14540 (26)</td>
<td>13010 (24)</td>
<td>13540 (36)</td>
</tr>
<tr>
<td></td>
<td>Day 14 (multiple dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>11</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>$\text{AUC}_{0-12}$ (\text{ng}\cdot\text{hr/mL})</td>
<td>49720 (31)</td>
<td>65860 (21)</td>
<td>61370 (28)</td>
</tr>
<tr>
<td>$\text{C}_{\text{max}}$ (\text{ng/mL})</td>
<td>18600 (27)</td>
<td>15930 (39)</td>
<td>19110 (24)</td>
</tr>
<tr>
<td>$\text{C}_{12}$ (\text{ng/mL})</td>
<td>535 (47)</td>
<td>958 (29)</td>
<td>711 (47)</td>
</tr>
<tr>
<td>$t_{\frac{1}{2}}$ (\text{hours})</td>
<td>9.13 (19)</td>
<td>12.2 (14)</td>
<td>14.2 (21)</td>
</tr>
<tr>
<td>$R_{\text{ac}}\cdot\text{AUC}$</td>
<td>1.27 (0.922–1.95)</td>
<td>1.33 (1.08–1.670)</td>
<td>1.35 (1.06–2.18)</td>
</tr>
<tr>
<td>$R_{\text{ac}}\cdot\text{C}_{\text{max}}$</td>
<td>1.28 (0.770–1.87)</td>
<td>1.16 (0.794–2.09)</td>
<td>1.36 (0.900–2.75)</td>
</tr>
</tbody>
</table>

$N =$ number of subjects; $R_{\text{ac}} =$ accumulation ratio

Geometric mean (\%CV) for all except: median (range) for $T_{\text{max}}$, $R_{\text{ac}}$ and $R_{\text{ac}}$; arithmetic mean (\%CV) for $t_{\frac{1}{2}}$

*presented at the 5th Int. workshop on Clinical Pharmacology of Hepatitis Therapy 23 June 2010, Boston, USA*
### Pharmacokinetic Results (Cont’d)

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Comparison (Test vs Reference)</th>
<th>Test&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Reference&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ratio (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0–12&lt;/sub&gt; (ng•hr/mL)</td>
<td>Elderly vs young adults</td>
<td>65861.93</td>
<td>49718.48</td>
<td>132.47</td>
<td>110.01</td>
<td>159.51</td>
</tr>
<tr>
<td></td>
<td>Very elderly vs young adults</td>
<td>61367.81</td>
<td>49718.48</td>
<td>123.43</td>
<td>102.51</td>
<td>148.63</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>Elderly vs young adults</td>
<td>15927.47</td>
<td>18600.46</td>
<td>85.63</td>
<td>68.62</td>
<td>106.85</td>
</tr>
<tr>
<td></td>
<td>Very elderly vs young adults</td>
<td>19113.69</td>
<td>18600.46</td>
<td>102.76</td>
<td>82.35</td>
<td>128.23</td>
</tr>
<tr>
<td>R&lt;sub&gt;ac&lt;/sub&gt;, AUC</td>
<td>Elderly vs young adults</td>
<td>1.35</td>
<td>1.32</td>
<td>102.26</td>
<td>89.67</td>
<td>116.62</td>
</tr>
<tr>
<td></td>
<td>Very elderly vs young adults</td>
<td>1.40</td>
<td>1.32</td>
<td>106.63</td>
<td>93.50</td>
<td>121.60</td>
</tr>
<tr>
<td>R&lt;sub&gt;ac&lt;/sub&gt;, C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Elderly vs young adults</td>
<td>1.23</td>
<td>1.29</td>
<td>95.42</td>
<td>78.45</td>
<td>116.06</td>
</tr>
<tr>
<td></td>
<td>Very elderly vs young adults</td>
<td>1.41</td>
<td>1.29</td>
<td>109.13</td>
<td>89.72</td>
<td>132.73</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted geometric mean values; <sup>b</sup>Ratio of adjusted geometric means

*presented at the 5<sup>th</sup> Int. workshop on Clinical Pharmacology of Hepatitis Therapy 23 June 2010, Boston, USA*
Overview of Safety Results

- There were no deaths or SAEs
- No subject discontinued due to an AE or had a dose reduction or temporary discontinuation of treatment due to an AE
- No clinically important, treatment-related changes in safety laboratory test results, vital sign measurements, or ECGs were observed

AE = adverse event; SAE = serious adverse event

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Conclusions

- Steady-state filibuvir exposures ($\text{AUC}_{0-12}$) were 1.3-fold and 1.2-fold higher in the elderly and very elderly populations, respectively, relative to young adults.

- No clinically significant differences were noted in steady-state $C_{\text{max}}$ for both elderly age groups relative to the young adults.

- The observed pharmacokinetic differences were not considered clinically meaningful and dose adjustments are not necessary in the elderly.

- Multiple doses of filibuvir were well tolerated by the young adult, elderly, and very elderly subjects evaluated in this study.
Pharmacokinetics, Safety and Tolerability of a Single Oral Dose of Filibuvir in Subjects with Hepatic Impairment

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³Pfizer, Clinical Development, New London, USA
⁴Vertex Pharmaceuticals, Clinical Pharmacology, Cambridge, USA

presented at the 5th Int. workshop on Clinical Pharmacology of Hepatitis Therapy 23 June 2010, Boston, USA
Rationale and Objective

- Filibuvir is predominately metabolized, thus its clearance may be reduced with hepatic impairment.

- The objectives of this study are to investigate the pharmacokinetics, safety and tolerability of a single 200 mg dose of filibuvir in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function.
Study Design

- Open-label, single-dose, non-randomized, sequential study
- N=24 subjects (8 per group)
  - Healthy volunteers (normal hepatic function)
  - Mild hepatic impairment (Child-Pugh A)
  - Moderate hepatic impairment (Child-Pugh B)
- Regimen – filibuvir 200 mg single oral dose (fasted)
- Groups enrolled sequentially (mild hepatic impairment → moderate hepatic impairment → normal subjects)
- Pharmacokinetics samples were collected up to Day 8
- Safety assessments were made throughout the study
- One-way analysis of variance (ANOVA) was used to compare the natural log-transformed \( \text{AUC}_{\text{inf}} \) and \( \text{C}_{\text{max}} \) for each hepatic impairment group (mild and moderate) (Test) to the normal hepatic function group (Reference)
Pharmacokinetic Results – Median Plasma Concentrations.

- Normal
- Mild Hepatic Impairment (Child-Pugh A)
- Moderate Hepatic Impairment (Child-Pugh B)
# Pharmacokinetic Results

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Normal hepatic function</th>
<th>Mild hepatic impairment</th>
<th>Moderate hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>( AUC_{\text{inf}} , (\text{ng}\cdot\text{hr/mL}) )</td>
<td>37977 (37)</td>
<td>38632 (52)</td>
<td>87654 (49)</td>
</tr>
<tr>
<td>( C_{\text{max}} , (\text{ng/mL}) )</td>
<td>11073 (37)</td>
<td>7487 (53)</td>
<td>15142 (35)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Comparison</th>
<th>Test(^a)</th>
<th>Reference(^a)</th>
<th>Ratio(^b) (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>( AUC_{\text{inf}} , (\text{ng}\cdot\text{h/mL}) )</td>
<td>Mild vs normal</td>
<td>38631.54</td>
<td>37977.47</td>
<td>101.72</td>
<td>(63.17%, 163.80%)</td>
</tr>
<tr>
<td></td>
<td>Moderate vs normal</td>
<td>87654.22</td>
<td>37977.47</td>
<td>230.81</td>
<td>(143.33%, 371.67%)</td>
</tr>
<tr>
<td>( C_{\text{max}} , (\text{ng/mL}) )</td>
<td>Mild vs normal</td>
<td>7486.60</td>
<td>11072.59</td>
<td>67.61</td>
<td>(43.89%, 104.16%)</td>
</tr>
<tr>
<td></td>
<td>Moderate vs normal</td>
<td>15141.59</td>
<td>11072.59</td>
<td>136.75</td>
<td>(88.77%, 210.65%)</td>
</tr>
</tbody>
</table>

\(^a\)Geometric mean (%CV) for all

\(^b\)Ratio of adjusted geometric means
Overview of Safety Results

- There were no deaths and no permanent discontinuations from the study due to AEs.

- No subject required a dose reduction or temporary discontinuation due to AEs.
  - One SAE was reported in the moderate hepatic impairment group (exacerbation of pre-existing anemia) but was not considered to be due to study drug.

- Slightly more subjects in the moderate hepatic impairment group had laboratory test abnormalities (without regard to baseline abnormality), but none were considered clinically significant.
Conclusions

- Filibuvir exposures ($\text{AUC}_{\text{inf}}$) were not altered in subjects with mild hepatic impairment and were 2.3-fold higher in subjects with moderate hepatic impairment compared to subjects with normal hepatic function.

- No consistent trend was noticed for changes in C$_{\text{max}}$ with hepatic impairment.

- Overall, administration of single oral doses of 200 mg of filibuvir was considered safe and well tolerated in healthy subjects and subjects with mild and moderate hepatic impairment.

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