Modeling and Simulation of Time to Pain Relief of a Fast-Absorbing Acetaminophen Formulation

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Objectives: To develop pharmacokinetic (PK)-pharmacodynamic (PD) models relating acetaminophen (ACM) plasma concentrations to the hazard of pain relief events and to derive the probability of success (POS) of a significantly faster pain relief of a fast-absorbing ACM formulation compared with commercial formulations of ACM and ibuprofen.

Methods: A PK model for ACM was developed using concentration data from two studies in healthy volunteers and one dental pain study in patients using NONMEM 7.2. Data from 164 subjects receiving 1000 mg ACM as fast-absorbing (F-ACM) or standard (S-ACM) tablets with 1801 detectable plasma concentrations were included in the PK analysis.

Time-to-event models were developed linking concentrations of ACM to the hazard of confirmed perceptible pain relief (CPPR) and meaningful pain relief (MPR) as recorded using the double stopwatch method in the dental pain study (N=60/arm). Patients received either placebo, 1000 mg acetaminophen as F-ACM or S-ACM tablets, or 400 mg ibuprofen as liquid-filled capsules (L-IBU). Different hazard models, including Weibull, Gompertz and Bateman were evaluated on the placebo data to describe the drug-free hazard. Several functions were tested to explore the drug effect as a concentration-dependent increase in the hazard.

The PKPD models were used to simulate CPPR and MPR in hypothetical trials with the number of patients per treatment group ranging from 60 to 150. Five hundred trial replicates were simulated, and the POS to obtain a significant Wilcoxon test (p<0.05) in the pairwise comparison of treatments, including an unstudied dose of 650 mg F-ACM, was calculated.

Results: A two-compartment disposition model with two parallel absorption pathways, each comprising sequential zero-first order absorption and a lag-time on one of the two pathways best described the ACM PK data. ACM from the F-ACM formulation was significantly faster absorbed than from S-ACM tablets, as indicated by a 48% shorter lag-time and a 115% faster absorption rate constant. The hazard of CPPR and MPR after receiving placebo was best described with a Bateman function. The concentration-hazard relationship was described by a power function. The key results of the simulations are shown in the table below.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Comparison (Reference - Test)</th>
<th>N=60</th>
<th>N=90</th>
<th>N=120</th>
<th>N=150</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPPR</td>
<td>L-IBU 400 – F-ACM 1000</td>
<td>82.0</td>
<td>93.4</td>
<td>94.2</td>
<td>96.0</td>
</tr>
<tr>
<td></td>
<td>L-IBU 400 – F-ACM 650</td>
<td>80.8</td>
<td>87.8</td>
<td>93.4</td>
<td>95.8</td>
</tr>
<tr>
<td></td>
<td>S-ACM 1000 - F-ACM 1000</td>
<td>42.8</td>
<td>59.2</td>
<td>69.4</td>
<td>74.2</td>
</tr>
<tr>
<td></td>
<td>S-ACM 1000 - F-ACM 650</td>
<td>36.6</td>
<td>46.8</td>
<td>56.6</td>
<td>65.6</td>
</tr>
<tr>
<td>MPR</td>
<td>L-IBU 400 – F-ACM 1000</td>
<td>63.6</td>
<td>81</td>
<td>87.5</td>
<td>90.1</td>
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<tr>
<td></td>
<td>L-IBU 400 – F-ACM 650</td>
<td>7.3</td>
<td>8.5</td>
<td>10.3</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>S-ACM 1000 - F-ACM 1000</td>
<td>17.8</td>
<td>23.6</td>
<td>36.0</td>
<td>37.0</td>
</tr>
<tr>
<td></td>
<td>S-ACM 1000 - F-ACM 650</td>
<td>0</td>
<td>0.2</td>
<td>0</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Conclusions: With 120 patients/group, simulations showed a high chance for F-ACM 1000 mg to have a significantly faster time to CPPR and MPR compared with L-IBU 400 mg. POS of faster CPPR dropped to ~70% comparing F-ACM 1000 mg to S-ACM 1000 mg. The POS of showing a faster MPR for F-ACM compared to S-ACM was low.

References: none