Population Pharmacokinetics of AZD-5847 in Patients with TB

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Introduction

• AZD5847 is an oxazolidinone antibiotic, with *in vitro* activity against *Mycobacterium tuberculosis*

• Recently completed a phase II EBA study

• EBA activity was very modest
Objective

• Develop a population pharmacokinetic model for AZD-5847 using data from the Phase 2 EBA study
Study Design

- The study includes 60 subjects receiving AZD-5847

- Study included 4 different AZD arms, 15 subjects per arm
  - 500 mg QD
  - 500 mg BID
  - 800 mg BID
  - 1200 mg QD
Study Design

Participants Evaluated
N= 106

Excluded (did not meet entry criteria)
N=31

Randomized
N=75

Rifafour e-275 mg at standard dosing
N=15
Completed drug intake
N=15
Completed follow-up
N=15

AZD5847 at 500 mg once daily
N=15
Completed drug intake
N=15
Completed follow-up
N=15

AZD5847 at 500 mg twice daily
N=15
Completed drug intake
N=15

AZD5847 at 1200 mg once daily
N=15
Completed drug intake
N=15
Completed follow-up
N=15

AZD5847 at 800 mg twice daily
N=15
Completed drug intake
N=15
Completed follow-up
N=15
Sampling

- Participants underwent intensive PK sampling for 24 to 48 hours after dosing on days 1 and 14.

- Trough concentrations also were measured within 30 minutes prior to dosing on days 3, 5, and 10.
Modeling

- Modeling performed using Monolix 4.3 (SAEM)

- First, model data for day 1 only

- NCA results showed F might be dose dependent; initially F was fixed at 1
Modeling

• Dose was modeled as a categorical covariate for F

• First, develop model for day 1, then predict concentrations on day 14 to assess any time dependent changes in Cl/F or F
Results

- Total number of observations is 1723
- Average body weight was 53.6 kg and average age was 35 years
- The study included 10 females and 50 males receiving AZD-5847.
Results

• Data were adequately described with a two compartment model and tlag for absorption

• Dose added as a covariate for F

• F is capped at 800 mg dose

• F at 1200 mg is 67 %
Predicting day 14
Modeling full data

• Then, all data were modeled simultaneously:

• Two compartment and tlag with dose as covariate for F
Modeling full data

• Typical values (relative standard error %) were:
  • Tlag 0.27 hours (18%)
  • Ka 0.38 hour⁻¹ (9%)
  • Cl 8.0 L/hour (3%)
  • V1 43.3 L (7%)
  • Q 8.9 L/hour (13%)
  • V2 31.9 L (9%)
Modeling full data

- The coefficient of variation (r.s.e. %) were:
  - Tlag  68.6 % ( 22% )
  - Ka     21.6 % ( 19% )
  - Cl      22.0% ( 10% )
  - V1      14.9% ( 36% )
  - Q       47.1% ( 28% )
  - V2      55.6% ( 13% )
Diagnostics
Diagnostics
Typical profile
<table>
<thead>
<tr>
<th>Dose</th>
<th>Observed AUC</th>
<th>Predicted AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg QD</td>
<td>56</td>
<td>63</td>
</tr>
<tr>
<td>500 mg BID</td>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>800 mg BID</td>
<td>93</td>
<td>100</td>
</tr>
<tr>
<td>1200 mg QD</td>
<td>96</td>
<td>100</td>
</tr>
</tbody>
</table>
Predicted AUC / MIC

- Protein binding is 80%; MIC in the EBA study ranged from 1-2 mcg/ml

- In the mouse model, a minimum fAUC / MIC > 20 was required for bactericidal activity
# Predicted AUC / MIC

<table>
<thead>
<tr>
<th>Dose</th>
<th>$f_{AUC}/MIC$ (MIC = 1)</th>
<th>$f_{AUC}/MIC$ (MIC = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg QD</td>
<td>12.5</td>
<td>6</td>
</tr>
<tr>
<td>500 mg BID</td>
<td>12.5</td>
<td>6</td>
</tr>
<tr>
<td>800 mg BID</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>1200 mg QD</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>
Summary

• AZD-5847 shows biphasic elimination, and saturable (non-linear) absorption; administering doses above 800 mg might not be beneficial

• In the mouse model, a minimum fAUC / MIC > 20 was required for bactericidal activity
Summary

• This could help explain the poor bactericidal activity observed in the phase II study

• Given the saturable absorption of AZD-5847, it is difficult to achieve favorable PK/PD targets