AZD5847
Oxazolidinone for the treatment of Tuberculosis

Scott Butler
Infection Innovative Medicines Group
AstraZeneca R&D, Boston
Key Features of AZD5847

Product Concept: Oxazolidinone suitable for use in combination therapies to treat DS and/or MDR/XDR tuberculosis (+HIV co-infected)

- AZD5847 binds 50S ribosomal subunit and blocks initiation of protein synthesis
- Bactericidal against *M. tuberculosis*: susceptible, MDR- and XDR-TB isolates
- AZD5847 is active against extracellular, intracellular, rapidly dividing, and slowly dividing mycobacteria in mouse models
- In vitro data suggests low DDI risk with likely combination drugs (including antiretrovirals)
- Generally safe and well tolerated over 14 days (volunteers and patients)
Phase 2a: EBA Study (Sponsored by NIAID)

Short duration (14 days) monotherapy with AZD5847 in patients with drug sensitive TB

- Ongoing in South Africa (TASK, Andreas Diacon)

Inclusions/exclusions; HAINE test to for sensitivity to rifampin and isoniazid; Baseline safety labs

Active pulmonary tuberculosis documented by positive sputum smear x 2

Randomization

1 2 3 4 5

Treatment: 14 days
- Daily quantitative sputum culture for \textit{M. tuberculosis}
- Days 0-2 = early bactericidal activity
- Days 3-14 = sterilizing activity

PK sampling days 1 and 14, trough levels days 5 and 10
Safety labs on days 7 and 14

Initiate SOC for DS-pulmonary TB

Treatment groups (total enrollment ~75: **15 per arm**)

1. AZD5847 500mg qd
2. AZD5847 500mg bid
3. AZD5847 1200mg qd
4. AZD5847 800mg bid
5. Rifafour 1 tab PO qd (weight based)

**Endpoint:** Rate of change in sputum colony forming unit (CFU) counts (bactericidal activity) during the entire 14 days of study drug administration (EBA0-14)
Phase 2a: EBA Study Status

• As of September 25:
  o 57 patients enrolled
  o 36 have completed the protocol
  o Generally very well tolerated
  o Last patient expected to complete follow up in December

• Final study report expected ~April 2014

From September monthly report:

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study Drug Arm</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rifafour (EHRZ)</td>
<td>AZD5847 500 mg qd</td>
<td>AZD5847 500 mg bid</td>
<td>AZD5847 1200 mg qd</td>
<td>AZD5847 800 mg bid</td>
<td>N=48</td>
</tr>
<tr>
<td></td>
<td>n=10</td>
<td>n=10</td>
<td>n=9</td>
<td>n=10</td>
<td>n=9</td>
<td></td>
</tr>
<tr>
<td>Demographic:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs), median (IQR)</td>
<td>41 (27)</td>
<td>26 (21)</td>
<td>29 (9)</td>
<td>36 (11)</td>
<td>35 (8)</td>
<td>35 (19)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>7 (70)</td>
<td>9 (90)</td>
<td>6 (67)</td>
<td>7 (70)</td>
<td>8 (89)</td>
<td>37 (77)</td>
</tr>
<tr>
<td>Clinical:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg), median (IQR)</td>
<td>45 (6)</td>
<td>52 (8)</td>
<td>47 (20)</td>
<td>54 (10)</td>
<td>56 (7)</td>
<td>51 (13)</td>
</tr>
<tr>
<td>BMI (kg/m²), median (IQR)</td>
<td>17 (4)</td>
<td>19 (2)</td>
<td>17 (5)</td>
<td>20 (3)</td>
<td>20 (3)</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (gm/dL), median (IQR)</td>
<td>12 (2)</td>
<td>12 (4)</td>
<td>12 (3)</td>
<td>12 (1)</td>
<td>12 (1)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>WBC (10^3 cells/mm³), median (IQR)</td>
<td>13 (5)</td>
<td>10 (7)</td>
<td>9 (2)</td>
<td>9 (2)</td>
<td>8 (3)</td>
<td>9 (4)</td>
</tr>
</tbody>
</table>

BMI = Body Mass Index, weight was measured in kilograms (kg) and height in meters (m).
WBC = White-blood-cell count; IQR = Interquartile Range.
### 90 Day Chronic Toxicology - Mouse

- **Study Sponsored by DMID, NIAID**
- **In life completed**

<table>
<thead>
<tr>
<th>Treatment Level (mg/kg)</th>
<th>Dose Conc. (mg/ml)</th>
<th># Animals</th>
<th>Day 91</th>
<th>Day 182</th>
<th>No. Undosed Females for Mating</th>
<th>No. TK Satellite Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>10 M/10 F</td>
<td>6 M/6 F</td>
<td>16F</td>
<td></td>
<td>3 M/3 F</td>
</tr>
<tr>
<td>50</td>
<td>5</td>
<td>10 M/10 F</td>
<td>---</td>
<td>16F</td>
<td></td>
<td>9 M/9 F</td>
</tr>
<tr>
<td>250</td>
<td>25</td>
<td>10 M/10 F</td>
<td>---</td>
<td>16F</td>
<td></td>
<td>9 M/9 F</td>
</tr>
<tr>
<td>1000</td>
<td>100</td>
<td>10 M/10 F</td>
<td>10 M/10 F</td>
<td>16F</td>
<td></td>
<td>9 M/9 F</td>
</tr>
<tr>
<td><strong>Total No. Animals</strong></td>
<td></td>
<td><strong>40 M/40 F</strong></td>
<td><strong>16 M/16 F</strong></td>
<td><strong>64 F</strong></td>
<td></td>
<td><strong>30 M/30 F</strong></td>
</tr>
</tbody>
</table>

- **Overall, AZD 5847 was well tolerated in male and female CD-1 mice after repeat oral gavage administration of 50, 250, or 1000 mg/kg for 90 days**

- **Draft Histopathology report due 14 Oct 2013.**

- **Draft final report due 31 Jan 2014.**
90 Day Chronic Toxicology - Dog

• Study Sponsored by DMID, NIAID
• In life study is ongoing

<table>
<thead>
<tr>
<th>Treatment Level (mg/kg)</th>
<th>Dose Conc. (mg/ml)</th>
<th>No. Animals Sacrificed</th>
<th>Day 91</th>
<th>Day 182</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>3 M/3 F</td>
<td>3 M/3 F</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>3 M/3 F</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>3 M/3 F</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>30</td>
<td>3 M/3 F</td>
<td>3 M/3 F</td>
<td></td>
</tr>
<tr>
<td>Total No. Animals</td>
<td></td>
<td>12 M/12 F</td>
<td>6 M/6 F</td>
<td></td>
</tr>
</tbody>
</table>

• To date, AZD 5847 has been well tolerated in male and female beagle dogs after repeat oral capsule administration of 5, 20, or 60 mg/kg for 90 days

• Main necropsy scheduled for 18 Sept 2013

• Draft final report due 30 Apr 2014.
AZD5847 and Linezolid show similar efficacy in combination with SOC

• New novel combination studies ongoing in mouse chronic infection and relapse model (E. Nuermberger, sponsored by Global Alliance for TB)
Looking Toward Phase 2b Studies

• **Pharmaceutical Development**
  - DMID sponsored formulation development and manufacture of capsules to support Ph2b studies

• **Understanding potential Drug-Drug Interactions**
  - AZD5847 is a substrate of P-gp/BCRP and acid metabolite is a substrate of OATP1B1/1B3
  - AZD5847 inhibits OATP1B1 (IC$_{50}$ 33 µM)
  - In vitro studies on UGT1A1 and several transporters, including OATP1B1, OAT1, OAT3, OCT2, BCRP, and others
  - Confirm the proposed major route of elimination through hepatic metabolism by human $^{14}$C ADME
Development Pathways

**Ph2a**
14 day EBA

**Ph2b**
AZD Combo(s)
DS and MDR TB
2 week, 8 week

**Ph3**
AZD Combo
DS and MDR TB

**Interim analysis of MDR patients**
AZD Combo vs OBT
24 week data

**Accelerated Approval**
AZD combo Treatment of MDR TB

Registration
Combination for Treatment of DS and MDR TB

**Accelerated Approval**
AZD+ OBT Treatment of MDR TB

**Ph3**
AZD + OBT vs OBT
MDR
24 week
Summary

• Oxazolidinones offer a promising (clinically validated) addition to future combination regimens
  • MDR/XDR treatment or simplified/reduced duration SOC

• AZD5847 has potential to differentiate among oxazolidinones:
  • Active against slowly dividing *M. tuberculosis*
  • Active against intracellular *M. tuberculosis*
  • Potential for improved safety profile

• AZD5847 is generally safe and well tolerated at predicted efficacious doses

• Phase 2a trial to finish clinical phase in December 2013
  • Final study report ~April 2014

• Work ongoing to position AZD5847 for Phase 2b by mid 2014
  • With safety coverage for up to 90 days treatment