AZD5847

Phase 1 completed in healthy volunteers

- Bactericidal vs. multiple physiological states of TB bacteria: an uncommon attribute among TB drugs
- Well tolerated at predicted therapeutic dose in healthy volunteers
- Hematologic toxicities, a key risk seen at exposures above the predicted therapeutic dose

Risk versus benefit is the key question
Key Pre-clinical Data

**Excellent intracellular and in vivo efficacy vs TB**

- **Efficacy in the Mice Model of TB**
- **Efficacy in the Macrophage Model of TB**

**MIC Distribution - 163 Mtu Isolates**
- (84 sensitive, 18 SDR, 36 MDR & 25 XDR)

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**MIC Distribution - 163 Mtu Isolates**
- (84 sensitive, 18 SDR, 36 MDR & 25 XDR)
AZD5847 retains PKPD index vs. rapidly dividing and slowly dividing Mtu in mouse lung TB model

- AZD5847 and linezolid are equally effective versus rapidly dividing Mtu in mouse lung TB model
- But, AZD5847 has superior activity versus slowly dividing Mtu, that is key to achieving sputum sterilization.

Once daily oral dosing for 4 weeks

Effect in Mice Lung TB Model

Log_{10} CFU/lung

AUC_{0-24} uM.hr

Days post infection
Key Clinical Data: Phase 1

- The maximum dose administered was 1200mg PO q12h x 14 days
  - Maximum gmean daily AUC: 524.6 µM.hr (fAUC 104.9 µM.hr)
  - Maximum gmean Cmax: 31.8 µM (fCmax 6.4 µM)
- Bioavailability decreases with increasing dose, but largely compensated if taken after meals
Key Clinical Data

Exposures in Phase 1 correspond to efficacious level in the mouse model

Modelling of Ph1 Data for Likely Attainment of Preclinical PD Target

- Inter-subject PK variability and the MIC distribution for *M. tuberculosis* are taken into account
- Monte-Carlo simulation is used to calculate target attainment in ≥85% patients

800 mg qd / 400 mg q12 likely to give efficacy
Key Safety Data: **Mitochondrial Protein Synthesis** inhibition

- For linezolid, the linkage to myelotoxicity, lactic acidosis and neuropathy may be MPS inhibition$^{1,2,3}$
- At the approved dosage (600mg PO q12h), linezolid plasma levels are above the *in vitro* IC$_{50}$ for MPS during the entire dosing interval, which may explain its toxicity upon use >14 days$^4$
- AZD5847 offers an increased margin vs. in vitro MPS. Longer term studies will be required to determine the clinical significance of this observation.

**AZD5847: Phase 1 data**

Salient Features

Mechanism of action
• AZD5847 targets bacterial protein synthesis
• Bactericidal vs. clinical *M. tuberculosis* (Mtu) isolates (susceptible, MDR- and XDR-isolates)
• AZD5847 demonstrates activity vs. extracellular, intracellular, rapidly dividing and slowly dividing Mtu in mouse model of tuberculosis

PK/PD
• Efficacy in the mouse lung TB model is linked to AUC/MIC
• AZD5847 is not an inducer or inhibitor of major CYPs
• Human PK data show that food enhances bioavailability such that therapeutic exposure levels predicted from PK/PD modeling have been achieved.

Safety
• AZD5847 generally well tolerated over 14 days in healthy volunteers
• Reversible changes in WBC and reticulocyte counts seen at exposure > predicted therapeutic
• Improved *in vitro* margin vs. inhibition of mitochondrial protein synthesis for AZD5847 vs. linezolid
• Inhibits human Monoamine oxidase A *in vitro*
Phase 2a: (Supported by NIAID)

Study to be conducted in South Africa
Principal Investigators:
Andreas Diacon, Cape town, S. Africa; Henry Boom, Case Western Reserve, Cleveland, USA

Active pulmonary tuberculosis documented by positive sputum smear x 2
Inclusions/exclusions; HAINIE test to document sensitivity to rifampin and isoniazid; Baseline safety labs

Randomization
1. Treatment x 14 days
   Daily quantitative sputum culture
2. PK sampling days 1 and 10, trough levels an all other days
3. Safety labs on days 7 and 14
4. Initiation of SOC treatment for DS-pulmonary TB

Treatment groups with Diol
1. AZD5847 500mg qd
2. AZD5847 500mg bid
3. AZD5847 1200mg qd
4. AZD5847 800mg bid
5. Rifafour 1 tab PO qd

<table>
<thead>
<tr>
<th>AZD5847 Dosing regimens</th>
<th>Cmax range (µM)</th>
<th>Total Daily AUC range (µM.hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg, QD</td>
<td>9.5-11</td>
<td>131 -146</td>
</tr>
<tr>
<td>500 mg, BID</td>
<td>12-15</td>
<td>250 - 304</td>
</tr>
<tr>
<td>1200 mg, QD</td>
<td>17-21</td>
<td>228 - 288</td>
</tr>
<tr>
<td>800 mg, BID</td>
<td>17-21</td>
<td>352 - 430</td>
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</tbody>
</table>
Current Development Strategy for AZD5847

Next step: Phase 2a EEBA study via NIAID support
**Platform of evidence**
- Bactericidality, activity against resistant TB, and efficacy in mouse models of TB
- Effective against intra- and extracellular TB
- Confidence in oxazolidinone class as effective clinical anti-TB agents
- Predicted therapeutic range covered in GLP toxicology in rats and dogs

**Pre-clinical: AZ**
- Demonstrated from Phase1 Single and multiple (14 days) day dosing studies (max dose 1200mg PO q12h x 14 days) - tolerated exposures in healthy volunteers exceeded predicted efficacious exposures, as predicted by preclinical PD models
- Food (irrespective of type of food) enhanced bioavailability.

**Ph1: AZ**
- Ph2a planned with NIAID to demonstrate bactericidal activity of AZD5847, following 14-day monotherapy in DS TB patients. Bactericidal activity and acceptable tolerability profile will enable progression to Ph2b
- Adequate oral bioavailability in tablet (needs to be established)
- Ph2b objective (to be partnered): Objective -Superiority over placebo in combination with background regimen in MDR-TB patients.
  - Faster rate of sputum negativity achieved in MDR patients in the AZD5847 arm
  - Higher percentage of patients achieve sputum negativity in the AZD5847 arm

**Ph2a: NIAID Ph2b: seeking partners**
- Subpart H approval from FDA based on Ph2b outcome
- AZD5847 as part of novel combination(s) for achieving sputum sterilization and reduce duration of treatment in comparison to SOC.

**Ph3: seeking partners**

**Vision**
A safe, effective antituberculosis agent with options for novel combinations treating drug-sensitive and drug-resistant TB patients, including HIV co-infected patients, and offering a public health benefit from reduced infectivity.