Clofazimine in Clinical Trials for Tuberculosis

Resurrecting Clofazimine
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TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT
1. Background to Enthusiasm at the TB Alliance
   – Regimen studies in the mouse – more to come
2. Riminophenazine Backup Program
   – How can clofazimine be improved?
3. Recent and Ongoing Clinical Trials in Pulmonary Tuberculosis
Riminophenazine Class: Clofazimine

**Attributes:**
- Potent anaerobic and intracellular activity
- Efficacious against acute and chronic murine TB models
- Synergy effect in combo studies in mouse
- Low frequency of resistance development
- Novel MOA (ox. phos.) – active against M(X)DR-TB

**Challenges:**
1. CV liability
   - hERG IC50 <1 uM
   - Clinical QTc prolongation finding:
     - TMC207+CLF 32 ms (TMC207 alone 12.3 ms)*
2. PK and tissue distribution/accumulation
   - Human T\(_{1/2}\) > 10 days – high accumulation
   - Crystalline formation in tissue, intracellular precipitation
   - Intrinsic color (skin discoloration)
3. Limited “modern” safety/tox/DMPK data available

* Dannemann B. ICAAC 2012
# Clofazimine *In Vitro* Data

<table>
<thead>
<tr>
<th>Assay</th>
<th>Units</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous Solubility pH 1</td>
<td>ug/mL</td>
<td>5</td>
</tr>
<tr>
<td>Aqueous Solubility pH 6.8</td>
<td>ug/mL</td>
<td>&lt;1</td>
</tr>
<tr>
<td>pKa</td>
<td></td>
<td>8.4</td>
</tr>
<tr>
<td>logP (ClogP)</td>
<td></td>
<td>5.3 (7.7)</td>
</tr>
<tr>
<td>PPB, (H, M, D, R and Ms)</td>
<td>%</td>
<td>99.9 (99.9~99.96)</td>
</tr>
<tr>
<td>Caco-2 A-B</td>
<td>10^{-6} cm/s</td>
<td>NA (solubility)</td>
</tr>
<tr>
<td>Caco-2 B-A</td>
<td>10^{-6} cm/s</td>
<td>NA (solubility)</td>
</tr>
<tr>
<td>Microsomal Clint (H, D, R and Ms)</td>
<td>% remaining, 30 min</td>
<td>96, 39, 94, 95</td>
</tr>
<tr>
<td>CYP3A4 IC_{50} (TDI)</td>
<td>uM</td>
<td>&lt;0.5 (&lt;1)</td>
</tr>
<tr>
<td>CYP2D6 IC_{50}</td>
<td>uM</td>
<td>&gt;20</td>
</tr>
<tr>
<td>CYP2C19 IC_{50}</td>
<td>uM</td>
<td>&gt;10</td>
</tr>
<tr>
<td>CYP2C9 IC_{50}</td>
<td>uM</td>
<td>&gt;1</td>
</tr>
<tr>
<td>hERG IC_{50}</td>
<td>uM</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
Clofazimine – Potent Bactericidal and Sterilizing Activity in Murine Regimen Studies

• Data that support TB Alliance choice of regimens to evaluate will be presented by E. Nuermberger, JHU
Recent and Ongoing Clinical Trials of Note

• 2010 – Publication of Success with the “Bangladesh” Regimen in MDR TB  
  [Van Deun A. Am J Respir Crit Care Med 2010; 182:684-692]  
  – 88% “successful outcome” in non-randomized cohort of 206 patients that included clofazimine and gatifloxacin

• 2012 – Initiation of the STREAM Protocol  
  – Sponsored by the IUATLD; funded by DMID  
  – A RCT of the modified Bangladesh Regimen vs SOC

• 2012 – Initiation of TB Alliance NC-003 Trial  
  – See subsequent slides

• 2013 – Initiation of Janssen Phase 3 Trial of Bedaquiline  
  – RCT of Bedaquiline vs placebo on modified Bangladesh Regimen

• 2013 – Hope for a Thorough QT Trial of Clofazimine
Clinical Study NC-003

EBA Study with Clofazimine Alone and in Novel Regimens
NC-003 Key Development Objectives

• Establish the Early Bactericidal Activity (EBA) of 14 Days Monotherapy of:
  – Pyrazinamide
  – Clofazimine
• Further characterize the safety of clofazimine in a controlled setting
  – Investigator Brochure written by TB Alliance for clofazimine to summarize relevant information for investigators
• Evaluate the EBA of the J-C and J-Z Backbones
• Evaluate the EBA of 4 complete 3-4 drug regimens
  – J-Pa-C+/−Z contains 3 drugs with no pre-existing resistance
Third Novel Combo EBA: NC-003

Participants with newly diagnosed smear positive DS TB

Z
C
J-C-Z
J-Pa-C
J-Pa-Z
J-Pa-C-Z
Rifafour

14 daily doses

15 per group

Randomize

Serial 16 hour pooled sputum samples for CFU Count

Z=pyrazinamide, C=clofazimine, Pa = PA-824, J = TMC207

Primary Endpoint: $EBA_{CFU}(0-14)$ - the rate of change in logCFU per ml sputum
Clofazimine Regimen for NC-003

• Usual dose for treatment of patients with Leprosy is 100 mg/day given for months – years
• High doses of 300-400 mg/day, administered for months, reported in the literature
  – Generally tolerated, but rare reports of bowel obstruction/perforation
• For NC-003 aim is to have majority of 14 day period at exposure close to 100 mg/day when at steady state
• PK modeling suggests that 300 mg/day X 3 days, followed by 100 mg/day for 11 days will achieve close to steady state in first week
  – This regimen should be well tolerated
Predicted plasma exposure after multiple oral doses of clofazimine

- 100 mg daily dose: Cmax on day 1, 14 and 50 are 277, 756 and 1030 nM.
- 3x200 mg/day followed by 100 mg daily: Cmax on day 1 and day 14 are 555 and 826 nM.
- 3x300 mg/day followed by 100 mg daily: Cmax on day 1 and day 14 are 833 and 895 nM.
Clofazimine in Clinical Trials – Parting Thoughts

• Is clofazimine a viable drug to use in new regimen development programs?
  – For MDR patients?
  – For a shortened regimen for all patients w/TB sensitive to the regimen?

• Stay tuned for more information over 2013...