Status of TB Drug Pipeline: Clinical Development

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Open Forum 4
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# Current TB Therapy and Unmet Needs

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Current Therapy</th>
<th>Unmet Needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-Susceptible DS-TB</td>
<td>4 drugs; ≥6 month therapy (2RHZE + 4RH)</td>
<td>Shorter, simpler therapy</td>
</tr>
<tr>
<td>Drug-Resistant M(X)DR-TB</td>
<td>Few drugs (including injectables); ≥18 months; toxicities</td>
<td>Totally oral, shorter, more efficacious and safer therapy</td>
</tr>
<tr>
<td>TB/HIV Co-Infection</td>
<td>Drug-drug interactions (DDI) with ARVs</td>
<td>No or low DDI, co-administration with ARVs</td>
</tr>
<tr>
<td>Latent TB Infection</td>
<td>6-9 months H</td>
<td>Shorter, safer therapy</td>
</tr>
</tbody>
</table>

* Rifampin (R), Isoniazid (H), Pyrazinamide (Z), Ethambutol (E)

- Need shorter, simpler therapies against both DS and DR-TB
- To accomplish, will need to replace all or most current drugs
TB Drugs in Clinical Development

Sources: WGND & clintrials.gov
TB Drugs in Clinical Development

- gatifloxacin: TDR, Oflotub
- moxifloxacin: TB Alliance, UCL
- TMC207 - MDR: J&J/Tibotec, TB Alliance
- TMC207 - DS: TB Alliance, J&J/Tibotec
- OPC67683: Otsuka
- PA-824: TB Alliance
- rifapentine: s-a/CDC

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- **PA-824**: TB Alliance
- **rifapentine**: s-a/CDC
- **SQ109**: Sequella
- **PNU100480**: Pfizer
- **AZD5847**: Astra Zeneca

Sources: WGND & clintrials.gov

Phase I (3) | Phase II (4) | Phase III (2)
TB Drugs in Clinical Development

Sponsors:
- OFLOTUB Consortium
- IRD--C. Lienhardt coordinator
- LSHTM, MRC SA, KEMRI, NTPs Benin, Senegal, Guinea, European Commission, WHO/TDR, Inst. of Tropical Med (B)
- Lupin Pharma

Drug class:
- Fluoroquinolone

Most advanced Ph III program
1st trial ↓ RX to 4 mo; Follow-up=2 yrs
1 EP: % failure + relapse
Enrollment = 1,836
Completed
Data not yet available

Sites:
- Benin, Guinea, Kenya, Senegal, S. Africa

Sources: WGND & clintrials.gov
TB Drugs in Clinical Development

Sponsor: UCL & TB Alliance supported by EDCTP & Bayer

Drug class: Fluoroquinolone

REMox TB (Ph III)
Largest registration trial ever for TB
↓ RX to 4 months
2 experimental arms:
H◄M, E◄M
1 EP: %fail+relapse @ 12 months post Rx
Enrolled > 600
Target = 2,400

Sources: WGND & clintrials.gov
| Drug Name | Sponsor | Drug class | Study C208 (Ph II) | Results | Stage 2: OBR+TMC 400 mg qd (2wks) →200 mg 3X/wk (22wks) (n = 150 in stage 2) 2 yr. f/u; safety/PK + relapse 6-mo results from Stage 2 available soon  
|-----------|---------|------------|-------------------|---------|
| TMC207-MDR | J&J/Tibotec | Diarylquinoline | OBR+TMC 400 mg qd (2wks) →200 mg 3X/wk (6wks) (n = 47 completed Stage I)  
|          |         |            |                   | Culture conversion after 8 wks → 48 vs 8% (TMC+OBR vs pbo+OBR) |
| OPC67683   |         |            |                   |         |
| PA-824     |         |            |                   |         |
| rifapentine |         |            |                   |         |
| SQ109      |         |            |                   |         |
| PNU100480  |         |            |                   |         |
| AZD5847    |         |            |                   |         |

Sources: WGND & clintrials.gov

Ongoing (C209): Open label study with TMC + OBR N=225 pts; Rx duration=6 mo F/U: 19 mo on OBR
TB Drugs in Clinical Development

- **gatifloxacinc**
- **moxifloxacinc**
- **TMC207 - MDR**
- **TMC207-DS**
- **OPC67683**
- **PA-824**
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- **AZD5847**

**Sponsor:** TB Alliance

**Drug class:** diarylquinoline

**DDI study completed:**
Compared the effects of 2 CYP3A4 inducers R and P on plasma conc of TMC in healthy subjects

**Results:** both R and P cause ~50% reduction

**Phase II 14-day EBA study initiated:**
In patients with newly diagnosed, smear +, drug sensitive pulmonary TB
Given doses of TMC to achieve Cav (Days 2-14) of ~ 500, 1000, 1500 & 2000 ng/mL
Enrollment is completed
Data anticipated in 4Q 2010

A phase II 14-day combo EBA study is being planned

Sources: WGND & clintrials.gov
TB Drugs in Clinical Development

**Sponsor:** Otsuka

**Drug class:** Nitro-dihydro-imidazooxazole

Phase I SD & MD studies completed

Two EBA studies completed

**Ph II dose ranging study:**

430 MDR pts enrolled & Rxd for 8 wks with Pbo or OPC 100/200 mg BID + OBR

1 EP = Sputum conversion

Results not yet available

**Ongoing:**

Open-label dose escalation trial to assess The S/T/PK & Efficacy in MDR patients

250-400 mg BID + OBR

N=30

Recruiting in Latvia and Lithuania

Sources: WGND & clintrials.gov
**TB Drugs in Clinical Development**

**Sponsor:** TB Alliance

**Drug class:** Nitroimidazooxazine

Several Phase I studies completed

**Key results:**
- Well tolerated & PK c/w 1X/day or less freq dosing
- No significant food effect at anticipated clinical dose
- Not a significant inhibitor/inducer of CYP3A4

**Phase II:**
- Two 14-day EBA studies in patients with newly diagnosed, smear +, drug sensitive pulmonary TB
- First study showed equivalent efficacy of all doses (200, 600, 1000, 1200 mg/d) evaluated.
- Second study evaluated 50, 100, 150 & 200mg/d
- Preliminary data analysis revealed evidence of dose-dependent efficacy

A phase II 14-day combo EBA study is being planned

Sources: WGND & clintrials.gov
TB Drugs in Clinical Development

**Sponsor:** CDC & sanofi-aventis

**Drug class:** Rifamycin

**TBTC S29B:**
In healthy subjects:
Determine S/T of ↑ doses (5, 10, 15 & 20 m/kg/d) as well as effects on induction of metabolizing enzymes
N=36 (M+F)

**TBTC S29:**
RHZE vs PHZE in patients with pulmonary TB
Both R & P at 10m/kg/d
N=480 (M+F)
1 EP = culture conversion after 8 wks (40 doses)

**TBTC S26 (LTBI):**
Open label study comparing effectiveness of weekly P/H for 3 mos to daily H for 9 mos
In PPD high risk reactors with no active TB
N=8000 (M+F, > 2yr old)

Sources: WGND & clintrials.gov
TB Drugs in Clinical Development

**Sponsor:** Sequella supported by NIH

**Drug class:** Ethylenediamines

**Phase I:**
- Single ↑ dose study completed
  - N=62 (M+F)
  - Doses up to 300 mg well tolerated
  - 61 hr. half-life
- Multiple dose study completed
  - 75 and 150 mg for up to 14 days
  - N=30 (M +F)
  - Well tolerated and PK data indicated
  - Steady state was reached by day 7
- Based on the data, plan to evaluate 300mg/d for 14 days in healthy subjects

Sources: WGND & clintrials.gov
###TB Drugs in Clinical Development

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<th>Drug Class</th>
<th>Compared to LZD</th>
<th>Phase I</th>
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<tr>
<td>gatifloxacin</td>
<td>Pfizer</td>
<td>oxazolidinone</td>
<td>↓MIC50 and ↑MPS IC50</td>
<td>SD and MD studies completed</td>
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TB Drugs in Clinical Development

**Sponsor:** AstraZeneca

**Drug Class:** oxazolidinone

**Phase I:**
- Single dose study in healthy subjects completed
- Food effect also assessed
- Data not yet published

**Phase II:**
- Multiple dose study in healthy subjects enrolling
- Daily dosing up to 14 days
- N=60 (M+F)
- Next study likely to be a Phase II EBA study in patients with pulmonary TB

Sources: WGND & clintrials.gov
Summary

- Great need for new drugs to address the challenges and unmet needs in TB therapy
- Need for a stronger and more robust global TB drug pipeline
  - Resurgence in TB drug R&D
- Need a new approach to the clinical development of novel anti-TB drug regimens
  - Will be reviewed in the next session
Thank you