Status of the TB Drug Pipeline: Clinical Candidates

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Global Alliance for TB Drug Development

Open Forum III
Delhi, India
5-6 May 2008
Global TB Drug Portfolio: 7 clinical candidates

- gatifloxacin (Oflotub, TDR)
- moxifloxacin (Bayer, TB Alliance)
- TMC207 (J&J/Tibotec)
- OPC67683 (Otsuka)
- PA-824 (TB Alliance (Novartis))
- LL-3858 (Lupin)
- SQ109 (Sequella)

- Phase I
- Phase II
- Phase III
Gatifloxacin
Gatifloxacin

- Phase III, pivotal trial
- Open-label, randomized, controlled
- Non-inferiority design, comparing:
  - test: 2 months GHRZ / 2 months GHR
  - control: 2 months EHRZ / 4 months RH
- Sample size: 1035 patients/arm
- Follow-up: 2 years after completion of treatment
- Trial sites: Benin, Guinée, Kenya, Senegal, South Africa

G = gatifloxacin; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol
Primary End-points

**Efficacy:**
- Percent unfavourable outcome (bacteriological failures and relapses) at 24 months following the end of treatment

**Safety:**
- Percent adverse events in each arm
Gatifloxacin Phase III trial: status

- > 2/3 enrolled (FPI - June 2005)

- Due to reported early effect on glucose homeostasis with potentially severe hypo- or hyperglycemia:
  - Tightened exclusion criteria
  - Monitoring for dysglycemia
Partners involved in the gati project

The **OFLOTUB** Consortium:

- Hopital Ignace Deen, Conakry, Guinée
- Institute of Tropical Medicine, Belgium
- IRD, France: C. Lienhardt (Trial Coordinator)
- KEMRI, Kenya
- LSHTM, London, UK
- MRC, South Africa
- National TB Control programme, Benin
- National TB Control Programme, Senegal
- St George's Hospital Medical School, London, UK
- Hôpital de Garches, France

The European Commission

WHO/TDR

Lupin Pharmaceuticals Ltd, India
Moxifloxacin
### Overview of Clinical Development

**Plan: Initial Studies**

<table>
<thead>
<tr>
<th>Trial (sponsor)</th>
<th>Study Design</th>
<th>Countries</th>
<th>Total # subjects</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBTC #27 (CDC)</td>
<td>Moxi replaces Ethambutol (PII)</td>
<td>USA, Canada, Uganda, South Africa</td>
<td>336</td>
<td>Completed 6/05</td>
</tr>
<tr>
<td>JHU</td>
<td>Moxi replaces Ethambutol (PII)</td>
<td>Brazil</td>
<td>170</td>
<td>Completed 6/07</td>
</tr>
<tr>
<td>TBTC #28 (CDC)</td>
<td>Moxi replaces Isoniazid (PII)</td>
<td>USA, Canada, Uganda, South Africa, Brazil, Spain</td>
<td>433</td>
<td>Completed 5/07</td>
</tr>
<tr>
<td>REMox TB (UCL/MRC)</td>
<td>Moxi replaces Isoniazid (PIII)</td>
<td>Kenya, Tanzania, South Africa, Zambia (and….)</td>
<td>2400</td>
<td>FPI 1/08</td>
</tr>
<tr>
<td></td>
<td>Moxi replaces Ethambutol (PIII)</td>
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</table>
REMox TB Final Trial Design

Regimen 1

| HERZ + Mpbo | HR + Mpbo | HR |

Regimen 2

| MERZ + Hpbo | MR + Hpbo | Hpbo Rpbo |

Regimen 3

| MHRZ + Epbo | HR + M | Hpbo Rpbo |

Comparison 1
M subst for H (4 vs 6 mos.):
Non-inferior Failure/Relapse rate:

Comparison 2
M subst for E (4 vs 6 mos.):
Non-inferior Failure/Relapse rate:

Visits

Months

Screening | Intensive | Continuation |

Active Phase | Follow-Up
REMoxTB: Study Design

• Non-inferiority; randomized, double blind, controlled trial
• Primary endpoint: Treatment failure plus relapse within 12 months of rx end
• Assumptions
  – 80% culture negative at 2 months in control arm
  – 12% failure/relapse in control arm
  – 6% acceptable non-inferiority margin
  – 800 patients enrolled in each arm
  – 90% power, one tailed significance at the 1.25% level would require 727 evaluable patients/arm
REMoxTB: Study Design

Phase III Pivotal trial

- Intensive microbiology protocol
  - All laboratories are accredited locally and participate in international quality assurance schemes
- Study sites will be GCP/GLP compliant
- Looking to expand geographic representation for ultimate global registration
REMox Sites

• Current (enrolling)
  – Lusaka, Zambia
  – Cape Town, SA (2)
  – Durban, SA

• Site initiation prep. in progress/discussion
  – Moshi, Tanzania
  – Mbeya, Tanzania
  – Kampala, Uganda
  – Hong Kong
  – Vellore, India
  – Beijing, China
  – Tianjin, China
  – Kenya – on hold due to unrest

• Looking for total of 20-30 sites, minimum
Moxifloxacin

Future Plans: 2008-2011

- Global registration, if data supportive
  - Facilitate and oversee conduct of REmox TB pivotal trial
  - Build additional clinical trial capacity
  - Continue to meet with regulatory agencies
  - Initiate second Phase III trial if needed, and/or stand alone studies in HBCs as needed for global registration

- Consider high dose rifamycin/moxi development program at appropriate time
Laying the Groundwork

• Evaluation of moxifloxacin for TB indication
• Addressing AAA issues
  – Affordability commitment by industry partner
  – Already marketed drug
  – Manufacturing costs considered
• Testing and expanding clinical trial capacity
• Pursuing regulatory guidelines and harmonization
• Bringing together multiple parties to define global clinical development program
TMC-207
TMC207 - Phase I PK Findings

- Linear PK
- Positive food effect (2-fold increase in exposure)
- Metabolism by CYP3A4
- Administration of rifampin lowers TMC207 levels 50%
- Steady state levels not achieved by day 14
TMC207 - EBA

**1 week**
- TMC207 25mg
- TMC207 100mg
- TMC207 400mg
- Rifampin 600mg
- Isoniazid 300mg

**6 months**
- Standard treatment

**Daily sputum collection overnight**

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TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Open Forum 3
5-6 May 2008
TMC207 EBA Results

Day

Log Fail

0 1 2 3 4 5 6 7 8 9

TMC207 25MG
TMC207 100MG
TMC207 400MG
RIFAMPIN 600MG
ISONIAZID 300MG

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Open Forum 3
5-6 May 2008
TMC207 - Clinical Safety

- 189 subjects treated with TMC207 in all trials to date (except current trial C208)
- No serious adverse events related to TMC207
**TMC207: C208 MDR TRIAL**

- **Confirmed MDR**
- **Start BR + TMC207 or BR + placebo**
- **End TMC207, placebo**

- **1w R washout**
- **8 weeks Stage I n=50**
- **24 weeks Stage II n=150**

- **Double-blind phase**
- **BR alone**
- **2 y follow-up 18-24 month MDR-TB treatment total**
OPC-67683 - in Phase II
PA-824
# PA-824: Phase I Synopsis

<table>
<thead>
<tr>
<th>Study</th>
<th>CL-001</th>
<th>CL-002</th>
<th>CL-003</th>
<th>CL-004</th>
<th>CL-005</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Single-dose</td>
<td>Multi-dose</td>
<td>Fed-Fasted single dose</td>
<td>ADME</td>
<td>Renal Effects Study</td>
</tr>
<tr>
<td><strong>Doses</strong></td>
<td>50, 250, 500, 750, 1000, 1250, 1500 mg</td>
<td>200, 600, 1000, (1400) mg 7 days</td>
<td>1000 mg</td>
<td>[14C]- PA-824 OS</td>
<td>800, 1000 mg 8 days</td>
</tr>
<tr>
<td><strong>Population (N)</strong></td>
<td>Males only (53)</td>
<td>Males and females (24)</td>
<td>Males (9) and Females (7)</td>
<td>Males only (6)</td>
<td>Males and Females (46)</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>MDS Lincoln, NE</td>
<td>MDS Neptune, NJ</td>
<td>MDS Lincoln, NE</td>
<td>Covance, Madison, WI</td>
<td>DaVita, Minneapolis</td>
</tr>
<tr>
<td><strong>Main Results</strong></td>
<td>Well tolerated, no dose-limiting AEs or abnormal laboratory results Tmax 4-5 hrs. T ½ ~ 18 hrs.</td>
<td>1000 mg/d, moderate creatinine elevation: reversed during 7-day washout period. No consistent effect on BUN. 1400-mg cohort not enrolled Tmax 4-5 hrs. T ½ ~ 17 hrs.</td>
<td>t$_{1/2}$ = 19-20 in fed and fasted Tmax = 7 hr in fasted, 5 hr in fed state. Exposures higher in fed than fasted state.</td>
<td>91% of dose recovered in urine and feces ~65% urine ~26% feces Metabolite analysis in process Tmax 4.5 hrs. T ½ ~ 17 hrs.</td>
<td>Serum/plasma creatinine level ↑ (up to 30%) during treatment; levels declined during ensuing 7-day washout. No effect during treatment on GFR, ERPF, FF, BUN, UA</td>
</tr>
</tbody>
</table>
PA-824-CL-007: Phase IIa Extended EBA Study

- **Trial Design:**
  - two-center, partially double-blinded (PA-824 groups double-blinded as to dosage), randomized clinical trial.

- **Treatments:**
  - test: once daily doses of 200mg, 600mg, 1000mg and 1200mg for 14 consecutive days.
  - control: RHZE; Rifafour® e-275 (South African first-line TB treatment)

- **Patient Population:**
  - male and female - 4 groups of 15 participants receiving PA 824, 1 group of 8 participants - Rifafour® e-275
  - aged 18 and 64 years
  - newly diagnosed, uncomplicated, smear-positive, pulmonary TB.

- **Trial sites:**
  - Tiervlei CTU, Karl Bremer Hospital, Cape Town. Dr. A. Diacon
  - Lung Institute, University of Cape Town, Cape Town. Dr R. Dawson
CL-007: End-points

Efficacy outcomes

Primary:
- The extended EBA of PA-824 determined by the rate of change in logCFU over the period Day 0-14

Secondary:
- standard EBA of PA-824 determined by rate of change in logCFU in sputum over the period Day 0-2
- extended EBA of PA-824 determined by mean rate of change in logCFU in sputum for the periods Day 0-14 and Day 2-14
- change in time to sputum culture positivity (MGIT)
CL-007: End-points (cont’d)

Secondary outcomes:
Pharmacokinetics:
- Cmax,
- Tmax,
- AUC(0-t),
- AUC(0-inf),
- ratio of AUC(0-t) to AUC(0-inf) - AUCR,
- terminal elimination rate constant (Kel),
- apparent terminal elimination phase half-life (t½).

Safety:
- Severe adverse events and proportion of participants who discontinue due to an adverse event
## PA-824-CL-007 Study Timelines

<table>
<thead>
<tr>
<th>Event</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Patient Randomised</td>
<td>15-Aug-07</td>
</tr>
<tr>
<td>Last Patient Out</td>
<td>14-Dec-07</td>
</tr>
<tr>
<td>Database final lock</td>
<td>09-May-08</td>
</tr>
<tr>
<td>Final clinical study report released</td>
<td>10-Jun-08</td>
</tr>
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</table>
Regulatory Milestones Achieved

- **FDA Orphan Drug Designation**
  - granted July 5, 2007

- **EU Orphan Medicinal Product Designation**
  - granted October 17, 2007

- **FDA Fast Track Designation**
  - granted October 22, 2007
LL-3858
(Sudoterb)
LL-3858

• Pyrrole; novel mechanism of action
  – Equally potent in vitro against drug-sensitive and drug-resistant strains
• Single dose, dose escalation study completed to 1000 mg – well-tolerated
• Multiple dose, dose escalation study to at least 600 mg/day; well-tolerated
• Drug interaction study with HRZ; 1 case of jaundice at 400 mg
SQ-109
SQ-109

• 1,2-ethylene diamine; novel mechanism of action

• Completed Phase I, single dose, dose escalation study
  – doses up to 300 mg well-tolerated
  – $t_{1/2} = 61$ hr

• Plan:
  – Multiple dose, dose escalation study: mid ’08
  – Begin Phase II: end ‘08
Thank you
CL-005: Results Summary

- Consistent and reversible increase in plasma/serum creatinine.
- No significant effect on GFR or ERPF
- No effect on other indices of kidney function (BUN and serum uric acid)
- Mechanism for creatinine increase likely due to tubular secretion, not impairment of kidney function (i.e., not clinically significant or pathological)
- PK data similar to previous studies
TB Alliance Drug Portfolio

- **Moxifloxacin**
  - Screening: Bayer
  - Preclinical: Bayer

- **PA-824**
  - Screening: TB Alliance
  - Preclinical: TB Alliance

- **Quinolones**
  - Screening: KRICT/Yonsei
  - Preclinical: ACSRC/UIC

- **Nitroimidazoles**
  - Screening: GSK
  - Preclinical: GSK

- **Pleuromutilins**
  - Screening: GSK
  - Preclinical: GSK

- **MtB DNA Gyrase Inhibitors**
  - Screening: GSK
  - Preclinical: GSK

- **InhA Inhibitors**
  - Screening: GSK
  - Preclinical: IMM/BTTTRI

- **Multifunctional Molecules**
  - Screening: Cumbre/CSU
  - Preclinical: Cumbre/CSU

- **Riminophenazines**
  - Screening: IMM/BTTTRI
  - Preclinical: IMM/BTTTRI

- **Malate Synthase Inhibitors**
  - Screening: GSK/TAMU
  - Preclinical: GSK/TAMU

- **Phenotypic screening**
  - Screening: UIC
  - Preclinical: UIC

- **Energy Metabolism Inhibitors**
  - Screening: UPenn
  - Preclinical: UPenn

- **Protease Inhibitors**
  - Screening: IDRI
  - Preclinical: IDRI
REMox TB: Study Timeline

- Investigators’ Meeting: Nov 07
- First Patient In: Jan. 08
- Last Patient In: July 09 T
- Last Patient Out: Jan. 11 T

*Added ~ 6 months with increase from N=1500 to 2400*

NOTE: BfArM has requested 2 yr follow-up post-treatment (but data not required at time of filing); also requested QTc substudy