University of St. Andrews & University College London, UK

Radboud University Nijmegen Medical Centre, The Netherlands

University of Munich Medical Center, Germany

University College London, UK
Medical Research Council at UCL, UK
African PanACEA Partners:

- University of Zambia (UNZA)
- Medical School (UNZA)
- Albert Schweitzer Hospital Medical Research Unit
- Koninklijke Universiteit van Gent (KUG)
- Medical School (UNZA)
- Bagamoyo - Ifakara Health Research and Development Centre
- University of Witwatersrand (WITS)
- Medical School (UNZA)
- Mbarara Medical Research Programme (MMRP)
- Kibong’oto National Tuberculosis Hospital (KCMC)
- National Tuberculosis Unit (NTLP)
- Instituto de Medicina de Zárate (INS)
- Instituto National de Saute (INS)
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### The PanACEA portfolio

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase I + IIa</th>
<th>Phase IIb</th>
<th>Phase III, GATB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moxifloxacin</strong></td>
<td>Max. tolerated dose 20mg up to 40mg</td>
<td>2 months RIF&lt;sub&gt;20mg&lt;/sub&gt; 2 months RIF&lt;sub&gt;15mg&lt;/sub&gt; 3 months RIF&lt;sub&gt;35mg&lt;/sub&gt; 3 months RIF&lt;sub&gt;20mg&lt;/sub&gt; + moxifloxacin 3 months RIF&lt;sub&gt;20mg&lt;/sub&gt; + SQ109&lt;sub&gt;300mg&lt;/sub&gt; 3 months SQ109&lt;sub&gt;300mg&lt;/sub&gt;</td>
<td>4 months moxifloxacin for E or H (REMoX)</td>
</tr>
<tr>
<td><strong>Rifampicin</strong></td>
<td>Safety of 3 doses of SQ109 75, 150, 300mg DDI with RIF</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SQ109</strong></td>
<td>Safety of 3 doses of SQ109 75, 150, 300mg DDI with RIF</td>
<td>SAD &amp; MAD studies</td>
<td></td>
</tr>
<tr>
<td><strong>Q203 (Qurient)</strong></td>
<td>Completion of toxicology</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BTZ043 (HKI/DZIF)</strong></td>
<td><strong>BTZ043</strong> suzoloid, thioridazine high dose PZA faropenem, high dose moxifloxacin, timcodar</td>
<td><strong>High dose rifampin SQ109</strong></td>
<td><strong>moxifloxacin participate in GATB Phase III</strong></td>
</tr>
</tbody>
</table>
What is the right dose of rifampicin?

Martin Boeree, MD, PhD
Associate Professor
Radboud University Medical Centre
Nijmegen, the Netherlands

On behalf of the PanACEA consortium

Berlin, June 29, 2014
The game plan

• HR1
• HR2
• MAMS 1
• MAMS 2
• HR Phase III
HIGHRIF 1 (HR1) study design
HR1 study

- One control group with standard 10 mg/kg RIF (N=8)
- 4 consecutive arms of each 15 patients:
  - 20 mg RIF/kg
  - 25 mg RIF/kg
  - 30 mg RIF/kg
  - 35 mg RIF/kg
Grade 3 – Adverse Events

- Control: 0
- 20 mg/kg: 1 possibly related event (transient hyperkalemia)
- 25 mg/kg: 0
- 30 mg/kg: 1 unrelated event (pleural effusion)
  1 possibly related (LFT in week 2)
- 35 mg/kg: 1 possibly related (LFT in week 2)
• Few grade 3, no grade 4 and grade 5 events

• High dose rifampin is safe and tolerated in this study
CFU EBA 0-14 days

TTP EBA 0-14 days
Conclusions

• In this study RIF up to 35 mg/kg is safe and tolerated.

• There is a suggestion of an increasing decline on log10 CFU/ml and an increasing growth in TTP with dose, especially for 30 and 35 mg/kg.

• PK: “superproportional” increase in AUC and C_{max} (nonlinear PK) without ceiling.
# HIGHRIF 2 (HR2) study

<table>
<thead>
<tr>
<th>Title</th>
<th>Pharmacokinetics and pharmacodynamics of high versus standard dose rifampicin in patients with pulmonary tuberculosis in Tanzania.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Phase II, double blind, randomized, controlled, three arm,</td>
</tr>
<tr>
<td>Treatment</td>
<td>• Intensive phase : 2 mo RHZE (total RIF doses: 600, 900, 1200 mg) No weight bands.</td>
</tr>
</tbody>
</table>
| Parameters | • Safety and tolerability (biochemistry, haematology, AEs)  
• Pharmacokinetics (PK)  
• EBA, RNA in blood and sputum |
| # Patients | 150 (50 per arm) |
HR2 – study design

0 mg RIF + RHZE (600 mg RIF)

300 mg RIF + RHZE (900 mg RIF)

600 mg RIF + RHZE (1200 mg RIF)

Standard TB treatment (RIF + INH)

Day

0 1 2 3 4 5 6 7 8 12 14 15 18 21 22 28 29 35 36 42 43 49 56 57

Week

0 1 2 3 4 5 6 7 8 9 10 11 12 26

Intensive phase

Continuation phase
## Grade 3 AEs

<table>
<thead>
<tr>
<th>Grade 3 AEs</th>
<th>600 mg R</th>
<th>900 mg R</th>
<th>1200 mg R</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAT + ALAT INCREASED</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>COUGH</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>DENTAL CARIES</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>DYSPNEA</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>FEVER</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HICCUPS</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LYMPHOCYTE COUNT DECREased</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>ORAL PAIN</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PLATELET COUNT DECREASED</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>VOMITING</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>
SAEs

- Grade 3: equally distributed through all arms
- Grade 4: none
- Grade 5: 3 deaths, one in each dose group, all had severe advanced disease
Time to culture conversion on MGIT

Kaplan-Meier survival estimates

Number at risk
- dose = 600: 48, 47, 46, 39, 28, 22, 14, 8, 8, 8, 8
- dose = 900: 47, 46, 41, 31, 23, 19, 13, 7, 7, 7, 7
- dose = 1200: 47, 46, 40, 28, 18, 15, 12, 6, 6, 6, 6

Dose levels:
- Blue line: dose = 600
- Red line: dose = 900
- Green line: dose = 1200

Analysis time (in weeks):
- 0, 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154
Time to culture conversion on LJ

Kaplan-Meier survival estimates

Number at risk
- dose = 600: 39, 28, 23, 18, 11, 7, 4, 2, 2, 2, 2
- dose = 900: 38, 32, 21, 17, 12, 7, 5, 3, 3, 3, 3
- dose = 1200: 40, 32, 22, 15, 9, 6, 3, 1, 1, 1, 1

- blue line: dose = 600
- red line: dose = 900
- green line: dose = 1200
Modelling slopes of logCFU and logTTP over time

- Fractional polynomials in a mixed effects model.
- Negative cultures imputed with limited of detection (TTP=42 days; CFU=1)
  - Work ongoing to properly account for censoring for limit of detection
Fitted Log(TTP) over time
Fitted Log(CFU) over time
Conclusions: preliminary results

• Modest, non-significant reduction in time to culture conversion on both MGIT and LJ with increasing dose.
• Increase in slope of logTTP over time with increasing dose.
• Analysis work in progress.
**Median plasma concentrations per dose group**

![Graph showing median plasma concentrations per dose group](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose rifampicin (mg)</th>
<th>P-value (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>600</td>
<td>900</td>
</tr>
<tr>
<td><strong>AUC(_{0-24h} (h*mg/l))</strong></td>
<td>23.9 (9.14-118)</td>
<td>48.4 (18.9-101)</td>
</tr>
<tr>
<td><strong>C(_{\text{max}} (mg/l))</strong></td>
<td>5.32 (1.98-23.3)</td>
<td>9.27 (4.86-55.4)</td>
</tr>
<tr>
<td><strong>T(_{\text{max}} (h))</strong></td>
<td>4.0 (2.0-6.1)</td>
<td>4.0 (2.0-6.1)</td>
</tr>
<tr>
<td><strong>CL (l/h)</strong></td>
<td>25.1 (5.06-65.6)</td>
<td>18.6 (8.89-47.7)</td>
</tr>
<tr>
<td><strong>V(_d (l))</strong></td>
<td>69.0 (17.6-213)</td>
<td>69.5 (41.8-131)</td>
</tr>
<tr>
<td><strong>T(_{1/2} (h))</strong></td>
<td>1.91 (1.07-4.48)</td>
<td>2.59 (1.39-3.77)</td>
</tr>
<tr>
<td><strong>No. patients with C(_{\text{max}} &gt; 8.0 \text{mg/l} (%))</strong></td>
<td>5 (21.7)</td>
<td>14 (70.0)</td>
</tr>
</tbody>
</table>
Preliminary conclusions HR2

• Doses of 900 and 1200 mg of RIF combined with standard TB drugs for 2 months are safe and equally well tolerated as the standard dose RIF.

• PK shows again a nonlinear, superproportional increase in AUC and Cmax, though less outspoken as in HR1

• Efficacy: modest non-significant difference
And next….

• 40 mg/kg in HR1: follow up just finished

• MAMS
MAMS

- Multiple arm, multiple stage design
- Several combinations in phase II
- Several interim analyses
- “Poor” arms discontinue, “better” arms continue
- Phase III selection design
Hypothetical MAMS Design
Example for 6-arm TB Trial

Start of recruitment
1\textsuperscript{st} Interim
2\textsuperscript{nd} Interim
3\textsuperscript{rd} Interim
End of recruitment
### MAMS TB 01 in PanACEA

<table>
<thead>
<tr>
<th>Control: HRZE</th>
<th>isoniazid (H), rifampicin Std (R), pyrazinamide (Z), ethambutol (E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1: HRZQ</td>
<td>isoniazid (H), rifampicin 10 mg (R), pyrazinamide (Z), SQ109 300mg(Q)</td>
</tr>
<tr>
<td>Arm 2: HRZQ</td>
<td>isoniazid (H), rifampicin 20 mg (R), pyrazinamide (Z), SQ109 300mg (Q)</td>
</tr>
<tr>
<td>Arm 4: HRZM</td>
<td>isoniazid (H), rifampicin 20 mg (R), pyrazinamide (Z), moxifloxacin (M)</td>
</tr>
</tbody>
</table>

Each arm 64 patients, control 128 patients, total 384 patients
Endpoints

Primary Endpoint
Time to stable culture conversion to negative in liquid media:
*Time to the first of two negative weekly sputum cultures without an intervening positive culture in liquid media*

![Graph showing probability of sputum conversion over days on therapy (Control vs Moxi)](Rustomjee, Int J Tuberc Lung Dis 2008)
PanACEA MAMS TB 01

• Enrolment ended

• Follow up will end after summer

• First presentation of results anticipated CROI 2015
Acknowledgements

- Gibson Kibiki, Hadija Semvua, Charles Mthabo, Jossy van den Boogaard, Stellah Mpagama, KCRI, Moshi, Tanzania
- Klaus Reiter, Salim Abdullah, Ifakara HRDC, Bagamoyo, Tanzania
- Andreas Diacon, Jeannine Du Bois, Armour Venter, Stellenbosch University, RSA
- Rod Dawson, Kim Narunsky, University of Cape Town, RSA
- Sunita Rehal, Patrick Phillips, Andrew Nunn, MRC, London, UK
- Michael Hoelscher, Norbert Heinrich, Ludwig Maximilian University, Munich, Germany
- Stephen Gillespie, University of St Andrews, UK
- Tim Mc Hugh, University College of London

- Rob Aarnoutse, Georgette Plemper van Balen, Radboud University Nijmegen Medical Centre, the Netherlands
We are very grateful to the EDCTP for funding and facilitating this study