PanACEA SUDOCU trial: sutezolid as part of a 4-drug combination

PD Dr Norbert Heinrich
Unit head, TB drug and diagnostic trials

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On behalf of the PanACEA consortium
Sutezolid – better and safer than Linezolid?

- Sutezolid – an oxazolidinone drug candidate developed by Sequella and Global TB Alliance
- Previously evaluated up to phase 2A (14d monotherapy)
- Less mitochondrial toxicity predicted
- 7 sutezolid-treated subjects (14%) experienced mild or moderate increases in alanine transaminase (grade 1-2; Wallis, 2014)

MPS IC50:
- Sutezolid 15.5 µg/ml
- Major metabolite 4.4 µg/ml
- Minor metabolite 6.7 µg/ml
- Linezolid 5.5 µg/ml

Metabolism: CYP3A4, flavine monooxogenases

SUDOCU – sutezolid dose-finding and combination development

Objectives:
- Exposure – response modelling
- Exposure - toxicity modelling
- Select sutezolid dose with good safety and efficacy
- Assess CYP 3A4 enzyme induction potential

Primary Endpoint:
- Change in bacterial load as measured by MGIT TTP, over 12 weeks

Randomization
- STZ 0 mg QD – BDM – 15 Pat
- STZ 600 mg QD – BDM – 15 Pat
- STZ 1200 mg QD – BDM – 15 Pat
- STZ 600 mg BID – BDM – 15 Pat
- STZ 800 mg BID – BDM – 15 Pat

Continuation phase to complete 6 months treatment course in government programmes

Day 0
- STZ 600 mg QD – BDM – 15 Pat
- STZ 0 mg QD – BDM – 15 Pat

3 months
- STZ 800 mg BID – BDM – 15 Pat

6 months
- Continuation phase to complete 6 months treatment course in government programmes

STZ – sutezolid. BDM – bedaquiline, delamanid, moxifloxacin at standard doses.
Northern Partners:
- Radboud University (RUMC)
- University of Munich (LMU)
- University College London (UCL)
- Liverpool School of Tropical Medicine
- Swiss TPH
- UCSF
- Sequella, Inc
- Otsuka
<table>
<thead>
<tr>
<th></th>
<th>Arm 1: U0</th>
<th>Arm 2: U600</th>
<th>Arm 3: U1200</th>
<th>Arm 4: U600BD</th>
<th>Arm 5: U800BD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%) unless otherwise stated</td>
<td>16</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>15</td>
<td>75</td>
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<tr>
<td><strong>Total randomized</strong></td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Female</td>
<td>3 (18.8%)</td>
<td>4 (26.7%)</td>
<td>3 (21.4%)</td>
<td>5 (33.3%)</td>
<td>4 (26.7%)</td>
<td>19 (25.3%)</td>
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<tr>
<td>Male</td>
<td>13 (81.2%)</td>
<td>11 (73.3%)</td>
<td>11 (78.6%)</td>
<td>10 (66.7%)</td>
<td>11 (73.3%)</td>
<td>56 (74.7%)</td>
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<tr>
<td><strong>Age</strong></td>
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<tr>
<td>Median [Min, Max]</td>
<td>30.0 [20.0, 54.0]</td>
<td>33.0 [21.0, 48.0]</td>
<td>35.0 [22.0, 53.0]</td>
<td>36.0 [22.0, 58.0]</td>
<td>34.0 [22.0, 54.0]</td>
<td>33.0 [20.0, 58.0]</td>
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<tr>
<td><strong>Race</strong></td>
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<tr>
<td>Black</td>
<td>16 (100%)</td>
<td>15 (100%)</td>
<td>14 (100%)</td>
<td>15 (100%)</td>
<td>15 (100%)</td>
<td>75 (100%)</td>
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<tr>
<td>Other</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<td><strong>Ethnicity</strong></td>
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<tr>
<td>Hispanic or Latino</td>
<td>0 (0%)</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>16 (100%)</td>
<td>15 (100%)</td>
<td>14 (100%)</td>
<td>15 (100%)</td>
<td>15 (100%)</td>
<td>75 (100%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Median [Min, Max]</td>
<td>54.9 [45.0, 75.5]</td>
<td>50.0 [43.6, 65.0]</td>
<td>55.2 [47.0, 76.5]</td>
<td>54.8 [42.2, 75.0]</td>
<td>49.1 [42.5, 65.0]</td>
<td>53.0 [42.2, 76.5]</td>
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<tr>
<td><strong>HIV Status</strong></td>
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</tr>
<tr>
<td>Positive</td>
<td>1 (6.7%)</td>
<td>0</td>
<td>0</td>
<td>1 (11.1%)</td>
<td>0</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>Negative</td>
<td>14 (93.3%)</td>
<td>15 (100.0%)</td>
<td>14 (100.0%)</td>
<td>14 (93.3%)</td>
<td>15 (100.0%)</td>
<td>72 (97.3%)</td>
</tr>
</tbody>
</table>

*No HIV info for patient 103026
### Safety

- **NO neuropathy**
- 1 grade 4 neutropenia - 600BD (possible „benign ethnic neutropenia“)
- 1 grade 4 DILI - 600 BD
- 1 COVID-19 related death - 600 BD
- 4 events of QT prolongation >60ms (no prolongation >500ms absolute)

#### Table: Safety Summary

<table>
<thead>
<tr>
<th></th>
<th>Arm 1: U0</th>
<th>Arm 2: U600</th>
<th>Arm 3: U1200</th>
<th>Arm 4: U600 BD</th>
<th>Arm 5: U800 BD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total randomized</strong></td>
<td>16</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>15</td>
<td>75</td>
</tr>
<tr>
<td>Number of AEs reported</td>
<td>10</td>
<td>12</td>
<td>12</td>
<td>22</td>
<td>8</td>
<td>64</td>
</tr>
<tr>
<td>Number of Participants with AEs</td>
<td>6 (37.5%)</td>
<td>5 (33.3%)</td>
<td>7 (50%)</td>
<td>7 (46.7%)</td>
<td>4 (26.7%)</td>
<td>29 (38.67%)</td>
</tr>
<tr>
<td>Number of SAEs reported</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Number of Participants with SAEs</td>
<td>0</td>
<td>1 (6.67%)</td>
<td>1 (7.1%)</td>
<td>4 (26.7%)</td>
<td>1 (6.67%)</td>
<td>7 (9.3%)</td>
</tr>
<tr>
<td><strong>Number of AEs by Severity</strong></td>
<td>Arm 1: U0</td>
<td>Arm 2: U600</td>
<td>Arm 3: U1200</td>
<td>Arm 4: U600 BD</td>
<td>Arm 5: U800 BD</td>
<td>Total</td>
</tr>
<tr>
<td>Grade 1: Mild</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Grade 2: Moderate</td>
<td>3</td>
<td>7</td>
<td>5</td>
<td>9</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>Grade 3: Severe</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Grade 4: Life Threatening</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Grade 5: Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
QTcF intervals

Days of Treatment

Days of Treatment

QTcF intervals

Days of Treatment
AESIS: Hepatic safety - ALT (U/I)

preliminary – please don’t distribute
Hepatic safety: ALT (U/l) – Grade 4 Hepatotoxicity
## Pharmacokinetics

- Exposure metrics derived from population pharmacokinetic model

<table>
<thead>
<tr>
<th>Sutezolid dose</th>
<th>Median Sutezolid AUC0-24 (min-max) [mg/L*h]</th>
<th>Median Sutezolid Cmax (min-max) [mg/L]</th>
<th>Median Sutezolid-Sulfoxide AUC0-24 (min-max) [mg/L*h]</th>
<th>Median Sutezolid-Sulfoxide Cmax (min-max) [mg/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 mg QD</td>
<td>3.52 (1.56-6.85)</td>
<td>0.59 (0.19-1.27)</td>
<td>18.25 (12.98-24.21)</td>
<td>2.35 (1.36-3.01)</td>
</tr>
<tr>
<td>1200 mg QD</td>
<td>6.79 (3.35-9.91)</td>
<td>1.04 (0.59-1.42)</td>
<td>33.13 (23.21-47.61)</td>
<td>3.67 (2.76-5.87)</td>
</tr>
<tr>
<td>600 mg BD</td>
<td>8.29 (2.36-12.36)</td>
<td>0.84 (0.29-1.14)</td>
<td>35.00 (20.92-50.95)</td>
<td>3.04 (1.48-3.67)</td>
</tr>
<tr>
<td>800 mg BD</td>
<td>11.18 (4.42-20.04)</td>
<td>1.05 (0.39-1.71)</td>
<td>48.50 (27.11-82.01)</td>
<td>3.68 (1.62-5.60)</td>
</tr>
</tbody>
</table>
### Pharmacokinetics

- Exposure metrics derived from population pharmacokinetic model

<table>
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<td></td>
</tr>
<tr>
<td>1200 mg QD</td>
<td>6.79 (7.13)*</td>
<td>1.04 (1.97)*</td>
<td>33.13 (36.82)*</td>
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</tr>
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<tr>
<td>800 mg BD</td>
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</tbody>
</table>

Primary efficacy Endpoint: Median TTP (ITT population)
Primary efficacy Endpoint: Median TTP (ITT population)

!!MAMS trial: historical comparison from similar sites, similar patient population!!
Exposure-response modelling - methods

- Mixed-effects methodology
- TTP continuous variable censored at 25 or 42 days
- Bi-linear model with estimated node point at ~8 weeks
- Negative values included with model for probability of being above censoring limit
Exposure-response modelling

- Baseline bacterial load correlated with first slope \((p = 0.008)\)
- Ralph-score quantifying lung damage correlated with second slope \((p<0.001)\)
- Sutezolid AUC0-24h correlated with both slopes \((p=0.04)\)
- Approx 40% steeper slope for highest observed AUCs
Summary

Safety:
- Good safety of the combination +/- sutezolid
- 4 SAEs QTcF prolongation: due to 60ms cutoff; no measurements beyond 470 ms
- 1 case of grade 4 liver toxicity, 1 case of neutropenia

Efficacy:
- BDM backbone similar to HRZE in historical comparison;
- PK-PD: 40% steeper slope for highest observed sutezolid exposures
- Sutezolid added efficacy to BDM
- No plateau in exposure or efficacy seen in SUDOCU
Outlook: DECODE

Objectives:
• Exposure – response modelling
• Exposure - toxicity modelling
• Select delpazolid dose with good safety and efficacy


Sustained SCC by WK 08:
• no treatment – observe for relapse
SCC not sustained by WK 08:
• HR continuation treatment in NTP

Day 0
- DPZ 0 mg QD – BDM – 15 Pat
- DPZ 400 mg QD – BDM – 15 Pat
- DPZ 800 mg QD – BDM – 15 Pat
- DPZ 1200 mg QD – BDM – 15 Pat
- DPZ 800 mg BID – BDM – 15 Pat

4 months

12 months

LPI Sep 2022
Soft Database Lock imminent
Thank you for your attention!

Special thanks to:

- Study participants
- The PanACEA consortium, led by Martin Boeree/RUMC
- The PIs and their teams:
  - Christina Manyama, MMRC
  - Stellah Mpagama, KIIDH/KCRI
  - Francis Mhimbira, IHI
  - Modulakgotla Sebe, Aurum
  - Tim McHugh, Leticia Wildner, UCL
  - The LMU team – esp. Larissa Hoffmann
  - Sequella, Inc., Otsuka

Funding:

- EDCTP: European and Developing Countries Clinical Trials Partnership
- BMBF: German Government, DZIF: German Center for Infection Research