Tuberculosis in 2017: Searching for new solutions in the face of new challenges

6th TB Symposium – Ministry of Health of the Republic of Belarus, Republican Scientific and Practical Center for Pulmonology and Tuberculosis, and Médecins Sans Frontières

1-2 March, 2017, MINSK, BELARUS

Clinical update- landscape of new TB drugs

Cathy Hewison
Médecins Sans Frontières

MEDECINS SANS FRONTIERES
Overview

• What are we talking about
• What new drugs are on the horizon
• What new combinations are being tested
• What can we expect in the next 5-10 years
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What are we talking about

- Pre-clinical phases (trials on animals)
  - many steps *
  - difficult to be fund...often called THE DEATH VALLEY

- Clinical phases (human trials):
  - Phase I: healthy volunteers, safety, tolerability, pharmacokinetics.
  - Phase II: small numbers of sick patients, efficacy, more safety
  - Phase III: large numbers of patients, safety and efficacy

*ADME profile, GMP manufacture, API, toxicology, make the tablets, preparation of regulatory documents
### Global TB Drug Pipeline

#### Discovery

**Lead Optimization**
- Diaryquinolines
- DprE Inhibitors
- InhA Inhibitor, Ureas
- Macrolides, Azaindoles
- Mycobacterial Gyrase Inhibitors
- Pyrazamide Analogs
- Ruthenium(II) Complexes
- Spectinamides
- Translocase-1 Inhibitors, Clp, Mmp13, Oxazolidinones, Pyrimidines DprE1, Aryl Sulfonamides, PKS13, Squaramides

#### Preclinical Development

<table>
<thead>
<tr>
<th>Early Stage Development</th>
<th>GLP Tox.</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI-166</td>
<td>BTZ-043*</td>
<td>Q203*</td>
<td>Sutezolid (PNU-100480)</td>
<td>Rifapentine - Moxifloxacin for Drug Sensitive TB</td>
</tr>
<tr>
<td>CPZEN-45*</td>
<td>PBTZ-169*</td>
<td>PBTZ169*</td>
<td>Linezolid EBA</td>
<td>Delamanid (OPC-67683) with OBR for MDR-TB</td>
</tr>
<tr>
<td>1599*</td>
<td>TBA-7371*</td>
<td>OPC-167832*</td>
<td>High Dose Rifampicin for DS-TB</td>
<td></td>
</tr>
<tr>
<td>SATB-082*</td>
<td>GSK-070*</td>
<td></td>
<td></td>
<td>Pretomanid-Moxifloxacin-Pyrazinamide Regimen (STAND)</td>
</tr>
</tbody>
</table>

#### Clinical Development

- Bedaquiline (TMC207)-Pretomanid (PA-824) - Pyrazinamide Regimen
- Levofloxacin with OBR for MDR-TB
- Bedaquiline-STREAM MDR-TB Trial Stage 2 with oral OBR (9 mo) or OBR with injectables (6 mo)
- Bedaquiline-Linezolid with OBR for MDR-TB (NExT Trial)

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**Chemical classes:** fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diaryquinoline, benzothiazinone, imidazopyridine amide. New chemical class

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1 Details for projects listed can be found at [http://www.newtbdrugs.org/pipeline.php](http://www.newtbdrugs.org/pipeline.php) and ongoing projects without a lead compound series identified can be viewed at [http://www.newtbdrugs.org/pipeline-discovery.php](http://www.newtbdrugs.org/pipeline-discovery.php)

2 OBR = Optimized Background Regimen

[www.newtbdrugs.org](http://www.newtbdrugs.org)  
*Updated: October 2016*
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OPC-167832

3,4-carbostyril derivative

- Ostuka, announced union TB conference 2016
- DS and DRTB effective in mouse models
- Different mechanism of action than all currently approved TB drugs
- Otsuka working on a PAN-TB (DS and DRTB) combination with Dlm + other TB drugs

Where are we?

- Public-private partnership
- Fast track status from FDA
- Dosing study started October 2016

http://www.professionalabstracts.com/union2016/ipanner/#/grid
Sutezolid (PNU-100480)

Oxazolidinone

- Inhibit protein synthesis
- Like linezolid but early testing:
  - more potent in vitro and in the mouse
  - less toxic

Where are we?

- Early study results published in 2014, BUT NO FURTHER DEVELOPMENT
- Geneva, 25 January 2017 — Medicines Patent Pool signed a licence with Johns Hopkins University to facilitate the clinical development sutezolid
**SQ-109**

<table>
<thead>
<tr>
<th>Ethambutol analogue</th>
<th>Where are we?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocks cell wall synthesis AND prevents efflux of companion drugs from macrophages</td>
<td>phase 1 complete</td>
</tr>
<tr>
<td>10 times more active than Ethambutol in preclinical studies</td>
<td>Phase II (high dose R with H- or H-Z-Mfx): complete</td>
</tr>
<tr>
<td>Synergistic with H, R and Bdq and active against E resistant strains</td>
<td></td>
</tr>
</tbody>
</table>

**Where are we?**

- phase 1 complete
- Phase II (high dose R with H- or H-Z-Mfx): complete
**PBTZ169**

<table>
<thead>
<tr>
<th>Benzothiazinone</th>
<th>Where are we?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Active against DS and DRTB</td>
<td>• Phase I (Nearmedic, Russia)</td>
</tr>
<tr>
<td>• Synergy with Cfz and Bdq</td>
<td>– completed July 2016</td>
</tr>
<tr>
<td>• Compatible with other drugs</td>
<td>– safety, tolerability and pharmacokinetics up to 640 mg.</td>
</tr>
<tr>
<td></td>
<td>• Phase I (Innovative Medicines For Tuberculosis (iM4TB), Switzerland</td>
</tr>
<tr>
<td></td>
<td>– planned 2017</td>
</tr>
<tr>
<td></td>
<td>• Phase IIa planned toward end of 2016</td>
</tr>
</tbody>
</table>
Where do we stand with our drug candidate PBTZ 169?

we are here!

Transformation of molecule into soluble powder
ADME profile: drug behaviour in the body and what body does to drug
Formulation development: production of tablets
Regulatory documents filling/review
First human clinical trials

2014 pre-clinical phase 2016

ClinicalTrials.gov
A service of the U.S. National Institutes of Health
Try our beta test site

Phase 1 Study of PBTZ169

This study has been completed.
Sponsor:
Nearmedic Plus LLC
Collaborator:
OCT LLC
Information provided by (Responsible Party):
Nearmedic Plus LLC

Full Text View Tabular View No Study Results Posted
Q203

Imidazopyridine

• Developed by Qurient (Korea)
• Blocks growth of TB bacilli
• Targets respiratory cytochrome bc1 complex,

Where are we?

• Phase 1: Dose-Escalation Study to Evaluate Safety, Tolerability and Pharmacokinetics of Single Doses of Q203 in Normal, Healthy, Male and Female Volunteers

• Phase IB: Dose-Escalation Study to Evaluate Safety, Tolerability and Pharmacokinetics of Multiple Doses of Q203 in Normal Healthy Male and Female Volunteers
Drugs you already know...

<table>
<thead>
<tr>
<th>Nitroimidazoles</th>
<th>Diarylquinoline</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PA-824 (pretonamid)</td>
<td>• Bedaquiline (TMC207)</td>
</tr>
<tr>
<td>• Developed by Global TB alliance</td>
<td></td>
</tr>
<tr>
<td>• Under testing for DS and DRTB</td>
<td></td>
</tr>
<tr>
<td>• Delamanid (OPC-67683)</td>
<td></td>
</tr>
<tr>
<td>– Inhibits mycolic acid synthesis</td>
<td></td>
</tr>
<tr>
<td>– Phase III completed, results 2018</td>
<td></td>
</tr>
<tr>
<td>– Recommended by WHO from 6 years</td>
<td></td>
</tr>
<tr>
<td>old</td>
<td></td>
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</tbody>
</table>
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What new combinations are being tested

- [http://www.resisttb.org/?page_id=1602](http://www.resisttb.org/?page_id=1602)
Combinations of new drugs for MDRTB: BEDAQUILINE

<table>
<thead>
<tr>
<th>In the shortened regimen</th>
<th>• STREAM 2 (ongoing)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>9m:</strong> Km, Mfx, Cfz, E, Z, HdH, Pto</td>
<td></td>
</tr>
<tr>
<td><strong>9m:</strong> Lfx, Cfz, E, Z, HdH, Pto</td>
<td></td>
</tr>
<tr>
<td><strong>6 m:</strong> Km, Lfx, Cfz, Z, HdH</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No injectable (6-9 months)</th>
<th>• NeXT (enrolling)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lzd, LFx, Eto, HdH, Z</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pretonamid + Linezolid (XDRTB, 6-9 m)</th>
<th>• Nix ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• PRACTECAL (enrolling)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>With Pretonamid + Mfx + Z</th>
<th>• NC-005 (fully enrolled)</th>
</tr>
</thead>
</table>
# Combinations of new drugs for MDRTB: DELAMANID

<table>
<thead>
<tr>
<th>Bedaquiline and Delamanid</th>
<th>• DELIBERATE (open)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-drug interactions, QT</td>
<td></td>
</tr>
<tr>
<td>In children</td>
<td>• Otsuka: 233 &lt; 6 yrs (open)</td>
</tr>
<tr>
<td>In children with HIV</td>
<td>• Otsuka: 232</td>
</tr>
<tr>
<td></td>
<td>- 6-11 yr, 12-17 yr complete</td>
</tr>
<tr>
<td></td>
<td>- 3-5 yr open</td>
</tr>
<tr>
<td></td>
<td>- 0-2 yr to be decided</td>
</tr>
<tr>
<td>Lzd + Lfx + Z (9-12 m)</td>
<td>• MDR-end: enrolling Korea</td>
</tr>
</tbody>
</table>
Combinations of with repurposed or TB drugs: DR and DSTB

<table>
<thead>
<tr>
<th>MDRTB: Increased dose of Lfx</th>
<th>• Opti Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>H resistant TB: High dose H</td>
<td>• ACTG5312</td>
</tr>
<tr>
<td>MDRTB: molecular testing Z</td>
<td>• China PZA trial</td>
</tr>
<tr>
<td>DSTB: rifapentine +/- MFX to shorten DSTB treatment 4m</td>
<td>• TBTC study/A5349: enrolling</td>
</tr>
<tr>
<td>DSTB: higher dose rifampicin to shorten DSTB treatment</td>
<td>• PanACEA, HIRIF, ReDEFINe</td>
</tr>
</tbody>
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In the next 4-5 years...maybe...

- New MDRTB regimens: shorter, all oral, less adverse events (but requiring monitoring) and better than conventional treatments
- Some new drugs ready to be used under CU

=> get ready

  - Compassionate use a good tool for early use
  - Strengthen patient monitoring and aDSM now
  - Innovate on how to get the drugs to patients «patient orientated».... Drugs are not the only problem!!
Data sources and references

- https://clinicaltrials.gov
- http://www.resisttb.org/
- http://www.newtbdrugs.org/pipeline
- WHO global report 2016
- AIDS clinical rounds, UCSan Diego, Constance A. benson: New drugs and nevel approaches to treatment shortening in DS and DRTB