THE TB DRUG LANDSCAPE AND CHALLENGES

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PATIENT PATHWAY ANALYSIS INDICATES MULTIPLE OPPORTUNITIES FOR IMPROVEMENT

BMGF PORTFOLIO OF INTERVENTIONS FOCUSES ON KEY GAPS IN CARE CASCADE
## DEVELOPMENT OPTIONS IN TB

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Convenience/Duration</th>
<th>Lower Cost</th>
<th>Development Time</th>
<th>Risk of Resistance</th>
<th>Example</th>
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</thead>
<tbody>
<tr>
<td>Add-on to OBR (MDR)</td>
<td>√</td>
<td>X</td>
<td>X</td>
<td>√</td>
<td>√</td>
<td>X</td>
<td>BDQ, DLM</td>
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<tr>
<td>Substitution (MDR)</td>
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<td>?</td>
<td>?</td>
<td>?</td>
<td>√</td>
<td>X</td>
<td>STREAM 1</td>
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<td>Last Resort (XDR/ MDR)</td>
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<td>√</td>
<td>√</td>
<td>?</td>
<td>√</td>
<td>√</td>
<td>BDQ-Pa-L</td>
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<tr>
<td>Single Substitution (RS)</td>
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<td>?</td>
<td>√</td>
<td>?</td>
<td>X</td>
<td>√</td>
<td>ReMox</td>
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<tr>
<td>Unified (MDR/RS)</td>
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<td>√</td>
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<td>?</td>
<td>X</td>
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<td>tbd</td>
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</tbody>
</table>

=BMGF Focus
UNIFIED DEVELOPMENT PATH: RS AND RR TOGETHER

Testing Model

Mouse Model
- Single drug
- Combo in regimen
- Relapse-free sterilizing activity

Healthy Subjects
- Single drug
- Single and repeat dose
- Safety, tolerability
- PK
- DDI

Mono EBA
- Single drug
- Dose ranging
- RS patients only

Combo EBA
- Optimized dose regimen
- Test various regimens
- RS patients only

Regimen 2-Month Study
- RS and RR patients
- RS vs HRZE standard
- RR for consistency

Phase 3
- 4-6 month treatment
- RS vs HRZE for non-inferiority
- RR for consistency

Study Attributes

PK to support daily dosing
Clear effect to reduce CFU count
CFU Slope Better than HRZE standard
Culture Conversion Better Than HRZE
OPTIONS FOR ACCELERATING TB DRUG DEVELOPMENT

• Option 1: Combine MAD and EBA
  • Patients are used in Phase 1 in other therapeutic areas (oncology, virology)
  • Obtain safety data in population of interest

• Option 2: Link monotherapy and combination 14-day EBA
  • Evaluate additional contribution of combination to antibacterial activity
  • Obtain safety, DDI information on potential regimens
  • Prerequisites for evaluation of novel combinations
    • Diligence on potential for overlapping toxicities with recommendations for clinical monitoring
    • Consider need for preclinical toxicology studies on combinations

• Option 3: Combine Options 1 and 2

• Option 4: Adaptive Phase 2/3 designs
  • Assess antibiotic activity after 4-8 weeks of treatment to select most promising regimens
  • Requires treatment response biomarkers with faster turnaround time than current CFU assay
THE HUNT FOR A PAN-TB REGIMEN

• Shorter (<6 months)
• Simpler
  ▪ Initiate treatment upon diagnosis (no requirement for DST)
  ▪ All oral, once daily (long acting injectables may be considered)
  ▪ Fixed dose combinations where feasible
• Safer
  • No or very limited clinical or laboratory monitoring
  • No need for dose adjustments (enables development of FDCs)
  • Low DDI liability (esp with ARV and anti-diabetics)

At an affordable cost
Global New TB Drug Pipeline

Preclinical Development

Early Stage

- Caprazene nucleoside (CPZEN-45*)
- Cyclopeptide (SATB082*)
- Spectinamide 1810*
- Riminophenazine (TBI-166)
- Oxazolidinone (TBI-223)
- Gyrase Inhibitor (SPR-720 (pVXc-486*))
- Oxazole TB-47*

GLP Tox.

- BTZ-043*
- TBA-7371*
- GSK-070*
- TBAJ-587

Phase 1

- OPC-1678321
- PBTZ169*
- Q203*

Phase 2

- Delpazolid (LCB01-0371)
- SQ-109*
- Sutezolid (PNU-100480)

Phase 3

- Bedaquiline (TMC-207)
- Delamanid (OPC-67683)
- Pretomanid (PA-824)

Clinical Development

= BMGF-supported

New chemical class*  Known chemical classes are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide.

1 New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline/discovery

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CHALLENGES OF THE NEW TB DRUG LANDSCAPE

- The TB drug pipeline is increasing in number and diversity
  - Nitroimidazoles, diarylquinolones, oxazolidinones, Dpre1 inhibitors, MmpL3 inhibitors, Leucyl-tRNA synthesis inhibitor, cytochrome C oxireductase inhibitor
  - Need holistic approach to data from in vitro, in vivo and clinical studies to identify most promising regimens for late-stage evaluation
- Short duration studies (<2 months) may not reduce risk of failure for treatment-shortening regimens
  - Treatment response biomarker would revolutionize drug development and, potentially, indicate which patients have achieved cure with shorter regimens
    - Sputum and non-sputum assays
    - Imaging
    - Immune Response Marker
- Risk of drug resistance requires regimen development
  - Are preclinical combination safety toxicology studies helpful?
  - How best to identify the most promising combinations?
Over 10mm patients are waiting for better treatment.

Note: 11 countries include India, China, Indonesia, Nigeria, Pakistan, S Africa, Bangladesh, Myanmar, DRC, Mozambique, and Ethiopia.

Source: Global Tuberculosis Report 2016; WHO (2015); End TB Strategy (2016)