Approaches to TB Drug Development
An Industry Perspective

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Conflict of Interest Disclosure

- The presenter, Charles D. Wells, M.D., works for Sanofi.
Approaches to TB Drug Development

- Approaches taken from industry-based development programs:
  - 2005-2014, onward to future
- Regimens studied and why
- Trial design, endpoints and outcome definitions used
- Nuances of combination drug development, given background therapy (ex. MDR-TB)
- Challenges/barriers in development programs
- Moving through registration/application process
- Path forward
Industry Considerations - Background

- For industry, expediency – clock is ticking
  - Patent protection time-limited (development 10-12 yrs.)
  - Reason-to-believe – quick path to/through Proof of Concept (PoC)

- *M. tuberculosis* biology works against expediency
  - Previously with TB trials
    - 6 months (treatment) + 2 years follow-up; relapse as endpoint
    - Sensible from public health perspective; challenge for developers
  - Animal models and EBA (≤ 14 days) early tools, but with limitations
  - Sputum culture conversion (SCC) as surrogate marker
    - Earlier SCC clinically meaningful; important for public health
    - But when? 2 mo vs. later? – debate continues
    - Practical considerations – slow, contamination, capacity
## Target Product Profile: New TB Drug/Regimen Development Pathway to Target Label

### Description of the Mechanism of Action
- Novel mechanism of action active against current resistant strains
- No cross resistance between drugs in the regimen
- Active on resistant strains to all available treatment

### Indications & Target population
- Patients with active tuberculosis irrespective of HIV status:
  - Minimum case  ➔  1\textsuperscript{st} line treatment for active M(X)DR TB\(^\dagger\)
  - Base case  ➔  1\textsuperscript{st} line treatment of DS-TB\(^\ddagger\), M(X)DR TB

### Dosage and administration
- Oral fixed dose combination tablet; once daily

### Efficacy
- M(X)DR-TB: Superior to SoC / optimized background regimen (OBR)
- DS-TB: Non-inferior to SoC with shortened treatment duration (<< 6 months)

### Safety
- Safer than SoC/OBR
- Limited QT prolongation

\(^\dagger\)M(X)DR-TB – Multidrug/Extensively Drug Resistant Tuberculosis
\(^\ddagger\)DS-TB – Drug Susceptible Tuberculosis
Development Strategies for New TB Agents/Regimens

Target Patient Population

- **M(X)DR-TB**
  - Unmet medical need - better efficacy & shorter/easier/safer regimens
  - Superiority design (Sacks LV, Behrman RE. Tuberculosis, 2008):
    - “..exploring efficacy…in setting of drug resistant disease may present certain opportunity”
    - “..possibility of accelerated approval based on a surrogate endpoint”
  - Confers efficiency, but field steadily changing….

- **DS-TB**
  - RIPE highly efficacious
  - Shortening treatment (profoundly) as essential goal
  - Non-inferiority design
Development of New Tuberculosis Agents Setting Stage for M(X)DR-TB as Pathway, Pre-2005

- Green Light Committee (GLC)† /Global Fund launch and expansion, for M(X)DR-TB, 1999-2005:
  - Limited access to treatment
    - Cumulative total: ≤ 20,000 patients worldwide
  - Limited diagnostic/DST capacity
  - Large reservoir of “chronic” patients (previous 2nd-line treatment)
  - Weaker 2nd-line drugs – early gen. fluoroquinolones, etc.
  - 24 months for treatment with high toxicity
  - Lack of experience with clinical trials/GCP

- Best programs in early years‡:
  - 2-month SCC = 30%
  - Cure: ≤ 65%; mortality: 10%-20%

Time to SCC vs. Treatment History in MDR-TB Patients, Latvia, 2000† - Previous 2nd-line Treatment with Lower/Later SCC

* log-rank test of the equality of the 3 survival curves

P value <0.001*  N=167

M(X)DR-TB as initial target for Bedaquiline and Delamanid

- GLC sites as network and labs/liquid media;¹⁻³
- Stringent definitions for SCC/outcomes from WHO
- SCC as endpoint from FDA & EMA (2009/2010); accelerated pathway
- Design: optimized background regimen (OBR) + test agent vs. OBR
  - Bedaquiline (N=160): 6-mos. SCC: 79% vs. 58%⁴
  - Delamanid (N=481): 2-mos. SCC: 45% vs. 30%⁵
- Limited datasets → restricted label/patient population

Drug-drug interaction and treatment optimization trials of new agents have followed⁶,⁷

However, field is steadily transforming…..

⁷ NCT02754765 Evaluating Newly Approved Drugs for Multidrug-resistant TB (endTB)
Field for M(X)DR-TB – Progressive Improvements

- Expanding treatment capacity – GLC/Global Fund
  - >100,000 M(X)DR-TB patients treated annually
  - Decreased population of chronic patients

- Better diagnosis – from months to days - huge impact!

- Better drugs/access
  - Existing: Moxifloxacin, Linezolid, Clofazamine
  - New: Bedaquiline, Delamanid

- Shorter regimens among patients without previous 2nd-line treatment†
  - Bangladesh, 9-month regimen; N=206, Cure: 88%

- Greatly improved treatment success…
  - WHO reports overall‡: 52%
  - Mature MDR-TB treatment programs: ≥ 80%±; XDR-TB: ≥ 60%

†Van Deun A, et al. Am J Respir Crit Care Med 2010
M(X)DR-TB Outcomes from PETTS, 2005-2008†‡

- † PETTS – Preserving Effective TB Treatment Study
- Multinational prospective cohort study - N=1244 patients; 9 countries/26 sites
- Treatment: 5-drug intensive phase (6-8 mos.); total 20-24 mos.

### Patients With Known Treatment Outcomes (n = 973)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Successful Outcome, No. (%)</th>
<th>Poor Outcome, No. (%)</th>
<th>P Value</th>
<th>Risk Ratio (95% CI) for Treatment Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLC approval</td>
<td>503 (82.9)</td>
<td>104 (17.1)</td>
<td>&lt;.001</td>
<td>1.39 (1.27–1.52)</td>
</tr>
<tr>
<td>No‡</td>
<td>219 (59.8)</td>
<td>147 (40.2)</td>
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<tr>
<td>No. of SLDs tested in local laboratory</td>
<td></td>
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<tr>
<td>0–2</td>
<td>288 (65.7)</td>
<td>150 (34.2)</td>
<td>&lt;.001</td>
<td>Reference</td>
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<tr>
<td>3</td>
<td>281 (79.1)</td>
<td>74 (20.8)</td>
<td>&lt;.001</td>
<td>1.20 (1.10–1.31)</td>
</tr>
<tr>
<td>4–7</td>
<td>153 (85.0)</td>
<td>27 (15.0)</td>
<td>&lt;.001</td>
<td>1.29 (1.18–1.42)</td>
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<tr>
<td>Previous treatment history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>111 (82.8)</td>
<td>23 (17.2)</td>
<td>.002‡</td>
<td>Reference</td>
</tr>
<tr>
<td>First-line drugs</td>
<td>525 (74.1)</td>
<td>184 (26.0)</td>
<td>.03</td>
<td>0.89 (.82–.98)</td>
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<tr>
<td>SLDs</td>
<td>86 (66.2)</td>
<td>44 (33.9)</td>
<td>.002</td>
<td>0.80 (.69–.93)</td>
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</tbody>
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Improvement in M(X)DR-TB Treatment Outcomes, Republic of Korea, 1996 - 2010†

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>(n = 86)</td>
<td>(n = 125)</td>
<td>(n = 123)</td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>46 (53.5)</td>
<td>86 (68.8)</td>
<td>103 (83.7)</td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>43 (50.0)</td>
<td>64 (51.2)</td>
<td>92 (74.8)</td>
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<tr>
<td>Completed</td>
<td>3 (3.5)</td>
<td>22 (17.6)</td>
<td>11 (8.9)</td>
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<tr>
<td>Unfavourable outcomes</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>40 (46.5)</td>
<td>39 (31.2)</td>
<td>20 (16.3)</td>
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<tr>
<td>Failure</td>
<td>24 (27.9)</td>
<td>16 (12.8)</td>
<td>7 (5.8)</td>
<td></td>
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<tr>
<td>Relapse</td>
<td>3 (3.5)</td>
<td>3 (2.4)</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>9 (10.5)</td>
<td>10 (8.0)</td>
<td>5 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Default</td>
<td>4 (4.6)</td>
<td>10 (8.0)</td>
<td>6 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Relapse rate (cases per 1000 person-years)</td>
<td>10.9</td>
<td>6.9</td>
<td>8.2</td>
<td>0.174</td>
</tr>
</tbody>
</table>

- Improved outcomes with more frequent use of later generation FQs and linezolid
- Linezolid for those refractory to 3-6 months Rx and/or XDR-TB (21%), 2006-2010

Improving SCC/Outcomes for XDR-TB, 2005-2014

Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis†

<table>
<thead>
<tr>
<th></th>
<th>Immediate Start (n=19)</th>
<th>Delayed Start (n=20)</th>
<th>Overall Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sputum Culture Conversion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-month</td>
<td>15/19 (79%)</td>
<td>7/20 (35%)</td>
<td>34/39 (87%)</td>
</tr>
<tr>
<td>6-month</td>
<td></td>
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<td></td>
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<tr>
<td><strong>Treatment Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td></td>
<td></td>
<td>27/38 (71%)</td>
</tr>
<tr>
<td>Lost to f/u</td>
<td></td>
<td></td>
<td>3/38 (8%)</td>
</tr>
<tr>
<td>Failure</td>
<td>4/38 (11%)</td>
<td>4/38 (10%)</td>
<td></td>
</tr>
<tr>
<td>Withdrew</td>
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Immediate Start (n=19) vs. Delayed Start (n=20)

- XDR vs. MDR (Individualized treatment)
  - XDR: 37 cases, 18 (49%) cured, 8 (22%) death
  - MDR: 494 cases, 372 (75%) cured, 39 (8%) death

- XDR vs. MDR (Individualized treatment + 2nd-line DST)
  - XDR: 14 cases, 11 (78%) cured, 1 (7%) death
  - MDR: 334 cases, 264 (79%) cured, 26 (8%) death

Management of Extensively Drug-Resistant Tuberculosis‡ in Peru: Cure Is Possible

Delamanid for Extensively Drug-Resistant Tuberculosis ±

- 2-month SCC
  - DLM+OBR: 7/16 (44%)
  - OBR: 1/10 (10%)

Mortality at 24 months
- ≥ 6 mos. DLM – 0/17 (0%)
- ≤ 2 mos. DLM – 2/9 (22%)

Advances in non-clinical realm to improve translational accuracy for selection/development of new regimens†

- Models – “Of Mice (Kramnik), Marmosets and Men” + hollow fiber infection
- Better details on drug synergy/antagonism, cross resistance, differential and complementary PK, etc.

Patient population – given better diagnosis, new agents and evolving standards

- Pre-XDR/XDR-TB – superiority, but which comparator(s) – regimens with linezolid, bedaquiline, delamanid +/- clofazamine?
- MDR-TB – shortened (9-month) regimen if no resistance to fluoroquinolones/injectables
- DS-TB – non-inferiority trials with RIPE as comparator - treatment shortening

Culture-based endpoints remain obstacle – limitations/inefficiencies

- Slow results - solid medium, 4-6 weeks; MGIT, 42 days
- Quantitative cultures
  - Most reliable method to determine bacillus number
  - High workload → serial dilutions, limited labs with capacity
- Liquid medium – MGIT Time to Detection (TTD) – semi-quantitative
  - Correlation between agar CFU/TTD changes during treatment†‡
  - Likely reflecting recovery of TB bacilli from exposure to TB drugs during treatment

EBA (14-day) – proof of activity; but with limitations

- Some drugs, limited EBA (PZA, LZD) – but robust treatment effect

Early SCC for M(X)DR-TB – easier to achieve with new agents…

Combination rules for TB regimen development

- Demonstrating contribution of each drug in combination to extent possible (not sufficiently from existing data)
- Requires regimen EBA +/- regimen SCC studies – factorial design
- Time and resource intensive – more limited # of regimens evaluated

Better tools for measuring treatment effect/endpoints

- PET/CT imaging: early quantitative measure of anti-TB drug efficacy
  - Sputum Lipoarabinomannan (LAM)
    - Quantitative (vs. MGIT/TTD)
    - Potential pharmacodynamic biomarker
    - Immunoassay to measure concentration with “real time” read going through qualification process for drug development tool

1. Guidance for Industry – Codevelopment of Two or More investigational Drugs for use in Combination; US DHSS FDA CDER 2013;
4. ClinicalTrials.gov: NCT02371681; NextGen EBA;
Pathway Forward – New Agent/Regimen Development (3)
Trial Design Options

● Conventional design (up to 10 years)
  ▪ SAD/MAD + PoC (EBA of combinations + 2-month combinations)
  ▪ Phase 3 with fixed/balanced randomization

● Adaptive trial designs → greater efficiency
  ▪ Bayesian (vs. balanced) adaptive design (i.e. endTB).
  ▪ Multi-arm multi-stage (MAMS) design (i.e. PANACEA)
  ▪ Both use information (i.e. SCC) to ‘adapt’ trial
    – Bayesian adaptive more efficient if >1 effective regimen
    – MAMS more efficient if only 1 effective regimen

● Key choice for strategy, thresholds, reliance on markers (LAM, EBA):
  ▪ Relaxing standards → high % of candidates go through; false +’s
  ▪ Calibrate screening → no false +’s; exclude viable treatments
Bayesian Response-Adaptive Trial in MDR-TB: endTB Trial†

• Phase 3 non-inferiority trial of MDR-TB treatment using Bayesian adaptive randomization to examine 5 new shorter experimental regimens:‡

<table>
<thead>
<tr>
<th>#</th>
<th>Bdq</th>
<th>Dlm</th>
<th>Cfz</th>
<th>Lzd</th>
<th>FQ</th>
<th>Z</th>
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<tbody>
<tr>
<td>1</td>
<td>Bdq</td>
<td></td>
<td></td>
<td>Lzd</td>
<td>Mfx</td>
<td>Z</td>
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<tr>
<td>2</td>
<td>Bdq</td>
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<td>Lzd</td>
<td>Lfx</td>
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<td>3</td>
<td></td>
<td>Dlm</td>
<td></td>
<td>Lzd</td>
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<td>4</td>
<td></td>
<td>Dlm</td>
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<td>Cfz</td>
<td>Lzd</td>
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<td>Z</td>
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</table>

Table 1. Six regimens proposed for testing in endTB trial.

Bdq: bedaquiline; Dlm: delamanid; Cfz: clofazimine; Lzd: linezolid; FQ: fluoroquinolone; Mfx: moxifloxacin; Lfx: levofloxacin; Z: pyrazinamide.

• Reduced trial size (< 1,000 pts.) and duration with multiple superior regimens potentially identified; from simulation:
  • 27% fewer than balanced randomization
  • 80% power to detect up to 2 novel regimens non-inferior (margin 12%) to control (70% efficacy) at 73 weeks post randomization.
  • Up to 25% more participants would receive non-inferior regimens.

†ClinicalTrials.gov Identifier: NCT02754765 Evaluating Newly Approved Drugs for Multidrug-resistant TB.
Envisioned Impact of Adaptive Trial Design + “Real Time” LAM: Potentially Shortens Development Time by 2-3 Years†

- Phase 1: SAD/DDI; MAD to include target population (EBA)
- Seamless Phase 2/3 trial with adaptive design of combinations

Broader Considerations in Moving Forward To Registration

- Early engagement of authorities – seek critical feedback on design of programs/trials in face of steadily evolving field and pay attention!
  - Patient population, comparator arm, endpoints, follow-up
  - Trial design - special protocol assessments
  - Combination rules† – in vivo models + EBA for individual agents sufficient?

- Regulatory Harmonization across authorities – essential to making new treatments available to broader swath of patients, sooner
  - EMA, PMDA, and FDA met in Vienna in April 2017; agreement to align certain data requirements to stimulate development to fight antimicrobial resistance (AMR) and protect global public health.

- TB is “priority pathogen” in fight against AMR
  - Push/pull mechanisms to encourage and support new TB drug/regimen development are crucial

†Guidance for Industry – Codevelopment of Two or More investigational Drugs for use in Combination; US DHSS FDA CDER 2013
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