MDR-TB Clinical Trials Landscape
Overview: Current and Future Trials

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Outline

• New and repurposed drugs for MDR-TB treatment
• Ongoing Phase 2 MDR-TB trials
• Treatment regimens currently in Phase 3 trials
• MDR-TB Trials of the future
2018 Global New TB Drug Pipeline

Preclinical Development

- Early Stage
  - Caprazene nucleoside CPZEN-45
  - Spectinamide 1810
  - Gyrase inhibitor SPR-720 (pVXc-486)
  - Pyrazolopyridine carboxamide TB-47
  - Fluoroquinolone DC-159a

  GMP/GLP Tox.

  - BTZ-043
  - TBAJ-587
  - TBI-223
  - GSK-286

Clinical Development

- Phase 1
  - TBI-166
  - Macozinone (PBTZ-169)
  - Q203
  - GSK-656 (070)
  - TBA-7371

- Phase 2
  - Delpazolid (LCB01-0371)
  - Sutezolid (PNU100480)
  - SQ-109

- Phase 3
  - Bedaquiline* (TMC-207)
  - Delamanid* (OPC-67683)
  - Pretomanid* (PA-824)

Contezolid (MRX-4/MRX-1)

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

* 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

Updated: March 2018

Working group on new TB drugs
www.newtbdrugs.org
Phase 2 Trials to optimize dosing and Minimize DDI and Adverse Effects

- ACTG 5312: High dose INH for inhA mutations (2019)
- ACTG 5343: BDQ and DLM QT interactions (2019)
- Janssen C211 Study: Pediatric PK of BDQ (2019)*
- Otsuka 233: Pediatric 6-month open label DLM (2020)
- ZeNiX: Optimization of linezolid dosing (2020)
- ACTG 5356: Optimization of linezolid dosing (2021)*
- IMPAACT P1108 Trial: Pediatric PK of BDQ (2020)*

*not yet started        *partial results being presented at Union Meeting
Phase 3 Clinical Trials for MDR-TB
Trials to replace injectable

- NEXT Trial – Phase 3 (2019)
- MDR-END Trial—Phase 2/3 (2021)
- STREAM Stage 2 Trial—Phase 3 (2021)
- endTB Trial – Phase 3 (2022)
NeXT Trial (Phase 3)

- Description: 6-9 month trial of bedaquiline in combination with other oral agents (duration dependent on culture conversion)
- Regimens: BDQ+LZD+LFX+ETA/INHH+PZA (6-9 Mo)
  MXF+ETH+TER+KM+PZA (21-24 Mo)
- Sponsors: MCC
- Target population: MDR-TB, adults
- Outcome: “favorable outcome” at 24 months
- Size: 300 patients; 108 enrolled (on hold)
- Sites: South Africa
- Expected results: 2019
MDR-END Trial (Phase 2/3)

- Description: Injectable-free DLM-based regimen vs SOC
- Regimens:
  - SOC (WHO 20-24 months)
  - DLM+LZD+LFX+PZA for 9-12 months
- Sponsor: Korean government
- Target population: smear+ MDR-TB, adults 18+
- Outcome: Failure, relapse, default or death
- Size: 204 Patients; 75% enrolled
- Sites: Korea
- Expected results: 2021
STREAM Trial, Stage 2 (Phase 3)

- Description: Addition of two new arms to STREAM
- Regimens:
  - SOC (continues both WHO and Bangladesh)
  - BDQ+CFZ+EMB+LFX+PZA+4(INH$_H$+PTO) – 9 mos
- Sponsor: USAID, others
- Target population: smear+ MDR-TB, adults
- Outcome: Failure, relapse, default or death
- Size: 550 patients; 330 enrolled
- Sites: Ethiopia, Vietnam, South Africa, Mongolia
- Expected results: 2021
endTB Trial (Phase 3)

- Description: Combination regimens, adaptive randomization
- Regimens: WHO SOC (20-24 months)
  - BDQ+LZD+MXF+PZA for 9 months
  - BDQ+CF+LZD+LFX+PZA for 9 months
  - BDQ+DEL+LZD+LFX+PZA for 9 months
  - DEL+CF+LZD+LFX+PZA for 9 months
  - DEL+CF+MFX+PZA for 9 months
- Sponsor: MSF/UNITAID
- Target population: smear+ MDR-TB, adults 15+
- Outcome: Failure, relapse, default or death
- Size: 750 patients; 159 enrolled
- Sites: India, Pakistan, Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
- Expected results: 2022
Trials to shorten duration

- NiX-TB Trial (2018)
- TB-PRACTECAL Trial (2022)
- SimpliciTB (2022)
NiX-TB (Phase 2/3)

- Description: 6 month trial of Pretomanid in combination with Bedaquiline and Linezolid
- Regimen: BDQ+PTM+LZD (Single Arm)
- Sponsor: GATB
- Target population: XDR-TB, adults
- Outcome: relapse-free cure
- Size: 100 patients; completed November 2017
- Sites: South Africa
- Expected results: This Thursday, OA03-213-25, 14:00 in KWA Plenary Hall
TB-PRACTECAL Trial (Phase 2/3)

- Description: Staged trial of BDQ/PTM/LZD regimens:
  - SOC (WHO 20-24 month regimen)
  - BDQ+PTM+LZD+MFX for 6 months
  - BDQ+PTM+LZD+CF for 6 months
  - BDQ+PTM+LZD for 6 months
- Sponsor: MSF
- Target population: smear/Xpert+ MDR-TB, adults 18+
- Outcome: Failure, relapse, default or death
- Size: 630 Patients; 115 enrolled
- Sites: Uzbekistan, Swaziland, Belarus
- Expected results: 2022
SimpliciTB Trial (Phase 3)

- Description: Staged trial of BDQ/PTM/LZD regimens:
  - BDQ+PTM+MFX+PZA for 4 months (DS)
  - BDQ+PTM+MFX+PZA for 6 months (MDR)
  - HRZE for 6 months
- Sponsor: GATB
- Target population: DS (randomized) and MDR (not randomized)
- Outcome: Failure, relapse, default or death
- Size: 300 DS, 150 MDR; 15 enrolled
- Sites: Georgia
- Expected results: late 2022
Phase 3 MDR-TB trial in preparation: endTB-Q

• Population: FQ-resistant MDR-TB
• Regimen: BDQ+DEL+LZD+CF
• Durations: 24 or 39 weeks
• Sites: India, Pakistan, Kazakhstan, Kyrgyzstan, Lesotho, Peru, South Africa
• To Start: 2019
Phase 3 MDR-TB trial in preparation: BEAT-TB

- Population: MDR-TB
- Regimen of BDQ, DEL, LFX, LZD and CF
- Duration: 6 months
- Site: South Africa
- To start 2019
Timeline for an MDR-TB Clinical Trial

• Enrollment phase: 2-3 years
• Follow-up phase: 18 months
• Overall duration: 3-4 years
• Opportunities for shortening:
  – Enroll faster (doubling the rate reduces enrollment phase by half)
  – Surrogate endpoint (shortens follow-up phase by as much as half)
MDR-TB Trials of the future

• New Oxazolidinones
  – Sutezolid, Tedazolid, Delpazolid, Contazolid
• Benzothiazinones:
  – BTZ 043, Macozinone (PBTZ 169)
• Telacebec (Q203)
• Additional regimen shortening?
• Prevention of emergence of drug resistance?
Conclusions

• The pipeline for new TB drugs has been productive since 2000
• Six new drugs (4 new classes) are now in Phase 2 & 3 clinical trials
• Six additional new drugs (3 additional new classes) have recently entered Phase 1 trials
• The duration of MDR-TB Phase 3 trials is a substantial barrier to progress
• Additional site capacity could shorten trial duration and accelerate progress
To follow developments in MDR-TB diagnosis and treatment:

RESIST-TB Clinical Trials Progress Report

www.resisttb.org