

*New Drugs and Regimens
for Drug-Resistant TB*

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Outline

- New and repurposed drugs for TB
- Phase 2 Trials focused on DR-TB
- Phase 3 trials for treatment of DR-TB
- Novel DR-TB trial designs

Goals of DR-TB Treatment Trials

- Optimize dosing
- Minimize adverse drug reactions
- Maximize compatibility with antiretrovirals
- Shorten duration of treatment
- Increase cure proportion
- Decrease relapse
- Minimize emergence of resistance

2018 Global New TB Drug Pipeline ¹

Discovery

Preclinical Development

Clinical Development

Lead Optimization

Early Stage Development

GMP/
GLP Tox.

Phase 1

Phase 2

Phase 3

Diarylthiazoles

DprE1 Inhibitors

InhA Inhibitor

Macrolides

Mycobacterial Gyrase
Inhibitors

Arylsulfonamides

Inhibitors of MmpL3,
Translocase-1, Clp,
PKS13

Oxazolidinones

Pyrimidines

Squaramides

CPZEN-45*

Spectinamide
- 1810*

SPR-720
(pVXc-486)*

TB-47*

DC-159a

BTZ-043*

TBAJ-587
TBI-223

GSK-286*

TBI-166*

Macozinone*
(PBTZ-169)

OPC-167832*

Q203*

GSK-656 (070)*

Contezolid
(MRX-4/MRX-1)

TBA-7371*

Delpazolid
(LCB01-0371)

SQ-109*

Sutezolid
(PNU-100480)

Macozinone*
(PBTZ-169)

Bedaquiline*
(TMC-207)

Delamanid*
(OPC-67683)

Pretomanid*
(PA-824)

**Underline = new to Phase
since October 2017**

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

¹New 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>



www.newtbdrugs.org

Updated: March 2018

New Antituberculosis Drugs in Clinical Development, 2019

<u>Drug</u>	<u>Class</u>	<u>Company</u>	<u>Status</u>
Bedaquiline	Diarylquinolone	Janssen	Phase 3
Delamanid	Imidazooxazole	Otsuka	Phase 3
Pretomanid	Imidazooxazine	GATB	Phase 3
Sutezolid	Oxazolidinone	Sequella	Phase 2
Delpazolid	Oxazolidinone	LegoChem	Phase 2
Macozinone	Piperazinobenzo- thiazinone	iM4TB	Phase 2

Repurposed Antituberculosis Drugs in Clinical Development, 2019

<u>Drug</u>	<u>Class</u>	<u>Company</u>	<u>Status</u>
Rifampicin	Rifamycin	Various	Phase 2
Levofloxacin	Fluoroquinolone	Various	Phase 2
Clofazimine	Iminophenazine	Novartis	Phase 3
Linezolid	Oxazolidinone	Pfizer	Phase 2
Rifapentine	Rifamycin	Sanofi-Aventis	Phase 3
Moxifloxacin	Fluoroquinolone	Bayer/GATB	Phase 3

Phase 2 Trials to optimize dosing and Minimize DDI and Adverse Effects

- ACTG 5307 (Essentiality of INH)
- ACTG 5312 (High dose INH for inhA mutations)
- Opti-Q (optimization of levofloxacin dosing)
- ACTG 5356 (optimization of linezolid dosing)
- ACTG 5343 (BDQ and DLM QT interactions)
- C211 Study (Pediatric PK of BDQ)
- IMPAACT P1108 Trial (Pediatric PK of BDQ)
- Otsuka Pediatric PK Trial (Pediatric PK of DLM)

Clinical Trials for MDR-TB

Goal: Shorten treatment and improve upon
~75% relapse-free cure

Trials to shorten duration

- NiX-TB Trial and ZeNiX Trials– Phase 2/3 (2018, 2020)
PTM+BDQ+LZD for 6 months
- TB-PRACTECAL – Phase 3 (2020)
SOC vs.
BDQ+PTM+LZD±MFX or CF for 6 months

Pretomanid (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
- Sites: South Africa

Status of Participants in Nix-TB (as at 11 Oct'18)

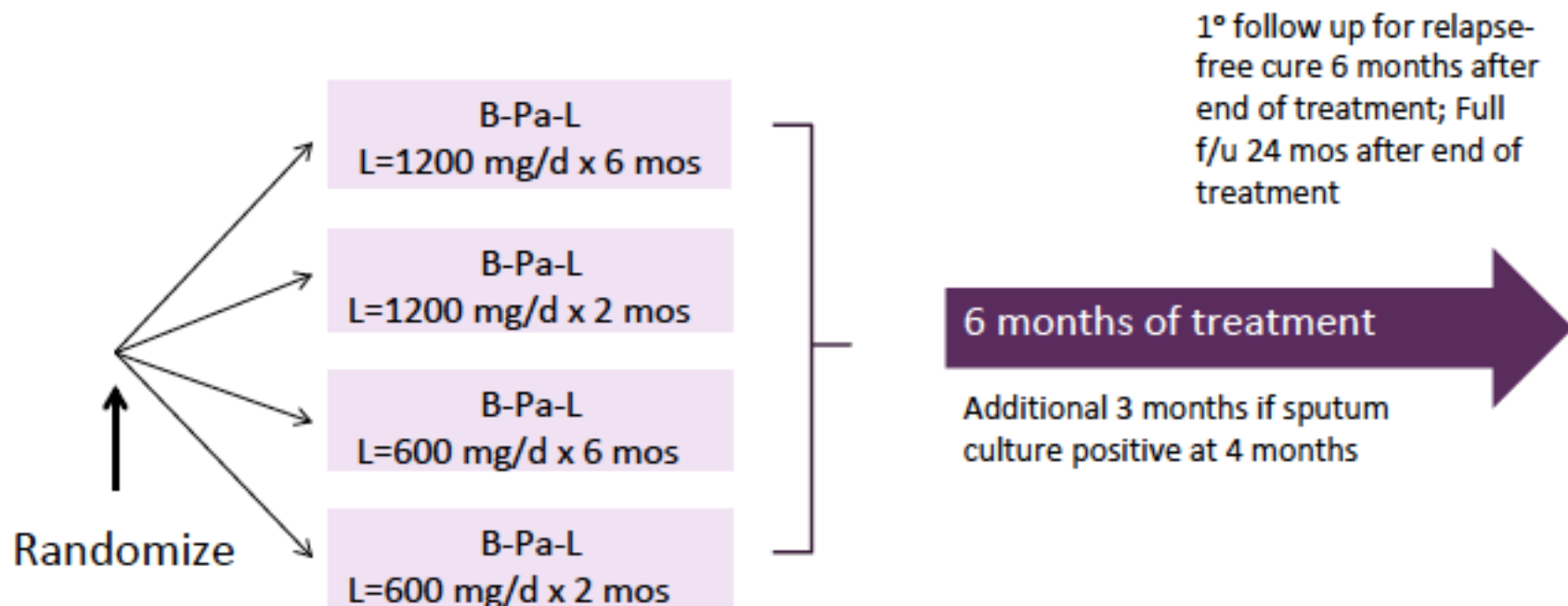
- Enrollment ended November 15, 2017 (ZeNix trial began enrolment subsequently)
 - 109 enrolled
 - 102 have completed treatment
 - 92 have reached their primary endpoint (6 months after end of treatment)
 - 31 patients have completed 24 months follow up
- Overall relapse-free cure of TB disease among the first 30 followed to primary endpoint 6 months after end of therapy:
 - 26 / 30 = 87% (vs. historical up to 30% success rate)
 - 4 deaths early in treatment



ZeNix: Linezolid Optimization Trial

ZeNix

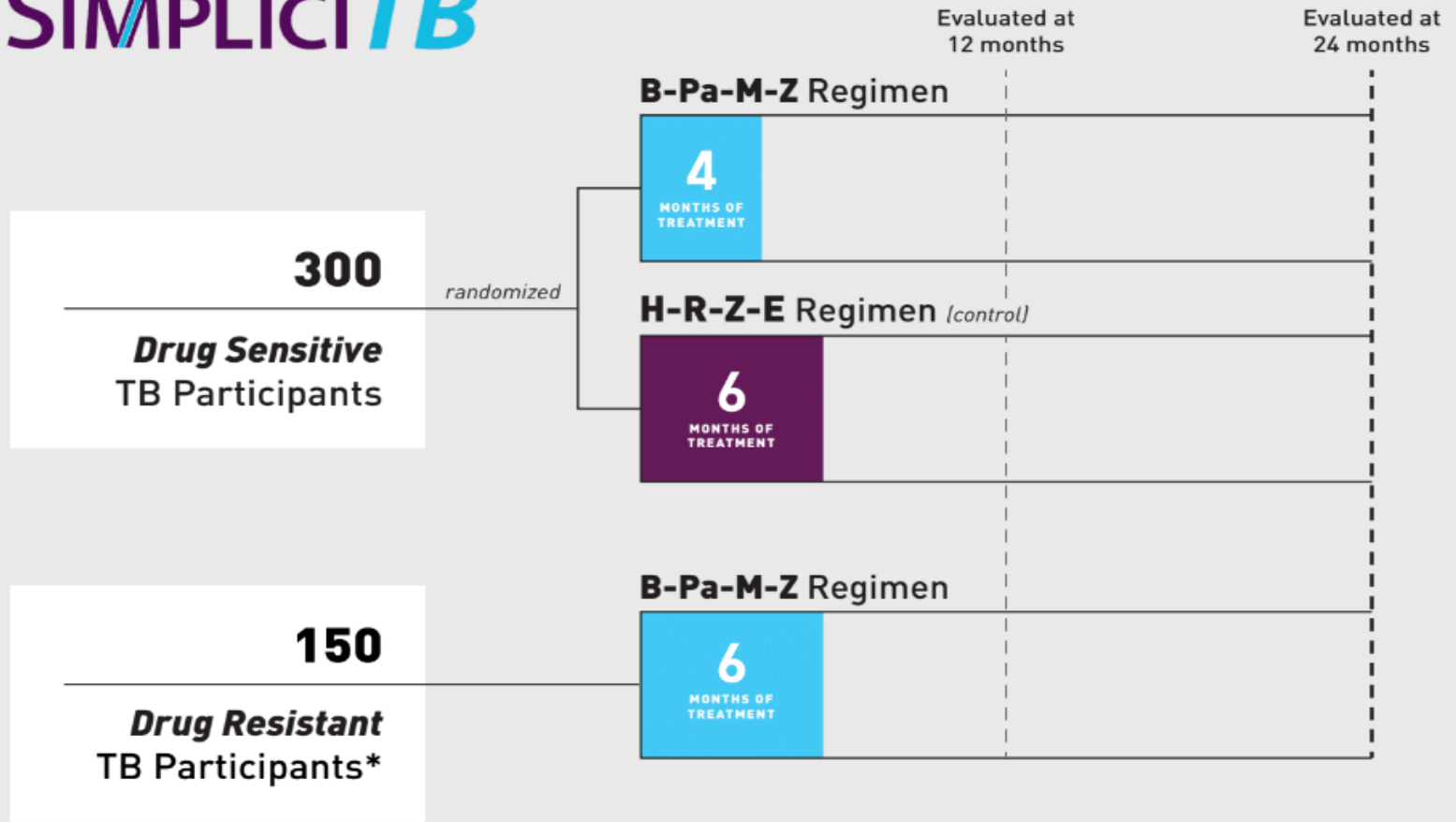
Patients with XDR-TB, Pre-XDR-TB or who have failed or are intolerant to MDR-TB treatment



N=30 XDR-TB per group AND
up to 15 pre-XDR or intolerant/non-responsive MDR-TB per group

Pa dose = 200 mg daily; B Dose = 200 mg daily x 8 weeks, 100 mg x 18 weeks

SIMPLICITB



B bedaquiline 200 mg x 8 weeks, then 100 mg | **Pa** pretomanid 200 mg | **M** moxifloxacin 400 mg | **Z** pyrazinamide 1500 mg
H isoniazid | **R** rifampin | **Z** pyrazinamide | **E** ethambutol

Status: fully enrolled

TB-PRACTECAL Trial (Phase 2/3)

- Description: *Adaptive design* 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, loss-to-follow-up or death
- Size: 630 Patients
- Sites: Uzbekistan, eSwatini
- Expected completion: 2021

Trials to replace injectable

- MDR-END Trial– Phase 2/3 (2019)
SOC vs.
DEL+LZD+LFX+PZA for 9-12 months
- NEXT Trial – Phase 3 (2020)
SOC vs.
BDQ+LZD+LFX+ETA/INH_H+PZA (6-9 Mo)
- STREAM Stage 2 Trial– Phase 3 (2020)
SOC vs.
BDQ+CFZ+EMB+LFX+PZA+4(INH_H+PTO) – 9 mos
- endTB Trial – Phase 3 (2021)
SOC vs.
Combinations of BDQ, DLM, LZD, FQ, PZA for 9 mos

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
- Sites: Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
- Expected completion: 2021

SMaRT Kids Trial (Phase 3)

- Description: Pediatric treatment shortening
- Regimens: 2mo (DLM+ CFZ+hdLZD+LFX+PZA) then 4mo (DLM+CFZ+sdLZD+LFX+PZA)
injectable/oral, 9-12-month WHO regimen
- Sponsor: IMPAACT
- Target population: HIV+/- children <15 years of age with confirmed or probable MDR or RR-TB;TBM excluded
- Outcome: Failure, relapse, default or death
- Size: 648
- Sites: South Africa, Philippines, Haiti, India
- Expected completion: ?

Novel TB Trial Designs

- MAMS Trial (TB PRACTECAL)
- Adaptive randomization Trial (endTB)
- Strategy Trial (MDR-END, NeXT-TB, InDEX)
- Pragmatic Trial (BEAT-TB, InDEX)

Pragmatic Trial

- Performed under programmatic conditions
- Broad inclusion criteria
- Goal is to move regimen into widespread practice

BEAT Tuberculosis Trial – Phase 3

- Description: Open label, randomized controlled pragmatic strategy trial; both the Study and the Control Strategies will be modified once fluoroquinolone sensitivity has been established.
- Regimens: BDQ+DLM+LNZ+LVX+CF for 6 months vs. South African Standard of Care for 9 months
- Target population: Pulmonary MDR/RR-TB, adults
- Outcome: Failure/Relapse
- Size: 1300 patients
- Sponsors: USAID
- Sites: South Africa
- Completion: 2024

InDEX Trial (Phase 4)

- Description: Strategy of individualized MDR-TB treatment based on WGS to a standardized regimen
- Regimens: South African SOC (9-24 months)

Individualized regimen based on WGS

- Sponsor: CAPRISA
- Target population: smear+ MDR-TB, adults 18+
- Outcome: Failure, relapse, default or death
- Size: 448 Patients
- Sites: South Africa
- Expected completion: 2021

Conclusions

- A broad spectrum of clinical trials for MDR/XDR-TB are in the field or in the planning stages
- New and repurposed TB drug classes may increase TB disease treatment responses and shorten treatment duration
- Tolerability of a number of the new and repurposed agents remains to be defined, especially when used in combination
- Continued improvement in the MDR-TB SOC makes comparative trials challenging