

Treatment of XDR-TB

Focus on the Nix-TB and ZeNix Trials

RESIST-TB Webinar 11 January 2018

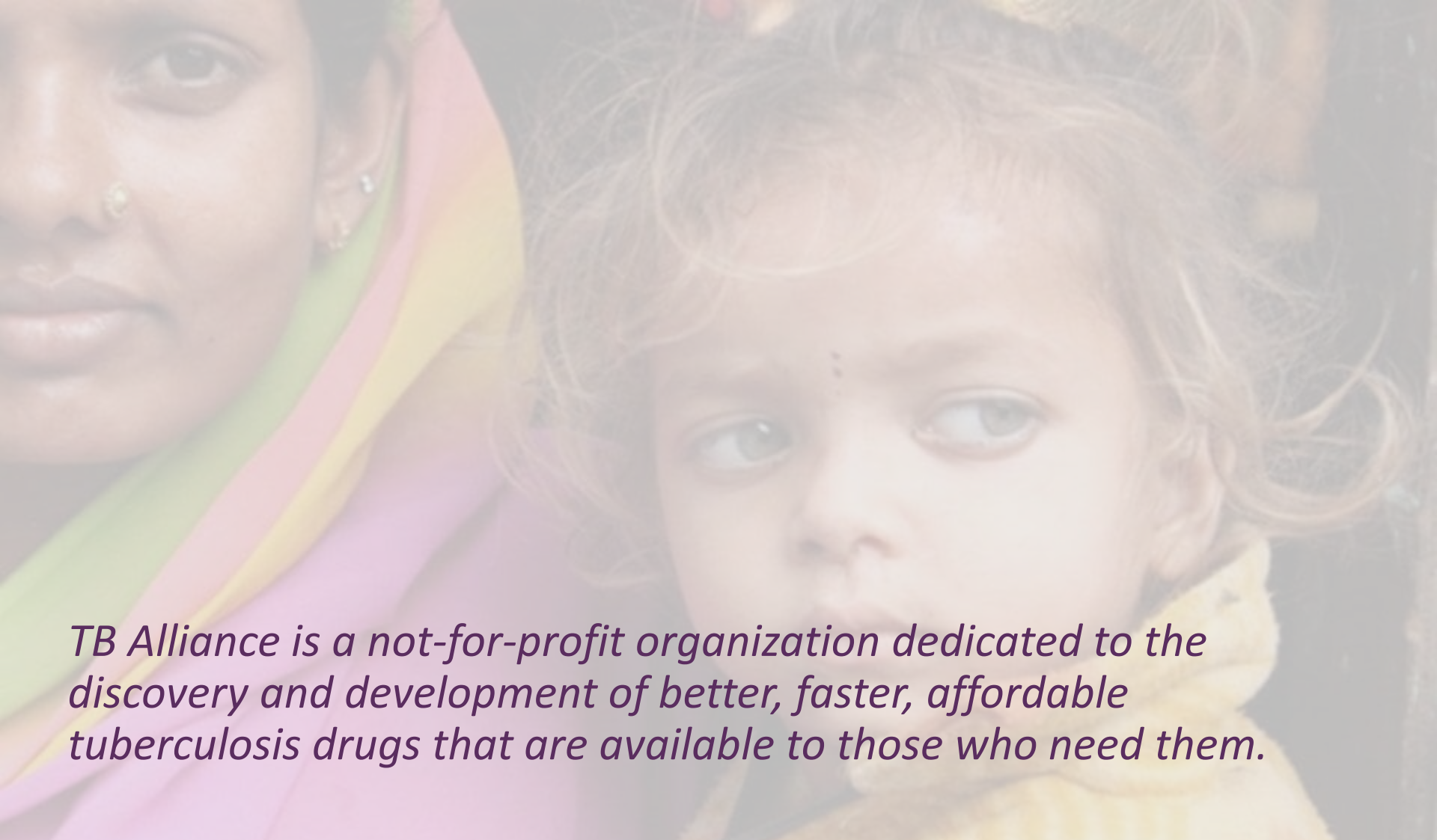
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Global Alliance for TB Drug Development



Outline of Discussion

- TB Alliance Approach to Treatment for All forms of TB
- Background to the Trials of the B-Pa-L Regimen to Treat XDR-TB
 - Linezolid 14 day EBA Study
 - Mouse Model of Infection
- Update on the Nix-TB Trial
- Update on the ZeNix Trial
- Additional Related Research Efforts
 - TB Practecal with MSF
 - Newer Oxazolidanones to Improve Safety over Linezolid
 - Sutezolid
 - TBI 223



TB Alliance is a not-for-profit organization dedicated to the discovery and development of better, faster, affordable tuberculosis drugs that are available to those who need them.

Current TB Therapy

OLD

Arsenal of drugs developed mostly in 1960s.

LONG

TB treatment today takes 6-30+ months.

COMPLEX

Many pills must be taken daily; Drug-resistant treatment includes daily injections.

EXPENSIVE

Drug-resistant TB drugs can cost > \$10,000 per treatment.

INADEQUATE

Breeds resistance & default; incompatible with some HIV treatments; DR-TB treatment often fails.



One day of treatment for drug-resistant TB

AAA Mandate

TB Alliance access strategy

Our commitment to patients, providers, and programs ensures our efforts benefit TB patients around the world. TB Alliance products will be:



Adopted

into treatment
policies and drug
registries

Available

in public and
private sectors

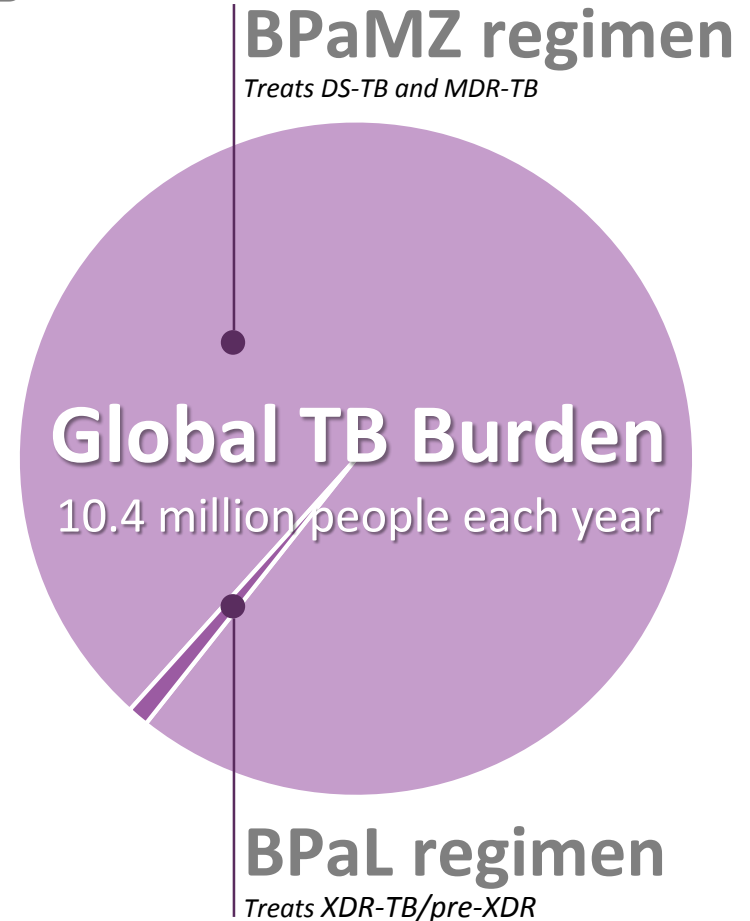
Affordable

cost effective for
patients, countries,
and donors

Treatment for All

Two drug regimens can treat all people with TB

- Countries may soon have the short, all-oral, and affordable drug regimens needed to treat all people with TB.
- The treatment landscape could be reshaped by a common therapy for virtually everyone with drug-sensitive (DS-) and multi-drug resistant TB (MDR-TB), and a closely related treatment for those with extensively drug-resistant (XDR-) TB.
- Treatments now in late-stage development could be deployed in the context of currently available diagnostics.



B = Bedaquiline

Pa = Pretomanid

L = Linezolid

M = Moxifloxacin

Z = Pyrazinamide

Shorter, Simpler Treatment for XDR-TB



One day of XDR treatment today
Treatment duration: 2+ years

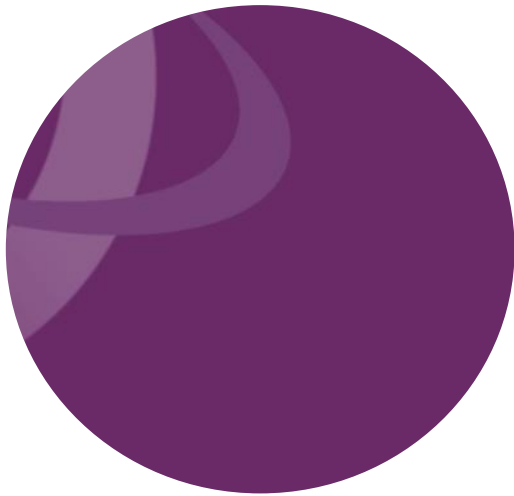


One day of BPaL regimen in Nix-TB trial
Treatment duration: 4-6 months

The Drugs in the BPaL Regimen

- Bedaquiline
 - A diarylquinoline
 - Inhibits energy metabolism
 - Approved as an add-on to SOC in many countries, starting 2012
- Pretomanid
 - A nitroimidazo-oxazine
 - Inhibits cell wall synthesis and kills through generation of reactive nitrogen species
 - In development as part of regimens to treat all forms of TB (DS, MDR, XDR)
- Linezolid
 - An oxazolidanone; inhibits protein synthesis in bacteria
 - Approved widely for up to 28 days treatment of serious bacterial infections
 - Limited for long term use by myelotoxicity and neurotoxicity

Background Research for the Nix-TB and ZeNix Trials



- Evaluate Linezolid dose
- Evaluate Linezolid duration

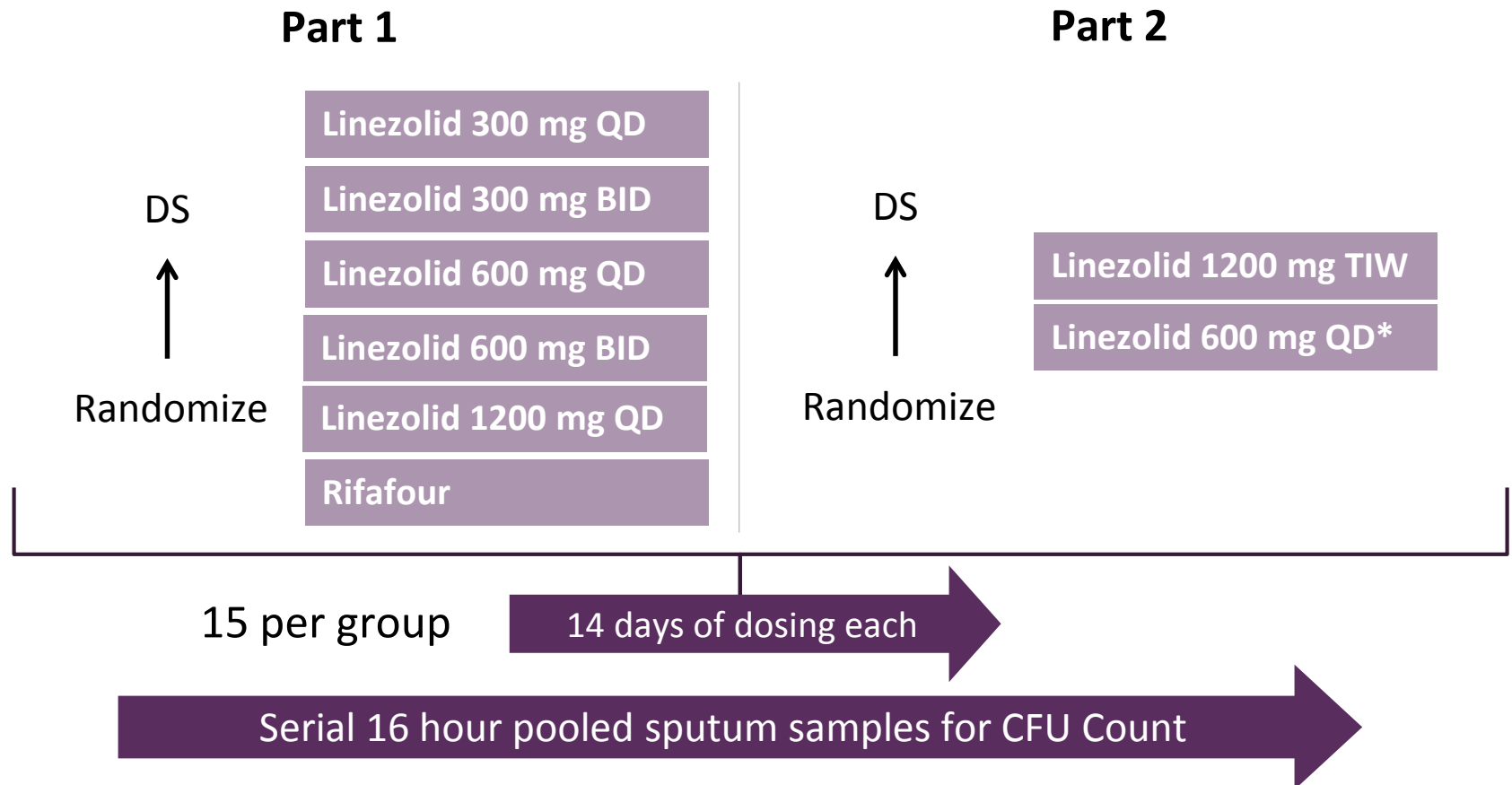
LIN-CL001 Linezolid Dose-Ranging 2-Week Study

- Linezolid has been linked to high rates of toxicity.
- This study sought to determine
 - The 2-week bactericidal activity of linezolid relative to the standard HRZE regimen
 - Whether the bactericidal activity is different when linezolid is administered once daily or divided into two daily doses 12 hours apart, or administered 3 days/week.
 - Whether the bactericidal activity differs across the total daily dosing range of 300 – 1200 mg.

LIN-CL001 Linezolid Dose-Ranging Study

2 Week Safety, Tolerability and Bactericidal Activity Study

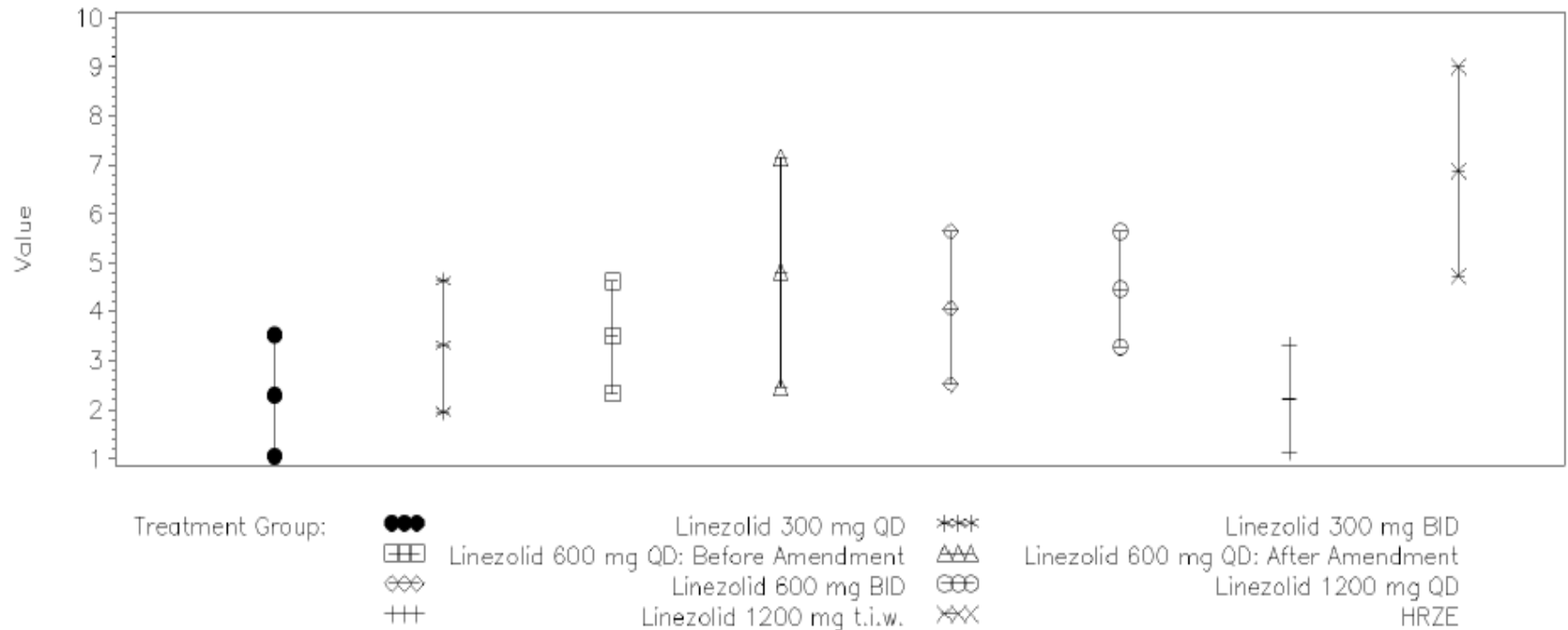
Participants with newly diagnosed smear positive DS TB



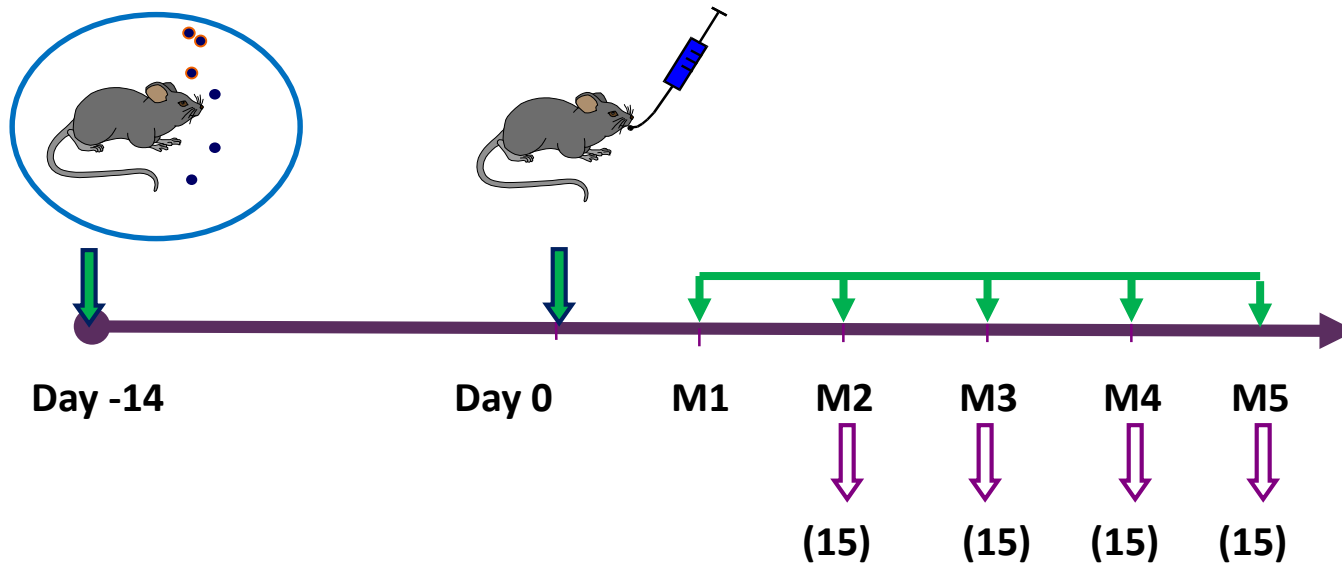
*An additional 15 were enrolled in part two at linezolid 600 mg QD for comparison for a total of 30 at 600 mg qd

LIN-CL001 Key EBA Findings

Posterior Estimates and 95% Bayesian Confidence Intervals of Mean Early Bactericidal Activity Time to Positivity, Days 0-14, Daily Percent Change



Scheme for Murine Relapse Experiments to Evaluate New Regimens



(15) mice held for (3) months without treatment and then sacrificed to determine permanent cure without relapse

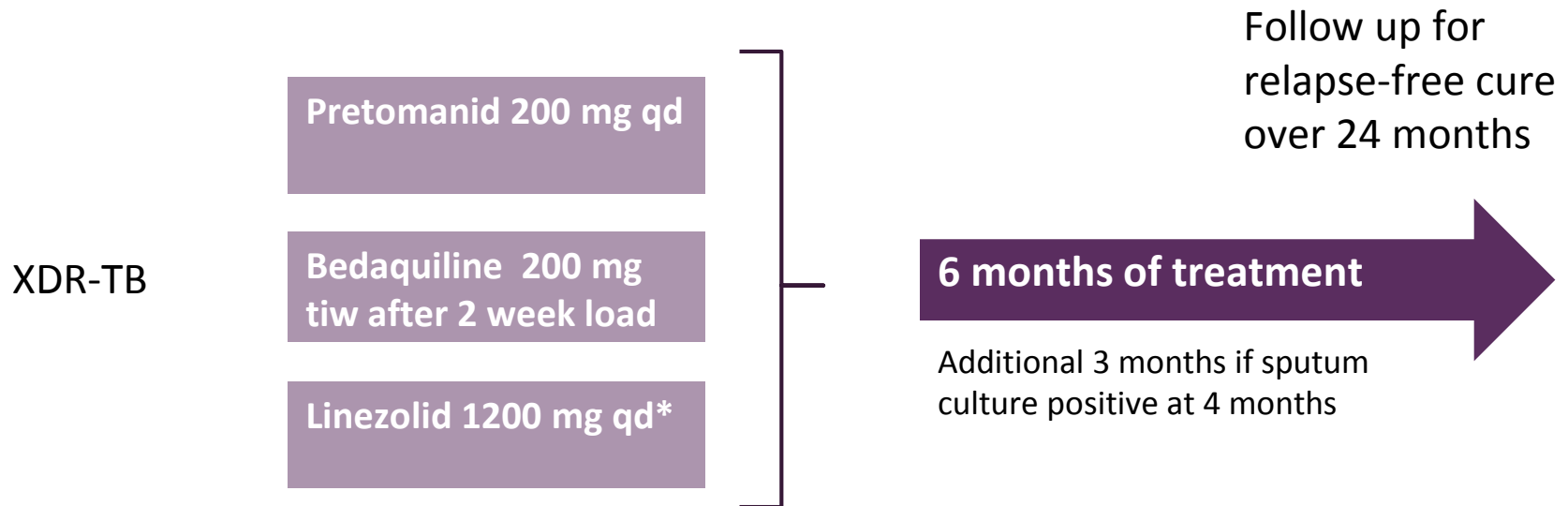
Linezolid (L) Sterilizing Activity on Background of Bedaquiline Plus Pretomanid (BPa) in BALB/c Mice— Data From Eric Nuermberger

| Regimen | Proportion relapsing after treatment for: | |
|------------|---|-----------------------|
| | 2 months | 3 months |
| 2RHZ/RH | | 8/14 (57%) |
| BPa | | 3/14 (21%) |
| 3BPaL | 6/15 (40%) | 0/15*† (0%) |
| 2BPaL/1BPa | | 0/15*† (0%) |
| 1BPaL/2BPa | 9/15 (60%) | 0/15*† (0%) |

*p = 0.11 vs. BPa; †p ≤ 0.001 vs. RHZ

Nix-TB Pilot Phase 3 Trial in XDR-TB

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



*Amended from 600 mg bid strategy

Sites

Sizwe Hospital, Johannesburg, South Africa

Brooklyn Chest Hospital, Cape Town, South Africa

King Dinuzulu Hospital, Durban, South Africa

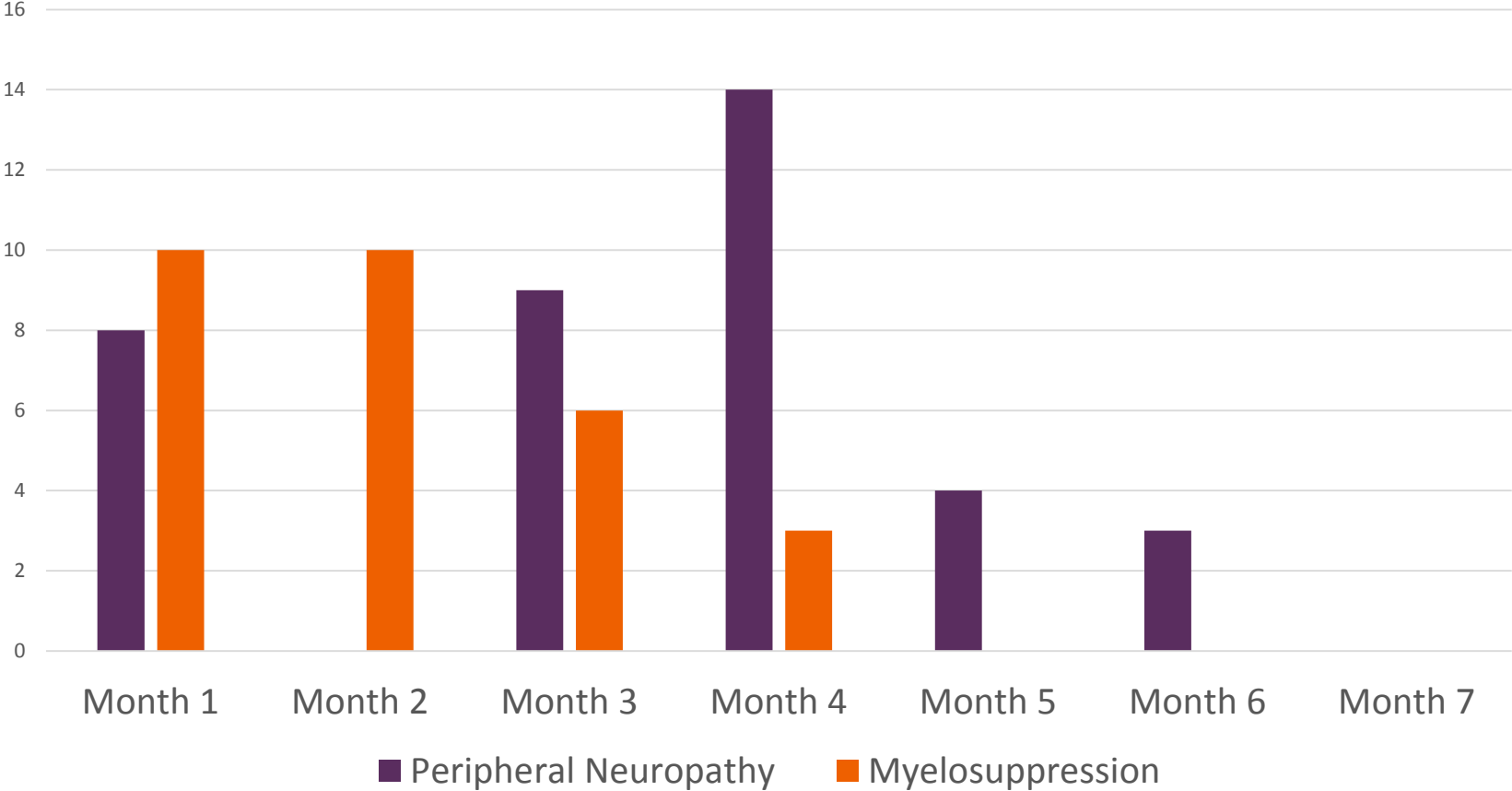
Status of Participants in Nix-TB

- 109 participants enrolled as of end enrollment November 15, 2017
 - 80 have completed treatment
 - 56 have reached their primary endpoint (6 months after end of treatment; NDA cutoff)
 - 10 patients have completed the study (Month 30)
- 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 85% failure rate)
- Enrollment ended November 15, 2017
 - Transition to ZeNix

Experience with Linezolid Toxicity

- 67% of Participants had at least one interruption of linezolid
 - Maximum mean duration of dose interruption = 23 days
- 55% had at least one reduction of linezolid dose
- 4 months was the minimum total amount of exposure time to linezolid
- Myelosuppression requiring interruption or reduction generally in the first 2-3 months
- Neuropathy requiring interruption or reduction generally in months 4-6
 - Data on resolution of neuropathies is evolving

Number and Type of Linezolid Adverse Events by Month



Characteristics of Anemia Course by Linezolid Interruption vs Reduction in First 50 Completing Therapy

- Interruption for anemia
 - N = 10
- Reduction in dose for anemia and no interruption
 - N = 8

| Interruption Vs Reduction | N | Day 1 Hgb | Nadir | % Decrease | Wks for 80% incr of reduction |
|---------------------------|----|----------------------------|------------------------|--------------------|-------------------------------|
| Interruption | 10 | Mean 12.1 (10-14.4) | Mean 8.7 (7.4-10) | Mean 27 (12-46) | Mean 3.1 (2-4) |
| Reduction | 8 | Mean 12.9 (11.8 – 14.4) | Mean 9.9 (6.8-11.8) | Mean 23 (5-45) | Mean 2.5 (1-5) |

BPaL Regimen: Moving Forward

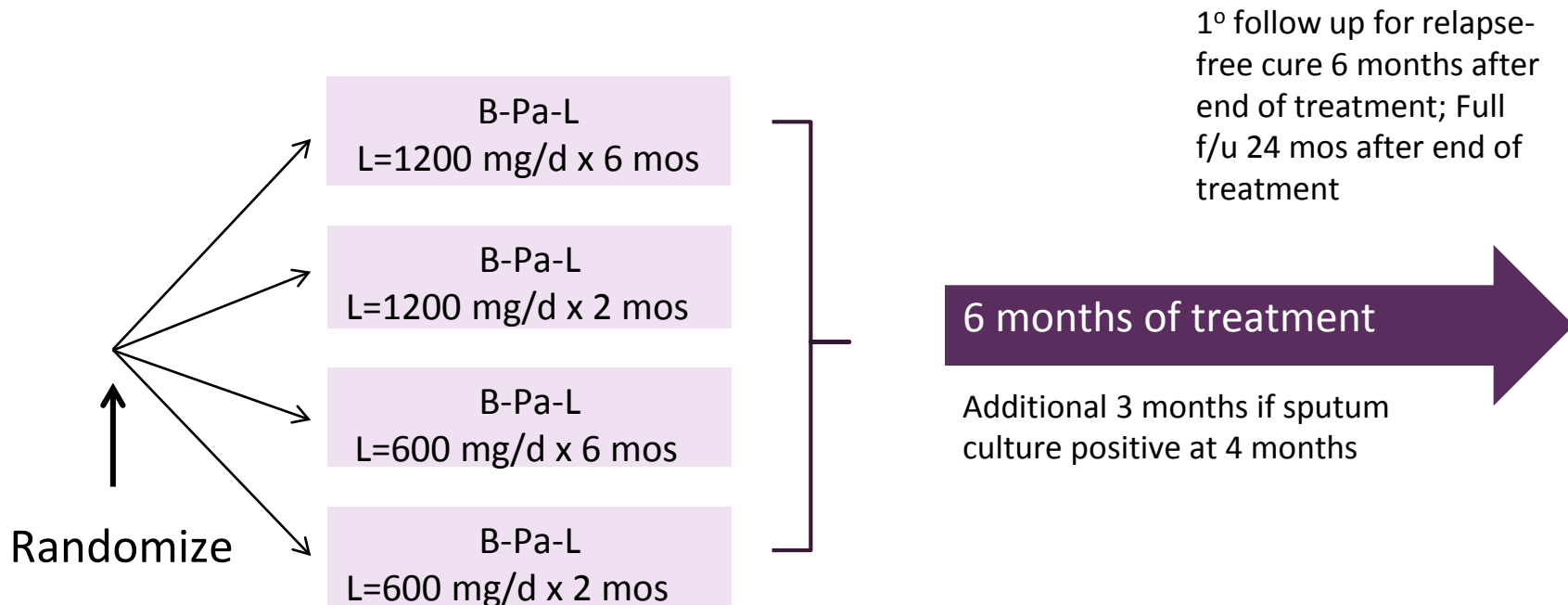
ZeNix Clinical Trial

- The ZeNix trial will seek to optimize linezolid as part of a novel regimen for those suffering from the most severe forms of drug-resistant TB.
- This trial will :
 - Evaluate the linezolid dose
 - Evaluate the linezolid duration
- Expected to be conducted across 10 trial sites in South Africa, Georgia, Belarus, and Russia.



ZeNix: Linezolid Optimization Trial

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

Status Update on the ZeNix Trial

- 1st Patient enrolled December, 2017 in Tbilisi, Georgia
- Screening is open at 3 sites in South Africa
- Regulatory and Central Ethics Approvals Complete
 - Russia and Belarus – Expect screening to start late February

Additional Evaluation of the BPaL Regimen

TB Practecal
-MSF



TB-PRACTECAL regimens rationale

Principles for designing future regimens for multidrug-resistant tuberculosis

Grania Brigden,^a Bern-Thomas Nyang'wa,^b Philipp du Cros,^b Francis Varaine,^c Jennifer Hughes,^d Michael Rich,^e C Robert Horsburgh Jr,^f Carole D Mitnick,^g Eric Nuermberger,^h Helen McIlleron,ⁱ Patrick P J Phillips^j & Manica Balasegaram^a

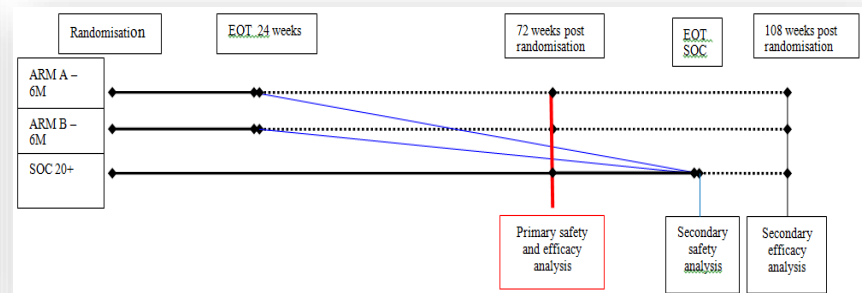
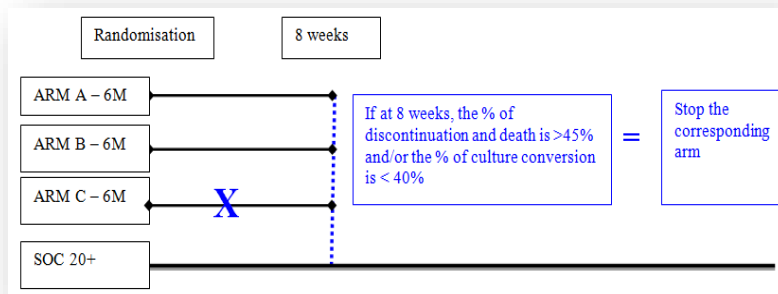
- At least one new class
- At least 3 and max 5 effective drugs
- Effective against MDR and XDR strains
- 6 - 9 months
- Oral
- Simple dosing schedule
- Good side effect profile, limited monitoring
- Minimal interaction with antiretrovirals

A RANDOMISED, CONTROLLED, OPEN-LABEL, PHASE II-III TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF DRUG REGIMENS CONTAINING BEDAQUILINE AND PRETOMANID FOR THE TREATMENT OF ADULT PATIENTS WITH PULMONARY MULTIDRUG RESISTANT TUBERCULOSIS

3 Investigational Arms:

- Bedaquiline + pretomanid + linezolid
- Bedaquiline + pretomanid + linezolid + moxifloxacin
- Bedaquiline + pretomanid + linezolid + clofazimine

Control arm: Locally accepted standard of care which is consistent with the WHO recommendations for the treatment of M/XDR-TB



Partners



Sponsor & Trial Management



Statistics



Developers of pretomanid



Clinical Monitoring



Overall Trial Support



Data management



Mycobacteriology Monitoring

Cardiac safety

TB Alliance Development of Sutezolid

Completed Sutezolid preclinical toxicity studies

- Safety pharmacology studies
- Genotoxicity studies
- 1-month rat toxicity
- 1-month monkey toxicity
- CMC activities

Global Alliance for TB Drug Development **SUTEZOLID** PHASE 1

Sutezolid-CL-001/P4005931

*"A **Phase 1**, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Sutezolid in Healthy Adult Subjects"*

Cohorts Doses

- The investigational product (Sutezolid and matching placebo) is supplied as 100, 200 and 600 mg tablets.

| Cohort | Dose (mg) | No. of Subjects | Fasting/Fed Conditions |
|--------|-----------|--------------------|------------------------|
| 1A | 300 | 2 active/1 placebo | Fasting |
| 1B | 300 | 5 active/1 placebo | Fasting |
| 2 | 600 | 6 active/2 placebo | Fasting |
| 3 | 1200 | 6 active/2 placebo | Fasting |
| 4 | 1800 | 6 active/2 placebo | Fasting |

First Patient Dosed 24th September 2017
n=8 (6 active)

**Towards Safer
Oxazolidinones as
components of Universal
Regimen for TB**

TBI 223



TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

TBI-223: Pharmacology

Reduce activity against MPS to effectively reduce bone marrow toxicity

- ***In vitro* Pharmacology**

- MIC against *Mtb* *in vitro* and in macrophages in the range of LZD.
- Active against drug-sensitive and drug-resistant *Mtb* strains
- No known pre-existing resistance or cross-resistance with clinical TB drugs – resistant mutation frequency (3.1×10^{-8}) comparable to LZD (7.6×10^{-9})
- Significantly weaker inhibitor of mammalian MPS
 - Mean IC_{50} from (7 trials) - $>74 \mu\text{M}$

- **ADME**

- Stable in liver microsomes and hepatocytes ($t_{1/2} >120$ min) *in vitro*
- No significant inhibition of 5 major human CYPs (20% at $30 \mu\text{M}$)
- No CYP induction

- **Preclinical PK**

- High oral bioavailability; exposures were dose proportional in general
- Relatively short half-life in mice ($t_{1/2} = 3$ hr compared to about 1.6 hr for LZD)

TBI-223 (O): *In vivo* Efficacy similar to Linezolid in Combination with Bedaquiline (J) and Pretomanid (Pa)

| | Time point and lung CFU (\log_{10} CFU) |
|---------------------|--|
| Initial CFU (D-14) | 4.1 \pm 0.1 |
| Pretreatment (D0) | 7.3 \pm 0.1 |
| Regimen | W8 (n=5) |
| JPa | 1.9 \pm 0.1 |
| JPaL ₅₀ | 0.0 \pm 0.0 |
| JPaL ₁₀₀ | 0.3 \pm 0.4 |
| JPaO ₁₀₀ | 0.4 \pm 0.5 |
| JPaO ₂₀₀ | 0.2 \pm 0.4 |

B, Bedaquiline; Pa, Pretomanid; L, Linezolid, O, TBI-223. Subscripted figures are daily doses of drugs in mg/kg

In Vivo Safety and Toxicity - MPS vs. Bone Marrow Toxicity and Hematological

Reduced activity against MPS led to reduced bone marrow toxicity

| Compound | Linezolid | OTB-223 |
|---|---|--|
| MIC ($\mu\text{g}/\text{mL}$) | 0.23 – 0.63 | 0.8 - 1.9 |
| MPS (μM) | 8.5 | > 74 |
| Mouse/human bone marrow progenitor cell suppression assay (μM) | 24-60 | >150 |
| MED AUC ($\text{hr}\cdot\mu\text{g}/\text{mL}$) | 131 | 179 |
| Bone Marrow Histopathology, platelet \downarrow , reticulocyte \downarrow (Rat 28 day study at mg/kg dose) | 150 mg/kg (AUC 425 $\mu\text{g}\cdot\text{hr}/\text{mL}$) NOAEL at 20 mg/kg (IB) | > 300 mg/kg (AUC 1685 $\mu\text{g}\cdot\text{hr}/\text{mL}$) |
| Bone Marrow Histopathology, platelet \downarrow , reticulocyte \downarrow (Dog 14 day study at mg/kg dose) | NOAEL at 20 mg/kg (IB) | > 150 mg/kg (AUC 789 $\mu\text{g}\cdot\text{hr}/\text{mL}$) |
| Comments | Death (day 11,12) at 300 mg/kg Death (day 21) at 150 mg/kg | |

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Thank You

