Research and Development Update

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TB Alliance Stakeholders Association Meeting
October 27, 2014
Barcelona, Spain

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

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2014 Q4

Discovery

LEAD IDENTIFICATION

- ATP Synthesis Inhibitors *Calibr*
- Whole-Cell Hit-to-Lead Program *Sanofi*
- Whole-Cell Hit-to-Lead Program *GSK*
- RNA Polymerase Inhibitors *Rutgers University*
- Energy Meta-bolism Inhibitors *AZ/Upenn*
- POA Prodrugs *Yonsei*
- InhA Inhibitors
- Hit ID Program *Takeda*
- Hit ID Program *Daiichi Sankyo*
- Hit ID Program *Shionogi*

LEAD OPTIMIZATION

- Macrolides *Sanofi*
- Ureas *Sanofi*
- Diarylquinolines *Janssen/University of Auckland/UIC*
- Indazoles *GSK*
- Thiophene Carboxamides *Calibr*
- Azaindoles AZ
- Cyclopeptides *Sanofi*
- Mmmpl3 Inhibitors

Early Development

PRECLINICAL DEVELOPMENT

- TBA-354
- Preclinical TB Regimen Development *JHU*

PHASE 1

- Pharmacokinetics of first-line drugs in children < 5kg *Stellenbsch University*

PHASE 2A

- NIX-TB
  - PA-824 / Bedaquiline / Linezolid

PHASE 2B

- NC-005
  - PA-824/ Bedaquiline/ Pyrazinamide

PHASE 3

- STAND
  - PA-824/ Moxifloxacin/ Pyrazinamide

Late Development

PHASE 4

- Optimized Pediatric Formulations
  - Ethambutol/ Rifampicin/ Pyrazinamide for children > 5kg
  - Isoniazid/ Rifampicin for children > 5kg
  - Ethambutol for children > 5kg
  - Isoniazid for children > 5kg
  - Pyrazinamide for children > 5kg

TB Alliance R&D Partners:

AstraZeneca (AZ)
Bayer Healthcare AG (Bayer)
Beijing Tuberculosis and Thoracic Tumor Research Institute
Calibr
Daiichi Sankyo
GlaxoSmithKline (GSK)
Institute of Materia Medica (IMM)
IMPAACT
Janssen [Johnson & Johnson]
Johns Hopkins University (JHU)
Medical Research Council (MRC)
New York Medical College
Rutgers University
Sanofi
Shionogi
Stellenbosch University
Takeda Pharmaceuticals
University College London (UCL)
University of Auckland
University of Illinois at Chicago (UIC)
University of Pennsylvania School of Medicine
Yonsei University

TB Alliance Overarching Clinical Strategy

- **Goal: entirely novel regimen, 2 months treatment duration**
  - PaMZ (STAND; Ph 3): One NCE (new chemical entity)
    - Target treatment duration 4 months
  - JPaZ (NC-005; Ph 2b): Two NCEs
    - Target treatment duration 3 months
  - JPaOx (NiX-TB; Ph 3): Three NCEs
    - Target treatment duration 6 weeks (with Z) to 3 months
  - Newer regimens: Three NCEs, safer
- Path forward
  - Forward development (EBA, etc)
  - Simultaneous reverse-direction development (phase 3 in XDR)
    - Information on duration of therapy obtained early on
    - Long-term safety obtained early on

Clinical Plans 2014

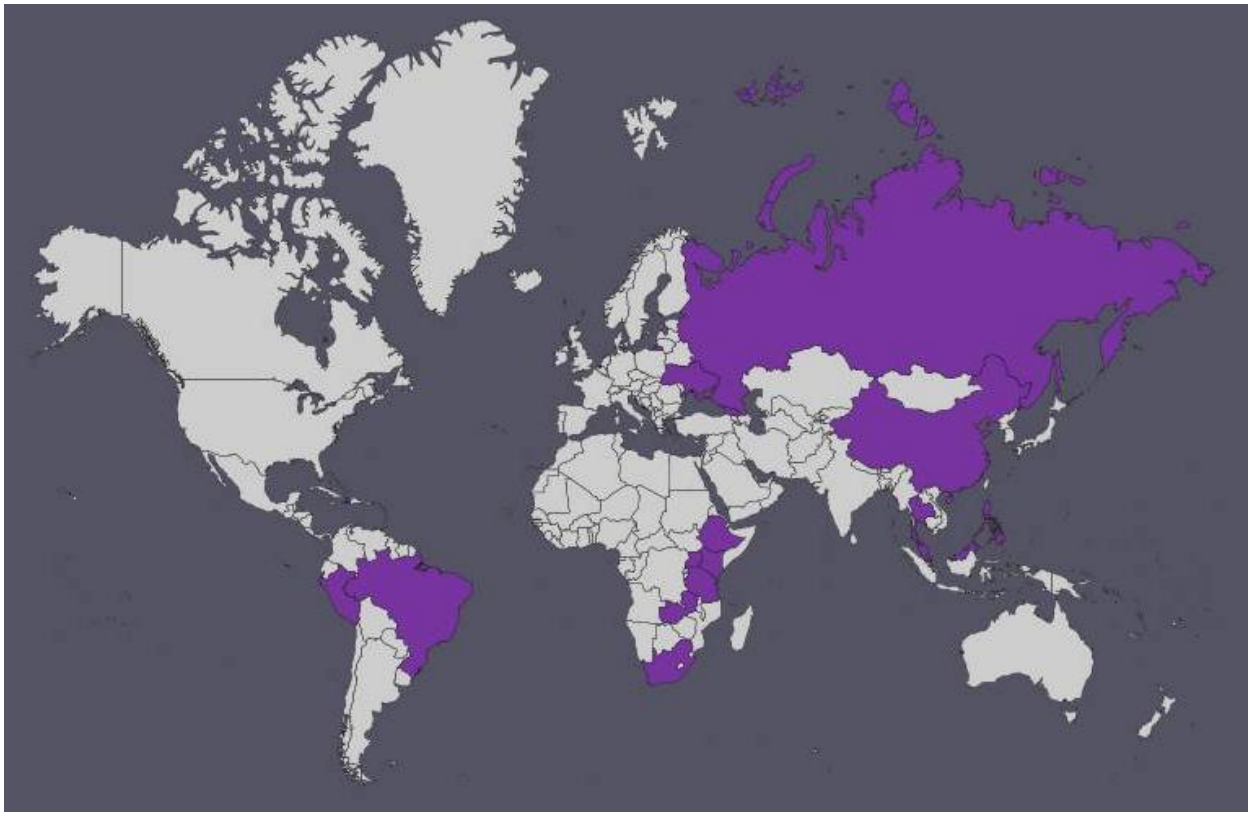
- PaMZ Phase 3 (STAND)
  - DS- and MDR-TB
  - Regulatory filing (stringent authorities) 2Q2018
- JPaZ Phase 2b (2-month study)
  - DS- and MDR-TB
  - Results 2Q2016
- NiX-TB Phase 3
  - XDR-TB
- Linezolid dose ranging EBA
  - Supporting NiX-TB
- TBA-354 Phase 1 First In Human
  - First new compound for TB to enter phase 1 in 5 years

STAND – PaMZ Phase 3

PaMZ Value Proposition

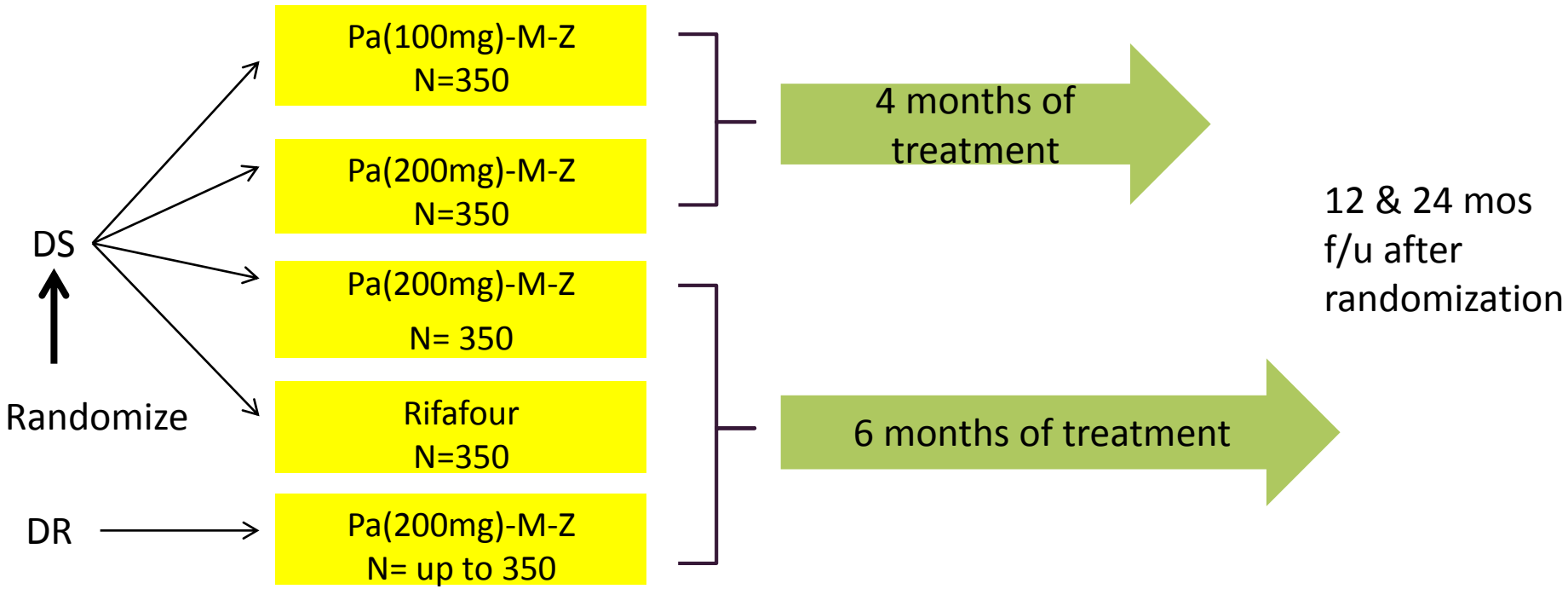
- Possible 4 month treatment for DS-TB
  - Requires DST in areas where MDR (or moxifloxacin resistance)
    - As does HRZE
    - GenXpert can serve as proxy DST for PZA resistance when DS
- Possible 4-6 month treatment for some MDR-TB
  - In patients whose *M.tb* is sensitive to PZA and moxifloxacin
  - Requires DST
- HIV/ART compatible
- Low cost of goods

Where in the World is STAND?



STAND: Phase 3 Trial of the Pa-M-Z Regimen

Participants with newly diagnosed smear positive DS- and MDR-TB



Z = pyrazinamide at 1500mg Pa = PA-824 M = moxifloxacin

PaMZ EOP2 FDA and EMA Meetings

Agreements on All Issues

- Contributions of individual drugs in the regimen demonstrated by mouse and early clinical (EBA) studies using factorial designs
- Additional non-clinical combination toxicology studies not needed
- Enrollment of subjects with MDR-TB without a concurrent SOC for MDR-TB agreed
  - EMA: MDR patients not needed for indication, “Treatment of TB”
- Length of follow up of subjects for the first regulatory file 12 months after beginning of treatment, with confirmatory data after 24 months
- Statistical non-inferiority margin for a novel regimen agreed at 12%
- True Modified Intention to Treat vs “MITT” vs Per Protocol analyses
- Rifampicin mono-resistant subjects can be allocated into the “MDR” treatment arm
- Isoniazid mono-resistant subjects cannot be allocated into the DS treatment arm for the primary analysis

What We Learned From REMox

- Length of follow up of subjects for the first regulatory file 12 months after beginning of treatment, with confirmatory data after 24 months
- Statistical non-inferiority margin for a novel regimen agreed at 12%
- True Modified Intention to Treat vs “MITT” vs Per Protocol analyses
- INH mono-resistant subjects cannot be allocated into the DS treatment arm for the primary analysis

- Operations, statistical algorithms
- Accept uncertainty as progress from Phase 2 to Phase 3
  - Address with trial design, sample size

NC-005 – JPaZ Phase 2b

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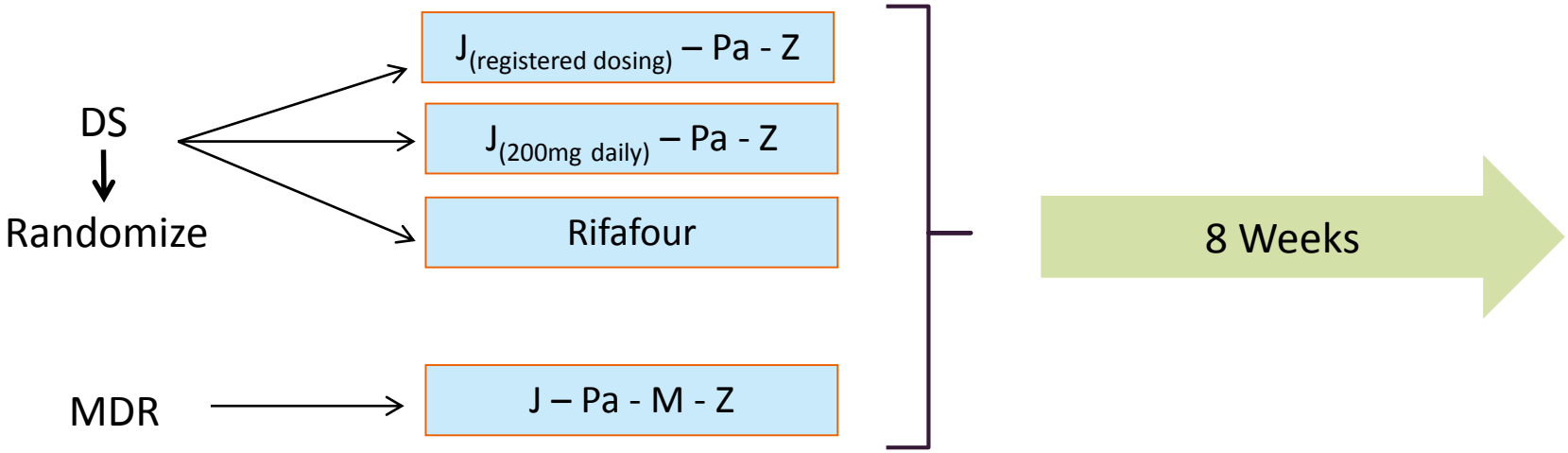
JPaZ Value Proposition

- Possible 3 month treatment for DS-TB and some MDR-TB
  - Requires DST in areas where MDR
    - As does HRZE
    - GenXpert can serve as proxy DST for PZA resistance when DS
- HIV/ART compatible
- Low cost of goods

NC005 Design – 8 week SSCC Study of J-Pa-Z

J, Pa, Z and M Containing Regimens

Participants with newly diagnosed smear positive DS- and MDR-TB



60 per DS group
Up to 60 MDR

Serial 16 hour pooled sputum samples for TTP/CFU Count

Z=pyrazinamide (1500mg daily), **M** = moxifloxacin 400mg daily, **Pa** = PA-824 200mg daily , $\mathbf{J_{(registered\ dosing)}}$ = bedaquilline 400mg for 14 days then 200mg three times a week, $\mathbf{J_{(200mg\ daily)}}$ = bedaquiline 200mg daily

NiX-TB – JPaOx Phase 3

JPaOx(Z) Value Proposition

- "Universal" regimen
- Possible 6-week treatment (when combined with Z) if Z sensitive for DS, MDR and XDR
  - 3 month treatment if Z resistant
  - Requires DST in areas where MDR
    - As does HRZE
    - GenXpert can serve as proxy DST for PZA resistance when DS
- HIV/ART compatible
- Low cost of goods

Linezolid as First Oxazolidinone in Regimen

- May not be safe enough for DS- or MDR-TB (first line)
  - Safer oxazolidinone to come?
- Initial study in XDR-TB
  - Learn safer ways to deliver?
- Definitive outcome study
  - Justified by lack of alternative therapy
  - May open door to compassionate use of PA-824 within a year

The Dismal Prognosis of Patients with XDR-TB

*Pietersen E et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. Lancet 2014. Published **Online** January 17, 2014 http://dx.doi.org/10.1016/ S0140-6736(13)62675-6*

107 Patients with XDR-TB in S. Africa dx'd 2002 – 2008

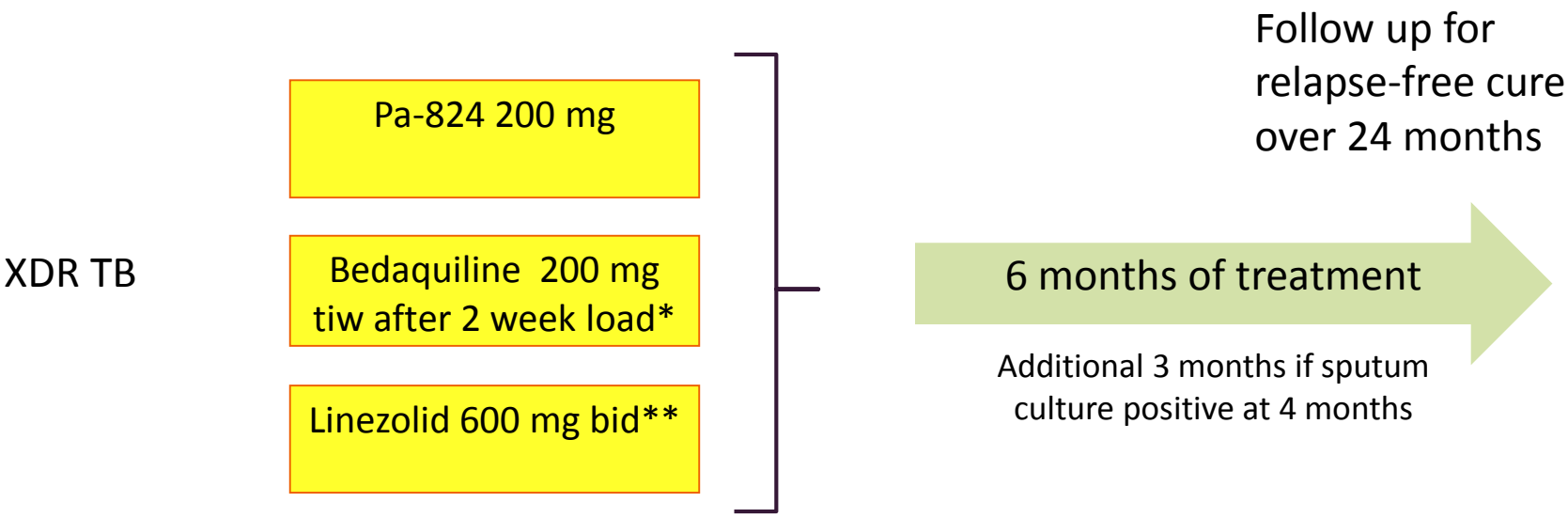
Treated empirically with median of 8 drugs

	Died	Failed Treatment	Defaulted	Cured or Continuing
24 mo f/u	**46%**	**23%**	**7%**	**16%**
60 mo f/u	**73%**	**10%**	**4%**	**11%**

NiX-TB "Rescue" Study

Patients with XDR-TB or Who Have Failed MDR-TB Treatment

14 year olds and up



*May adjust dosing Based on NC-005

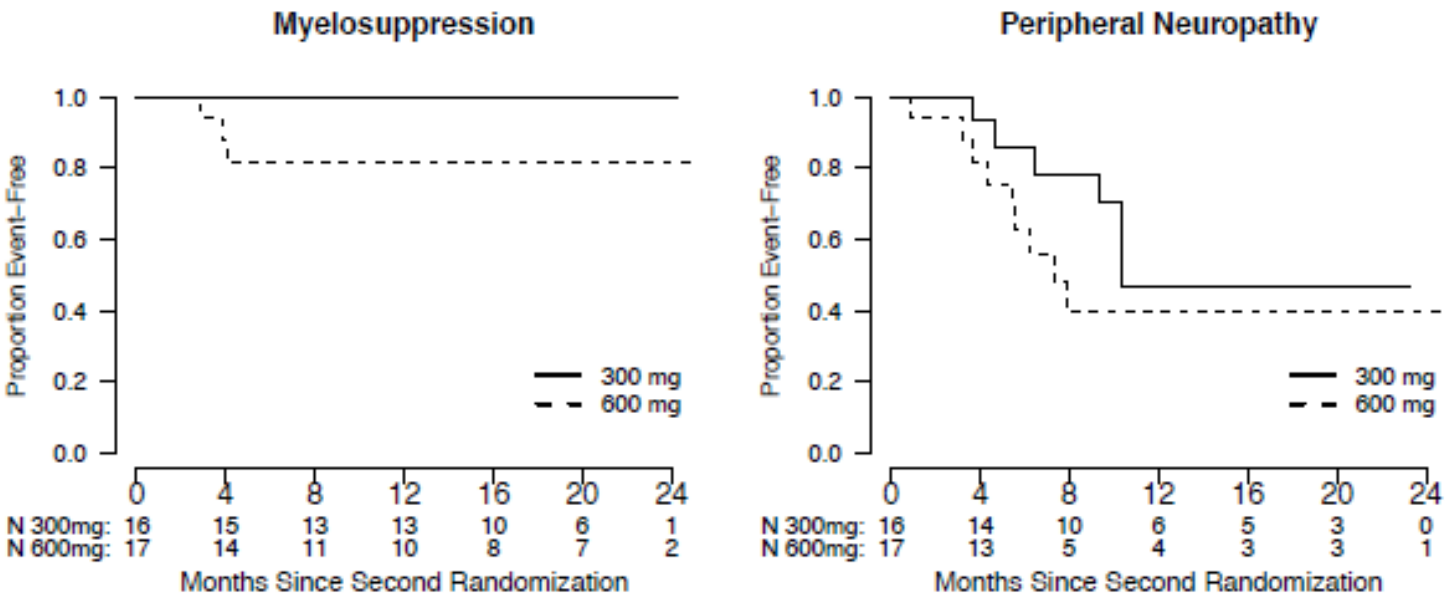
**May adjust based on linezolid EBA study

Sites: Durban, Sizwe, Brooklyn Chest, SA

Linezolid – Key Safety Concerns

- Bone Marrow Suppression with anemia, thrombocytopenia and/or leukopenia
- Peripheral Neuropathy
- Optic Neuropathy
- Others:
  - Lactic acidosis, serotonin syndrome, seizures

Time Course of Myelosuppression and Neuropathy on Long Term Linezolid



From Supplement to *Lee M, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med 2012;367:1508-18*

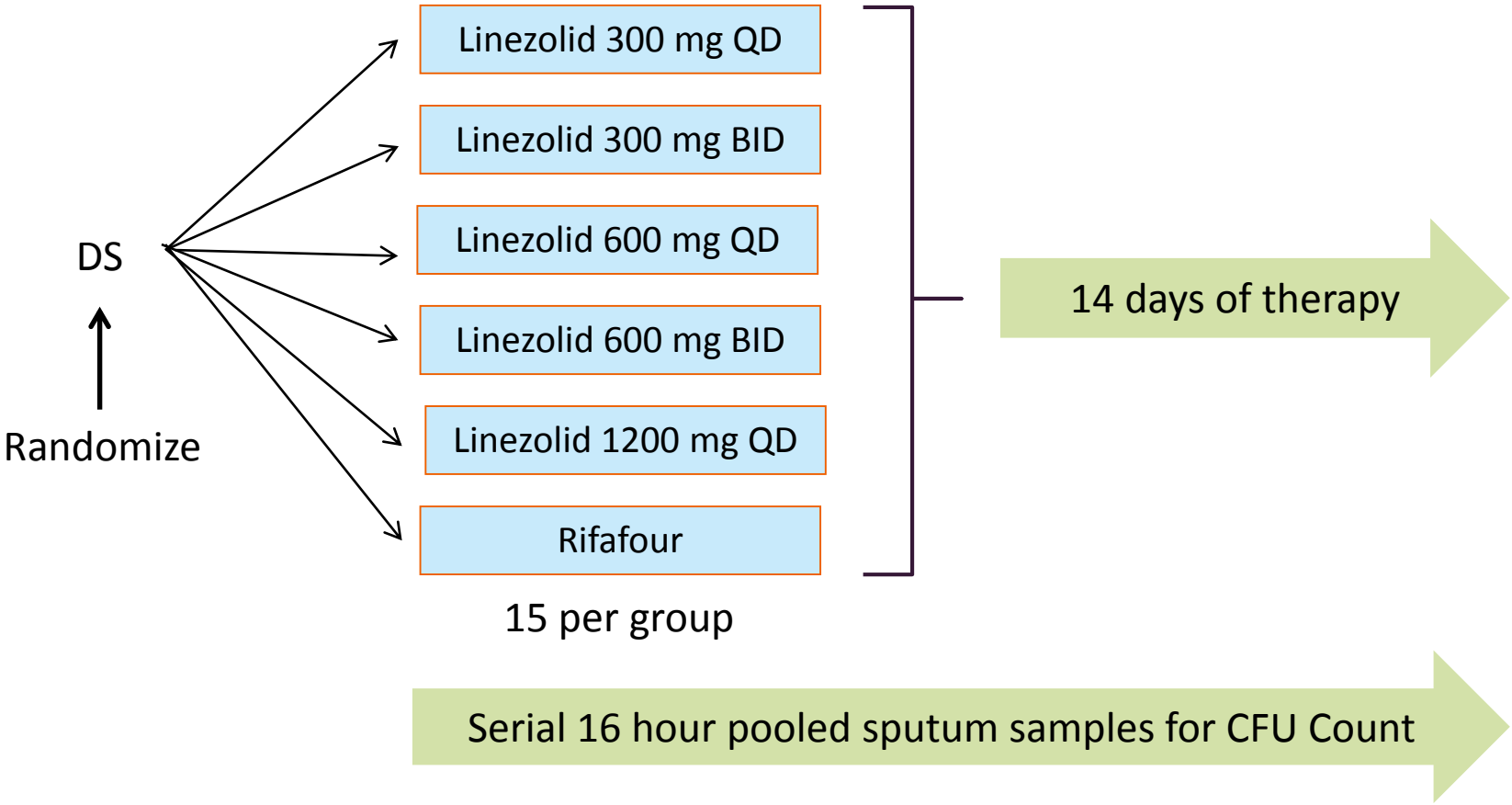
Approach to Safety Monitoring

- Start slowly
  - 1-2 sites initially with no more than 1-2 subjects/month
  - Add additional sites subsequently
- Screening assessments by PI:
  - Visual acuity and color vision
  - Peripheral neuropathy
- Ability to interrupt / lower the dose of linezolid and/or the bedaquiline/PA-824 combination
- Regular DSMC meetings and futility analysis
- Potential to amend protocol and replace linezolid with a newer oxazolidinone

LIN-CL001: Dose-Ranging Linezolid Study

2 Week Safety, Tolerability and Bactericidal Activity Study

Participants with newly diagnosed smear positive DS TB



Most Importantly

Thank you to the people with TB who selflessly agree to participate in clinical trials