TB Alliance Clinical Update

Stephen Murray, MD, PhD
Senior Medical Officer

April 5, 2016

CPTR

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Overarching Goal: Entirely Novel Regimen

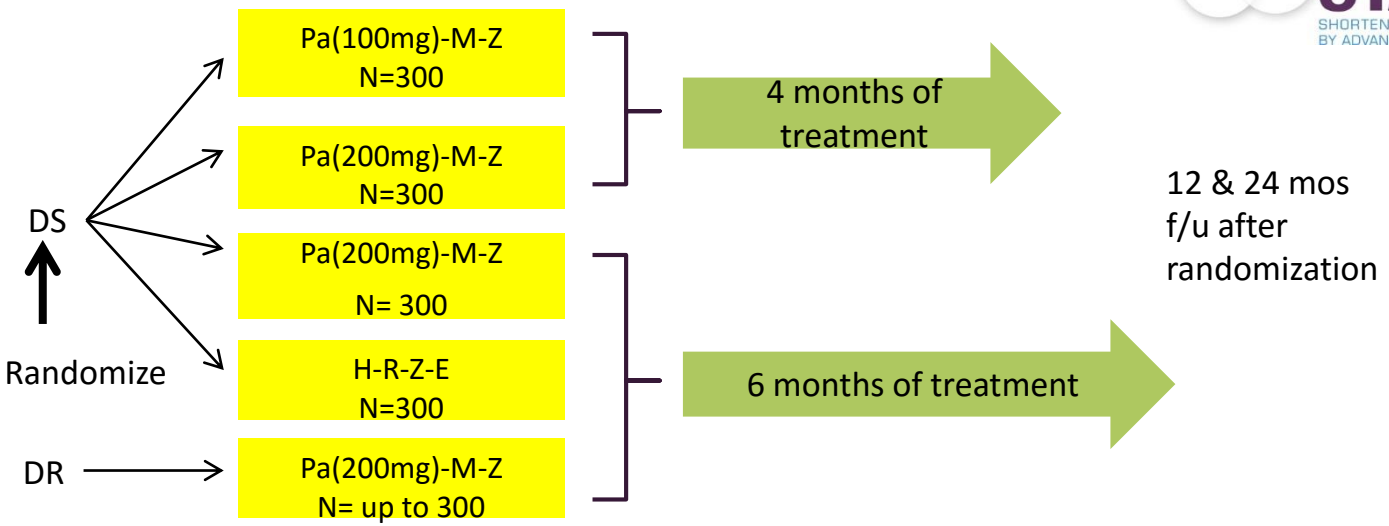
- **PaMZ (pretomanid, moxifloxacin and pyrazinamide)**
  - 1 NCE without pre-existing resistance
  - Target treatment duration 4 months
  - STAND Phase 3 Study
- **JPaZ (bedaquiline, pretomanid, pyrazinamide)**
  - 2 NCEs without pre-existing resistance
  - Target treatment duration 3 months
  - NC005 Study
- **JPaOx (bedaquiline, pretomanid, oxazolidinone)**
  - 3 NCEs without pre-existing resistance
  - Target treatment duration 3 months (6 weeks if Z sensitive and add Z)
  - Nix-TB Study

TB Alliance Clinical Program 2016

Title	Phase	Treatment duration	Population	Status
STAND (PaMZ)	3	4-6 months	DS- + MDR-TB	FPI FEB2015; enrollment on hold
NC-005 (BPaZ)	2b	2 months	DS- + MDR-TB	LPI DEC2015
Nix-TB (BPaOx)	2/3	6-9 months	XDR-TB	FPI APR2015
Linezolid dose-ranging EBA study	2a (supports Nix-TB)	2 weeks	DS-TB	Topline results SEP2015; extension planned
TBA-354 FIH / MAD	1	Single dose / 2 weeks	Healthy volunteers	MAD FPI NOV2015; program discontinued

STAND Trial - Phase 3 Trial of PaMZ

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



Pa = pretomanid **M = moxifloxacin 400 mg** **Z = pyrazinamide at 1500mg**

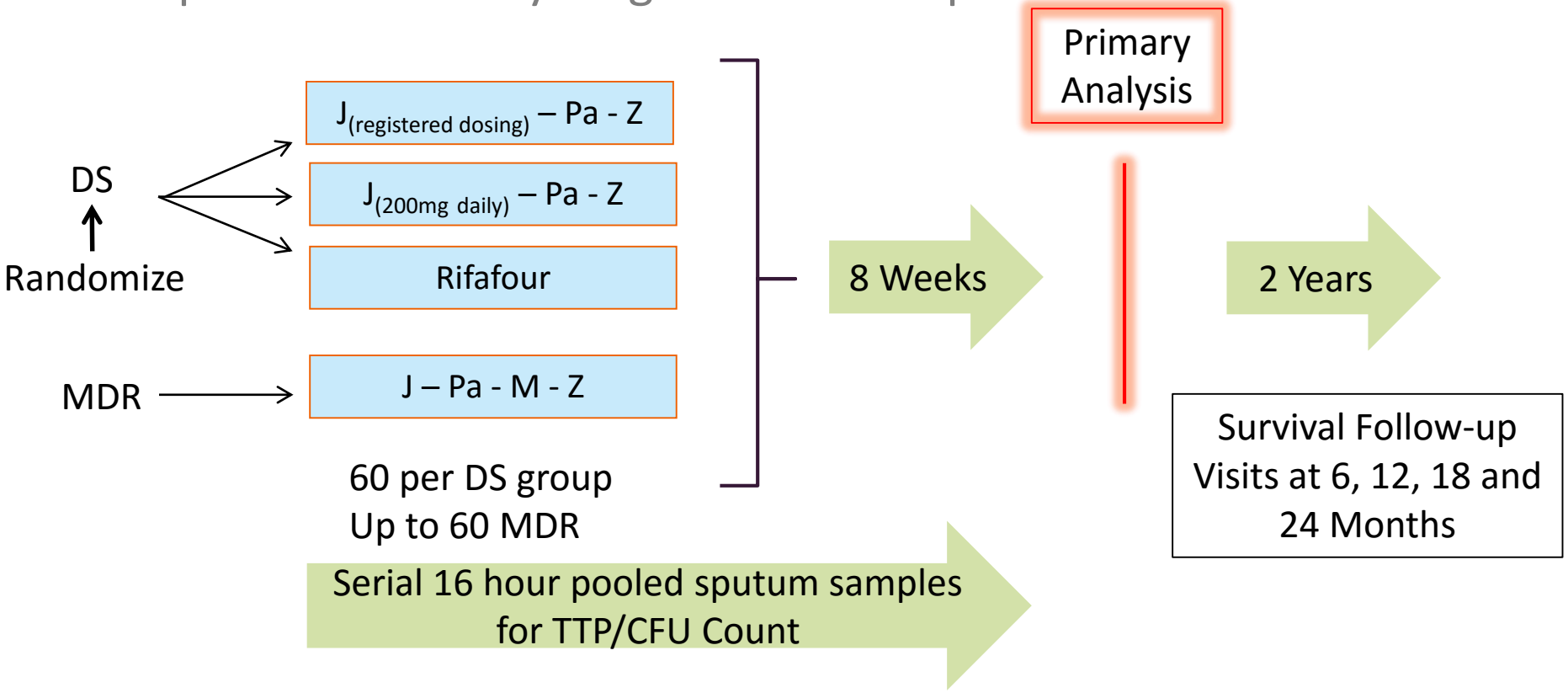
STAND Study Status

- Sept. 22: DSMC recommended enrollment suspension
  - High hepatic toxicity, including 3 deaths
  - FDA placed trial on partial clinical hold
- Nov. 12: DSMC recommended restart of enrollment, but initially excluding HIV positive patients
  - Increased safety features added to study
- Nov. 24: FDA teleconference
  - Permission for sponsor to unblind to hepatic safety data
- March 7: Informal submission to FDA of hold-release document
  - Next steps / timing depend on FDA and DSMC discussions

NC005 – 8 week SSCC Study of J-Pa-Z

J, Pa, Z and M Containing Regimens

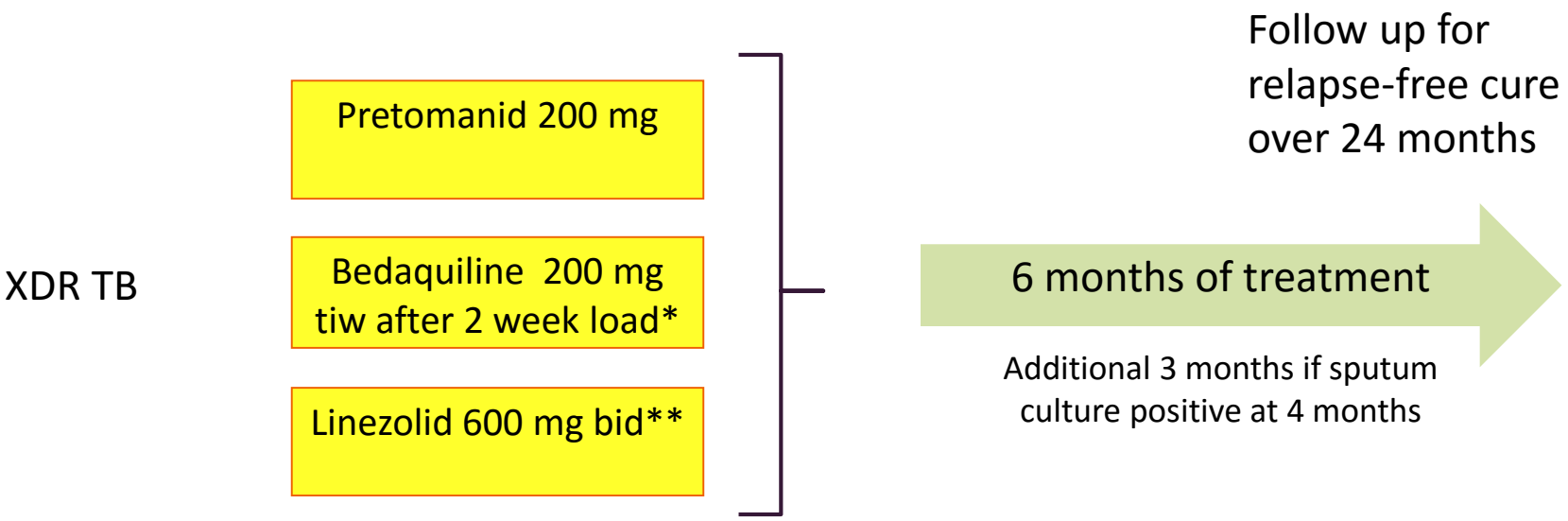
Participants with newly diagnosed smear positive DS and MDR TB



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 Pilot Phase 3 Trial

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



*May adjust dosing Based on NC-005
**May adjust based on linezolid EBA study

Sites: Sizwe and Brooklyn Chest, South Africa

Linezolid as First Oxazolidinone in Regimen

- L may not be safe enough for DS- or first line MDR-TB
  - Safer oxazolidinone to come?
- Initial study in XDR-TB is a “pilot” phase 3 study
  - Definitive outcome study
  - Risk : benefit of skipping phase 2
  - Study design based on preclinical and clinical models
  - Explore safer and more effective ways to deliver linezolid in pilot phase
    - Based on mouse model, dose-ranging clinical study

NiX-TB (BPaL) Study: Key Questions

- How long is L needed?
  - Driven by safety issues of neuropathy and myelotoxicity
- What dose of L is optimal?
- What dosing schedule of L is optimal?

Linezolid (L) Sterilizing Activity

Background of Bedaquiline Plus Pretomanid (BPa) in BALB/c Mice Data From Eric Nuermberger

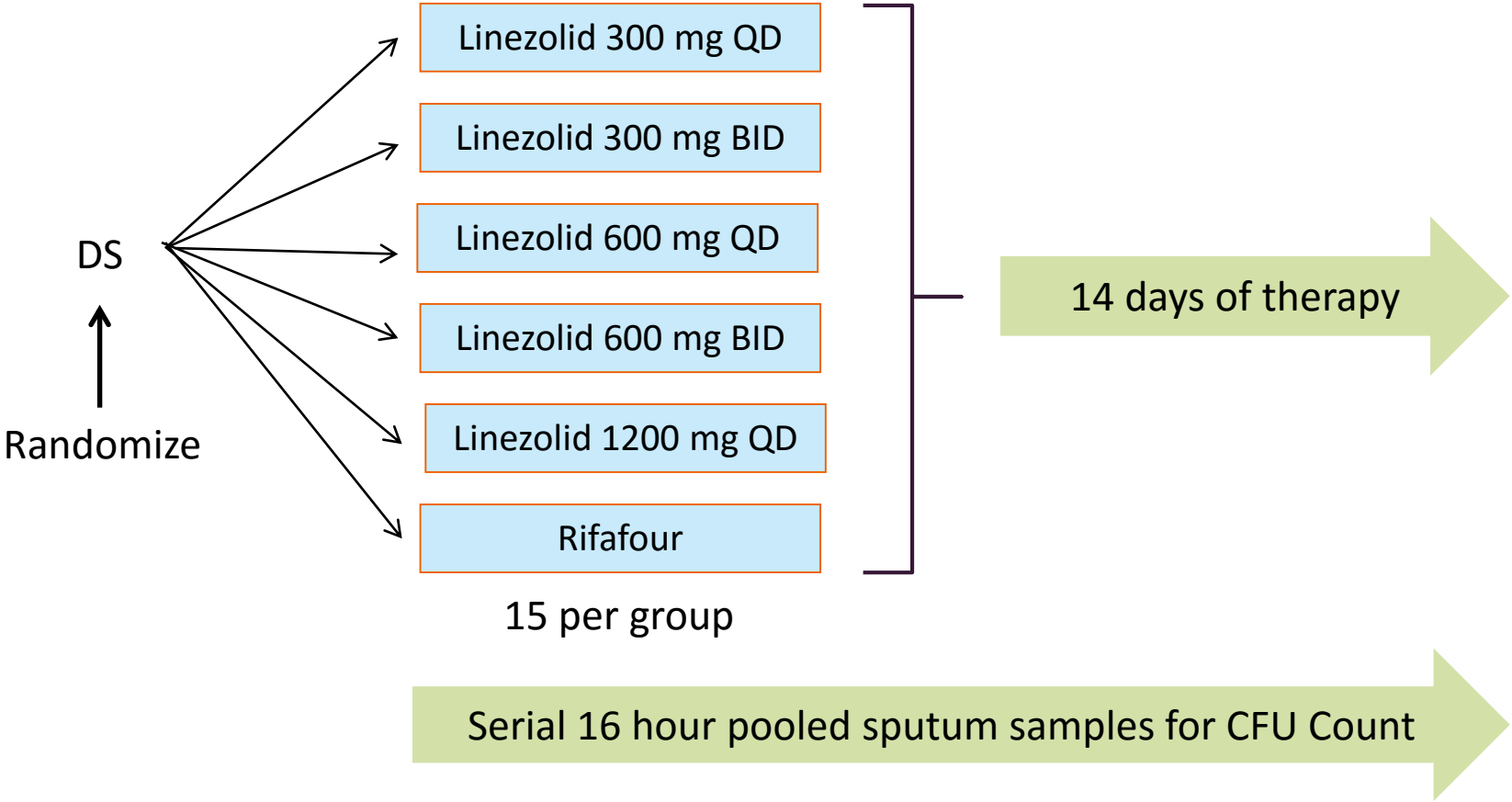
	Proportion relapsing after treatment for:	
Regimen	**2 months**	**3 months**
2RHZ/RH		**8/14 (57%)**
BPa		**3/14 (21%)**
3BPaL	**6/15 (40%)**	**0/15*† (0%)**
2BPaL/1BPa		**0/15*† (0%)**
1BPaL/2BPa	**9/15 (60%)**	**0/15*† (0%)**

*p = 0.11 vs. BPa; †p≤ 0.001 vs. RHZ

LIN-CL-001: Dose-Ranging Linezolid Study

2 Week Safety, Tolerability and Bactericidal Activity Study

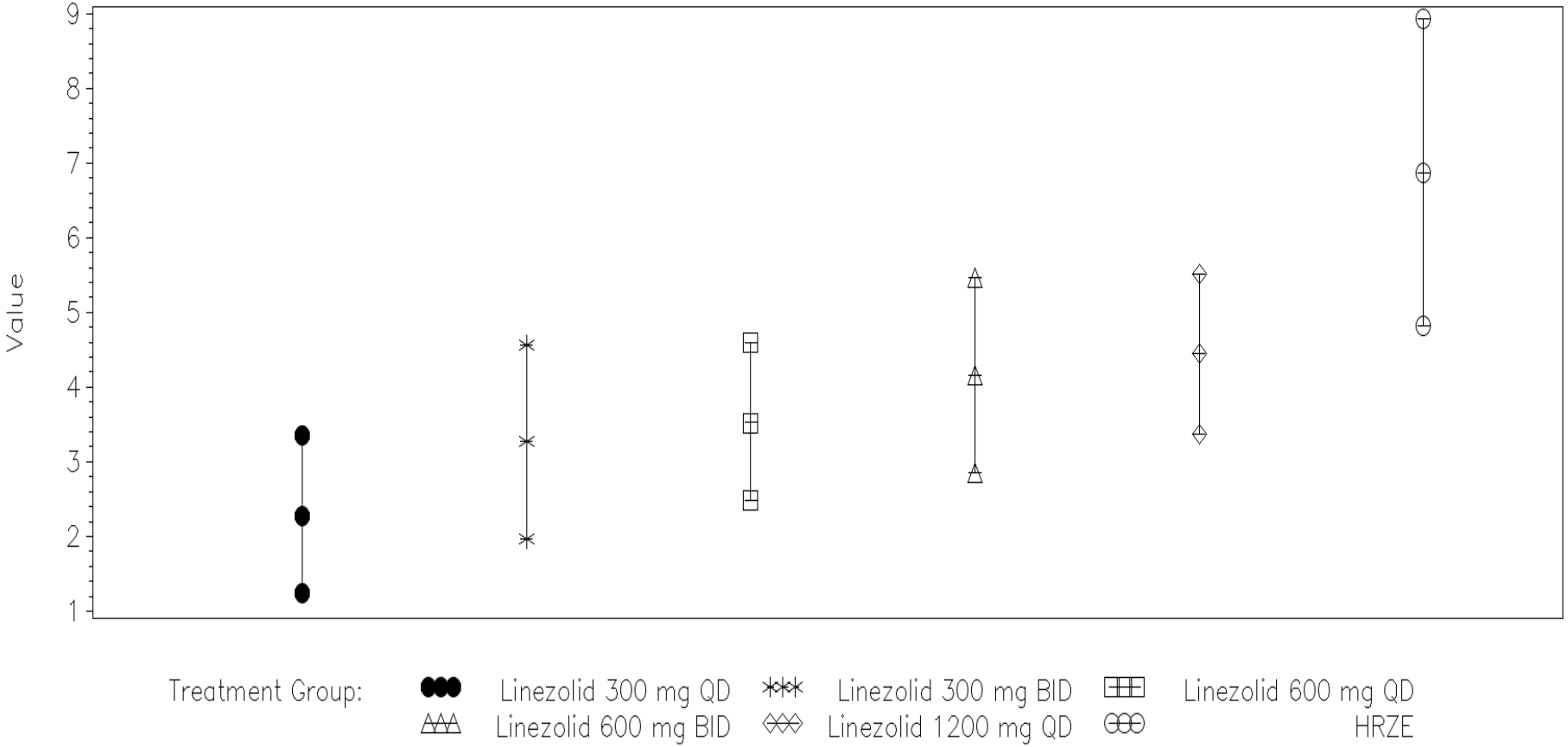
Participants with newly diagnosed smear positive DS TB



Posterior Estimates and 95% BCIs of Mean EBA_{TTP}(0-14)

LIN-CL-001: Data from Andreas Diacon and Rod Dawson

Bayesian NLME Regression Model



BPaL Dose-ranging and Preclinical Results

- Results show dose response between 300 mg and 1200 mg daily
  - Once daily and twice daily dosing of same total daily dose similar
- Mouse relapse results suggest L dosing may be needed for only one or two months, not entire treatment period
  - Similar to Z and E
  - Would help manage L toxicity
- These results informed NiXTB clinical trial

Progress in NiX-TB

- 37 patients enrolled
  - Interim analyses every 15 patients
  - Primary endpoint: culture and clinical status 6 mos after end of treatment
  - First interim analysis 3Q2016, but will have “feel” earlier
- 4 patients died early on in treatment
  - Causes linked to underlying disease
- All other patients doing well
  - Majority culture convert early on, almost all by week 8
  - All responding clinically, gaining weight, etc.
  - Some linezolid dose interruptions and decreases in dose beginning mainly at week 9, but linezolid toxicity manageable
  - 14 patients have completed treatment and have been discharged to home / community