Quo Vadimus?

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TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

TB ALLIANCE

Putting science to work for better, faster TB cures

The Global Need in the TB Market

Global Need

- Current TB treatment is too lengthy, too toxic, and not effective enough in programmatic settings
  - More apparent in MDR-TB
  - But also applies to DS-TB; otherwise MDR-TB would not be on the rise
- Getting a drug approved is not enough
  - Uptake of bedaquiline and delamanid as examples
  - Development plan must address a usage that will have a meaningful impact and be implemented

Key Learnings

- Phase 2 to phase 3 predictability
- Mouse model predictability
- Volumes drive commercial viability

Predictability of Phase 2 Data: Oflotub and REMoxTB Time to Culture Negativity

- Oflotub 2-month phase 2 data within confidence intervals of REMox 2-month data in phase 3
  - Oflotub hazard ratio 1.73 (95% CI, 1.15 – 2.60)
    - ✓Ph 2, **n = 60 / group**
  - REMox hazard ratio 1.25 (95% CI, 1.10 – 1.40)
    - ✓Ph 3, **n = 640 / group**
- Cf. relevance to 2-week EBA data

Mouse Relapse Data

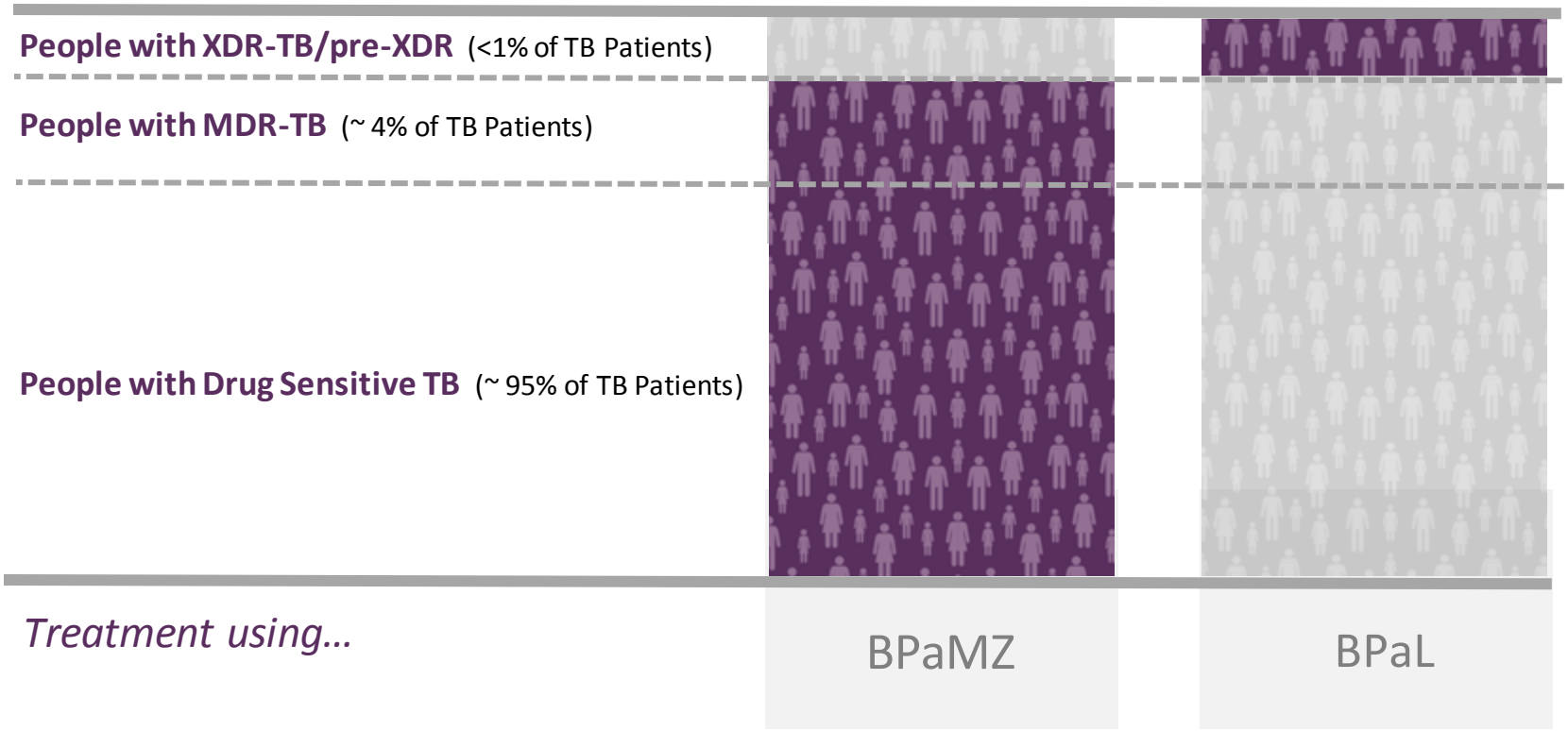
	M1.5 (+3)	M2 (+3)	M3 (+3)	M4 (+3)	M5 (+3)
RHZ				10/15	**2/15**
$Pa_{50}MZ$				6/14	0/14
PaMZ			10/14	**3/15**	
BPaM			2/15	**0/14**	
BPaZ	**13/14**	**0/15**	0/15		
BPaMZ	**3/15**	**0/15**	0/15		

Rank order BPaMZ > BPaZ > BPaM > PaMZ > RHZ same as clinical rank order; cf. BPaL

Other Predictions from Mouse and EBA Models

- Prospective predictions important
- Mouse relapse model predicts that L can be withdrawn from BPaL after 2 months, just like PZA from HRZE
  - Being tested in ZeNix
- EBA model predicts that L 600 mg almost as effective as L 1200 mg
  - Being tested in ZeNix

Treatment For All With Universal Backbone of B-Pa: Importance of Volumes

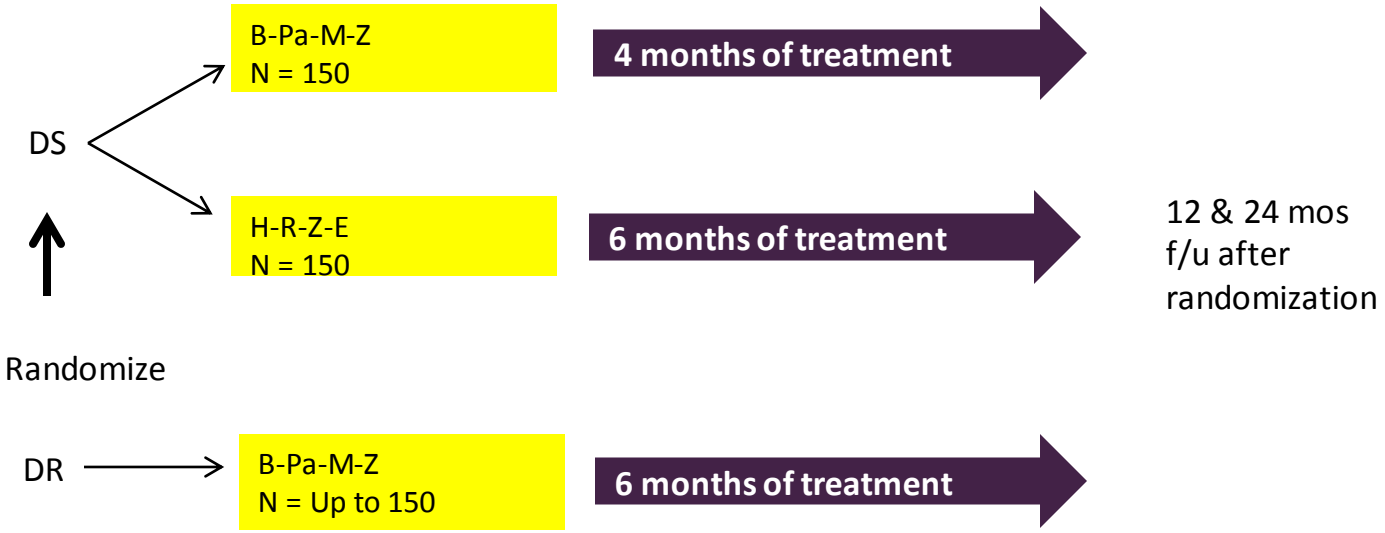


Other Learnings

- Efficiency of regimen development
  - Requires demonstration of individual contributions of all drugs in the regimen
    - Animal studies, EBA studies
  - Still requires non-inferiority phase 3 trial
- Efficiency of "unified pathway"
  - DS- and MDR-TB are different genotypes, not different diseases
    - Allows formal noninferiority comparison in DS subjects only
  - "Breakthrough" for MDR-TB not efficacy, but delivery and safety
    - Extremely precise comparison of new regimen efficacy vs MDR SOC not good use of resources
  - 80% cure with MDR SOC when DST incorporated
    - STREAM, Otsuka phase 3
    - Non-inferiority approach likely needed in MDR-only studies going forward
  - Volumes at launch

SimpliciTB Trial: BPaMZ

Participants with newly diagnosed DS- and MDR-TB



B = bedaquiline 200 mg x 8 wks, then 100mg Pa = pretomanid 200 mg

M = moxifloxacin 400 mg Z = pyrazinamide 1500mg

Regimen Development and Non-Inferiority Margin

- HRZM vs HRZE
- BPaMZ vs HRZE

Unified Pathway and Non-Inferiority Margin

- BPaMZ vs HRZE
- Non-inferiority studies against MDR SOC will be more difficult than against HRZE
  - Similar numbers, but harder population to recruit and study
- MDR SOC + B (shorter) vs MDR SOC + Pbo
- MDR SOC + B – injectables vs MDR SOC

Next Steps

- Universal regimen: not there yet, but
- On the verge of same or similar treatments for DS- and MDR-TB
  - Due to NCEs
  - Will no longer need separate health care systems, manufacturers, drug supplies, distribution channels for DS- and MDR-TB
    - Particularly impacts MDR- and XDR-TB, where drug costs are increased by low volumes and treatments are complex
  - Healthcare and drug delivery easier, cheaper, simpler, requiring fewer resources

Challenges

- Funding and resources, particularly for late-stage clinical development
- DS- and MDR-TB treatments siloed around globe
  - Different organizations and systems, each with vested interests
  - Combining will be transformative in freeing up resources and providing quality care, but will also be disruptive
- Pharma not “in the game”
  - Economics don’t justify
  - But opportunity to re-engage pharma
  - Economics different if large volumes and if clear and efficient path to development and regulatory approval

One More Thing: REMoxTB Data on Liquid Culture

- Difference in incidence and quality of "isolated positives" between solid and liquid culture
  - Adjustment in endpoint needed for liquid culture
  - Importance of clinical assessment

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