



Pediatric TB Clinical Trials and Treatment Regimens

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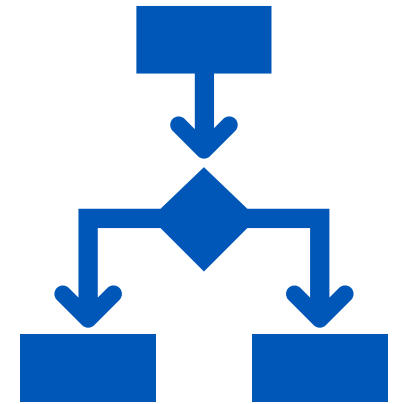
Disclosure:

No relevant financial disclosures to report. I will discuss off-label use of some TB medicines in children.

Overview

1. Approach to TB therapeutics in children
2. Regimens and trial evidence
 - DS-TB
 - MDR/RR-TB
3. Looking forward
 - Shorter, better treatment
 - New drugs and regimens

Framework for childhood TB therapeutics



Approach to study of TB treatment in children

Optimization
Different
regimen than
adults

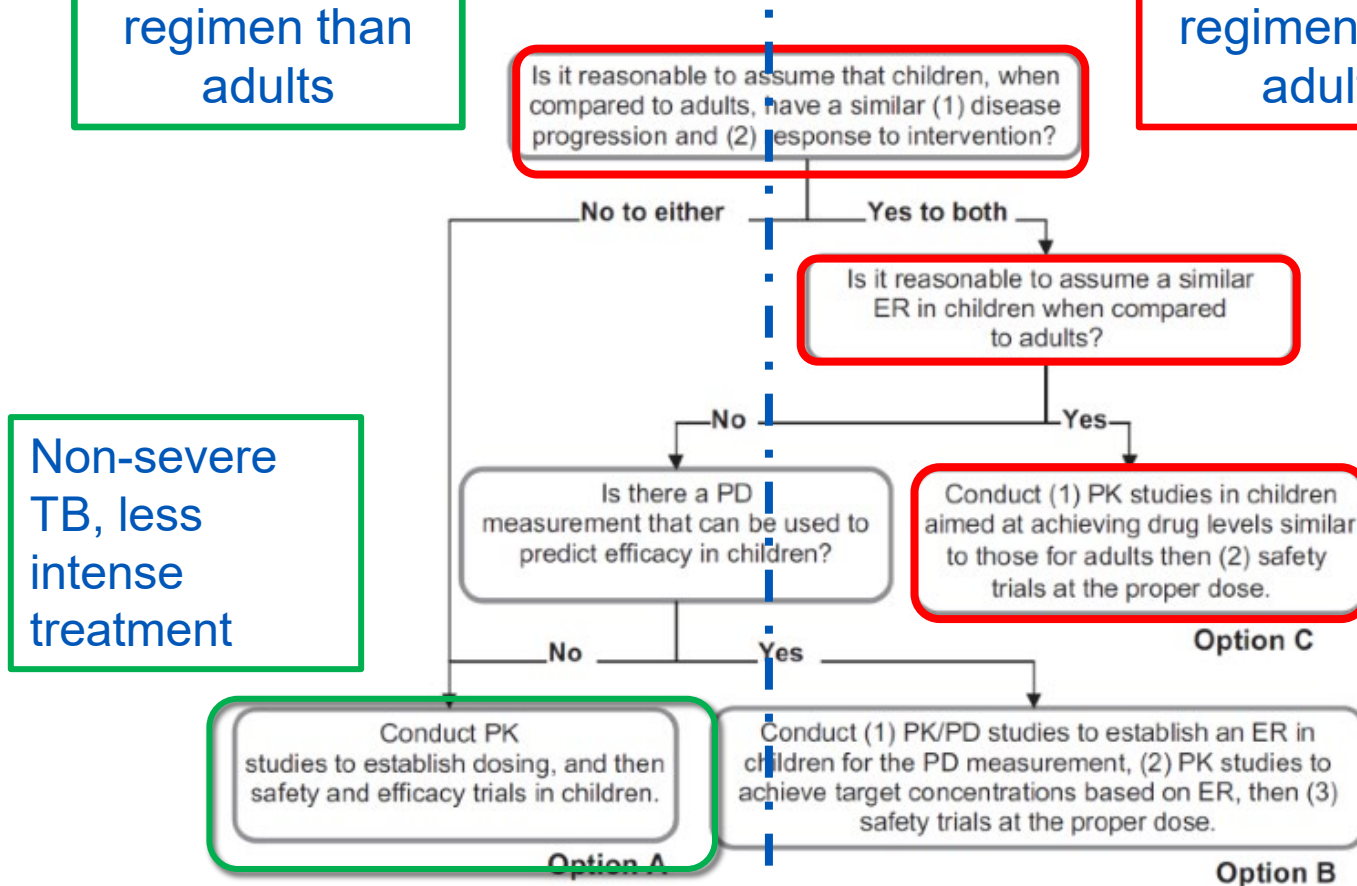
Access
Same drug or
regimen as in
adults

Access

1. Similar disease progression and similar response to intervention
2. Similar exposure response
3. Study: PK, safety

Optimization (for children)

1. Disease progression or response different in children
2. Study: Efficacy, safety

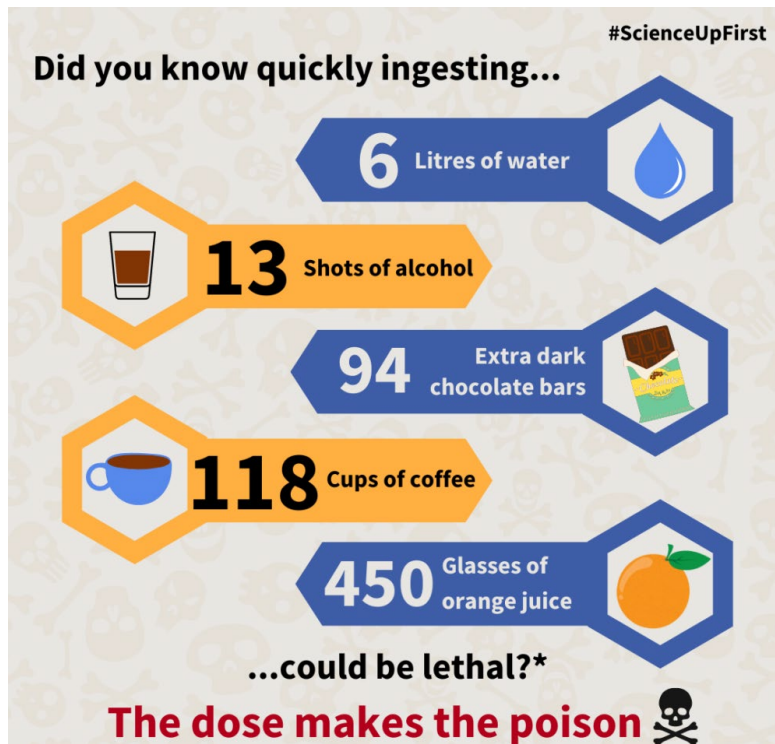


¹ Dunne J et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics (2011);

² FDA Guidance for Industry Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (2003)

Approach to study of TB treatment in children (2)

EXTRAPOLATION

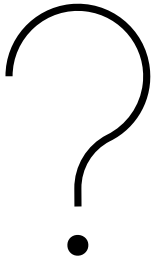


In TB, efficacy of a drug/regimen can be extrapolated from *adults* to *children* IF drug levels in *children* are the same as in *adults*

Exposure matching

- Identify dose in children resulting in same drug exposures/levels as adults
- Monitor safety at those exposures/levels

Polling Question



Is it necessary to do formal efficacy studies of a TB drug in children if efficacy has been demonstrated in adults?

A. Yes – formal efficacy studies in children are required

B. No – formal efficacy studies in children are NOT required

B. No – extrapolate efficacy in children are NOT required. PK, dose and safety of the drug must be established in children.

Priorities for enabling optimal RR-TB treatment in children

- Is it necessary to study individual TB drug efficacy in children if demonstrated in adults? **No – extrapolate efficacy from adults.**
- What is the priority? **Study of PK dose, safety and acceptability**
- The same mg/kg dose results in the same drug exposures for all children? **No – must consider weight and age effects**
- Are efficacy trials in children sometimes appropriate? – **Yes, in specific circumstances, e.g. treatment optimization**
- Way to deliver the drug – child-friendly formulation, other



Regimens for Pediatric TB Treatment

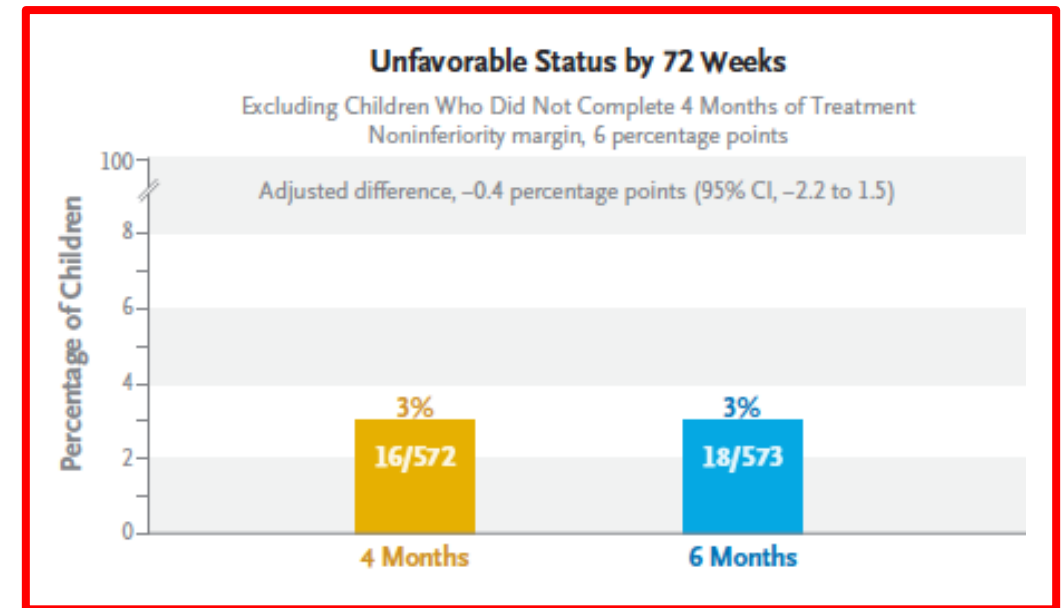


Regimens for DS- and MDR/RR-TB in children

	Regimen	Age range	Severity
DS-TB	26 weeks of HRZE (2HRZE/4HR)	All ages	Severe or non-severe PTB
DS-TB	16 weeks of HRZE (2HRZE/2HR)	3 months to <16 years	Non-severe PTB
DS-TB	17 weeks of HPMZ (2HPMZ/2HPM)	≥12 years of age	Severe or non-severe PTB
MDR/RR-TB	26 weeks of BPaL/M	≥14 years of age	Severe or non-severe PTB
MDR/RR-TB	26 weeks of BDLLC	All ages	Severe or non-severe PTB
MDR/RR-TB	9 months of BLMZ, BCLLfxZ, BDLLfxZ	All ages	Severe or non-severe PTB
*Consider: 1. drug susceptibility; 2. age; 3. location of disease (PTB vs EPTB); 4. severity			

DS-TB: SHINE TB Trial

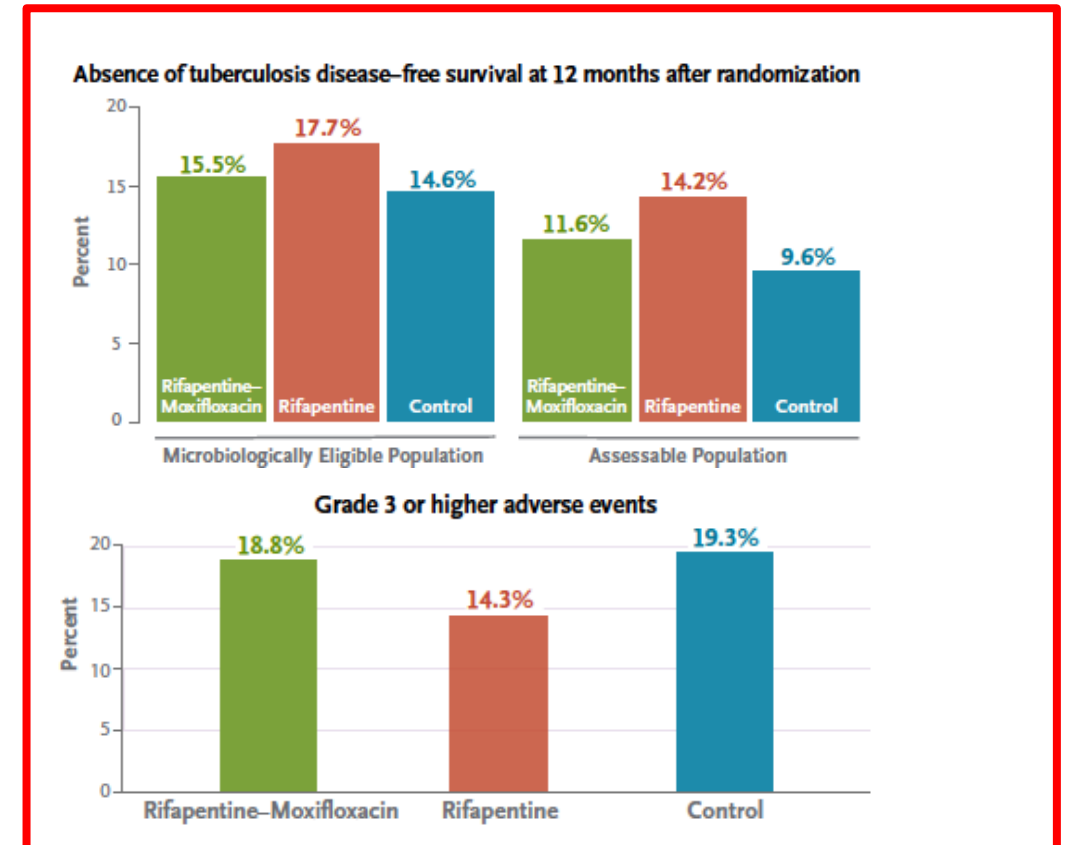
Design	Randomized controlled 2-arm non-inferiority trial
Eligibility	Age 0-16y Weight >3 kg Symptomatic non-severe TB*
Sample size	N=1204
Regimen	SOC 26 weeks (4HRZE/2HR) versus 16 weeks (2HRZE/2HR)
* Non-severe = ≤1 lobe on CXR; no cavities, complex pleural effusion, or airway obstruction; extrathoracic lymph nodes; smear negative	



- Rifampicin exposures low in some weight bands
- Challenges with determining disease severity in some settings

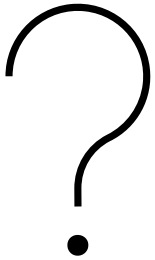
DS-TB: S31/A5349

Design	Randomized controlled 3-arm non-inferiority trial
Eligibility	Age ≥12 years Sputum AFB smear or rapid NAAT pos PTB No severe EPTB Weight ≥40 kg
Sample size	N=2516
Regimen	SOC 26 weeks (4HRZE/2HR) versus 17 weeks 2HPMZ/2HPM or 17 weeks 2HPZE/2HP



- RPT dose to approximate 1200 mg OD not known in children <12 years

Polling Question



5-year-old male with no significant medical history identified in a contact investigation to have 3 weeks of non-remitting cough, 10 days of fever, 2 kg weight loss over the last 4 weeks. His father who lives in the same home was diagnosed 1 month ago with pulmonary TB susceptible to all drugs tested (INH, RIF, PZA, EMB, MFX). His exam is non-focal, HIV test is negative, IGRA is positive, CXR shows B hilar adenopathy, with small RML opacification, gastric aspirates are AFB smear negative and Xpert negative. You diagnose PTB. What is your initial choice of treatment regimen?

A. 2HRZE/4HR

B. 2HRZE/2HR

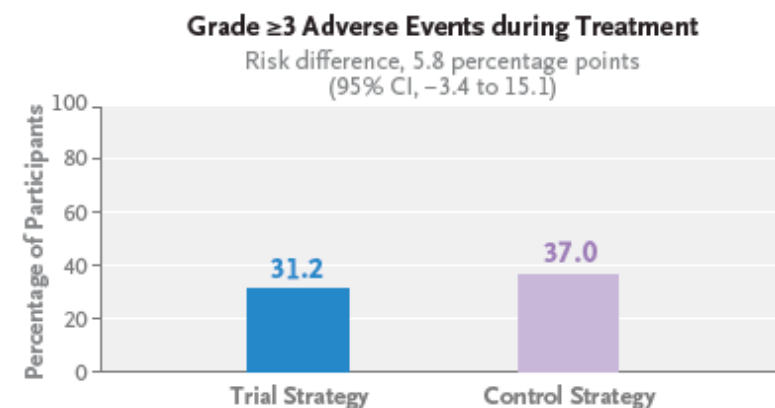
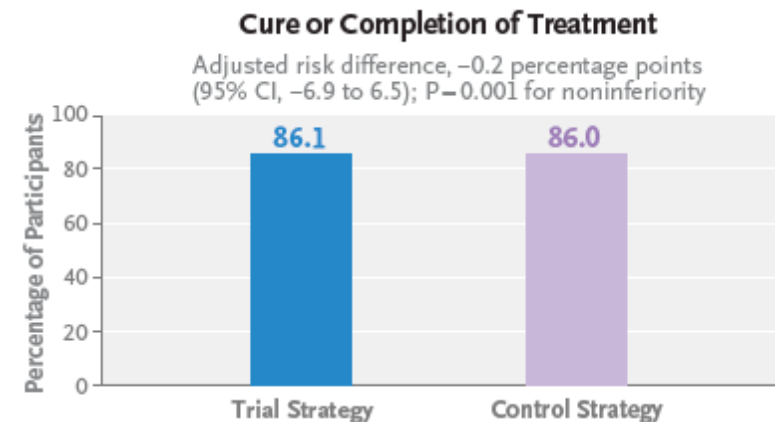
C. 2HPMZ/2HPM

D. 6BDLLfxC

B. Between 3m and 16 years with non-severe DS PTB without evidence of severe EPTB

MDR/RR-TB: BEAT-TB South Africa

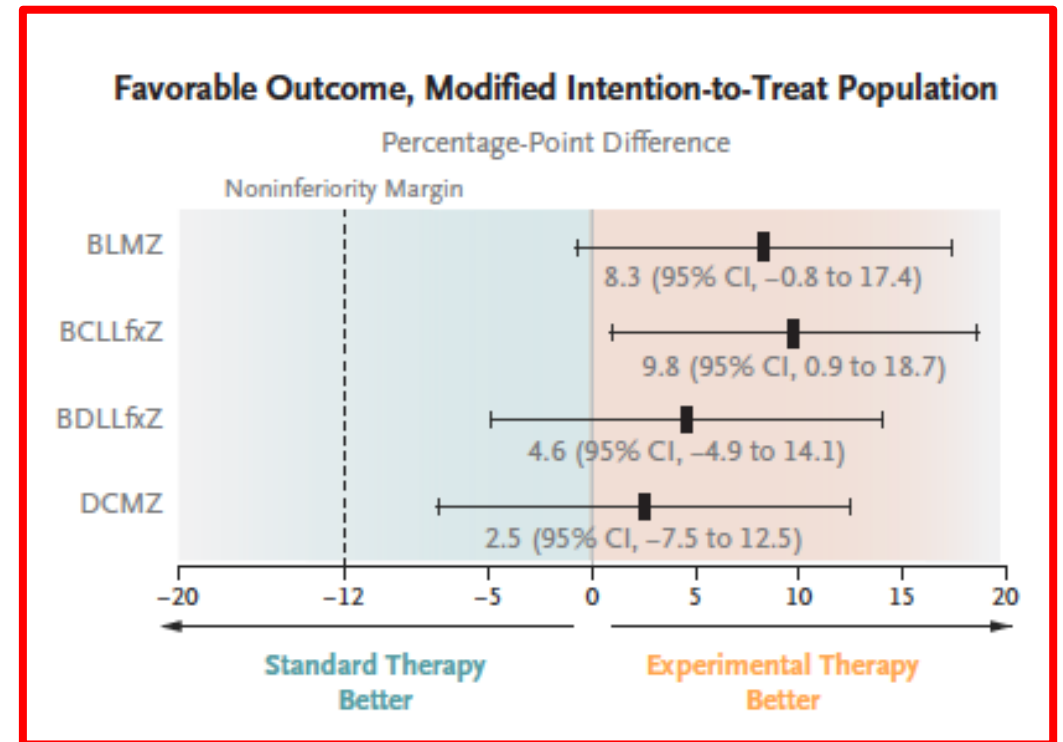
Design	Pragmatic, randomized controlled non-inferiority trial
Eligibility	Age ≥ 6 years of age Pulmonary TB with at least RIF-R
Sample size	N=403
Regimen	Local SOC (WHO 9m or longer) versus trial-strategy (BDLLfxC) • FQN-S: BDLLfx • FQN-U: BDLLfxC • FQN-R: BDLC



- Extrapolate to children of all ages

MDR/RR-TB: endTB

Design	Randomized controlled 6-arm non-inferiority trial
Eligibility	Age $\geq 15y$ Confirmed RR-TB with FQN-S
Sample size	N=754
Regimen	SOC versus 39 weeks of: BLMZ BCLLfxZ BDLLfxZ DCLLfxZ DCMZ



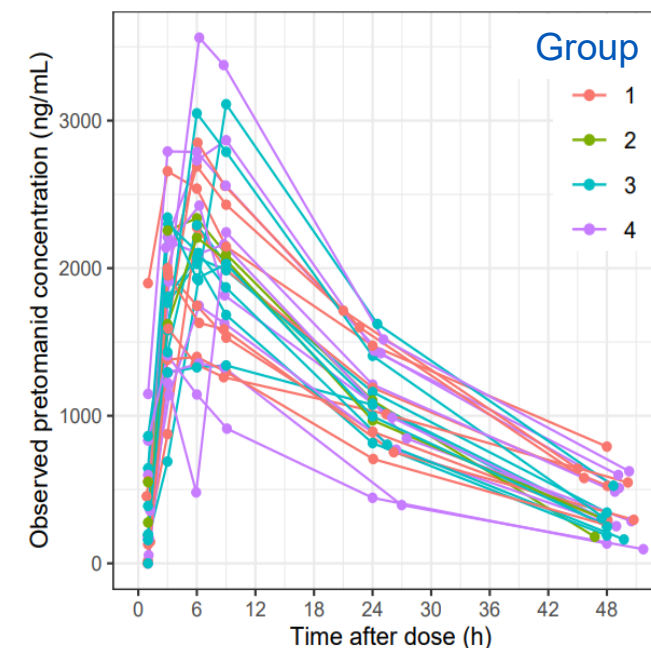
- Extrapolate results to children of all ages
- BLMZ > BCLLfxZ > BDLLfxZ
- Consider available drugs

MDR/RR-TB: Pretomanid (BPaL/M)

Current use	Pediatric data	Pediatric studies, status
• FDA approved, Component of Nix, other regimens under evaluation • WHO recommended in BPaLM/BPaL for MDR/RR-TB and XDR-TB in adults and adolescents (2022)	• Pediatric data delayed • Children <14 years • Male reproductive toxicity in rats • 2x dispersible tablet trial formulations developed	• IMPAACT 2034: PK, safety of single-dose of pretomanid in children with RR-TB (completed 2026) • Female children • Multiple dose study being planned (IMPAACT 2051)

IMPAACT 2034: PK, Safety, Acceptability of Single-Dose Pretomanid in Female Children with RR-TB

PK Parameter, median (range)	All (N=27)	Group 1 (n=8) 4 - <12kg	Group 2 (n=2) 12 - <20kg	Group 3 (n=8) 20 - <31kg	Group 4 (n=9) >31kg
Pretomanid dose		8-<12kg: 50 mg (paeds) 6-<8kg: 35 mg (paeds) 4-<6kg: 20 mg (paeds)	50 mg	100 mg	≥40kg: 200mg 31-<40kg: 100mg
C _{max} (ng/mL)	2275 (1341-3562)	2124 (1399-3850)	2272 (2207-2338)	2295 (2060-2520)	2243 (1354-3562)
AUC _{0-∞} (µg*h/mL) (model)	59.6 (28-95.9)	66.2 (45.9-94)	58.6 (58.1-59.1)	57.5 (46.8-85.5)	59.8 (28-95.9)



For reference, exposure median (range) in adult trials was:

C_{max} 1975 ng/mL (1120-3270) and steady-state AUC₀₋₂₄ 59.5 µg*h/mL (28.7-117)

Looking forward: shorter
regimens, new drugs



Key considerations for shorter regimens

1. Extrapolation
 - Reasonable to extrapolate efficacy of shorter regimens studied in adults
2. Can we treat TB in children with shorter durations than current regimens?
 - Likely yes
 - SHINE, adult trial results, nonclinical data
3. Are shorter duration regimens the most important goal?
 - No, important goal to balance with efficacy, safety, tolerability, acceptability
4. How to design TB treatment shortening trials for children
 - Tricky to decide on the treatment duration
5. Are there others ways we can effectively shorten treatment by reducing administration without shortening treatment exposure?
 - Long-acting formulations

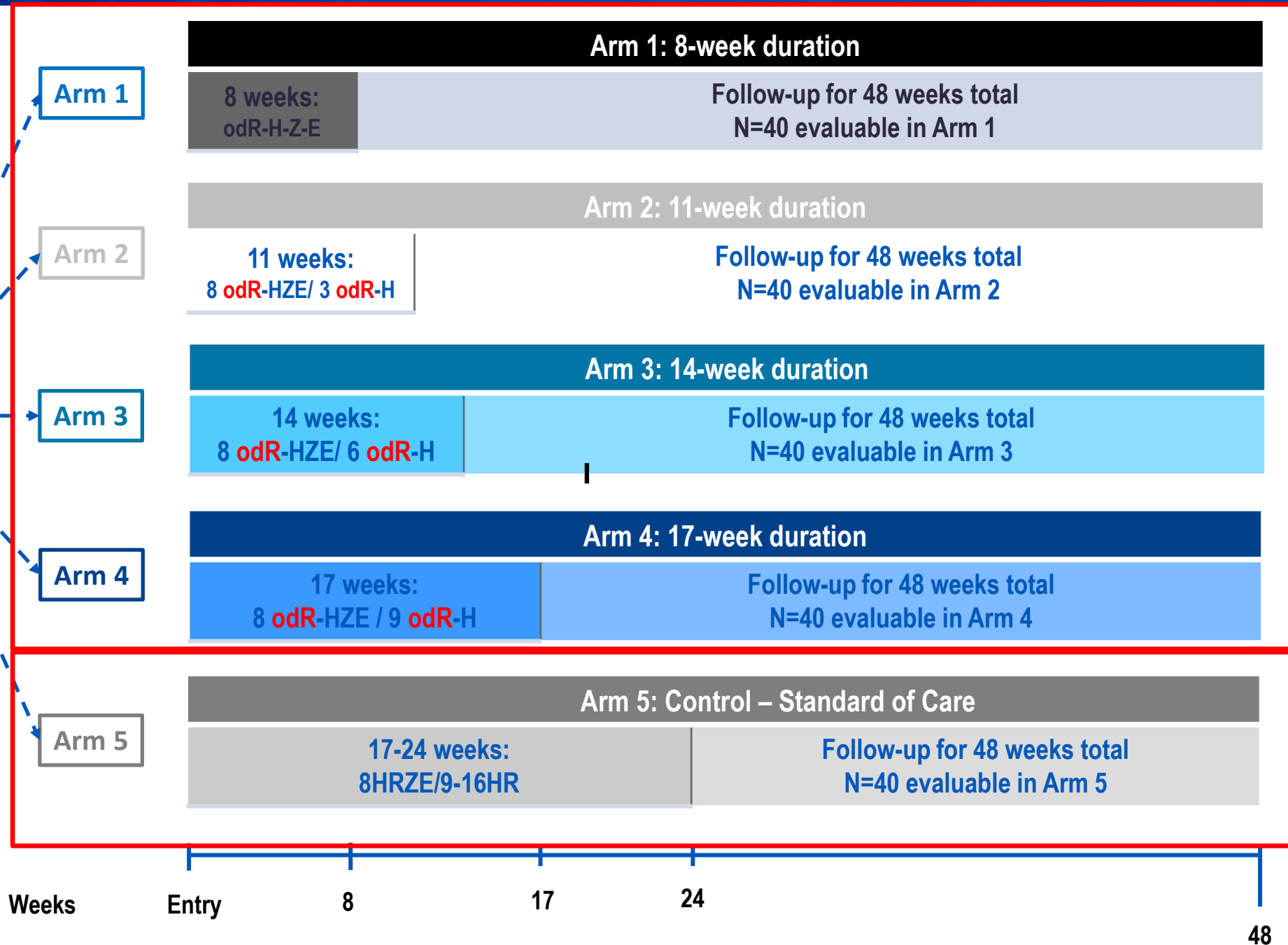
SMILE-TB Trial

- **Title:** Shortened RegiMen for Drug-susceptible TB in Children (SMILE-TB)
- **Design:** International, multicenter, randomized controlled, open-label, 2-arm, phase 3 noninferiority trial.
- **Population:** Children 3m to <10 years with pulm or lymph node DS-TB (n=860)
- **Intervention:** HPMZ (8 weeks) versus 2HRZE/2-4HR (Control)
- **Overall aim:** To determine if 2HPMZ has non-inferior efficacy compared to SOC treatment
- **Status:** Open and enrolling

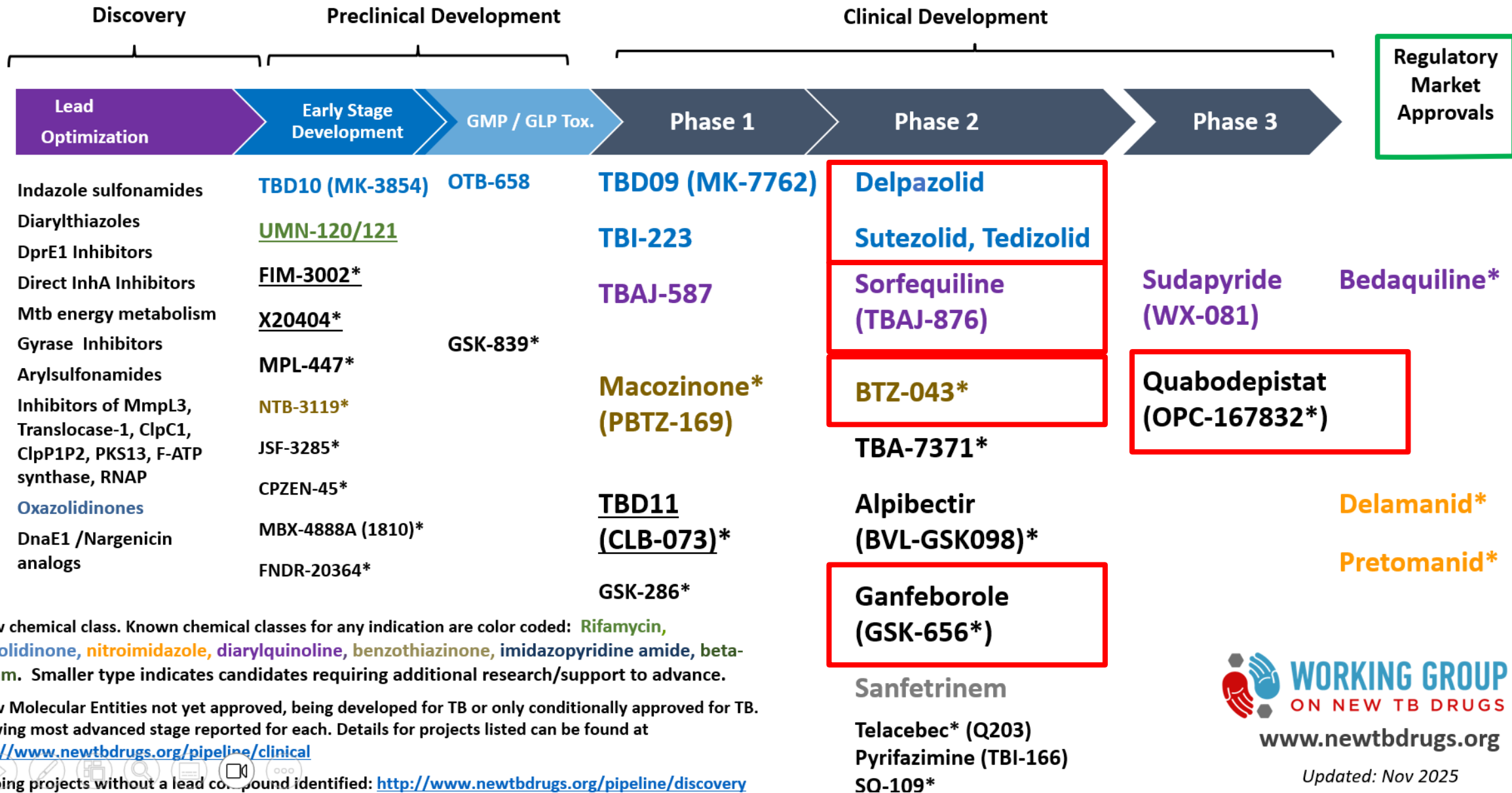
REDUCE-TB Trial

- **Title:** Re-evaluating the Duration in Children of TB Treatment (REDUCE TB)
- **Design:** Multi-arm open-label phase IIC trial with duration randomization
- **Population:** Children 3m to <10 years with pulm DS-TB (n=230)
- **Intervention:** hdRIF with HZE for differing durations (8-17 weeks)
- **Overall aim:** Identify the shortest duration study regimens that have acceptable efficacy and safety for evaluation in a phase III trial
- **Status:** To open in Q1 2027

Children 3
mo to
<10 years
with
confirmed
or clinically
diagnosed
DS-TB
[1:1:1:1:1]
[n=200]



2025 Global New TB Drug Pipeline¹



Challenges in access to new TB drugs and regimens for children

- Overall delays
 - 8–13-year delays between adult approvals and pediatric approvals across all ages
 - Start too late, take too long
 - CHEETA
- Access in the U.S.
 - Registration of drugs in the U.S.
 - Registration of child-friendly formulations



Questions and Answers





Thank you