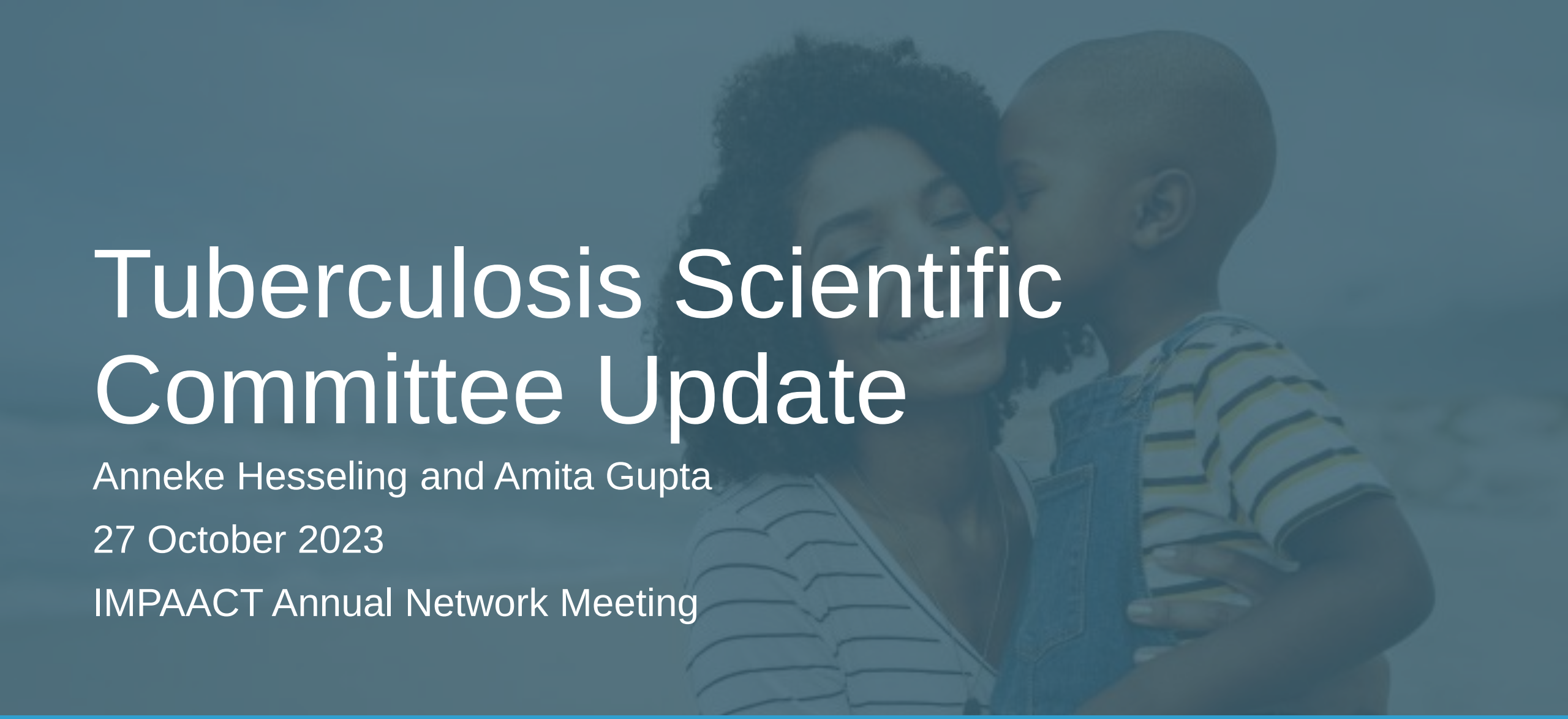

Tuberculosis Scientific Committee Update

Anneke Hesseling and Amita Gupta

27 October 2023

IMPAACT Annual Network Meeting

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

TBSC Goals and Overall Strategy

To evaluate novel approaches for TB prevention, diagnosis and treatment in HIV-positive and negative infants, children, adolescents, and pregnant and postpartum women that will lead to optimal dosing and regimens, global recommendations, licensing and improved care and access.

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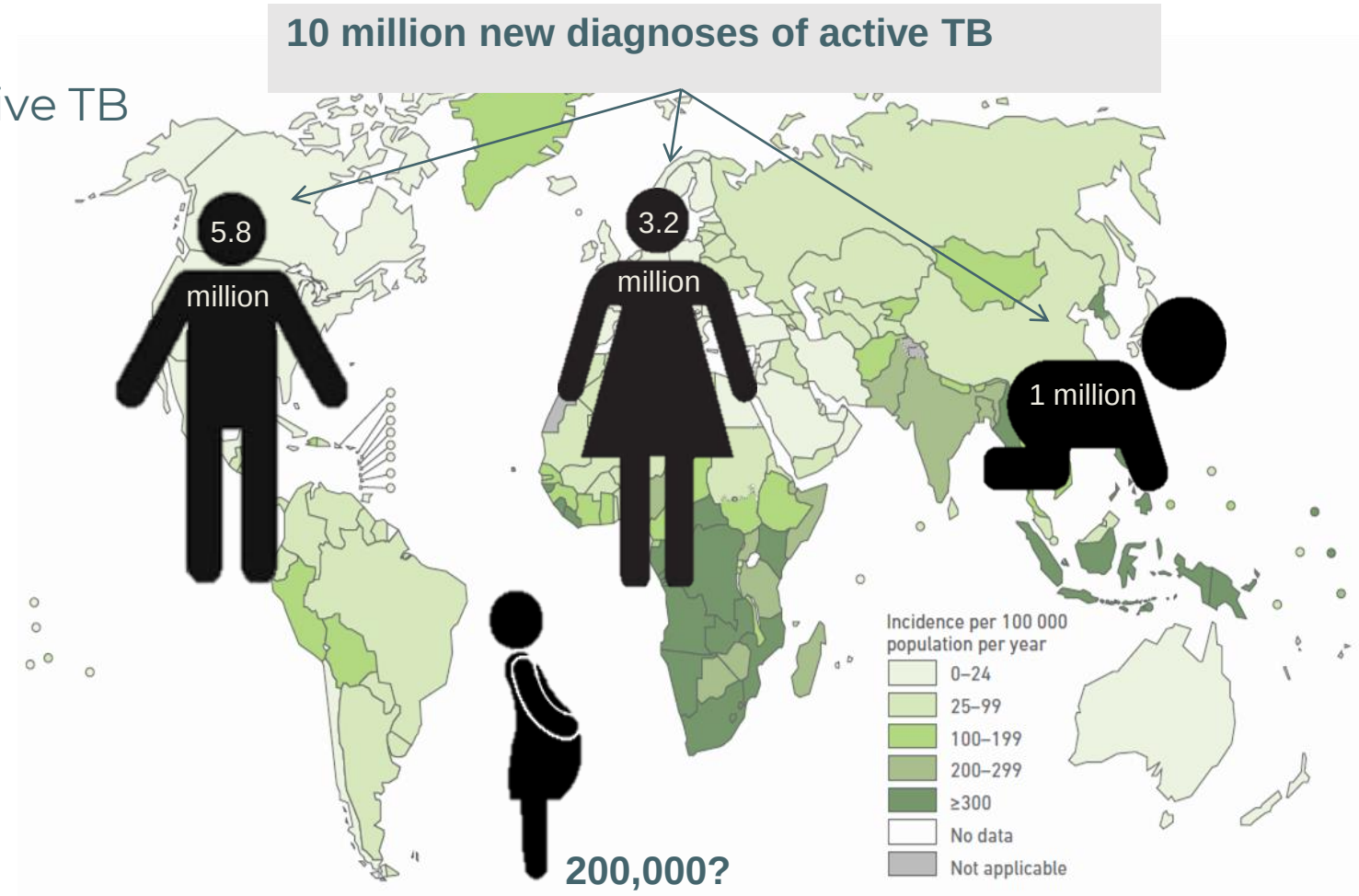
Global TB Burden

10.6 million new diagnoses of active TB



WHO 2022

WHO Global TB Report 2020, Sugarman Lancet GH 2014

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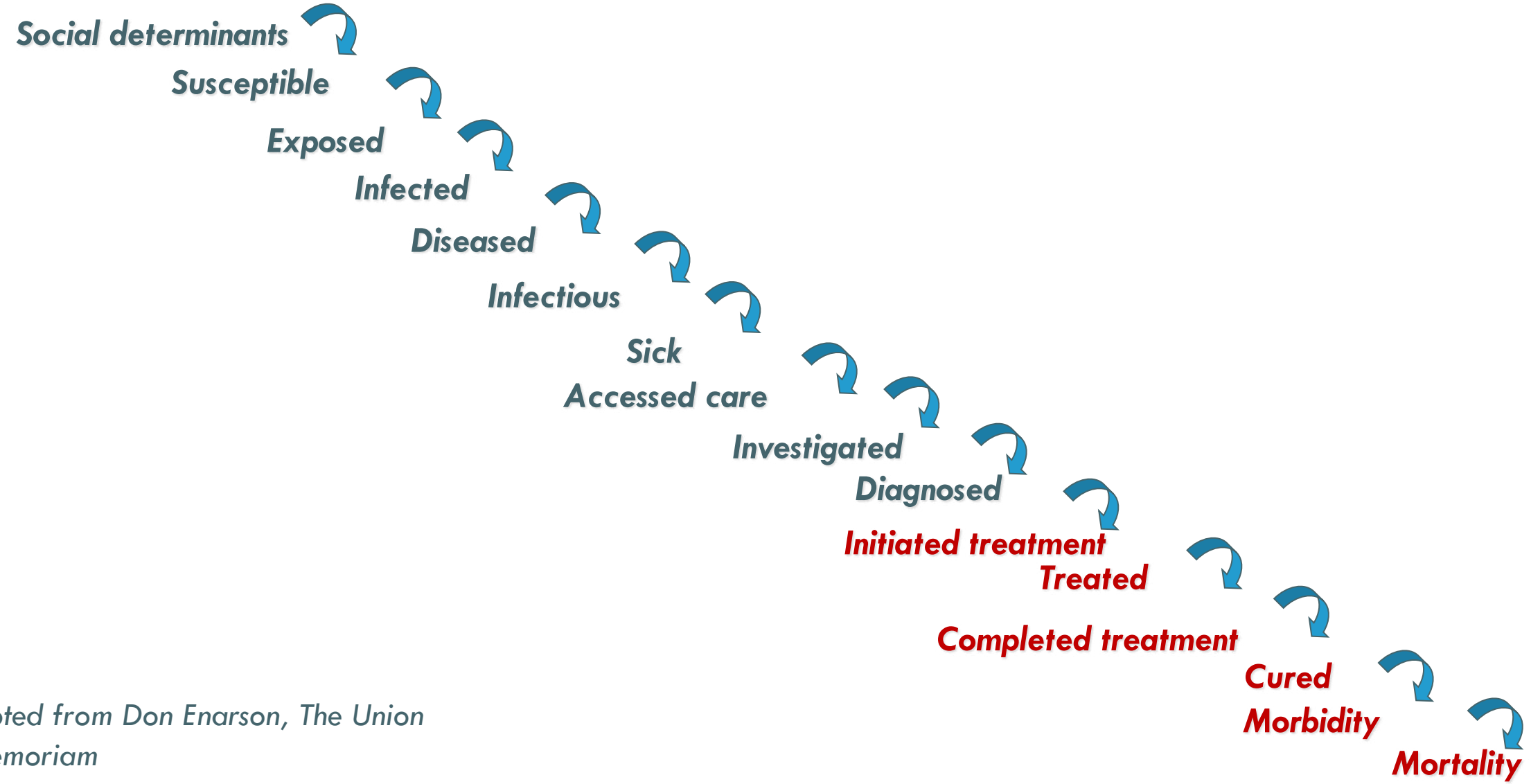
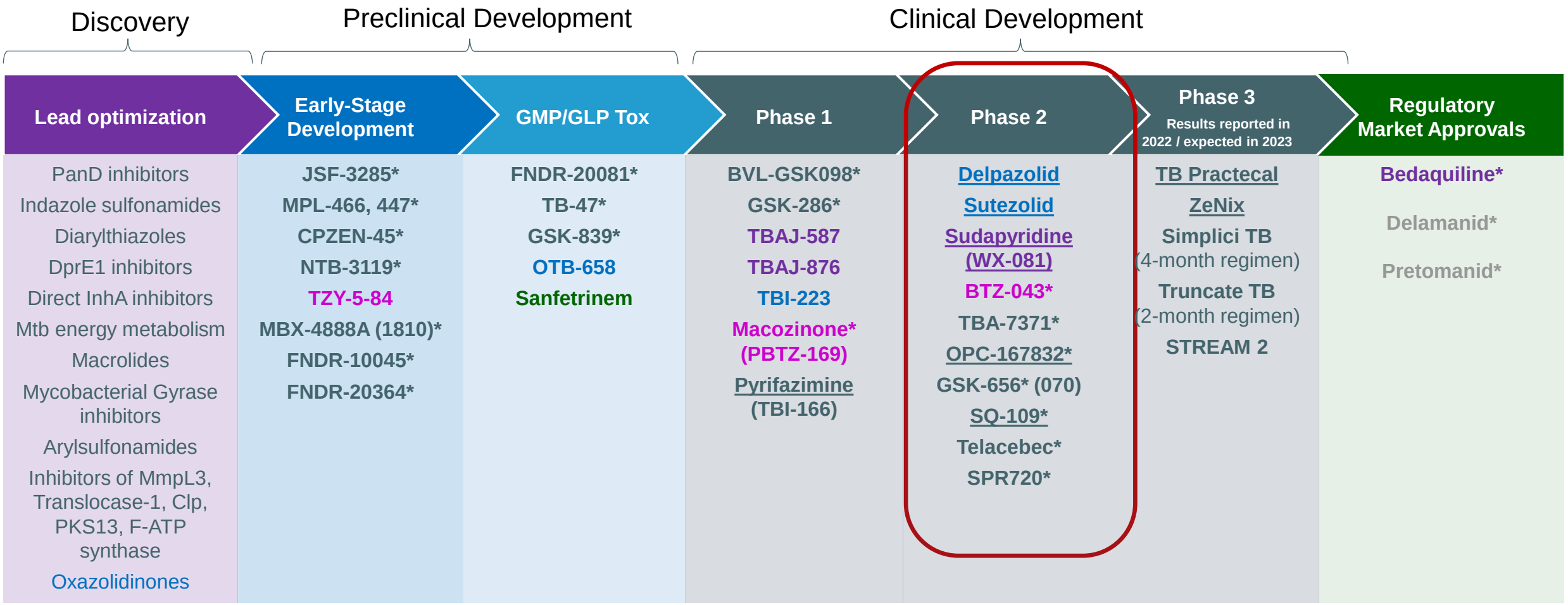
Key Transitions in Tuberculosis: Treatment



Adapted from Don Enarson, The Union
In memoriam

2022 Global Pipeline of New TB Drugs

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org
Updated: March 2022



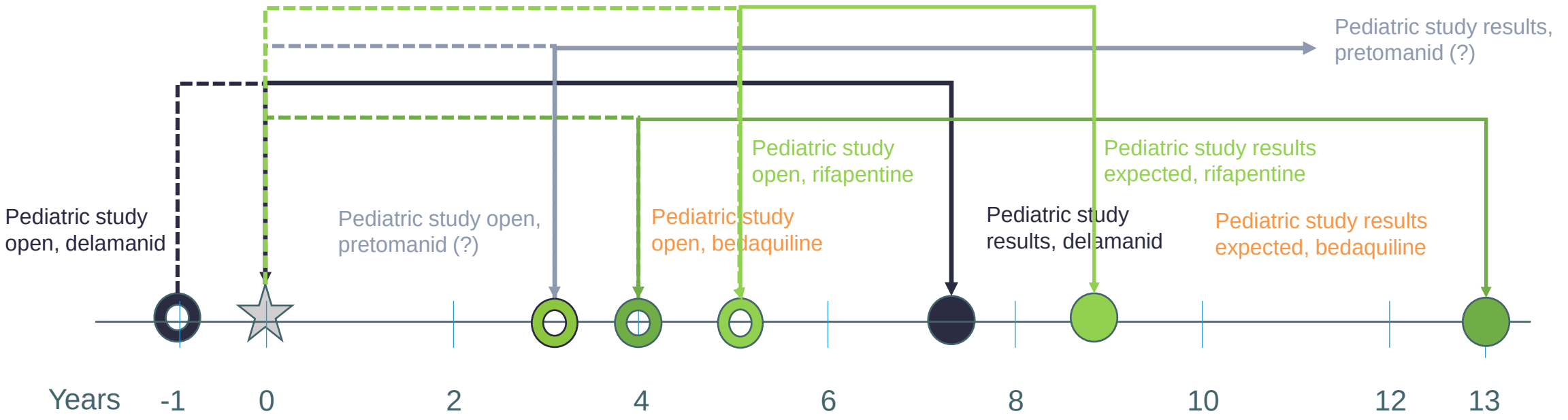
Underline = updates since October 2021

*New chemical class; known chemical classes for any indication are color-coded: oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, beta-lactam

[1]New molecular entities not yet approved, being developed for TB or only conditionally approved for TB (most advanced stage for each); details for projects listed can be found at www.newtbdrugs.org/pipeline/clinical; ongoing projects without a lead compound series identified: www.newtbdrugs.org/pipeline/discovery

DprE1, Decaprenylphosphoryl-β-d-ribose 2′-epimerase; GLP, Good Laboratory Practice; GMP, Good Manufacturing Practice; MmpL3, Mycobacterial membrane protein Large 3; Mtb, *Mycobacterium tuberculosis*; PKS13, polyketide synthase 13; TB, tuberculosis; tox, toxicity

Dramatically delayed paediatric TB treatment research and development prevent children from sharing in the benefits of scientific progress



Stringent Regulatory Authority (SRA) approval granted for adults, all drugs

Courtesy, Lindsay McKenna

Substantial Progress in TB Drug Evaluation in Children

	Evidence on PK, dose, safety, acceptability	Child-friendly formulation*
Moxifloxacin	√	√
Levofloxacin	√	√
Bedaquiline	√	√
Linezolid	√	√
Clofazimine	√	√
Delamanid	√	√
Pretomanid	P2034 (single dose)	
New compounds	X	X
Rifapentine	TBTC Study 35, TBTC Study 39, DOLPHIN Kids, P2024	
Rifampicin	X	X

WHO TB PADO Priorities: dispersible, scored, palatable paediatric formulations

Slide adapted, Tony Garcia-Prats.

TBSC Strategy

- Focus on therapeutic trials with high impact and programmatic relevance
- Continuous landscaping to ensure relevance and avoid redundancy, speaking to network strengths
- State of the art trial design PK methods
- Early engagement with industry to avoid long delays
- Alignment with WHO research priorities
- Innovations in formulation development work
- Socio-behavioral work relevant to policy and practice: acceptability, end-user preferences and formative work
- Leveraging additional funding: e.g. P1078 (Ro1), P2020 (Uo1 application)
- Strong focus on community engagement
- Ongoing participation in WHO platforms e.g. TB PADO, GAPf
- Mentored investigator programme

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Protocol chairs

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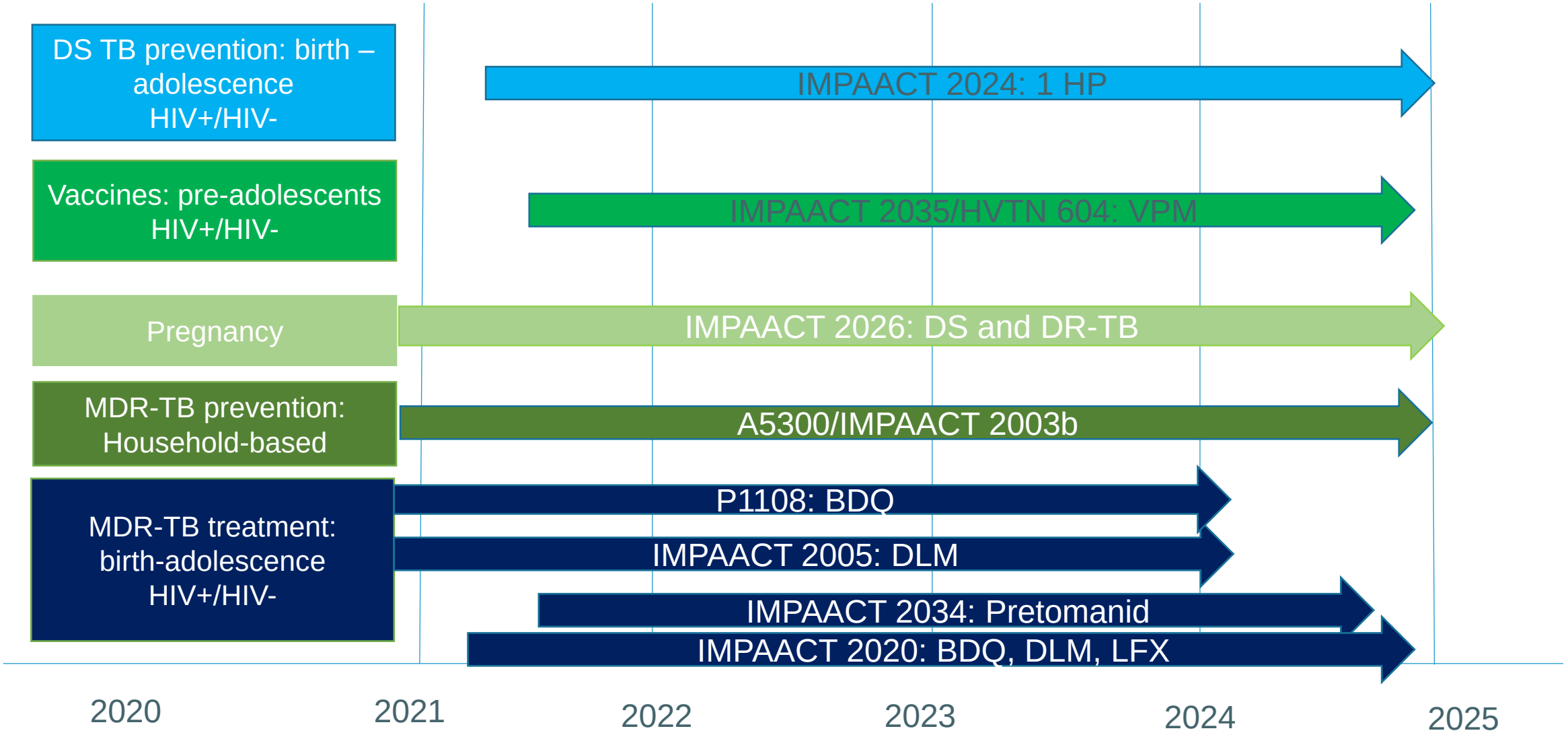
IMPAACT TBSC Roadmap 2023



Highlights

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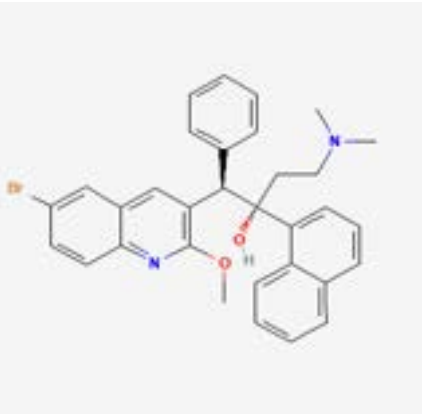
P1108: Phase I/II trial of PK, safety and tolerability of bedaquiline in infants, children, and adolescents with RR-TB with and without HIV



- Accrual completed: August 2023 (COVID pause: 2020)
- All 54 evaluable enrolled (52 at 3 South African sites, 2 Haiti)
- 6 interim analyses
- All PK and safety targets met across age cohorts
- Enrolment completed under version 1.0
- Data sharing WHO : 2018: BDQ recommended in children > 6 years.
- Data sharing with WHO: 2021/22: BDQ: recommended in children down to 0 years (May 2022)
- Dosing recommendations: weight banded: operational handbook
- 100 and 20 mg Formulation globally available through GDF

Chairs: Anneke Hesseling, Simon Schaaf

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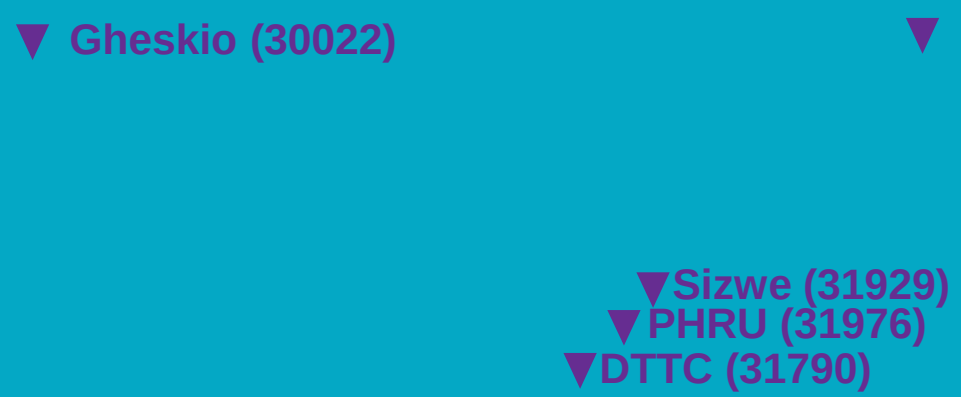
P1108: 5 sites



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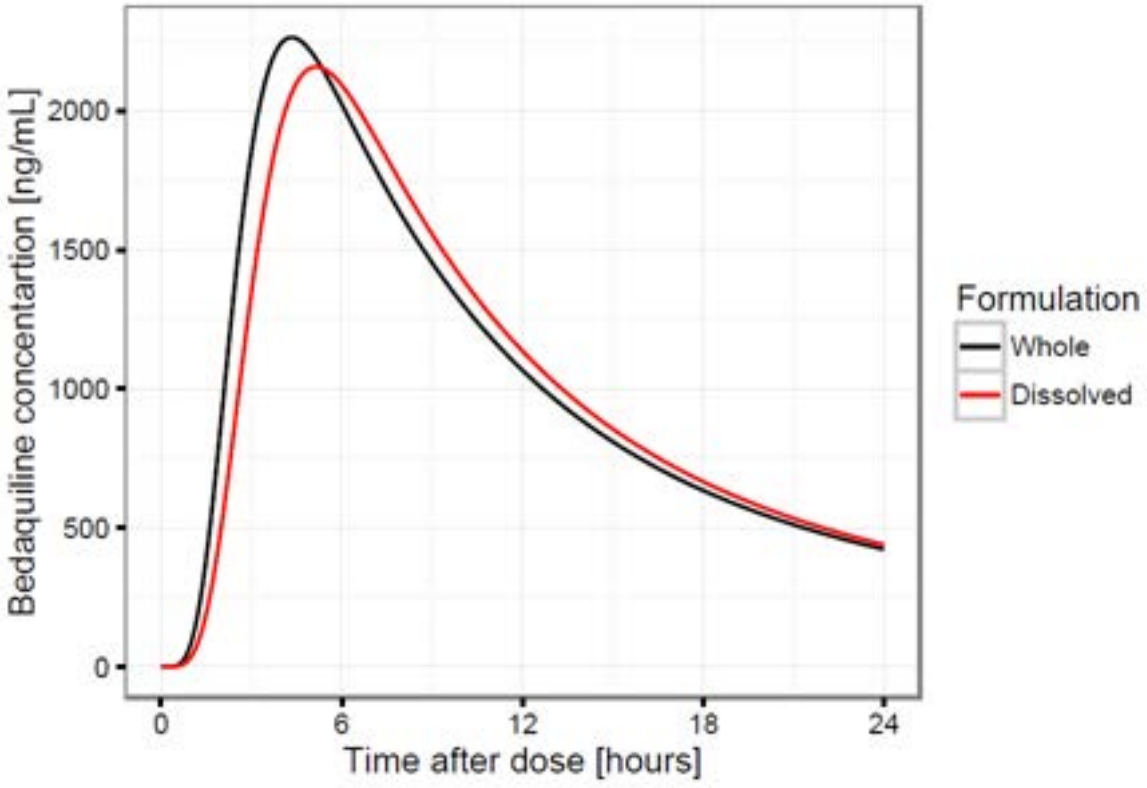
Need for bridging PK – lack of access to formulation
BDQ CRUSH Impact of dissolving on a typical BDQ PK profile



- Mean absorption time slightly longer for dissolved tablets: +23% (p=0.03, $CI_{95\%}$ 2.1-48%)
- T_{max}: 4.3 to 5.2h
- C_{max}: ↓ 5%

Difference in bioavailability dissolved vs whole tablets not statistically significant (p=0.92, $CI_{95\%}$ 94-108%)

→ **Bioequivalence criteria fulfilled**

Svensson, BJ Pharm 2018

Bedaquiline in children: universal recommendation

- **In children with MDR/RR-TB aged <6 years, an all-oral treatment regimen containing bedaquiline may be used: Based on PK and safety data from P1108**
  - Applies to and complements current WHO recommendations on shorter and longer regimens that contain bedaquiline
  - Complements the current WHO recommendation on longer regimens that contain delamanid

P1108 led to WHO recommendations in 2019 for access down to age 6, and again during 2022 for children down to age 0 while trial ongoing

These recommendations make it possible to build all oral regimens for children of all ages

BDQ dosing by WHO weight band		
3 to < 7 kg	0 to < 3 mo	30 mg / 10 mg
	≥ 3 mo	60 mg / 20 mg
7 to < 10 kg	0 to < 3 mo	30 mg / 10 mg
	3 to <6mo	60 mg / 20 mg
	≥ 6 mo	80 mg / 20 mg
10 < 16 kg	3 to <6mo	60 mg / 20 mg
	≥ 6 mo	120 mg / 60 mg
16 < 24 kg		200 mg / 100 mg
24 < 30 kg		200 mg / 100 mg

World Health Organization

Bedaquiline: Next steps

- Version 2.0 finalized and being implemented (shorter duration f/u, other)
- Data sharing with Janssen C211
- Trial dissemination
- Plan to assay other TB drugs (future use)
- BDQ (and DLM) once-daily modeling. - Elin Svensson, supplemental funding
- BDQ evaluated in context of a regimen (IMPAACT 2020)
- Ongoing data sharing with Janssen

UPPSALA UNIVERSITET

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Updated 2022 WHO recommendations for RR-TB treatment

	Recommended RR-TB regimen	Duration	Number of drugs	Simplicity
Adults	6BPaLM	6 mo	4	Once daily
Children	*4-6B·Lf·Cf·Z·Em·H^{h}·Et / 5Lf·C·Z·Em*	9-11 mo	7	Daily, 3x-weekly, 2x-weekly

Need for all-oral simpler effective 6 months once-daily regimen in children < 15 years of age:
WHO stated research priority
Pregnant women??????

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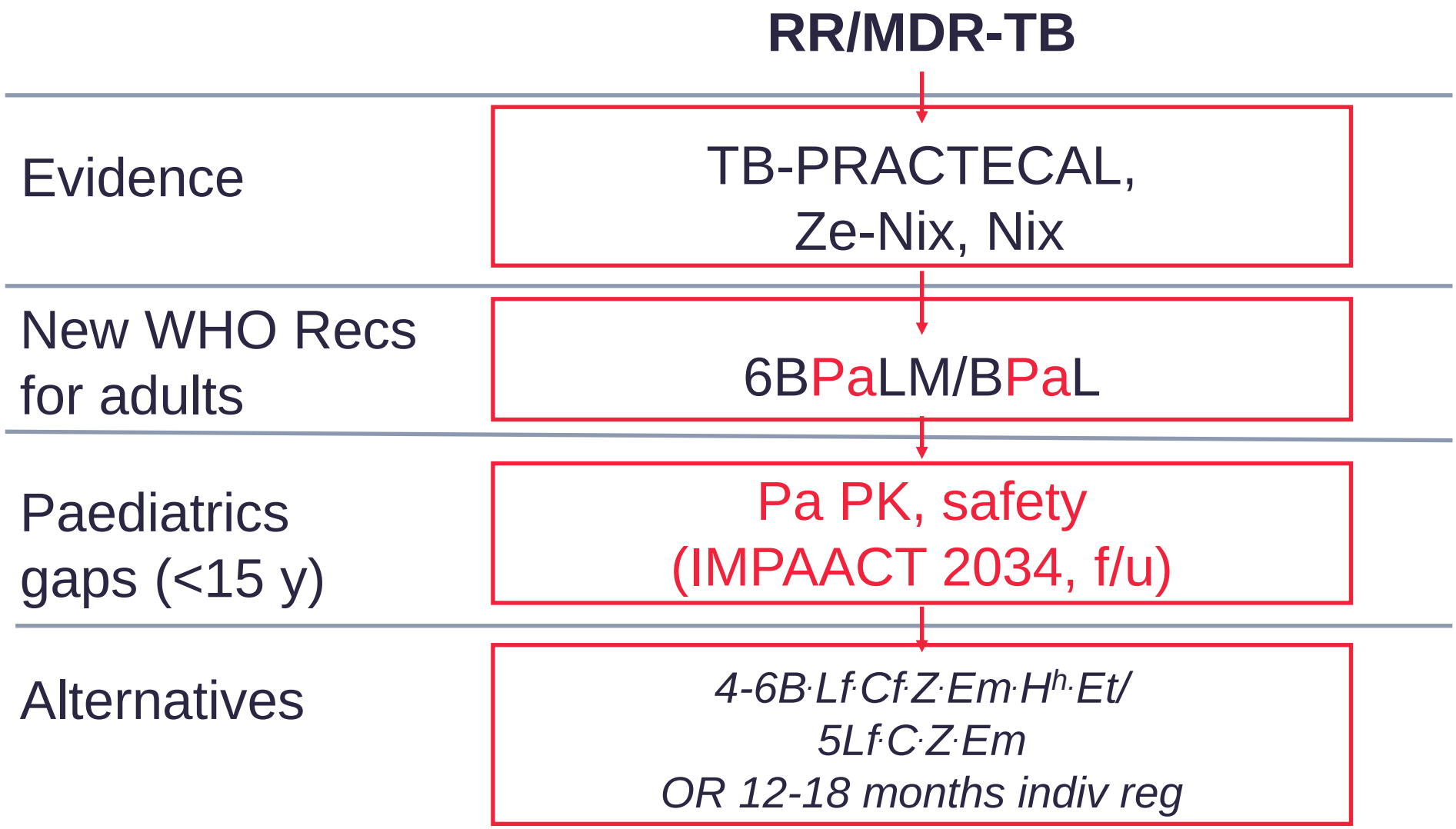
Better regimens for children with MDR/RR-TB



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IMPAACT 2020: A Phase II Study of Shortened Oral Novel Treatment for Rifampicin-Resistant Tuberculosis in Children

Protocol Chairs: Anneke Hesseling, MD, PhD and Anthony Garcia-Prats, MD, PhD

Protocol Vice-Chairs: Pauline Howell, MD and Megan Palmer, MD

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Updated 2022 WHO recommendations for RR-TB treatment

Challenges to use of BPaLM in children

1. Pretomanid access (IMPAACT 2034; single dose PK – opened 2023)
   - Barrier to extrapolation of efficacy
2. Linezolid duration – safety risk-benefit for children
   - Shorter duration → reduced AEs, better risk-benefit
   - Document safety, outcome
3. Complexity of dosing
   - BDQ once daily for adults, equivalent pediatric dose unknown
   - DLM once daily for adults, equivalent pediatric dose unknown

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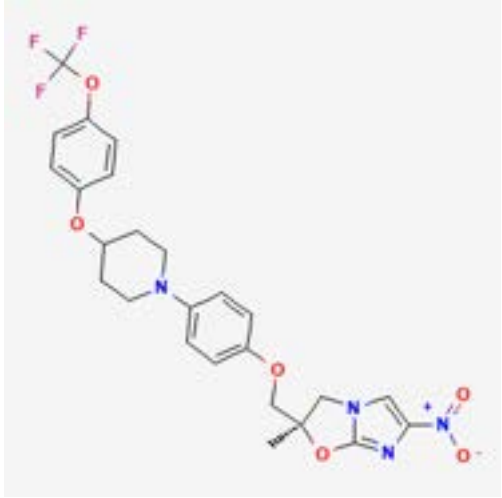
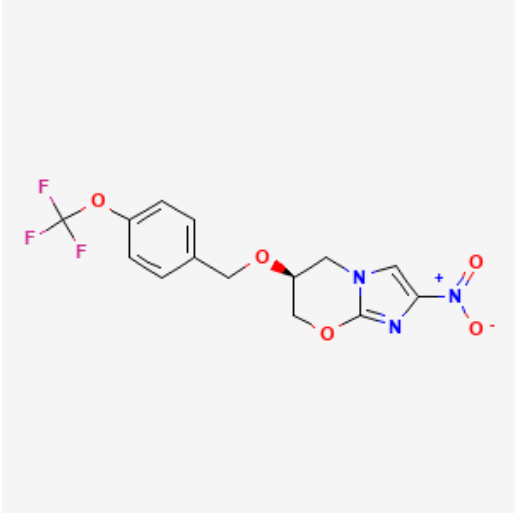
Extrapolation efficacy BPaLM and drug substitution



$C_{25}H_{25}F_3N_4O_6$



$C_{14}H_{12}F_3N_3O_5$

A tale of 2 drugs

Delamanid and Pretomanid

nitro-dihydro-imidazooxazole

"It was the worst of times, it was the best of times."

Charles Dickens. A tale of two cities

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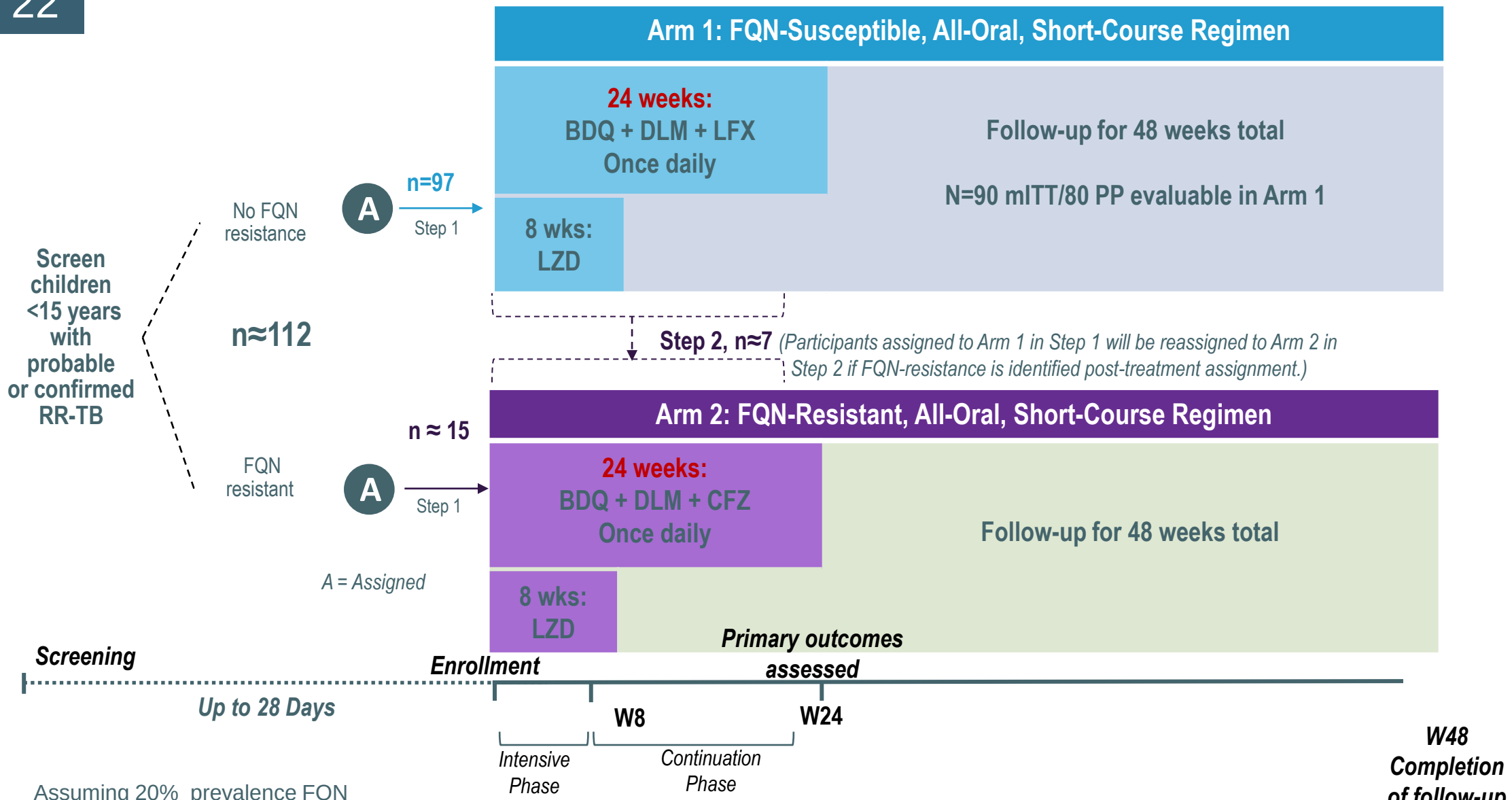
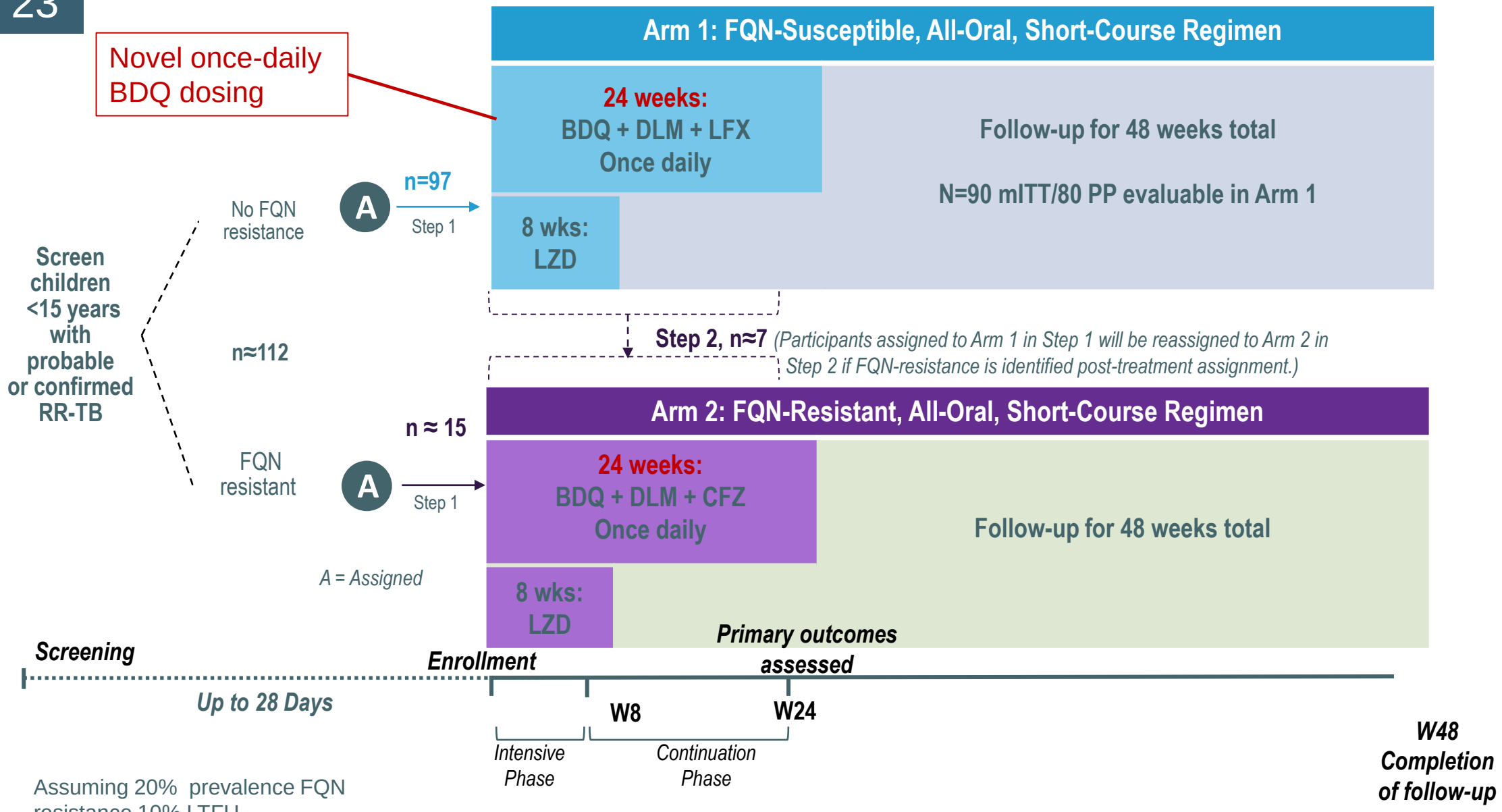
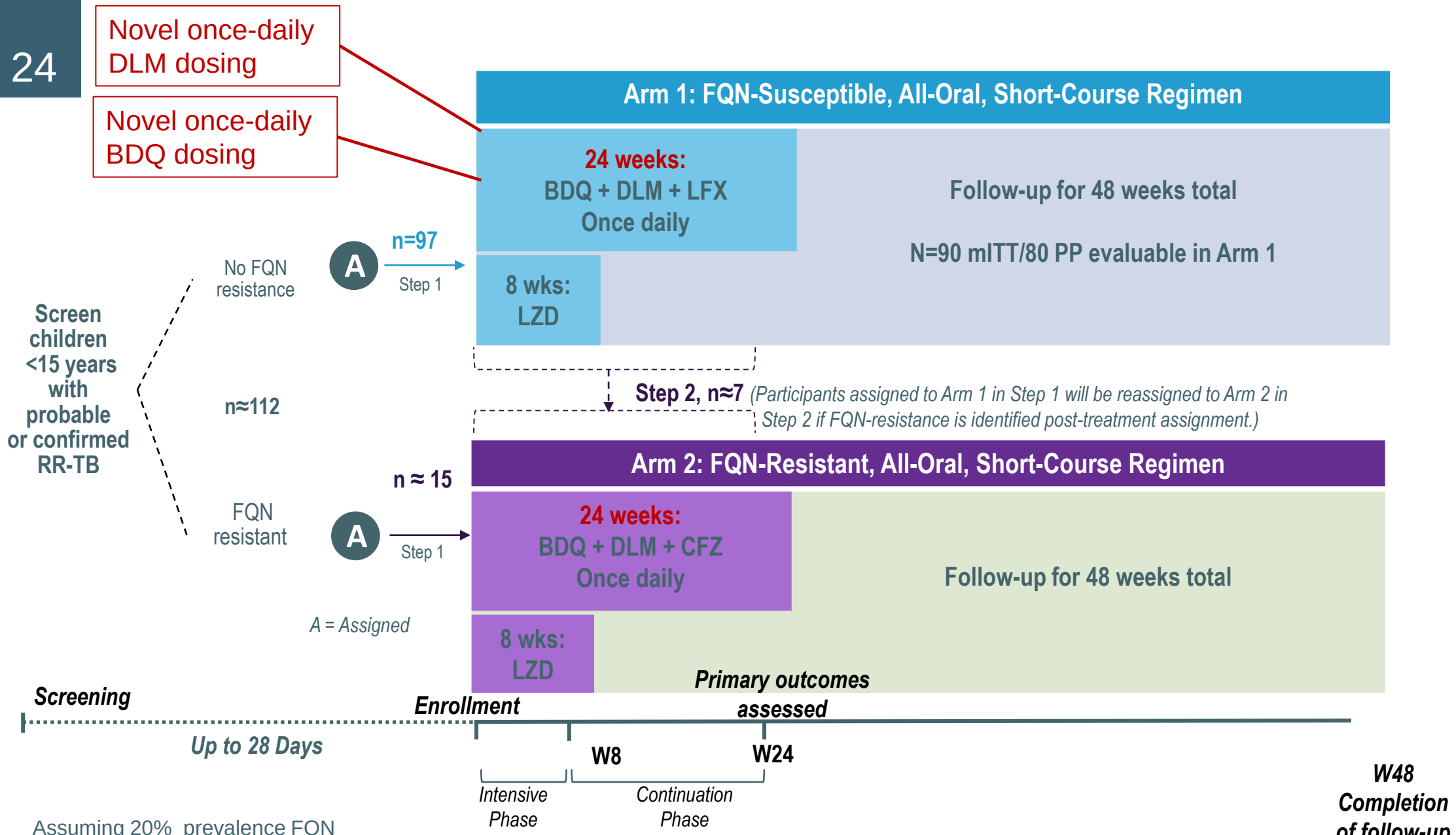


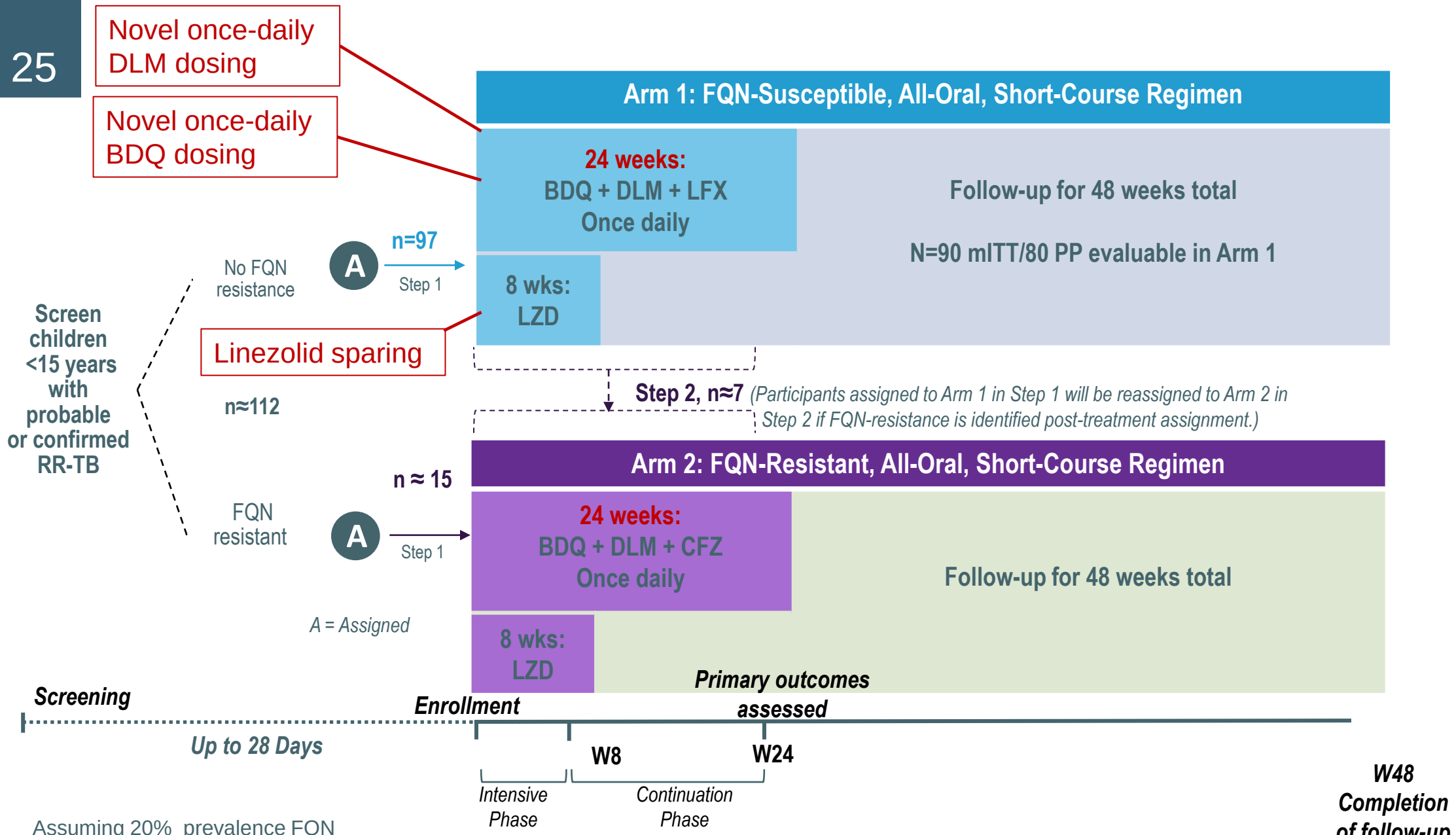
Assuming 20% prevalence FQN resistance 10% LTFU



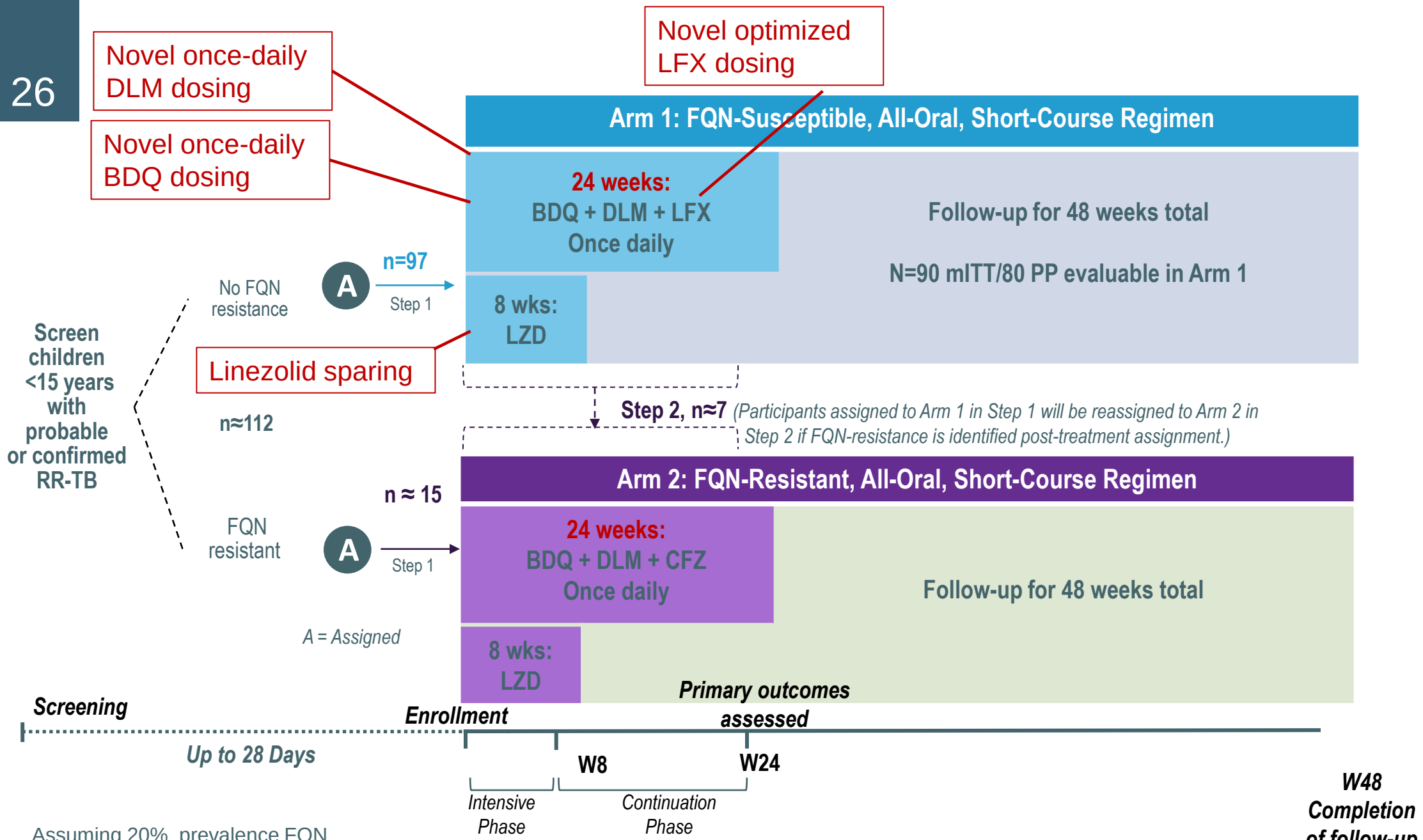
Assuming 20% prevalence FQN resistance 10% LTFU



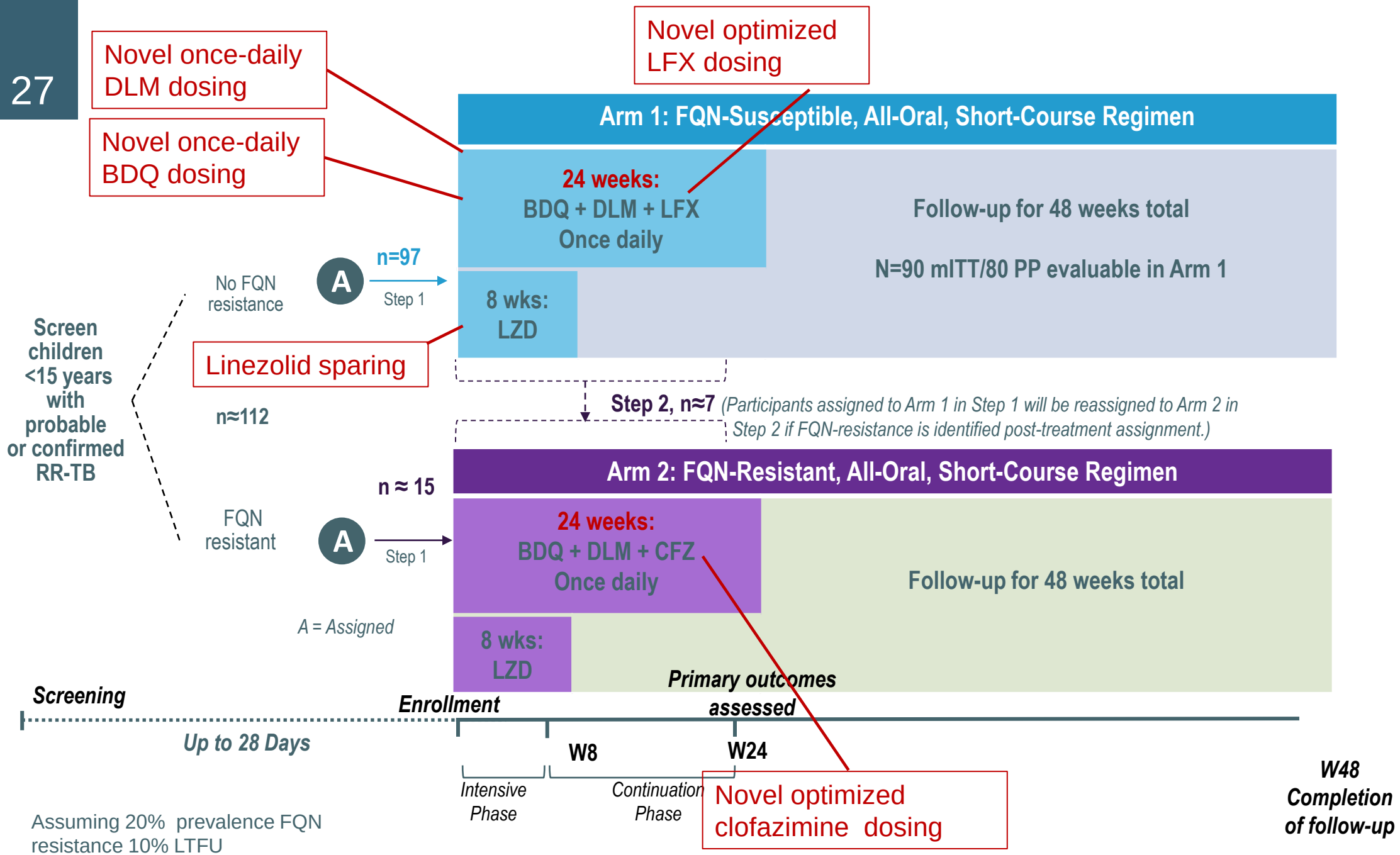
Assuming 20% prevalence FQN resistance 10% LTFU



Assuming 20% prevalence FQN resistance 10% LTFU



Assuming 20% prevalence FQN resistance 10% LTFU



Assuming 20% prevalence FQN resistance 10% LTFU

Study Population: Infants, children, and adolescents less than 15 years of age with confirmed or probable RR-TB (participants may have TB that is resistant to additional treatment agents and may or may not be living with HIV)

Sample Size: Approximately **112 children** and their caregivers

Design: Phase 2, open-label, multisite, two arm study; all age groups in parallel, weight banded dosing of all drugs

Interim analysis: PK

Arm 1 (FQN-susceptible): Approximately **97 participants** with no resistance to fluoroquinolones (FQN) identified prior to study entry will be entered into Arm 1. Approximately 7 of these participants are expected to be identified with FQN resistance after Entry into Arm 1 and reassigned to Arm 2. At least 90 Arm 1 participants are expected to be evaluable for primary study outcomes.

Arm 2 (FQN-resistant): Approximately **22 participants with** FQN resistance are expected to be entered into Arm 2, including approximately 15 with FQN resistance identified prior to study entry and approximately 7 with FQN resistance identified after entry into Arm 1.

Opening: 2024

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Primary Objective

- Among infants, children, and adolescents with confirmed or probable RR-TB with FQN susceptibility (RRfs-TB), to characterize the **safety and tolerability of** a novel, all-oral, short-course once-daily treatment regimen through Week 30.

Secondary Objectives

- Among infants, children, and adolescents with confirmed or probable RR-TB with FQN susceptibility (RRfs-TB), to characterize **outcomes** of a novel, all-oral, short-course once-daily treatment regimen through Week 48.

Secondary Objectives

Among infants, children, and adolescents who received the relevant drugs, to:

- Characterize the pharmacokinetics of once-daily BDQ, DLM, LFX, LZD, CFZ through Week 24
- Characterize the pharmacokinetics of antiretrovirals among participants with HIV through Week 24
- Characterize the cardiac safety of co-treatment with once-daily BDQ and DLM through Week 30

Among infants, children, and adolescents with confirmed or probable RR-TB with resistance to FQNs (RRfr-TB), to:

- Characterize the safety and tolerability of an all-oral, novel short-course one-daily treatment regimen through Week 30
- Characterize TB efficacy outcomes of an all-oral, novel short-course once-daily treatment regimen through Week 48

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IMPAACT 2034: Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a **Single Dose of Pretomanid** Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis

- Primary Objective: To **evaluate the PK of a single dose of pretomanid in children** with RR-TB to ***identify the weight-banded doses*** of pretomanid to be evaluated in a future multiple dosing study in children
- Secondary Objectives: To evaluate the two-week **safety/ tolerability** and **acceptability/ palatability** of a single dose of pretomanid in children with RR-TB
- Dose Selection Goal: to find doses that would yield, for children with different weights, exposures, as measured by **$AUC_{0-\infty}$ after a single dose, close to 50.9 µg*hr/mL**, the median value of steady-state AUC_{0-24} observed in the Nix-TB study (using scored 10 and 50 mg dispersible tabs)
- Population: N=36 to 72 children >28 days of age to <18 years of age with RR-TB, with or without HIV (weighing ≥4 kg)
- *Females only (pending further discussions with FDA)*

Chairs: Ethel Weld, Anthony Garcia-Prats, Pauline Howell

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Group	Weight	Formulation	Dose
1: ≥31 kg	≥40 kg	Adult	200 mg (one adult tablet)
	31-<40 kg	Dispersible pediatric	100 mg (two 50 mg dispersible tablets)
2: 20-<31 kg	20-<31 kg	Dispersible pediatric	100 mg (two 50 mg dispersible tablets)
3: 12-<20 kg	12-<20 kg	Dispersible pediatric	75 mg (one 50 mg dispersible tablet and half of one 50 mg dispersible tablet)
4: 4-<12 kg	8-<12 kg	Dispersible pediatric	50 mg (one 50 mg dispersible tablet)
	6-<8 kg	Dispersible pediatric	35 mg (half of one 50 mg dispersible tablet and one 10 mg dispersible tablet)
	4-<6 kg	Dispersible pediatric	20 mg (two 10 mg dispersible tablets)

First participant enrolled and dosed October 2023!
4 on study as of Oct 26, 2023

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

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IMPAACT 2034: 7 sites

▼BJMC (31441) (Pune)

▼Siriraj Hospital (5115) (Bangkok)

▼KCMC (5118) (Moshi)

▼UFRJ (5071) (Rio de Janiero)

▼Sizwe (31929)

▼PHRU (31976)

▼DTTC (31790)

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IMPAACT 2005

A Phase I/II Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen in Children with MDR-TB with and without HIV

Protocol chairs
Anthony Garcia-Prats, MD, PhD
Ethel D. Weld, MD, PhD
Kelly Dooley, MD, PhD

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IMPAACT 2005: Current Status

- **Revised model-adjusted dosing of DLM** for all ages
- Optimal DLM dose in young, small children (< 3 years)
- **Characterization of newly identified psychiatric AEs**
- Public health relevance, new adult RR-TB guidelines: DLM substituted for Pretomanid?
- N=22 enrolled/36
- Data highly relevant for optimized dosing in young children, CLWH, safety data and will inform IMPAACT 2020

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IMPAACT 2005: 7 sites

▼BJMC (31441) (Pune)

▼KCMC (5118)
(Moshi)

Gaborone, (12701); Molepolole (12702)
(Botswana)

▼▼Sizwe (31929)
▼PHRU (31976)
▼DTTC (31790)

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Data to be generated in 2005 important – not being generated by other studies

1. To confirm DLM dosing in <15kg & 3 years – Most important

- Only *conditional* WHO rec, made expecting the data from IMPAACT 2005
- Least data AND most uncertainty

2. Confirm currently recommended dosing strategy in older children

- Current dosing strategy *not yet confirmed in children*
- *Will inform IMPAACT 2020*
- Entirely *in silico*

3. Need to further characterize DLM neuropsychiatric safety signal

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IMPAACT 2005 accruing steadily, feasible to complete

Cohort (Age in years)	Enrolled before Nov 2022	Enrolled since Nov 2022	Assuming similar enrollment for next year (min goal = 9; max = 12)
Cohort 1 (12 -<18)	4	3	Meet min goal (n=10)
Cohort 2 (6 -12)	0	4	Do not meet min goal (n=8)
Cohort 3 (3 -<6)	0	4	Do not meet min goal (n=8)
Cohort 4 (0 -<3)	0	7	Meet max goal (n=12)

- November 2022 – November 2023
  - **Study enrolled 18 in that timeframe**
  - **Study did not meet any operational futility criteria**
- *Assuming similar accrual trends in the next year or so (as experienced since Nov 2022), we estimate:*
  - **Cohorts 1 and 4** could get to 9 enrollments each by **Q1 2024**
  - **Cohorts 2 and 3** could get to 9 enrollments each by **Q4 2024**

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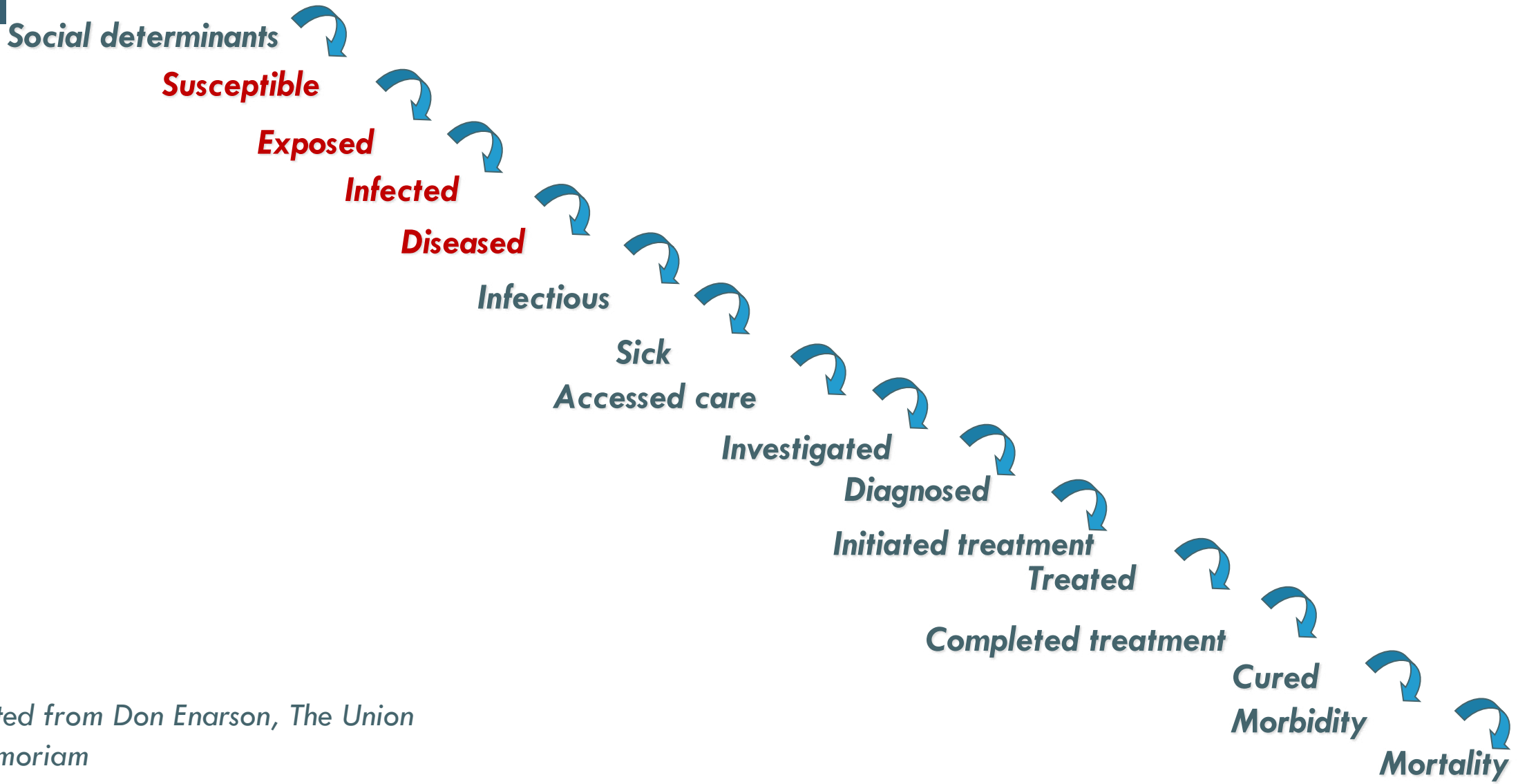
Key transitions in tuberculosis: prevention



Adapted from Don Enarson, The Union
In memoriam

IMPAACT 2024: Phase I/II Dose Finding, Safety and Tolerability Study of Daily Rifapentine Combined with Isoniazid (1HP) for Tuberculosis Prevention in Children Two to Less than 13 Years of Age with and without HIV

Protocol Chairs: *Nicole Salazar-Austin, MD, ScM and Christy Beneri, DO*

Gap:

- Ultra-short course TPT like 1HP have the potential to substantially improve adherence, completion rates and safety of TPT and could dramatically improve TPT delivery for children globally
- 1HP dosing not known for children < 13 years

Design: Phase I/II, multi-site, open-label, non-comparative dose finding study. Sequential cohorts

Primary Objectives:

- To determine the weight-band dosing of RPT taken as part of the 1HP regimen by evaluating:
  - PK RPT exposures among children with and without HIV (match to adult exposures seen in BRIEF-TB)
  - Safety and tolerability of the 1HP regimen among children with HIV while receiving BID DTG and without HIV
- To evaluate the effect of RPT taken as part of the 1HP regimen on the PK of DTG

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IMPAACT 2024

Current Status: CSRC Reviewed 5 October 2023

Anticipated Timeline: Open Q3 2024; Completion in 2027

Pharmaceutical Support: Sanofi to donate RPT

Anticipated Impact: Inclusion of 1HP for children 2-12 years in WHO TPT Guidelines

Cohort 1	Cohort 2
Living without HIV	Living with HIV
80 evaluable participants	30 evaluable participants

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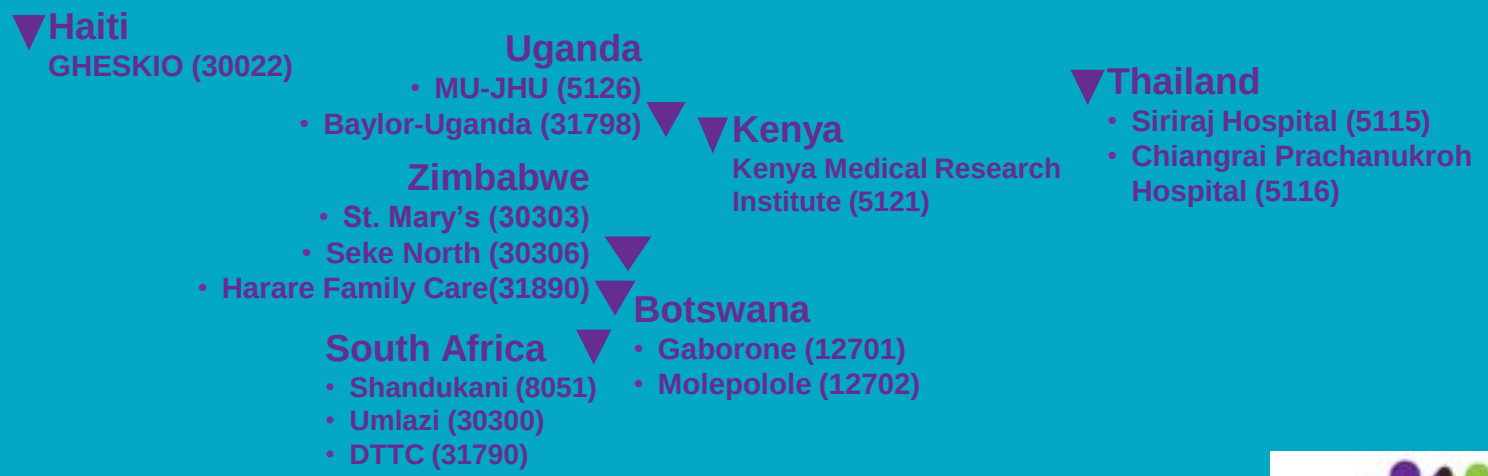
IMPAACT 2024: 14 Sites Selected



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MDR-TB Prevention

Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients

(A5300B/I2003B/PHOENIx)

Protocol Chairs
ACTG: GJ Churchyard, S Swindells
IMPAACT: AC Hesseling, A Gupta

ACTG AIDS CLINICAL TRIALS GROUP

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

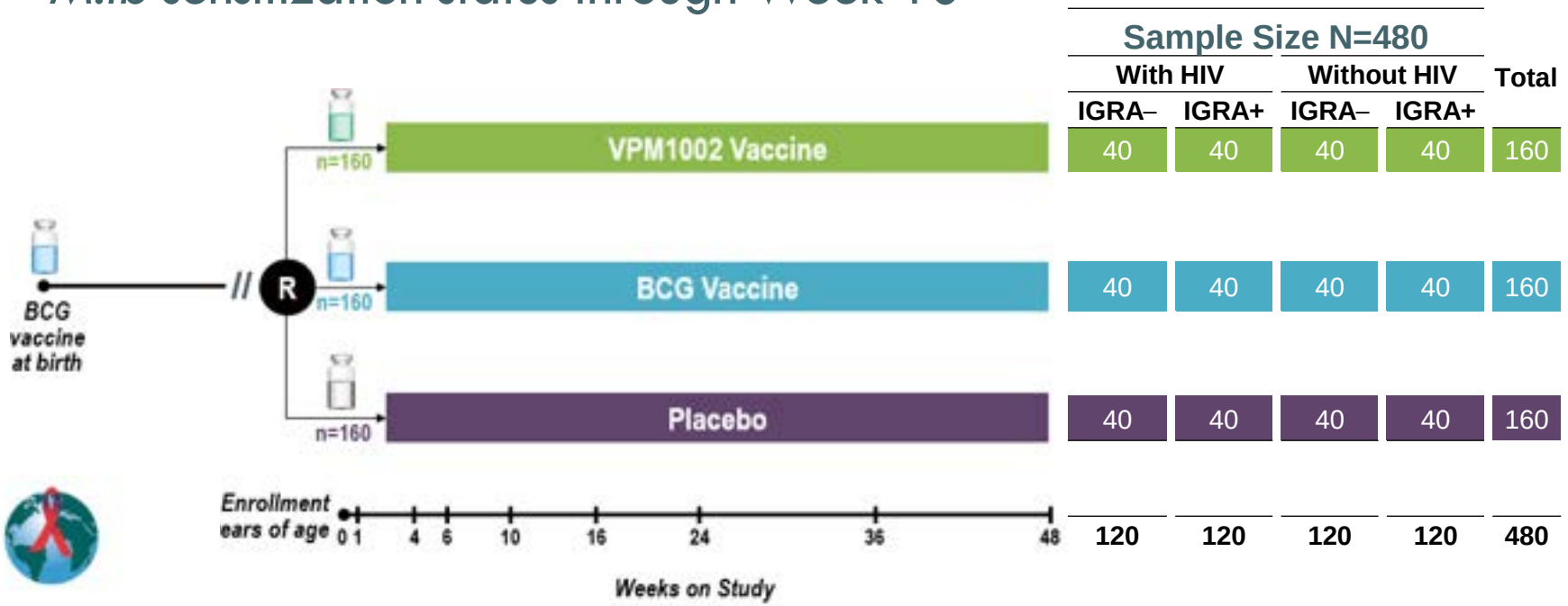
	TB-CHAMP	V-QUIN	PHOENIx
Intervention	LVF (novel paediatric dispersible formulation) vs. placebo daily for 6 months	LVF vs. placebo daily for 6 months	DLM vs standard dose INH daily for 26 weeks
Design	Cluster randomized; superiority Community-based	Cluster randomized; superiority Community-based	Cluster randomized; superiority Community-based
Target Population	• 0-4 years regardless of IGRA or HIV status • Only study powered for efficacy in children	• Adults, adolescents • TST + • Small group adolescents	• HIV + • Children <5 yrs • TST/IGRA + > 5 y
Assumptions	LVF decreases TB incidence from **7% to 2.8%** 80% power	LVF decreases TB incidence by 70% from 3% untreated 80% power	DLM decreases TB incidence by 50% from **5% to 2.5%** 90% power
Sample size	550 Households **1009 contacts**	1326 Households **2785 contacts**	1726 Households **3452 contacts**
Sites	South Africa DTTC, Shandukani, PHRU Matlosana, THINK, Isanga Lethemba	Viet Nam NTP	ACTG & IMPAACT sites 28 sites, 11 countries
Timelines to open	Completed Results 2023	Completed Results: 2023	Opened June 2019 N=2446 enrolled
Funder, PI	UNITAID BMRC, SA MRC SHIP Hesseling, Seddon, Schaaf	Woolcock,Viet Nam, Australia, Nguyen **Viet** Nhung, Greg Fox	ACTG/IMPAACT

VQUIN

IMPAACT 2035/ HVTN 604: LEAP Study

Primary Objectives:

1. To evaluate the safety of VPM1002 and BCG revaccination by HIV status through Week 48
2. To evaluate the cellular immunogenicity of VPM1002 and BCG revaccination by HIV and *M.tb* sensitization status through Week 10



	Sample Size N=480				
	With HIV		Without HIV		Total
	IGRA–	IGRA+	IGRA–	IGRA+	
VPM1002 Vaccine	40	40	40	40	160
BCG Vaccine	40	40	40	40	160
Placebo	40	40	40	40	160
	120	120	120	120	480

- Children with HIV: CD4 ≥200 & virologically suppressed on ART
- 9 IMPAACT & HVTN sites in South Africa
- Open to accrual ~Q1 2024

HIV VACCINE TRIALS NETWORK

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IMPAACT 2035/ HVTN 604:
Phase I/II Randomized, Placebo-Controlled Study of the Safety and Immunogenicity of VPM1002 Vaccination or BCG Revaccination against Tuberculosis in Pre-Adolescents Living with and without HIV in South Africa

Leveraging **E**arly **A**dolescence to **P**revent TB: **LEAP Study**

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HIV VACCINE TRIALS NETWORK

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Future plans and priorities

Priorities for pregnant and postpartum people

- DS-TB pregnancy treatment: 4-month RFPT/Moxi (Study 31) regimen for DS-TB in pregnancy: RADIANT-Moms
- RADIANT-Moms Formative work **(CS 5037)**
- TB vaccine trials – cross-network collaboration: ACTG, HVTN
- Socio-behavioural research
- Support novel formulation development

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RESEARCH SUMMARY

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

Dorman SE et al. DOI: 10.1056/NEJMoa2033400

CLINICAL PROBLEM

The standard treatment of drug-susceptible pulmonary tuberculosis is a 6-month course of a daily rifamycin-based antimicrobial regimen. A more potent regimen with improved rifamycin exposure might shorten treatment duration, potentially improving adherence and reducing adverse effects and costs.

CLINICAL TRIAL

Design: A randomized, open-label, noninferiority trial of two 4-month rifapentine-containing regimens, as compared with a standard 6-month rifampin-containing regimen, for the treatment of drug-susceptible tuberculosis.

Intervention: 2516 participants 12 years of age or older with newly diagnosed tuberculosis were randomly assigned to a 6-month control regimen, a 4-month regimen in which rifampin was replaced with rifapentine (rifapentine group), or a 4-month regimen in which rifampin was replaced with rifapentine and ethambutol with moxifloxacin (rifapentine–moxifloxacin group). The primary efficacy outcome was survival free of tuberculosis at 12 months after randomization, and safety was assessed through day 14 after the last dose of a trial drug.

RESULTS

Efficacy: The rifapentine–moxifloxacin regimen, but not the rifapentine regimen, was shown to be noninferior to the control regimen.

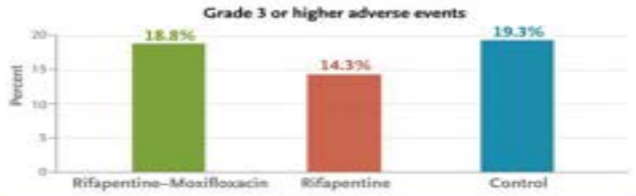
Safety: The percentages of patients who had adverse events of grade 3 or higher or who discontinued the assigned regimen prematurely did not differ significantly between the rifapentine–moxifloxacin group and the control group but were lower in the rifapentine group than in the control group.

LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- How the trial regimens perform in HIV-coinfected patients
- Whether the shorter treatment duration offsets the likely higher cost of the rifapentine–moxifloxacin regimen

Links: Full article | NEJM Quick Take | Editorial



CONCLUSIONS

A 4-month regimen containing rifapentine and moxifloxacin was noninferior in efficacy and similar in safety and premature discontinuation to a standard 6-month antimicrobial regimen for the treatment of tuberculosis.

WHO identified research gaps:

- Children < 12 years and pregnant women excluded: PK, safety needed
- TBTC will evaluate PK and safety in children < 12 years: Radiant-Kids

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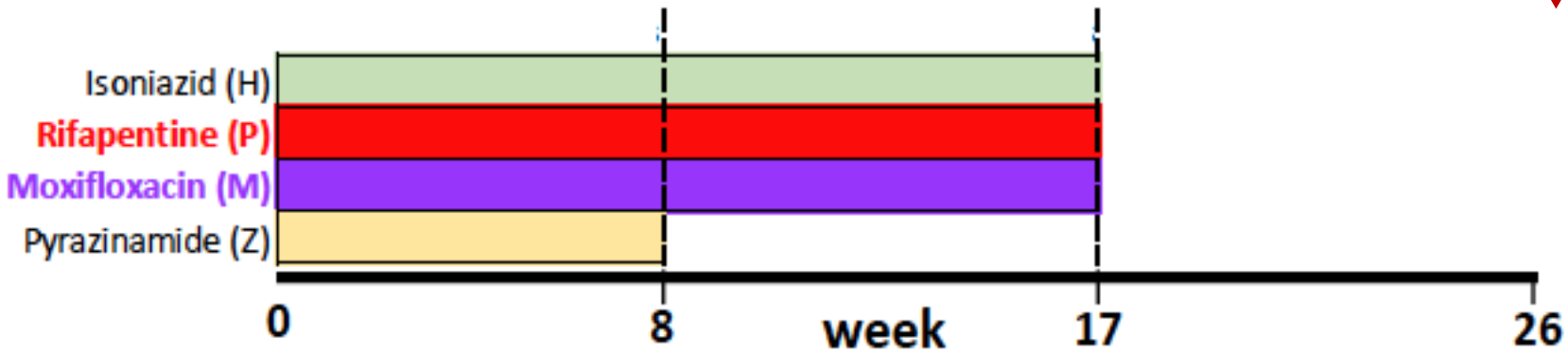
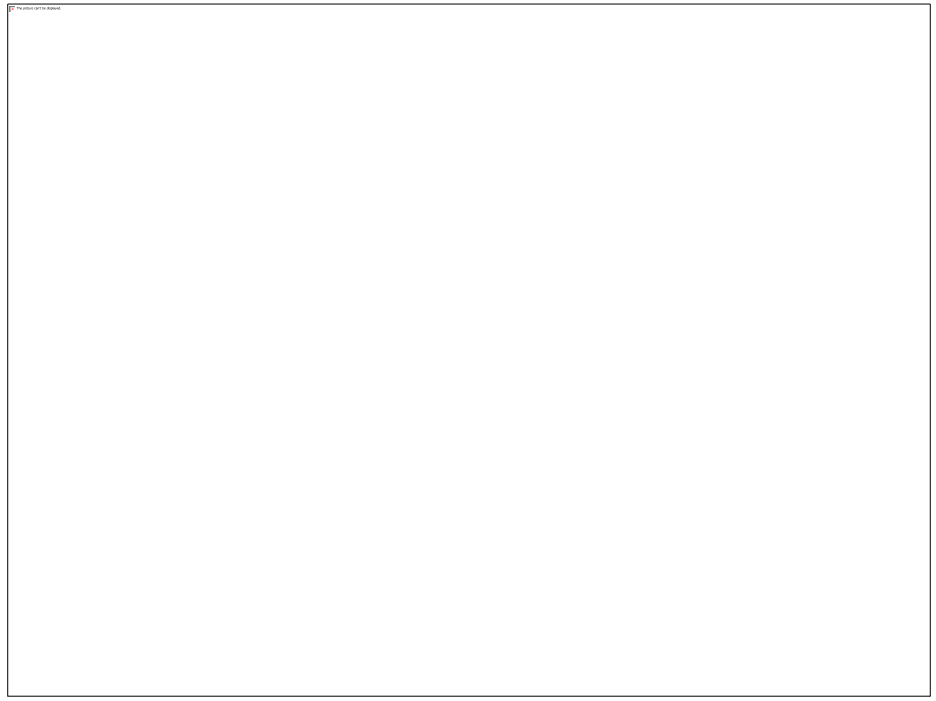
RADIANT-Moms PK and safety trial

- Multi-site open-label single arm pharmacokinetic and safety study, conducted over a 17-week treatment period of the Study 31 regimen for DS-TB
- PK, safety, tolerability, acceptability
- N=54 pregnant women with DS-TB
- Long-term maternal and infant outcomes

2HPZM / 2HPM
"RPT-MOX"



Thank you



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