Tuberculosis Scientific Committee

Anneke C. Hesseling, Amita Gupta

Annual Meeting IMPAACT Network meeting

24 June 2021

IMPAACT

International Maternal Pediatric Adolescent
AIDS Clinical Trials Network

Overall TB Scientific Committee Goals

"Evaluate novel approaches for TB prevention, diagnosis and treatment in HIV-infected and uninfected infants, children, adolescents, and pregnant and postpartum women that will lead to optimal dosing and regimens, licensing and improved care."

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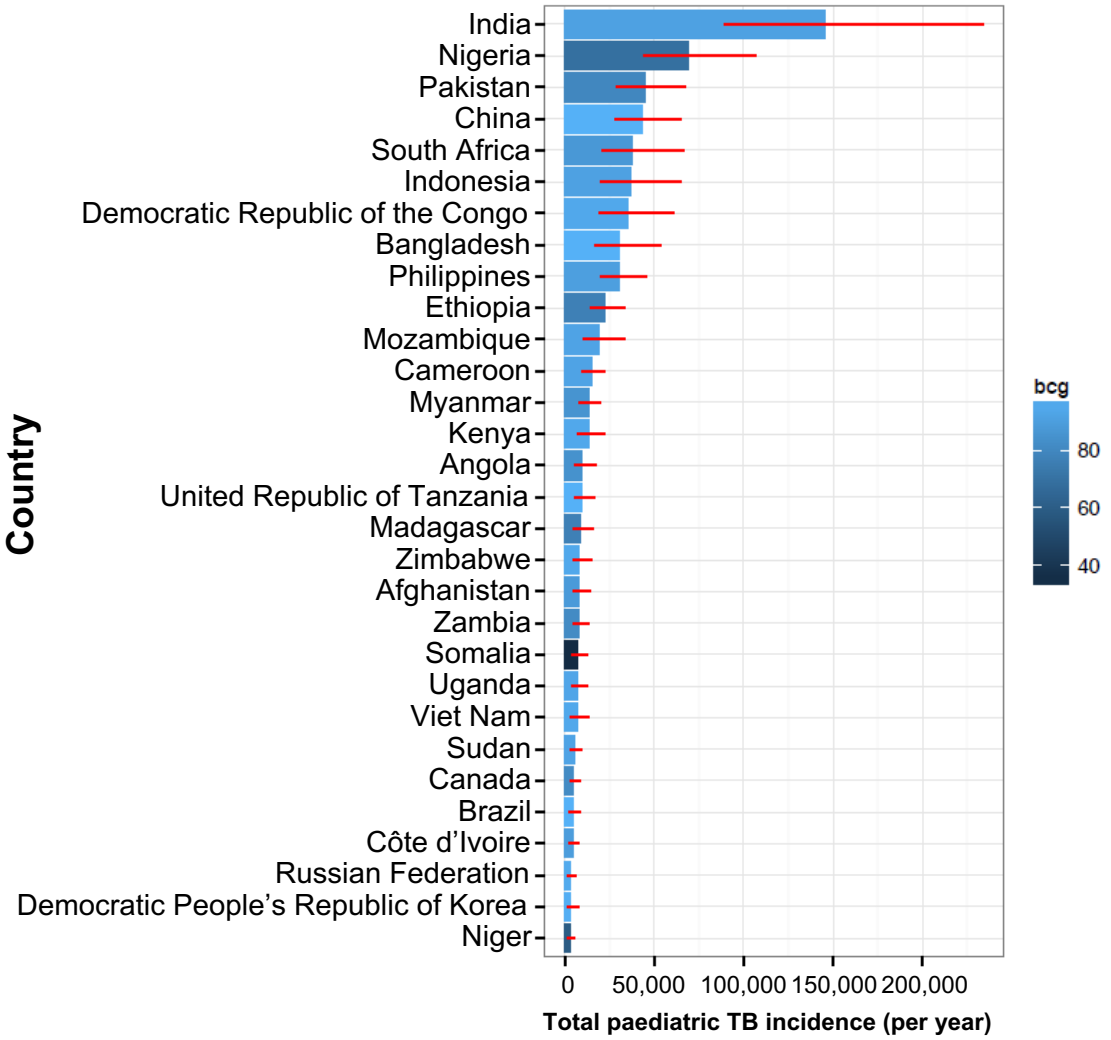
Global burden of TB in children (< 15 years)



- 12% global burden
- Estimates of incident TB disease
  - 999,800[2]
  - 847,000[1]
  - 1,190,000[3]
- >95% of disease burden is drug-susceptible TB
- Diagnosis remains challenging

Estimated mortality:

- <15 years: 240,000
- <5 years : 190,000
- **Excess TB mortality in HIV: 17%**
- **TB: a top 10 cause of deaths in children < 5 years**

1. Jenkins HE et al. Lancet 2014; 383: 1572-1579; 2. Dodd PJ et al. Lancet Glob Health 2014; 2: e453-459; 3. WHO Global Tuberculosis Report 2019

2021 Global New TB Drug Pipeline [1]

Discovery | Preclinical Development | Clinical Development

Lead Optimization → Early Stage Development → GMP / GLP Tox. → Phase 1 → Phase 2 → Phase 3 → Regulatory Market Approvals

Lead Optimization	Early Stage Development	GMP / GLP Tox.	Phase 1	Phase 2	Phase 3	Regulatory Market Approvals
PanD inhibitors	JSF-3285*	GSK-839*	BVL-GSK098*	SPR720*		
Indazole sulfonamides	MPL-446, 447*	OTB-658	GSK-286*	BTZ-043*		
Diarylthiazoles	CPZEN-45*	Sanfetrinem	TBAJ-587	TBA-7371*		Bedaquiline*
DprE1 Inhibitors	NTB-3119*		TBAJ-876	GSK-656* (070)		Delamanid*
Direct InhA Inhibitors	TB-47*		TBI-223	OPC-167832*		Pretomanid*
Mtb energy metabolism	TZY-5-84		Macozinone* (PBTZ-169)	Delpazolid	Rifapentine / Moxifloxacin (4-month regimen)	
Macrolides	FNDR-20081*		TBI-166	Sutezolid		
Mycobacterial Gyrase Inhibitors	Spectinamide – 1810*			Telacebec* (Q203)		
Arylsulfonamides				SQ-109*		
Inhibitors of MmpL3, Translocase-1, Clp, PKS13, F-ATP synthase				Macozinone*		
Oxazolidinones						

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical. Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

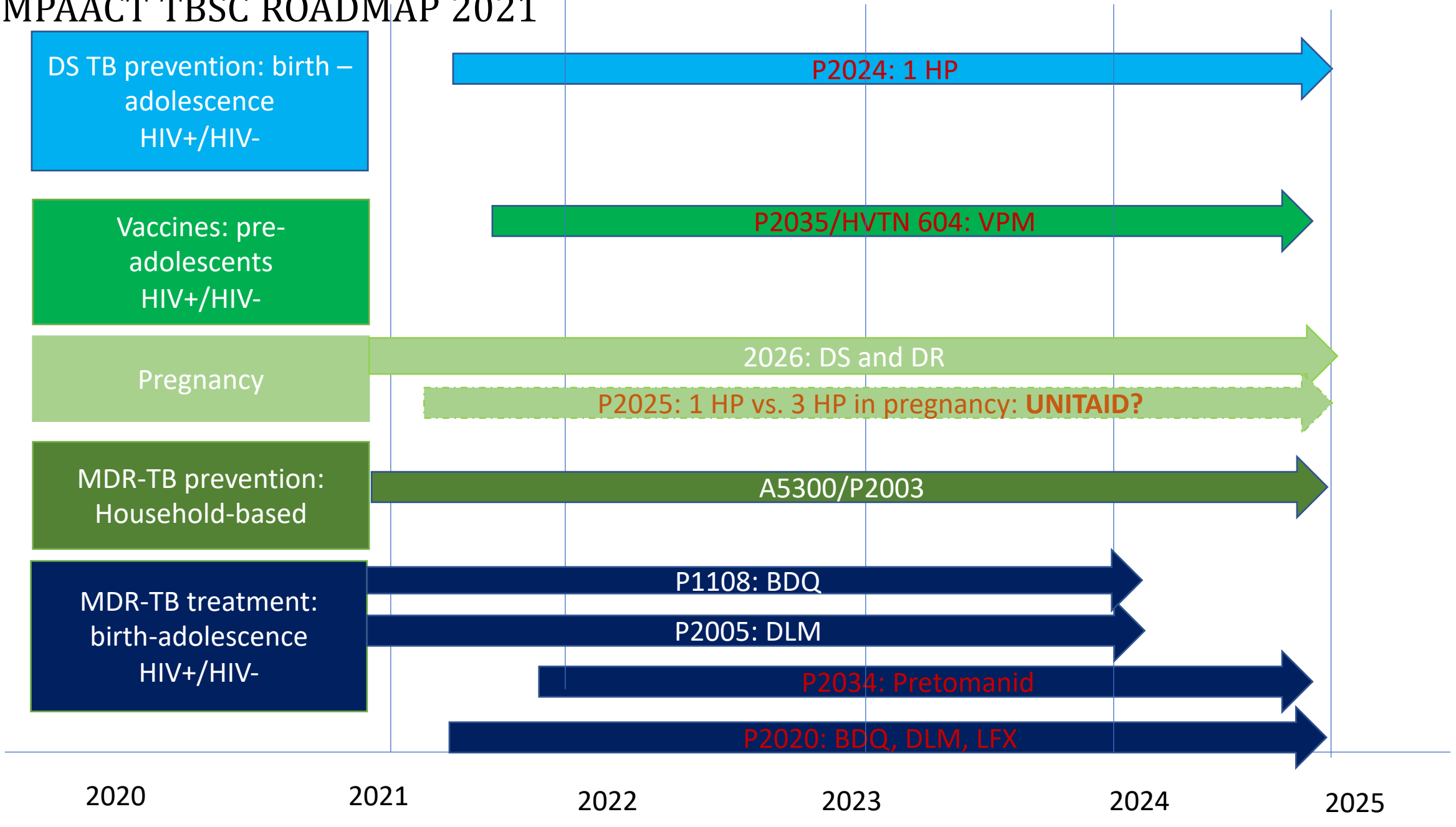
Underline = updates since November 2020

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2021

IMPAACT TBSC ROADMAP 2021



TB PREVENTION

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IMPAACT 2024: Phase I/II Dose Finding, Safety and Tolerability Study of Daily Rifapentine Combined with Isoniazid (1HP) for Tuberculosis Prevention in Infants, Children, and Adolescents

Protocol Chairs:

Nicole Salazar-Austin, MD, ScM

Christy Beneri, DO

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Design: Phase I/II, multi-site, open-label study with two sequential cohorts

Objectives:

Cohort 1:

- To evaluate the relative bioavailability of RPT film-coated tablet when administered as a crushed or whole tablet

Cohort 2:

- To determine the weight-band-based dosing of daily RPT, as part of the 1HP regimen, that achieves targeted plasma PK exposures for infants, children, and adolescents with and without HIV
- To evaluate the safety and tolerability of the 1HP regimen over 28 days among infants, children, and adolescents with and without HIV

- Children 6 to < 10 years of age
- N=12 PK-evaluable participants
- Children without HIV

- Children from birth to < 18 years of age
- N=154 PK-evaluable participants
- Children with (n=99) and without (n=55) HIV
  - HIV: DTG (n=69) or EFV (n=30) containing regimens
  - DTG will be dosed BID

Sites: International and National,

Timeline: MPRG pre-review (ongoing) → DAIDS Signoff Sept/Oct 2021 → Start Q2 2022

A5300B/IMPAACT2003B

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

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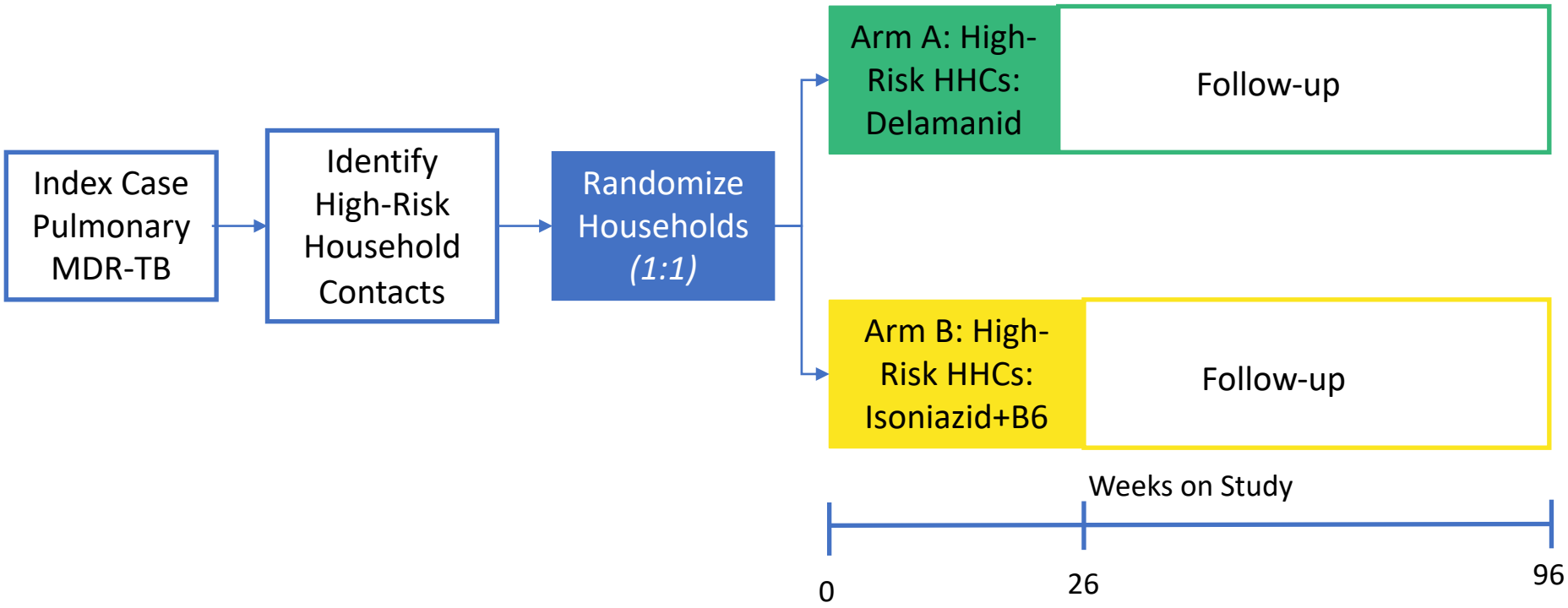
- Multi-center, cluster-randomized, superiority trial
- Cluster = eligible high-risk contacts from same HH
  - Randomization balanced by site
- All eligible HHCs in same HH receive the same treatment
- 3452 high risk HHCs, assuming 2 HHCs per index case

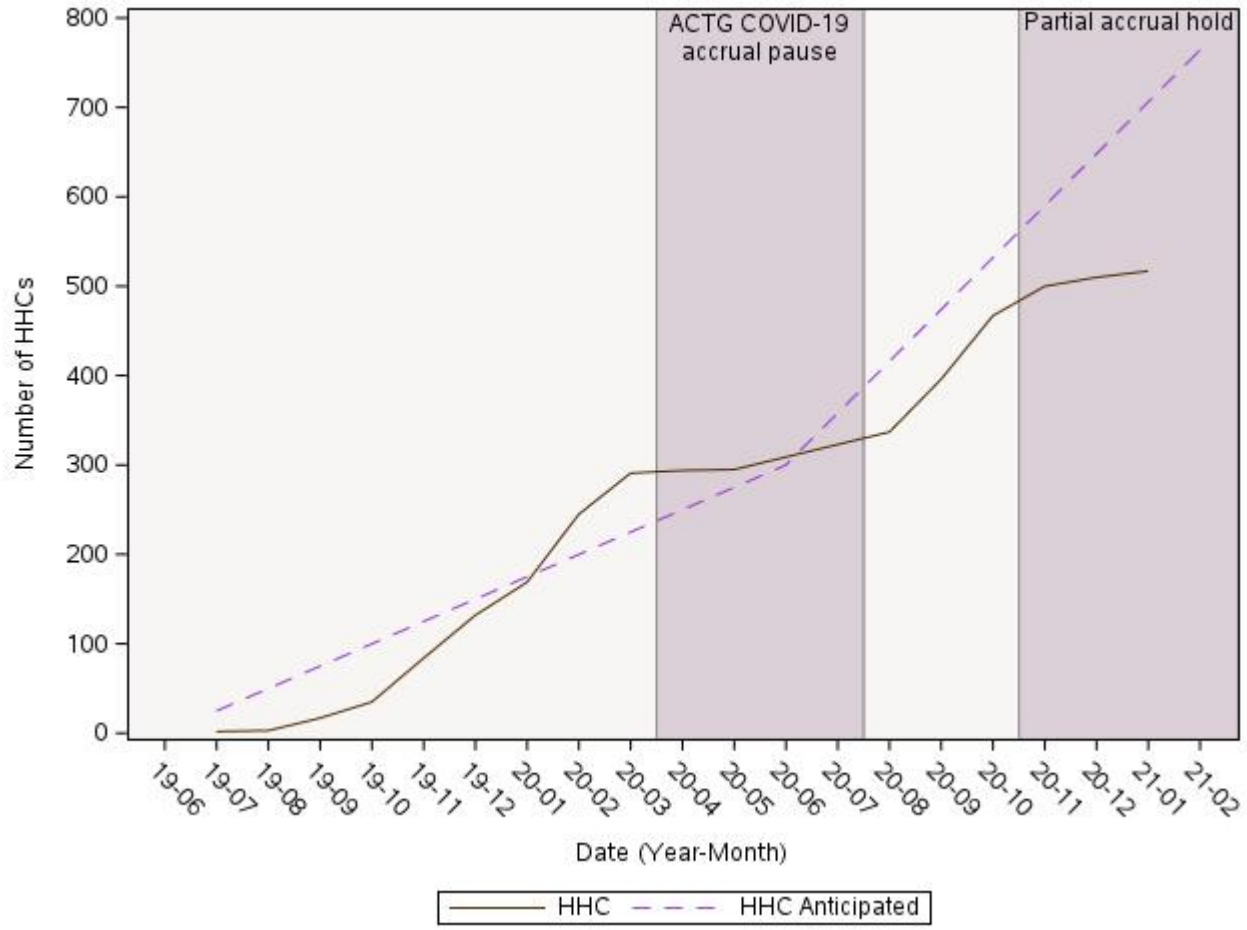


Household Contacts: Enrolment

- Accrual: 370 Index Cases and 587 Household Contacts
- Breakdown of HHC by age:
  - <5 y: 44
  - >=5 to <18 y: 136
  - >=18 y: 407



High-Risk Household Contacts Enrolment



IMPAACT 2035 / HVTN 604 : Phase I/II Study of the Safety and Immunogenicity of VPM1002 vaccination and BCG Revaccination against Tuberculosis in South African Pre-Adolescents Living with and without HIV

"**L**everaging **E**arly **A**dolescence to **P**revent TB"
LEAP

Protocol Chairs:
Lisa Cranmer, MD, MPH, IMPAACT
Protocol Vice-Chairs: Cheryl Day, PhD, IMPAACT, Steven Innes, MD, PhD (HVTN)

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HIV VACCINE TRIALS NETWORK

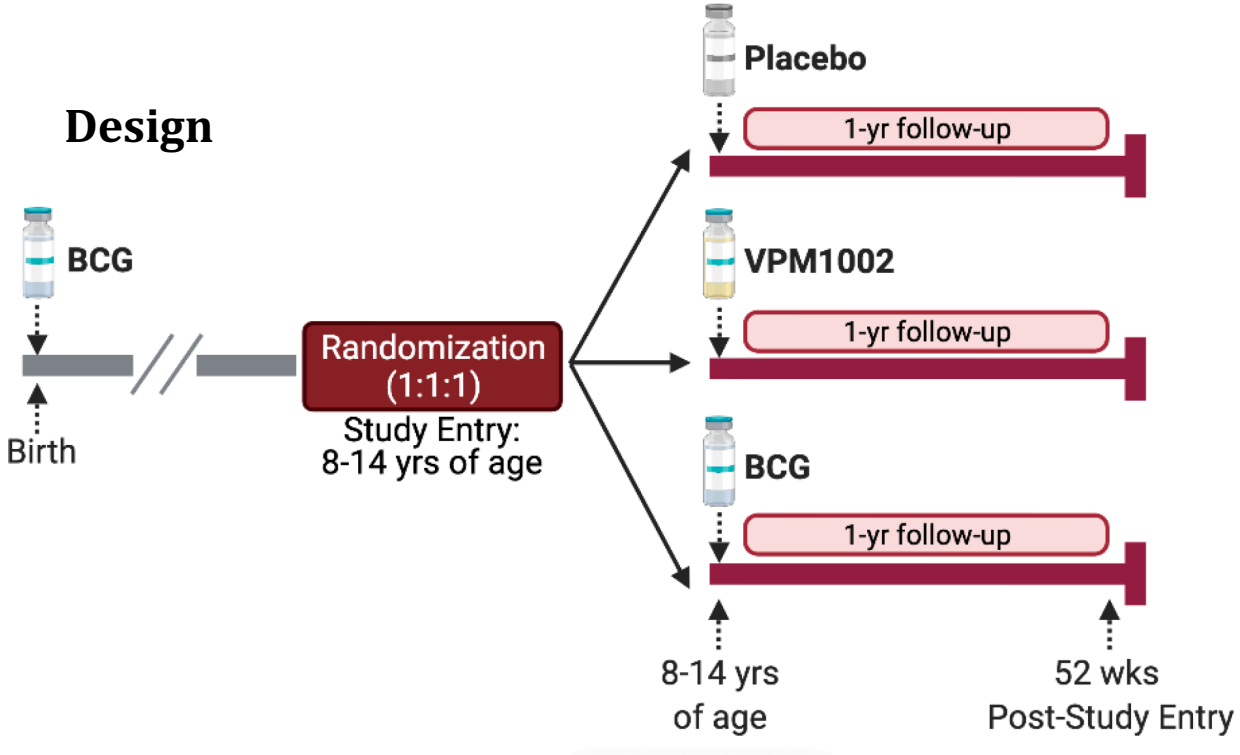
LEAP Trial

Primary Objectives:

1. To evaluate the safety and tolerability of VPM1002 and BCG revaccination

2. To evaluate the cellular immunogenicity of VPM1002 and BCG revaccination

Design



Randomized 1:1:1

Double-blinded

Each arm stratified by HIV and IGRA status:

- HIV−, IGRA− (n=40)
- HIV−, IGRA+ (n=40)
- HIV+, IGRA− (n=40)
- HIV+, IGRA+ (n=40)

160 per arm, 480 Total

Timeline: Protocol Development (current) → MPRG/SRC (Aug/Sept) → Start (June '22) International sites

TUBERCULOSIS TREATMENT

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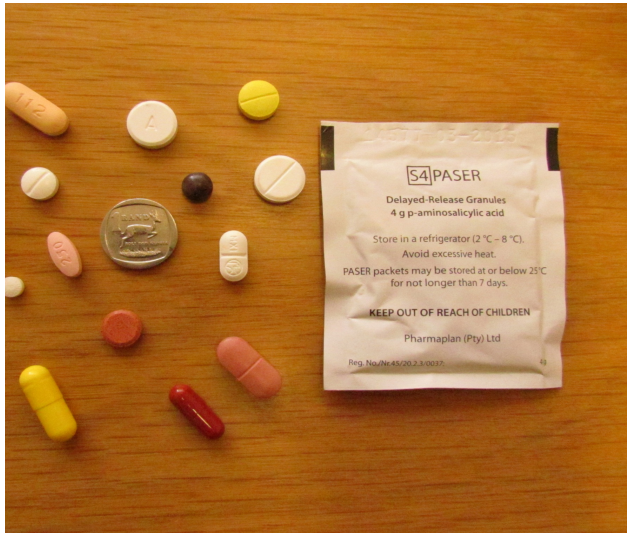
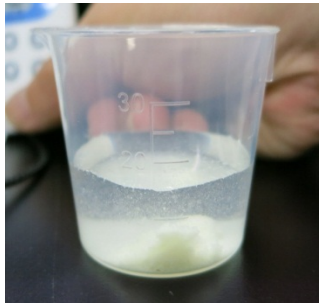
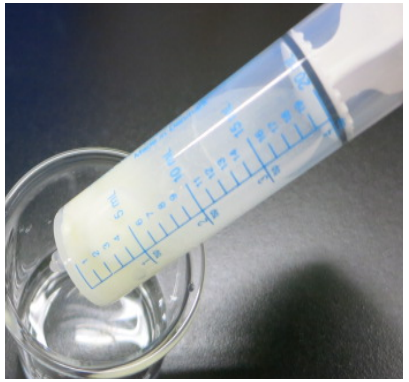
TB TREATMENT RESEARCH (DR-TB)

Study Name	Duration	For Treatment of	BDQ	DLM	PTD	LZD	CFZ	FQ	PZA	Other(s)	Estimated to Complete
SimpliciTB NCT03338621	6 months	MDR-TB (DS-TB)	X		X			M	X		February 2022 [fully enrolled]
Nix-TB NCT02333799	6-9 months	XDR-TB, pre-XDR-TB, TI/NR MDR-TB	X		X	X					Final results presented CROI 2021
ZeNix NCT03086486	6-9 months	XDR-TB, pre-XDR-TB, TI/NR MDR-TB	X		X	X					December 2021 [fully enrolled]
TB-PRACTECAL NCT02589782	6 months	MDR-TB Pre-XDR-TB XDR-TB	X		X	X	(X)	(M)			February 2023
BEAT-Tuberculosis NCT04062201	6 months	RR-TB	X	X		X	(X)	(Lx)			March 2023
endTB NCT02754765	9 months	MDR-TB	X	X		X	X	M/Lx	X		January 2023
endTB-Q NCT03896685	6-9 months	FQ-R MDR-TB	X	X		X	X				September 2023
NEXT NCT02454205	6-9 months	MDR-TB	X			X		Lx	X	Eto or HdH or Tzd	December 2020 [fully enrolled]
STREAM stage II NCT02409290	6-9 months	MDR-TB	X				X	Lx	X	HdH; Pto or Kan; +/- Emb	July 2022 [fully enrolled]
MDR-END NCT02619994	9-12 months	MDR-TB		X		X		Lx	X		June 2021

Focused on shortening treatment to 6–12 months and improving outcomes and tolerability by optimizing linezolid dose and duration, and/or by evaluating different combinations of new and repurposed medicines (e.g., J, D, Pa, C, M, Lx, Lz).

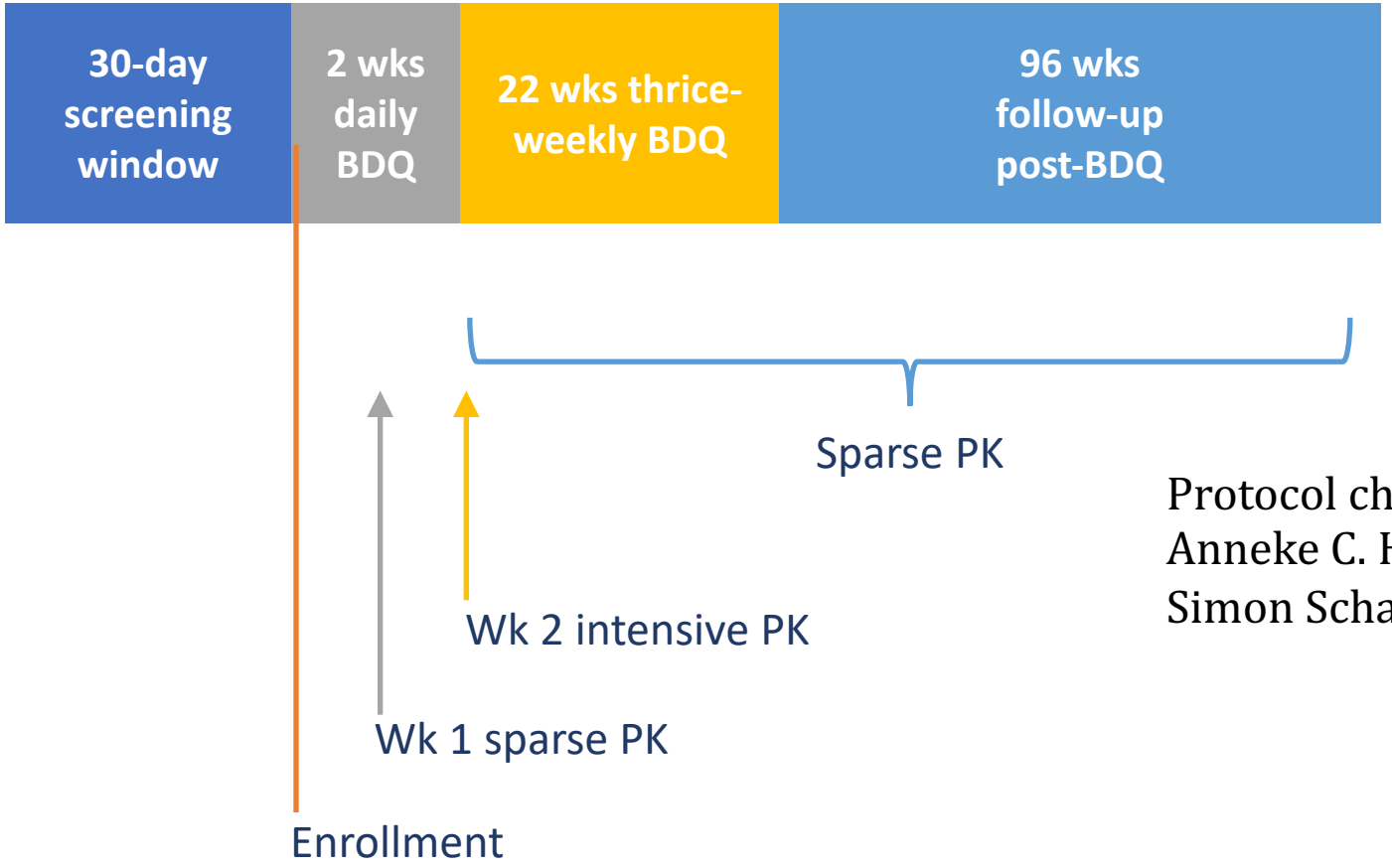

S4 PASER
Delayed-Release Granules
4 g p-aminosalicylic acid
Store in a refrigerator (2 °C – 8 °C).
Avoid excessive heat.
PASER packets may be stored at or below 25°C
for not longer than 7 days.
KEEP OUT OF REACH OF CHILDREN
Pharmaplan (Pty) Ltd






100
250

IMPAACT P1108: Phase I/II: PK, safety and tolerability of BDQ in HIV+ and -children with RR-TB



Protocol chairs:
Anneke C. Hesseling, MD, PhD
Simon Schaaf, MD, PhD

- Modified age de-escalation trial: 0-17 years; n=54
- Younger cohorts open in parallel (0-2 and 3-5 years)
- Dose-finding; PK modeling, dose adjustment; adaptive design, semi-real time PK modeling in mini-cohorts, real time safety assessment
- Adult formulation: whole/crushed (access)
- Long-term safety; treatment outcome. Sites: South Africa, Haiti, India

Cohort	Age and	BDQ Dosing
Cohort 1 up to 24 participants to achieve 18 evaluable (nine in each weight band)	≥ 6 to < 18 years ☐30 kg	400 mg once per day for two weeks and then 200 mg three times per week on Monday, Wednesday, and Friday for 22 weeks
	≥ 6 to < 18 years ☐15 to <30 kg	200 mg once per day for two weeks and then 100 mg three times per week on Monday, Wednesday, and Friday for 22 weeks
Cohort 2 up to 24 participants to achieve 18 evaluable	≥ 2 to < 6 years ☐7 kg	Participants >7 to ≤ 30 kg: 200 mg once per day for two weeks and then 100 mg three times per week on Monday, Wednesday, and Friday for 22 weeks Participants 7 kg: 100 mg once per day for two weeks and then 50 mg three times per week on Monday, Wednesday, and Friday for 22 weeks
Cohort 3 up to 24 participants to achieve 18 evaluable	≥ 0 to < 2 years ☐3 kg	Participants >7 to ≤ 30 kg: 200 mg once per day for two weeks and then 100 mg three times per week on Monday, Wednesday, and Friday for 22 weeks Participants ≥ 3 to ≤ 7 kg: 100 mg once per day for two weeks and then 50 mg three times per week on Monday, Wednesday, and Friday for 22 weeks

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P1108 highlights

Paused to accrual: March 2020: COVID-19
- Re-opened: February 2020: Cohorts 2 and 3 in parallel
- First participant < 6 years enrolled in November 2020
- Accrual targets met: interim analysis: May 2021: cohort 2
- SMC review completed: May 2021: targets met for for PK and safety
- Data shared with WHO upon request: May 2021
- Cohort 3 targets met for accrual and interim analysis: June 2021
- N=8 enrolled cohort 3, n=8 enrolled, cohort 2 (min = 6 “mini-cohort”)
- Collaboration with Janssen: data sharing
- Version 2.0 to be released to sites: July 2021: paediatric BDQ formulation, broader eligibility

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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 for MDR-TB in Children with and without HIV

Chairs: Ethel Weld, MD, Pharm D,
Anthony Garcia-Prats, MD, PhD
Kelly Dooley, MD, Pharm D,

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- **Primary objectives**
  - To evaluate the PK of DLM at doses determined most likely to achieve exposures similar to those achieved in adults with 100 mg twice-daily
  - To evaluate the safety of DLM when added to OBR over 24 weeks of children
- **Design**
  - Phase I/II open-label, single—arm, multisite study
  - Sites: India (BJMC), Botswana (Gaborone, Molepolole), South Africa (DTTC, Sizwe, PHRU Matlosana), Tanzania (KCMC)
- **Accrual status:** n=4, Paused to accrual pending approval of protocol amendment
- **Challenges**
  - After pause for protocol amendment to revise dosing based on emerging data, paused to due to COVID
  - Paused for protocol amendment to address unexpected new safety signal
- **Other**
  - Evaluating model-optimized dosing strategy across the weight spectrum, based on data from Otsuka's 232/233 trials
  - Will identify DLM dosing in smallest children, current critical knowledge gap

IMPAACT 2034: Phase I Study of the Pharmacokinetics, Safety, and Acceptability of Pretomanid in Children with Rifampicin-Resistant Tuberculosis

Protocol chairs:
Ethel Weld, MD, Pharm D,
Pauline Howell, MD,
Anthony Garcia-Prats, MD, PhD

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- **Objectives**
  - Primary: Evaluate the **pharmacokinetics** of a **single-dose of pretomanid** in children with RR-TB
  - Secondary: Evaluate the **safety, tolerability, acceptability and palatability** of a **single-dose of pretomanid** in children with RR-TB
- **Design:** Phase I, multi-site, open-label, single-dose study
  - Minimum: n= 36 evaluable children in 4 weight groups
- **Status**
  - In protocol development, sites TBD
  - For MPRG review Q3 2021
- **Other**
  - Collaboration with TB Alliance
  - FDA IND, EMA
  - Followed by a multiple-dose study, pending safety data from adult male fertility study

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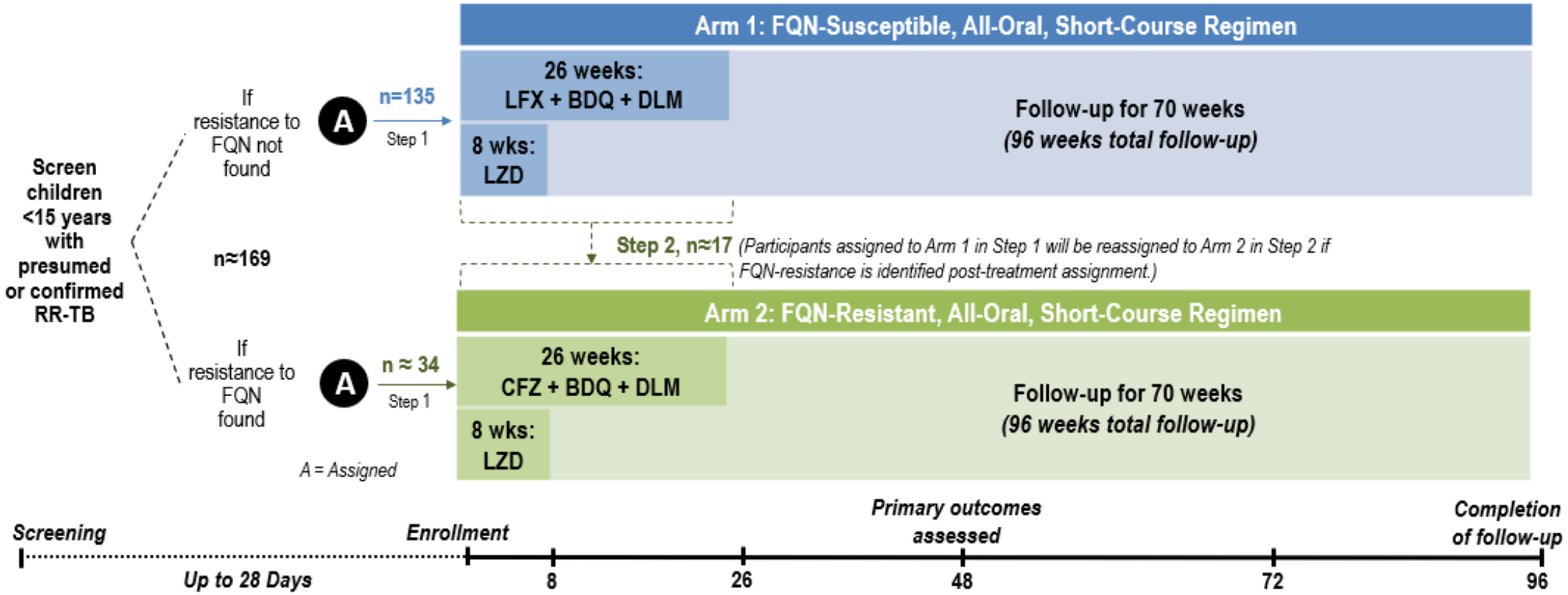
IMPAACT 2020:All oral short course treatment for RR-TB in children and adolescents



Advancing priority new studies: addressing gaps for treatment of DS TB

- Disease burden (>95%); 75% PTB
- Considerable existing investment in DR-TB – at cost of DS-TB
- Different disease spectrum vs. adults; paucibacillary, lymph nodes
- Priority: treatment shortening: building on results of SHINE and TBTC Study 31 (Q4 2020): 4 months non-inferior to 6 months
- Optimizing role of rifamycins

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SHINE: PHASE III TRIAL - EFFICACY AND SAFETY OF 4 MONTHS STANDARD TB TREATMENT

Children aged <16 years with minimal TB (n=1200)

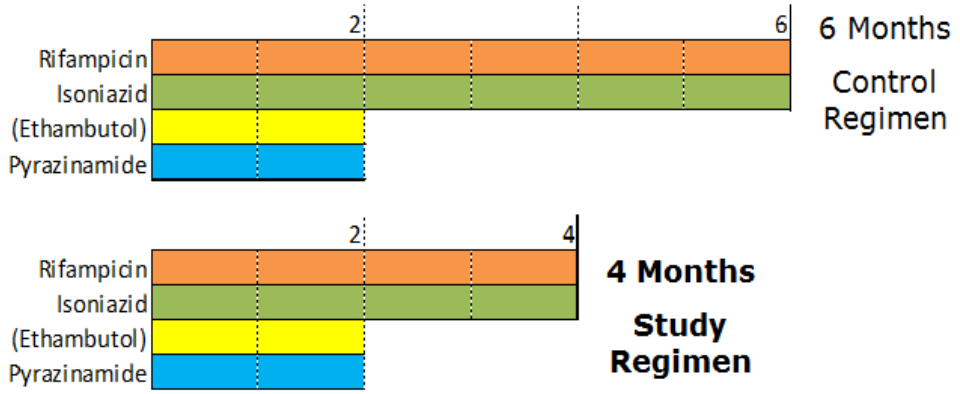
Randomisation (1:1)

6 month (n=600)
Intensive phase: 8 weeks
Continuation phase: 16 weeks

4 month (n=600)
Intensive phase: 8 weeks
Continuation phase: 8 weeks

72 weeks follow-up for primary outcome assessment

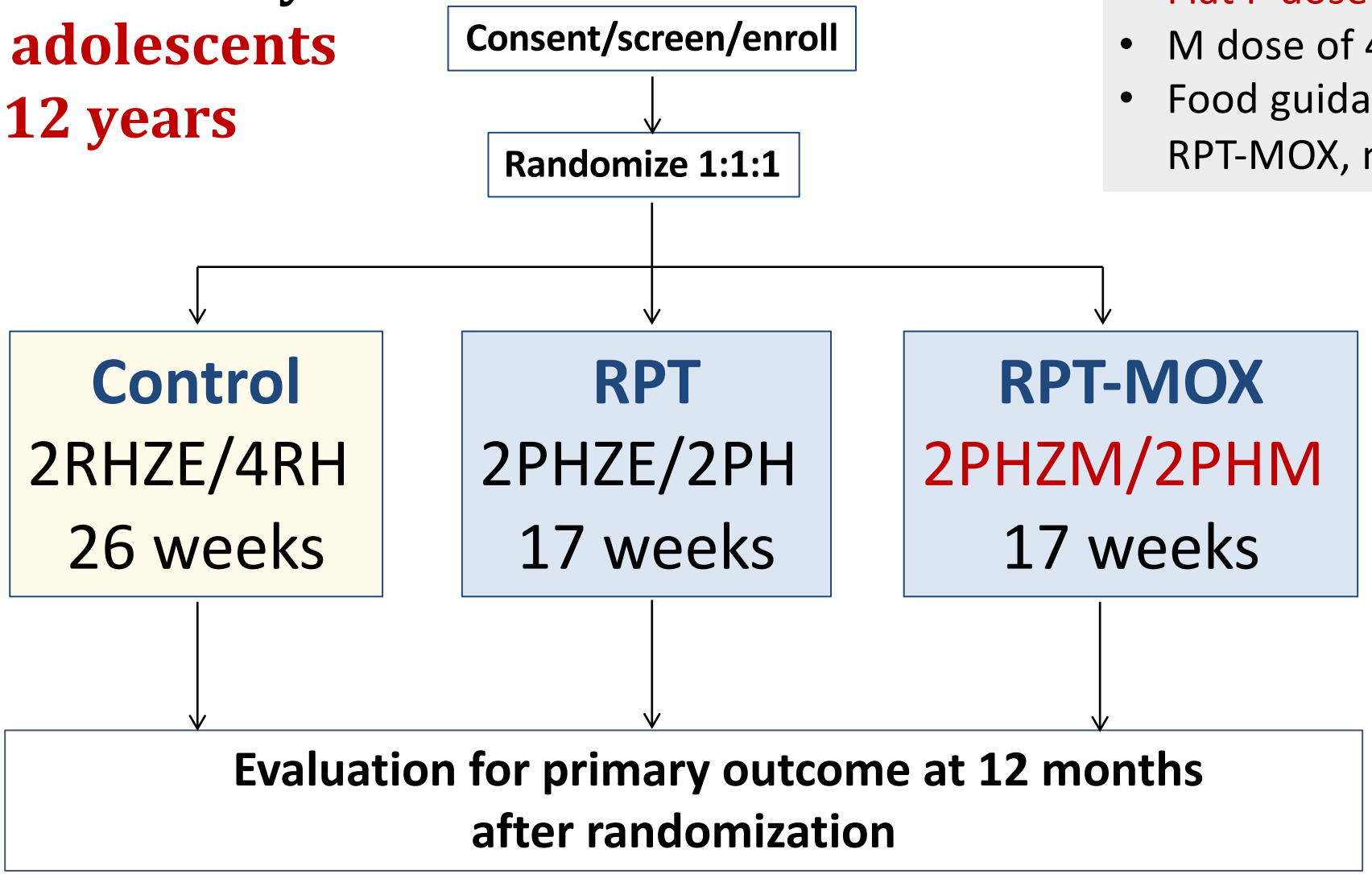
Nested PK substudies undertaken in selected centres



Primary Outcome Measure(s)	**Main Trial:** Efficacy: Unfavourable outcome, defined by the composite endpoint of TB treatment failure, relapse (or re-infection) or death Safety: Grade 3/4 adverse events **Pharmacokinetic Studies:** Pharmacokinetic (PK) parameters (AUC, Cmin, Cmax) of HRZ(E) and of antiretrovirals (ARVs), from full pharmacokinetic curves determined per age group and by HIV status

TBTC S31/A5349
Design Summary
Adults adolescents
>= 12 years

Notes:
- All treatment: daily 7/7
- Flat P dose of 1200 mg
- M dose of 400 mg
- Food guidance: food with RPT-MOX, no food with RPT



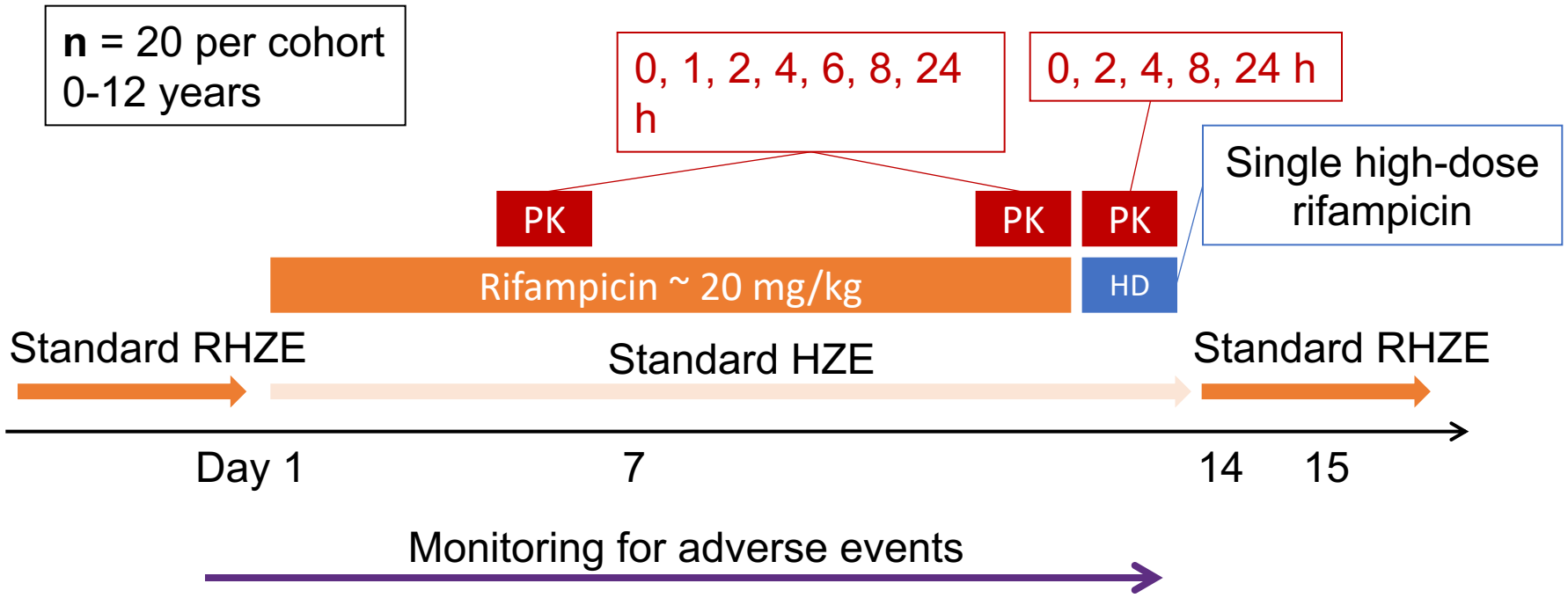
No daily RFPT PK in children

Optimizing rifamycin exposure in children

Cohort 1
15-20 mg/kg
(Days 1-14)
35 mg/kg (Day 15)

Cohort_2
~35 mg/kg
(Days 1-14)
~50 mg/kg
(Day 15)

Cohort 3
~60 mg/kg
(Days 1-14)
~75 mg/kg
(Day 15)



Svensson, under review

Advancing TB therapeutics: priority studies

1. Rifapentine PK and safety (high-dose; 1200 mg daily): bridging TBTC S31: high dose daily RFPT, with MFX

2. Rifampicin: PK and safety, tolerability of high dose rifampicin: long-term

Other priorities

1. Vaccine trials: following VPM: subunit vaccines? ID-93, inclusion of HIV+
2. Diagnostic studies: POC, in context of clinical algorithms non sputum based - diagnostic and treatment response

TBSC mentored investigator programme (and graduates)

- Ethel Weld
- Yael Hirch-Moverman
- Sylvia La Course
- Lisa Cranmer
- Jyothi Mathad
- Jeff Tornheim
- Mandar Paradkar
- Pauline Howell
- Christy Beneri
- Jennifer Hughes
- Nicole Salazar-Austin
- Louvina van der Laan
- Graeme Hoddinott
- Jennifer Hughes
- Megan Palmer
- Marije van Schalkwyk

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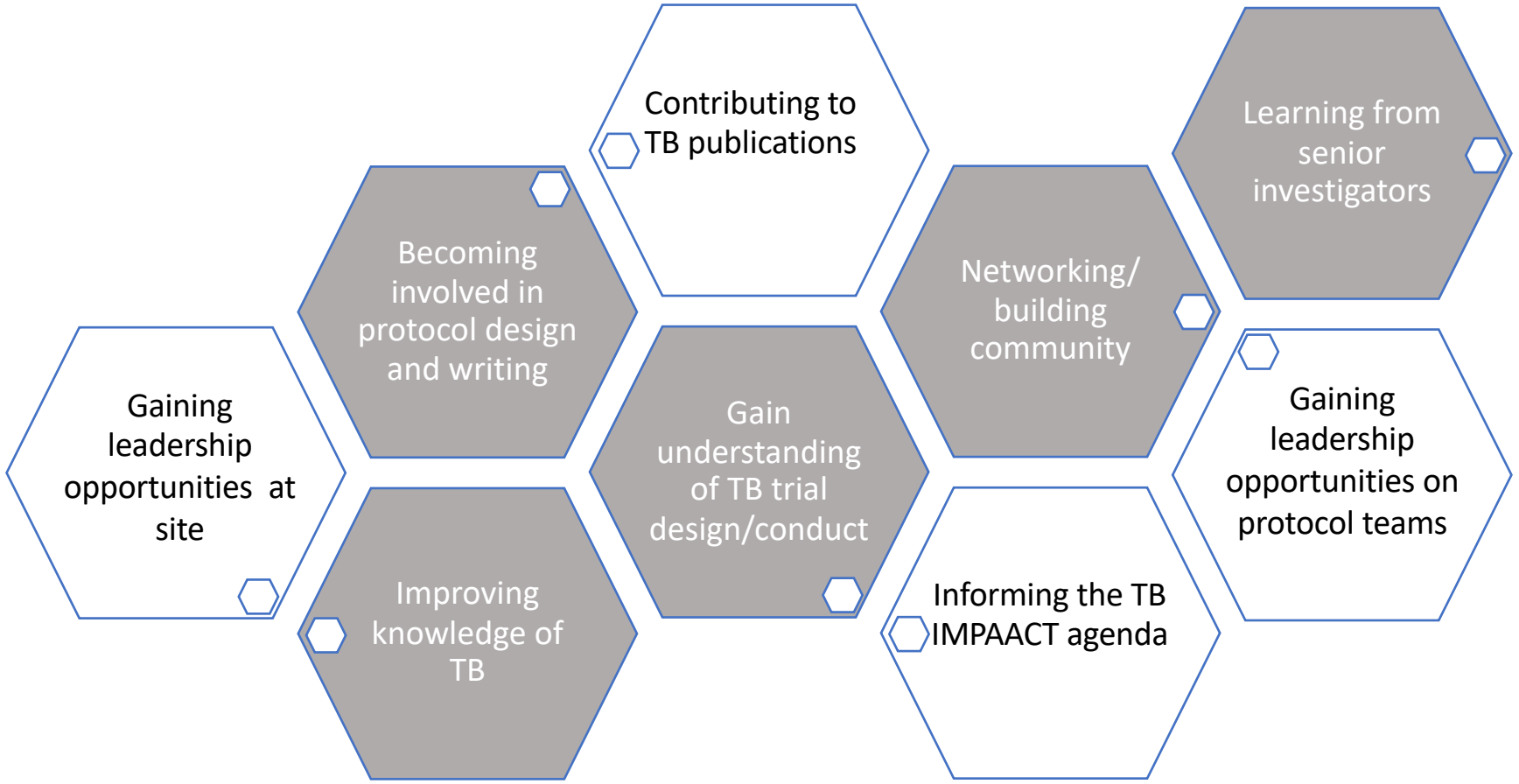
Motivations for joining and benefits of program participation



THANK YOU

Photo taken with permission, Sue Purchase
Desmond Tutu TB Centre, Cape Town, South Africa

Elin Svensson
Lindsay McKenna
Tony Garcia-Prats
Ethel Weld
Nicole Salazar-Austin
Christy Beneri