IMPAACT P1108

A Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) Given in Combination with an Individualized Rifampin-Resistant Tuberculosis (RR-TB) Therapy in Infants, Children and Adolescents with RR-TB Disease, Living with or without HIV

June 2023

Protocol Version 2.0

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Protocol Version 2.0 Implementation Requirements

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Protocol Version 2.0 Implementation Requirements

The following must be completed at each site prior to implementing protocol Version 2.0:

1. All site-specific required regulatory approvals must be obtained for protocol Version 2.0 and associated site-specific informed consent and assent forms.
2. A protocol Version 2.0 Implementation Notice must be issued by the Operations Center.
3. Laboratory Center confirmation that all laboratory requirements for protocol Version 2.0 have been completed.

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Protocol Version 2.0 Implementation Requirements

After all implementation requirements for protocol Version 2.0 have been met at a site, protocol Version 2.0 should be immediately implemented.

Participants enrolled under protocol Version 1.0 who will continue follow-up under protocol Version 2.0 must re-consent and re-assent (if applicable) at the next study visit using the site-specific Version 2.0 informed consent and assent forms, including for specimen storage and future use. This should take place prior to performing any study visit procedures.

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Protocol Version 2.0 Implementation Requirements

For participants who completed the Week 96 visit under protocol Version 1.0, an End of Study visit will need to be conducted as soon as possible to complete follow-up following procedures specified in Section 6.9 of protocol Version 2.0.

Participants must re-consent and re-assent (if applicable), including for specimen storage and future use, using the site-specific Version 2.0 informed consent and assent forms prior to performing the End of Study visit procedures.

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Protocol Team

- Chair: **Anneke Hesseling**
- Vice-Chair: **Simon Schaaf**
- Medical Officers: **Patrick Jean-Philippe** (DAIDS); **Renee Browning** (DAIDS); **Sai Majji** (NICHD); **Jack Moye** (NICHD)
- Clinical Research Managers: **Sarah Bradford** and **Iris Mustich**
- Statisticians: **Paula Britto** and **Grace Montepiedra**
- DAIDS Protocol Pharmacists: **Andrea McMunn** and **Thucuma Sise**
- Pharmacometrician**: Elin Svensson**
- Protocol Data Managers: **Mattie Bartlett** and **Amanda Golner**
- Microbiologist: **Anne-Marie Demers**

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Protocol Team

- Laboratory Data Managers: **Madison Green** and **Kyle Whitson**
- Laboratory Technologists: **Vandana Kulkarni** and **Neeta Pradhan**
- Laboratory Center Representative: **Diane Costello**
- Pharmacologist: **Kelly Dooley**
- Community Advisory Board Representative: **Gwynneth Hendricks**
- Community Program Manager: **Rhonda White**

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Study Resources

- **IMPAACT P1108 Study Webpage**: https://www.impaactnetwork.org/studies/p1108
- **Protocol Version 2.0**, dated 21 September 2022
- **Study-specific Manual of Procedures (MOP)**
- **Study-specific Laboratory Processing Chart**
- **eCRF Completion Guide and Print Matrix**: www.frontierscience.org
- **IMPAACT Network MOP**: https://www.impaactnetwork.org/resources/manual-procedures
- **DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, dated July 2017**: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables
- **DAIDS SCORE Manual and Related Training**:

  https://www.niaid.nih.gov/research/daids-score-manual
  https://www.niaid.nih.gov/daids-ctu/score

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Protocol Version 2.0 Key Updates

- Bedaquiline (BDQ) 20 mg pediatric formulation is added as option for Cohorts 2 and 3
- Shorter follow-up duration with removal of Week 120 visit (now ~96 weeks of follow-up)
- Modified eligibility criteria for clarity and to minimize barriers to enrollment
- All participants will have one respiratory specimen collected at Screening for TB microbiology testing
- Antiretroviral genotypic resistance testing added for participants living with HIV that have a viral load ≥ 1,000 copies/mL
- Removal of urine collection for future biomarkers, local lactate, and lactate/pyruvate evaluations
- TSH and fT4 testing only required if participants taking PAS or Ethionamide
- Intensive PK sampling will take place at Week 1 or Week 2 visit based on when a participant initiates BDQ daily dosing, including any non-study BDQ prior to study enrollment
- Updated clinical management guidance for participant safety monitoring
- Updated TB treatment outcome classifications and evaluation requirements

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Study Rationale

- RR-TB treatment in children can be improved with new, effective, and safer drugs, with the goal of further shortening RR-TB therapy using shorter and acceptable injectable-sparing regimens and reducing adverse effects and poor tolerability.
- Adults: BPaLM/BPaL for MDR/XDR-TB for six months
- The World Health Organization (WHO) recommends BDQ 20 mg and 100 mg tablets for RR-TB treatment in children down to six years of age. As of March 2022, WHO has conditionally recommended BDQ in children with MDR/RR-TB below six years of age, based on preliminary data from P1108. However, further data on dosing and safety are needed.

Hypothesis: BDQ will be well tolerated and will demonstrate an acceptable safety and PK profile in infants, children, and adolescents with RR-TB, living with and without HIV.

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Groups & steps	Medicine	
Group A: Include all three medicines	Levofloxacin *or* Moxifloxacin	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine *OR*	Cs
	terizidone	Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	imipenem–cilastatin *OR*	Ipm–Cln
	Meropenem	Mpm
	amikacin	Am
	(*OR* streptomycin)	(S)
	ethionamide *OR*	Eto
	Prothionamide	Pto
	p-aminosalicylic acid	PAS

Primary Objectives

- Determine the BDQ doses that achieve similar weekly exposure (AUC) of BDQ compared to adults taking BDQ at the current standard recommended WHO dose.
- Evaluate the safety and tolerability of BDQ over a 24-week dosing period.

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Secondary and Exploratory Objectives

Secondary Objectives

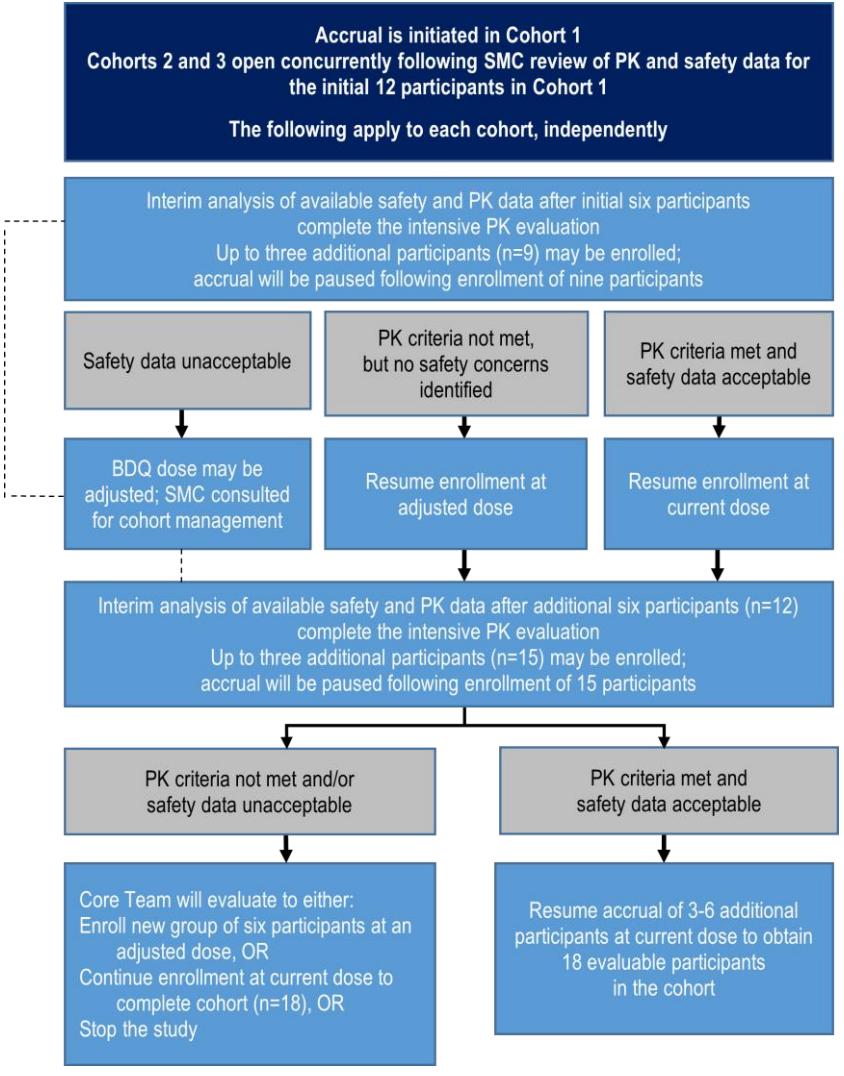
- Evaluate the PK of BDQ over the 24-week dosing period, by HIV status.
- Describe the long-term safety and tolerability of BDQ over a 96-week total follow-up period, by HIV status.
- Describe BDQ concentrations following BDQ discontinuation and through 72 weeks after BDQ discontinuation, by HIV status.
- Describe the RR-TB treatment response up to 96 weeks from initiation of the study, by HIV status.

Exploratory Objective

- Explore longitudinal biomarkers of TB treatment response in children treated for RR-TB.

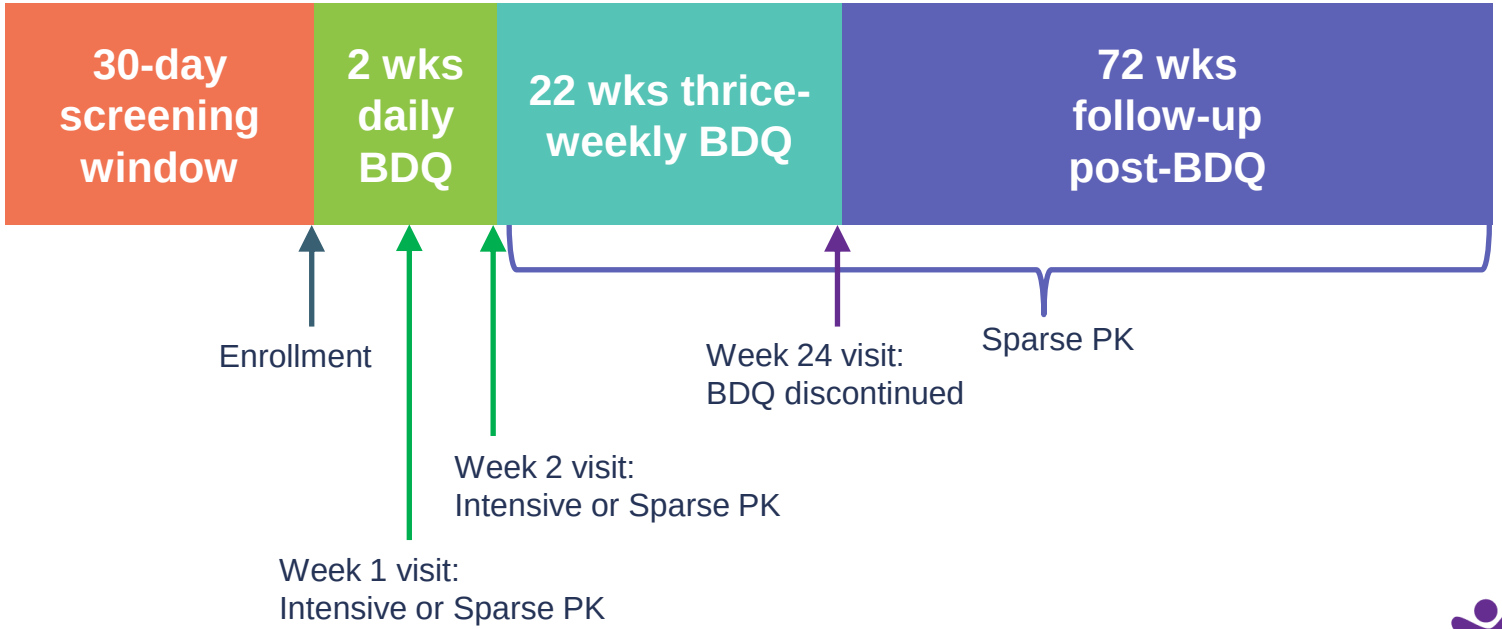
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Study Design



IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Study Duration



**Intensive PK will be performed at either the Week 1 or Week 2 visit based on when the participant initiated BDQ daily dosing (refer to protocol Section 6)*

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Age Cohorts and BDQ Dosing

Cohort	Age and Weight	BDQ Dosing
Cohort 1 Up to 24 participants to achieve 18 evaluable (approximately nine in each weight band)	≥ 6 to < 18 years ≥30 kg	*Participants ≥30 kg:* 400 mg once per day through the intensive PK sampling visit*, then 200 mg three times per week on Monday, Wednesday, and Friday through the Week 24 visit *Participants >7 to <30 kg* 200 mg once per day through the intensive PK sampling visit*, then 100 mg three times per week on Monday, Wednesday, and Friday through the Week 24 visit *Participants ≥ 3 to ≤ 7 kg:* 100 mg once per day through the intensive PK sampling visit*, then 50 mg three times per week on Monday, Wednesday, and Friday through the Week 24 visit
	≥ 6 to < 18 years ≥15 to <30 kg	
Cohort 2 Up to 30 participants to achieve 18 evaluable	≥ 2 to < 6 years >7 kg	
Cohort 3 Up to 30 participants to achieve 18 evaluable	≥ 0 to < 2 years ≥3 kg	

*Intensive PK sampling will be performed at the Week 1 or Week 2 visit following receipt of at least 14 and no more than 17 BDQ daily doses, including any non-study BDQ doses taken prior to study entry.

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Any questions?

Contact the P1108 Core Team:
impaact.p1108core@fstrf.org

Clinical questions: CMC

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network