P1108 UPDATE

A PHASE I/II, OPEN-LABEL, SINGLE ARM STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY, OF BEDAQUILINE (BDQ) IN COMBINATION WITH OPTIMIZED INDIVIDUALIZED MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB) ON IN HIV-INFECTED AND HIV-UNINFECTED INFANTS, CHILDREN AND ADOLESCENTS WITH MDR-TB DISEASE

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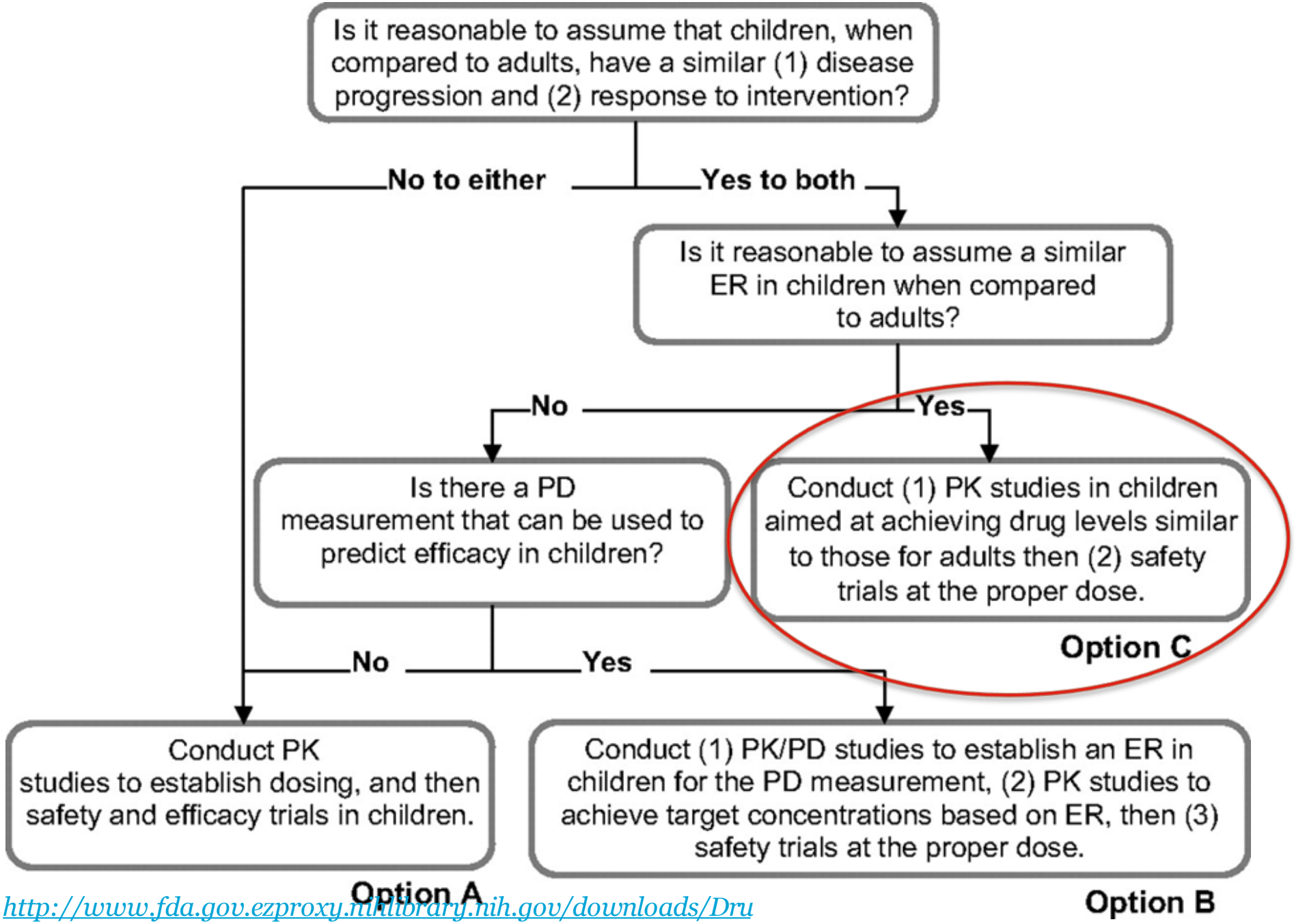
18 JUNE 2018

IMPAACT TBSC



http://www.fda.gov.ezproxy.nihlibrary.nih.gov/downloads/Drugs/

PRIMARY OBJECTIVES

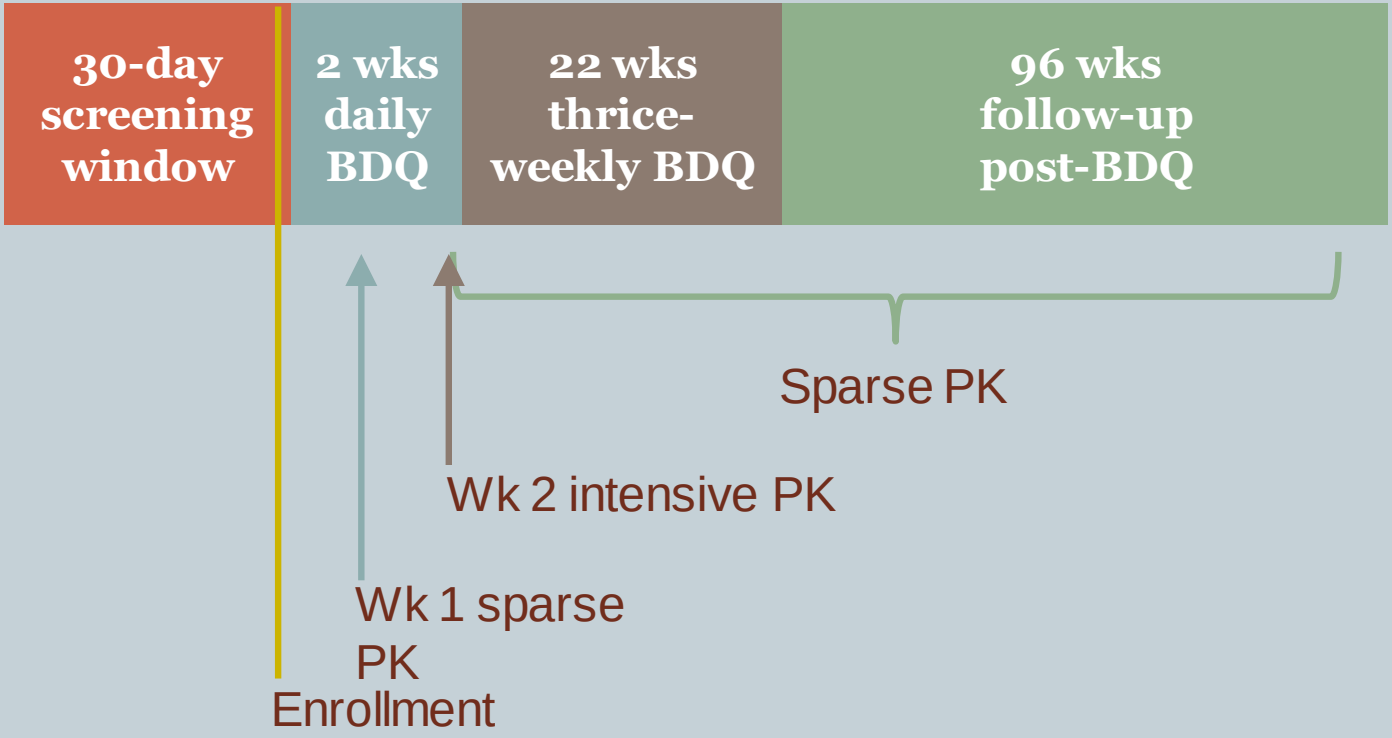
1. To determine the BDQ doses that achieve similar weekly exposure (area under the curve; AUC) of BDQ compared to adults taking BDQ at the standard recommended dose.
2. To evaluate the safety and tolerability of BDQ over 24 weeks from the initiation of study treatment

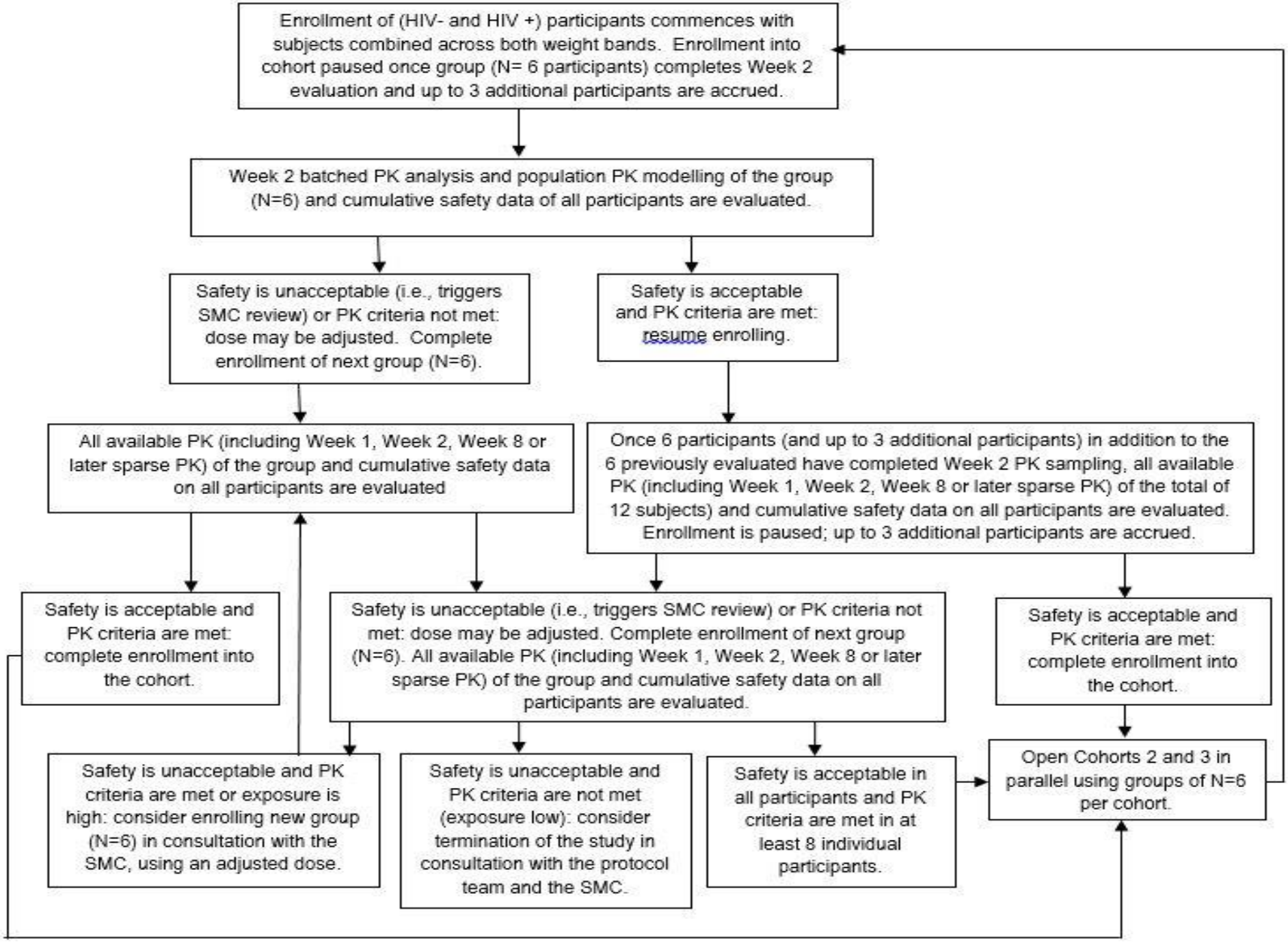
SECONDARY AND EXPLORATORY OBJECTIVES

Secondary Objectives:

1. To evaluate the PK of BDQ over the 24-week dosing period, by HIV status.
2. To describe the long-term safety and tolerability of BDQ over a 120-week (30-month) total follow-up period, by HIV status.
3. To describe BDQ concentrations following BDQ treatment discontinuation at 24 weeks, from study Weeks 24 to 120, by HIV status.
4. To describe the MDR-TB treatment response up to 120 weeks from the initiation of the study, by HIV status

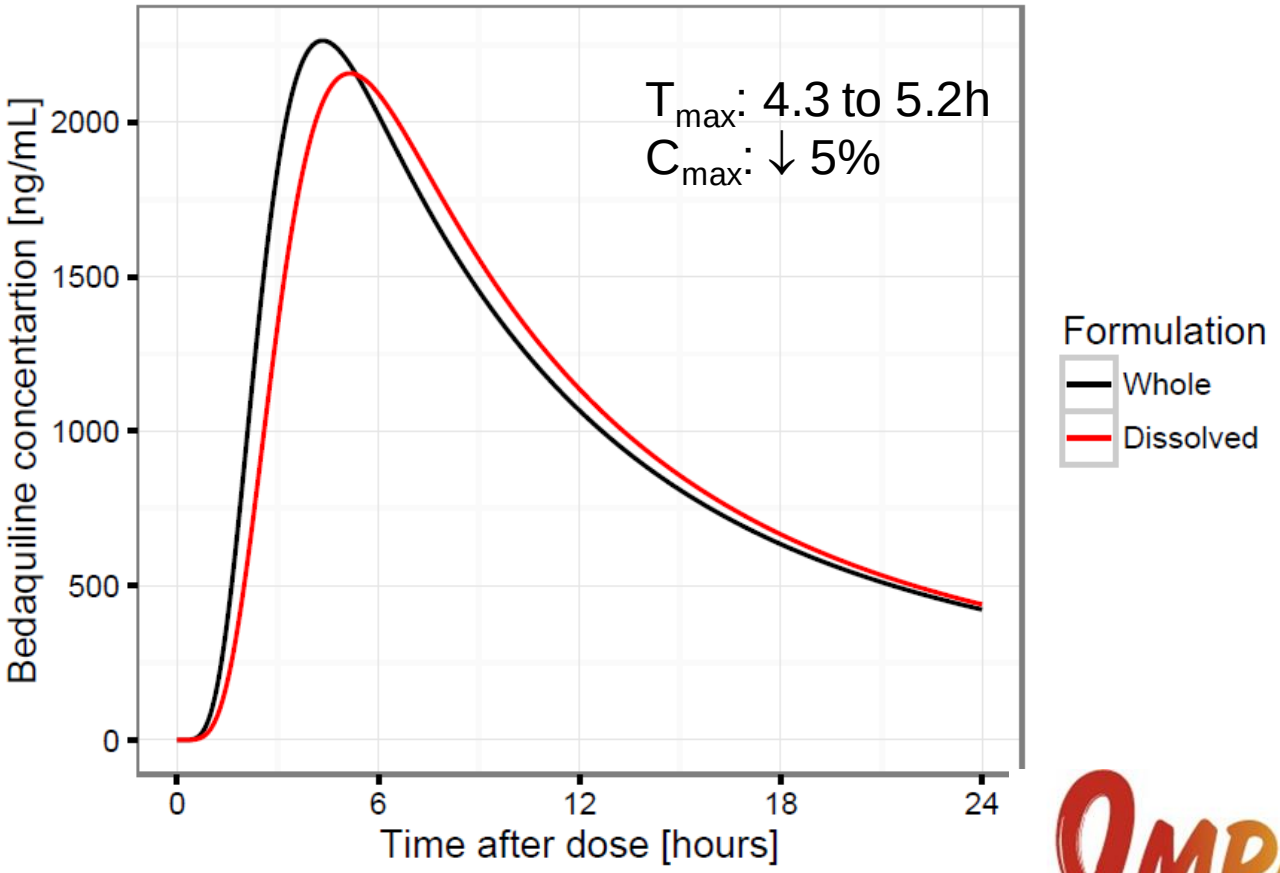
IMPAACT P1108




Enrollment of (HIV- and HIV +) participants commences with subjects combined across both weight bands. Enrollment into cohort paused once group (N= 6 participants) completes Week 2 evaluation and up to 3 additional participants are accrued.
Week 2 batched PK analysis and population PK modelling of the group (N=6) and cumulative safety data of all participants are evaluated.
Safety is unacceptable (i.e., triggers SMC review) or PK criteria not met: dose may be adjusted. Complete enrollment of next group (N=6).
Safety is acceptable and PK criteria are met: resume enrolling.
All available PK (including Week 1, Week 2, Week 8 or later sparse PK) of the group and cumulative safety data on all participants are evaluated
Once 6 participants (and up to 3 additional participants) in addition to the 6 previously evaluated have completed Week 2 PK sampling, all available PK (including Week 1, Week 2, Week 8 or later sparse PK) of the total of 12 subjects) and cumulative safety data on all participants are evaluated. Enrollment is paused; up to 3 additional participants are accrued.
Safety is acceptable and PK criteria are met: complete enrollment into the cohort.
Safety is unacceptable (i.e., triggers SMC review) or PK criteria not met: dose may be adjusted. Complete enrollment of next group (N=6). All available PK (including Week 1, Week 2, Week 8 or later sparse PK) of the group and cumulative safety data on all participants are evaluated.
Safety is acceptable and PK criteria are met: complete enrollment into the cohort.
Safety is unacceptable and PK criteria are met or exposure is high: consider enrolling new group (N=6) in consultation with the SMC, using an adjusted dose.
Safety is unacceptable and PK criteria are not met (exposure low): consider termination of the study in consultation with the protocol team and the SMC.
Safety is acceptable in all participants and PK criteria are met in at least 8 individual participants.
Open Cohorts 2 and 3 in parallel using groups of N=6 per cohort.

Cohort	Age and Weight	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 then 200 mg three times per week for 22 weeks
	≥ 6 to < 18 years ≥15 to <30 kg	200 mg once per day for two weeks then 100 mg three times per week for 22 weeks
Cohort 2 up to 24 participants to achieve 18 evaluable	≥ 2 to < 6 years ≥7 kg	Calculated using model-based dose selection
Cohort 3 up to 24 participants to achieve 18 evaluable	≥ 0 to < 2 years ≥3 kg	Calculated using model-based dose selection

Impact of dissolving on a typical bedaquiline PK profile



Enrolment status

- Opened Q4 2018: 9 participants enrolled : 7 from Desmond Tutu TB Centre, 2 from PHRU Matlosana CRS.
- In April 2018, accrual temporarily paused for an interim look at the PK and safety data.
- Reviewed available evaluable PK (evaluable for this analysis is defined as having week 2 PK data) and safety data and determined that a dose modification for the study drug was not needed per protocol
- Study re-opened on May 8, 2018, to accrue into Cohort 1; PK and safety interim analysis will be done after 12 participants have week 2 PK data available in this cohort

Baseline characteristics: first interim analysis: n=9

- 60% Black Non-Hispanic (African)
- All HIV-uninfected to date
- Ages: 6-17 years: median age at entry: 14 years
- Median weight and height at entry was 38 kilos and 156 cms respectively
- All 9 enrolled had bacteriologically confirmed TB (PTB) and started MDR-TB medication prior to study entry
- All had proof of at least RMR-TB

Next steps

- Complete n=12 in cohort 1 and complete formal safety and PK evaluation
- Data sharing with Janssen (CTA): C211
- Access to paediatric formulation
- Data shared with WHO (MDR TB guidelines)
- Open cohorts 2, 3 in parallel (5 sites), 2018