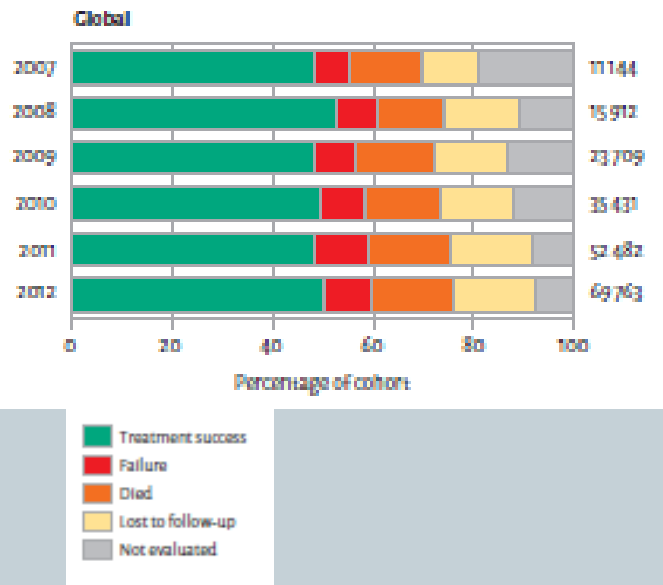
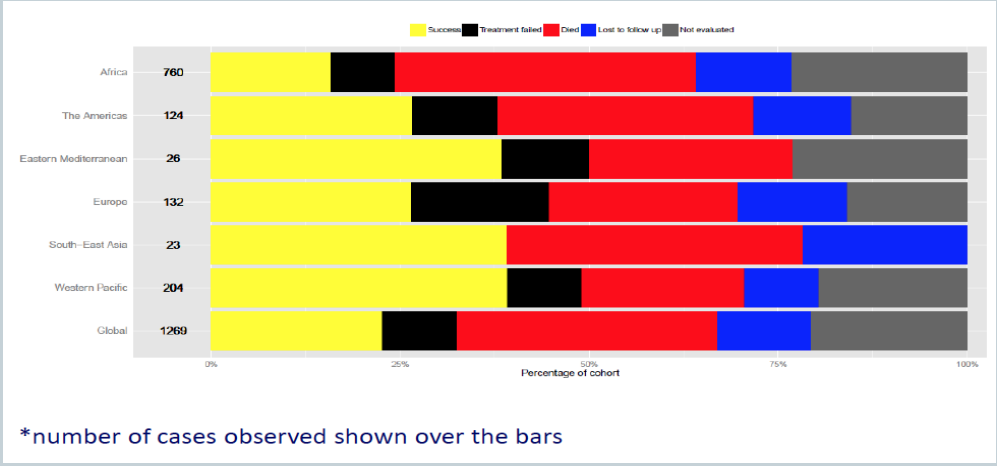
IMPAACT
International Maternal Pediatric
Adolescent AIDS Clinical Trials Network

IMPAACT P1108

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) THERAPY IN HIV-INFECTED AND HIV-UNINFECTED INFANTS, CHILDREN AND ADOLESCENTS WITH MDR-TB DISEASE

Low Treatment Success and High Mortality





*number of cases observed shown over the bars

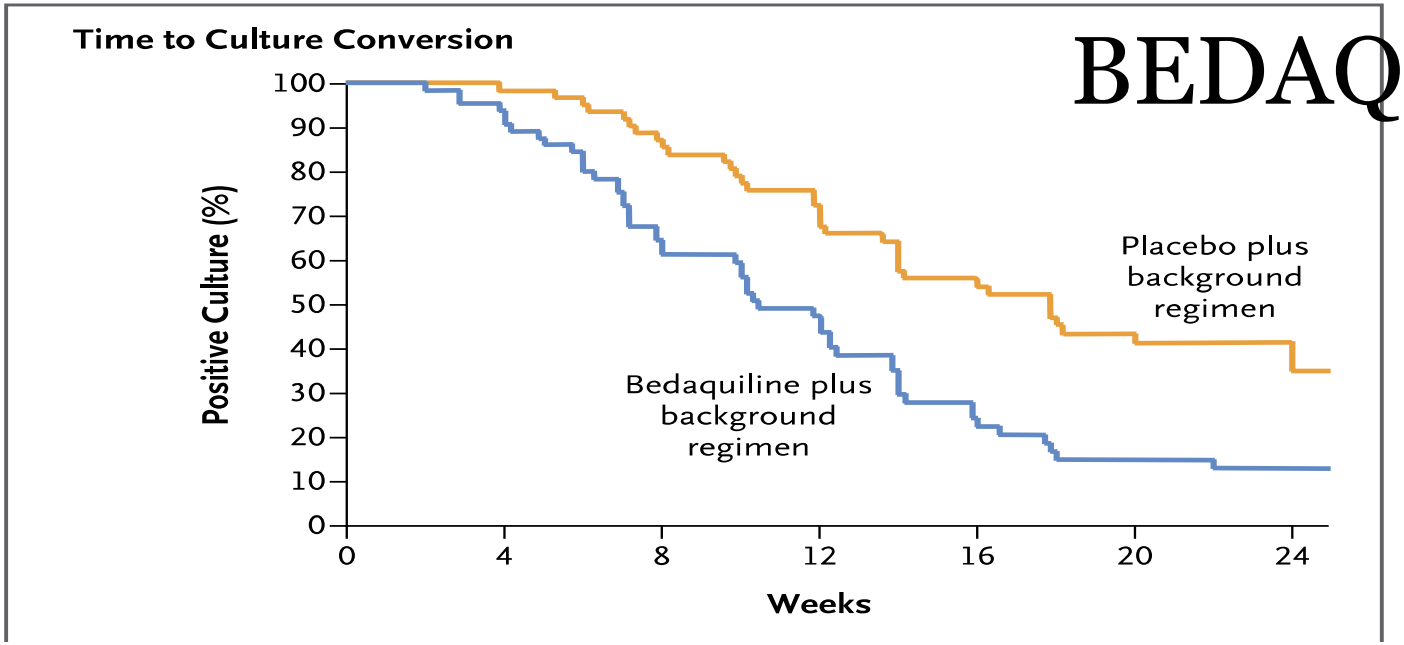
MDR TB: 50% treatment success, 16% death

XDR TB: 24% treatment success, 30% death

WHO Global TB Report 2015


ETO
PZA
Levoflox
Bedaquiline
INH
Terizidone
EMB

BEDAQUILINE



Conditional approval: FDA
MCC: 2014
India
Black box warning

Table 2. Adverse Events during 120 Weeks in the Intention-to-Treat Population.*

Variable	Bedaquiline (N = 79)	Placebo (N = 81)
Median duration of overall treatment phase (range) — wk	91.7 (2.0–120.0)	94.1 (2.0–137.3)
Adverse event — no. (%)		
Any	78 (99)	79 (98)
Related to treatment	55 (70)	56 (69)
Grade 3 or 4†	34 (43)	29 (36)
Leading to discontinuation of treatment	4 (5)	5 (6)
Serious adverse events — no. (%)‡	18 (23)	15 (19)
Adverse event occurring in ≥20% of patients — no. (%)		
Nausea	32 (41)	30 (37)
Arthralgia	29 (37)	22 (27)
Vomiting	23 (29)	22 (27)
Headache	23 (29)	18 (22)
Hyperuricemia	20 (25)	27 (33)
Hemoptysis	16 (20)	14 (17)

Diacon, NEJM, 2015

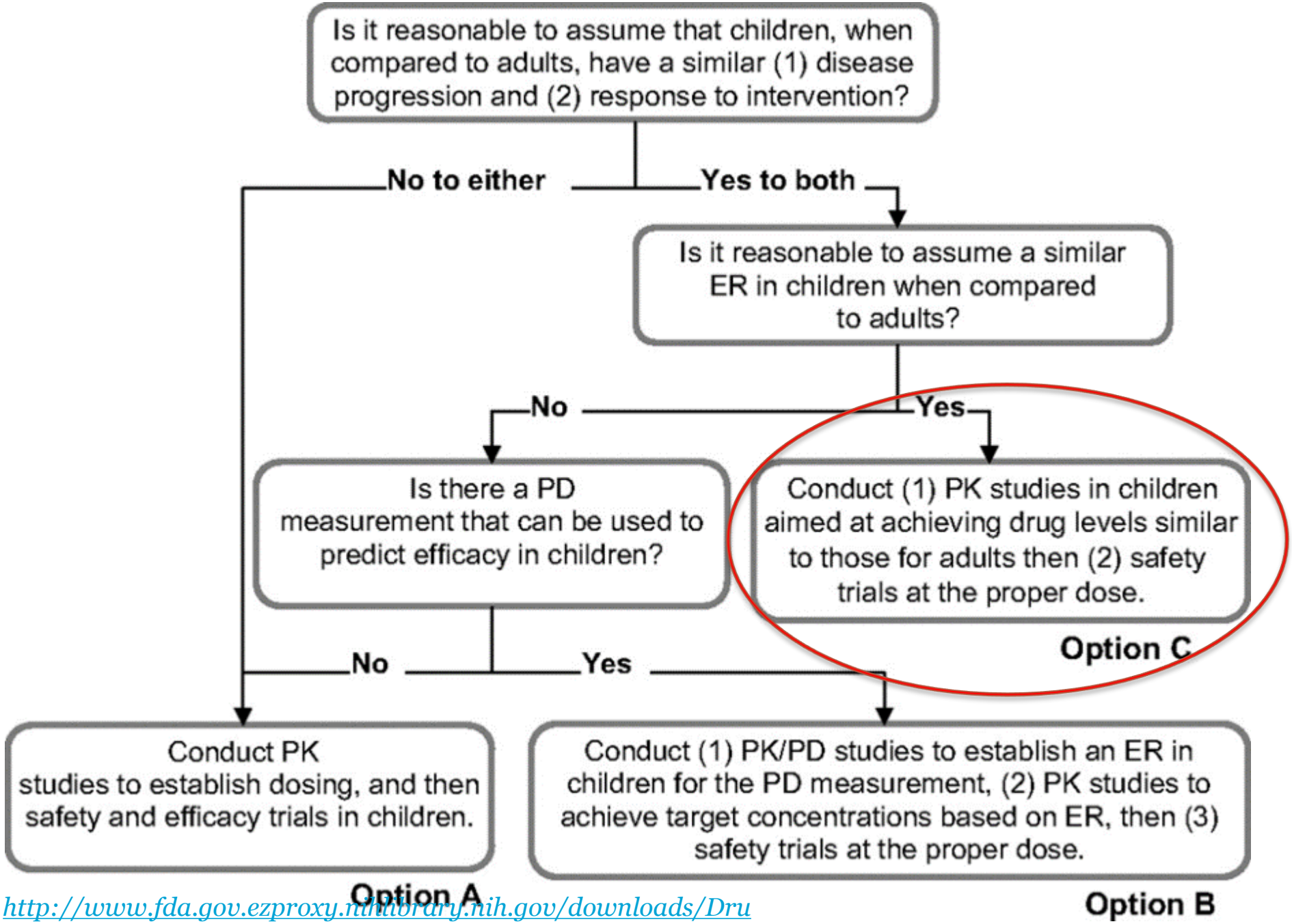
PRIMARY OBJECTIVES

In HIV-infected and HIV-uninfected infants, children and adolescents receiving BDQ plus optimized background regimens (OBR) for MDR-TB:

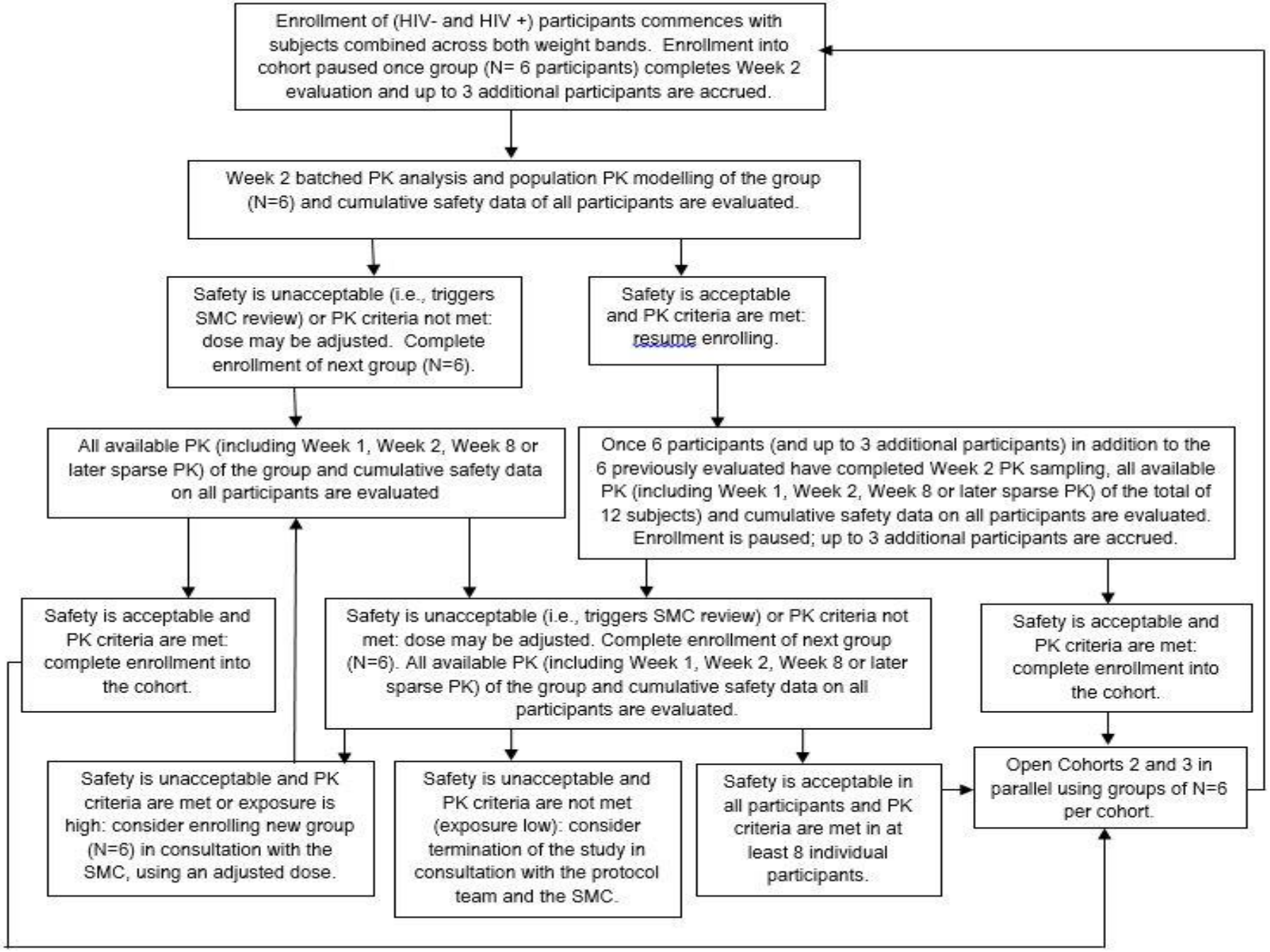
- To determine the BDQ doses that achieve similar weekly exposure (area under the curve; AUC) of BDQ compared to adults taking BDQ at the standard recommended dose
- To evaluate the safety and tolerability of BDQ over 24 weeks from the initiation of study treatment

SECONDARY OBJECTIVES

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



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


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

Participating sites

Current study status

- Protocol Version 1 released:

  March 3, 2016

- Projected Open to Accrual:

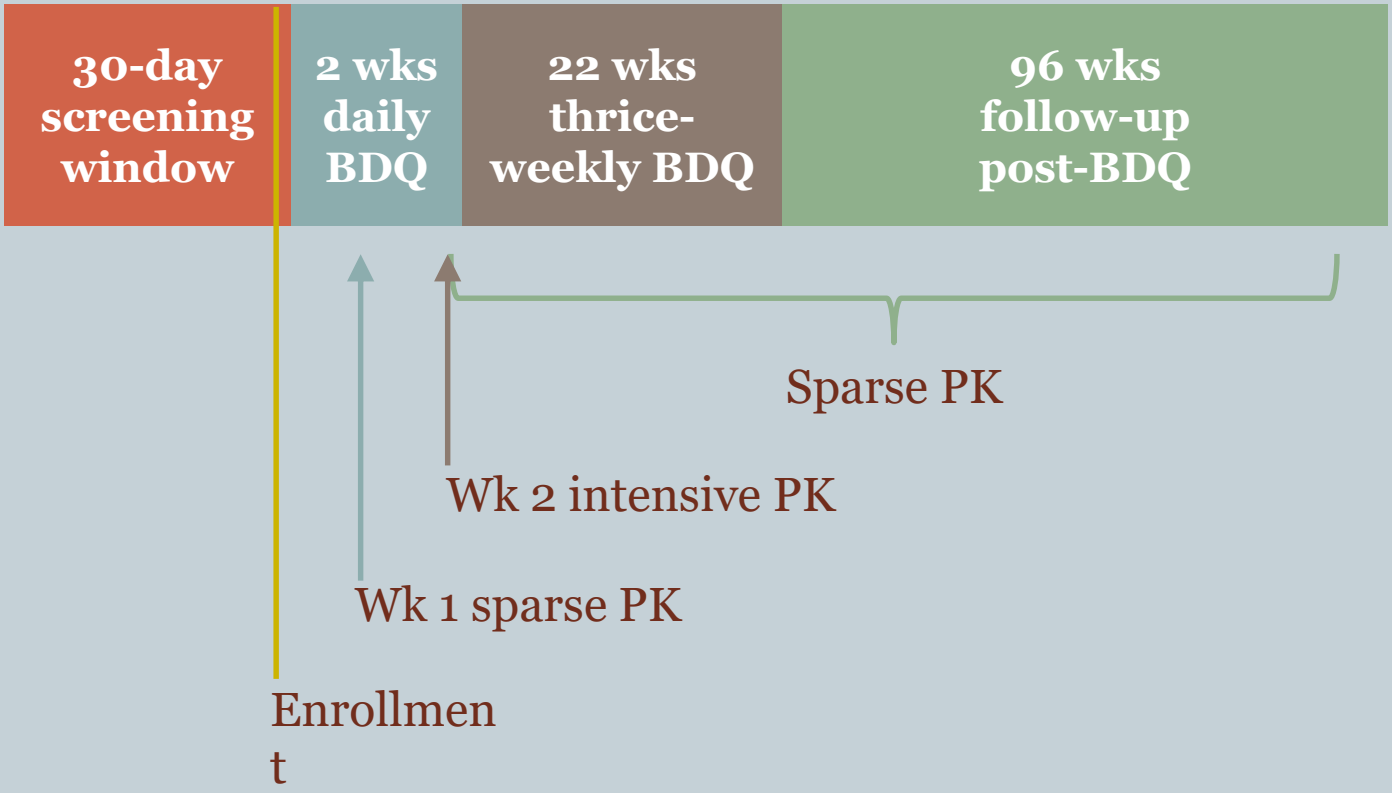
  June 2017

- Projected First Participant Enrolled:

  June 2017

- Under FDA IND
- CTA with Janssen: access to paediatric formulation

Study design and duration



Sample Size

- Up to 72 participants will be enrolled to achieve at least 54 evaluable participants
  - Cohort 1: ≥ 6 to < 18 years of age at enrollment (Balanced by weight: ≥ 15 to < 30 kg AND ≥ 30 kg)
  - Cohort 2: ≥ 2 to < 6 years of age at enrollment
  - Cohort 3: ≥ 0 to < 2 years of age at enrollment
- All evaluations to be done in groups of 6
- In each cohort, at least six participants will be HIV-infected

Appendix I: Schedule of Evaluation for All Cohorts (1, 2 and 3)

	Screening	On treatment visits										Unsch Visit	Early BDQ D/C or Study D/C
		Entry/ Day 0	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24		
CLINICAL EVALUATIONS													
Informed consent	x												
Documentation of HIV status[1]	x												
History	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical exam	x	x	x	x	x	x	x	x	x	x	x	x	x
Pill dispensing		x	x	x	x	x	x	x	x	x			
Adherence assessment		x	x	x	x	x	x	x	x	x	x		x
TB disease status and severity	x	x		x			x				x		x
Tuberculin Skin Testing[2]	x						x						
ECG	x	x		x	x		x	x	x	x	x		x
CXR	x						x		x		x		x
Audiology		x					x		x		x		
LABORATORY EVALUATIONS													
Hematology	1.0mL	1.0mL	1.0mL	1.0mL	1.0mL		1.0mL	1.0mL	1.0mL	1.0mL	1.0mL		1.0mL
Chemistries	2.0mL	2.0mL	2.0mL	2.0mL	2.0mL		2.0mL	2.0mL	2.0mL	2.0mL	2.0mL		2.0mL
LFT	x	x	x	x	x		x	x	x	x	x		x
TSH (fT4 if TSH is elevated)		2.0mL					2.0mL		2.0mL		2.0mL		
Serum biomarkers (storage)	0.5-1 mL	0.5-1.0mL		0.5-1.0mL	0.5-1.0mL		0.5-1.0mL		0.5-1.0mL		0.5-1.0mL		
Cohort 1: lactate[3] to local lab		2.0mL			2.0mL						2.0mL		
Cohort 1: lactate/ pyruvate		2.0mL			2.0mL						2.0mL		
Pregnancy test	x	x			x		x		x		x		x
Specimens for TB micro lab		x			x		x	x	x	x	x		
Urinalysis		x			x		x	x	x	x	x		x
Urine biomarker (storage)	x	x		x	x		x		x		x		
Intensive PK				2.5-5.0mL									
Sparse PK			0.5-1.0mL		0.5-1.0mL		0.5-1.0mL	0.5-1.0mL	0.5-1.0mL	0.5-1.0mL	0.5-1.0mL		0.5-1.0mL
HIV-Infected only													
HIV-1 RNA PCR (viral load)		3.0mL						3.0mL			3.0mL		
Lymphocyte subsets		1.0mL			1.0mL			1.0mL			1.0mL		1.0mL
TOTAL BLOOD VOLUMES (*higher volumes for HIV+*)													
Cohort 1	4.0mL	10-14.0mL	4.0mL	9.0mL	9-10mL	0mL	7.0mL	4-8.0mL	7.0mL	4.0mL	11-15mL	0mL	4-5.0mL
Cohort 2	4.0mL	6-10.0mL	4.0mL	9.0mL	5-6mL	0mL	7.0mL	4-8.0mL	7.0mL	4.0mL	7-11mL	0mL	4-5.0mL
Cohort 3	3.5mL	5.5-9.5 mL	3.5mL	6.0 mL	4-5.0mL	0mL	6.0mL	3.5-7.5mL	6.0mL	3.5mL	6-10.0mL	0mL	3.5-4.5mL

Appendix I (cont.): Schedule of Evaluation for All Cohorts (1, 2 and 3)

	Off treatment visits							Unsched. Visit	Early Study D/C
	Week 32 (8 wks post BDQ)	Week 40 (16 wks post BDQ)	Week 48 (24 wks post BDQ)	Week 60 (36 wks post BDQ)	Week 72 (48 wks post BDQ)	Week 96 (72 wks post BDQ)	Week 120/ End of Study (96 wks post BDQ)		
CLINICAL EVALUATIONS									
History	x	x	x	x	x	x	x	x	x
Documentation of HIV status[1]			x				x		x
Physical exam	x	x	x	x	x	x	x	x	x
TB treatment outcome							x		
ECG		x							x
CXR		x			x		x		
LABORATORY EVALUATIONS									
Hematology	1.0 mL	1.0 mL	1.0 mL	1.0 mL	1.0 mL	1.0 mL	1.0 mL		1.0 mL
Chemistries	2.0 mL	2.0 mL	2.0 mL	2.0 mL	2.0 mL	2.0 mL	2.0 mL		2.0 mL
LFT	x	x	x	x	x	x	x		x
TSH (fT4 if TSH is elevated)	2.0mL		2.0mL		2.0mL				
Serum biomarkers (storage)							0.5-1.0mL		
Cohort 1: lactate[3] to local lab						2.0mL			
Cohort 1: lactate/ pyruvate						2.0mL			
Pregnancy test	x	x	x	x	x	x	x		x
Specimens for TB micro lab	x	x	x	x	x				x
Urinalysis	x	x	x	x	x	x	x		x
Urine biomarkers (storage)			x				x		
Sparse PK	0.5-1.0mL	0.5-1.0mL	0.5-1.0mL	0.5-1.0mL	0.5-1.0mL	0.5-1.0mL	0.5-1.0mL		0.5-1.0mL
HIV-Infected only									
HIV-1 RNA PCR							3.0mL		
Lymphocyte subsets	1.0 mL		1.0 mL			1.0 mL	1.0 mL		
TOTAL BLOOD VOLUMES (*higher volumes for HIV+*)									
Cohort 1	6-7.0mL	4.0mL	6-7.0mL	4.0mL	6.0mL	8-9.0mL	5-9.0mL		4.0mL
Cohort 2	6-7.0mL	4.0mL	6-7.0mL	4.0mL	6.0mL	4-5.0mL	5-9.0mL		4.0mL
Cohort 3	5.5-6.5mL	3.5mL	5.5-6.5mL	3.5mL	5.5mL	3.5-4.5mL	4-8.0mL		3.5mL

(1) Refer to protocol section 4.3 for acceptable documentation of HIV status at screening. In the absence of such documentation, HIV testing should be conducted as part of the screening process and may entail the collection of up to 6 mL depending on type of tests validated for use at the site. Documentation of HIV status of HIV-exposed participants in Cohort 3 is required at Week 48 (24 weeks post BDQ) and Week 120/End of Study. If acceptable documentation is not available, additional blood may need to be collected.

(2) If TST is not available at the site, IGRA may be done. This would require that an additional 3-4.0 mL of blood be collected at these time points.

(3) If lactate is >3mmol/L, additional 2.0mL for repeat test will be necessary; refer to LPC and Appendix IX: Toxicity Management of Specific Toxicities: Lactate.