IMPAACT 2017
SC Meeting

01 June 2017

IMPAACT
International Maternal Pediatric
Adolescent AIDS Clinical Trials Network

BACKGROUND

Study Rationale

- Many safe, potent, daily, antiretrovirals (ARVs)
- But still challenge of sustaining adherence to ARVs for some (esp adolescents)
- Desire for further treatment simplification
- Interest in NRTI sparing regimens

Long-Acting/Extended Release Medications

- A rapidly growing approach with many promising applications, mostly in adults

- Long-acting agents used as contraceptives and in management of other chronic diseases

Long-Acting/Extended Release ARVs

- Long-acting cabotegravir (CAB LA) is an integrase strand transfer inhibitor
- Long-acting rilpivirine (RPV LA) is a non-nucleoside reverse transcriptase inhibitor
- CAB LA + RPV LA are currently being studied in two Phase III adult clinical trials

PRIOR RESEARCH

LATTE-2 Objectives

- Establish proof of principle for the first ever long-acting (LA) injectable HIV treatment regimen
- **Primary Objectives**
  - Evaluate the safety and efficacy of CAB LA + RPV LA as maintenance therapy
  - Select a dosing schedule of CAB LA + RPV LA for progression into phase III studies
- **Key Secondary Objectives**
  - Characterize pharmacokinetics after depot injections
  - Evaluate the tolerability and acceptability of intramuscular dosing

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

Ongoing Phase 3 adult studies

FLAIR

Treatment-naïve patients given a 20-week daily oral dolutegravir/abacavir/lamivudine (Triumeq®) regimen, and then randomised to switch to a regimen of CAB-LA and RPV-LA, OR remain on oral therapy

ATLAS

Treatment-experienced patients with suppressed viral load randomised to switch from their existing cART to CAB-LA and RPV-LA OR remain on oral cART

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Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

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STUDY OBJECTIVES

Primary Objectives

Cohort 1

- To confirm the doses for oral CAB followed by injectable CAB LA in HIV-infected, virologically suppressed adolescents by evaluating (Cohort 1C):
  - Safety and multiple dose PK of oral CAB through Week 4
  - Safety and multiple dose PK of CAB LA through Week 16
- To confirm doses for injectable RPV LA in HIV-infected, virologically suppressed adolescents by evaluating safety and multiple dose PK of RPV LA through Week 16 (Cohort 1R)

Cohort 2

- To assess the safety of injectable CAB LA + RPV LA through Week 24 in HIV-infected, virologically suppressed adolescents

Secondary Objectives
Cohort 1

- To evaluate the tolerability and acceptability of CAB LA or RPV LA when given as single intramuscular injections every four weeks over an eight-week period to HIV infected, virologically suppressed HIV-infected adolescents both from the standpoint of the study participants receiving the injections as well as their parent/caregivers and site staff.

- To characterize long-term safety and washout PK through 48 weeks following permanent discontinuation of CAB LA or RPV LA

- To evaluate safety and multiple dose PK of oral RPV through Week 4 in HIV-infected, virologically suppressed adolescents

Secondary Objectives
Cohort 2

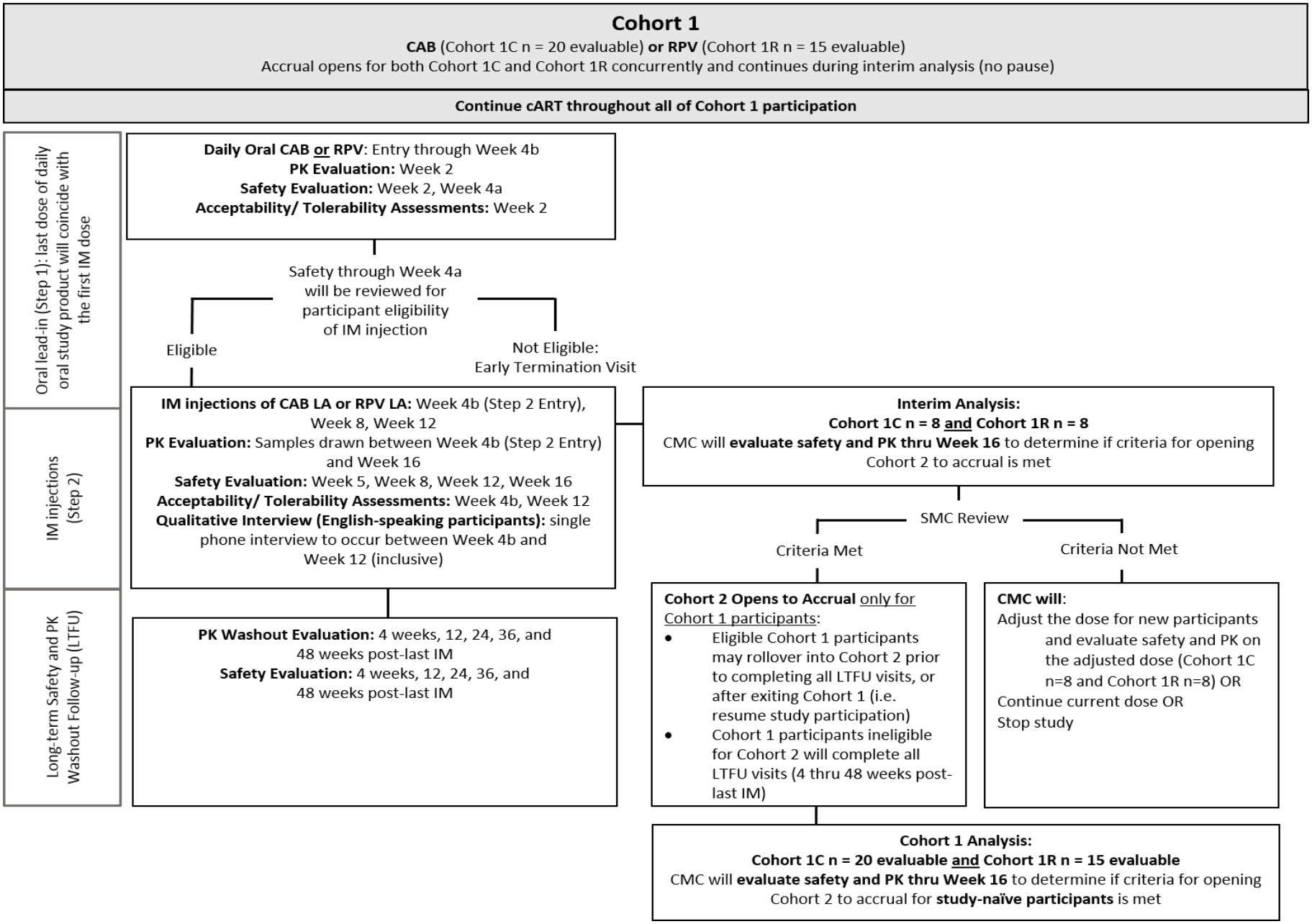
- To assess safety through Week 48, when given as single intramuscular injections every four weeks to HIV-infected, virologically suppressed adolescents

- To evaluate the tolerability and acceptability of CAB LA + RPV LA through week 48 when given as single intramuscular injections every four weeks to HIV-1 infected, virologically suppressed HIV-infected adolescents both from the standpoint of the study participants receiving the injections as well as their parent/caregivers and site staff.

- To assess antiviral activity of injectable CAB LA + RPV LA through Week 24, and through Week 48, when given as single intramuscular injections every four weeks to HIV-infected, virologically suppressed adolescents

- To determine the long term (≥ 48 weeks) safety and tolerability of CAB LA + RPV LA in HIV-1 infected, virologically suppressed adolescents eligible to receive these agents beyond 48 weeks as part of the study extension phase

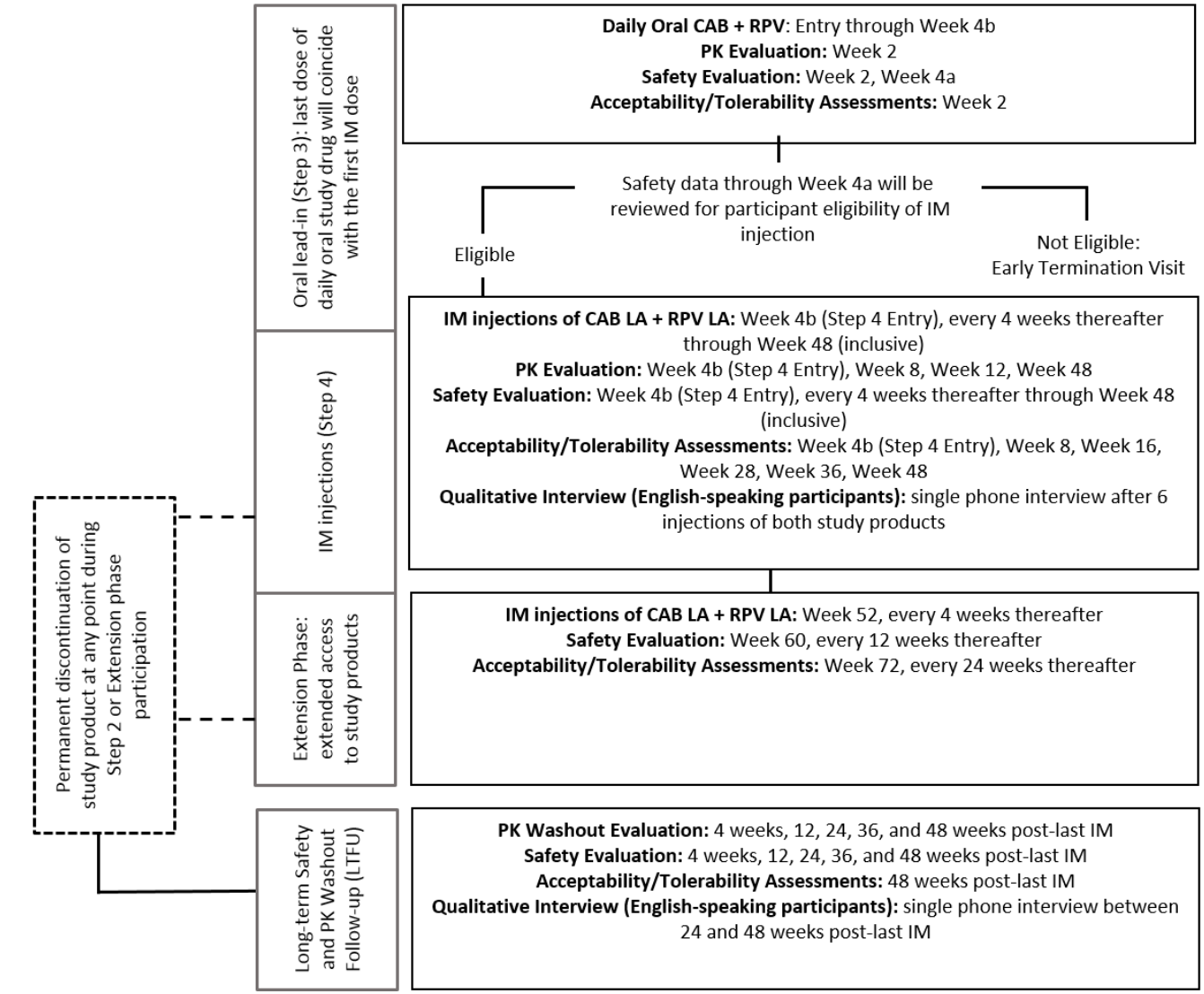
STUDY DESIGN


Cohort 1
CAB (Cohort 1C n = 20 evaluable) or RPV (Cohort 1R n = 15 evaluable)
Accrual opens for both Cohort 1C and Cohort 1R concurrently and continues during interim analysis (no pause)
Continue cART throughout all of Cohort 1 participation
Oral lead-in (Step 1): last dose of daily oral study product will coincide with the first IM dose
IM injections (Step 2)
Long-term Safety and PK Washout Follow-up (LTFU)
Daily Oral CAB or RPV: Entry through Week 4b
PK Evaluation: Week 2
Safety Evaluation: Week 2, Week 4a
Acceptability/ Tolerability Assessments: Week 2
Safety through Week 4a will be reviewed for participant eligibility of IM injection
Eligible
Not Eligible: Early Termination Visit
IM injections of CAB LA or RPV LA: Week 4b (Step 2 Entry), Week 8, Week 12
PK Evaluation: Samples drawn between Week 4b (Step 2 Entry) and Week 16
Safety Evaluation: Week 5, Week 8, Week 12, Week 16
Acceptability/ Tolerability Assessments: Week 4b, Week 12
Qualitative Interview (English-speaking participants): single phone interview to occur between Week 4b and Week 12 (inclusive)
PK Washout Evaluation: 4 weeks, 12, 24, 36, and 48 weeks post-last IM
Safety Evaluation: 4 weeks, 12, 24, 36, and 48 weeks post-last IM
Interim Analysis:
Cohort 1C n = 8 and Cohort 1R n = 8
CMC will evaluate safety and PK thru Week 16 to determine if criteria for opening Cohort 2 to accrual is met
SMC Review
Criteria Met
Criteria Not Met
Cohort 2 Opens to Accrual only for Cohort 1 participants:
Eligible Cohort 1 participants may rollover into Cohort 2 prior to completing all LTFU visits, or after exiting Cohort 1 (i.e. resume study participation)
Cohort 1 participants ineligible for Cohort 2 will complete all LTFU visits (4 thru 48 weeks post-last IM)
CMC will:
Adjust the dose for new participants and evaluate safety and PK on the adjusted dose (Cohort 1C n=8 and Cohort 1R n=8) OR
Continue current dose OR
Stop study
Cohort 1 Analysis:
Cohort 1C n = 20 evaluable and Cohort 1R n = 15 evaluable
CMC will evaluate safety and PK thru Week 16 to determine if criteria for opening Cohort 2 to accrual for study-naïve participants is met

Cohort 2

CAB + RPV (n = 100 with at least 70 evaluable who had not previously participated in Cohort 1)
Accrual first opens only for Cohort 1 participants (based on Cohort 1 interim analysis); then opens for new participants (based on Cohort 1 full analysis)

Discontinue cART during Step 3, Step 4, and Extension Phase (resume cART during LTFU)



Cohort 1

Study Visit	CT 1 Screen	Step 1 (oral phase)			Step 2 (injection phase)								
		CT 1 Entry	CT 1 Wk 2	CT 1 Wk 4a	CT 1 Wk 4b (Step 2 Entry)	CT 1 Wk 5	CT 1 Wk 6	CT 1 Wk 8	CT 1 Wk 9	CT 1 Wk 12	CT 1 Wk 13	CT 1 Wk 14	CT 1 Wk 16
Study Product													
Daily oral study product (for up to 6 wks)		X	*	*									
Administer injection study product					X			X		X			
Pharmacology Evaluation													
PK Sampling			X		X	X	X	X	X	X	X	X	X

Cohort 1 participants who complete the final IM injection at Week 12 will have a combined Week 16 and 4 weeks post-last IM visit.

Cohort 1 participants will enter into LTFU upon permanent product discontinuation, including completion, of IM injectable regimen.

Long-Term Safety and Washout PK Follow-Up (LTFU)

Study Visit	4 weeks post-last injection	12 weeks post-last injection	24 weeks post-last injection	36 weeks post-last injection	48 weeks post-last injection/ Study Exit
Pharmacology Evaluations					
PK Sampling	X	X	X	X	X

Cohort 2

Study Visit	CT 2 Screen	Step 3 (oral phase)			Step 4 (injection phase)						Extension Phase	
		CT 2 Entry	CT 2 Wk 2	CT 2 Wk 4a	CT 2 Wk 4b (Step 4 Entry)	CT 2 Wk 5	CT 2 Wk 8	CT 2 Wk 9	Q4 weeks	CT 2 Wk 48	CT 2 Wk 52	Q4 weeks
Study Product												
Daily oral study product (for up to 6 wks)		X	*	*								
Administer injection study product					X		X		X	X	X	X
Pharmacology Evaluation												
PK Sampling			X		X		X	X	X	X		

Long-Term Safety and Washout PK Follow-Up (LTFU)

Study Visit	4 weeks post-last injection	12 weeks post-last injection	24 weeks post-last injection	36 weeks post-last injection	48 weeks post-last injection/ Study Exit
Pharmacology Evaluations					
PK Sampling	X	X	X	X	X

Eligible Cohort 1 participants may enroll into Cohort 2. These participants might not complete LTFU visits post-last IM in Cohort 1, or might exit study, prior to resuming study participation in Cohort 2.

Study-naïve participants will enroll into Cohort 2 after the Cohort 1 analysis and dose confirmation is complete.

Participants will enter into LTFU upon permanent product discontinuation of IM injectables.

STUDY START-UP TIMELINE

Projected IMPAACT 2017 Timeline

June

- Protocol development
- Site selection

July-September

- Submit for IMPAACT and DAIDS reviews

October/ November

- Version 1.0 released to U.S. sites
- Study-specific trainings and site activation

January 2018

- Open to Accrual

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Questions?

Thank you for your interest in IMPAACT 2017!

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