Project Brief: IMPAACT 2017

Full Title of Study/Programme	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
Technical Focus Area/Key Words	Research in Paediatrics
Rationale	The IMPAACT 2017 is a Phase I/II study being conducted to establish if adolescents (and later younger children), infected with HIV-1 who are currently virologically suppressed on ART, remain suppressed upon switching to a two-drug intramuscular (IM) long-acting (LA) regimen of CAB LA plus RPV LA. The initial age group studied will be adolescents aged 12 to < 18 years and results from this initial age cohort may inform the study details in a protocol amendment at a later date for a younger population.
Primary Objectives	Cohort 1 (continuing a background cART regimen) • To confirm the doses for oral CAB followed by injectable CAB LA in HIV-infected, virologically suppressed adolescents by evaluating: 1. Safety and multiple dose PK of oral CAB through Week 4; 2. 2.1.1.2 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 2 (discontinuing a background cART regimen) • To assess the safety of 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 through Week 16 in HIV infected, virologically suppressed adolescents. • To evaluate the tolerability and acceptability of RPV LA through Week 16 in HIV infected, virologically suppressed adolescents. • Cohort 2 • To assess safety of oral CAB + oral RPV followed by CAB LA + RPV LA through Week 48 in HIV-infected, virologically suppressed adolescents. • To evaluate repeat-dose pharmacokinetics of CAB LA + RPV LA through Week 24, and through Week 48 in HIV-infected, virologically suppressed adolescents. • To assess antiviral activity of CAB LA + RPV LA through Week 24, and through Week 48 in HIV-infected, virologically suppressed adolescents.

Exploratory Objectives	• To evaluate the tolerability and acceptability of CAB LA + RPV LA through Week 24, through Week 48, and through Week 96 in HIV-infected, virologically suppressed adolescents (Cohort 2). • To evaluate the safety, antiviral and immunologic activity, and characterize PK of CAB LA + RPV LA through Week 96 in HIV-infected, virologically suppressed adolescents (Cohort 2). • To evaluate adolescent participant's experience of CAB LA and/or RPV LA, and parent/caregiver's experience and perceptions of adolescent acceptability and tolerability of CAB LA and/or RPV LA (Cohort 1 and Cohort 2). 2.5.4 To evaluate the tolerability and acceptability, and characterize long-term safety and PK through 48 weeks following permanent discontinuation of CAB LA or RPV LA (Cohort 1)
Primary Endpoint/Outcome	Safety through Week 4 for oral CAB, through Week 16 (CAB LA or RPV LA) for Cohort 1 Safety Outcome: All adverse events, regardless of grade • Number of participants who: 1. Had Grade 3 or higher adverse events 2. Had Grade 3 or higher adverse events assessed as related to study product/s 3. Had serious adverse events meeting ICH criteria assessed as related to study product/s 4. Permanently discontinued study product due to adverse events assessed as related to study product/s 5. Died due to adverse events assessed as related to study product/s Safety through Week 24 for CAB LA+RPV LA for Cohort 2 Safety Outcome: All adverse events, regardless of grade • Number of participants who: 1. Had Grade 3 or higher adverse events 2. Had Grade 3 or higher adverse events assessed as related to study product/s 3. Had serious adverse events meeting ICH criteria assessed as related to study product/s 4. Permanently discontinued study product due to adverse events assessed as related to study product/s 5. Died due to adverse events assessed as related to study product/s
Secondary Endpoint/Outcome	Tolerability of CAB LA or RPV LA through Week 16 for Cohort 1 • Tolerability measures will include measures of side effects, pain during and after injections, injection site reactions, and perceptions of injections from comprehensive surveys of adolescents Acceptability of CAB LA or RPV LA through Week 16 for Cohort 1

	• Acceptability measures will include assessments of motivation for changing regimens, satisfaction with treatment, preferences for injectable versus oral regimen, quality of life, changes in attitudes towards the study products from comprehensive surveys of adolescents Safety through Week 48 for CAB LA+RPV LA for Cohort 2 Safety Outcome: All adverse events, regardless of grade 1. Number of participants who: 2. Had Grade 3 or higher adverse events 3. Had Grade 3 or higher adverse events assessed as related to study product/s 4. Had serious adverse events meeting ICH criteria assessed as related to study product/s 5. Permanently discontinued study product due to adverse events assessed as related to study product/s 6. Died due to adverse events assessed as related to study product/s Virologic activity of CAB LA+RPV LA through Weeks 24 and 48 for Cohort 2 • Outcome – Plasma HIV-1 RNA • Number of participants with HIV-1 RNA >200 copies/mL, missing HIV-1 RNA, study treatment discontinuations
Study Design (R)	This is a Phase I/II, multi-center, open-label, non-comparative study to confirm the dose and evaluate the safety, tolerability, acceptability, and PK of oral CAB, long-acting injectable CAB (CAB LA), and long-acting injectable RPV (RPV LA) among up to 155 virologically suppressed HIV-1 infected children and adolescents aged 12 to < 18 years. Up to 60 parents/caregivers of adolescent participants will also be enrolled to take part in in-depth qualitative interviews. The study design includes two cohorts of participants and two steps of study participation in each cohort. Cohort 1, Step 1 and Cohort 2, Step 3 are both a lead-in phase in which participants will receive oral formulations of the study products for at least 4 weeks, and up to 6 weeks (maximum). In Cohort 1, Step 2 and Cohort 2, Step 4, participants will receive injectable formulations of the study products. In each cohort, participants will enter the study in the oral lead-in phase (Step 1, or Step 3) and then transition to the injectable phase (Step 2, or Step 4) if eligibility criteria for the injectable phase are met. Cohort 1 Step 2 and Cohort 2 Step 4 participants, including those who prematurely permanently discontinue injectable study product, will continue on-study for an additional 48 weeks after their last study product injection, per the long-term safety and washout PK follow-up (LSFU) schedule.

Study arms (R)	Cohort 1: Up to 55 adolescents to achieve approximately 35 evaluable receiving the oral followed by the LA dose of CAB (Cohort 1C) or RPV (Cohort 1R), in addition to cART, which, passing safety and PK guidelines, are recommended as dosing for Cohort 2. Cohort 1C and Cohort 1R assignment is based on the adolescent's prestudy cART regimen. • Cohort 1C: Up to 30 adolescents to achieve approximately 20 evaluable for CAB. The evaluable population will include at least 4 female adolescents, at least 4 male adolescents, at least 5 adolescents weighing 35 kg to less than 50 kg at study entry, and at least 5 adolescents weighing at least 50 kg at study entry. • Cohort 1R: Up to 25 adolescents to achieve approximately 15 evaluable for RPV. The evaluable population will include at least 4 female adolescents, at least 4 male adolescents, at least 5 adolescents weighing 35 kg to less than 50 kg at study entry, and at least 5 adolescents weighing at least 50 kg at study entry. Cohort 2: Up to 155 adolescents may participate in Cohort 2. Up to 100 adolescents, who had not previously participated in Cohort 1, to achieve approximately 70 evaluable, who had not previously participated in Cohort 1, receiving the final recommended oral followed by the LA doses of CAB and RPV. Adolescents who participated in Cohort 1 (up to 55 participants) may continue study participation in Cohort 2, if eligible, in addition to the up to 100 Cohort 2 participants newly enrolled to the study.
Study population (R)	HIV-1 infected children and adolescents, 12 to < 18 years
Study sample size (R)	Up to 155 adolescents in total
Follow up/duration	Adolescents in Cohort 1 will be followed for up to 64 weeks. Adolescents will be followed for at least four weeks in Step 1 (oral phase) and at least 12 weeks in Step 2 (injection phase). All Step 2 adolescents will be followed (on cART, off study product) for up to an additional 48 weeks as part of long-term safety and washout PK follow-up after their last study product injection. Adolescents in Cohort 2 will be followed for up to 144 weeks. Adolescents will be followed for at least four weeks in Step 3 (oral phase) and 92 weeks in Step 4 (injection phase). After completing 92 weeks of follow-up in Step 4 (injection phase), Cohort 2 adolescents may continue access to injectable study products through a mechanism external to the protocol, and will exit the study
Study/Programme sites	Wits RHI Shandukani Research Centre (SRC)
Study/Programme duration	Approximately 5 years total. Accrual into Cohort 1 is expected to require approximately three months. Following review of data from Cohort 1 through Week 16, accrual into Cohort 2 is expected to require approximately nine months. Adolescents in Cohort 2 will be followed for up to three years
Intervention (R)	Cohort 1:

	Cohort 1C: 30 mg CAB once daily orally for at least four weeks (up to a maximum of 6 weeks) in addition to cART (Step 1 oral phase), followed by single intramuscular injections of CAB LA every four weeks over an eight-week period (600 mg first injection, 400 mg second and third injections) in addition to cART (Step 2 injection phase). • Cohort 1R: 25 mg RPV once daily orally for at least four weeks (up to a maximum of 6 weeks) in addition to cART (Step 1 oral phase), followed by single intramuscular injections of RPV LA once every four weeks over an eight-week period (900 mg first injection, 600 mg second and third injections) in addition to cART (Step 2 injection phase). Dose adjustments are not anticipated but may occur as described in protocol Section 9 and 10. Cohort 2: 30 mg CAB + 25 mg RPV once daily orally for at least four weeks, and up to a maximum of 6 weeks, during Step 3 oral phase, followed by intramuscular injections of CAB LA + RPV LA once every four weeks for 92 weeks (for CAB LA 600 mg first injection and 400 mg subsequent injections; for RPV LA 900 mg first injection, 600 mg subsequent injections) during Step 4 injection phase.
Operations	Study specific
Investigators	• Dr Faeezah Patel, Principal Investigator • Dr Lee Fairlie, Sub Investigator • Dr Masebole Masenya, Sub Investigator • Dr Elizea Horne, Sub Investigator
Other Partners & Collaborators	• Texas Children's Hospital • University of California, UC San Diego • Lurie Children's Hospital of Chicago • Pediatric Perinatal HIV Clinical Trials Unit • Boston Medical Center Pediatric HIV Program • Jacobi Medical Center • Seattle Children's Research Institute • San Juan City Hospital • SUNY Stony Brook • Emory University School of Medicine • The University of Southern California- LA • University of Florida- Jacksonville • South Florida CDTC Ft. Lauderdale • Rush University Cook County Hospital • University of Colorado- Denver • Johns Hopkins University • David Geffen School of Medicine at UCLA • St. Jude Children’s Research Hospital • Bronx-Lebanon Hospital Center • University of Puerto Rico Pediatric HIV/AIDS Research Program
Sponsors/Donors	• The National Institute of Allergy and Infectious Diseases (NIAID) • The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Linked Sub Studies and post grad projects	IMPAACT 2017

Publications/key presentations to date	None as yet
Progress Update as at Jul 2020	Protocol V 3.0 approved, Training for all site staff will be conducted on the 23rd and 24th March 2021 Faeezah approved as PI
Frequency of donor narrative report	Monthly
Overall Study/Project Contact	Faeezah Patel (fpatel@wrhi.ac.za) Hermien Gous (hgous@wrhi.ac.za)
Briefing owner and date	Dr Hermien Gous and Faeezah Patel; May 2019