Project Brief: IMPAACT 2019

Full Title of Study/Programme	IMPAACT 2019 Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age Version 2.0 dated 04 Sep 2019 with CM 1 dated 11 Jun 2020 and CM 2 dated 14 Aug 2020
Technical Focus Area/Key Words	Research in Paediatrics
Rationale	Overall Rationale To date, DTG has only been studied as a single ARV formulation in children. ABC/DTG/3TC (immediate release tablet marketed as Triumeq®) is a safe, effective, and well-tolerated "one pill, once daily" regimen approved by the FDA and EMA for use in adults and children weighing at least 40 kg (the EMA approval for pediatric use is limited to children at least 12 years of age). DTG has rapidly become a "preferred" agent for initial treatment of HIV in adults, and more recently, children and adolescents six years of age and older. Much of the safety, PK and dosefinding evaluation for DTG in children was completed in the ongoing IMPAACT P1093 and ODYSSEY studies. Internationally, the WHO supports harmonization of ARV regimens across populations including using the same regimen of ARVs in adult and pediatric populations. As more experience with INSTIs become available, it is presumed that this drug class will be identified as the candidate for a universal regimen for adults, pregnant women and children. To facilitate this goal, the safety and PK of dispersible tablet ABC/DTG/3TC in young children must be defined. This Phase I/II study will investigate the PK, safety and tolerability of ABC/DTG/3TC in HIV infected children less than 12 years of age. Given that DTG has demonstrated excellent virologic activity in P1093 and has an increasing role as initial ARV therapy in adults and older children, this study will include both ART-naïve and ART-experienced children. ABC/DTG/3TC will be dosed by weight bands across the age spectrum, consistent with the intended future marketing of the product. Age-based quotas have been specified to help ensure that adequate PK, safety, and tolerability data are collected among children less than six years of age as well as children six years of age and older. Previous experience in adults has demonstrated that the exposure to DTG, ABC and 3TC in a fixed dose combination formulation is consistent with each drug administered individually. This information was provided as part of the application for Triumeq®. Therefore, the DTG dosing recommendations from IMPAACT P1093 are not expected to differ when DTG is administered in a fixed dose combination. Nonetheless, a subset of children in each weight band will undergo intensive PK approximately one week

	after initiating ABC/DTG/3TC to evaluate for similar exposure to DTG. Population PK will be evaluated among all study participants. Rationale for Initial Dose Selection The DTG doses selected for evaluation in this study are expected to achieve DTG exposures similar to those observed with DTG 50 mg twice-daily in adults. The DTG doses are higher than those previously evaluated but consistent with doses currently being studied in IMPAACT P1093. The higher expected exposures of DTG are due to the coformulation of DTG, ABC, and 3TC in a single tablet; whereas the doses of 3TC and ABC increase in sync to each other with body weight, the increase is not the same for DTG. Safety data available from adults with higher DTG doses and exposures support the DTG doses selected for evaluation in this study (31-33). The DTG doses selected for evaluation in this study are specified within weight bands and are expected to be applicable to children less than 12 years of age who weigh at least 6 kg. However, as of the date of this protocol, limited data are available on DTG dosing for children less than six months of age. Additional data from the IMPAACT P1093 and ODYSSEY studies are expected to become available for this age group in the near future. When these data become available, the IMPAACT 2019 Protocol Team will review them to determine whether the dosing specified for this study is appropriate for children less than six months of age. Until this review is conducted, accrual into this study will be restricted to children six months of age and older. Once this review is conducted, if the Protocol Team determines that the dosing specified for this study is appropriate for children less than six months of age, the restriction on accrual will be lifted. If the Protocol Team determines that the dosing is not appropriate for children less than six months of age, the restriction on accrual will be maintained while alternative dosing and/or other protocol modifications are developed for children less than six months of age. Study sites will be notified of the outcome of the team's review and decision-making via email. The doses of ABC/3TC proposed for use in this study are consistent with WHO recommended doses of ~16 mg/kg for ABC and ~8 mg/kg for 3TC in children. Exposures from these doses are expected to achieve AUCs similar to those measured in ARROW, PENTA13, and PENTA15, which examined the PK and efficacy of once-daily ABC/3TC in pediatric patients. A relative bioavailability study is planned to provide reassurance of similar exposures of ABC/3TC with use of the dispersible fixed dose combination tablet compared with the marketed immediate release fixed dose combination tablet. Rationale for PK Targets

	A minimum of five children in each weight band will undergo intensive PK sampling with real time testing and review of intensive PK outcomes for ABC, DTG, and 3TC to confirm appropriate dose selection for each weight band. Dose confirmation for each weight band will be based on PK (AUC0-24h for ABC, DTG, and 3TC, in addition to C24h for DTG) and safety outcomes. Dose confirmation based on all three agents reflects ViiV's currently agreed PIP and PSP. The DTG targets are similar to current targets for IMPAACT P1093. These targets will continue to be evaluated and updated if needed based on new findings from P1093. The weight band target AUC0-24h target range for DTG is based on the lower and upper bounds of the 90% CIs for once and twice-daily DTG dosing in adults, respectively. The weight band target C24h target range for DTG is based on 60% of once-daily geometric mean exposures and 140% of twice-daily geometric mean exposures in adults. The ABC and 3TC AUC0-24h targets are based on the minimum lower and maximum upper bounds of the 90% CIs for predicted exposures with once daily ABC/3TC weight band dosing with the tablet formulation in children (summarized Table 3). If the geometric mean AUC0-24h for ABC, DTG, or 3TC and/or C24h for DTG among the dose evaluable (refer to Section 3.2) children in each weight band falls outside of the targeted range, the Protocol Team will re-evaluate the dose for that weight band using all available PK data from this study in addition to PK results from previous and ongoing studies of ABC, DTG, and 3TC. Individual dose adjustments may also be performed if a child's DTG AUC0-24h or C24h falls outside of the individual target ranges outlined in Table 5. If a child requires an individual dose adjustment, a repeat PK assessment may be performed for that child, with an appropriate sampling hstrategy determined by the Protocol Pharmacologists. Rationale for Deferred Enrollment of Children Switching from an NNRTI-Containing Regimen Children switching to the study drug regimen from an NNRTI-containing regimen (particularly a regimen containing etravirine, efavirenz, or nevirapine) will not be included in the intensive PK sampling as they may have decreased DTG exposure subsequent to enzymatic induction by these agents. These children, however, will have additional sparse sampling to better understand the PK of DTG when switching from an NNRTI-containing regimen. A sub-study in adult patients switched from efavirenz or nevirapine to DTG with rilpivirine (SWORD 1 and 2) examined trough levels at Weeks 2, 4, 8, 24, and 48 following the switch, and revealed that DTG trough concentrations were similar to levels in patients not on an NNRTI regimen by Week 4 (34). No dose adjustments to DTG were made following the transition from efavirenz or nevirapine to DTG with rilpivirine, and trough levels remained above the DTG IC90 at all time points examined.

	Note: Under certain pre-specified conditions, and in consultation with the Study Monitoring Committee (SMC), the Protocol Team may consider expanding intensive PK sampling to children switching to the study drug regimen from an NNRTI-containing regimen; refer to Section 9.5.1 for more information regarding this potential option. Rationale for Exploratory Evaluations In addition to plasma PK evaluations, this study will characterize phosphorylated 3TC and ABC moieties in PBMCs and dried blood spots (DBS). The active moieties of ABC and 3TC are found intracellularly and have been shown to correlate with ARV activity in previous studies (28). Thus, examining intracellular levels of carbovir-triphosphate and lamivudine-triphosphate in PBMCs may provide additional insight into exposure-response relationships at the site of action with these agents. DBS will be collected to characterize drug levels in this matrix and compare levels to self reported adherence. This approach has been studied with tenofovir disoproxil fumarate, tenofovir alafenamide, and emtricitabine, for which concentrations of the phosphorylated moieties can serve as measures of long- and short-term adherence to ARV therapy, respectively (35-37). Tenofovir-diphosphate concentrations increase proportionally with the number of doses taken per week, and thus this measure has been integrated as a surrogate measure of adherence and treatment outcomes in several HIV pre-exposure prophylaxis (PrEP) (25, 38-40) and treatment (41, 42) studies. This same approach could be applied with the phosphorylated moieties of ABC and 3TC. Pharmacogenetic analyses will focus on single nucleotide polymorphisms (SNPs) in genes that encode drug transporters and metabolizing enzymes involved in the PK disposition of ABC, DTG, and 3TC. The primary focus for initial pharmacogenetic analyses will focus on SNPs that influence the PK of DTG, such as UGT1A1 (rs8175317), for which individuals with low and reduced activity (presence of *28 and/or *37 alleles) exhibit slower clearance and higher DTG exposure (43). Rationale for Adherence Evaluations A variety of methods will be used to evaluate adherence to daily administration of ABC/DTG/3TC in this study. For all children, questionnaires will be administered at time points designated in the Schedule of Evaluations. In addition, for children undergoing intensive PK sampling, more objective methods of assessing adherence such as texted video, video streaming, and in-person directly observed therapy will be used to confirm daily dosing between enrollment and the day of intensive PK sampling. Data obtained through these methods will assist with determining whether failure to reach PK targets is due to challenges with adherence or

	administration versus actual PK differences in the pediatric study population. Relationships between PK-based adherence measures and other adherence measures will be explored, which may provide useful insights into selection of adherence measures to be used in future pediatric studies.
Primary Objectives	The primary objectives of this study are to: • Determine the steady-state AUC0-24h, Cmax, and C24h of ABC, DTG, and 3TC and confirm the dosing of ABC/DTG/3TC dispersible and immediate release tablets that achieves • protocol-defined PK targets for ABC, DTG, and 3TC in children less than 12 years of age • Evaluate the safety profile of 24 weeks of treatment with ABC/DTG/3TC dispersible • tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age
Secondary Objectives	The secondary objectives of this study are to: • Determine the PK of ABC, DTG, and 3TC, and clinical covariates that influence PK disposition, among children less than 12 years of age using population PK analysis of intensive and sparse PK samples collected over 48 weeks of treatment with ABC/DTG/3TC dispersible and immediate release tablets • Evaluate the safety profile of 48 weeks, and additionally up to 144 weeks, of treatment • with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age • Evaluate virologic and immunologic responses at 4, 24, and 48 weeks, and additionally up to 144 weeks, of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age • Evaluate changes in lipid profiles at 24 and 48 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age • Evaluate adherence to and palatability and acceptability of ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age at 4, 24 and 48 weeks of treatment • Evaluate HIV-1 genotypes and phenotypes among children less than 12 years of age who experience virologic failure while receiving treatment with ABC/DTG/3TC dispersible tablets or ABC/DTG/3TC immediate release tablets
Exploratory Objectives	The exploratory objectives of this study are to: • Describe central nervous system effects, including sleep and behavioral changes, that may occur over 24 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age

	• Describe pharmacogenetic associations among children less than 12 years of age receiving treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets • Determine concentrations of phosphorylated ABC and 3TC anabolites in PBMCs and DBS over 48 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age • Examine relationships between PK-based adherence measures and other adherence measures
Primary Endpoint/Outcome	Geometric mean AUC0-24h, Cmax, and C24h for ABC, DTG, and 3TC based on analysis of intensive PK samples collected at Week 1 (AUC0-24h and C24h to be compared within each weight band to the PK targets specified All adverse events occurring through Week 24 Participants with the following through Week 24: - Grade 3 or Grade 4 adverse events assessed as related to study drug - Grade 5 adverse events assessed as related to study drug - Life-threatening adverse events assessed as related to study drug - Serious adverse events assessed as related to study drug - - Adverse events assessed as related to study drug that lead to permanent discontinuation of study drug
Secondary Endpoint/Outcome	AUC0-24h, C0h, C24h, Cmax, Tmax, CL/F, and t1/2 derived from population PK modeling with sampling through Week 48 All adverse events occurring through Week 48 • Participants with the following through Week 48: - Grade 3 or Grade 4 adverse events assessed as related to study drug - Grade 5 adverse events assessed as related to study drug - Life-threatening adverse events assessed as related to study drug - Serious adverse events assessed as related to study drug - Adverse events assessed as related to study drug that lead to permanent discontinuation of study drug • All adverse events occurring through Week 144 • Participants with the following through Week 144: - Grade 3 or Grade 4 adverse events assessed as related to study drug - Grade 5 adverse events assessed as related to study drug - Life-threatening adverse events assessed as related to study drug - Serious adverse events assessed as related to study drug - Adverse events assessed as related to study drug that lead to permanent discontinuation of study drug HIV-1 RNA through Week 48

	• HIV-1 RNA through Week 144 • Participants with: - HIV-1 RNA ≥200 copies/mL at Weeks 4, 24, and 48 (snapshot algorithm) - HIV-1 RNA ≥50 copies/mL at Weeks 4, 24, and 48 (snapshot algorithm) • CD4+ cell count and percentage at Weeks 4, 24, and 48 • CD4+ cell count and percentage through Week 144 • Total cholesterol, HDL, LDL, and triglycerides at Weeks 24 and 48 • Parent/guardian reported adherence to study drug at Weeks 4, 24, and 48 • Parent/guardian reported tolerability (i.e., palatability and acceptability) of study drug at Weeks 4, 12, 24, and 48 • ARV resistance mutations at time of virologic failure (and at entry for children with resistance identified at time of virologic failure)
Study Design (R)	This is a Phase I/II, multi-site, open-label, multiple dose, non-comparative PK and safety study ofABC/DTG/3TC dispersible tablets and immediate release tablets in ART-naïve and ART experienced HIV-1-infected children less than 12 years of age. The study will be conducted among at least 50 and up to 75 children. At least 25 children will be less than six years of age and at least 25 will be six to less than 12 years of age. Children will be enrolled in weight bands. Two alternative dispersion volumes for preparation of dispersible tablets will be considered. Accrual into all weight bands will occur concurrently, and the age-based quotas will apply across weight bands. Accrual into the study overall will continue until study drug dosing has been confirmed for each weight band and the age-based quotas have been met. There is no prespecified maximum number of children who may be enrolled in each weight band; the Protocol Team will closely monitor accrual into each weight band and may pause and subsequently close or resume accrual into individual weight bands in an effort to assure balance across the weight bands. At the outset of study implementation, accrual into weight band #1 will be restricted to children six months (180 days) of age and older . Once the Protocol Team has confirmed that data are available to support the specified weight band dosing for children less than six months of age, this restriction will be lifted. If the Protocol Team determines that the specified dosing is not appropriate for children less than six months of age, the restriction on accrual will be maintained while alternative dosing and/or other protocol modifications are developed for children less than six months of age.

	ART-naive children will initiate treatment with the study drug regimen, ABC/DTG/3TC, at enrollment. ART-experienced children will switch from their pre-study ART regimen to ABC/DTG/3TC at enrollment. For all children, the first dose of study drug is expected to be taken on the day of enrollment or the day after enrollment. Use of ABC/DTG/3TC and evaluations to assess safety, adherence, tolerability (i.e., palatability and acceptability), virologic and immunologic response, and lipid profiles will continue through 48 weeks of follow-up. Specimen collection for PK evaluations will also continue through 48weeks of follow-up. Scheduled follow-up is generally expected to be completed at the Week 48 Visit, but may be continued for up to an additional 96 weeks for children who are deriving benefit from ABC/DTG/3TC but do not otherwise have access to ABC/DTG/3TC from a non-study source. For these children once ABC/DTG/3TC becomes available from a non-study source, study participation will be discontinued with transition into local standard HIV care and treatment. For children who are not deriving benefit from ABC/DTG/3TC, or who are deriving benefit and have access to ABC/DTG/3TC from a nonstudy source, the transition into local standard HIV care and treatment will occur upon completion of the Week 48 Visit.
Study arms	Single arm open label
Study population (R)	This study will be conducted among at least 50 and up to 75 HIV-1-infected children who will be selected At least 25 children will be less than six years of age and at least 25 will be six to less than 12 years of age.
Study sample size (R)	This study will be conducted among at least 50 and up to 75 HIV-1-infected children who will be selected At least 25 children will be less than six years of age and at least 25 will be six to less than 12 years of age.
Follow up/duration	Scheduled follow-up is generally expected to be completed at the Week 48 Visit, but may be continued for up to an additional 96 weeks for children who are deriving benefit
Study/Programme sites	SHANDUKANI RESEARCH CENTRE
Study/Programme duration	48 Weeks or up to 144 Weeks if children are found to be deriving benefit from continuing on study
Intervention (R)	Dispersible tablets containing 60 mg ABC, 5 mg DTG, and 30 mg 3TC and immediate release tablets containing 600 mg ABC, 50 mg DTG, and 300 mg 3TC, administered for at least 48 weeks and up to 144 weeks in weight bands as follows: Weight Band - Formulation (Daily Dose of ABC/DTG/3TC) #1 6 to less than 10 kg - 3 dispersible tablets

	(180/15/90 mg) #2 10 to less than 14 kg - 4 dispersible tablets (240/20/120 mg) #3 14 to less than 20 kg - 5 dispersible tablets (300/25/150 mg) #4 20 to less than 25 kg - 6 dispersible tablets (360/30/180 mg) #5 25 kg or greater - 1 immediate release tablet (600/50/300 mg)
Operations	Study specific
Investigators	Dr Faeezah Patel Dr Elizea Horne Dr Maysseb Masenya Dr Stacy Lee Sigamoney Dr Mrinmayee Dhar Dr Gabriella Benade Othusitse Segalo Tiffany Seef
Other Partners & Collaborators	NIAID VIIV GSK DAIDS
Sponsors/Donors	NIAID NICHD
Linked Sub Studies and post grad projects	NIl
Publications/key presentations to date	None as yet
Progress Update as at Mar 2021	Active and enrolling currently
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; March 2021