IMPAACT 2019: PK & Safety of Dispersible ABC/DTG/3TC in Children with HIV 6 to <14kg

Kristina M. Brooks,[1] Jennifer J. Kiser,[1] Yasha Rani,[2] Gaerolwe R. Masheto,[3] Faeezah Patel,[4] Iris Mustich,[5] Barbara Heckman,[6] Mark Lojacono,[6] Dwight E. Yin,[7] Sai Majji,[8] Hardik Chandasana,[9] Helena Rabie,[10] Patricia Flynn,[11] on behalf of the IMPAACT 2019 Team

[1]Deparment of Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO, USA [2]Frontier Science & Technology Research Foundation (FSTRF), Brookline, MA, USA [3]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, USA [4]WRHI Shandukani Research Centre, Johannesburg, South Africa [5]FHI 360, Durham, NC, USA [6]Frontier Science & Technology Research Foundation (FSTRF), Inc., Amherst, NY, USA [7]National Institute of Allergy and Infectious Diseases, Rockville, MD, USA [8]National Institute of Child Health and Human Development, Bethesda, MD, USA [9]GlaxoSmithKline, Collegeville, PA, USA [10]University of Stellenbosch, Stellenbosch, South Africa, USA [11]St. Jude Children's Research Hospital, Memphis, TN, USA

BACKGROUND

- There is limited availability of pediatric-friendly fixed dose combination (FDC) antiretroviral formulations.
- Abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) is only available as an immediate-release FDC tablet for use in adults and children ≥40 kg.[1]
- IMPAACT 2019 is examining the pharmacokinetics (PK), safety, and tolerability of ABC/DTG/3TC in immediate- and dispersible-release FDC form.
- Doses of individual components align with WHO weight band dosing.
- We previously confirmed dosing for the immediate-release, adult strength FDC tablet in children weighing ≥25 to <40 kg, and the novel dispersible-release FDC tablets in children weighing 14 to <25 kg.[2,3]
- Here, we report PK and week 4 safety results in children weighing 6 to <14 kg.

OBJECTIVES

- To determine steady-state area under the concentration time curve over 24 hours ($AUC_{0\text{-}24h}$), maximum concentration (C_{max}), and concentration at 24 hours post-dose (C_{24h}) of ABC, DTG, and 3TC.
- To confirm dosing of ABC/DTG/3TC dispersible- and immediate-release tablets that achieve protocol-defined PK targets for ABC, DTG, and 3TC.

METHODS

- Phase I/II, multi-site, open-label, non-comparative dose confirmation study (NCT03760458)
- Study sites in Botswana, South Africa, Thailand and the United States
- Plasma ABC, DTG, and 3TC concentrations quantified using liquid chromatography mass spectrometry (LC/MS) methods
- PK parameters calculated using noncompartmental methods (Phoenix WinNonlin®, Certara, Inc.)

Key Eligibility Criteria:

- Age <12 years
- Weight 6 to <40 kg
- Confirmed HIV infection
- Treatment-naïve **or**
- Treatment-experienced with HIV VL <200 copies/mL on a stable non-NNRTI-containing ARV regimen for ≥6 months

FIGURE 1. IMPAACT 2019 Weight Bands

WB1 (6 to <10 kg)	ABC 180mg/DTG 15mg/3TC 90mg • 3 DT dispersed in 15 mL water
WB2 (10 to <14 kg)	ABC 240mg/DTG 20mg/3TC 120mg • 4 DT dispersed in 20 mL water
WB3 (14 to <20 kg)	ABC 300mg/DTG 25mg/3TC 150mg • 5 DT dispersed in 20 mL water
WB4 (20 to <25 kg)	ABC 360mg/DTG 30mg/3TC 180mg • 6 DT dispersed in 20 mL water
WB5 (≥25 kg)	ABC 600mg/DTG 50mg/3TC 300mg • 1 IR tablet swallowed whole

DT: dispersible-release tablet; IR: immediate-release; WB: weight band.

Dosing of dispersible release ABC/DTG/3TC FDC tablets was confirmed in alignment with WHO weight band recommendations in children 6 to <14 kg

METHODS

FIGURE 2. Dose Confirmation Approach

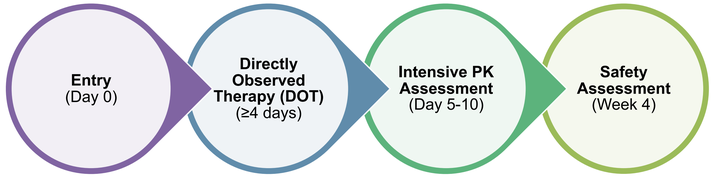


TABLE 1. Individual & Weight Band Targets

Drug	PK Parameter	Individual Target	Weight Band Target[a]
DTG	$AUC_{0\text{-}24h}$ (µg·h/mL)	25.0[b]-134	35.1[c]-134[d]
	C_{24h} (µg/mL)	≥0.5[b]	0.67[e]-2.97[f]
ABC	$AUC_{0\text{-}24h}$ (µg·h/mL)	--	6.3-50.4[g]
3TC	$AUC_{0\text{-}24h}$ (µg·h/mL)	--	6.3-26.5[g]

[a]Geometric mean for the weight band must fall within these targets [b]Estimated DTG $AUC_{0\text{-}24h}$ and C_{24h} values to produce EC_{90} [c]Lower 90% CI bound for once-daily DTG exposures in adults [d]Upper 90% CI bound for twice-daily DTG exposures in adults [e]Targets based on 60% of once-daily DTG exposures in adults [f]Targets based on 140% of twice-daily DTG exposures in adults [g]Minimum lower and maximum upper 90% CI bounds for predicted once-daily ABC and 3TC exposures in children based on population PK modeling of ARROW, PENTA13, PENTA15, and other single-dose PK studies in children

PK and safety criteria had to be met for dose confirmation within each WB

RESULTS

- 16 participants were enrolled for dose confirmation, of which two (1 in WB1 and 1 in WB2) withdrew prior to the intensive PK assessments due to palatability issues. Resulting data reflect those who underwent intensive PKs.

TABLE 2. Participant Demographics & DOT Methods

Characteristic	WB1 (N=7)	WB2 (N=7)
Sex at birth, n(%)		
Female	5 (71%)	4 (57%)
Male	2 (29%)	3 (43%)
Age (year), median (range)[a]	1.6 (1.1-2.0)	3.6 (2.1-4.0)
Weight (kg), median (range)[a]	9.5 (8.3-9.8)	13.1 (11.2-14.2)
Treatment-Experienced, n(%)	5 (71%)	7 (100%)
DOT method, n(%)[b]		
In-person	84 (100%)	42 (44%)
Real-time video	--	54 (56%)
Recorded timestamped video	--	--

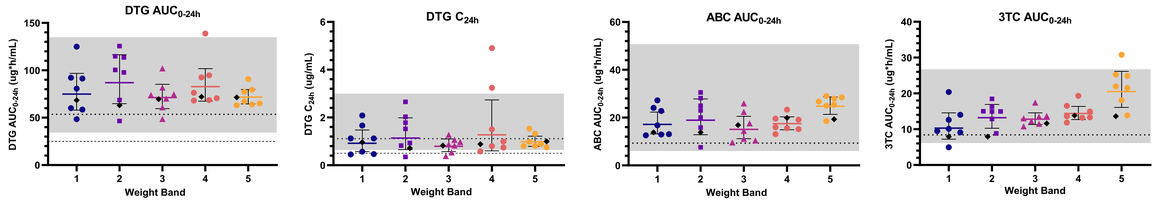
[a] On day of intensive PK [b] n(%) reflective of total number of dosing events

TABLE 3. Weight Band Dosing & Primary PK Results

WB	Dose (mg)	Dose by Weight (mg/kg)[a]	$AUC_{0\text{-}24h}$ (µg·h/mL)[b]	C_{max} (µg/mL)[b]	C_{24h} (µg/mL)[b]
DTG					
1	15	1.58 (1.53-1.81)	75.9 (33.7%)	7.4 (28%)	0.91 (67.6%)
2	20	1.53 (1.41-1.79)	91.0 (36.5%)[c]	8.9 (21.3%)	1.22 (77.5%)
ABC					
1	180	18.9 (18.4-21.7)	17.7 (33.8%)	7.3 (20.5%)	0.003 (125%)
2	240	18.3 (16.9-21.4)	19.8 (50.6%)[c]	8.4 (43.7%)	0.005 (128%)
3TC					
1	90	9.47 (9.18-10.8)	10.7 (46.0%)	2.3 (39.8%)	0.06 (39.5%)
2	120	9.16 (8.45-10.7)	14.2 (23.9%)[c]	3.6 (18.7%)	0.05 (48.3%)

Key: $AUC_{0\text{-}24h}$ = area under the concentration vs. time curve from time 0 through 24 hours post-dose; C_{max}: maximum plasma concentration; C_{24h} = concentration at 24 hours post-dose. [a] Reported as median (range) or [b] geometric mean (geometric CV%) [c] Pre-dose (time 0) sample was not available due to clotting in 1 participant and was replaced with concentration results from 24-hour time point to generate PK parameter estimates.

FIGURE 3. PK Results by Weight Band with Comparison to PK Targets and Historical Data



Key: dashed lines (---) indicate individual DTG target (minimum). Gray shading (▒) indicates weight band target ranges. Dotted lines (•••) indicate GM measures in adults with HIV receiving DTG 50 mg, ABC 600 mg, or 3TC 300 mg once-daily. Black diamond (♦) indicates predicted GM measures in children with HIV receiving same weight band doses of each component (compiled from FDA Clinical Pharmacology Reviews). Data presented from all five weight bands for side-by-side comparison of dose confirmation results.[2,3] Two participants in WB1 (0.47 and 0.45 ug/mL) and one participant in WB2 (0.35 ug/mL) did not meet the individual DTG C_{24h} targets but met the individual $AUC_{0\text{-}24h}$ targets. All C_{24h} were above the EC_{90} of 0.3 ug/mL for DTG and no individual dose adjustments were made.

RESULTS (CONTINUED)

- No grade 3 or higher AEs related to study drug
- No children discontinued study drug due to AEs
- No AEs required intervention

TABLE 4. Summary of AEs through Study Week 4

WB	Grade	Event	Time on Study Drug	Relationship	Time to Resolution
1	3	Fever (due to tonsilitis)	2+ weeks	Not related	Same day
	2	eGFR decrease[a]	4 weeks	Related to DTG	Ongoing
	1	SCr increase[a]	4 weeks	Related to DTG	Ongoing
1	1	ALT increase	4 weeks	Related to DTG, ABC, and 3TC	~4 weeks

Key: ALT = alanine transaminase; eGFR = estimated glomerular filtration rate; SCr = serum creatinine.
[a]In same participant; severity grading based on change from baseline; absolute values were within normal limits.

CONCLUSIONS

- PK targets were met for dispersible release ABC/DTG/3TC in children 6 to <14 kg.
- This formulation was well tolerated, and results provide reassurance for dosing of this FDC formulation.
- Longer-term safety, tolerability, and efficacy data through 48 weeks in all weight bands are forthcoming.
- Findings expected to support global efforts to expand the availability of pediatric-friendly DTG-containing FDCs in alignment with WHO weight band dosing.

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