Pharmacokinetics and Safety of Dispersible and Immediate Release FDC Abacavir/Dolutegravir/Lamivudine in Children with HIV Weighing ≥14 kg: Preliminary Results from IMPAACT 2019

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BACKGROUND

- The availability of pediatric-friendly fixed dose combination (FDC) antiretroviral formulations is limited. Abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) is currently only available as an immediate-release FDC tablet and is only FDA-approved for use in adults and children ≥40 kg.[1] ABC/DTG/3TC is a Paediatric Antiretroviral Drug Optimization (PADO)-4 priority for development.[2]
- IMPAACT 2019 is examining the pharmacokinetics, safety, and tolerability of ABC/DTG/3TC in immediate- and dispersible-release FDC form. The immediate-release, adult strength tablet is being examined in children weighing ≥25 to <40 kg, and the novel dispersible-release tablets are being assessed in children weighing 6 to <25 kg. Doses of the individual components align with WHO weight band dosing for each of these drugs.

Dosing of dispersible and immediate release ABC/DTG/3TC FDC tablets was confirmed in alignment with WHO weight band recommendations for children ≥14 to <40 kg

OBJECTIVES

Objectives of these analyses were to:

- 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
- Study sites in Botswana, South Africa, Thailand and the United States
- Plasma DTG, ABC, and 3TC concentrations quantified using LC/MS-MS
- PK parameters calculated using noncompartmental methods (Phoenix WinNonlin®, Certara, Inc.)
- Intensive PK results from Weight Bands 3, 4, and 5 are presented

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 <14kg)	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 <25kg)	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.

FIGURE 2. Dose Confirmation Approach

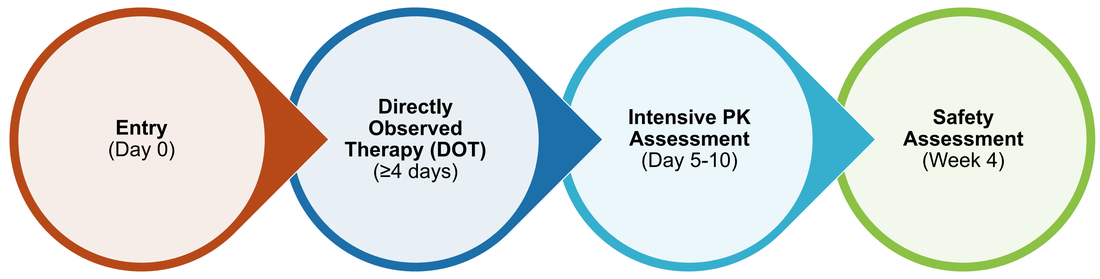


TABLE 1. Individual & Weight Band Targets

Drug	PK Parameter	Individual Target Range	Weight Band Target Range[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_{95} [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

Both PK and safety criteria had to be met for dose confirmation within each weight band

RESULTS

TABLE 2. Participant Demographics & DOT Methods

Characteristic	WB3 (N=7)	WB4 (N=7)	WB5 (N=7)
Sex at birth, n(%)			
Female	4 (57%)	3 (43%)	3 (43%)
Male	3 (43%)	4 (57%)	4 (57%)
Age (year), median (range)[a]	7.4 (5.8-9.6)	8.0 (6.4-8.9)	10.3 (9.3-11.3)
Weight (kg), median (range)[a]	18.8 (16.5-19.5)	21.6 (19.8-24.4)	28.0 (25.9-37.1)
Treatment-Experienced, n(%)	7 (100%)	7 (100%)	7 (100%)
DOT method, n(%)[b]			
In-person	4 (13%)	3 (11%)	0 (0%)
Real-time video	26 (87%)	21 (75%)	32 (100%)
Recorded timestamped video	0 (0%)	4 (14%)	0 (0%)

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

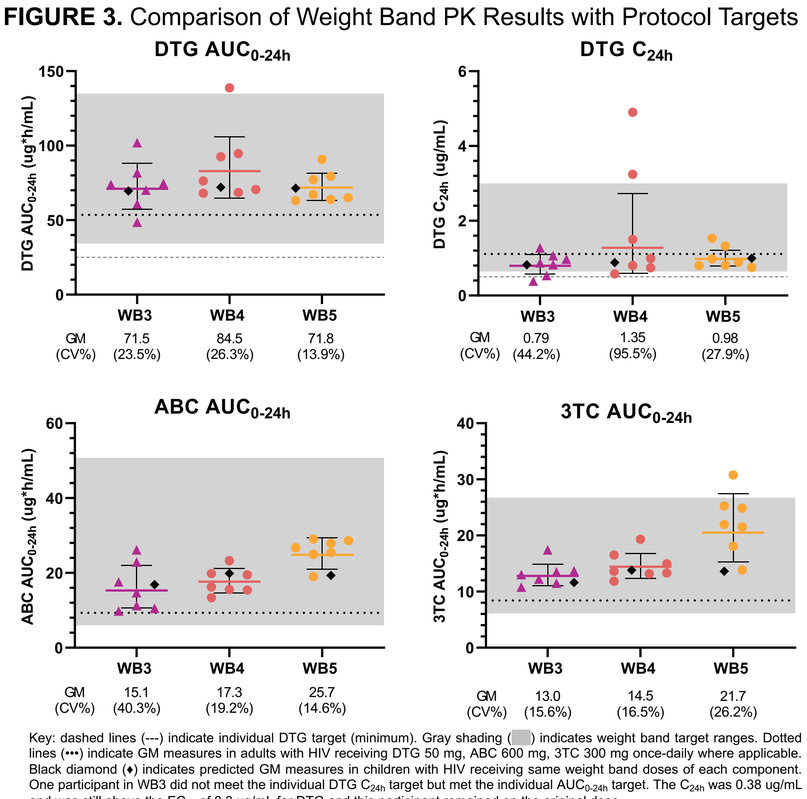
Pharmacokinetics

TABLE 3. Weight Band Dosing & Primary PK Results

WB	Dose (mg)	Dose by Wt (mg/kg)[a]	$AUC_{0\text{-}24h}$ (µg·h/mL)[b]	C_{max} (µg/mL)[b]	C_{24h} (µg/mL)[b]
DTG					
3	25	1.33 (1.28-1.52)	71.5 (23.5%)	7.04 (17.0%)	0.79 (44.2%)
4	30	1.39 (1.23-1.52)	84.5 (26.3%)	7.29 (16.7%)	1.35 (95.5%)
4[c]	30	1.37 (1.23-1.52)	75.1 (13.9%)	7.18 (11.3%)	0.87 (36.9%)
5	50	1.79 (1.35-1.93)	71.8 (13.9%)	6.25 (20.6%)	0.98 (27.9%)
ABC					
3	300	16.0 (15.4-18.2)	15.1 (40.3%)	6.3 (31.0%)	0.003 (108%)
4	360	16.7 (14.8-18.2)	17.3 (19.2%)	6.7 (27.7%)	0.004 (84.9%)
5	600	21.4 (16.2-23.2)	25.7 (14.6%)	9.0 (21.9%)	0.011 (229%)
3TC					
3	150	8.0 (7.7-9.1)	13.0 (15.6%)	2.92 (23.0%)	0.06 (36.6%)
4	180	8.3 (7.4-9.1)	14.5 (16.5%)	2.99 (31.9%)	0.06 (18.2%)
5	300	10.7 (8.1-11.6)	21.7 (26.2%)	4.15 (29.3%)	0.08 (35.0%)

[a] Reported as median (range) [b] Reported as geometric mean (geometric CV%) [c] Results with elevated C_{24h} results excluded to determine whether WB4 targets were met for dose confirmation.

FIGURE 3. Comparison of Weight Band PK Results with Protocol Targets



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, 3TC 300 mg once-daily where applicable. Black diamond (♦) indicates predicted GM measures in children with HIV receiving same weight band doses of each component. One participant in WB3 did not meet the individual DTG C_{24h} target but met the individual $AUC_{0\text{-}24h}$ target. The C_{24h} was 0.38 ug/mL and was still above the EC_{90} of 0.3 ug/mL for DTG and this participant remained on the original dose.

Safety

- No grade 3 or higher AEs related to study drug
- No children discontinued study drug due to AEs
- No AEs required intervention
- Nearly all AEs reported through week 4 resolved

TABLE 4. Summary of AEs through Study Week 4

WB	Grade	Event	Time on Study Drug	Relationship	Time to Resolution
3	3	SCr increase[a]	4 weeks	Not related	~3 weeks
	3	eGFR decrease[a]		Not related	
4	2	Sleep disturbance (nightmares)[b]	4 days	Related to DTG	~4 weeks
	2	eGFR decrease[b]	3 weeks	Related to DTG	Ongoing
5	1	Headache	1 day	Related to DTG	~6 weeks

[a]In same participant; based on change from baseline; SCr within normal range and eGFR was grade 1 based on absolute value
[b]Both events occurred in the same participant; eGFR decrease based on change from baseline

CONCLUSIONS

- PK targets were met for immediate- and dispersible-release ABC/DTG/3TC in children ≥14 kg and these formulations were well-tolerated. These results provide reassurance for dosing of these FDC formulations.
- Longer-term safety, tolerability, and efficacy data through 48 weeks and PK/safety data in children <14kg 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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