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

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

[1]TRIUMEQ® [package insert]. Research Triangle Park, NC: GlaxoSmithKline/ViiV Healthcare. 03/2021.
[2]World Health Organization. Paediatric Antiretroviral Drug Optimization (PADO) Meeting 4 Meeting Report. 2018 Dec 10-12.

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Objectives

Among children living with HIV <12 years of age:

- To determine steady-state $AUC_{0\text{-}24h}$, C_{max}, and 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

$AUC_{0\text{-}24h}$: area under the concentration time curve over a 24-hour dosing interval; C_{max}: maximum (peak) concentration; C_{24h}: concentration at 24 hours post-dose

Study Overview

- Phase I/II, multi-site, open-label, non-comparative dose confirmation study
- Study sites in Botswana, South Africa, Thailand and the United States

Key Eligibility Criteria:

- Children <12 years of age
- Treatment-naïve **or**
- Treatment-experienced with HIV VL <200 copies/mL on a stable non-NNRTI-containing ARV regimen for ≥6 months

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 tablets; IR: immediate-release tablet; NNRTI: non-nucleoside reverse transcriptase inhibitor; VL: viral load; WB: weight band.

Dose Confirmation Approach

Entry
(Day 0)
- Treatment-experienced participants switched to ABC/DTG/3TC

Directly Observed Therapy
(≥4 days)
- Confirmed dosing ≥4 days prior to intensive PK
- In-person, real-time video or timestamp video

Intensive PK Assessment
(Days 5-10)
- Fasted (low fat light snack permitted >2 hrs prior to observed dose)
- Individual real-time monitoring of DTG PK
- Weight band assessment of DTG, ABC, and 3TC (n=5-7)

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

Safety Assessment
(Week 4)

Acceptable safety criteria:
- No deaths/life-threatening adverse events (AEs) related to study drug, and
- Grade 3+ AEs or permanent d/c due to study drug in <2 participants

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

[a]Geometric mean contained within each target range

Participant Demographics & DOT Methods

Characteristic	Weight Band 3 (n=7)	Weight Band 4 (n=7)	Weight Band 5 (n=7)
Sex at birth, n(%) Female Male	 4 (57%) 3 (43%)	 3 (43%) 4 (57%)	 3 (43%) 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%)
Directly observed therapy (DOT) type, n(%)[b] In-person Real-time video Recorded timestamped video	 4 (13%) 26 (87%) 0 (0%)	 3 (11%) 21 (75%) 4 (14%)	 0 (0%) 32 (100%) 0 (0%)

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

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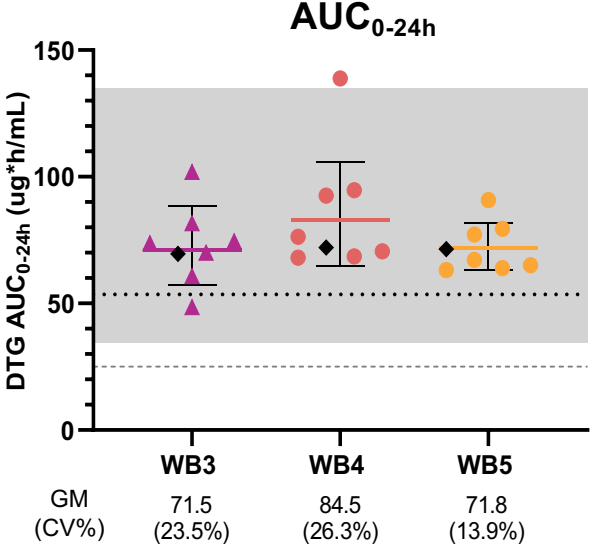
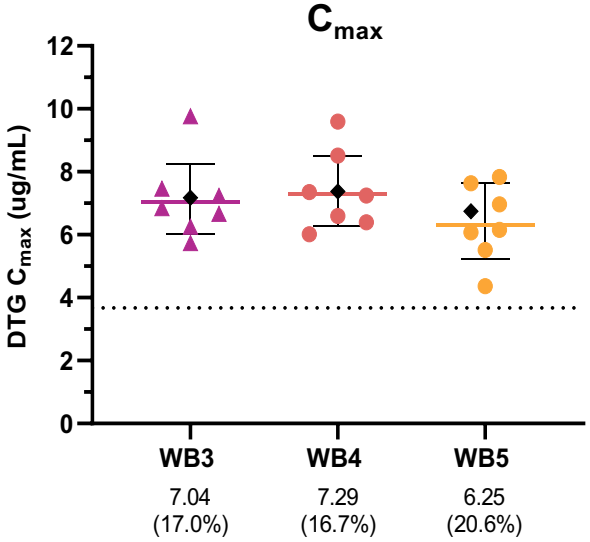
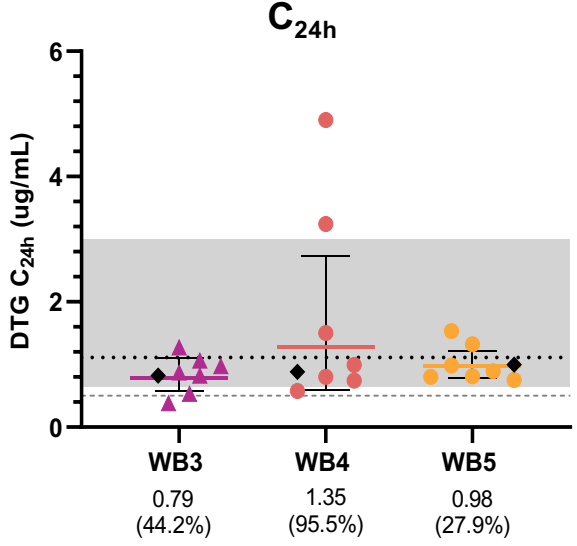
Dolutegravir PK

WB	Dose (mg)	Dose by Weight (mg/kg)[a]
3	25	1.33 (1.28-1.52)
4	30	1.39 (1.23-1.52)
5	50	1.79 (1.35-1.93)

WB = weight band. [a]Reported as median (range)







--- Individual target (minimum)
Weight band target ranges
⋯ GM measures in adults with HIV receiving DTG 50 mg once-daily (from Tivicay® Package Insert – *population PK modeling of SPRING-1 and -2*).
♦ Predicted GM measures in children with HIV receiving same single entity DTG formulations/doses (from Singh et al. HIV Pediatrics 2020 – *population PK modeling of ODYSSEY and P1093*).

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Dolutegravir PK

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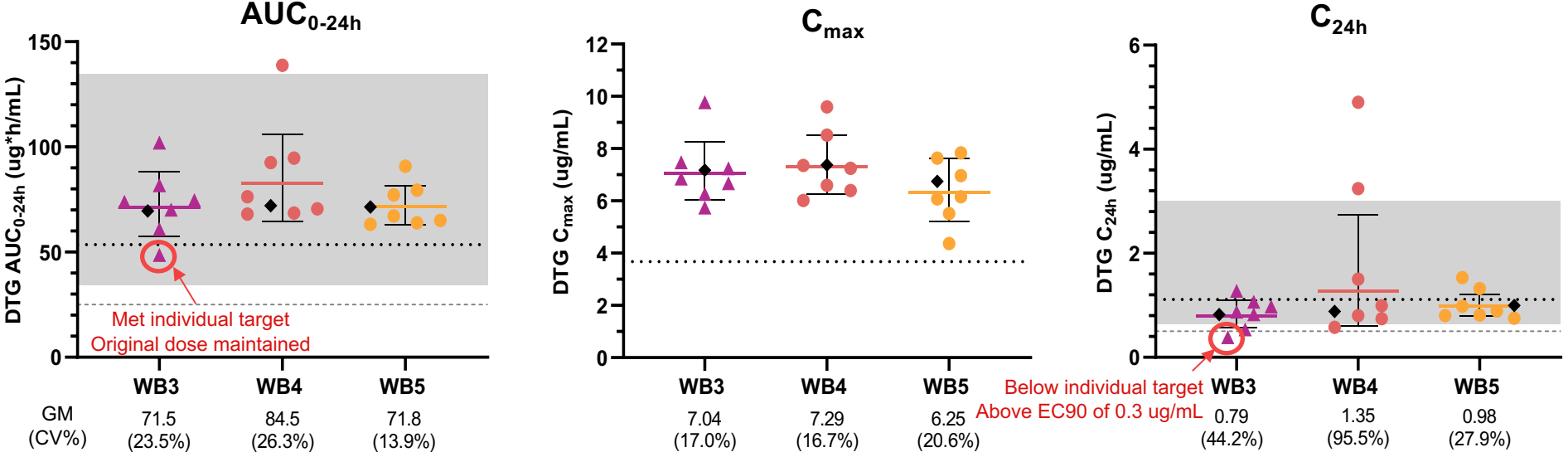

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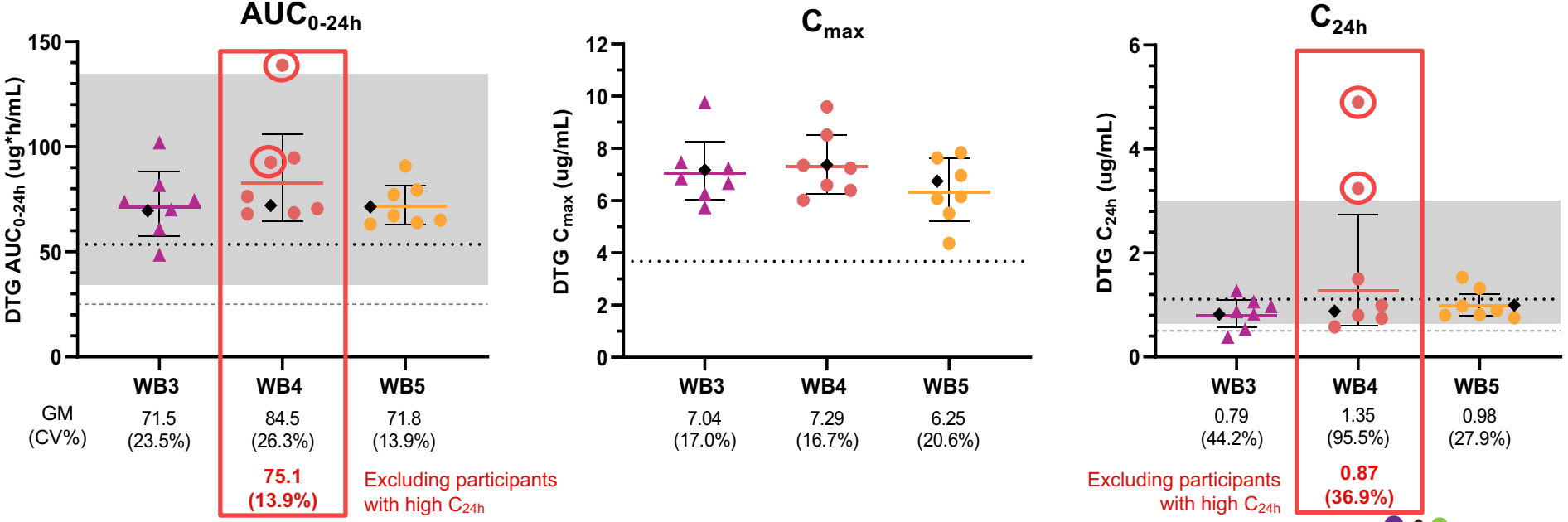

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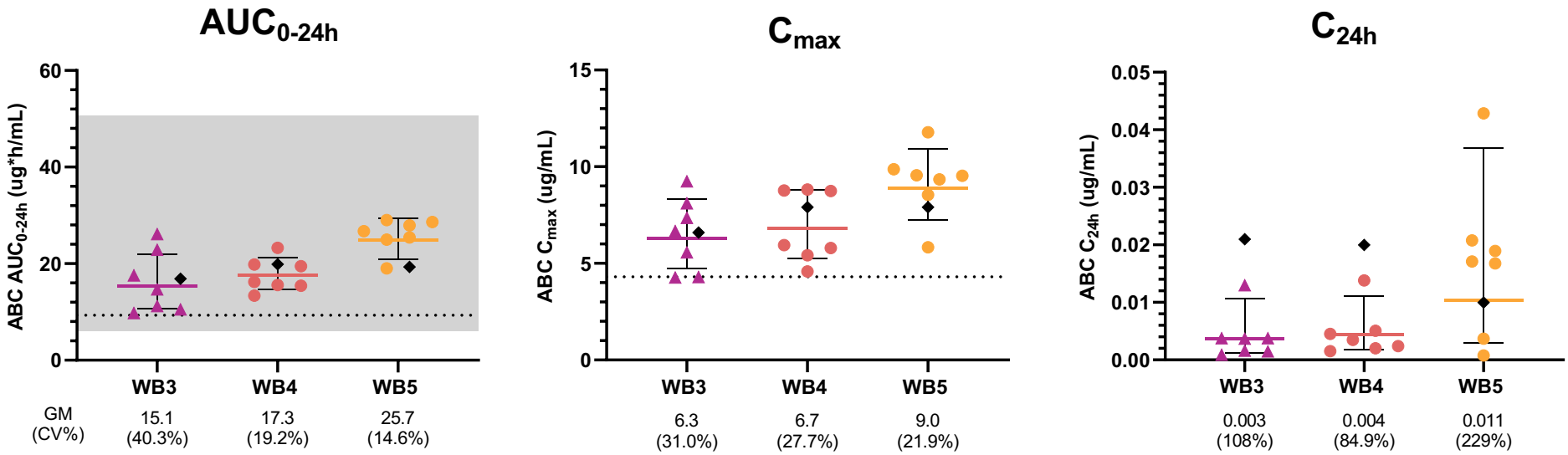
Abacavir PK

WB	Dose (mg)	Dose by Weight (mg/kg)[a]
3	300	16.0 (15.4-18.2)
4	360	16.7 (14.8-18.2)
5	600	21.4 (16.2-23.2)

WB = weight band. [a]Reported as median (range)



Weight band target ranges

⋯ geometric mean PK measure in adults with HIV receiving ABC 600 mg once-daily

♦ Predicted median measures in children with HIV receiving same once-daily WB doses (from Clinical Pharmacology Review for Ziagen® (abacavir sulfate) and Epivir® (lamivudine))

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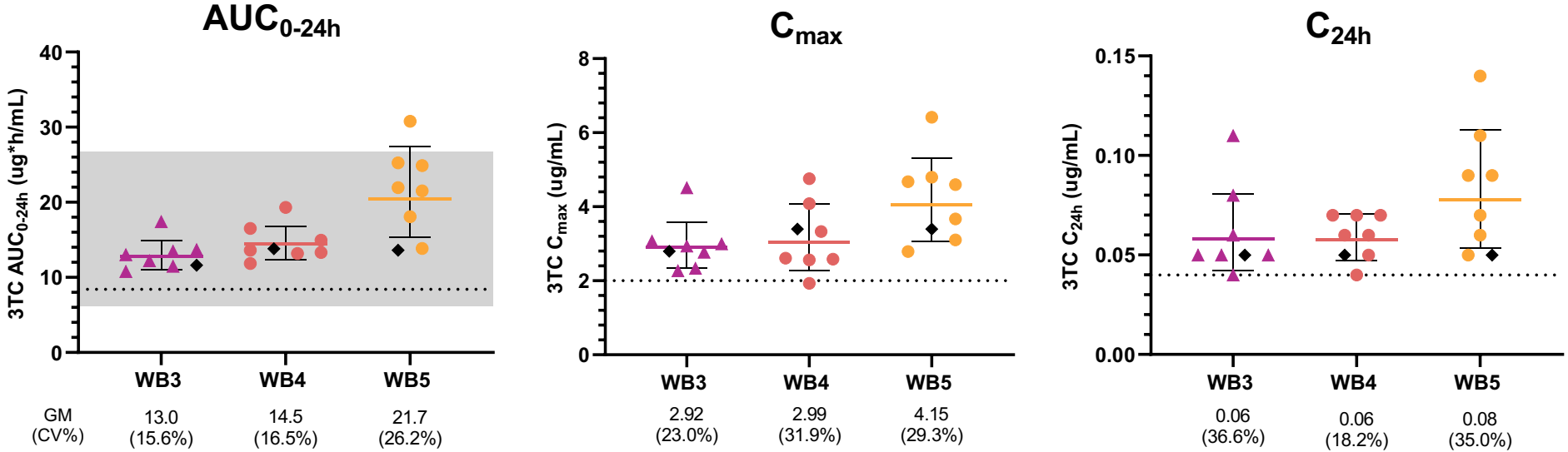
Lamivudine PK

WB	Dose (mg)	Dose by Weight (mg/kg)[a]
3	150	8.0 (7.7-9.1)
4	180	8.3 (7.4-9.1)
5	300	10.7 (8.1-11.6)

WB = weight band. [a]Reported as median (range)



Weight band target ranges

⋯ geometric mean PK measure in adults with HIV receiving 3TC 300 mg once-daily

♦ Predicted median measures in children with HIV receiving same once-daily WB doses (from Clinical Pharmacology Review for Ziagen® (abacavir sulfate) and Epivir® (lamivudine))

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Week 4 Safety Results

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

Week 4 Safety Results

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

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Conclusions

- PK targets were met for immediate- and dispersible-release ABC/DTG/3TC in children ≥14 kg and these formulations were well-tolerated
- Results provide reassurance for dosing of these FDC formulations in children weighing ≥14 kg
- 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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Acknowledgments

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