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HIV

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Waalewijn H, Chan M K, Bollen P D J, et al. Dolutegravir dosing for children with HIV weighing less than 20 kg: pharmacokinetic and safety substudies nested in the open-label, multicentre, randomised, non-inferiority ODYSSEY trial. *Lancet HIV* 2022; published online Feb 18. https://doi.org/10.1016/S2352-3018(21)00292-7.

Dolutegravir dosing for children with HIV weighing less than 20 kg: pharmacokinetic and safety substudies nested in the multicentre, randomised ODYSSEY trial.

Supplementary appendix

Content

Supplementary Table 1. Dolutegravir dosing and administration details in the pharmacokinetic substudies for children weighing 3 to less than 20kg

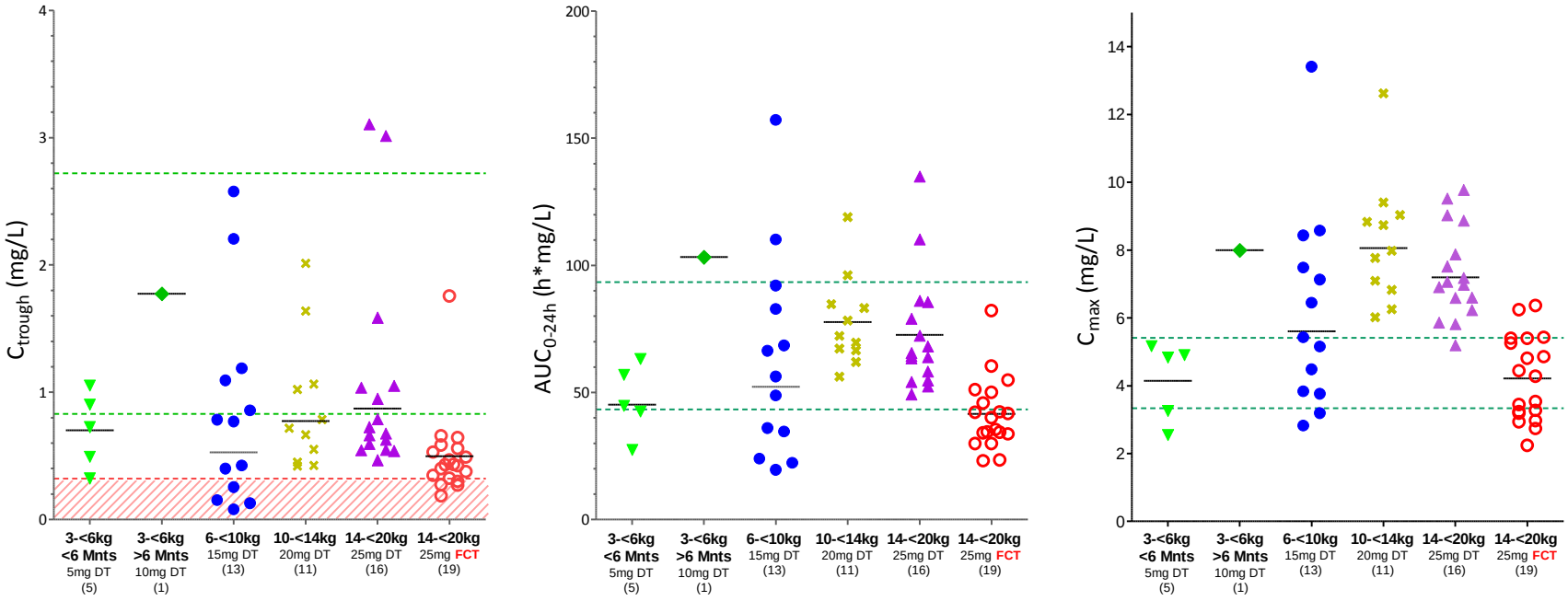
Weight band	Dose in mg	Formulation type and amount of tablets	Administration details	Food restrictions	Blood draw volume
3 to <6kg; <six months old	5	1 dispersible tablet	Dispersed in 10 mL water; rinsed with 10 mL water	Preferred fasting: 2 hours before dose, 1 hour after dose	0·5 ml sample at 7 time points
3 to <6kg; >six months old	10	2 dispersible tablets	Dispersed in 10 mL water; rinsed with 10 mL water	Preferred fasting: 2 hours before dose, 1 hour after dose	0·5 ml sample t 7 time points
6 to <10kg	15	3 dispersible tablets	Dispersed in 10 mL water; rinsed with 10 mL water	Preferred fasting: 2 hours before dose, 1 hour after dose	1 ml sample at 7 time points
10 to <14kg	20	4 dispersible tablets	Dispersed in 10 mL water; rinsed with 10 mL water	Mandatory fasting: At least 3 hours before dose; 2 hours after dose	2 ml sample at 7 time points
14 to <20kg	25	5 dispersible tablets	Dispersed in 15 mL water; rinsed with 10 mL water, followed up with 75 mL water (100 mL in total)	Mandatory fasting: at least 3 hours before dose; 2 hours after dose	2 ml sample at 7 time points
14 to <20kg	25	1 film-coated tablet	Taken with 100 mL water	Mandatory fasting: at least 3 hours before dose; 2 hours after dose	2 ml sample at 7 time points

Supplementary table 2. Children in Weight band 3 to <6kg older than 6 months taking 10mg dispersible tablet, not reported in main paper due to limited data of this group.

ID	WEIGHT (KG)	AGE (YEARS)	DOSE (MG)	FORMULATION	C_{TROUGH} (MG/L)	AUC_{0-24} (H*MG/L)	C_{MAX} (MG/L)	CL/F (L/H)	$T_{1/2}$ (H)	V_D/F (L)
1	5·7	0·61	10	DT	1·77	103·20	8·00	0·10	10·36	1·45

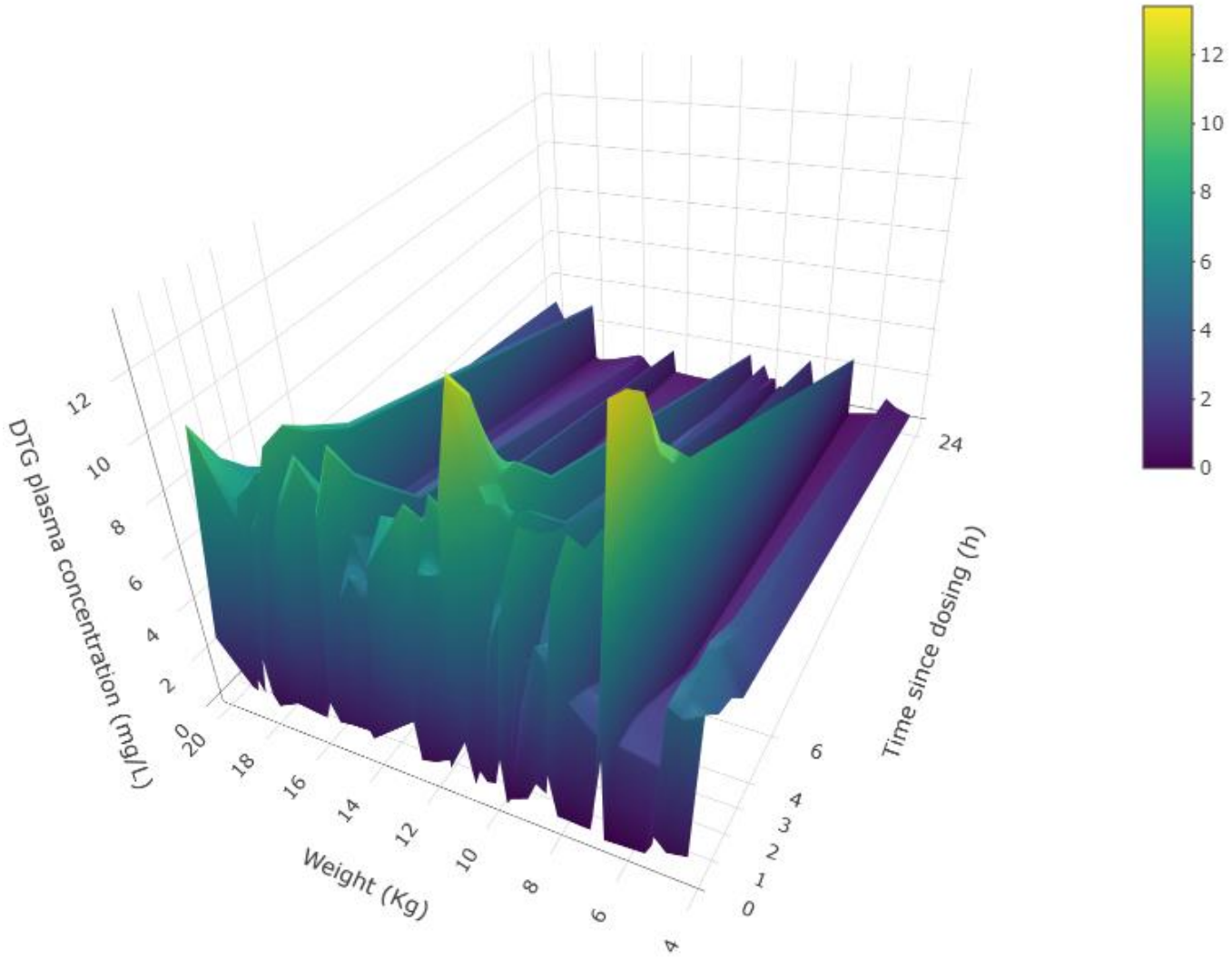
C_{trough}: dolutegravir trough concentration, AUC_{0-24}: area under the concentration-time curve from 0 to 24 hours. C_{max}: maximum concentration, CL/F: apparent clearance. DT: dispersible tablet

Supplementary figure 1. Individual dolutegravir Ctrough, AUC0–24h, and Cmax in children weighing 3 kg to less than 20 kg taking dispersible tablets (DT) or film-coated tablets (FCT), including one child weighing 3 to less than 6kg older than 6 months taking 10mg dispersible tablets.



Horizontal black lines indicate geometric means per dose. Red line indicates dolutegravir in-vivo EC90. Green dashed lines indicate published geometric mean adult reference values for 50 mg once-daily (lower line) and twice-daily doses (upper line). Ctrough=trough concentration. AUC0–24h=area under the concentration-time curve from 0 to 24 h. Cmax=maximum concentration. EC90=the effective concentration at which 90% of maximal viral inhibition is achieved in a 10-day monotherapy study.

Supplementary figure 2. Surface plot showing dolutegravir plasma concentrations by participant weight and time since dolutegravir dosing for all participants receiving dolutegravir dispersible tablets.



Supplementary table 3. Individual PK parameters of children ineligible for pharmacokinetic analysis with reasons for exclusion

ID	WEIGHT (KG)	AGE (YEARS)	DOSE (MG)	FORMULATION	C_{TROUGH} (MG/L)	AUC_{0-24} (H*MG/L)	C_{MAX} (MG/L)	CL/F (L/H)	$T_{1/2}$ (H)	V_D/F (L)	REASON FOR EXCLUSION
1	4·60	0·29	10	DT	1·41	88·95	7·60	0·11	9·11	1·48	Wrong dose for age and weight band
2	4·90	0·52	10	DT	0·49	32·72	2·62	0·31	8·96	3·95	Concomitant medication (Zinc Sulphate)
3	5·20	0·61	10	DT	1·10	80·57	6·92	0·12	8·17	1·46	Non-adherence
4	5·30	0·43	10	DT	4·62	180·64	12·29	0·06	17·65	1·41	Wrong dose for age and weight band
5	7·00	0·42	10	DT	2·43	127·60	9·47	0·08	11·17	1·26	Wrong dose for weight band
6	7·80	2·65	15	DT	1·07	78·27	7·46	0·19	7·91	2·19	Non-adherence
7	8·70	1·98	15	DT	0·54	54·15	5·24	0·28	6·47	2·59	Non-adherence
8	10·20	1·47	20	DT	1·06	73·21	6·55	0·27	8·66	3·41	Participant did not fast
9	11·90	2·66	20	DT	0·80	61·76	5·84	0·32	7·90	3·69	Non-adherence
10	14·70	4·68	25	FCT	0·95	56·14	4·33	0·45	9·99	6·42	DTG intake out of allowed dosing window
11	15·00	5·13	25	FCT	c.n.b.d.	c.n.b.d.	6.09	c.n.b.d.	c.n.b.d.	c.n.b.d.	DTG intake out of allowed dosing window
12	16·40	5·58	20	FCT	0·56	38·55	3·56	0·52	8·42	6·30	Wrong dose for weight band
13	17·00	7·61	25	FCT	0·06	8·95	1·48	2·79	5·75	23·18	Concomitant medication (iron supplement)
14	18·30	4·37	20	FCT	0·20	21·46	2·43	0·93	6·45	8·67	Major ineligibility as child was enrolled as ART-naïve when was taking ART supplied by an alternative clinic
14	19·00	4·96	25	DT	0·58	51·50	5·56	0·49	7·19	5·04	Major ineligibility as child was enrolled as ART-naïve when was taking ART supplied by an alternative clinic
15	18·50	8·85	25	FCT	0·09	21·32	3·63	1·17	4·67	7·90	Non-adherence
16	18·80	5·38	25	DT	0·18	35·11	4·52	0·71	4·85	4·98	Concomitant medication (valproic acid)
17	20·10	7·48	25	DT	1·47	84·70	6·88	0·30	9·65	4·11	DTG intake out of allowed dosing window

C_{trough}: dolutegravir trough concentration, AUC_{0-24}: area under the concentration-time curve from 0 to 24 hours. C_{max}: maximum concentration, CL/F: apparent clearance, C.n.b.d.: could not be determined· DT: dispersible tablet, FCT: film-coated tablet, DTG: dolutegravir. Dosing window: between 20 and 28 hours after previous DTG dose.

Supplementary table 4. Detailed summary of adverse events by weight band and dolutegravir dose and formulation

Dose‡	Total -	3-<6kg,<6m 5mgDT	3-<6kg,≥6m 10mgDT	6-<10kg 15mgDT	10-<14kg 20mgDT	14-<20kg 25mgFCT	 25mgDT	20-<25kg 30mgDT	Non-Per Protocol -
Follow-up[α], weeks									
No. of Participants	**71**	**8**	**5**	**28**	**18**	**25**	**19**	**2**	**14**
Median	24·0	11·3	10·9	15·6	24·0	24·0	24·0	11·3	5·4
(IQR)	(24·0-24·0)	(6·6-12·0)	(4·0-12·0)	(12·0-24·0)	(12·0-24·0)	(24·0-24·0)	(23·6-24·0)	(0·4-22·1)	(1·9-11·7)
[Range]	[1·0-48·0]	[1·3-12·0]	[1·0-20·1]	[0·0-24·0]	[0·0-24·0]	[12·7-24·0]	[0·6-24·0]	[0·4-22·1]	[0·1-23·4]
Number of SAEs (No. of Participants)##	**13 (11)**	**2 (2)**	**2 (2)**	**3 (3)**	**1 (1)**	**2 (2)**	**0 (0)**	**0 (0)**	**3 (1)**
Haematological	**1 (1)**	**1 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Thrombocytopenia+Neutropenia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Infectious Disease	**9 (8)**	**1 (1)**	**1 (1)**	**2 (2)**	**1 (1)**	**2 (2)**	**0 (0)**	**0 (0)**	**2 (1)**
Acute diarrhoea not investigated+Dehydration	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Acute febrile episode - undiagnosed	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Chronic diarrhoea with no pathogen	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastroenteritis	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Measles+Chest infection	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Plasmodium falciparum malaria	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Pneumonia no organism identified	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Pneumonia no organism identified+acute otitis media	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tuberculosis - pulmonary - smear negative or not done	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Non HIV related deaths	**1 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**1 (1)**
Traumatic *	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Systemic	**2 (2)**	**0 (0)**	**1 (1)**	**1 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Chest infection+Severe malnutrition	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Kwashiorkor *	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Number of grade ≥3 events (No. of Participants)###	**29 (19)**	**3 (2)**	**3 (2)**	**7 (5)**	**8 (4)**	**3 (3)**	**1 (1)**	**0 (0)**	**4 (2)**
Biochemical	**2 (2)**	**0 (0)**	**0 (0)**	**0 (0)**	**2 (2)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Raised AST	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Raised alkaline phosphatase (ALK)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Haematological	**7 (5)**	**2 (1)**	**0 (0)**	**1 (1)**	**3 (2)**	**0 (0)**	**0 (0)**	**0 (0)**	**1 (1)**
Anaemia with no clinical symptoms	4 (4)	0 (0)	0 (0)	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)	1 (1)
Neutropenia	2 (2)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Infectious Disease	**15 (12)**	**1 (1)**	**1 (1)**	**5 (4)**	**3 (2)**	**2 (2)**	**1 (1)**	**0 (0)**	**2 (1)**
Acute diarrhoea not investigated	2 (2)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Acute febrile episode undiagnosed	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Acute otitis media	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Chest infection	2 (2)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Chronic diarrhoea with no pathogen	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastroenteritis	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatitis A	2 (2)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)**	0 (0)	0 (0)
Measles	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Plasmodium falciparum malaria	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Pneumonia no organism identified	2 (2)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Tuberculosis - pulmonary - smear negative or not done	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Nervous System	**1 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**1 (1)**	**0 (0)**	**0 (0)**	**0 (0)**
Epilepsy, fits, convulsions	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Non HIV related deaths	**1 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**1 (1)**
Traumatic *	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Systemic	**3 (3)**	**0 (0)**	**2 (2)**	**1 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**
Dehydration	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Kwashiorkor *	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Severe malnutrition	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

‡ Exposed to DTG QD or BID dose with RIF. Numbers exposed to DTG BID: 1 child 3-6kg <6months 10mg DT BID (non-per protocol dose); 3 children 6-<10kg 15DT BID; 2 children 10-<14kg 20DT BID; 1 child 14-<20kg 25DT BID; 2 children 14-<20kg 25FCT BID.

*2 children died: 1 due to Kwashiorkor; 1 due to traumatic accident.

**** 1 event (Hepatitis A) resulted in discontinuation of dolutegravir.

α Follow-up based on time-updated dose. Dose changes were primarily the result of increased weight and moving to the intended PK dose in second PK substudy.

SAEs are analysed as episodes, with all components of the same clinical SAE presented as one episode (e.g. "Thrombocytopenia+Neutropenia").

For grade ≥3 clinical and laboratory adverse events, each component of the same episode is analysed as a separate event."

Note: 13 children participated in the first (25mg FCT) and second (25mg DT) pharmacokinetic substudies (14-20Kg) with no overlap; 1 child was exposed to and completed pharmacokinetic profiles on dispersible 15mg while 6-<10kg (12 weeks safety follow-up; 2 grade ≥3 events reported as components of the same clinical SAE) and 20mg while 10-<14kg (24 weeks safety follow-up; no events reported); 1 child was exposed to and completed pharmacokinetic profiles on dispersible 10mg (non per protocol dose; 3 weeks safety follow-up) and 5mg (24 weeks safety follow-up) while 3-<6kg <6months (no events reported); 1 child was exposed to and completed pharmacokinetic profiles on dispersible 20mg FCT (non per protocol dose; 21 weeks safety follow-up) and 25mg DT (24 weeks safety follow-up) while 14-<20kg (no events reported).

SAEs, serious adverse events; **IQR,** interquartile range; **DTG,** dolutegravir; **QD,** once daily; **BID,** twice daily; **DT,** dispersible tablet; **FCT,** film-coated tablet; **<6m**, less than 6 months old; **≥6m**, over 6 months old.

Supplementary table 5. Listing of adverse events reported

ID	Weight	Dose	DTG Exposure (wks)[#]	DTG Dose/Weight Group Exposure (wks)[‡]	SAE	Category	Event	Grade	ART Modifying	Relatedness to ART (ERC)
3	**3-<6kg**	**5mg DT**	2	2	Yes[1]	Haematological	Thrombocytopenia**^**	Grade 4	No	No
3	**3-<6kg**	**5mg DT**	2	2		Haematological	Neutropenia**^**	Grade 4	No	No
14	**3-<6kg**	**5mg DT**	11	11	Yes	Infectious Disease	Gastroenteritis	Grade 3	No	No
2	**3-<6kg**	**10mg DT**	1	1	Yes	Systemic	Kwashiorkor**	Grade 5	No	No
13δ	**3-<6kg**	**10mg DT**	7	7	No	Haematological	Anaemia with no clinical symptoms**^**	Grade 3	No	No
15	**3-<6kg**	**10mg DT**	3	1	Yes[3]	Infectious Disease	Acute diarrhoea not investigated	Grade 3	No	No
15	**3-<6kg**	**10mg DT**	3	1		Infectious Disease	Dehydration	Grade 3	No	No
19*	**3-<6kg**	**10mg DT**	1	1	Yes	Infectious Disease	Pneumonia no organism identified	Grade 3	No	No
19*	**3-<6kg**	**10DT BID**	3	0.1	Yes	Infectious Disease	Tuberculosis - pulmonary - smear negative or not done	Grade 4	No	No
19*	**3-<6kg**	**10DT BID**	18	15	Yes	Non-HIV related deaths	Traumatic¥	Grade 5	No	No
1	**6-<10kg**	**15mg DT**	2	2	No	Infectious Disease	Acute diarrhoea not investigated	Grade 3	No	No
6	**6-<10kg**	**15mg DT**	10	10	Yes[2]	Systemic	Chest infection	Grade 3	No	No
6	**6-<10kg**	**15mg DT**	10	10		Systemic	Severe malnutrition	Grade 4	No	No
10	**6-<10kg**	**15mg DT**	3	3	No	Haematological	Anaemia with no clinical symptoms**^**	Grade 3	No	No
12	**6-<10kg**	**15mg DT**	8	8	Yes	Infectious Disease	Chronic diarrhoea with no pathogen	Grade 4	No	No
17	**6-<10kg**	**15mg DT**	3	3	Yes[4]	Infectious Disease	Acute otitis media	Grade 3	No	No
17	**6-<10kg**	**15mg DT**	3	3		Infectious Disease	Pneumonia no organism identified	Grade 3	No	No
4	**10-<14kg**	**20mg DT**	2	2	No	Haematological	Anaemia with no clinical symptoms**^**	Grade 3	No	No
7	**10-<14kg**	**20mg DT**	22	22	No	Infectious Disease	Raised AST	Grade 3	No	No
7	**10-<14kg**	**20mg DT**	22	22	No	Infectious Disease	Hepatitis A	Grade 3	No	No
11	**10-<14kg**	**20mg DT**	15	15	No	Biochemical	Raised alkaline phosphatase (ALK)**^**	Grade 3	No	No
11	**10-<14kg**	**20mg DT**	14	13	No	Haematological	Neutropenia**^**	Grade 4	No	No
11	**10-<14kg**	**20mg DT**	3	3	No	Haematological	Anaemia with no clinical symptoms**^**	Grade 3	No	No
18	**10-<14kg**	**20mg DT**	10	10	Yes[5]	Infectious Disease	Measles	Grade 3	No	No
18	**10-<14kg**	**20mg DT**	10	10		Infectious Disease	Chest infection	Grade 3	No	No
8	**14-<20kg**	**25mg FCT**	19	19	No	Nervous System	Epilepsy, fits, convulsions	Grade 3	No	No
16	**14-<20kg**	**25mg FCT**	14	14	Yes	Infectious Disease	Plasmodium falciparum malaria	Grade 3	No	No

5	**14-<20kg**	**25mg DT**	24	1	No	Infectious Disease	Hepatitis A	Grade 4	Yes	No
9€	**14-<20kg**	**25FCT BID**	19	15	Yes	Infectious Disease	Acute febrile episode - undiagnosed	Grade 3	No	No

DTG exposure from randomisation

2 children died: **1 due to Kwashiorkor; ¥1 due to traumatic accident.

‡ From start of DTG DT following randomisation for <14kg, or start of 25mg FCT (QD or BID) or 25mg DT (QD or BID) for participants participating in first (25mg FCT) and second (25mg DT) pharmacokinetic substudies (14-20Kg)

^ Asymptomatic laboratory event

***** Non-per protocol dose: <6 months 10DT QD received for 3 weeks before increasing to 10DT BID with RIF use.

δ Non-per protocol dose: <6 months 10mg DT

€ 20.1kg and receiving 25FCT BID dosing with RIF use

Note: SAEs are analysed as episodes, with all components of the same clinical SAE presented as one episode.

1 Components of the same clinical SAE (Thrombocytopenia and Neutropenia)

2 Components of the same clinical SAE (Chest infection and Severe malnutrition)

3 Components of the same clinical SAE (Acute diarrhoea not investigated and Dehydration)

4 Components of the same clinical SAE (Pneumonia no organism identified and Acute otitis media)

5 Components of the same clinical SAE (Measles and Chest infection)

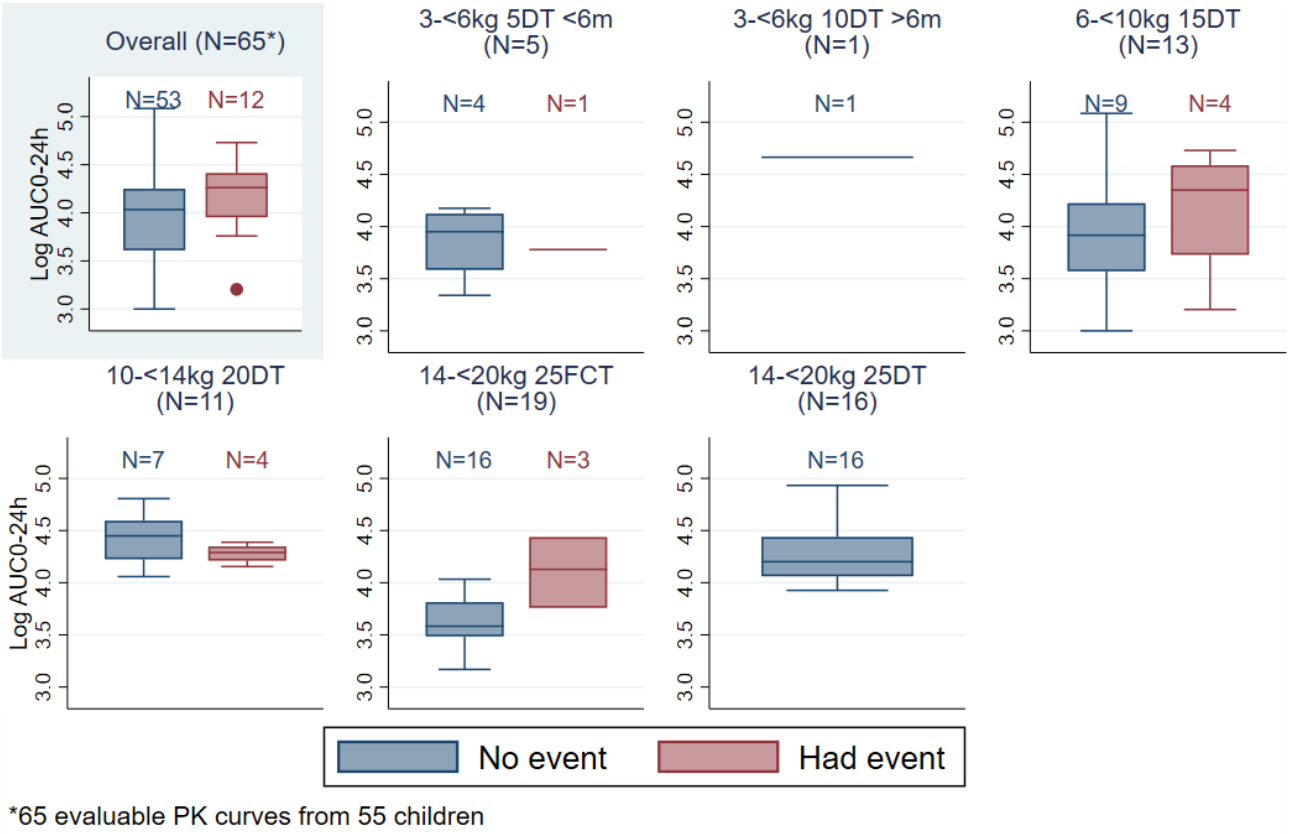
SAEs, serious adverse events; **DTG,** dolutegravir; **DT,** dispersible tablet; **FCT,** film-coated tablet; **QD,** once daily; **BID,** twice daily; **ERC,** endpoint review committee.

Supplementary table 6. Association between log $AUC_{0\text{-}24h}$ or log C_{max} and occurrence of adverse events

	Odds Ratio*	95% CI	P-value
Log $AUC_{0\text{-}24h}$			
Unadjusted	2.0	(0.5, 8.5)	0.327
Adjusted for weight band	3.0	(0.5, 17.0)	0.222
Log C_{max}			
Unadjusted	2.7	(0.5, 14.3)	0.245
Adjusted for weight band	5.4	(0.6, 52.8)	0.144

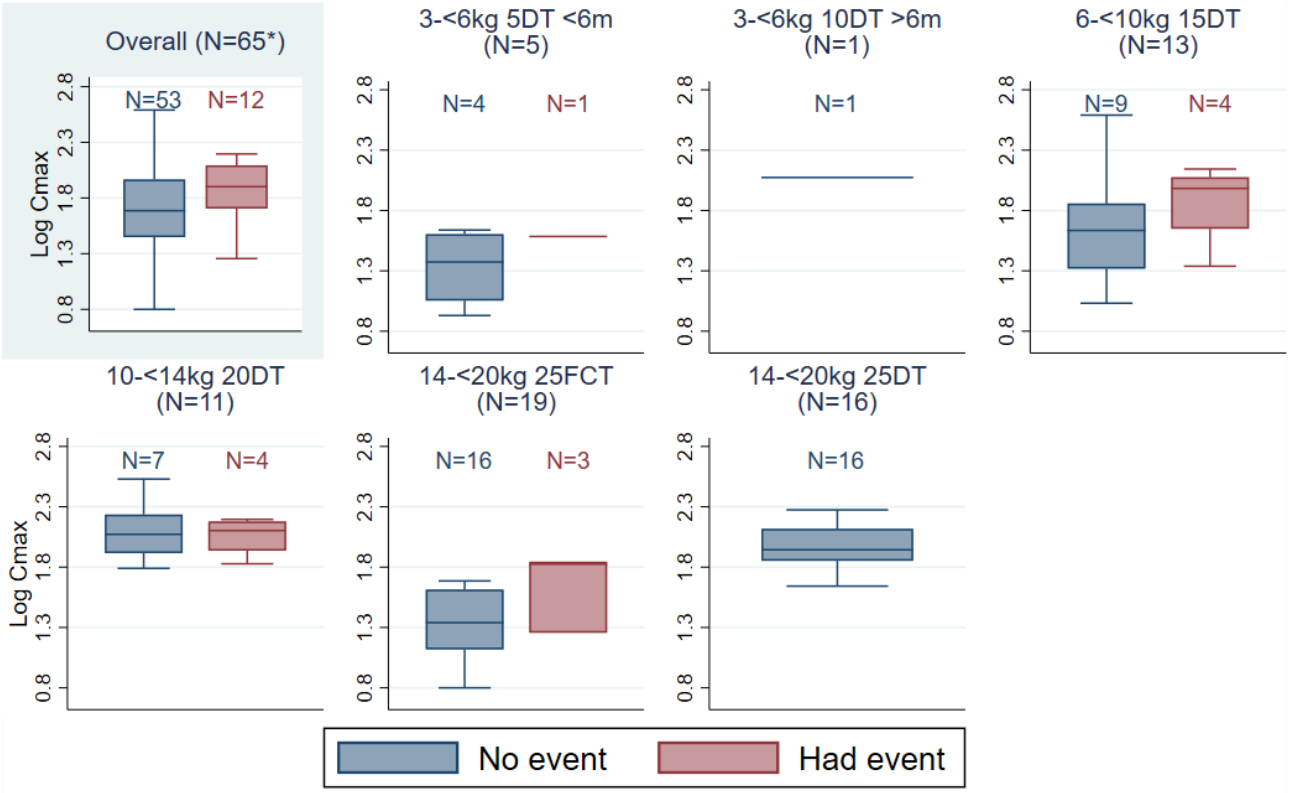
* Odds ratio of adverse event is for each 1-unit increase in log $AUC_{0\text{-}24h}$ or log C_{max}. Unadjusted odds ratios are estimated by fitting logistic regression models with the occurrence of adverse event (binary yes/no) as the outcome variable and log $AUC_{0\text{-}24h}$ or log C_{max} as the continuous predictor variables. Adjusted models are adjusted for weight band.
Log, natural logarithm; **$AUC_{0\text{-}24h}$,** area under the concentration-time curve from 0 to 24 h; **C_{max},** maximum plasma concentration; **95% CI,** 95% confidence interval.

Supplementary figure 3. Log $AUC_{0\text{-}24h}$ in children with vs without adverse events reported overall and by weight band



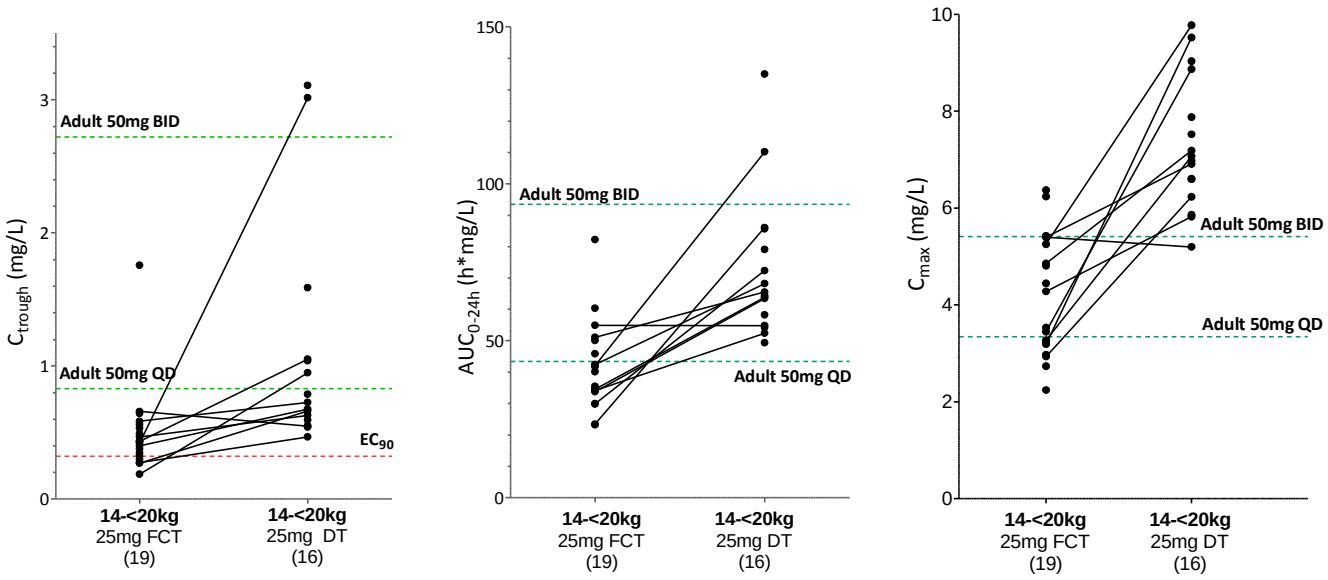
Boxplots are shown. Horizontal lines within the boxes show the median values (Quartile (Q) 2); boxes show interquartile ranges (IQR, Q1 to Q3); upper whiskers denote the uppermost value within Q3 + (IQR × 1·5); lower whiskers denote the lowermost value within Q1 − (IQR × 1·5). **Q1,** 25th percentile; **Q2,** 50th percentile (median); **Q3,** 75th percentile; **DT,** dispersible tablet; **FCT,** film-coated tablet; **Log,** natural logarithm; **$AUC_{0\text{-}24h}$,** area under the concentration-time curve from 0 to 24 h; **<6m**, less than 6 months old; **≥6m**, over 6 months old.

Supplementary figure 4. Log C_{max} in children with vs without adverse events reported overall and by weight band



Boxplots are shown. Horizontal lines within the boxes show the median values (Quartile (Q) 2); boxes show interquartile ranges (IQR, Q1 to Q3); upper whiskers denote the uppermost value within Q3 + (IQR × 1·5); lower whiskers denote the lowermost value within Q1 − (IQR × 1·5). **Q1,** 25th percentile; **Q2,** 50th percentile (median); **Q3,** 75th percentile; **DT,** dispersible tablet; **FCT,** film-coated tablet; **Log,** natural logarithm; **C_{max},** maximum plasma concentration; **<6m**, less than 6 months old; **≥6m**, over 6 months old.

Supplementary figure 5. Intra- and inter-subject comparison of pharmacokinetic parameters on 25mg film-coated tablets (FCT; reference) and 25mg dispersible tablets (DT; test)



Red line indicates dolutegravir in-vivo EC_{90}. Green dashed lines indicate published geometric mean adult reference values for 50mg once-daily (lower line) and twice-daily doses (upper line).C_{trough}=trough concentration. AUC_{0-24h}=area under the concentration-time curve from 0 to 24 h. C_{max}=maximum concentration. EC_{90}=the effective concentration at which 90% of maximal viral inhibition is achieved in a 10-day monotherapy study.

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