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Background

- Dolutegravir (DTG) film-coated tablets are EMA-approved for children aged >6 years weighing at least 15kg. However, doses for younger children and children who are unable to swallow tablets are unknown
- Dolutegravir 5mg dispersible tablets (DT) are small, child-friendly and scalable.
- We describe a **pharmacokinetic (PK) substudy of DTG 5mg DT in children weighing 6-<20kg** dosed by WHO weight bands conducted within ODYSSEY, an ongoing phase-II/III trial of DTG-based first- and second-line antiretroviral therapy (NCT02259127).
- The goal of this study is to achieve C_{trough} concentration similar to adult geometric mean (GM) C_{trough} values achieved on a QD 50mg film-coated tablet regimen.

Table 1. ODYSSEY PK substudy DTG doses.

WHO Weight bands	DTG DT once daily; number of tablets and daily dose, mg
6 to <10kg	3 (15mg)
10 to <14kg	4 (20mg)
14 to <20kg	5 (25mg)

Methods

- At steady-state, 24-hour PK profiles (7 samples) were constructed following observed intake of DTG DT.
- DTG plasma concentrations were measured using a validated UPLC-MS/MS method; WinNonlin 8.3 was used for non-compartmental analysis.
- Results were compared to historical PK parameters from adults taking 50mg DTG film-coated tablets (FCT) QD or BID, previous ODYSSEY PK data and published data on DT from the DTG registrational trial IMPAACT1093.
- Dolutegravir dispersible tablet (DT) formulation are **~1.6 to 2.0x more bioavailable** than film coated tablets (FCT)

Results

Demographics

- This PK substudy included 41 black-African children from **Uganda, Zimbabwe, and South Africa** of which **34 children** had evaluable PK curves and were included in the PK analysis (Table 2).
- 7 children were excluded from analysis for PK protocol deviations (n=4) or questionable adherence (n=3).

Pharmacokinetics

- PK results (Table 2) from weight bands **10-<14kg** and **14-<20kg** were **similar to** PK data from children receiving same DT doses in **IMPAACT1093** and GM C_{trough} values were **similar to** children 20-<40kg in ODYSSEY on DTG FCT 50mg and **adults** on 50mg DTG FCT QD (0.83 mg/L).
- Our data from the **6-<10kg** weightband showed **lower GM exposure** to DTG compared to IMPAACT1093 with **high variability** and 3 of 8 children had observed C_{trough} below EC_{90} (0.32mg/L).

Table 2. Patient demographics and main PK parameters for DTG in the ODYSSEY PK substudy and published reference PK parameters in adults [2,3].

WHO weightband	ODYSSEY PK substudy			Reference adults [2,3]	
	6-<10kg	10-<14kg	14-<20kg	≥ 40kg	≥ 40kg
DTG dose (N)	15mg DT QD (11)	20mg DT QD (10)	25mg DT QD (13)	50mg FCT QD (10 ^a)	50mg FCT BID (24 ^b)
Sex male	3 (27%)	3 (30%)	7 (54%)	-	-
Age (years)	1.4 (0.6-3.0)	2.4 (1.6-4.2)	6.0(4.9-8.5)	-	-
Weight (kg)	8.4 (6.7-9.7)	11.2 (10.0-12.6)	18.0 (14.9-19.9)	-	-
Dose (mg/kg)	1.8 (1.5-2.2)	1.8 (1.6-2.0)	1.4 (1.3-1.7)	-	-
C_{trough} (mg/L)	0.48 (167)	0.82 (55)	0.85 (67)	0.83 (26) ^a	2.72 (70) ^b
AUC_{0-24h} (mg*h/L)	49.3 (77)	77.0 (22)	69.5 (30)	43.4 (20) ^a	93.4 (50) ^b
C_{max} (mg/L)	5.4 (50)	8.0 (22)	7.1 (21)	3.3 (16) ^a	5.4 (40) ^b

Pharmacokinetic parameters are expressed as geometric mean with coefficient of variation (%) median (range) for age, weight and dose/weight. FCT, film-coated tablet; DT, dispersible tablet; BID, twice daily; QD, once daily. ^aFasted HIV-positive adults. ^bFasted healthy HIV-negative adults. ^cHIV-positive treatment experienced adults, fed state not specified.

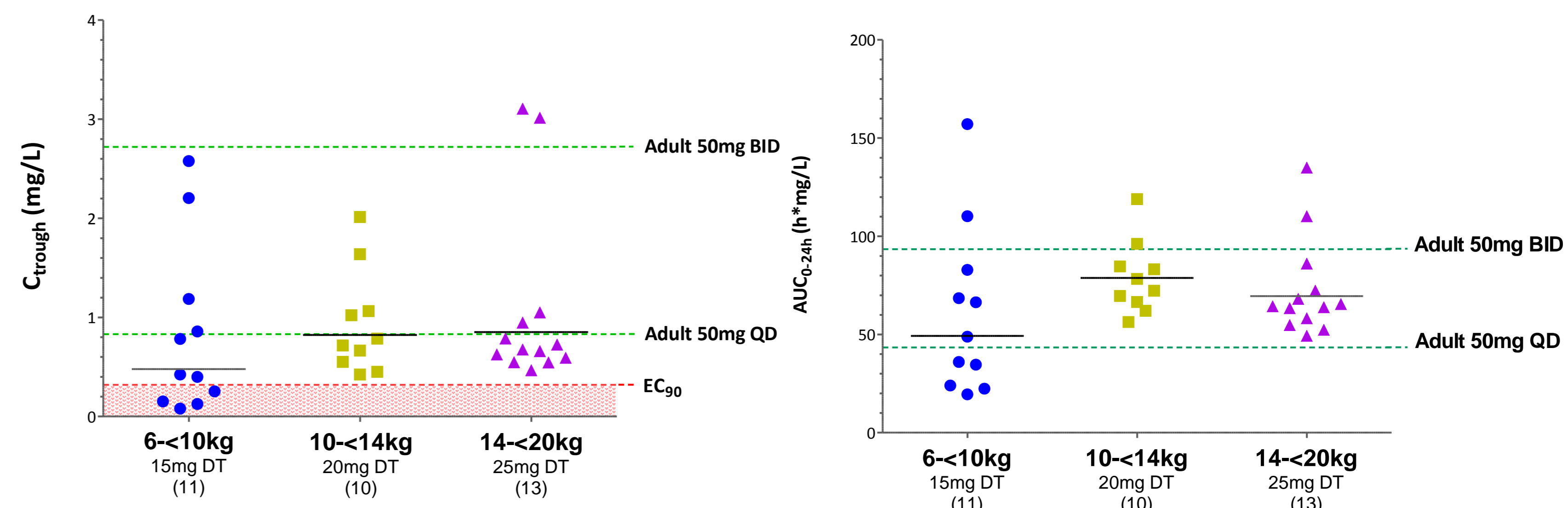


Figure 1. Individual C_{trough} and AUC_{0-24h} at PK day of each weight band. Black horizontal lines indicate geometric mean. Dashed lines indicate reference geometric mean value for dolutegravir film-coated tablets in adults and the EC_{90} . [2,3]

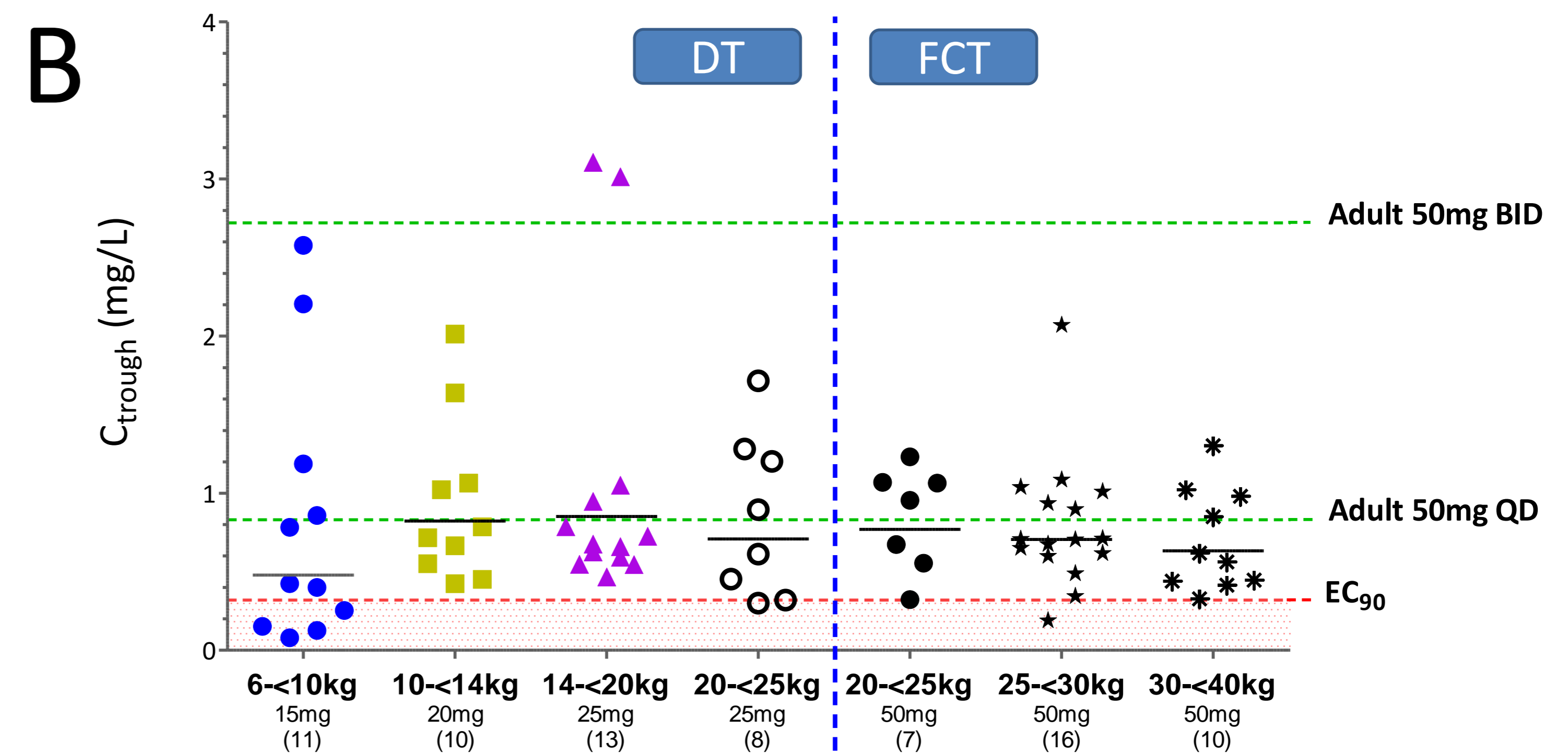
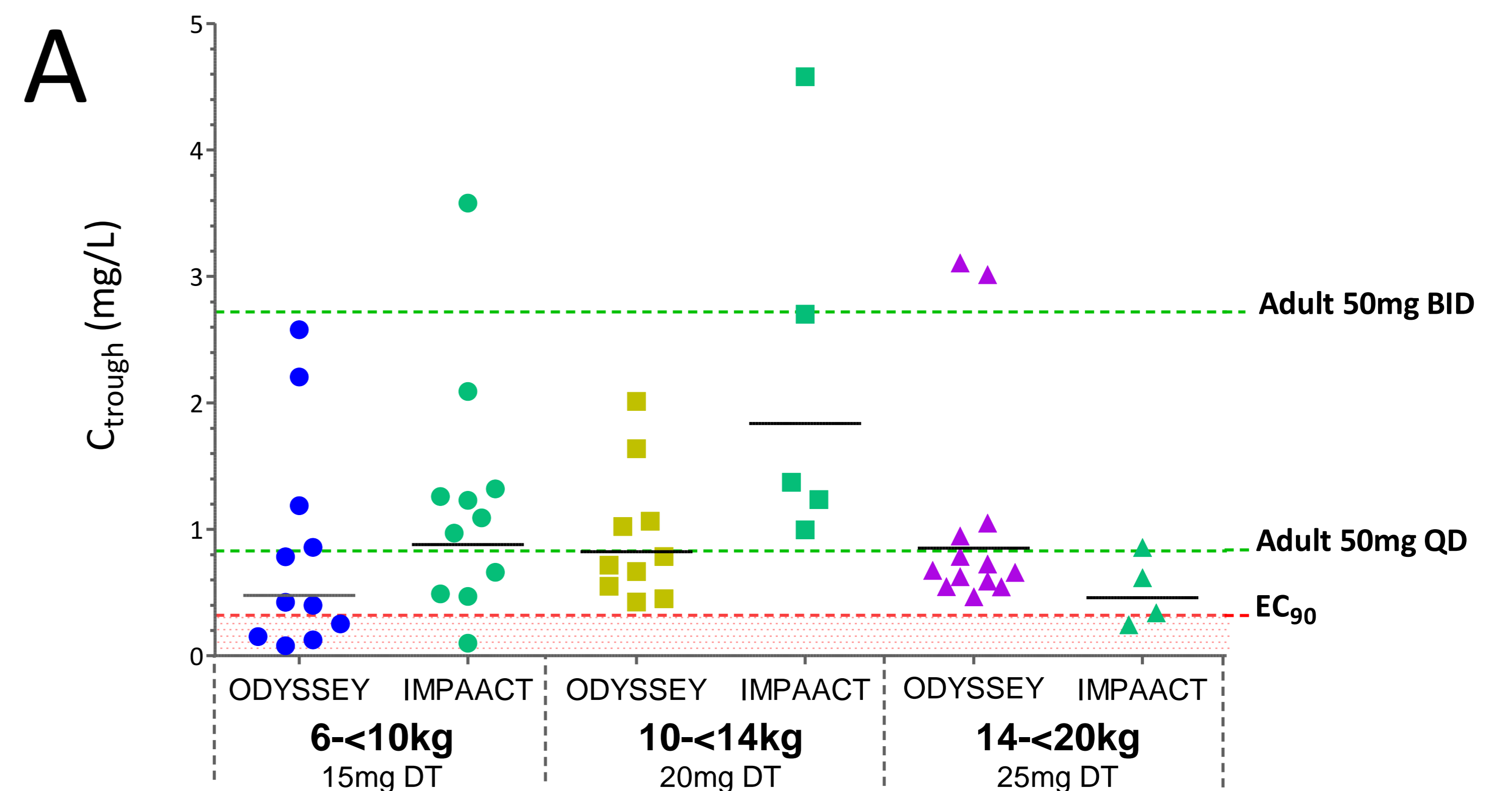


Figure 2.A Individual C_{trough} Odysseey compared to IMPAACT 1093. 2.B Individual C_{trough} of all weight bands currently studied within Odysseey. Black horizontal lines indicate geometric mean. Dashed lines indicate reference geometric mean value for dolutegravir FCT in adults and the EC_{90} . [2,3]

Conclusions

- DTG DT in children weighing 10-<20kg, dosed QD in WHO weight bands achieves similar C_{trough} to adults and older children on the adult DTG dose and young children on DT in IMPAACT1093.**
- This data will be submitted along with IMPAACT data to EMA and FDA**
- Some children in the 6-<10kg weight band had C_{trough} levels below EC_{90} , and PK profiles showed high variability in this weight band. Further PK data collection in children 3-<10kg are ongoing and all children are being followed up for safety.**

References

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