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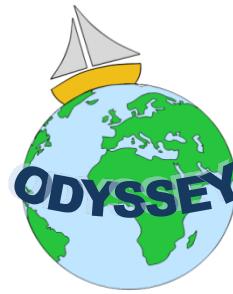


10TH IAS CONFERENCE ON HIV SCIENCE
Mexico City, Mexico  21-24 July 2019



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Pharmacokinetics of dolutegravir 5mg dispersible tablets in children weighing 6 to <20kg dosed using WHO weight bands

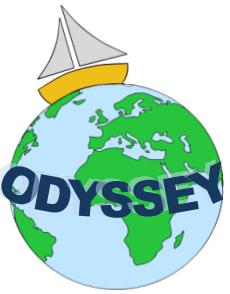
H. Waalewijn, P.D.J. Bollen, C. Moore, A. Kekitiinwa, P. Amuge, H. Mujuru, E. Chidziva, V. Musiime, E. Kaudha, A. Lugemwa, S. Makumbi, A. Violari, E. Variava, S. Ali, C. Giaquinto, P. Rojo, A. Colbers, D.M. Gibb, D. Ford, A. Turkova, D. Burger, and the ODYSSEY trial team



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Disclosures



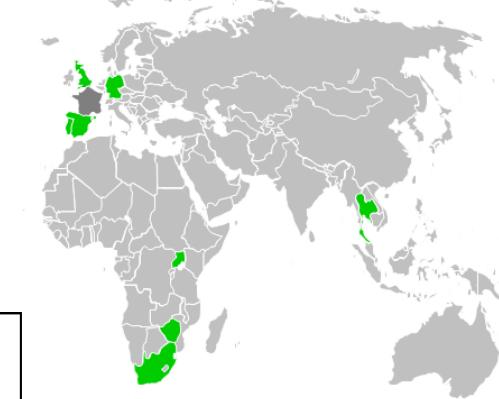
- The trial is sponsored by Penta Foundation
- ViiV Healthcare funded the main trial and PK substudies
- The funder had no direct role in the study design, data collection, analysis, interpretation, or the decision to submit for this conference



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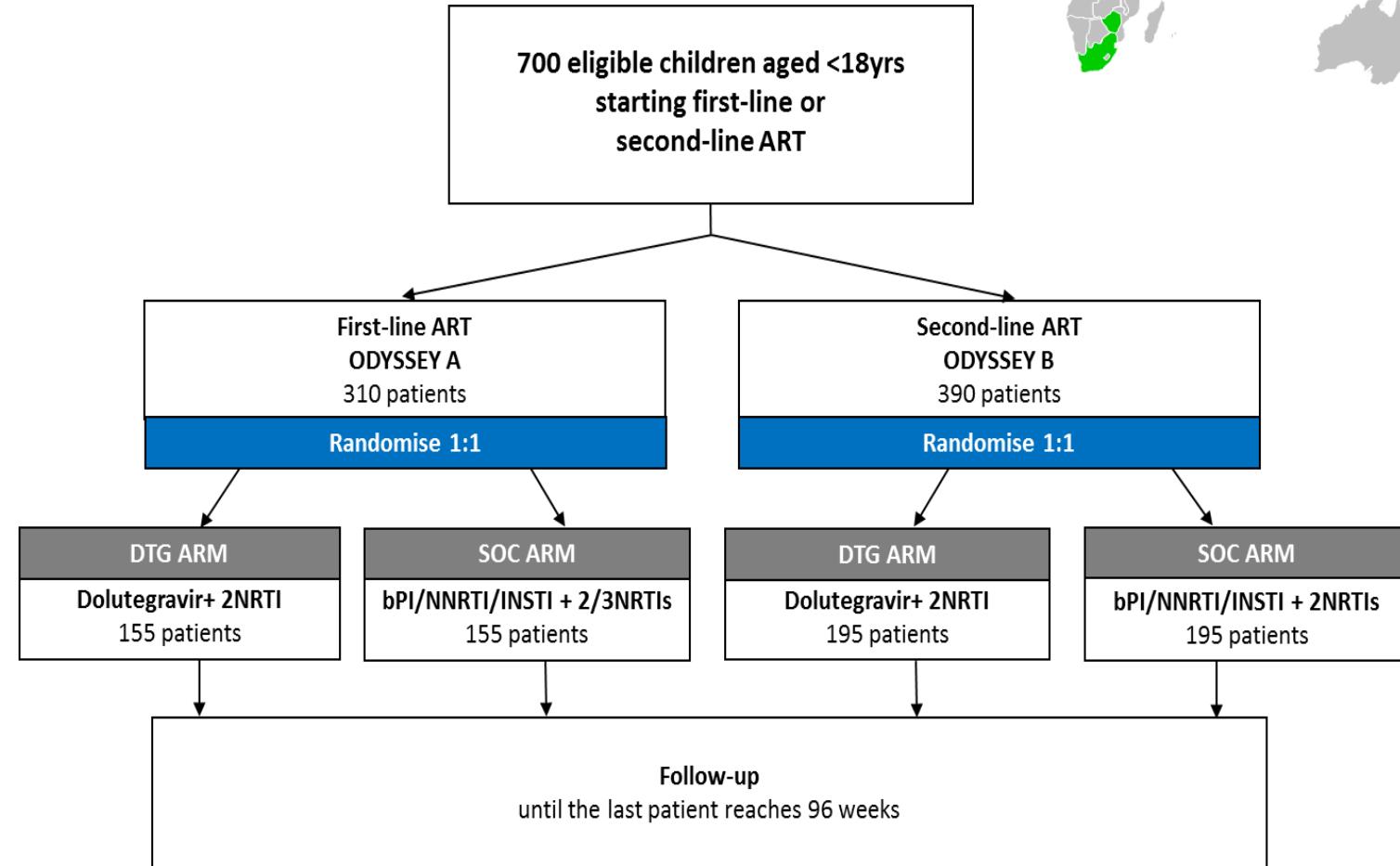


Background



ODYSSEY is a randomised, non-inferiority trial evaluating efficacy and safety of 1st and 2nd line dolutegravir-based ART vs standard of care in HIV-infected children <18 years

- **700 children $\geq 14\text{kg}$**
- **Additional 80 children $<14\text{kg}$ (recruitment ongoing)**



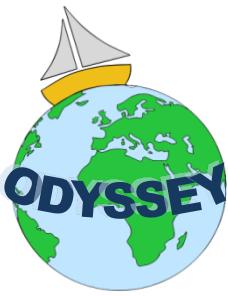
Dosing table

WHO Weight bands, kg	DTG DT* once daily number of tablets and daily dose, mg
3 to <6 (<6 months old)**	1 (5mg)
3 to <6 (>6 months old)**	2 (10mg)
6 to <10	3 (15mg)
10 to <14	4 (20mg)
14 to <20	5 (25mg)
20 to <25**	6 (30mg)

*Dolutegravir dispersible tablet (DT) formulation; DT are ~1.6 to 2.0x more bioavailable than film coated tablets (FCT)

**Not part of this presentation; 20 to <25kg data presented at CROI 2019 by Bollen et al.





PK reference values

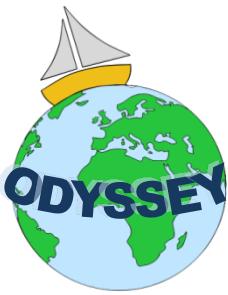
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Individual levels above EC₉₀ (0.32 mg/L) and/or IC₉₀ (0.06 mg/L)
- C_{max} : Compared to adult data on 50mg BID
- AUC: Compared to adult data on QD and BID

Adult reference values			
		Min et al. AIDS 2011	VIKING-3*
Weight band		≥ 40kg	≥ 40kg
Dose	Mg	50 FCT QD	50 FCT BID
N		10	24
C_{trough} (CV%)	mg/L	0.83 (26)	2.72 (70)
AUC _{0-24h} (CV%)	mg*h/L	43.4 (20)	93.4 (50)
C_{max} (CV%)	mg/L	3.34 (16)	5.41 (40)

* ViiV data available on Clinicaltrials.gov
id: NCT00950859



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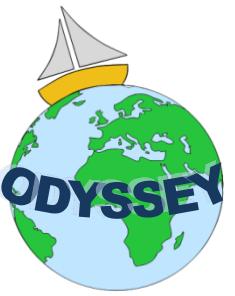
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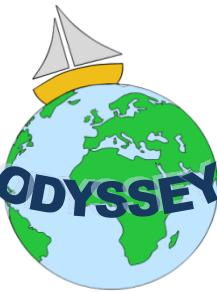
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Methods



- Steady-state 24h PK curves were constructed after DTG DT given for ≥ 7 days
- Taking DTG with food increases absorption

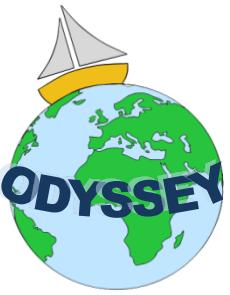
Fasting <10kg	Fasting $\geq 10kg$
2-hr fast pre- and 1-hr post dose preferred but not obligatory*	Overnight fast (preferred) or minimum 3 hrs fasted pre-dose
*All but one child was able to fast successfully	

- Quantification method: Liquid Chromatography-Mass spectrometry
- PK analysis: Non-compartmental analysis (WinNonLin)
- PK-sampling: Samples taken at $t=0$ (prior to DTG dose), $t= 1, 2, 3, 4, 6$ and 24h





Results



- 41 black-African children from Uganda, Zimbabwe and South Africa
 - Uganda: JCRC Lubowa, JCRC Mbarara, Baylor
 - Zimbabwe: UZCRC
 - South Africa: Soweto, Klerksdorp-Tshepong Hospital Complex
- **34** children had evaluable PK curves
- 7 were not evaluable due to non-adherence (3), incorrect dose (1), not fasted (1), previous dose not taken within dosing window (1), prohibited comedication (1)

Weight band	N	Median (IQR) age (y)	Median (IQR) weight (kg)	n/N (%) male
6-<10kg	11	1.4 (0.9-2.0)	8.4 (7.0-9.0)	3/11 (27%)
10-<14kg	10	2.4 (2.0-3.3)	11.2 (10.3-12.0)	3/10 (30%)
14-<20kg	13	6.0 (5.2-6.8)	18.0 (15.9-18.5)	7/13 (54%)
Total	34	3.1 (2.0-5.6)	11.5 (9.0-17.0)	13/34 (38%)



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Results

		ODYSSEY Weight Bands			Reference adults	
WHO weight band		6-<10	10-<14	14-<20	≥ 40kg	≥ 40kg
Dose	(mg) and formulation	15 DT	20 DT	25 DT	50 FCT QD*	50 FCT BID**
N		11	10	13	10 ^a	24 ^b
Dose/weight (range)	mg/kg	1.8 (1.5-2.2)	1.8 (1.6-2.0)	1.4 (1.3-1.7)	-	-
C _{trough} (CV%)	mg/L	0.48 (167)	0.82 (55)	0.85 (67)	0.83 (26) ^a	2.72 (70) ^b
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*Min et al. AIDS 2011

** ViiV data available on Clinicaltrials.gov
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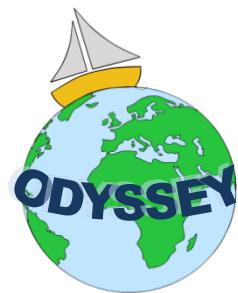
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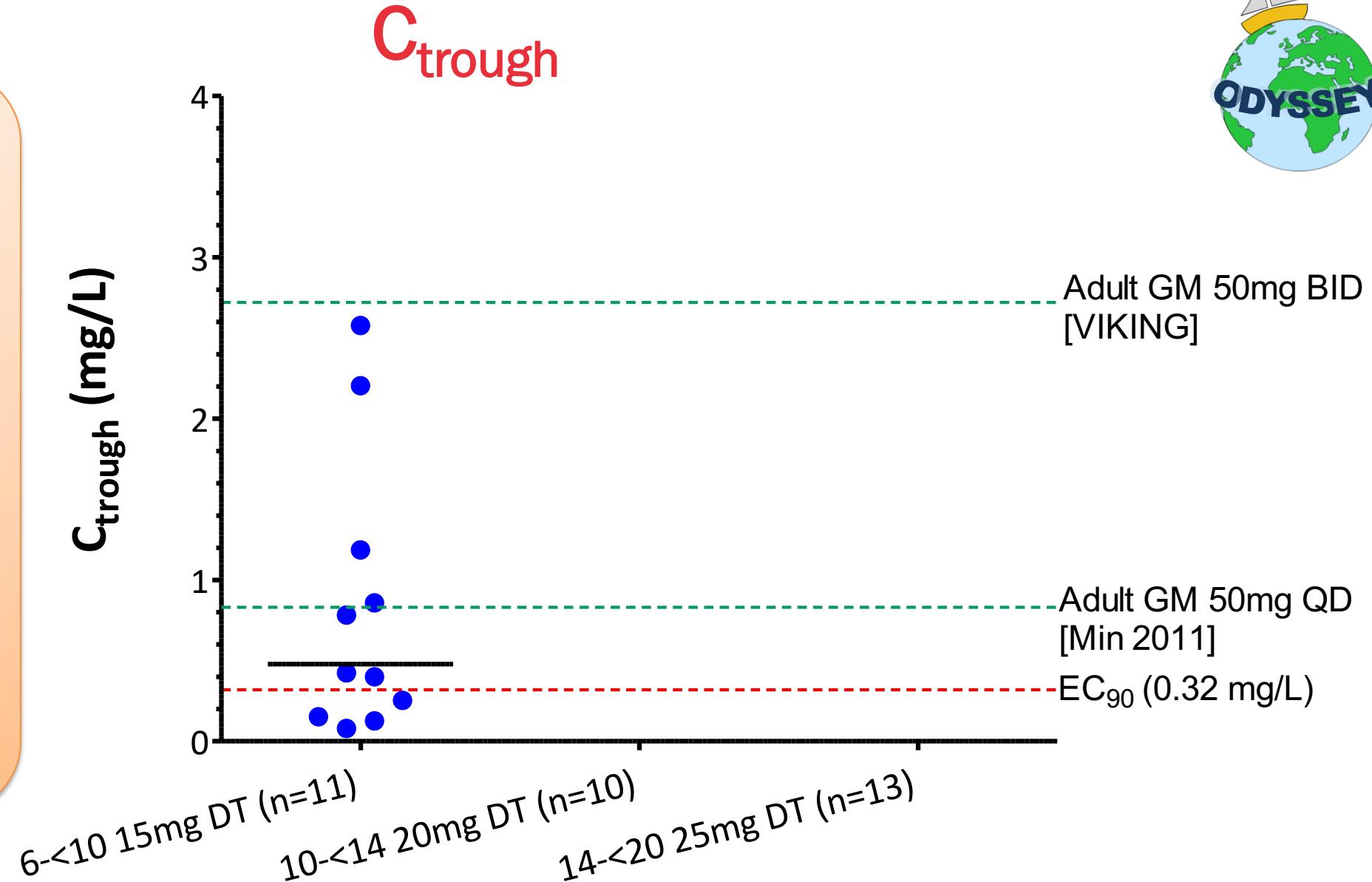
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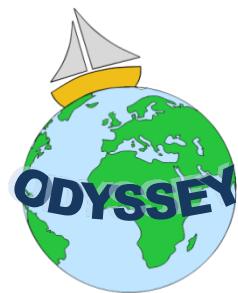


C_{trough} 6 to <10kg

4/11 (36%) had C_{trough} values below EC₉₀ (0.32 mg/L)

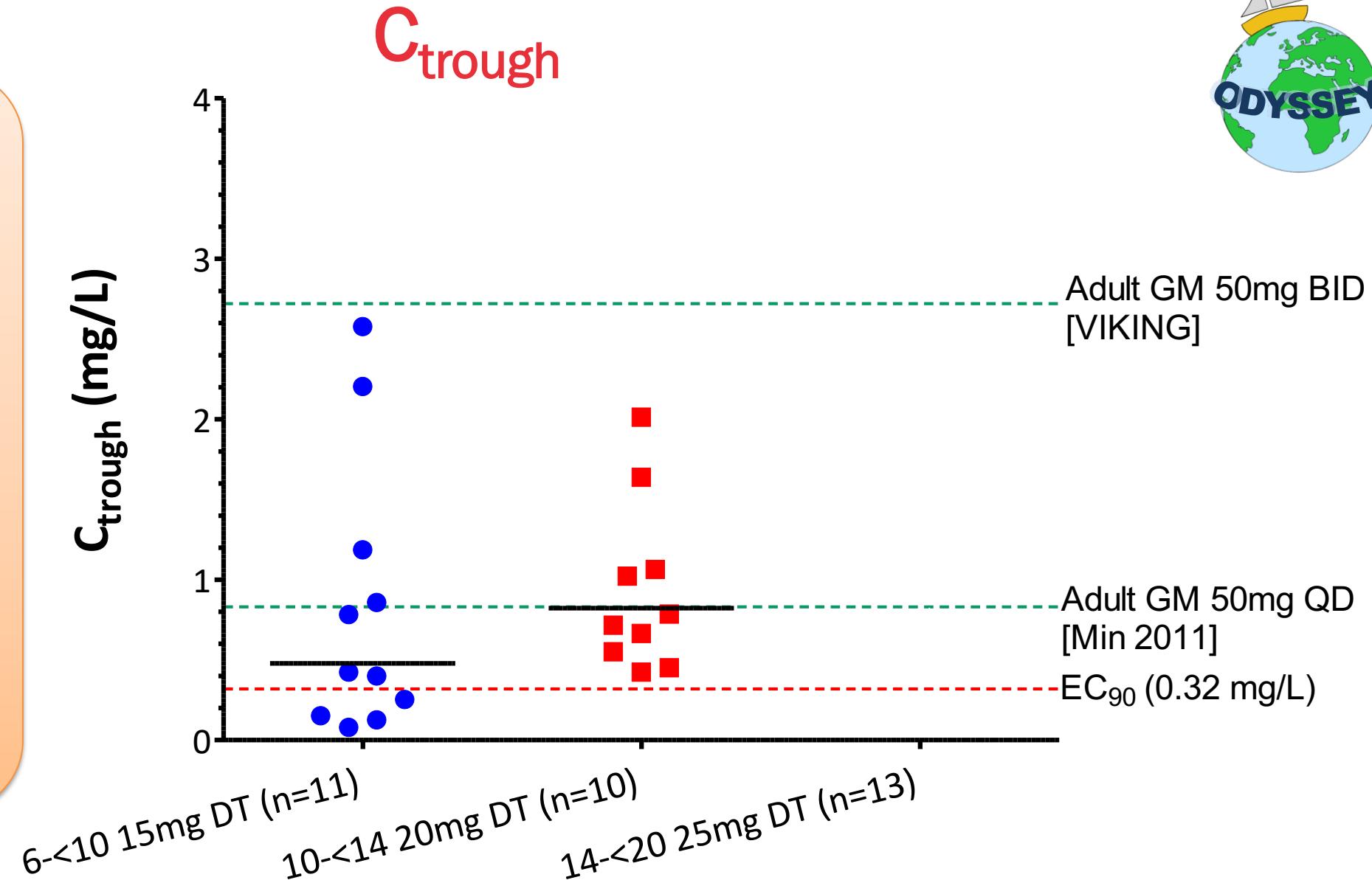
All C_{trough} values remained above IC₉₀ (0.06 mg/L)





C_{trough} 10 to <14kg

Geometric Mean
 C_{trough} similar to adults

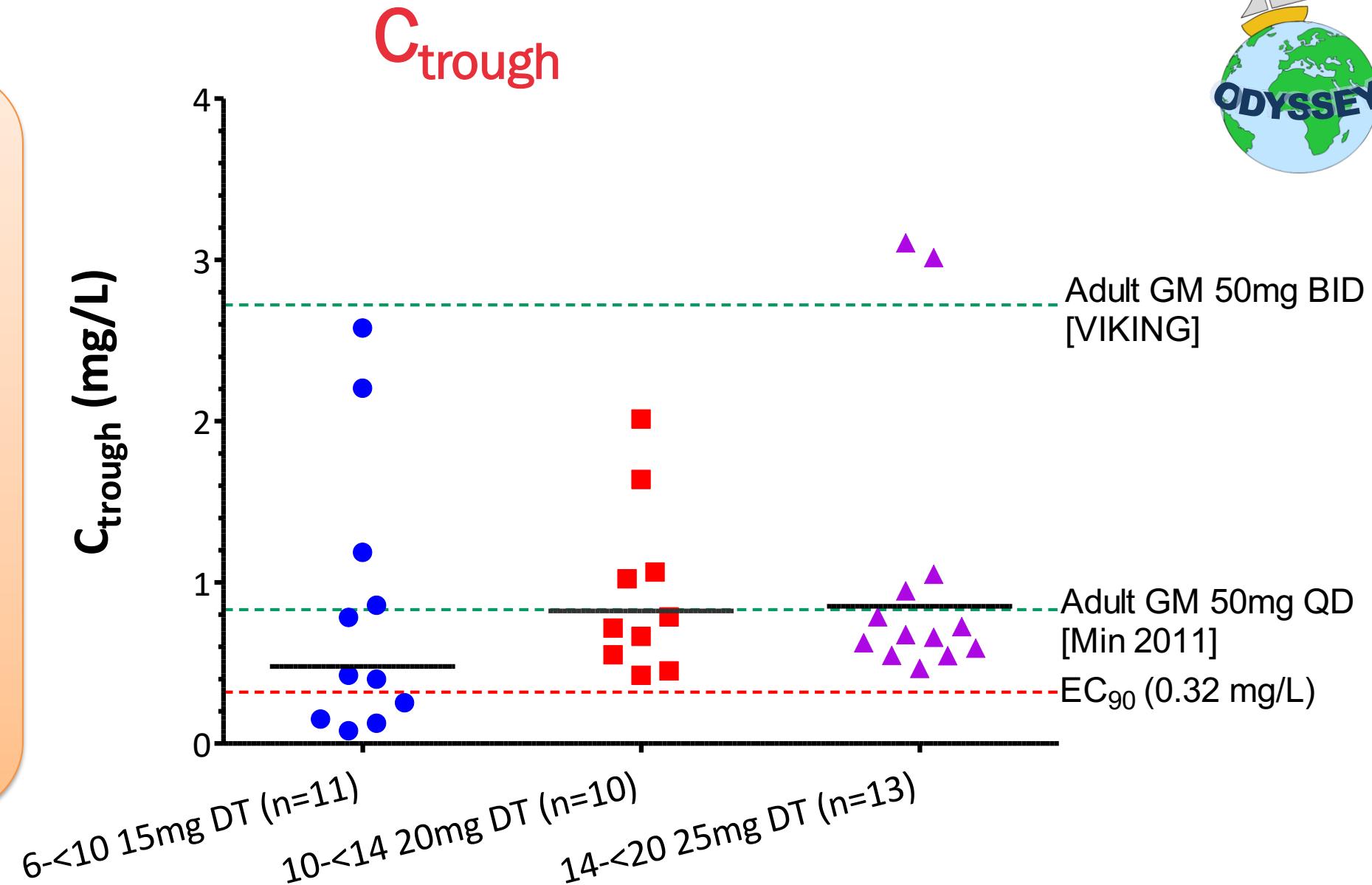


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C_{trough} 14 to <20kg

Geometric Mean
 C_{trough} similar to adults



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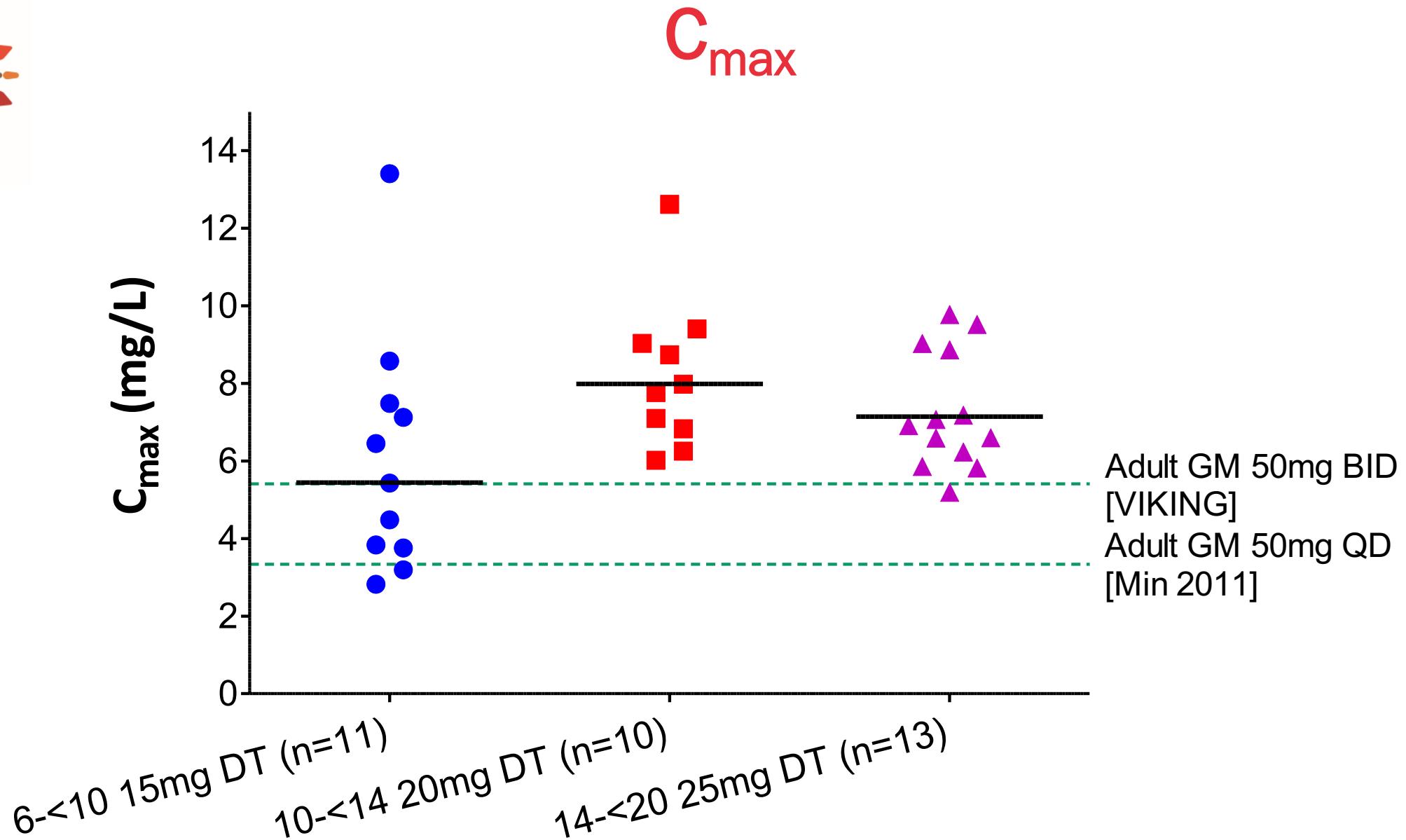
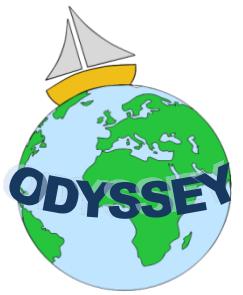
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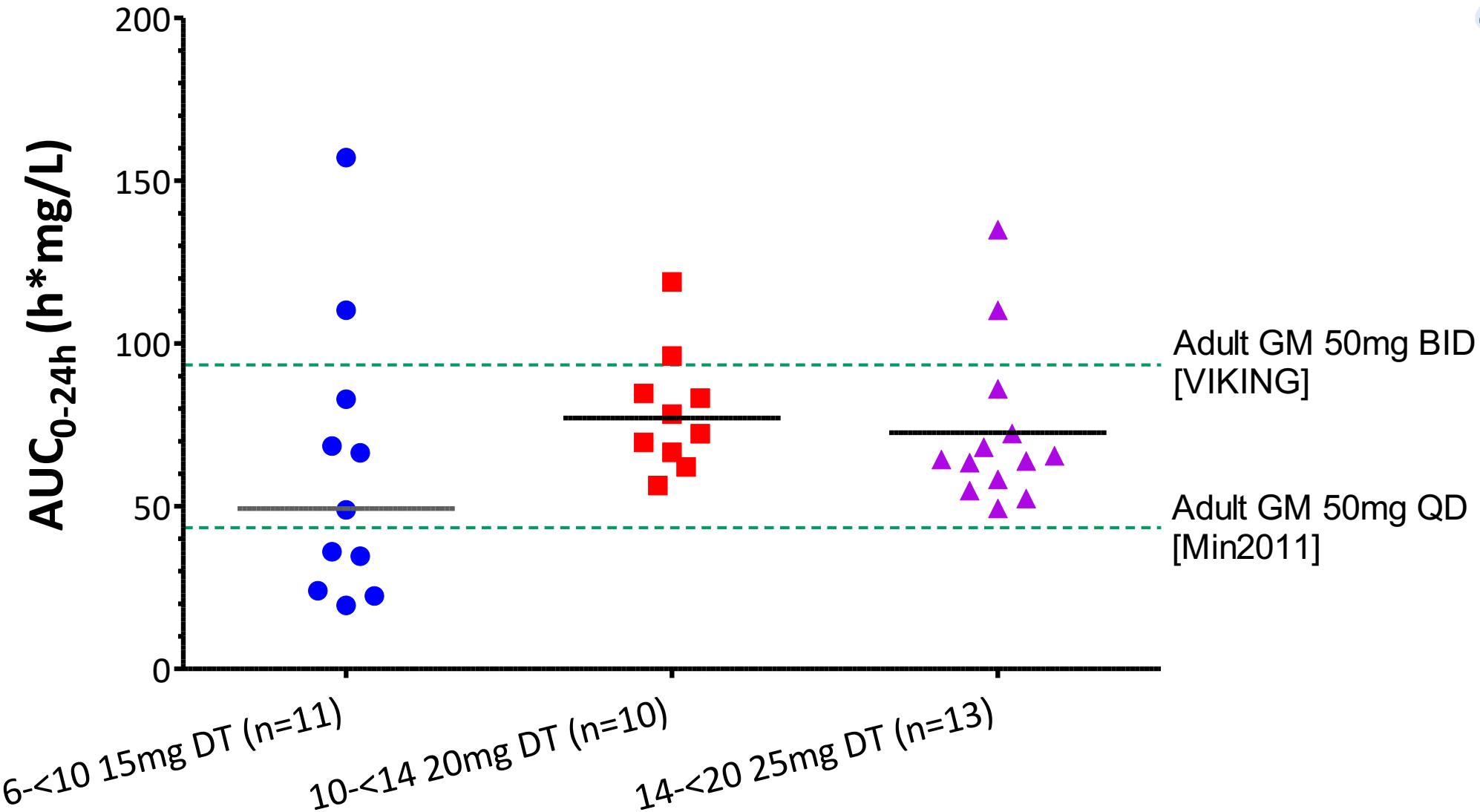
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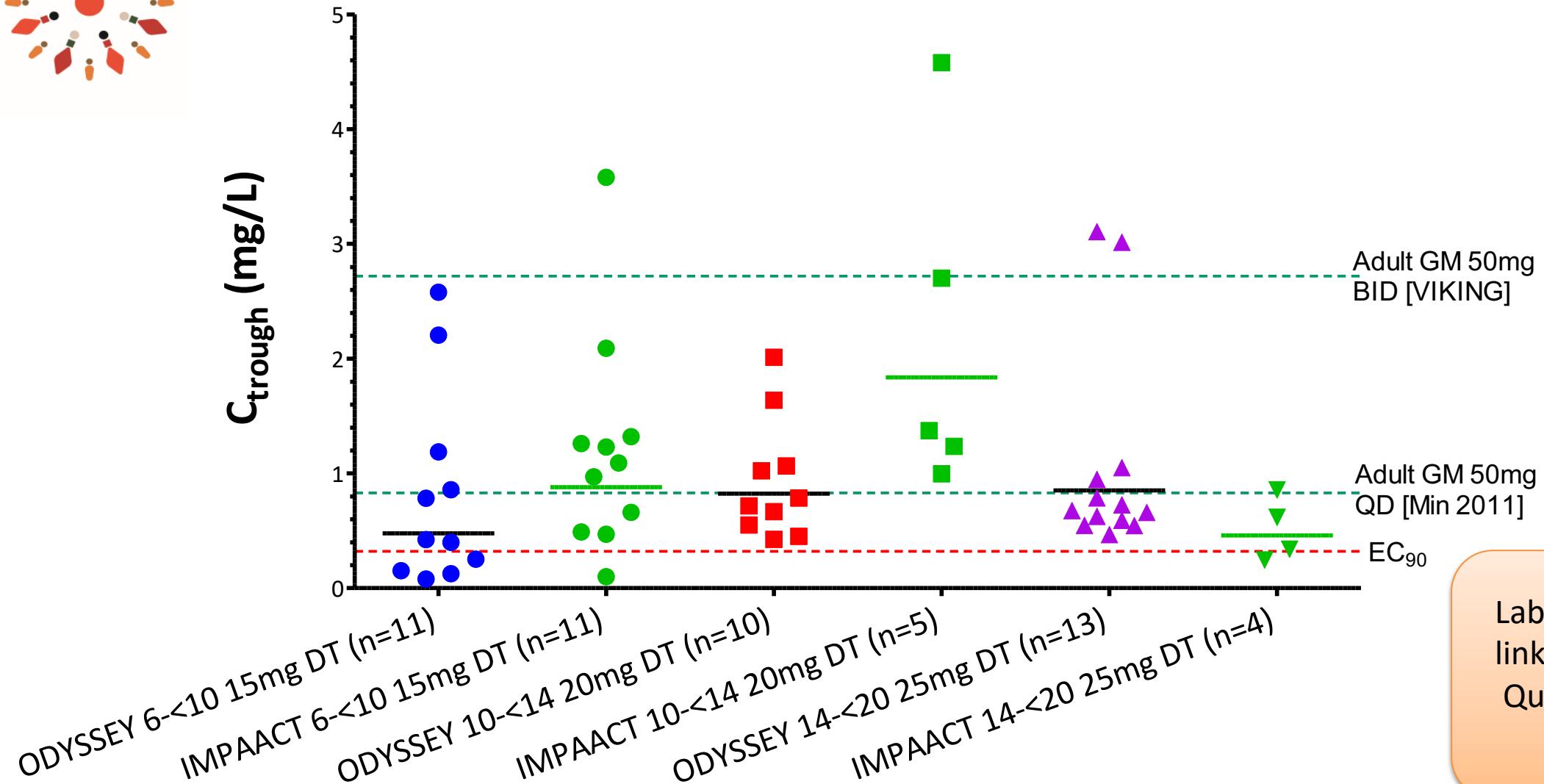
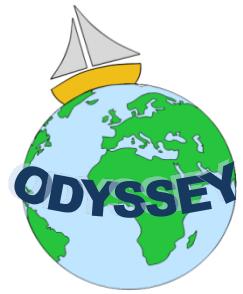
AUC between adult QD and BID values



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ODYSSEY and IMPAACT P1093



Laboratories are linked through a Quality Control program



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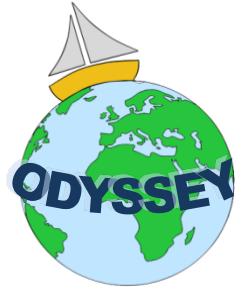
Discussion and conclusion



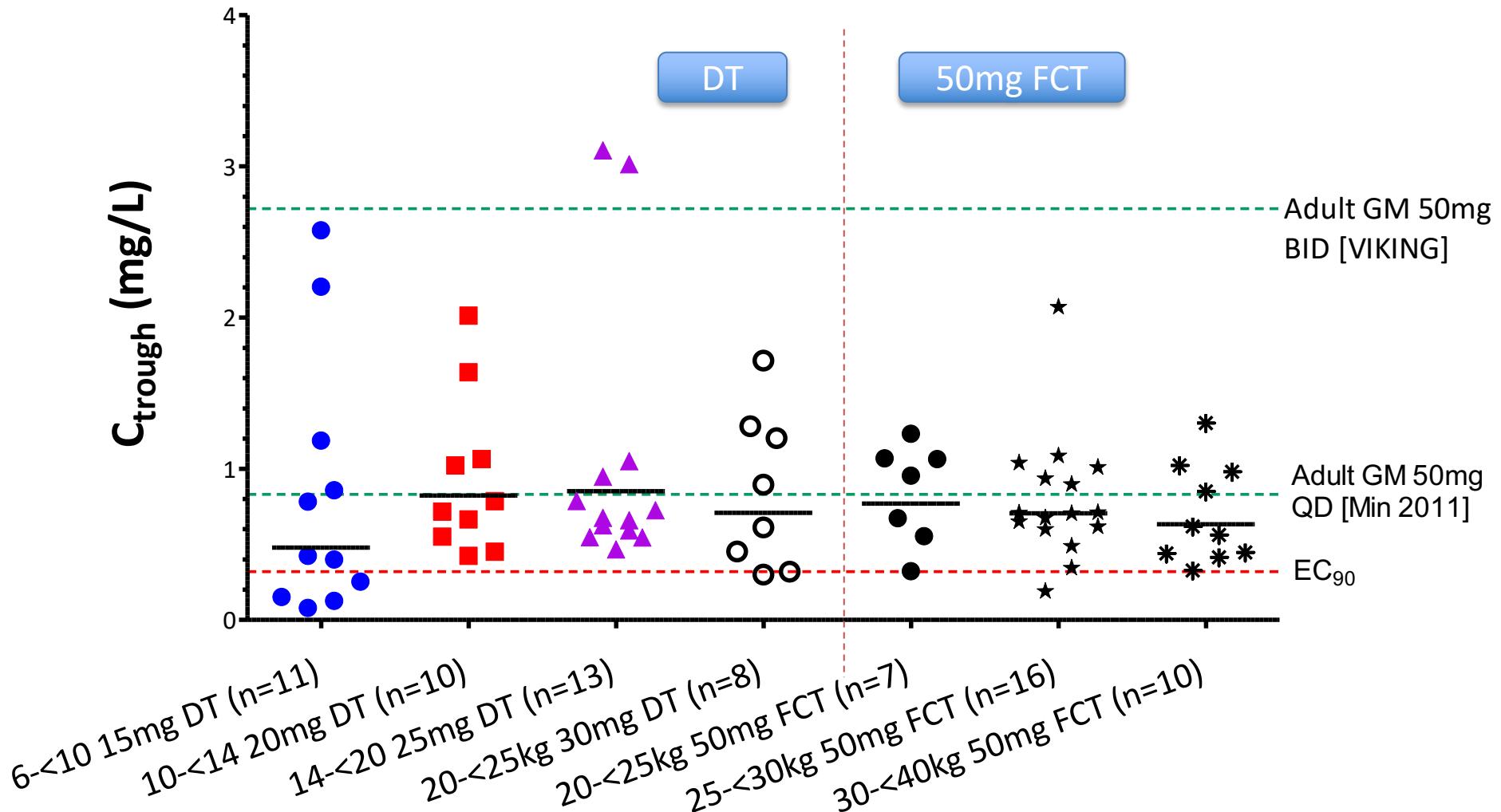
- DTG DT in children weighing **10-<14kg & 14 -<20kg**, dosed QD in WHO WBs achieves similar C_{trough} to adults
- Children in the **6-<10kg** WB had lower GM C_{trough}, more frequent C_{trough} levels below EC90 and PK profiles showed **high variability**
- High variability was seen in both ODYSSEY and IMPAACTp1093, especially in children <14kg
- Further PK data collection in children 3-<6kg is ongoing
- All children in ODYSSEY are being followed for **safety** and **efficacy**
- ODYSSEY and IMPAACT p1093 PK data will be included in **submission** to FDA and EMA
- ODYSSEY PK data show that 2 DTG formulations with simplified weight band dosing can be used **across the pediatric age range**



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ODYSSEY PK overview



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Acknowledgements

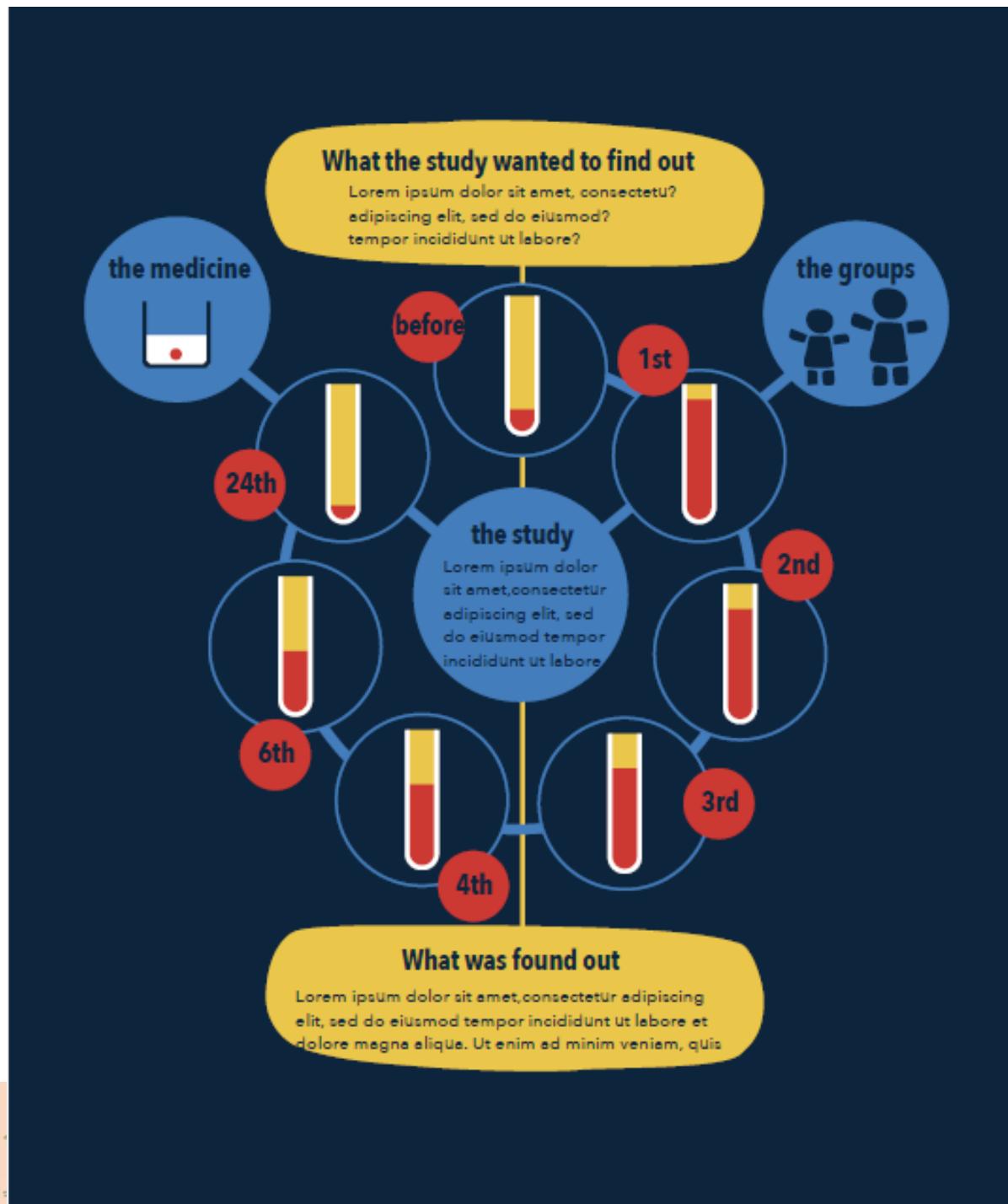


- ODYSSEY PK participants
- ODYSSEY PK sites and investigators
- Radboud University Medical Center, Nijmegen
- Trial Management Team
- Trial Steering Committee
- IDMC
- PENTA management team
- ViiV, Mylan
- IMPAACT P1093 investigators and ViiV PK experts
- Presenter received a scholarship from IAS to attend this event



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<http://odysseytrial.org/>



Backup slides



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Short term safety

- Follow up is still only short term and toxicity and efficacy monitoring is continuing.
- So far only serious adverse events have been looked at, not adverse events.
- 4 serious adverse events have been reported and are all hospitalisations with various infections.
- All look unrelated to DTG and DTG has continued in all. 2/4 have been reviewed by the endpoint review committee blind to arm.



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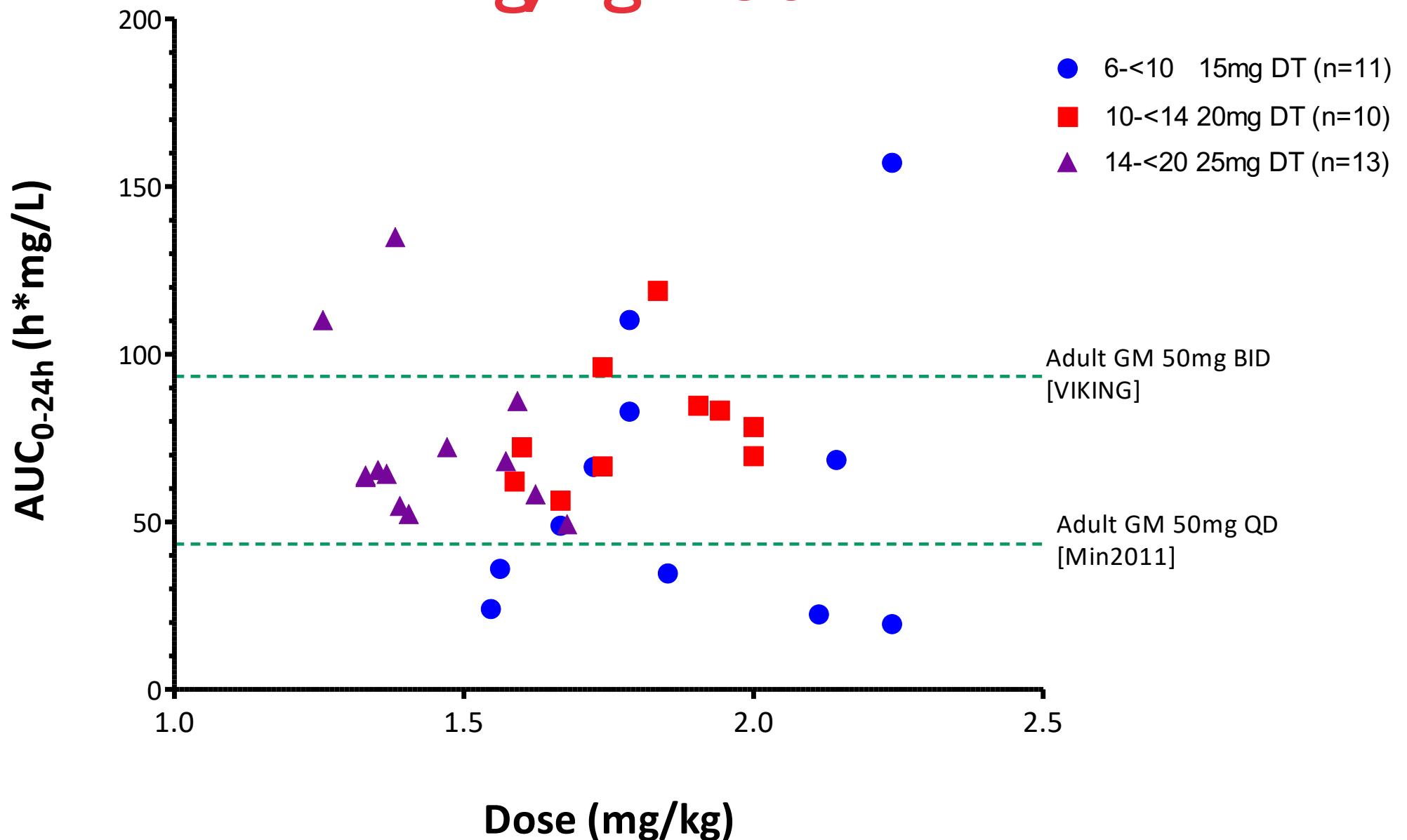
Methods

- Informed consent was obtained for all children
- **Inclusion criteria:**
 - <18 years on the PK visit
 - Randomised to DTG-group in ODYSSEY A or B
 - Weighing 6 to <20kg
- **Exclusion criteria:**
 - Illnesses that could influence PK, i.e. severe diarrhoea, vomiting, renal disease or liver disease
 - Concomitant medication known to have interactions with DTG
 - Severe malnutrition WHO Z score lower than -2
- **PK samples were considered not evaluable for PK analysis if:**
 - >1 PK sample was haemolytic
 - >1 PK samples were missing
 - Adherence was questionable based on PK results (e.g. low pre-dose plasma concentration (C_{0h}) compared with C_{trough})

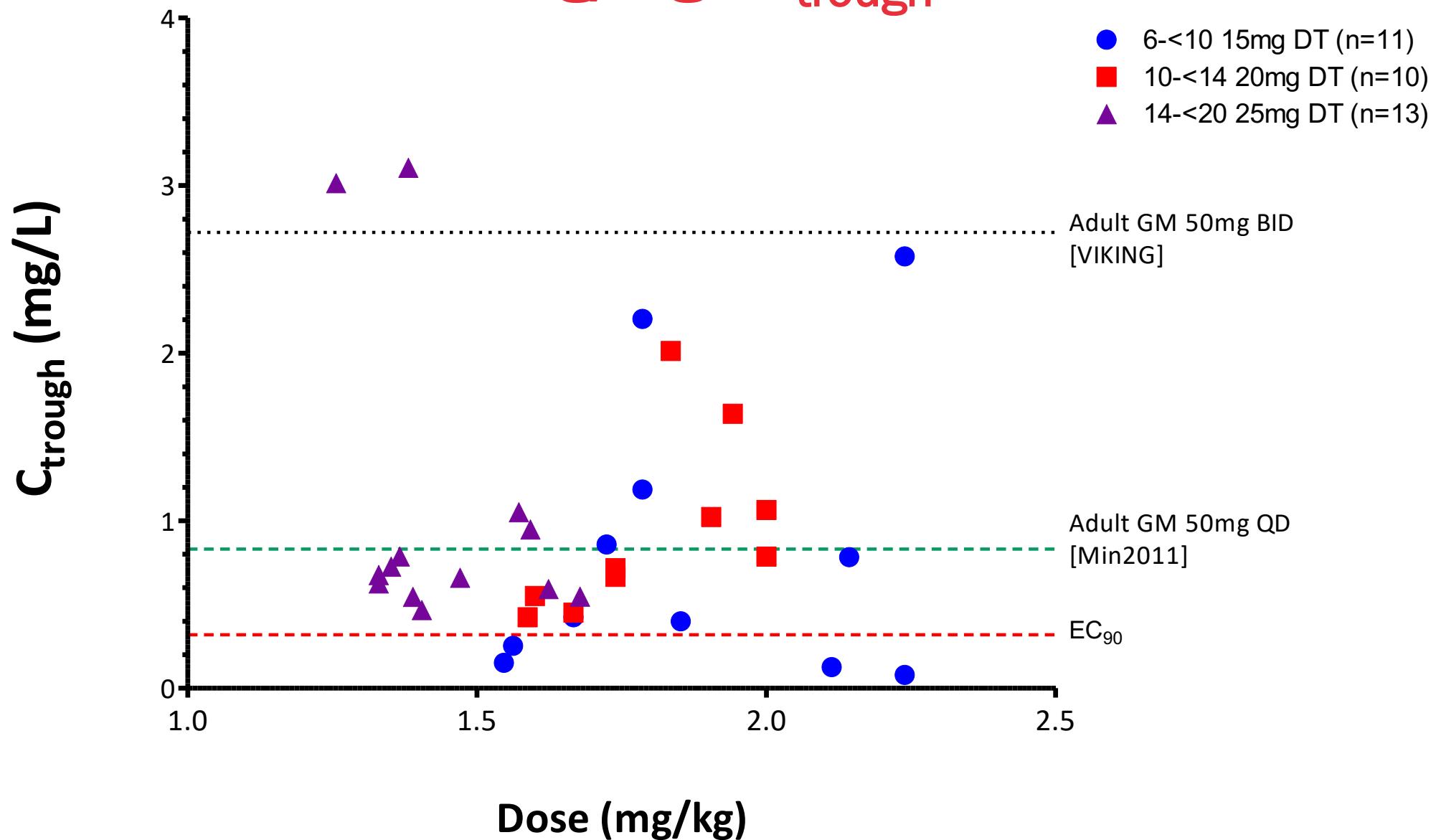


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Mg/kg~AUC



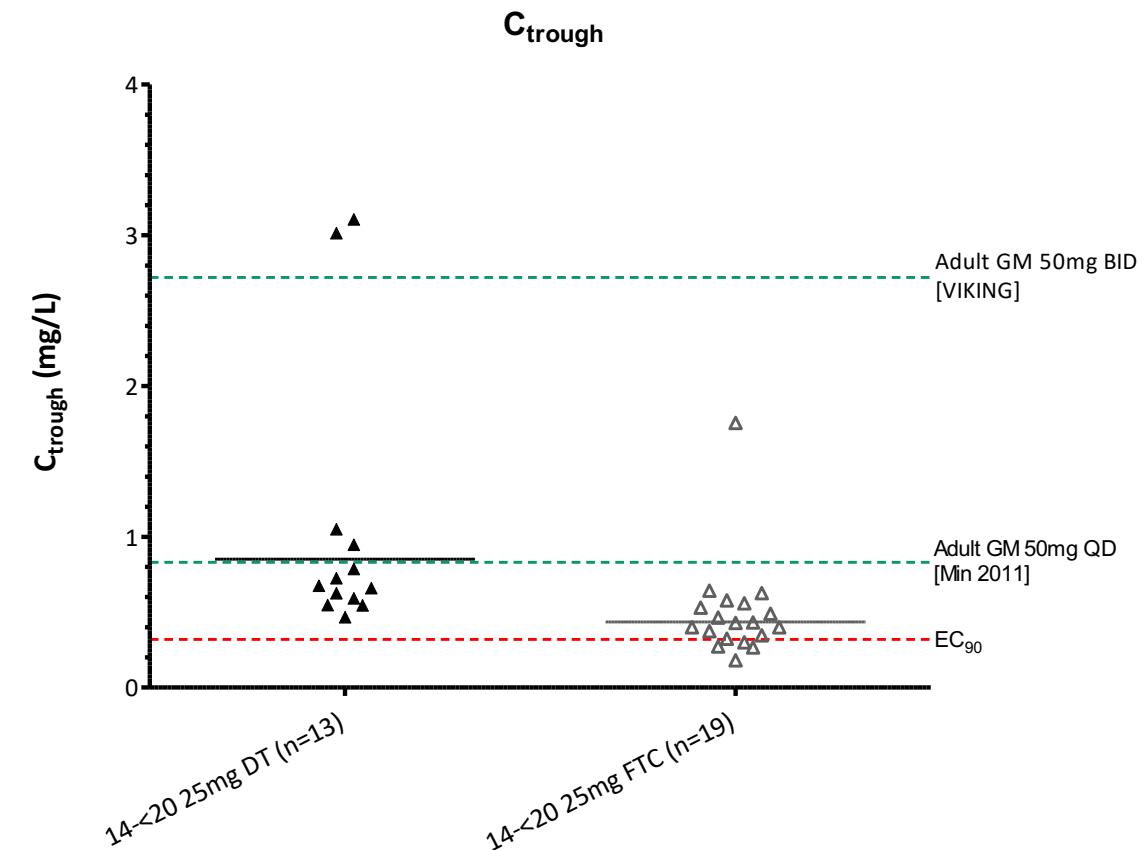
Mg/kg~C_{trough}



FCT vs DT

- DT is about 1.6 – 2.0 times more bioavailable than FCT

WHO weight band	14-<20kg	14-<20kg
Dose (mg) and formulation	25 FCT	25 DT
N	19	13
Dose/weight (mg/kg)	1.5 (1.3-1.8)	1.4 (1.3-1.7)
C _{trough} (mg/L)	0.43 (50)	0.85 (67)
AUC _{0-24h} (mg*h/L)	39.57 (32)	69.5 (30)
C _{max} (mg/L)	4.03 (31)	7.1 (21)
Pharmacokinetic parameters are expressed as geometric mean with coefficient of variation (%), median (IQR) for age and mean (range) for dose/weight. Doses represent once daily doses, unless otherwise specified. FCT, film-coated tablet; DT, dispersible tablet. ^a Fasted HIV-positive adults. ^b Fasted healthy HIV-negative adults. ^c HIV-positive treatment experienced adults, fed state not specified.		



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