

# Steady-state pharmacokinetics and early safety data in HIV-infected African children weighing $\geq 25\text{kg}$ after switching to 50mg film-coated dolutegravir tablets in the ODYSSEY trial



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10th International Workshop on HIV Pediatrics, Amsterdam, 20-21<sup>st</sup> July 2018



# Disclaimer



- 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 workshop



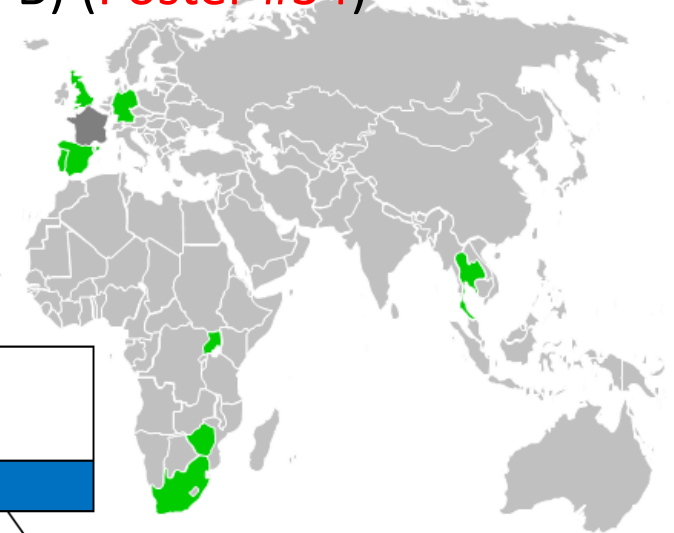
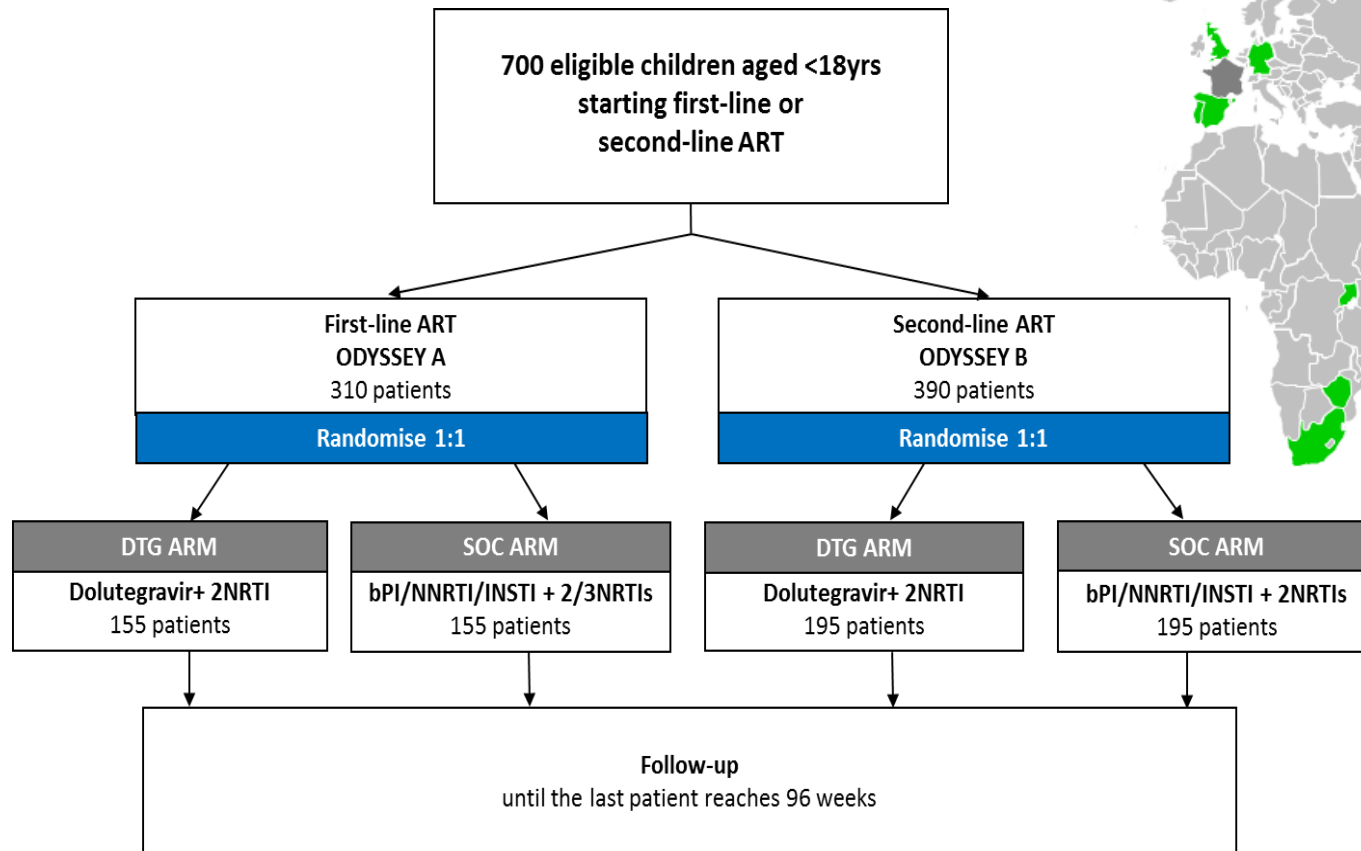
**10th International Workshop on HIV Pediatrics,  
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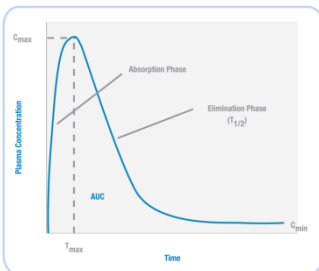


# Background



- ODYSSEY is an open-label, randomised, non-inferiority trial evaluating the efficacy and safety of DTG-based ART in 700 HIV-infected children <18 years starting first-line ART (ODYSSEY A) or switching to second-line ART (ODYSSEY B) (**Poster #34**)





# ODYSSEY PK substudies



## WB-PK1 ONGOING

Pharmacokinetics of dolutegravir in children in WHO weight bands 3-<25kg

3-<14kg (Lower WB-PK): dispersible DTG formulations

14-<25kg (part I): film-coated DTG formulations (**Poster #22**)

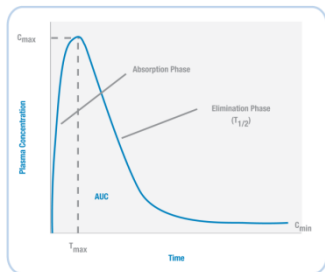
14-<25kg (part II): dispersible and film-coated DTG (increased dose)

## WB-PK2 COMPLETED

**A crossover pharmacokinetics substudy of dolutegravir in children weighing 25-<40kg with dose change to adult dose DTG 50mg QD (film-coated tablet)**

## TB-PK substudy ONGOING

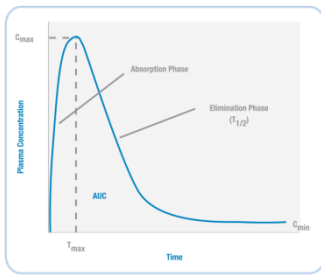
Pharmacokinetics of dolutegravir co-administered with rifampicin in HIV/TB co-infected children



## WB-PK 2: Crossover PK substudy of DTG in children 25 to <40kg



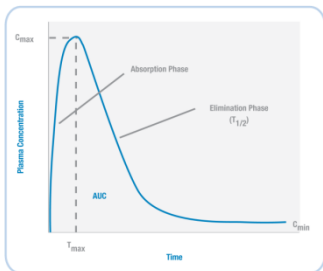
- Children were switched from current FDA and EMA-approved DTG doses to DTG 50mg QD (adult dose) in order **to simplify DTG administration for patients and programmes**
- The study provides within-patient comparative PK and safety data
- We aimed to achieve PK parameters **comparable to adult data** ( $C_{\text{trough}}$  not lower than adult  $C_{\text{trough}}$  on QD DTG under fasted conditions and  $AUC_{0-24h}$  and  $C_{\text{max}}$  not exceeding adult references on BID DTG)



# Methods



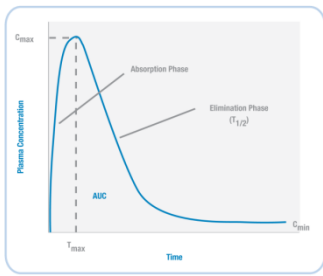
- Informed consent was obtained for all children
- **Inclusion criteria:**
  - Receiving DTG
  - <18 years on both PK visit(s)
  - Weight 25-<40kg and remaining in the same weight band through both PK days
- **Exclusion criteria:**
  - Illnesses that could influence PK results
  - Concomitant medications known to have interactions with DTG
  - Severe malnutrition
- **PK samples were considered not evaluable for PK analysis if:**
  - >1 PK sample was haemolytic or missing
  - Adherence was questionable based on PK results



# Methods



- Children had received studied DTG dose for  $\geq 7$  days to achieve steady-state
- They were fasted overnight (min for  $\geq 3$  hours) prior to PK days
- PK samples (t=0, 1, 2, 3, 4, 6 and 24h) were taken on the initial doses and after the switch to film-coated DTG 50mg:
  - PK day 1: DTG 25mg in **weight band 25-<30kg**  
DTG 35mg (10mg+25mg tablets) in **weight band 30-<40kg**
  - PK day 2: DTG 50mg
- Dolutegravir plasma concentrations were measured using a validated UPLC-MS/MS method
- Non-compartmental PK analysis was performed to calculate PK parameters with WinNonlin 6.3 software
- Laboratory and clinical safety were evaluated after switch to the 50mg dose at 2, 4 and 12 weeks and then every 12 weeks
- Safety data up to 30 weeks after switch are reported



# Results



- **28** black-African children from Uganda and Zimbabwe
- 61% male

	25-<30kg	30-<35kg	Total
<b>n</b>	18	10	<b>28</b>
<b>Age at first PK day, years</b>			
<b>Median</b>	10.7	11.2	<b>11.0</b>
<b>Range</b>	7.5-17.9	9.8-17.8	<b>7.5-17.9</b>
<b>Weight at first PK day, kg</b>			
<b>Median</b>	27.5	31.0	<b>29.0</b>
<b>Range</b>	25.0-30.7	29.9-38.2	<b>25-38.2</b>

- **24** children had evaluable PK curves on **both PK days** allowing for within-child PK comparison
  - n=15 (25-<30kg) and n=9 (30-<40kg)
- **Four** additional children had evaluable **a single PK curve**
  - 2 on 25mg (25<30kg) and 2 on 50mg (25-<30kg and 30<50kg)



# 25-<30kg: Selected PK parameters and reference adult data

ODYSSEY WB 25-<30kg			Reference adults HIV+		
	25 mg (n=17) →	<b>50mg (n=16)</b>	GMR (90% CI) 50mg vs. 25mg	50mg QD*	50mg BID**
Dose/weight, mg/kg	0.9 (0.8-1.0)	<b>1.8 (1.6-2.0)</b>	-		
C <sub>trough</sub> , mg/L	0.38 (48)	<b>0.75 (42)</b>	1.9 (1.6-2.2)	0.83 (26)	2.72 (70)
AUC <sub>0-24h</sub> , h*mg/L	33.1 (23)	<b>58.7 (27)</b>	1.7 (1.5-1.9)	43.4 (20)	93.4 (50)
C <sub>max</sub> , mg/L	3.16 (24)	<b>5.41 (25)</b>	1.7 (1.5-1.9)	3.34 (16)	5.41 (40)

Numbers are expressed as mean (range) for dose/kg and geometric mean with coefficient of variation (%) for C<sub>trough</sub>, C<sub>max</sub> and AUC<sub>0-24h</sub>

\*Min et al.2011: Fasted HIV-positive adults

\*\*VIKING (112961): HIV-positive treatment experienced adults, fed state not specified

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# 30-<40kg: Selected PK parameters and reference adult data

ODYSSEY WB 30-<40kg			Reference adults HIV+		
	35 mg (n=9) →	<b>50mg (n=10)</b>	GMR (90% CI) 50mg vs. 25mg	50mg QD*	50mg BID**
Dose/weight, mg/kg	1.1 (0.9-1.2)	<b>1.5 (1.3-1.7)</b>	-		
C <sub>trough</sub> , mg/L	0.45 (63)	<b>0.63 (49)</b>	1.4 (1.1-1.7)	0.83 (26)	2.72 (70)
AUC <sub>0-24h</sub> , h*mg/L	40.3 (35)	<b>53.5 (32)</b>	1.3 (1.2-1.5)	43.4 (20)	93.4 (50)
C <sub>max</sub> , mg/L	3.98 (28)	<b>5.22 (25)</b>	1.3 (1.2-1.5)	3.34 (16)	5.41 (40)

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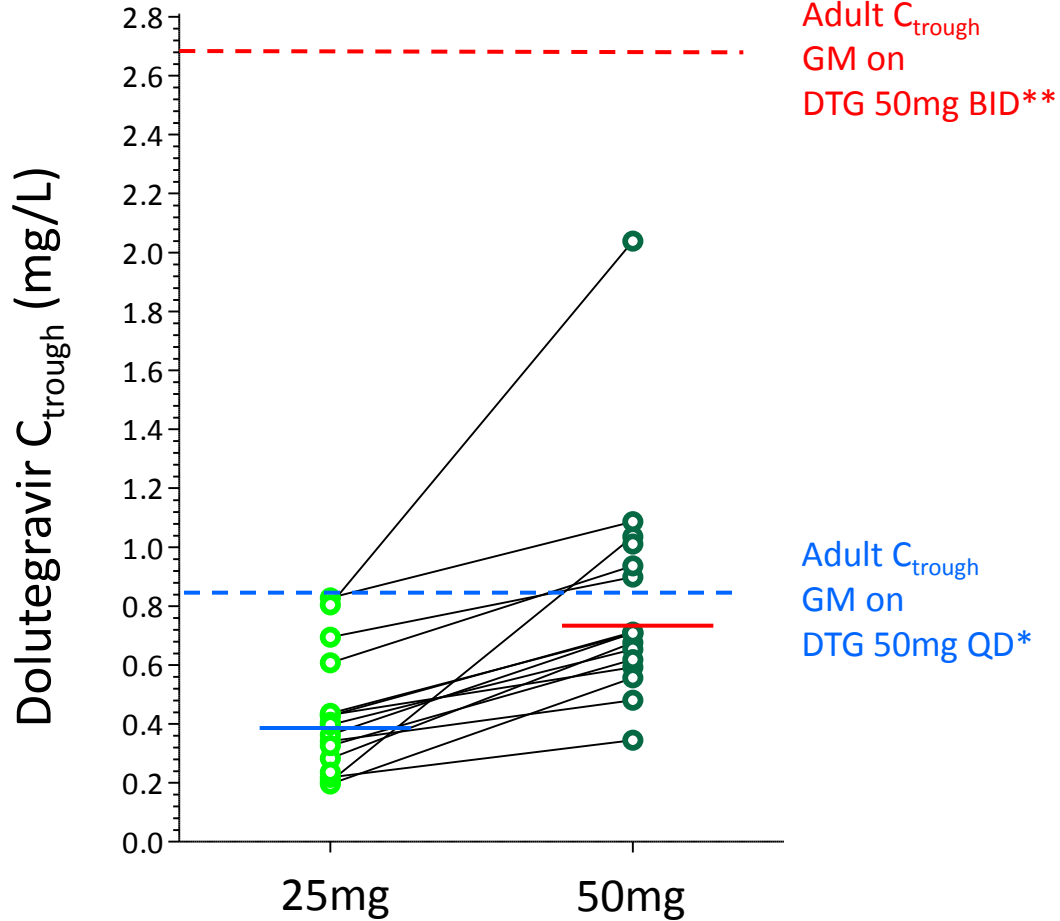
Numbers are expressed as mean (range) for dose/kg and geometric mean with coefficient of variation (%) for C<sub>trough</sub>, C<sub>max</sub> and AUC<sub>0-24h</sub>

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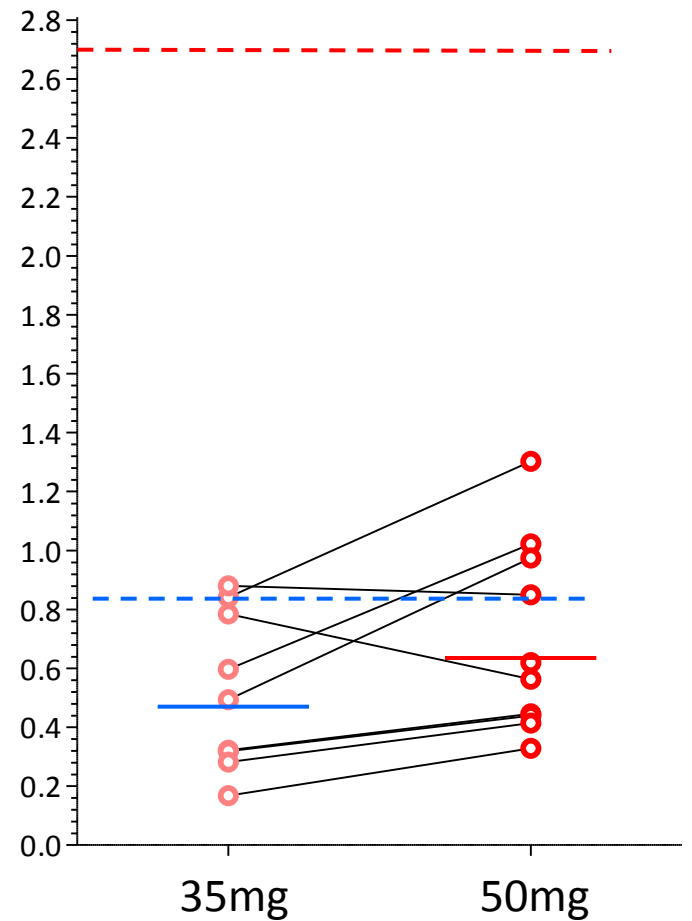
\*\*VIKING (112961): HIV-positive treatment experienced adults, fed state not specified

# $C_{trough}$

## 25-<30kg



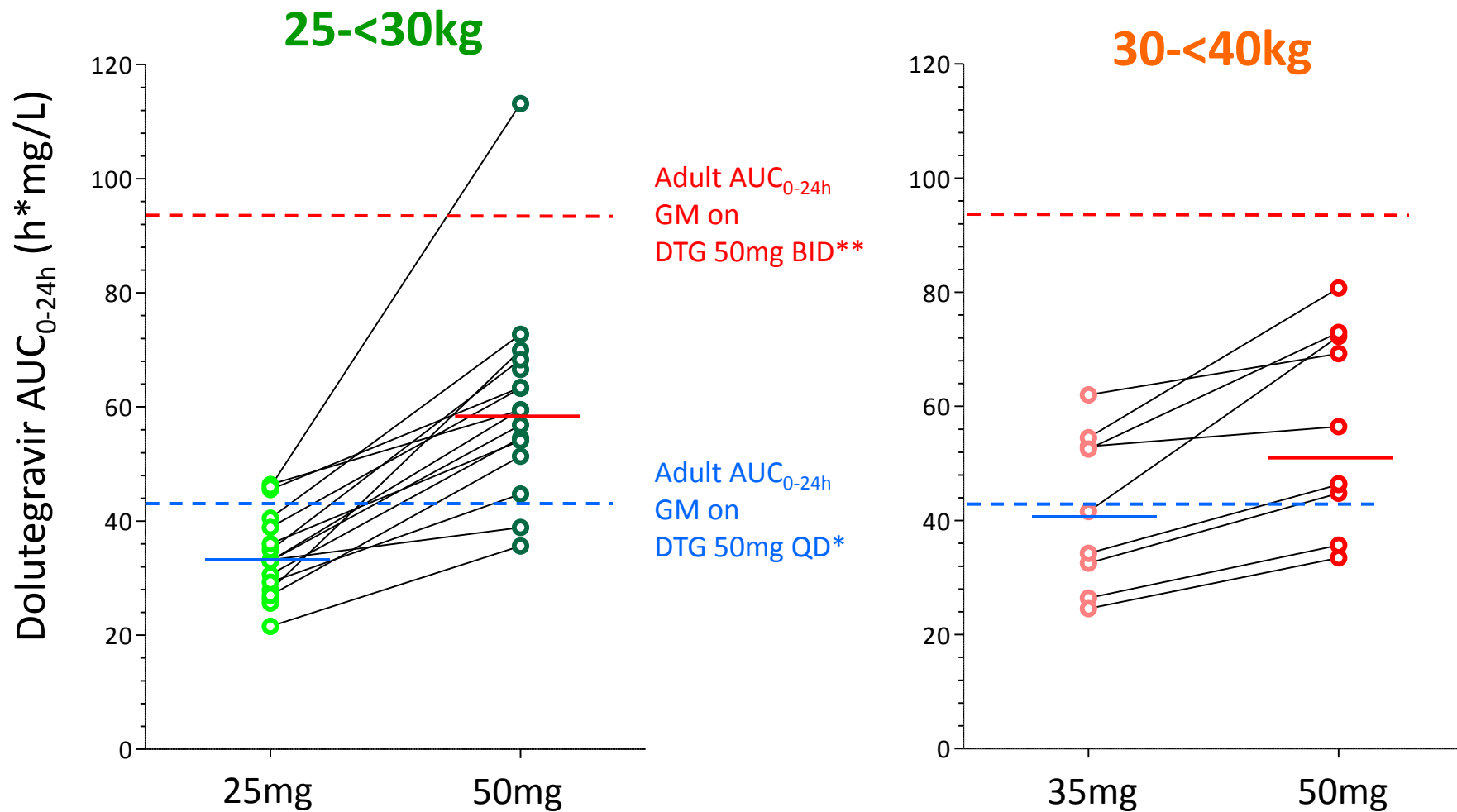
## 30-<40kg



\*Min et al.2011: Fasted HIV-positive adults

\*\*VIKING (112961): HIV-positive treatment experienced adults, fed state not specified

# AUC<sub>0-24h</sub>



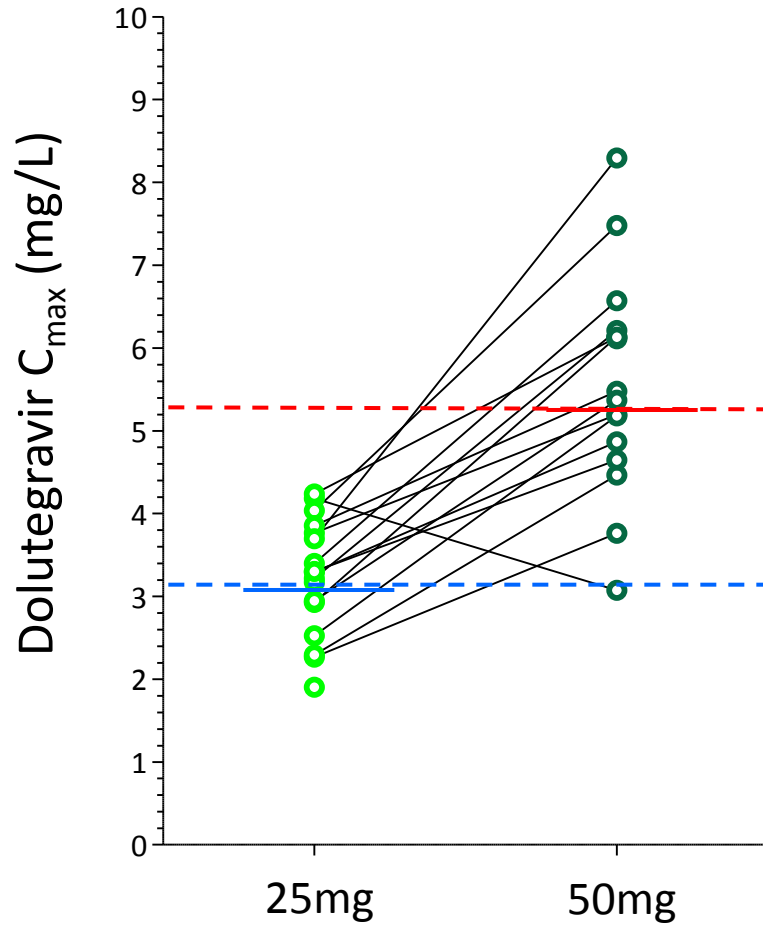
\*Min et al.2011: Fasted HIV-positive adults

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**C<sub>max</sub>**

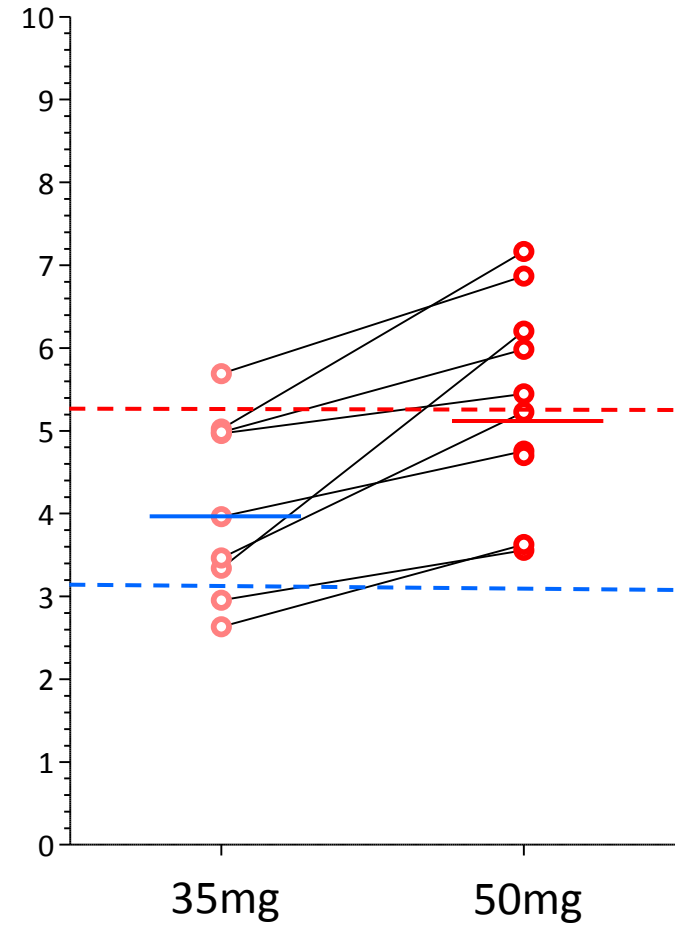
25-<30kg



Adult C<sub>max</sub>  
GM on  
DTG 50mg BID\*\*

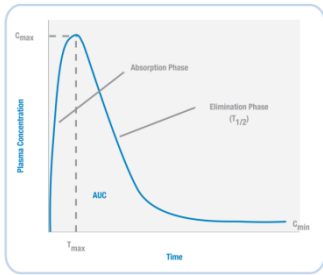
Adult C<sub>max</sub>  
GM on  
DTG 50mg QD\*

30-<40kg



\*Min et al.2011: Fasted HIV-positive adults

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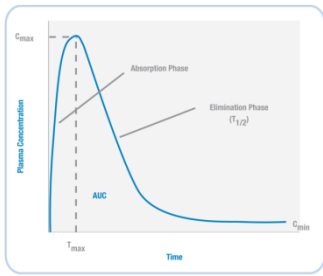


# Safety results

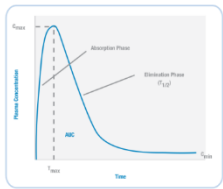


- 28 children in WB-PK2 who had successfully completed either PK day were included
- Over a median follow-up of 30 weeks (range 12-30) on DTG 50mg, 3 participants had reportable events
  - 1 participant had cryptococcal meningitis (SAE/WHO 4/DAIDS grade 4)
  - 1 participant had asymptomatic anaemia (DAIDS grade 3)
  - 1 participant had neutropenia (DAIDS grade 3)
- No events resulted in a modification of ART
- All events have been reviewed by an independent blinded endpoint review committee and were considered to be unrelated to DTG

# Conclusion and next steps



- Film-coated DTG 50mg tablets provide a practical way of dosing for children  $\geq 25$ kg
- Dosing with DTG 50 mg makes adult DTG formulations accessible to children  $\geq 25$ kg and aligns with adult ABC/3TC for children  $\geq 25$ kg
- PK results are acceptable in terms of comparison of PK parameters to adult references
- Short-term safety data are reassuring and revealed no safety concerns
- Children in the main ODYSSEY trial weighing  $\geq 25$ kg are switched to DTG 50mg tablets
- Longer-term safety data on DTG 50mg in children will be evaluated in the main trial



# Acknowledgements:

## PK sites and investigators



- **Uganda**

**JCRC Lubowa:** Cissy Kityo, Victor Musiime, Elizabeth Kaudha, Annet Nanduudu, Emmanuel Mujyambere, Paul Ocitti, Shamim Nakabuye, Charles Isabirye, Josephine Namusanje, Ritah Mbabazi; Kyobutungi Priscilla and Phyllis Mwesigwa

**JCRC Mbarara:** Abbas Lugemwa, Lorna Atwine, Miriam Kasozi, Shafic Makumbi, Baker Rubinga, Emily Ninsiima, Edridah Keminyeto, Mercy Tukamushaba, Rogers Ankunda, Ian Natuhurira,

**Baylor:** Adeodata Kekitiinwa, Pauline Amuge, Dickson Bbuye, Herbert Murungi, Geoffrey Onen, Winnie Akobye, Muzamil Nsibuka Kisekka, Rogers Sekabira, Gerald Agaba



- **Zimbabwe**

**UZCRC:** James Hakim, Hilda Mujuru, Mutsa Bwakura-Dangarembizi, Ennie Chidziva, Shepherd Mudzingwa, Misheck Nkalo Phiri, Ruth Nhema, Buxton Ndemera



- **Netherlands**

**Radboud University Medical Center, Nijmegen:**

Pauline Bollen, Hylke Waalewijn, Angela Colbers, David Burger





# 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
- P1093 investigators and ViiV PK experts

**THANK  
YOU!**

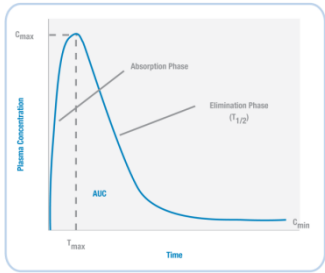
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Check out the ODYSSEY posters:

**#22: Steady-state pharmacokinetics and early safety data in HIV-infected African children weighing 14 to <25kg on film-coated dolutegravir 25mg tablets (P Bollen)**

**#34: ODYSSEY: design, current status and baseline characteristics (C Moore)**

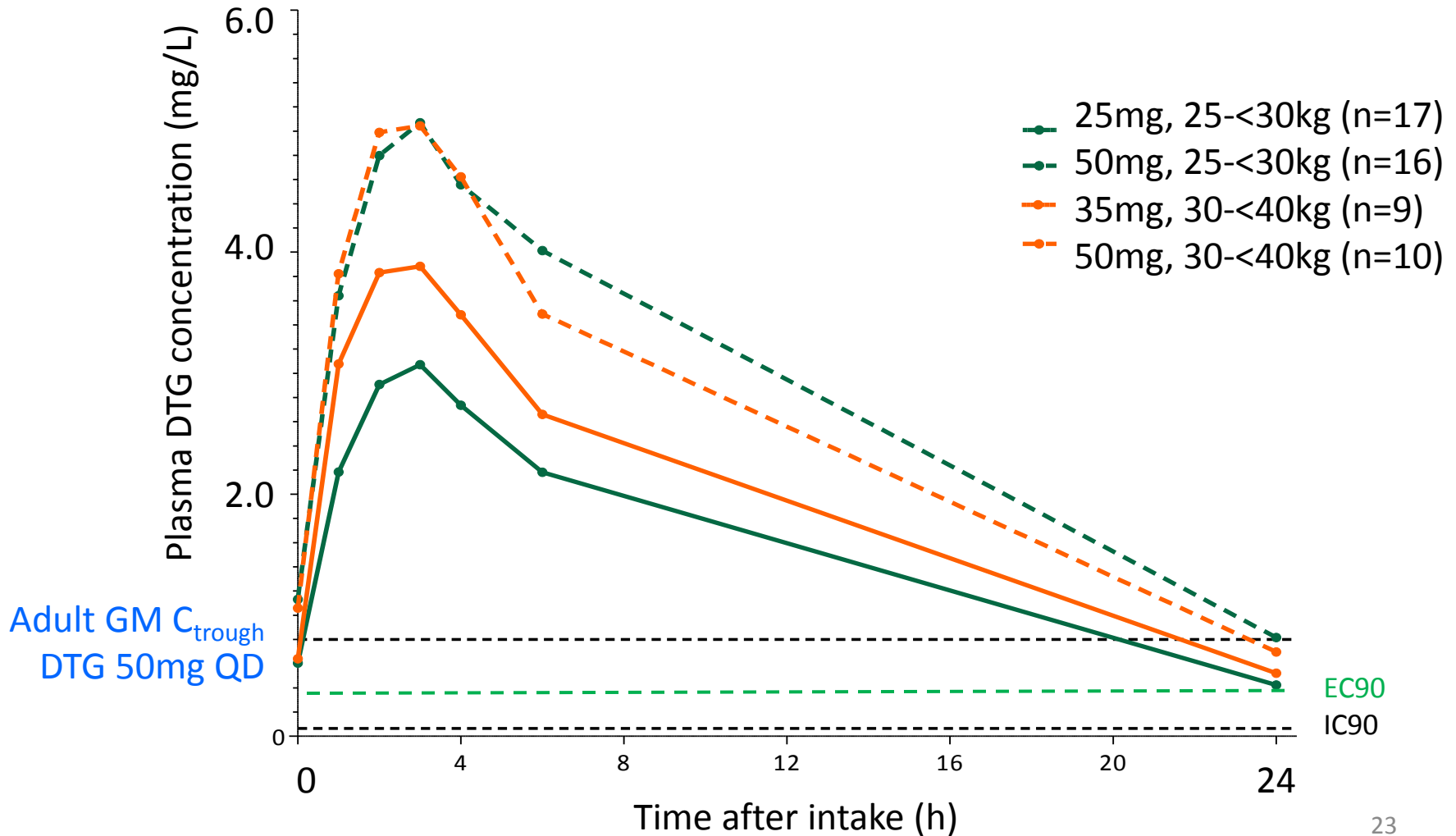
**#117: “I failed to take them as I should and now I’m scared”: How can we support adolescents’ adherence on second line HIV treatment (S Bernays)**



Additional slides



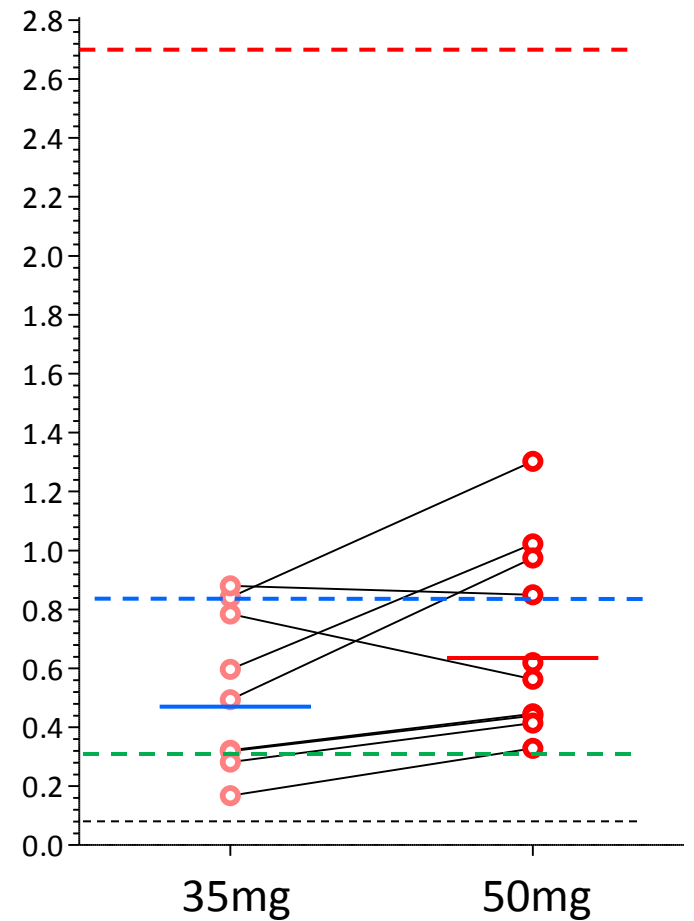
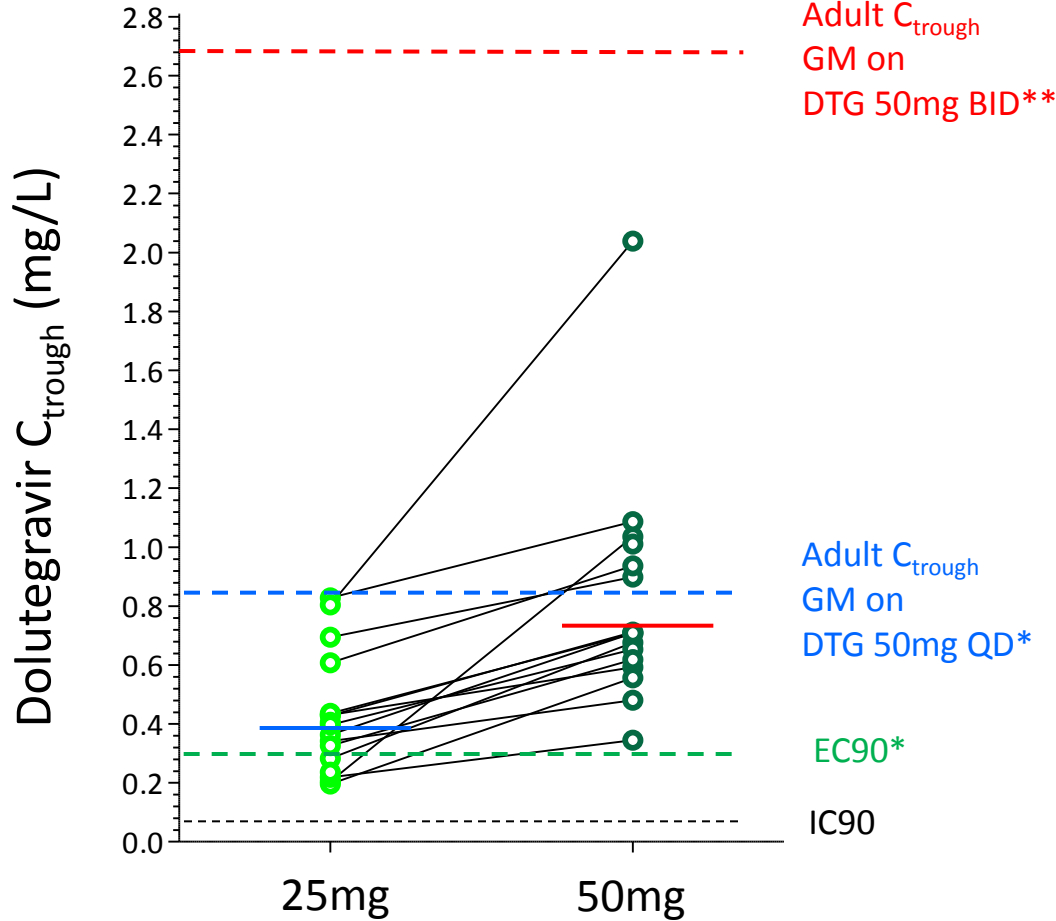
# Mean plasma concentration versus time curve per weight band per dose



**C<sub>trough</sub>**

**25-<30kg**

**30-<40kg**

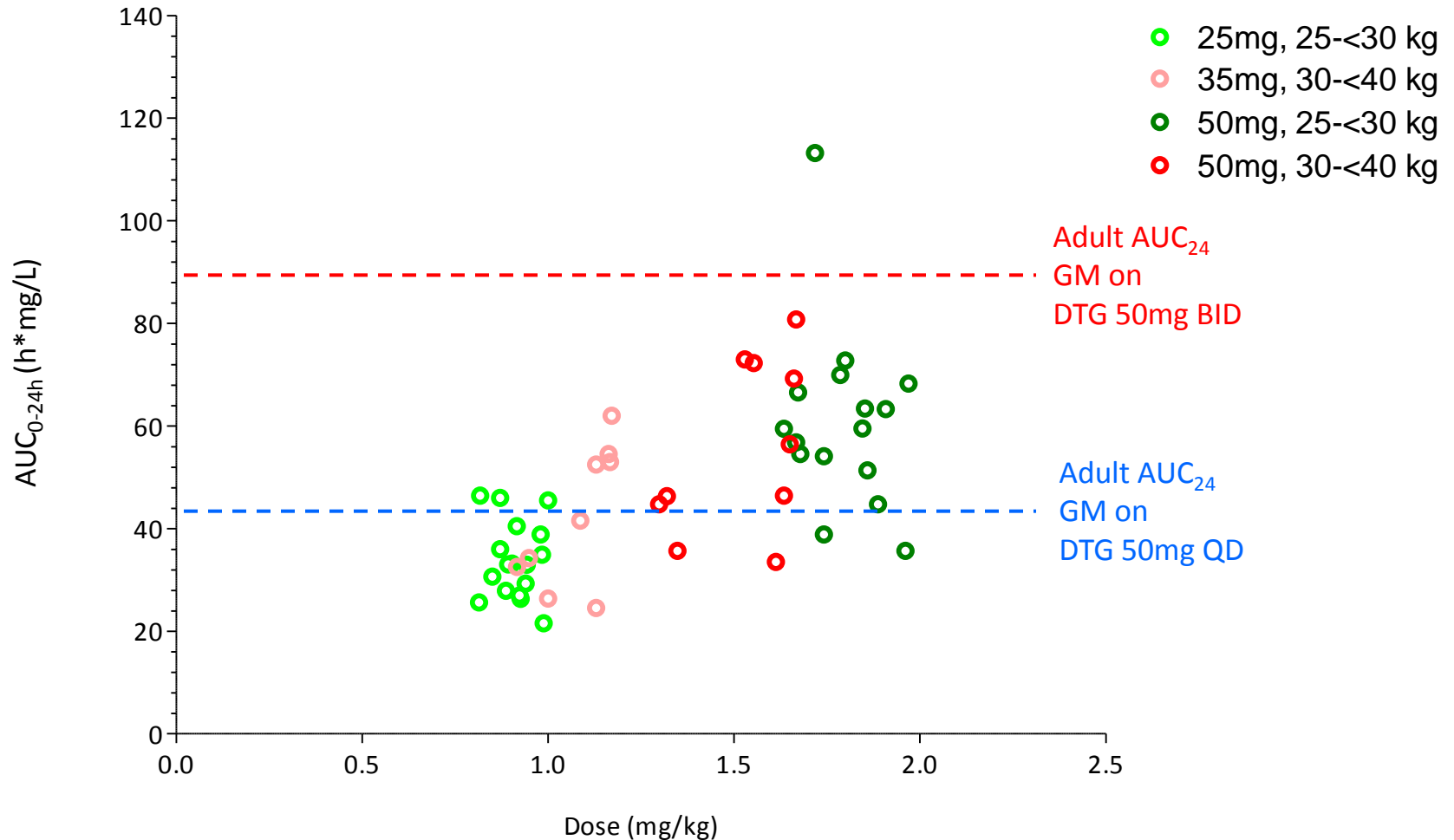


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# AUC<sub>0-24h</sub> versus DTG dose mg/kg for 25- <30kg and 30-<40kg



# $C_{max}$ versus DTG dose mg/kg for **25-<30kg** and **30-<40kg**

