Steady-state pharmacokinetics and early safety data in HIV-infected Africa children weighing 14 to <25kg on film-coated dolutegravir 25mg tablets

P#22

Pauline DJ Bollen[1], Anna Turkova[2], Hilda Mujuru[3], Victor Musiime[4], Pauline Amuge[5], Abbas Lugemwa[6], Angela Colbers[1], Moira J Spyer[2], Sarah Lensen[2], Cecilia L Moore[2], James Hakim[3], Cissy Kityo[4], Dickson Bbuye[5], Lorna Atwine[6], Carlo Giaquinto[7], Deborah Ford[2], Diana M Gibb[2], David M Burger[1], and the ODYSSEY trial team

[1]Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands. [2]Medical Research Council Clinical Trials Unit at University College London, London, United Kingdom. [3]University of Zimbabwe Clinical Research Centre, Harare, Zimbabwe. [4]Joint Clinical Research Centre, Kampala, Uganda. [5]Baylor College of Medicine, Kampala, Uganda. [6]Joint Clinical Research Centre, Mbarara, Uganda. [7]University of Padova, Padova, Italy.

mrcctu.trial-odyssey@ucl.ac.uk

Background

- ODYSSEY (*ClinicalTrials.gov;* NCT02259127) is an ongoing international randomised trial evaluating dolutegravir (DTG)-based antiretroviral therapy (ART) versus standard-of-care in HIV-infected children starting first- or second-line ART (poster #34).
- Within this trial a pharmacokinetic (PK) substudy was undertaken to assess PK and safety data for a simplified pediatric DTG dosing approach using WHO weight bands 14 to <20kg and 20 to <25kg. This approach differs from the EMA approved pediatric dose recommendations for DTG (Table 1) [1].

Table 1. *ODYSSEY PK substudy doses versus EMA approved pediatric DTG doses.*

ODYSSEY PK substudy doses		EMA approved doses (age ≥6 years)	
14-<25 kg:	25 mg QD (Taken as one film-coated 25mg tablet)	15 -< 20 kg:	20 mg QD (Taken as two 10 mg tablets)
		20 -< 30 kg:	25 mg QD

Methods

- Steady state 24-hour PK curves (t=0, 1, 2, 3, 4, 6 and 24h) were constructed from data on children weighing 14-<25kg after observed intake of a 25mg film-coated DTG tablet under fasted conditions. Intensive PK sampling was conducted in four clinics in Uganda and Zimbabwe. Informed consent was obtained for all children.
- The aim was to compare DTG PK parameters to historical PK parameters achieved in HIV-positive adults, taking DTG 50mg film-coated tablets once daily, for which PK was evaluated under fasted conditions (Min *et al.* 2011 [2]).
- DTG plasma concentrations were measured using a validated UPLC-MS/MS method with a lower limit of quantification of 0.01 mg/L. Non-compartmental PK analysis was performed to calculate PK parameters with WinNonlin 6.3 software.
- Laboratory and clinical safety were evaluated at 2 (only mandatory for 14 to <20kg), 4 and 12 weeks, and then every 12 weeks. Adverse events up to 30 weeks are reported.

Results I

Demographics

- This PK substudy included 39 black-African children from Uganda and Zimbabwe of which 33 children were included in the PK and safety analysis (Table 2).
- 6 children (8 PK curves) were excluded from analysis for PK protocol deviations (n=5), questionable adherence (n=2) or haemolysed PK blood samples (n=1).

Table 2. *Patient demographics and characteristics at PK day.*

WHO weight band	14-<20kg, n=19	20-<25kg, n=14
Sex male	13 (76%)	7 (50%)
Age (years)	6.2 (5.1-7.4)	9.5 (7.6-10.6)
Weight (kg)	17.0 (16.0-18.6)	23.4 (22.9-23.9)
Height (cm)	107 (103-110)	126 (124-129)
BMI (kg/m^2)	14.5 (13.9-15.5)	14.6 (14.3-15.0)
BMI-for-age Z score		
-3 to <-2	0 (0%)	2 (14%)
-2 to <0	14 (74%)	12 (86%)
>=0	5 (26%)	0 (0%)

Table entries are n(%) or median (IQR).

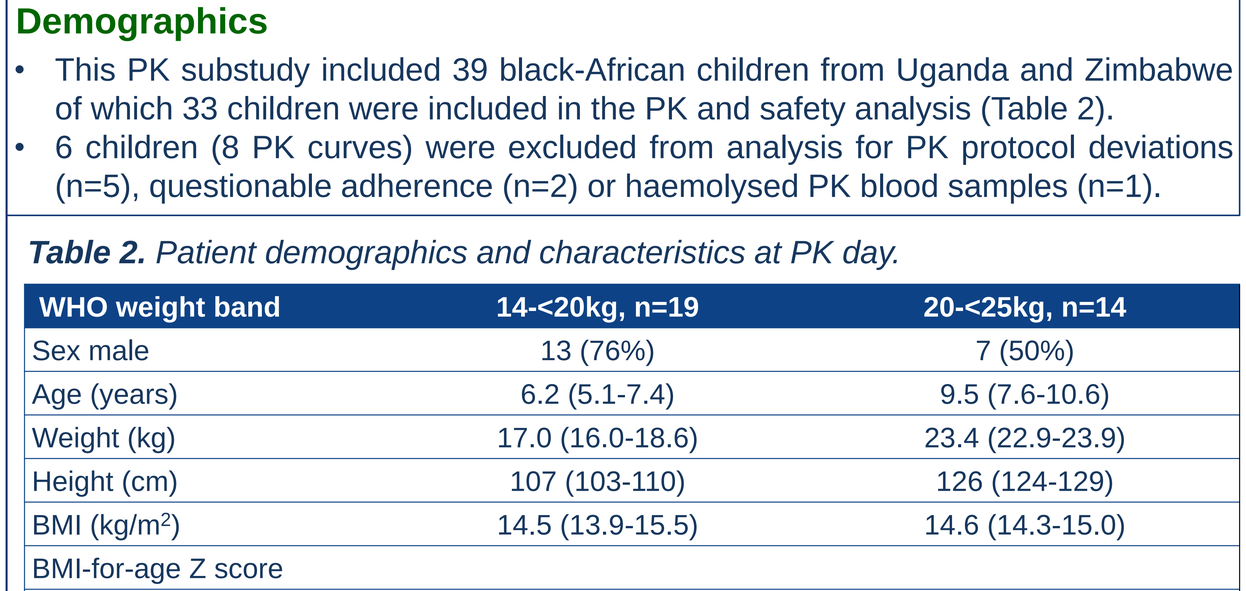

Figure 1. *Mean plasma concentration versus time profile per weight band.*

Results II

Pharmacokinetics

- In children weighing 14 to <20kg geometric mean (GM) C_{trough} and $AUC_{0\text{-}24h}$ on a 25mg DTG dose were 48% and 9% lower, respectively, compared to historical adult C_{trough} and $AUC_{0\text{-}24h}$ on DTG 50mg QD.
- In children weighing 20 to <25kg GM C_{trough} and $AUC_{0\text{-}24h}$ on a 25mg DTG dose were 61% and 31% lower, respectively, compared to C_{trough} and $AUC_{0\text{-}24h}$ on DTG 50mg QD in adults (Table 3 and Figure 2).

Table 3. *Main PK parameters for DTG in the ODYSSEY PK substudy and published reference PK parameters in adults [2].*

	ODYSSEY PK substudy		Reference adults [2]
WHO weight band	14-<20kg	20-<25kg	≥ 40kg
N	19	14	10
Dose (mg)	25	25	50
Dose (mg/kg)	1.5 (1.3-1.8)	1.1 (1.0-1.2)	-
C_{trough} (mg/L)	0.43 (50)	0.32 (94)	0.83 (26)
$AUC_{0\text{-}24h}$ (mg*h/L)	39.6(32)	30.1 (41)	43.4 (20)
C_{max} (mg/L)	4.03 (31)	3.20 (40)	3.34 (16)

Pharmacokinetic parameters are expressed as geometric mean with coefficient of variation (%). Dose (mg/kg) is expressed as mean (range). Doses represent once daily doses.

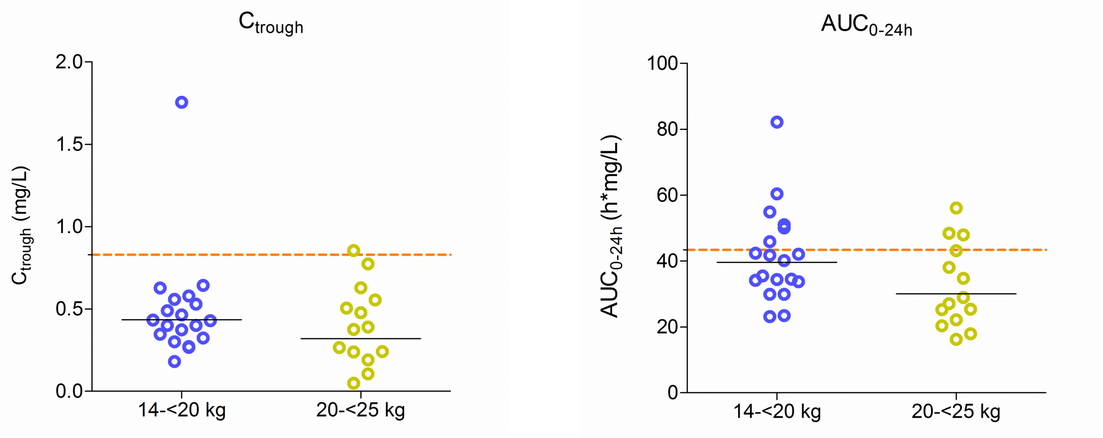

Figure 2. *Individual C_{trough} and $AUC_{0\text{-}24h}$ at PK day. Black horizontal line indicates geometric mean. Orange line indicates reference geometric mean value for dolutegravir in adults on 50mg QD film-coated tablets (Min et al. 2011 [2]).*

Results III

Safety data

- After a median (IQR) follow-up of 24.0 (23.6-30.0) weeks on the 25mg tablet dose, six patients had reportable adverse events: one participant had an SAE (malaria, grade 3), one participant had raised liver enzymes with thrombocytopenia (grade 3), one participant had a neutropenia (grade 3), and three participants had a confirmed or possible IRIS event (pulmonary TB, one grade 2 and two grade 3).
- Five events were reviewed by an independent blinded endpoint review committee (ERC); two events (both IRIS TB grade 3) not yet reviewed by the ERC were reviewed by the trial clinician.
- All events were judged to be unrelated or unlikely related to DTG. No events have resulted in modification of ART.

Conclusions

- **In children weighing 14 to <25kg on 25mg DTG, taken once daily as one film-coated tablet, C_{trough} and $AUC_{0\text{-}24h}$ were considerably lower compared to C_{trough} and $AUC_{0\text{-}24h}$ on DTG 50mg once daily in adults. Safety data on a 25mg dose were acceptable.**
- **For children weighing 14 to <25kg, we plan to increase DTG doses and/or change DTG formulation to dispersible tablets, for which bioavailability is higher, while maintaining practical dosing. PK studies within the ODYSSEY trial will be repeated and longer-term safety data will be evaluated.**

References

[1] SPC Tivicay, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002753/WC500160680.pdf, accessed on: 07/04/2018.

[2] Min et al. AIDS 2011; 25(14):1737-45.

CONTACT | Pauline Bollen, Radboud University Medical Center Nijmegen, The Netherlands. E: Pauline.Bollen@radboudumc.nl, T: +31 24 361 7744