Adult dolutegravir 50mg film-coated tablets in children living with HIV weighing 20 to <25 kg

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P# 0830

Background

- ODYSSEY (*ClinicalTrials.gov;* NCT02259127) is a phase III 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.
- The EMA recommended DTG dose of 25mg film-coated tablets (FCT) once daily in children weighing 20 to <30kg, has previously shown to lead to lower DTG exposures compared with those seen in adults[1,2].
- In adults, the use of dispersible tablets (DT) results in higher DTG bioavailability compared to FCT (ratio 1.5-1.8)[3].

Objectives

- This pharmacokinetic (PK) substudy assessed PK and safety of once daily DTG adult 50mg FCT and pediatric 30mg DT in children weighing 20 to <25kg.
- The aim was to achieve a geometric mean (GM) DTG trough concentration (C_{trough}) comparable to historical adult GM C_{trough} for 50mg FCT once daily under fasted conditions[4].
- PK parameters were compared to historical PK parameters achieved in HIV-positive adults, taking DTG 50mg FCT once[4] or twice daily[5], and to children weighing 20 to <25kg on 25mg FCT once daily within ODYSSEY[2].

Participants and Methods (I)

Inclusion for PK substudy

- Children weighing 20 to <25kg taking DTG in ODYSSEY at PK-sites in Uganda and Zimbabwe, and who gave additional informed consent for the PK substudy, were eligible for inclusion.
- Exclusion criteria were severe acute malnutrition, diarrhoea or vomiting, the use of concomitant medications known to have drug-drug interactions with DTG and suffering from an illness that may affect PK.

Pharmacokinetics

- Steady state 24-hour DTG PK profiles (t=0, 1, 2, 3, 4, 6 and 24h) in fasted children (≥3 hour fast) taking once daily DTG 50mg FCT or 30mg DT (6x5mg) were recorded ≥7 days after switch from 25mg FCT (main trial dose). We aimed to have at least 8 evaluable PK curves per DTG formulation.
- PK profiles were included in PK summary statistics if at least 4 samples were available (incl. C_{max}), and were excluded if treatment non-adherence was suspected (C_0:C_{trough} ratio ≥15).
- DTG plasma concentrations were measured using a validated UPLC-MS/MS with an LLOQ of 0.01 mg/L[6].
- Non-compartmental PK analysis was performed with WinNonlin 8.1 software.

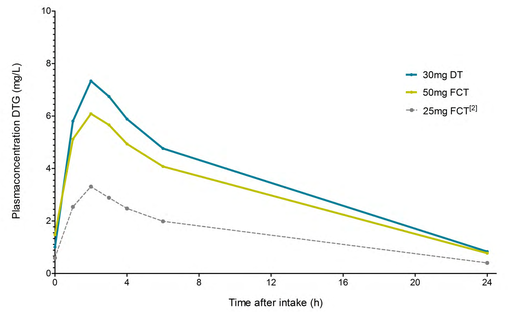
Participants and Methods (II)

Safety

- Laboratory and clinical serious adverse events (AE), grade 3/4 AE and ART modifying events (any grade) were evaluated at 2, 4 and 12 weeks, and then every 12 weeks. AE up to 24 weeks after start of the PK dose are reported.
- AE were reviewed by an independent blinded endpoint review committee (ERC).

Results (I)

Figure 1: Mean plasma concentration versus time curves for children on 30mg DT, 50mg FCT, and 25mg FCT within ODYSSEY.



Results (II)

Pharmacokinetics

- 15 African children were enrolled in Zimbabwe and Uganda and were included in the PK and safety analysis (Table 1).
- Mean plasma concentration versus time profiles for 50mg FCT (n=7) and 30mg DT(n=8) are shown in Figure 1.
- The 50mg FCT and 30mg DT doses both resulted in a GM C_{trough} value that was very similar and comparable to adults on 50mg FCT once daily, and was higher compared to children weighing 20 to <25kg on 25mg FCT (Table 1 and Figure 3).
- GM C_{max} on both doses exceeded adult GM values for DTG 50mg once and twice daily (Figure 2).
- GM $AUC_{0\text{-}24h}$ for both doses was between values observed in adults taking DTG 50mg once daily and 50mg twice daily (Table 1 and Figure 3).

Safety

- After median (IQR) follow-up of 12.9 (11.1-24.0) and 12.0 (6.6-18.6) weeks on 50mg FCT and 30mg DT respectively*, no children experienced grade 3/4, serious AE or discontinued DTG.

**median (range) on DTG before starting the current dose was 34.8 (13.9-60.0) weeks.*

Table 1: Participant demographics and PK parameters by dose and formulation in children 20 to <25kg and adult reference populations.

	ODYSSEY		Ref. ODYSSEY[2]	Ref. Adults [4,5]	
WHO weight band	20 to <25 kg		20 to <25 kg	≥ 40kg	
Dose (mg) and formulation	30 DT	50 FCT	25 FCT	50 FCT	50 FCT BID
N	8#	7#	14#	10[a]	24[b]
Sex male, n (%)	4 (50%)	4 (57%)	7 (50%)	10 (100%)	18 (75%)
Age (years)	8.6 (6.8-11.3)	9.7 (8.1-11.7)	9.3 (7.1-11.3)	34 (22-53)	47 (33-68)
Weight (kg)	21.8 (20.3-22.7)	22.4 (20.5-24.5)	23.4 (20.2-24.3)	-	-
Dose (mg/kg)	1.4 (1.3-1.5)	2.2 (2.0-2.4)	1.1 (1.0-1.2)	--	-
C_{trough} (mg/L)	0.71 (74)[c]	0.77 (51)	0.32 (94)[d]	0.83 (26)	2.72 (70)
$AUC_{0\text{-}24h}$ (mg*h/L)	71.8 (28)	62.8 (30)	30.1 (41)	43.4 (20)	93.4 (50)
C_{max} (mg/L)	7.42 (25)	6.07 (29)	3.20 (40)	3.34 (16)	5.41 (40)

PK parameters are geometric means with coefficient of variation (%). Other data are mean (range) for age, dose mg/kg, and weight, unless otherwise indicated. [a]Fasted HIV-positive adults. [b]HIV-positive treatment-experienced adults, fed state not specified. [c]One participant had a C_{trough} of 0.30mg/L which is below the EC_{90} for DTG of 0.32mg/L. [d]Ten participants had C_{trough} below 0.32 mg/L (EC_{90}). # Two participants on 30mg DT and four participants on 50mg FCT participated also in the ODYSSEY PK substudy on 25mg FCT.

Results (III)

Figure 2: Individual C_{trough} (left) and C_{max} (right) per dose/formulation.

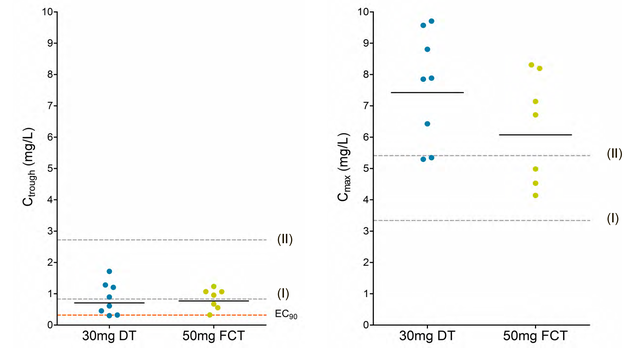
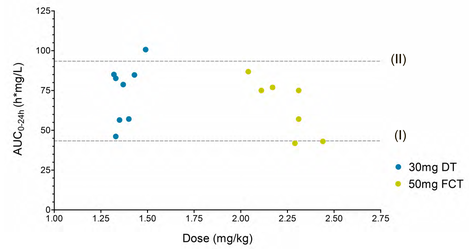


Figure 3: Individual $AUC_{0\text{-}24h}$ versus weight adjusted dose.



Grey lines indicate GM references in adults on 50mg QD (I) and 50mg BID (II). Black horizontal line indicates GM.

Conclusions

- **Daily DTG 50mg FCT and 30mg DT provide similar and appropriate PK profiles for children weighing 20 to <25kg, but C_{max} exceeds reference values for approved adult DTG dosing.**
- **Short-term safety data are reassuring and, provided ongoing longer-term safety is acceptable, these results support use of either 50mg FCT or DTG 30mg DT in this weight band.**
- **Adult DTG 50mg FCT could offer a practical and accessible dosing strategy for children 20 to <25kg allowing rapid alignment of WHO-preferred ART regimens for adults and children ≥20kg in low- and middle-income countries.**

References

[1] SPC Tivicay, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002753/WC500160680.pdf, accessed on: 04/02/2018. [2] 10th International Workshop on HIV Pediatrics, Amsterdam, 20-21st July 2018. P#22. [3] ViiV Clin Pharm Study Report 205893. [4] Min *et al.* AIDS 2011; 25(14):1737-45. [5] GSK Medicine, study ING112961(VIKING). [6] Bollen *et al.* J Chrom B 2019; 1105: *76-84.*

Acknowledgements

Presented at 2019 Conference on Retroviruses and Opportunistic Infections, March 4 to 7, 2019, in Seattle, Washington.

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