Adequate dolutegravir exposure dosed BID with rifampicin in children 6 to <18 years

P# 2835

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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.
- Currently, DTG is recommended as a preferred 3rd agent in antiretroviral regimens for children living with HIV for whom DTG dose is known.[1]
- While in adults there is evidence that the effect of rifampicin(RIF)-based TB treatment on DTG pharmacokinetics can be overcome by doubling DTG dose in adults.[3] In children there are currently no data available to support this approach.
- This pharmacokinetic (PK) substudy assessed all children received RIF-based TB treatment at PK sites.

Objectives

- To estimate the impact of RIF on DTG plasma concentrations in children using Geometric Mean Ratios (GMR) for twice daily weight-appropriate DTG dose given with RIF (DTG BID+RIF) over once daily DTG without RIF (DTG QD)
- To assess safety of DTG dose doubling in children

Participants and Methods (I)

Pharmacokinetics

- Children in ODYSSEY receiving DTG BID+RIF at PK sites in Uganda, Zimbabwe and South Africa, with additional informed consent, were included in the PK part of the substudy
- Children received (i) DTG 25mg or 50mg BID+RIF (PK day 1) followed by QD (PK day 2); DTG dosing depended on the current weight-appropriate DTG dose used in the ODYSSEY trial
- PK day 1: PK curve on DTG BID in the last month of RIF treatment PK day 2: PK curve on DTG QD ≥4 weeks after stopping RIF (**Figure 1**)
- PK parameters were compared to historical PK parameters achieved in HIV-positive adults, taking DTG 50mg FCT QD[3]
- GMRs were estimated using a mixed model method comparing DTG PK parameters between PK day 1 and 2.
- DTG plasma concentrations were measured using a validated UPLC-MS/MS with an LLOQ of 0.01 mg/L[4]

Safety

- All children at PK sites who received DTG BID+RIF aged 6-<18 years were included in the safety part of the substudy and were followed for serious adverse events (SAEs), grade 3/4 clinical and laboratory adverse events (AEs) and any AEs resulting in ART modification from start of DTG BID + RIF to 30 days after return to DTG QD
- AEs were reviewed by an independent blinded endpoint review committee (ERC) blinded to randomised allocation

Methods (II)

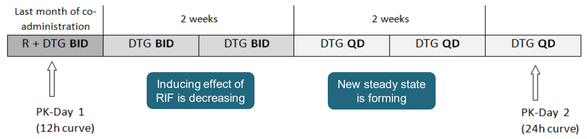

Figure 1: Sequential intrasubject pharmacokinetic sub-study. Samples taken at T=0,1,2,3,4,6, and 12 (PK day 1) or 24 (PK day 2)

Results (I)

Safety

- 31 children, median (range) age 12.2 (5.9-17.6), 16(52%) males, were followed for a median (IQR) of 30.7 (28.3, 39.6) weeks
- 13 adverse events were reported in 8 children
- Of 9 serious adverse events (SAEs), 1 was grade 2, 4 were grade 3, and 4 grade 4. All were hospitalizations with 1 event leading to DTG discontinuation (hepatitis A), 1 death (TB-related)
- Of 4 non-SAEs, all were grade 3; including 2 events of anaemia with clinical symptoms, 1 neutropenia and 1 disseminated/military TB
- All events were considered unlikely related to DTG by investigators and independent reviewers

Results (II)

Pharmacokinetics

- Of 31 eligible children, 17 were enrolled in the PK substudy
- 13/17 participants undertaking PK had ≥1 evaluable PK curve. 11 had evaluable PK on both PK days; 1 child evaluable PK on day 1; 1 child evaluable PK on day 2
- 10 PK curves in 6 children were not evaluable due to missed PK day (n=2), missed samples during PK day (n=1), suspected non-adherence to ART (n=7)
- Mean plasma concentration versus time profiles of DTG BID + RIF and DTG QD for 50mg (n=8) and 25mg (n=5) are shown in **Figure 2**
- Doubling of DTG dose in combination with RIF resulted in comparable $AUC_{0\text{-}24h}$ and C_{max}; GMR for C_{trough} was 1.56 (90%CI 1.09 – 2.25) (**Table 1**)
- Clearance of DTG is increased as expected by the inducing effect of RIF CL/F (GMR 1.36 for DTG 25mg, and 2.05 for DTG 50mg) and $T_{1/2}$ (GMR 0.60 for DTG 25mg, and 0.56 for DTG 50mg) (**Table 1**)
- For both DTG doses used in ODYSSEY C_{trough} values on DTG BID + RIF are higher than adult reference values (**Table 2**)

Table 1: Participant demographics and Geometric Mean Ratios (GMR) for DTG BID+RIF versus DTG QD by DTG dose in children 6-<18 years included in the PK part of the substudy in children 6-<18 years

Parameter		DTG 25mg (n=5)	DTG 50mg (n=8)	Overall (n=13)
Sex	Female/Male	3/2	5/3	8/5
Weight, kg	Median (range)	24.9 (19.8-27.7)	33.0 (28.1-48.5)	31.3 (19.8-48.5)
DTG BID dose, mg/kg	Mean (range)	2.1 (1.8-2.5)	2.8 (2.1-3.6)	2.5 (1.8-3.6)
C_{trough} (mg/L)*	GMR (90% CI)	2.10 (1.20-3.68)	1.25 (0.71-2.19)	1.56 (1.09-2.25)
$AUC_{0\text{-}24h}$ (h*mg/L)*	GMR (90% CI)	1.47 (0.99-2.19) †	0.98 (0.61-1.51) †	1.16 (0.88-1.54)
C_{max} (mg/L)*	GMR (90% CI)	1.02 (0.73-1.41)	0.86 (0.64-1.37)	0.93 (0.74-1.16)
$T_{1/2}$ (h)*	GMR (90% CI)	0.60 (0.46-0.78)	0.56 (0.39-0.80)	0.59 (0.49-0.72)
Vd/F (L)*	GMR (90% CI)	0.81 (0.48-1.37)	1.20 (0.75-1.94)	1.03 (0.73-1.45)
CL/F (L/h)*	GMR (90% CI)	1.36 (0.91-2.01)	2.05 (1.32-3.19)	1.72 (1.28-2.31)

* GMRs (90% CI) for DTG BID+RIF versus DTG QD (reference).
† Individual $AUC_{0\text{-}12h}$ while on BID dosing were multiplied by 2 for extrapolation to $AUC_{0\text{-}24h}$ and used for calculation of GMR for $AUC_{0\text{-}24h}$ on BID versus QD.
PK profiles were included in PK summary statistics if samples from at least 4 timepoints were available including Cmax, and were excluded if treatment non-adherence was suspected (C0:Ctrough ratio ≥15)

Table 2: PK parameters by dose in children 6 to <18 year old children and adult reference parameters.

Parameter		DTG 25mg BID + RIF (n=5)	DTG 50mg BID + RIF (n=7)	Adult reference DTG 50mg QD[2] (N=16)
C_{trough} (mg/L)	GM (CV%)	0.90 (16)	1.11 (99)	0.83 (26)
$AUC_{0\text{-}24h}$ (h*mg/L)	GM (CV%)	53.4 (21)	60.3 (63)	43.4 (20)
C_{max} (mg/L)	GM (CV%)	3.62 (24)	4.50 (47)	3.3 (16)

Results (III)

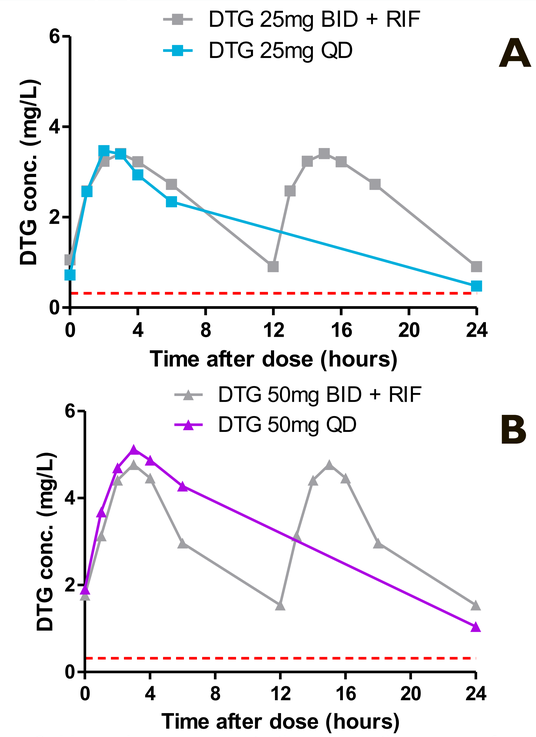

Figure 2: Mean plasma concentration versus time curves for children on DTG 25mg BID + RIF and DTG 25mg QD (**A**) and DTG 50mg BID + RIF and DTG 50 QD (**B**)

Conclusions

- **Twice daily DTG dosing was safe and sufficient to overcome RIF enzyme-inducing effect in children with HIV/TB co-infection aged 6-<18 years**
- **These results support doubling DTG dose for children aged 6 to <18 years treated for TB with RIF-containing regimens**
- **This study included no data on doubling adult DTG dose when it is given with RIF in children weighing <25kg**
- **Embedding PK substudies, including PK TB-HIV drug interaction studies, in phase II/III paediatric trials accelerates obtaining key data for treating children in timely manner**

References

[1] WHO dosing guidance 2019 https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/ [2] Dooley KE, *et al.* J Acquir Immune Defic Syndr 2013; 62:21–7 [3] Min *et al.* AIDS 2011; 25(14):1737-45. [4] Bollen *et al.* J Chrom B 2019; 1105: *76-84.*

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http://odysseytrial.org/