Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Turkova A, Waalewijn H, Chan MK, et al. Dolutegravir twice-daily dosing in children with HIV-associated tuberculosis: a pharmacokinetic and safety study within the open-label, multicentre, randomised, non-inferiority ODYSSEY trial. Lancet HIV 2022; published online July 19. https://doi.org/10.1016/S2352-3018(22)00160-6.
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### Table S1. Dolutegravir dosing in the ODYSSEY trial across different protocol versions

|                  | ODYSSEY v2.0* | ODYSSEY v3.0 | ODYSSEY v4.0 | ODYSSEY v5.0 onwards |
|------------------|---------------|--------------|--------------|---------------------|
| **Main trial participants** | 3–<6kg - | - | - | 5mg or 10mg DT\(^v\) |
|                  | 6–<10kg - | - | - | 15mg DT |
|                  | 10–<14kg - | - | - | 20mg DT |
|                  | 14–<15kg - | 20mg FCT\,* | 25mg FCT | 25mg DT |
|                  | 15–<20kg 20mg FCT\,* | 25mg FCT | 25mg FCT | 25mg DT |
|                  | 20–<25kg 25mg FCT | 25mg FCT | 25mg FCT | 25mg FCT or 50mg FCT\(\*\) |
|                  | 25–<30kg 25mg FCT | 50mg FCT | 50mg FCT | NA |
|                  | 30–<35kg 35mg FCT | 50mg FCT | 35mg FCT | NA |
|                  | 35–<40kg 35mg FCT | 50mg FCT | 35mg FCT | NA |
|                  | ≥40kg 50mg FCT | 50mg FCT | NA | 50mg FCT |

\(*\) DT = dispersible tablets, FCT = film-coated tablets.

* In May 2017 the EMA licensed the use of 20mg DTG in children 15 - <20kg and ≥6 years, following this, children were able to be recruited in this weight and age-band.

** From 1st of April 2018, after ethics notification, sites following protocol version 3.0 and above were recommended to increase the DTG dose of children 25 - <40kg to 50mg FCT QD at their next scheduled study visit based on the results of the WB-PK2. WB-PK2 participants remained on DTG 50mg with ongoing follow-up. Non-PK participants recruited after implementation were initiated on the 50mg film-coated DTG dose.

\(\*\) Infants <6 months of age received DTG 5mg QD while infants ≥6 months of age received DTG 10mg QD, both as dispersible tablets.

\(\*\) Both doses are examined in WB-PK1 part II substudy in this weight-band.

\(\*\) Children 15 - <20kg previously receiving DTG 20mg QD were changed to DTG film-coated 25mg tablets upon the approval of protocol v4.0. Subsequently all children 14–<20kg changed to DTG 25mg QD dispersible tablets following the review of WB-PK1 part I results and approval by the relevant ethical and regulatory authorities.

\(\*\) Children 20 - <25kg previously receiving DTG 25mg QD as one 25mg film-coated tablet changed to either DTG 30mg QD dispersible tablets or DTG 50mg QD film-coated tablet (depending on site) following the review of WB-PK1 part I results and approval by the relevant ethical and regulatory authorities.

\(\*\) Following the review of PK and safety data children 20–<25kg receiving DTG 30mg dispersible tablets should be switched to DTG 50mg film-coated tablets. Those who prefer to remain on DTG 30mg DT will be able to do so until they move weight band.
Table S2. Pharmacokinetic parameters of rifampicin of children with evaluable rifampicin pharmacokinetic curves by WHO paediatric TB weight band dosing

| WHO TB weight band | 8-<12kg | 12-<16kg | 16-<25kg | ≥25-<37kg† | ≥37kg | All eligible children‡ |
|--------------------|---------|---------|---------|----------|-------|------------------------|
| N                  | 1       | 1       | 4       | 8        | 4     | 18                     |
| Age at PK days, years | 2.1  | 6.2   | 7.2 (6.9-8.9) | 11.9 (10.4-13.1) | 15.9 (15.2-16.0) | 11.1 (7.5-14.5) |
| Weight, kg         | 9.5    | 14.6   | 20.1 (19.8-22.7) | 31.3 (27.9-31.8) | 45.6 (41.0-47.8) | 29.7 (20.5-33.8) |
| RIF daily dose, mg/kg | 15.8 | 15.4   | 14.9 (13.3-15.2) | 10.4 (9.6-14.2) | 11.6 (8.8-16.1) | 13.8 (9.6-15.2) |
| GM C\text{max}(CV%), mg/L* | 6.5  | 12.9   | 3.3 (56) | 4.7 (82) | 7.0 (36) | 5.1 (71) |
| AUC\text{0-6}   | 19.3    | 36.0   | 9.1 (55) | 14.0 (80) | 26.8 (27) | 15.9 (75) |

Data are median (IQR) for age, weight, and rifampicin doses, and geometric means (coefficient of variation %) for pharmacokinetic parameters, unless indicated otherwise. AUC\text{0-24h}=area under the concentration-time curve from 0 to 24 h. C\text{max}=maximum plasma concentration. PK=pharmacokinetic. RIF=rifampicin. SEM= standard error for the mean.
*Rifampicin C\text{max} range: optimal 8-24 mg/L, low 4-<8 mg/L, very low <4mg/L (Peloquin et al., 2002). Of total 18 children with evaluable rifampicin concentrations, 3 children (17%) had optimal rifampicin C\text{max}, 11(61%) had low C\text{max} and 4(22%) very low C\text{max}.
†7 children included for AUC\text{0-6} due to missed rifampicin sample at 6 hours after dose for one participant.
‡17 children included for AUC\text{0-6} due to missed rifampicin sample at 6 hours after dose for one participant.

Reference: Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs. 2002;62(15):2169-83.
Table S3. Listing of adverse events reported

| ID   | TB-PK participation | Time from DTG BID to event diagnosis (days) | DTG dose at event diagnosis date | SAE                      | System Level | Event Description                              | Event Grade | IRIS | ART Modifying | Relatedness to ART (ERC) |
|------|---------------------|--------------------------------------------|---------------------------------|--------------------------|--------------|-----------------------------------------------|-------------|------|---------------|--------------------------|
| 2    | Done TB-PK          | 40                                         | BID_35                          | Yes                      | Infectious Disease | Tuberculosis - disseminated/miliary           | 3           | Yes | No            | No                       |
| 4    | Done TB-PK          | 65                                         | BID_25                          | No                       | Haematological    | Neutropenia                                   | 3           | N/A | No            | No                       |
| 5    | Done TB-PK          | 184                                        | QD_25                           | No                       | Infectious Disease | Hepatitis A                                   | 4           | No  | Yes#          | No                       |
| 6    | Done TB-PK          | 105                                        | BID_25                          | Yes                      | Infectious Disease | Acute febrile episode - undiagnosed          | 3           | No  | No            | No                       |
| 7    | Done TB-PK          | 4                                          | BID_25                          | Yes‡                     | Infectious Disease | URTI                                           | 2           | N/A | No            | No                       |
| 7    | Done TB-PK          | 4                                          | BID_25                          | Yes‡                     | Skin             | Rash, maculopapular                           | 2           | N/A | No            | No                       |
| 7    | Done TB-PK          | 28                                         | BID_25                          | No                       | Haematological    | Anaemia with no clinical symptoms            | 3           | No  | No            | No                       |
| 8    | Done TB-PK          | 16                                         | BID_50                          | Yes                      | Nervous System    | Epilepsy, fits, convulsions                   | 3           | No  | No            | No                       |
| 8    | Done TB-PK          | 28                                         | BID_50                          | No                       | Haematological    | Anaemia with clinical symptoms               | 3           | No  | No            | No                       |
| 8    | Done TB-PK          | 28                                         | BID_50                          | Yes                      | Cardiovascular    | Deep vein thrombosis                          | 3           | No  | No            | No                       |
| 8    | Done TB-PK          | 126                                        | BID_50                          | No                       | Infectious Disease | Tuberculosis - disseminated/miliary          | 3           | Yes | No            | No                       |
| 1    | Not done TB-PK      | 28                                         | BID_20                          | Yes                      | Systemic         | Kwashiorkor                                   | 4           | Yes | No            | No                       |
| 1    | Not done TB-PK      | 59                                         | BID_20                          | Yes                      | Infectious Disease | Tuberculosis - disseminated/miliary*         | 5           | Yes | No            | No                       |
| 3    | Not done TB-PK      | 175                                        | BID_50                          | No                       | Haematological    | Neutropenia                                   | 3           | No  | No            | No                       |
| 9    | Not done TB-PK      | 34                                         | BID_35                          | Yes                      | Hepatic           | Drug induced liver injury                     | 4           | No  | No            | No                       |
| 10   | Not done TB-PK      | 1                                          | BID_50                          | Yes                      | Renal             | Renal failure - chronic                      | 4           | No  | No            | No                       |
| 11   | Not done TB-PK      | 104                                        | BID_10**                        | Yes                      | Non-HIV related death | Traumatic*                                   | 5           | No  | No            | No                       |

#DTG was stopped. This event was considered by the ERC to be unlikely/unrelated to DTG.
*SAE reported to have resulted in death.
‡Components of the same clinical SAE (Rash, maculopapular (grade 2) and URTI (grade 2))
¥Participant was returned to 25mg DTG once-daily 2 days before diagnosis of hepatitis A.
SAEs, serious adverse events; DTG, dolutegravir; BID, twice daily; ERC, endpoint review committee.
*All participants were receiving DTG film coated tablets at event diagnosis, except for **one child who was receiving 10mg dispersible tablets formulation.
Table S4. Summary of adverse events, frequency and rates by dolutegravir dose

| ART regimen* | Safety follow-up** (person years) | SAEs | Grade 3 or above |
|--------------|-----------------------------------|------|------------------|
|              | N [N children] | Rate p.100PYs [95% CI] | N [N children] | Rate p.100PYs [95% CI] |
| ≥40Kg        |                  |      |                  |                  |
| Approved DTG dose | 6.5              | 2    | 30.6             | 5                | 76.6             |
|              | [1]              | [3.7-110.7] | [2]             | [24.9-178.8]     |
| <40Kg        |                  |      |                  |                  |
| Previously approved / Lower DTG dose# | 10.1             | 6    | 59.6             | 8                | 79.5             |
|              | [5]              | [21.9-129.8] | [7]             | [34.3-156.6]     |
| Currently approved / Higher DTG dose## | 8.4             | 2    | 23.8             | 2                | 23.8             |
|              | [2]              | [2.9-86.1] | [2]             | [2.9-86.1]       |

* Weight-based DTG doses were given twice-daily, i.e., their daily dose was doubled when co-administered with rifampicin and until 2 weeks after rifampicin was stopped. Safety follow-up time is between starting twice-daily DTG and 30 days after returning to once-daily DTG or last follow-up visit if not returned to once-daily DTG. Two participants did not return to once-daily DTG due to death.

**Children contribute to follow-up whilst on a protocol-defined DTG dose in DTG arm. Follow-up and adverse events occurring whilst on non-per protocol doses or off these regimens do not contribute to this analysis (0.5 person years; no adverse events)

# Lower DTG doses: the ODYSSEY trial opened with children on doses evaluated by the IMPAACT dose-finding study and/or approved by FDA and/or EMA (20mg film-coated tablets (FCTs) in weight-band 15<20kg, 25mg in 20<30kg and 35mg in 30<40kg).

## Following ODYSSEY nested weight-band PK substudy results (Bollen et al., 2020; Waalewijn et al. 2022), children outside of the PK substudies were moved to higher DTG doses: 25mg DT in 14<25kg, 50mg FCT in 20<40kg. FDA and EMA dosing licenses were subsequently updated.

References:

Bollen PDJ, Moore CL, Mujuru HA, Makumbi S, Kekitiinwa AR, Kaudha E, et al. Simplified dolutegravir dosing for children with HIV weighing 20 kg or more: pharmacokinetic and safety substudies of the multicentre, randomised ODYSSEY trial. Lancet HIV. 2020;7(8):e533-e44.

Waalewijn H, Chan MK, Bollen PDJ, Mujuru HA, Makumbi S, Kekitiinwa AR, et al. Dolutegravir dosing for children with HIV weighing less than 20kg: pharmacokinetic and safety substudies nested in the multicentre, randomised ODYSSEY trial. Lancet HIV. 2022 Feb 18; S2352-3018(21)00292-7.
**Figure S1. Timing of pharmacokinetic day visits and dolutegravir dosing in relation to tuberculosis treatment**

| Last month of TB treatment | 2 weeks | 2 weeks |
|---------------------------|---------|---------|
| DTG BID + RIF             | DTG BID | DTG QD  | DTG QD  |

Pharmacokinetic day 1 (12h curve)

Pharmacokinetic day 2 (24h curve)

BID=twice daily. DTG=dolutegravir. QD=once daily. RIF=rifampicin. TB=tuberculosis
Figure S2. Within-subject comparisons per age group and per dolutegravir dose for AUC$_{0-24h}$, C$_{max}$ and C$_{trough}$ for twice-daily dolutegravir with rifampicin and once-daily dolutegravir.

C$_{trough}$=concentration at the end of the dosing interval. AUC$_{0-24h}$=area under the concentration-time curve from dose until 24 hours after dose. C$_{max}$=highest measured concentration in dosing interval. BID=twice daily. QD=once daily.
Figure S3. Individual dolutegravir pharmacokinetic parameters on double dose dolutegravir co-administered with rifampicin by dolutegravir formulation and dose

DT=dispersible tablets. FCT= film-coated tablets. $C_{\text{trough}}$: trough concentration. AUC$_{0-2\text{4h}}$: area under the concentration-time curve from 0 to 24 h. $C_{\text{max}}$: maximum concentration. EC90: concentration at which 90% of maximal viral inhibition was achieved in a 10-day monotherapy study (Min et al., 2011). Individual dolutegravir $C_{\text{trough}}$, AUC$_{0-2\text{4h}}$, and $C_{\text{max}}$ in children on twice-daily dolutegravir taking 25mg DT, 25mg FCT or 50mg FCT co-administered with rifampicin. Horizontal black lines indicate geometric means per dose and formulation. Red dotted line indicates dolutegravir in-vivo EC90. Green dashed lines indicate geometric mean adult reference values for 50mg once-daily (lower line) and twice-daily (upper line) doses.

Reference: Min S, Sloan L, DeJesus E, Hawkins T, McCurdy L, Song I, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. Aids. 2011;25(14):1737-45.