Model Informed Dolutegravir Dose Selection in Pediatrics with 1st Generation INSTI-Resistance

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Introduction

- Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) approved for once daily dosing in INSTI-naïve adults and children (≥4 weeks and ≥3 kg) living with HIV.
- For INSTI-experienced adults with certain INSTI-resistance (INSTI-r) substitutions or clinically suspected INSTI resistance, the recommended dose is 50 mg film coated tablet (FCT) twice daily (BID).
- However, dosing of DTG regimen for children with INSTI-r is not yet established.
- The objective of this work was to generate model-based pharmacokinetic (PK) data to inform DTG BID dosing in 1st generation INSTI-r children by weight bands (≥3 to <6 kg , ≥6 to <10 kg , ≥10 to <14 kg , ≥14 to <20 kg , ≥20 to <30 kg , and ≥30 to <40 kg).
- The efficacy and safety established in adults can be extrapolated to the pediatric population by matching the PK exposures, in accordance with FDA and EMA guidance.
- To understand possible risk with higher exposures, the modelled pediatric exposures from BID dosing should also be evaluated with reference to the pediatric and adult exposures observed in DTG drug development trials[1-4].

Methods

A population PK model was developed using the pediatric exposure data from IMPAACT P1093 (NCT01302847) and PENTA ODYSSEY (NCT02259127) studies and this was used for simulation of PK profiles in INSTI-r pediatric subjects[1].

Clinical trial simulations were performed using NONMEM®. This simulation with BID dosing included 1200 subjects (200 subjects per weight band/dose combination), with equal distribution of males and females. The DTG PK following BID dosing of Tivicay DT was predicted.

The target PK exposures were (Geometric mean(GM)) C12h >1.97 µg/mL & AUC0-12h >32.2 µg*h/mL in these pediatric subjects.

DTG Cmax exposures were also evaluated for safety, with reference to existing adult and pediatric data (IMPAACT P1093 & ODYSSEY).

Modelling informs DTG dose selection for pediatric patients with 1st generation INSTI-r and exposures predicted to achieve similar to those observed in adults with 50 mg FCT BID dosing

Results

Figure 1. Predicted C12h following BID dosing

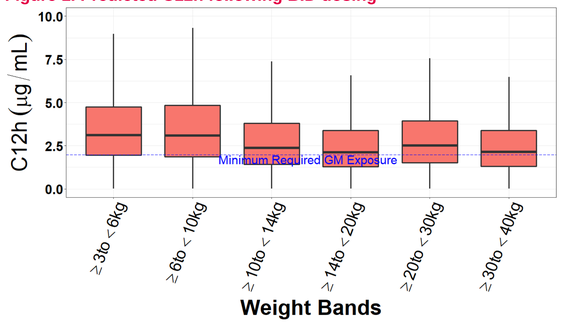
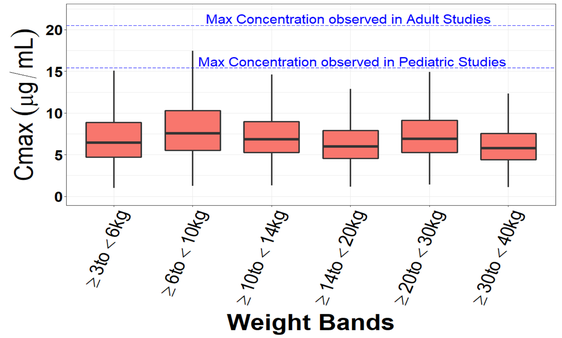


Figure 2. Predicted Cmax following BID dosing



- The predicted exposures for each weight band were well below observed Cmax values (Figure 2).

Table 1. DTG Model Based BID Dosing Regimen in 1st Generation INSTI-r Pediatric Subjects

Weight Band (kg)	Dispersible Tablet BID Dose	Cmax (µg/mL)	AUC0-12h (µg*h/mL)	C12h (µg/mL)
≥3 to <6	5 mg	**6.53** (3.06 – 14.22)	**50.28** (22.12 – 115.5)	**3.10** (0.94 – 9.15)
≥6 to <10	10 mg	**7.69** (3.64 – 16.73)	**56.24** (23.70 – 131.95)	**3.07** (0.82 – 9.97)
≥10 to <14	15 mg	**6.89** (3.64 – 13.42)	**47.56** (22.24 – 101.22)	**2.30** (0.62 – 7.15)
≥14 to <20	15 mg	**6.02** (3.14 – 11.66)	**41.81** (19.40 – 90.05)	**2.03** (0.55 – 6.33)
≥20 to <30	20 mg	**6.97** (3.66 – 13.54)	**48.65** (22.50 – 104.60)	**2.40** (0.67 – 7.32)
≥30 to <40	20 mg	**5.78** (3.00 – 11.29)	**40.81** (18.96 – 86.44)	**2.04** (0.57 – 6.13)

PK Parameters presented as a Geometric Mean (90% Prediction Interval)

- The proposed BID dosing (Table 1) yielded predicted exposures comparable to the target exposures.

Conclusions

- The proposed weight-band-based BID dosing of DTG DT for children achieved drug exposures comparable to those achieved in adults with BID dosing using the 50 mg FCT. Thereby these proposed doses are expected to provide similar efficacy as observed in adults.
- These doses per weight band are based on modelling, and not based on clinical observations: this is due to the difficulty of recruiting pediatric subjects with 1st generation INSTI-r disease.
- These modelled data could be the basis for DTG dose selection for pediatric patients with 1st generation INSTI-r.

References: 1. Singh R, et al. Pediatric dolutegravir (DTG) dosing recommendations derived from combined P1093 and ODYSSEY population pharmacokinetic analysis. Presented at: International Workshop on HIV Pediatrics 2020; November 16-17, 2020. **2.** Chen, Shuguang, et al. "Effect of a single supratherapeutic dose of dolutegravir on cardiac repolarization." Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 32.4 (2012): 333-339. **3.** Ruel, Theodore D., et al. "Pharmacokinetics, safety, tolerability, and antiviral activity of dolutegravir dispersible tablets in infants and children with HIV-1 (IMPAACT P1093): results of an open-label, phase 1–2 trial." The Lancet HIV 9.5 (2022): e332-e340. **4.** Bollen, Pauline D.J., et al. "Simplified dolutegravir dosing for children with HIV weighing 20 kg or more: pharmacokinetic and safety substudies of the multicentre, randomised ODYSSEY trial." The Lancet HIV 7.8 (2020): e533-e544.

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