A Single Once Daily ABC/DTG/3TC Tablet Predicts Safe and Effective Exposures in Children 3 to <6kg

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Introduction

- Abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) is a fixed-dose combination (FDC) tablet approved for adults and children with HIV weighing ≥6 kg and aged ≥3 months in the US.
- We evaluated whether a single FDC ABC/DTG/3TC (60 mg/5 mg/30 mg) dispersible tablet (DT) once daily would achieve therapeutic targets in children weighing ≥3 to <6 kg (aged ≥4 weeks) using population pharmacokinetic (PopPK) model approach.

Methods

- Drug-specific pediatric PopPK models were used for simulations[1-2].
  - ✓*ABC model adjusted with uridine diphosphate-glucuronosyltransferase 2B7 (UGT2B7) and alcohol dehydrogenase (ADH) enzyme maturation[3].*
  - ✓*DTG model with UGT1A1 maturation described previously[1].*
  - ✓*3TC model adjusted with renal maturation[4].*
- Simulations were performed with 1000 replicate trials of 200 participants. Exposure metrics (AUC0-24h, Cmax and C24h) were calculated for each drug and compared with geometric mean (GM) exposure target range previously used in pediatrics[5].
- Safety data from young children across weight bands from IMPAACT 2019 (≥6 kg)[5], P1093 (≥3 kg)[6] and ODYSSEY (≥3 kg)[7] were evaluated.
- Review of ABC and 3TC PK studies in neonates (including PETITE Study)[8-9] and infants <3 months were used to interpolate safety conclusions to infants 4 weeks to <3 months of age.

The Once Daily Single ABC/DTG/3TC DT (60 mg/5 mg/30 mg) Treatment Option May Be a Practical Solution for Infants Weighing ≥3 to <6 kg (Aged ≥4 Weeks) With Early HIV Diagnosis

Results

- Predicted exposures (Table 1) were within the target range (DTG C24h GM 0.697-2.26 µg/mL, ABC AUC0-24h GM 6.3-50.4 µg*h/mL, and 3TC AUC0-24h GM 6.3-26.5 µg*h/mL)[5].

Table 1. Predicted ABC/DTG/3TC DT Exposures in ≥3 to <6 kg

Entity	Dispersible Tablet Dose	AUC0-24h (µg*h/mL)	C24h (µg/mL)	Cmax (µg/mL)
ABC	60 mg	**17.84** (16.54, 19.24)	0.11 (0.09, 0.13)	4.73 (4.44, 5.03)
DTG	5 mg	57.79 (54.07, 61.56)	**1.32** (1.18, 1.46)	4.59 (4.36, 4.83)
3TC	30 mg	**11.36** (10.77, 11.97)	0.03 (0.02, 0.04)	1.80 (1.72, 1.89)

Note: AUC0-24h, Cmax and C24h presented as a GM (95% CI)

Figure 1. Comparison of Predicted ABC AUC0-24h in ≥3 to <6 kg With Approved FDC Doses in ≥6 kg

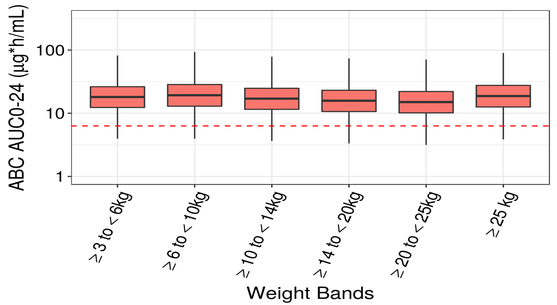


Figure 2. Comparison of Predicted DTG C24h in ≥3 to <6 kg With Approved FDC Doses in ≥6 kg

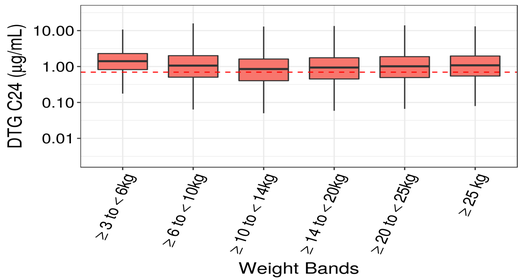
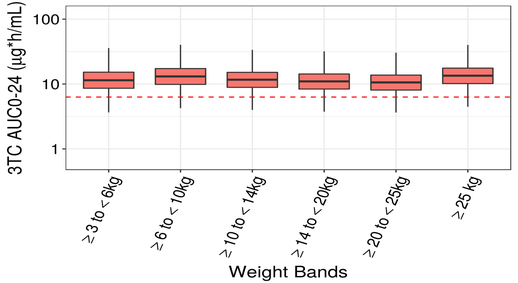


Figure 3. Comparison of Predicted 3TC AUC0-24h in ≥3 to <6 kg With Approved FDC Doses in ≥6 kg



- The predicted exposures of ABC/DTG/3TC in ≥3 to <6 kg with FDC tablet were comparable to other weight bands with approved FDC doses[5] (Figures 1 to 3).

Safety

- Use of 5 mg DTG as Dispersible Tablets in the ≥3 to <6 kg weight band in the P1093 and ODYSSEY studies led to approval of DTG based regimens from ≥4 weeks.
- Consideration of the benefit risk balance of ABC/DTG/3TC use in the ≥3 to <6 kg weight band was also supported by the existing safety data from subjects ≥6 kg taking ABC/DTG/3TC in IMPAACT 2019 study. These data did not reveal additional safety concerns with ABC/DTG/3TC compared to either what has been previously observed in adults or observed for the individual single entities in a pediatric population.
- Available literature references presenting safety data in neonates and infants <3 months, taken together with the DTG safety data in infants from 4 weeks of age from P1093, showed that the safety profile across weight bands treated with these DTG based regimens is similar.
- These safety data suggest no additional drug related safety issues in this age group compared to infants 6 kg and above (or 3 months and above), in addition to supporting the extension of the indication to the ≥3 to <6 kg weight band (≥4 weeks).

Conclusions

- Predicted exposures with single FDC ABC/DTG/3TC DT in infants weighing ≥3 to <6 kg (aged ≥4 weeks) were above the targets and expected to provide comparable efficacy observed in pediatrics and adults[5].
- The available safety data suggest a positive benefit-risk balance for use of single FDC ABC/DTG/3TC DT in the ≥3 to <6 kg weight band, and from 4 weeks of age.

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