PK AND 4-WEEK OUTCOMES OF DOLUTEGRAVIR DISPERSIBLE TABLETS IN HIV-INFECTED CHILDREN

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Background and Methods

BACKGROUND

Dolutegravir (DTG, S/GSK1349572) is recommended as first-line treatment for HIV-infected adults and children 6 years and older due to its potency, high barrier to resistance, convenience and tolerability (1). A 5 mg dispersible tablet (DTG-DT) formulation for children is being evaluated in IMPAACT P1093 (NCT01302847), an ongoing phase I/II open-label dose-finding study. The first DTG-DT dosing tested did not meet target drug exposures for Cohorts III and IV; the doses assessed in Cohort V met target exposures (2). Here we present the intensive pharmacokinetic (PK), 4-week safety and efficacy data of higher dosing for DTG-DT in children ages 6 months to <6 years.

METHODS

Children with HIV were either ART-experienced and failing or ART-naive. Enrollment was stratified into two age cohorts of 10 children (≥6 months to <2 years and ≥2 to <6 years). DTG-DT was dosed once daily by WHO weight-band (Table 1). Children received DTG-DT alone or added to stable-failing or empiric initial background regimens. Stage 1 intensive PK sampling was completed between days 5-10 under partial-fasting (no high fat food/liquid 2 hours prior, 1 hour after) conditions (Figure 1). Background regimens were optimized based on enrollment HIV genotypes. Safety, tolerability, and plasma HIV-1 RNA levels were assessed through 4 weeks.

FIGURE 1. P1093 Study Design and Dose Determination by Age Cohorts

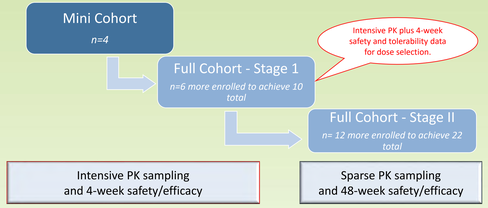


TABLE 1. DTG Dispersible Tablet Dosing

Weight Band (kg)	Revised Dose (mg)	Dose (mg/kg) for Weight Range		*Dose previously tested (mg)*
		Lower Weight	Upper Weight	
6 - <10	15	2.50	1.50	*10*
10 - <14	20	2.00	1.43	*15*
14 - <20	25	1.79	1.25	*15*

Results

BASELINE CHARACTERISTICS

- 10 children were enrolled to each age cohort.

TABLE 2. Baseline Demographics

Characteristic	≥2 years to <6 years (n=10)	≥6 months to <2 years (n=10)
Age (years)	3.6 (2.1, 6.0)	1.0 (0.5, 1.7)
Female	3	7
Weight (kg)	13.0 (9.3, 17.5)	7.5 (6.5, 9.5)
Region Africa	6	8
Asia	2	0
North America	1	1
South America	1	1
CD4 %	25.1 (0.3, 42)	31 (20, 49)
CD4 count (cells/mm^3)	1260 (1, 2463)	2359 (1352, 8255)
HIV-1 RNA [Log$_{10}$(copies/ml)]	4.3 (2.7, 5.9)	4.1 (2.5, 6.1)

Values are median (range) or n

PHARMACOKINETICS

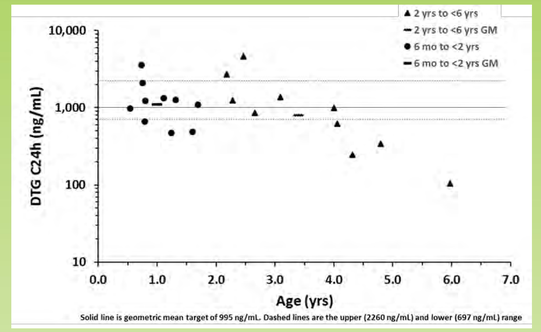
- The GM C_{24h} and AUC_{24h} and of each age cohort were within target range.
  [Based on adult data, exposure targets were geometric mean (GM) (range) C_{24h} of 995 (697-2260) ng/mL) and AUC_{24h} of 46 (37-134) mg.h/L].

TABLE 3. Intensive PK Results for DTG DT

Cohort (n=10 each)	Weight (kg)^	Dose (mg/kg)^	AUC_{24h} (mg x h/L)*	C_{max} (ng/mL)*	C_{24h} (ng/mL)*
≥2 years to <6 years	13 (8.6-17.5)	1.63 (1.4-2.0)	59.0 (62.2)	5181 (44)	791 (105.1)
≥6 months to <2 years	7.7 (6.8-9.5)	1.95 (1.58-2.21)	70.2 (49.6)	5702 (37.1)	1094 (70.4)

*^ Median (range); * Geometric mean (arithmetic CV%)*

FIGURE 2. Dolutegravir DT: 24 hour Trough by Cohort



VIROLOGY

- HIV-1 RNA levels were <400 c/mL in 16/20 and <50 c/ml in 8/20 participants after 4 weeks of treatment, with median decrease from BL of 2.38 log10 (c/mL) (IQR: 1.36, 3.11).

TABLE 4. Optimized Background Regimens

ARV regimens	≥2 years to <6 years	≥6 months to <2 years
ZDV, 3TC	4	
D4T, 3TC	1	
ABC, FTC	1	1
ABC, 3TC	1	8
ZDV, 3TC, LPV/r	1	
ABC, 3TC, LPV/r	1	1
3TC, EFV, DRV/r	1	

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Conclusions

4 WEEK SAFETY AND TOLERABILITY

- 3 participants experienced Grade 3 or 4 adverse events (AE), none of which were attributed to study drug
  - One experienced grade 4 neutropenia
  - One experienced grade 3 high lipase and grade 3 low bicarbonate
  - One suffered viral pneumonia, diarrhea, and mycobacterium avium complex infection
- No participants permanently discontinued study drug due to AE

DISCUSSION

- The increased weight-band DTG-DT dosing was successful in meeting the pre-specified AUC_{24h} and C_{24h} targets for both age cohorts among children 6 months to <6 years old.
- Previously reported DTG dosing met target concentrations in children 4 weeks to <6 months of age (Ruel, 2018).
- The DTG dispersible tablet formulation has been well-tolerated.
- Together with the additional PK, long-term safety and efficacy data collected, these novel results will support regulatory approval for DTG in these age groups and form the basis for World Health Organization weight-band based dosing recommendations for DTG-DT in children.

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REFERENCES

1. World Health Organization.. "Annex 3. Dosages of ARV drugs ", from https://www.who.int/hiv/pub/guidelines/ARV_Guidelines-2018-Annex3.pdf
2. Ruel T, et al. Pharmacokinetic and 4-week safety/efficacy of dolutegravir (S/GSK1349572) dispersible tablets in HIV-infected children aged 4 weeks to <6 years: results from IMPAACT P1093. XXII International AIDS Conference (Amsterdam, Netherlands) July 25, 2018. Poster Number: LBPED023

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