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

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Background and Methods

BACKGROUND

Dolutegravir (DTG) is recommended for first-line treatment of HIV-1 infected adults due to its potency, high barrier to resistance, and tolerability. It is approved for children 6-18 yrs of age, in many settings.

A 5 mg dispersible tablet (DTG-DT) pediatric formulation is being evaluated in IMPAACT P1093, an ongoing phase 1/2 open-label pharmacokinetic (PK), safety, and dose-finding study.

Here we present intensive PK and 4-week safety (primary outcome) and efficacy of the first doses of DTG-DT tested in the youngest age-defined cohorts (V: ≥4 weeks to <6 months, IV: ≥6 months to <2 years, III: ≥ 2 to <6 years).

METHODS

On enrollment, children received DTG-DT as monotherapy, or added to stable-failing or empiric initial background regimens and dosed using weight-band tables (Table 1). Intensive 24-hour PK sampling was completed between days 5-10, after which background regimens were optimized based on enrollment genotypes. Safety, tolerability, and plasma HIV-1 RNA levels were assessed through 4 weeks (Figure 1). From adult data, targets (range) for geometric mean (GM) exposures were AUC24h 46 (37-86) mgxh/L and C24h 750 (500-2260) ng/mL.

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

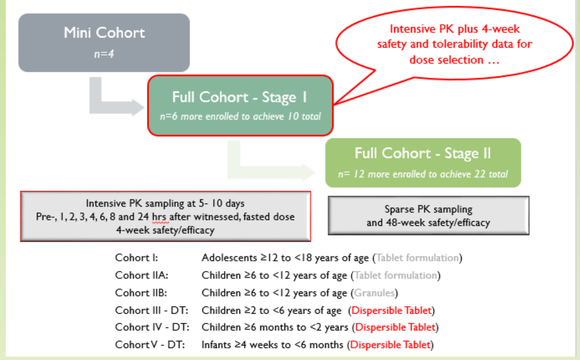


TABLE 1. Initial DTG Dispersible Tablet Dosing

Weight Band (kg)	Dose (mg)	Dose (mg/kg) for Weight Range	
		Lower Weight	Upper Weight
3-<6	5	1.67	0.83
6 - <10	10	1.67	1.00
10 - <14	15	1.50	1.07
14 - <20	15	1.07	0.75
20-<25	20	1.00	0.80

Results

BASELINE CHARACTERISTICS

In P1093 32 children were enrolled to achieve 30 (10 per age cohort) with evaluable data.

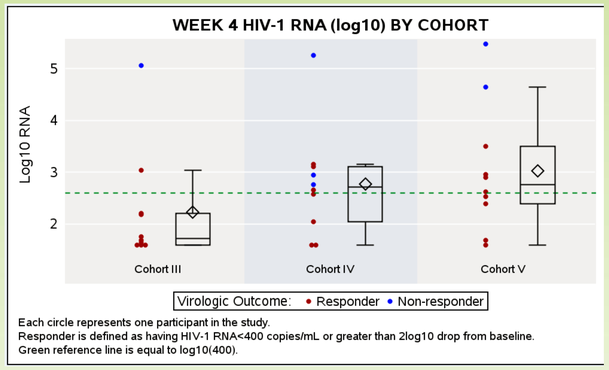
TABLE 2. P1093 Key Baseline Demographics N=30 (Cohorts III-DT,IV-DT, V-DT)

Characteristic	Median
Female	13 (43%)
CD4% >14	27 (90%)
Baseline CD4 cell count ≥500 c/mL	30 (100%)
Baseline HIV-1 RNA ≥50,000 c/mL	16 (53%)

ANTIVIRAL EFFICACY AT WEEK 4

At Week 4, 24/30 children had attained HIV-1 RNA <400 c/mL or achieved a >2 log decline from Baseline. Individual RNA decline /participant/Cohort is seen in Figure 2.

FIGURE 2. Week 4 Virologic Outcome for Cohort III, IV, and V



4 WEEK SAFETY AND TOLERABILITY

- No Grade 3 or 4 adverse events attributed to study drug
- Grade 3 events included low bicarbonate (2), low phosphate (1) , elevated systolic BP (1). One grade 4 low ANC was reported.
- No discontinuations due to adverse events
- DTG was generally well tolerated

PK

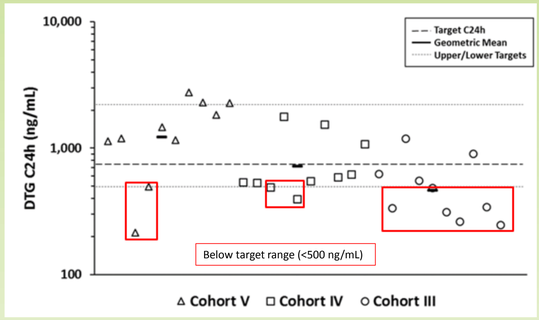
The GM AUC_{24h} and C_{24h} of each cohort were within target range, except for the C24h value in Cohort III (Table 1). From adult data, targets (range) for geometric mean (GM) exposures were **AUC_{24h} 46 (37-86) mgxh/L and C_{24h} 750 (500-2260) ng/mL.**

TABLE 3. Intensive PK Results for DTG DT

Cohort (n=10 each)˜	Age (yrs)^	Dose (mg/kg)^	AUC_{24h}* (mg x h/L)	C_{24h}* (ng/mL)
≥2 years to <6 years *(Cohort III)*	4.0 (2.1-5.9)	1.1 (0.8-1.6)	40 (36%)	461 (59%)
≥6 months to <2 years *(Cohort IV)*	1.2 (0.9-1.9)	1.2 (1.0-1.4)	51 (38%)	711 (60%)
≥4 weeks to <6 months *(Cohort V)*	0.34 (0.28-0.39)	1.2 (0.9-1.7)	61 (44%)	1207 (55%)

˜Enrolled 32 children to achieve 30 (10 per cohort) with evaluable data.
^ Median (range); * Geometric mean (arithmetic CV%);

FIGURE 3. Dolutegravir DT: 24 hour Trough by Cohort



DISCUSSION OF PK FINDINGS

The 5 mg and 10 mg DT doses assessed in the youngest children (Cohort V, 4 weeks to 6 months) achieved exposures comparable to adults. Enrollment into this cohort at these doses continues. The DTG doses assessed in children aged 6 months to <6 years (Cohorts III and IV) generally achieved doses in the protocol-defined range, however the C24h values trended lower. Higher doses in these cohorts are currently under assessment.

Exposures in children in the 6 to <10kg weight band were higher in younger children (i.e. <6 months of age). The age effect observed is not unexpected as clearances can be higher in older children (i.e. 2 to 6 years) than in infants (Anderson & Holford, 2008).

FEASIBILITY, TOLERABILITY, AND ACCEPTABILITY OF THE DTG DISPERSIBLE TABLET

Because the dispersible tablet is a new pediatric formulation of DTG, the feasibility of administration and acceptability were assessed. Few issues with administration of the dispersible tablet were reported. The dispersion was well-accepted by the children in this study.

Cohort (N=10 participants in each cohort)	Problems with swirling, dispersing or drawing up?	Overall Taste Assessment?	Problems taking?
≥2 yr to <6 yr *(III)* *n= 35 assessments*	Never: 34 "Infrequent/ sometimes": 1	Very good: 14 Good: 13 Average: 2 Very bad: 5	No: 33 Yes: 2
≥6 mo to <2 yr *(IV)* *n=32 assessments*	Never: 29 "Infrequent/ sometimes": 3	Very good: 7 Fair/Pleasant: 15 Acceptable: 8 Very bad: 2	No: 28 Yes: 4
≥4 wk to <6 mo *(V)* *n=28 assessments*	Never: 28 "Infrequent/ sometimes": 0	Very good: 9 Fair/Pleasant: 18 Acceptable: 2 Very bad: 0	No: 28 Yes: 0

Conclusions

- Data from these study cohorts will inform dosing of DTG in HIV-infected children 4 weeks to <6 years of age.
- Due to moderate inter-subject variability, DTG C24h resulted in some subjects having C24h values below the protocol-defined target range. Additional doses are currently under assessment.
- Good short term safety and efficacy were observed in these children at the doses assessed.

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REFERENCES & RELATED ABSTRACTS

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