Twenty-four week safety, tolerability and efficacy of dolutegravir dispersible tablets in children 4 weeks to <6 years old with HIV-1: results from IMPAACT P1093

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BACKGROUND

Dolutegravir (DTG) is recommended for first-line treatment of adults and children with HIV-1 due to its potency, high barrier to resistance, and tolerability. A 5mg dispersible tablet (DTG-DT) pediatric formulation is being evaluated in IMPAACT P1093 (NCT01302847), an ongoing phase I/II open-label dose-finding study. Here we present 24-week safety, tolerability and efficacy results among participants 4 weeks to <6 years old who received the dose proposed to regulatory authorities.

METHODS

Participants were ages 4 weeks to < 6 years, with HIV RNA >1000 copies/ml, enrolled into 3 age cohorts, ≥ 4 weeks to < 6 months**,** ≥ 6 months to < 2 years of age **,** ≥ 2 years to < 6 years. After initial 4-week dose evaluation with an intensive pharmacokinetic cohort, additional participants were enrolled to assess long term outcomes at proposed dosing. Participants received optimized background regimen that included 2 other agents, of which one had genotype predicted activity. Clinical and laboratory assessments occurred between day 5 and 13, and at weeks 4, 8, 12, 16, and 24 (+/-3 days). Safety analysis included cumulative data to April 30, 2019.

Table 1. DTG DT Dosing by WHO weight-band

Age	Weight Band (kg)	DTG DT Dose (mg)
≥ 4 weeks to < 6 months of age	3 to < 6	5
	6 to < 10	10
≥ 6 months of age	6 to < 10	15
	10 to < 14	20
	14 to < 20	25

RESULTS

51 children enrolled into the 3 age cohorts described.

Table 2. Participant characteristics at baseline

Characteristic (N= 51)	N(%) or Median(IQR)
Female	28 (55%)
Location	
Asia (Thailand)	6 (12%)
Africa (Botswana, Kenya, South Africa, Tanzania, Uganda, Zimbabwe)	36 (70%)
North America (USA)	2 (4%)
South America (Brazil)	7 (14%)
ART Naive	15 (29%)
HIV RNA Log_{10}(Copies/ml)	4.3 (3.3, 5.8)
CD4+ Cells	1866 (1189, 2384)
CD4%	24.2 (20.0, 31.0)

Once-daily weight-band dosing of DTG-DT well-tolerated with a favorable safety profile, a robust antiviral effect among children 4 weeks to <6 years old.

Efficacy

Virologic and immunologic outcomes were assessed in the 34 (67%) participants with 24 week RNA result at time of data freeze.

Figure 1. Proportion of participants with HIV RNA<400 c/mL over time

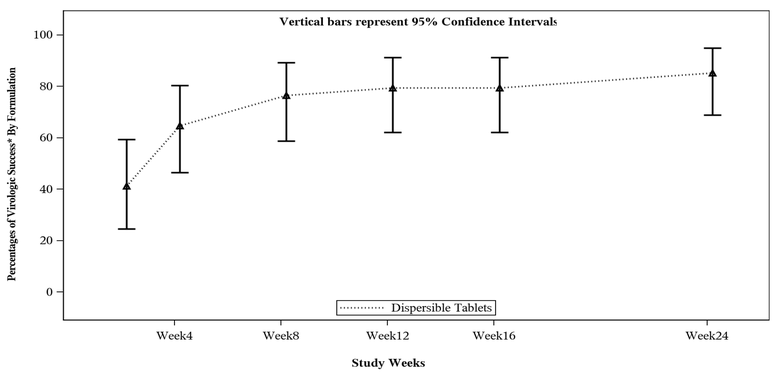

Table 3. Optimized Background Regimen

Regimen	n (%)
ABC, 3TC	24 (47%)
ZDV, 3TC	10 (20%)
ZDV, 3TC, LPV/r	6 (12%)
ABC, 3TC, LPV/r	5 (10%)
ABC, FTC	2 (4%)
D4T, 3TC, LPV/r	2 (4%)
D4T, 3TC	1 (2%)
3TC, EFV, DRV/r	1 (2%)

Table 4. Virologic and immunologic outcomes at week 24

Age Group	4 wks to <6 mo (n=17)	6 mo to <2 yrs (n= 9)	2 yrs to <6 yrs (n=8)
HIV RNA <50c/mL*	41% (18, 67)	67% (30, 93)	63% (25, 92)
HIV RNA <400c/mL*	88% (64, 99)	89% (52, 100)	75% (35, 97)
Δ CD4+ cells(cells/mm^3)˜	352 (-189, 926)	-221 (-962, 150)	76 (-173, 458)
Δ CD4 percent˜	5 (3, 9)	3 (-10, 7)	5 (-2, 9)

***Proportion (95% confidence interval); ˜Median (interquartile range) change from baseline**

Safety

- All children who received the proposed dose were included in safety analyses
- No Grade 3 or 4 adverse events (AE) *attributed to study drug*
- Study drug was never discontinued due to toxicity

Table 5. Number (%) of participants in each age group who experienced at least one grade 3/4 adverse event* by 24 weeks

	4 wks to <6 mo (n=23)	6 mo to <2 yrs (n=12)	2 yrs to <6 yrs (n=16)
# with grade 3 or greater **clinical** event(s), overall	3 (13%)	2 (17%)	1 (6%)
# with grade 3 or greater **laboratory** event(s), overall	13 (57%)	4 (33%)	3 (19%)

˜ DAIDS AE Grading Table, Version 1.0, December 2004, Clarification August 2009

- Youngest cohort experienced majority of events
- The most common Grade 3/4 laboratory AE were low neutrophil (n=11), bicarbonate (n=3), hemoglobin (n=3).
- One death due to acute gastroenteritis dehydration not attributed to study drug.

Tolerability

- DTG-DT palatability was average, good, or very good for 98% of respondents.

CONCLUSIONS

- DTG-DT was well tolerated with a favorable safety profile, and showed virologic efficacy among infants and children with diverse prior ART experience
- CD4 changes likely reflect multiple factors including recovery and age-related normal changes
- Results support the recent FDA approval of this pediatric formulation of DTG for the treatment of children with HIV

REFERENCES

- FDA updated Package Insert (June 18, 2020): www.accessdata.fda.gov/drugsatfda_docs/label/2020/213983s000lbl.pdf
- Protocol available at: https://impaactnetwork.org/studies/p1093.asp

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