Safety Pharmacokinetics and Efficacy of Dolutegravir in Treatment Experienced HIV + Children

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ABSTRACT

Background: IMPAACT P1093 is an ongoing Phase I/II multicenter open-label PK, safety, dose finding study of dolutegravir (DTG) plus optimized background regimen (OBR) in children and adolescents in age defined cohorts. Adequate pharmacokinetics (PK), safety and virologic efficacy have been described in children aged 12 to 18 years, leading to the recent FDA approval. Here we report the PK, safety and virologic efficacy of DTG in children ≥ 6 to < 12 years old. **Methods:** HIV infected treatment experienced children ≥6 to <12 yrs on a failing antiretroviral (ARV) regimen with an HIV RNA of ≥1000 copies/mL (c/mL) were enrolled in an intensive PK stage as part of the study. DTG tablets (10, 25, 50mg) at ≈1 mg/kg once a day (based on defined weight bands) were added to a stable, failing ARV regimen, with an OBR added after intensive PK (~Day5-10). Target PK exposures were $AUC_{(0\text{-}24)}$ range of 37-67 μg*h/mL (primary) and C_{24} range 0.77 – 2.26 μg/ml (secondary). Safety, tolerability, CD4 cell count and HIV-1 RNA were evaluated at Week 24. Virologic success was defined as achieving an HIV-1 RNA < 400 c/mL or ≥ 1 Log_{10} decline in HIV RNA by Week 24 based on the FDA snapshot algorithm, with an additional secondary endpoint of HIV-1 RNA <50 c/mL. **Results:** Eleven children were enrolled and completed the 24 week study visit. Demographics were as follows: 64% (7/11) male, 36% (4/11) African American, 27% (3/11) Caucasian, 18% (2/11) Asian, 36% (4/11) were of Hispanic ethnicity. Mean (SD) age was 9.5 yrs (±1.8); weight was 34.9 kg (±11.9). Median (IQR) baseline CD4+ cell count and % were 645 cells/μL (325, 732) and 19% (14, 26) respectively. Median (IQR) baseline HIV-1 RNA log_{10} was 5.0 log_{10} c/mL (3.5, 5.3). Five subjects (≥ 40 kg of weight) received DTG 50 mg, 2 subjects (30-< 40 kg) received DTG 35 mg and 4 subjects (20-<30 kg) received DTG 25 mg once daily. DTG geometric mean (CV%) $AUC_{(0\text{-}24)}$ and C_{24} were 50.46 (63%) μg*h/mL and 0.92 (89%) μg/mL respectively. Virologic success was achieved in 81.8 % (9/11; 95% CI: 48.2 % to 97.7%) at Week 24. Additionally, 63.6% (7/11; 95% CI: 30.8% to 89.1%) had an HIV RNA load < 50 c/mL at Week 24. Median (IQR) gain in CD4 cell count and % at Week 24 was 209 cells/μL (14, 403) and 8% (6%, 11%) respectively. DTG was well tolerated, with 3 subjects experiencing Grade 3 laboratory abnormalities; two developed unconjugated bilirubin elevation while on atazanavir as part of the OBR, and another subject developed neutropenia, which was deemed unrelated to treatment. There were no Grade 4 AEs, SAEs or study discontinuations due to AEs. **Conclusions:** DTG plus OBR had a favorable safety profile and achieved adequate mean AUC_{24} and C_{24} in HIV infected children ≥ 6 to < 12 years. DTG plus OBR provided good virologic efficacy through Week 24 in this pediatric population.

BACKGROUND

- IMPAACT P1093 is an ongoing Phase I/II multicenter open label Pharmacokinetics (PK), safety, dose finding study of dolutegravir (DTG) plus optimized background regimen (OBR) in children and adolescents in age defined cohorts.
- Adequate PK, safety and virologic efficacy up to 24 weeks have been described in children aged 12 to 18 years, leading to the recent FDA indication.
- Here we report the intensive PK, safety and virologic efficacy of DTG in children ≥ 6 to < 12 years old

STUDY DESIGN

- Inclusion Criteria
  - HIV-1 infected children aged ≥ 6 to < 12 yrs
  - Integrase Inhibitor (INI) naïve
  - HIV-1 RNA > 1000 copies/mL
  - ART treatment experienced
    - On ART, unchanged, failing regimen for at least 12 weeks or
    - Off ART treatment for 4 weeks
  - Must have at least 1 fully active drug for the OBR

STUDY DESIGN

Stage I
Intensive PK group n=11

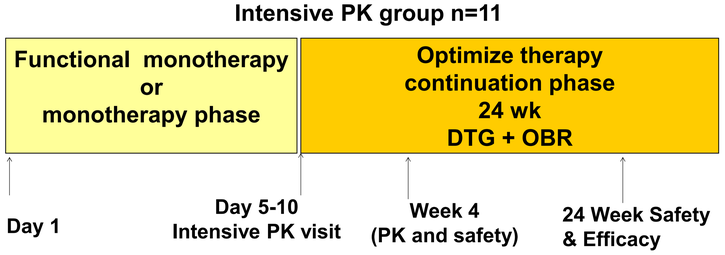


Table 1. Baseline Characteristics

	Cohort IIA (n=11)
Age (y), Median (IQR)	10 (8,11)
Gender, n (%)	
Male	7 (63.6)
Female	4 (36.4)
Race, n (%)	
Black or African American	4 (36.4)
White	3 (27.3)
Asian	2 (18.2)
Ethnicity, n (%)	
Hispanic or Latino	4 (36.4)
Not Hispanic or Latino	7 (63.6)
Plasma HIV RNA Log10 copies/mL, median (IQR)	5.0 (3.5, 5.3)
CD4+ cell count (cells/μL), median (IQR)	645 (325, 732)
CD4+ percent, median (IQR)	19 (14, 26)
Time on prior ART (years), median (IQR)	9.3 (6.4, 10.4)

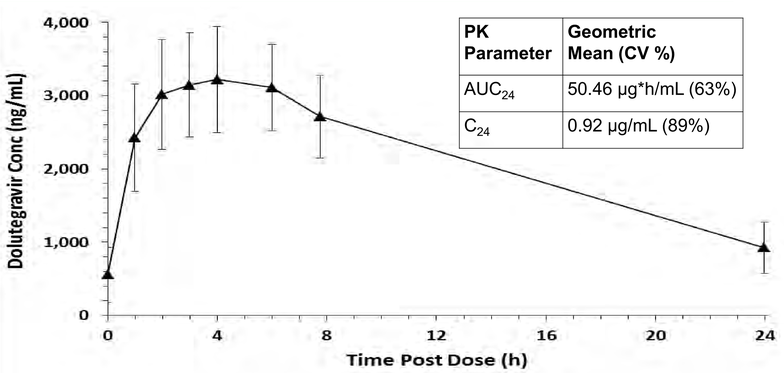
Prior Antiretroviral Therapy

ART Class	n (%)
NRTI	11 (100)
PI	11 (100)
NNRTI	6 (54.5)
Triple Class Experienced	6 (54.5)

TABLE 2. Optimized Background Therapy

ART	n (%)
Tenofovir DF, emtricitabine	2 (18)
Tenofovir DF, emtricitabine, atazanavir/r	2 (18)
Tenofovir DF, lamivudine, atazanavir/r	1 (9)
Zidovudine, lamivudine	1 (9)
Zidovudine, lamivudine, atazanavir/r	1 (9)
Zidovudine, lamivudine, indinavir/r	1 (9)
Zidovudine, abacavir, lopinavir/r	1 (9)
Stavudine, darunavir/r	1 (9)
Didanosine, emtricitabine, efavirenz	1 (9)
Total	11(100)

TABLE 3. PK Results: DTG Exposure in Cohort IIA



PK Parameter	Geometric Mean (CV %)
AUC_{24}	50.46 μg*h/mL (63%)
C_{24}	0.92 μg/mL (89%)

DTG Dose	Weight range	n=11
50 mg	≥ 40 kg	5
35 mg	30-< 40 kg	2
25 mg	20- <30 kg	4

FIGURE 1a. Efficacy: proportion of patients (95% CI) with HIV RNA ≤ 400 c/mL or ≥ 1 Log_{10} decline from baseline, ITT Approach

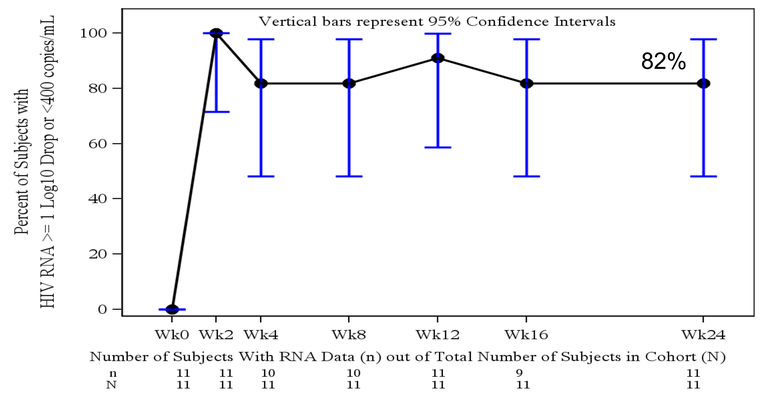


FIGURE 1b. Efficacy: proportion of patients (95% CI) with HIV RNA ≤ 50 c/mL, ITT Approach

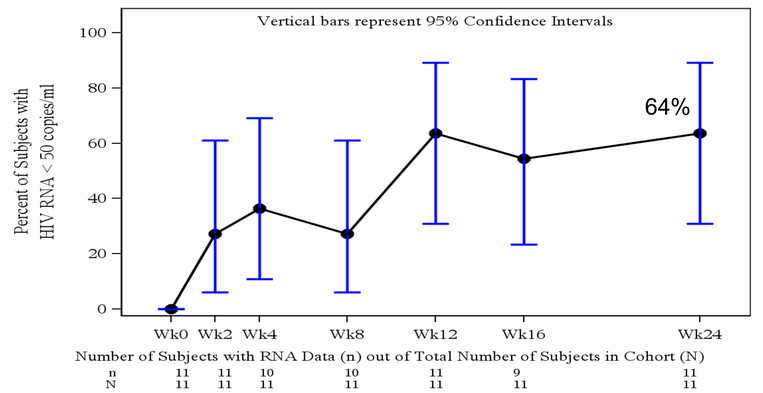


TABLE 4. Safety at 24 Weeks

- DTG was well tolerated
  - No discontinuations due to adverse events
  - No DTG-related AE
  - Two participants with unrelated grade 3 laboratory abnormality
    - Unconjugated bilirubin elevation associated with atazanavir
    - Asymptomatic lipase elevation
  - No trends in lab abnormalities

CONCLUSIONS

- DTG plus OBR had a favorable safety profile in HIV infected children
- DTG at doses of ≈1 mg/kg once a day achieved adequate mean AUC_{24} and C_{24} in HIV infected children ≥ 6 to < 12 years old
- In addition, DTG treatment as part of an OBR provided good virologic efficacy through week 24

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