Safety and Efficacy of Dolutegravir in HIV Treatment-Experienced Adolescents: 48-Week Results

Rolando M. Viani[1], Carmelita Alvero[2], Terry Fenton[2], Edward Acosta[3], Rohan Hazra[4], Ellen O'Gara[5], Barb Heckman[6], Debra Steimers[7], Sherene Min[7], Andrew Wiznia[8], and the P1093 Team

[1]University of California San Diego, CA, [2]Harvard School of Public Health, MA, [3]University of Alabama at Birmingham, AL, [4]NICHD, MD, [5]NIAID, MD, [6]Frontier Sciences Research Foundation Inc, NY, [7]GlaxoSmithKline, NC, [8]Jacobi Medical Center, NY, USA

CROI 2014 Poster # LB-2788

ABSTRACT

Background: P1093 is an ongoing Phase I/II multicenter open-label pharmacokinetic (PK), safety, dose finding study of dolutegravir (DTG) plus optimized background regimen (OBR) in children and adolescents in age defined cohorts. The pediatric weight band dosing of ~1 mg/kg once a day achieved PK exposure in adolescents comparable to those observed at 50 mg once daily in adults. **Methods:** HIV infected treatment experienced children ≥12 to <18 yrs on a failing antiretroviral (ARV) regimen with an HIV RNA of ≥1000 copies/mL (c/mL) were enrolled in Stage 1 (intensive PK) or Stage 2 (no PK, safety and efficacy). Stage 1: DTG was added to a stable, failing ARV regimen, with an OBR added after intensive PK (~Day 5-10); Stage 2: DTG was started with an OBR. Safety, tolerability, CD4 cell count and HIV-1 RNA were evaluated at Week 48. Virologic success was defined as achieving an HIV-1 RNA < 400 c/mL by Week 48 based on the FDA snapshot algorithm, with an additional secondary outcome of HIV-1 RNA <50 c/mL. **Results:** Twenty three adolescents (Stage 1, n=10; Stage 2, n=13) were enrolled and 22 (95.7%) completed the 48 week study visit. Demographics were as follows: 78% (18/23) female, 52% (12/23) African American, 35% (8/23) Caucasian, 26% (6/23) were of Hispanic ethnicity. Median age (range) was 14 yrs (12, 17) and median weight (range) was 52.2 kg (33, 91). Median (IQR) baseline CD4+ cell count and % were 466 cells/μL (297, 771) and 22% (18.4, 29.2), respectively. Median (IQR) baseline HIV-1 RNA $\log_{10}$ was 4.3 $\log_{10}$ c/mL (3.9, 4.6). Nineteen adolescents received 50 mg/day and 4 received 35 mg/day of DTG. Virologic success, an HIV RNA < 400 c/mL was achieved in 73.9 % (17/23; 95% CI: 51.6 % to 89.8%) at Week 48. Additionally, 60.9% (14/23; 95% CI: 38.5% to 80.3%) had an HIV RNA load < 50 c/mL at Week 48. Median (IQR) gain in CD4 cell count and % at Week 48 was 84 cells/μL (-81, 238) and 4.7% (0, 9.4%) respectively. DTG was well tolerated, with 2 subjects experiencing Grade 3 laboratory abnormalities: one developed unconjugated bilirubin elevation while on atazanavir as part of the OBR, and another subject developed asymptomatic lipase elevation, which was deemed treatment unrelated. One subject discontinued DTG after virologic failure due to inability to meet study related appointments. Invariably, all participants who experienced virologic failure had incomplete adherence based on three day pill recall questionnaire. There were no Grade 4 AEs, SAEs or discontinuations due to AEs. **Conclusions:** DTG plus OBR was safe and well tolerated in HIV infected adolescents. In addition, DTG treatment as part of an OBR provided good virologic efficacy through Week 48.

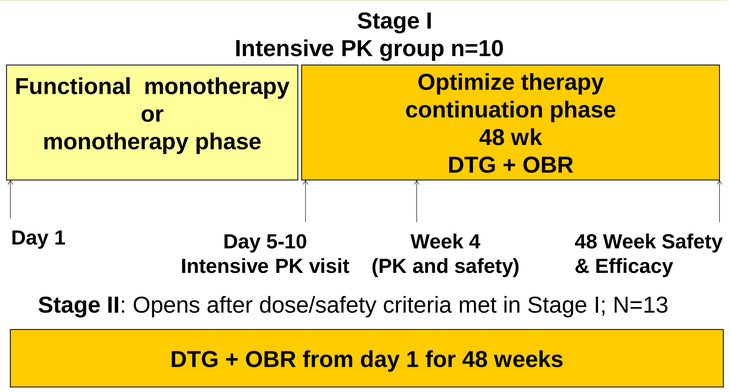
BACKGROUND

- 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 48 week safety and virologic efficacy of DTG in adolescents 12-18 y

STUDY DESIGN

- Inclusion Criteria
  - HIV-1 infected children and adolescents aged ≥ 12 to < 18 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 II: Opens after dose/safety criteria met in Stage I; N=13

DTG + OBR from day 1 for 48 weeks

Table 1. Baseline Characteristics

	Cohort 1 (n=23)
Age (y), Median (IQR)	15 (12,16)
Gender, n (%)	
Male	5 (21.7)
Female	18 (78.3)
Race, n (%)	
Black or African American	12 (52.2)
White	8 (34.8)
Asian	3 (13)
Ethnicity, n (%)	
Hispanic or Latino	6 (26.1)
Not Hispanic or Latino	17 (73.9)
Plasma HIV RNA Log10 copies/mL, median (IQR)	4.3 (3.9, 4.6)
CD4+ cell count (cells/μL), median (IQR)	466 (297, 771)
CD4+ percent, median (IQR)	22 (18, 29)
Time on prior ART (years), median (IQR)	12.53 (10.8, 14.0)
Prior Antiretroviral Therapy	
ART Class	n (%)
NRTI	23 (100)
PI	18 (78.3)
NNRTI	12 (52.2)
Triple Class Experienced	8 (34.8)
Enfuvirtide Experienced	2 (8.7)

TABLE 2. Optimized Background Therapy

ART	n (%)
Tenofovir DF, emtricitabine, darunavir/r	7 (30.4)
Abacavir, lamivudine, darunavir/r	3 (13)
Tenofovir, lamivudine, lopinavir/r	3 (13)
Tenofovir DF, emtricitabine, efavirenz	3 (13)
Tenofovir DF, emtricitabine	2 (8.7)
Tenofovir DF, emtricitabine, darunavir/r, etravirine	1 (4.3)
Tenofovir DF, atazanavir/r	1 (4.3)
Tenofovir DF, emtricitabine, atazanavir/r	1 (4.3)
Abacavir, lamivudine, atazanavir	1 (4.3)
Zidovudine, lamivudine, darunavir/r	1 (4.3)
Total	23 (100)

Dose & Safety at Week 48

Dose	n=23
50 mg for ≥ 40 kg	19 (82.6%)
35 mg for 30-< 40 kg	4 (17.4%)

- 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

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

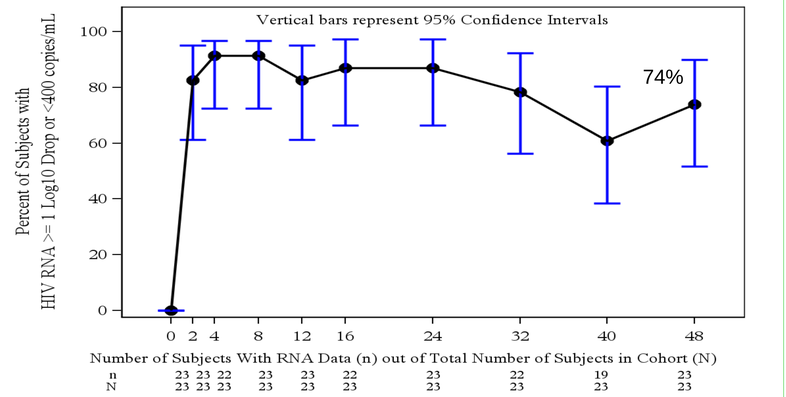


FIGURE 1b. Efficacy: proportion of patients (95% CI) with HIV RNA ≤ 50 c/mL, ITT Approach

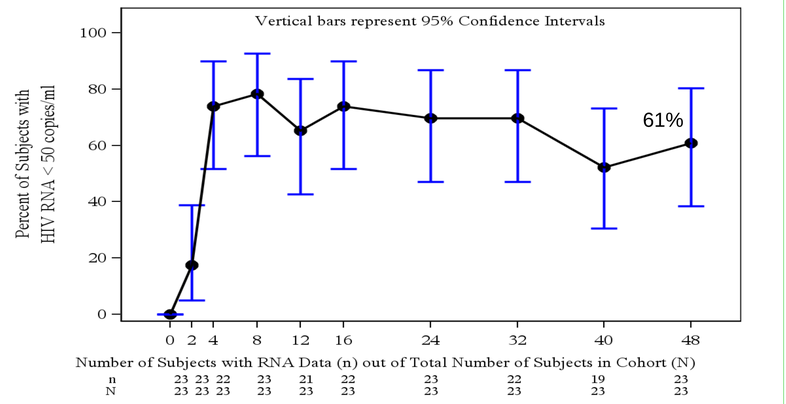
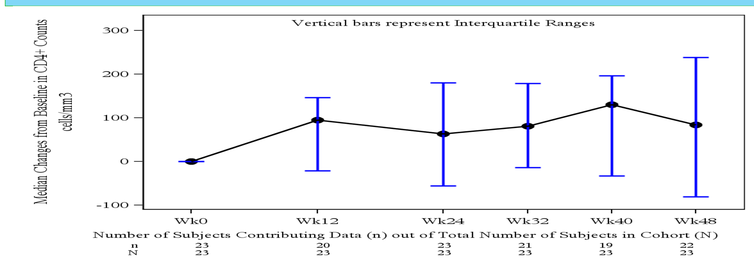


FIGURE 2. CD4+ cell count median changes (IQR) from baseline



CONCLUSIONS

- DTG plus OBR was safe and well tolerated in HIV infected adolescents.
- DTG plus OBR demonstrated virologic efficacy at week 48
- DTG is a new effective treatment option for adolescents aged 2 to 18 years

Funding: IMPAACT is funded by NIH, NIAID, NICHD, and NIMH
ViiV Healthcare

Correspondence: *Rolando M. Viani, MD, MTP*
University of California San Diego
9500 Gilman Drive, 0672
La Jolla, CA 92093-0672
Phone: (619) 471-9177
email: rviani@ucsd.edu