IMPAACT 1093: Dolutegravir in 6-12 Year Old HIV Infected Children: 48-Week Results

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CROI 2016 Poster # 816

ABSTRACT

Background: IMPAACT 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 in adolescents achieved PK exposure comparable to those observed at 50 mg once daily in adults.

Methods: Cohort IIA enrolled HIV infected treatment experienced, integrase naive children ≥6 to <12 years of age with an HIV RNA of ≥1000 copies/mL (c/mL) into Stage 1 (intensive PK) or Stage 2 (no PK, safety and efficacy). In Stage 1, DTG was added to a stable, failing ARV regimen, with OBR optimization after intensive PK (~Day 5-10); in Stage 2, DTG and OBR at study entry. Safety, tolerability, CD4 cell count and HIV-1 RNA were evaluated at Week 48,a primary objective. Virologic success was defined as achieving an HIV-1 RNA <400 c/mL by Week 48 based on the FDA snapshot algorithm and HIV-1 RNA <50 c/mL as a secondary outcome.

Results: Twenty three children (Stage 1, n=11; Stage 2, n=12) were enrolled and 21 (91.3%) completed the 48 week study visit. Demographics were as follows: 70% (16/23) male; 52% (12/23) African American, 17% (4/23) Caucasian; 26% (6/23) were of Hispanic ethnicity. Median age (range) was 10 yrs (6, 11) and median weight (range) was 30.0 kg (18, 54). Median (IQR) baseline CD4+ cell count and % were 645 cells/mm^3 (466, 732) and 24% (14.3%, 28.7%), respectively. Median (IQR) baseline HIV-1 RNA $\log_{10}$ was 5.0 $\log_{10}$ c/mL (4.5, 5.5). DTG weight band target dose was 1 mg/kg, (# participants/dose (mg)) distribution as follows: 1 (70); 5 (50); 6 (35); 8 (25); 3 (20) . Virologic success (wk 48): HIV RNA < 400 c/mL was achieved in 78.3 % (18/23); 95% CI: (56.3 % to 92.5%); HIV <50 c/m achieved in 73.9% (17/23); 95% CI: (51.6% to 89.8%). Median (IQR) gain in CD4 cell count and % at Week 48 was 387 cells/mm^3 (49, 575) and 9% (7 14), respectively. DTG was well tolerated; none of the four Grade 3 clinical adverse events nor three Grade 3 laboratory events were study drug related. Two subjects went off study: one for virologic failure, and one moved and was lost to follow-up. There were no Grade 4 AEs, SAEs or discontinuations due to AEs.

Conclusions: DTG plus OBR was safe, well tolerated and provided virologic efficacy through week 48 in HIV infected children 6-12 years of age.

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.
- Dolutegravir has regulatory approval for children 12-18 yrs of age in >50 countries worldwide
- Adequate PK, safety and virologic efficacy up to 24 weeks have been described in children aged 6-12 years of age, leading to the recent FDA submission.
- Here we report 48 week safety and efficacy data of DTG in children ≥ 6 to < 12 years of age

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

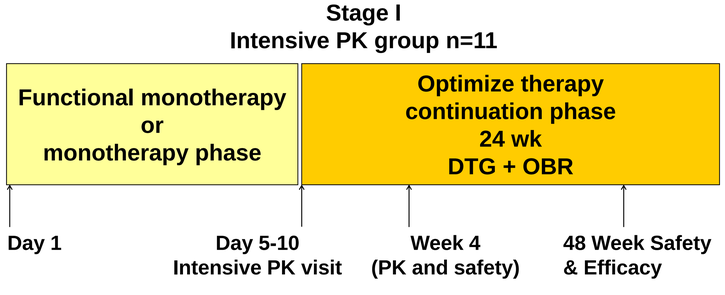


Table 1. Baseline Characteristics

	Cohort IIA (n=23) (Stage I (n=11)
Age (y), Median (IQR)	10 (6,11)
Gender, n (%)	
Male	16 (70)
Female	7 (30)
Race, n (%)	
Black or African American	12 (52)
White	4 (17)
Asian	3 (13)
Ethnicity, n (%)	
Hispanic or Latino	6 (26)
Not Hispanic or Latino	13 (56.5
Unknown	4 (17.4)
Plasma HIV RNA Log10 copies/mL, median (IQR)	5.0 (4.5, 5.5)
CD4+ cell count (cells/µL), median (IQR)	645 (466, 732)
CD4+ percent, median (IQR)	24 (14.3, 28.7)
CD4: ≤14	5 (21)
CD4: >14-≤25	7 (30)
CD4: ≥25	11 (48)
Time on prior ART (years), median (IQR)	9.3 (6.4, 10.4)
Enrollment Sites:	
United States: 14 Sites	16
South Africa	4
Thailand	3

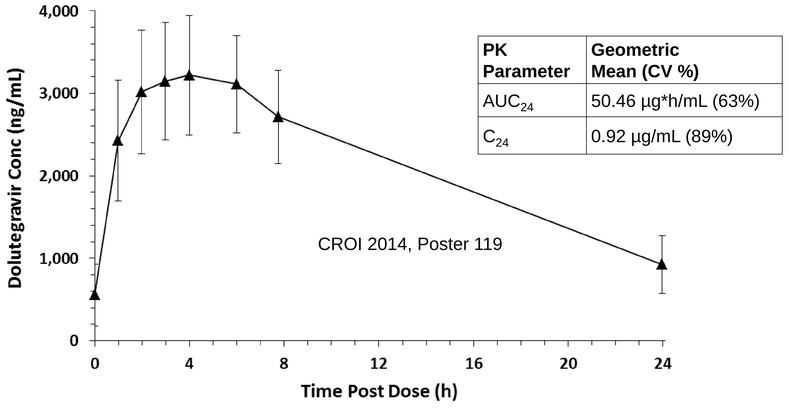
Prior Antiretroviral Therapy

ART Class	n (%)
NRTI/NNRTI/PI	8 (44)
NRTI/PI	6 (33)
NRTI/NNRTI	3 (17)
NRTI	1 (6)
Entry inhibitor	0

Cohort IIA: Participant Dosing (N=23)

Dolutegravir Dose (mg)	Weight range (kg)	Number participants
70	>40	1
50	>40	5
35	30-<=40	6
25	20-<=30	8
20	15-<=20	3

PK Results: DTG Exposure in Cohort IIA, Stage 1



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

FIGURE 1. Efficacy: *Proportion of Patients with HIV RNA <400 copies/mL (Cohort IIA) (FDA Snapshot algorithm)*

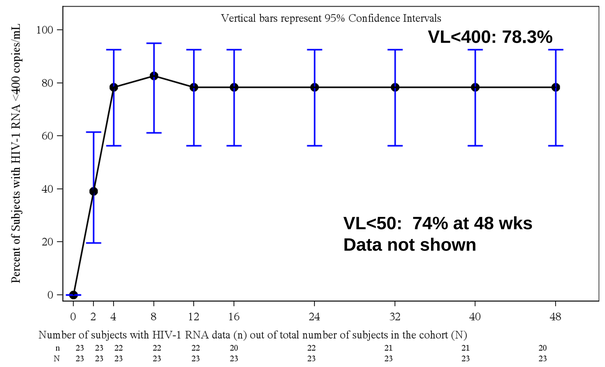
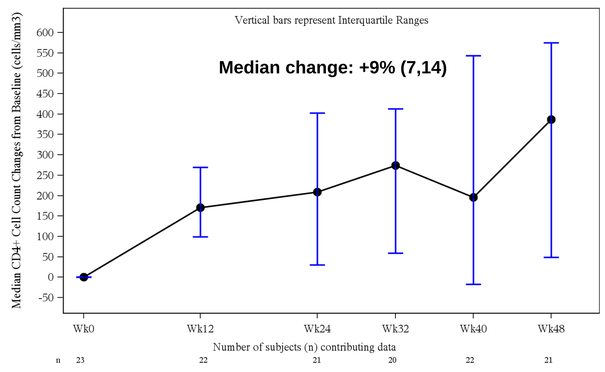


FIGURE 2. Efficacy: *Median CD4+ Cell Count Changes from Baseline (Cohort IIA):*



Safety at 48 Weeks

- DTG was generally well tolerated
  - No discontinuations due to adverse events
  - No DTG-related AE
  - Three participants with unrelated grade 3 laboratory abnormality
    - – Unconjugated bilirubin elevation associated with atazanavir
    - – Asymptomatic lipase elevation
    - – neutropenia
  - Four participants with unrelated grade 3 clinical events (abscess, pneumonia, abnormal behavior, extremity pain

CONCLUSIONS

- In children 6-12 years of age, DTG plus OBR treatment for 48 weeks had a:
  - – Favorable safety profile in HIV infected children
  - – Excellent and sustainable virologic efficacy
  - – Significant improvement in CD4 number and percentage.
- Study continuing to evaluate dolutegravir in children >4 weeks of age with pediatric appropriate formulations

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

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