FDA Analysis of CD4+ Cell Count Declines Observed in HIV-infected Children Treated with Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide

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ABSTRACT #2344

BACKGROUND

- A decline in mean CD4+ T cell count (CD4+ count) was identified in virologically suppressed HIV-infected 6 to <12 years old who switched from a stable antiretroviral drug regimen to elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide fumarate (TAF) (E/C/F/TAF) in Study GS-US-292-0106.
- E/C/F/TAF (Genvoya®) is FDA approved for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA < 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components.
- Data from study GS-US-292-0106 (Study 0106), sponsored by Gilead Sciences, were used to support approval for use in pediatric patients. Study 0106 is an ongoing study evaluating the pharmacokinetics (PK), antiviral activity, and safety of E/C/F/TAF in pediatric patients <18 years of age.
  - Cohort 1 enrolled treatment-naïve adolescents 12 to <18 years old (yo) and weighing ≥35 kg. All subjects received the adult formulation. Data through Week 24 were submitted to support approval of E/C/F/TAF in this age group.
  - Cohort 2 enrolled 23 perinatally infected, virologically suppressed (VS) subjects 6 to <12 yo and weighing ≥25 kg who switched from a stable antiretroviral (ARV) regimen to E/C/F/TAF. All subjects received the adult formulation. Data through Week 24 were submitted to support approval of E/C/F/TAF in this age group.
- The safety profile of E/C/F/TAF was similar between adults and adolescents studied in Cohort 1 of Study 0106.
- A decline in mean CD4+ T cell count (CD4+ count) occurred at Week 2 and persisted at Week 24 (Table 1).

Table 1: CD4+ Count Decline Analysis: Mean and % Change in CD4+ Count from Baseline (BL) to Week (Wk) 24 for Cohort 2

		Mean Change from BL					
	BL	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 24
CD4+ count (cells/uL)	966 (201)*	-162	-125	-134	-162	-133	-150
CD4%	40 (5.3)*	-0.5%	-0.1%	-0.8%	-0.8%	-0.5%	-1.5%

- *Mean (SD)

Methods

- FDA review focused on the 23 subjects in Cohort 2, aged 6 to <12 yo who had completed safety and efficacy data through Week (Wk) 24.
- FDA explored possible reasons for CD4+ count declines in Cohort 2 including:

1) Change in overall leukocyte (WBC) and absolute lymphocyte count (ALC) to determine whether declines in CD4+ count were caused by declines in overall leucocyte or lymphocyte count. Additional 48 week data requested from manufacturer.

2) Trends in subject-level CD4+ count to determine whether the mean decline was driven by outliers.

Additional follow-up data through Week 48 of E/C/F/TAF treatment were also requested from the manufacturer to identify trends in CD4+ count with ongoing exposure

3) Relationship between CD4+ count and PK of each drug in E/C/F/TAF to determine whether one specific component of the combination tablet was correlated with the observed declines in CD4+ count.

- Intensive PK in the pediatric subjects in Cohort 2 was performed at Week 4 and compared with PK in adult controls (intensive PK for EVG, COBI, and FTC, population PK for TAF and tenofovir [TFV]).
- FDA also reviewed prior ARV trials and literature to identify other instances of CD4+ count declines in pediatric and adult trials, and to evaluate for potential drug class effects.

RESULTS

Baseline Characteristics of Cohort 2

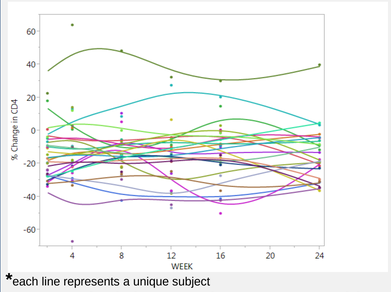
- All 23 subjects were VS with HIV-1 RNA < 50 copies/mL.
- Mean CD4+ count (range) was 966 cells/μL (603-1421); median CD4+ was 969 cells/μL.
- Subjects were 61% female and 78% Black/African American.
- Mean age (range) of subjects was 10 yo (8-11).
- Mean weight (range) was 31.6 kg (25.2-58.2). The median weight was 30.5 kg (Q1 27.5, Q3 33.0)
- 12 (52%) of the subjects were on zidovudine prior to the ARV switch.
- Prior to the ARV switch, in combination with NRTIs; 11 (48%) were on NNRTIs, 2 (9%) were on INSTIs, and 5 (22%) were on PIs.

CD4+ T Cell Count Findings for Cohort 2[1]

Mean change in CD4+ count decreased at Wk 2 and remained decreased throughout the 24-week study period (Table 1). In contrast, mean WBC and ALC count remained stable through Week 24:

- Mean WBC was 4.64 x 10^3/dL at BL and 4.39 x 10^3/dL at Week 24
- Mean ALC was 2.23 x 10^3/dL at BL and 1.99 x 10^3/dL at Week 24.
- The decreased CD4+ count changes were not driven by outliers; 21/23 subjects had declines in CD4+ count at Week 2 which persisted (Figure 1).
- All subjects had plasma viral load <50 copies/mL at all study points through Week 24.

Figure 1 : Percent Change in CD4+ Count by Week and Subject* for Cohort 2



*each line represents a unique subject

- FDA asked the manufacturer to provide CD4+ count data for the same 23 subjects beyond Week 24. These results show a trend toward baseline CD4+ count between Weeks 24 and 48. (Table 2).

Table 2: Mean Change in CD4+ Cell Count and Percentage at Each On-treatment Time Point from Week 24 to Week 48* for Cohort 2

	Mean Change from BL			
	Wk 24	Wk 32	Wk 40	Wk 48
CD4+ count (cells/uL)	-150	-88	-31	-90
CD4%	-1.5%	-1.1%	-0.9%	-1.3%

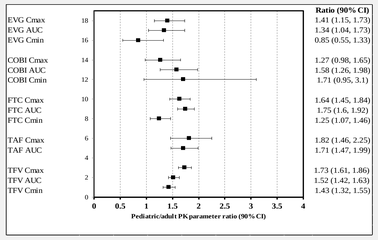
*Full safety and efficacy data at Week 48 not received for independent FDA analysis

- All subjects had HIV RNA < 50 copies/mL at Week 48.

Pharmacokinetics Analysis for Cohort 2[2]

- There was no association between CD4+ count and area under the concentration-time curve (AUC) of any of the components of E/C/F/TAF.
- Compared to historical adult data, exposures of the components of E/C/F/TAF were generally higher in subjects 6-12 yo relative to adults. (Figure 2)
- Exceptions where the upper 90% CI is between two and three include the cobicistat C_{min} and the TAF C_{max}.

Figure 2: Comparison of Exposures of the Components of E/C/F/TAF in HIV-infected Pediatric Subjects 6-<12 yo (n=23) and Adult (n=19) Subjects (note: TFV=tenofovir)



Evaluation of Prior ARV Trials

- In Cohort 1 of Study 0106 (an adolescent treatment-naïve cohort), the mean baseline CD4+ cell count was 471 cells/uL and at Week 24 there was a mean increase of +224 cells/uL.
- Adults virologically suppressed in Study GS-US-292-0109 and switched to E/C/F/TAF had a mean increase of +33 cells/uL at Week 24. This pediatric population was VS whereas the approval for E/C/F/TAF in older subjects was based on a treatment-naïve population.
- Approval of dolutegravir and raltegravir in a similar age range were not based on all subjects being VS at baseline. In dolutegravir and raltegravir pediatric studies, CD4+ counts increased above 70 cells/uL at 24 Weeks.
- Limited clinical data about use of cobicistat in this pediatric patient population are available.

Evaluation of Literature

Recombinase Activating Genes 1 and 2 (RAG 1/2) Inhibition by Integrase Inhibitors

- V(D)J recombination is the mechanism of genetic recombination that occurs in developing lymphocytes during the early stages of T and B cell maturation.
- Site-specific cleavage of chromosomal DNA by RAG 1/2 is needed to make functional immunoglobulins and T cell receptor genes by V(D)J recombination.
- HIV-1 Integrase has structural similarities with RAG 1[3].
- Nishana and colleagues[4] found that the integrase inhibitors, elvitegravir and raltegravir, interfered with biochemical functions of RAGs such as DNA binding, cleavage, and hairpin formation. Interference with functions of RAGs by raltegravir were limited.
- Nishana and colleagues[4] found significant reductions in mature B lymphocytes in mice exposed to EVG and COBI.

Conclusions

- CD4+ count declines were observed in 23 children aged 6 to <12 yo, who had mean CD4+ count declines of -150 cells/uL that began at Week 2 and persisted for 24 weeks in VS subjects receiving the adult strength tablet of E/C/F/TAF.
- Persistent declines in mean CD4+ count is a unique finding in this pediatric study of E/C/F/TAF and the etiology remains unclear.
- The sponsor reports the CD4+ count declines at 48 Weeks (mean CD4+ decline of 90 cells/uL) were less than initial declines.
- Compared to historical adult data, exposures of the components of E/C/F/TAF were generally higher in pediatric subjects relative to adults, but there was no association between CD4+ count and AUC of any of the components of E/C/F/TAF.
- Inhibition of RAG1/2 by EVG may play a role in CD4+ count reduction, but further research is needed.
- The FDA describes safety and efficacy data from this pediatric cohort in the US Package Insert for Genvoya® (E/C/F/TAF) and Descovy® (F/TAF) to inform clinicians of this finding so that additional monitoring can be performed, as needed
- FDA and the manufacturer of E/C/F/TAF are collaborating to investigate other possible mechanisms.
- Data for use of E/C/F/TAF in children >2 years of age will provide further evaluation of the trend in CD4+ count in more pediatric patients.

References

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