Cross-Discipline Team Leader Review

Date	December 6, 2021
From	Su-Young Choi, Pharm.D., Ph.D
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	207561 (b) (4) S-29
Applicant	Gilead Sciences, Inc
Date of Submission	March 29, 2021
PDUFA Goal Date	September 29, 2021
Proprietary Name	GENVOYA
Established or Proper Name	Fixed Dose Combination of elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF)
Dosage Form(s)	Tablet
	(b) (4)
Recommendation on Regulatory Action	Approval for S-29 Efficacy supplement supporting the labeling changes with long term data in pediatric patients and negative findings from the PK study that was used to fulfill the Written Request
Recommended Indication(s)/Population(s) (if applicable)	Not applicable – (b) (4)
Recommended Dosing Regimen(s) (if applicable)	Not applicable – (b) (4)

1. Introduction

The Applicant submitted this supplemental NDA (b) (4) . Currently, GENVOYA full dose tablet is approved as a complete regimen 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 less than 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 of GENVOYA.

[redacted] the Applicant submitted Cohort 3 results of GS-US-292-0106, a single multicenter, single-arm, open-label study evaluating PK, antiviral activity, and safety of GENGOYA in pediatric patients 2 to less than 6 years. As with other antiretroviral drugs, the effectiveness of GENVOYA in pediatric patients can be extrapolated from adults by demonstrating comparable drug exposures between adults and pediatrics [redacted].

Upon the review of the submission, the review team has concluded that Ctau of EVG in pediatric subjects receiving the low dose tablet of GENVOYA was substantially lower than those observed in adults. Therefore, efficacy cannot be extrapolated from adults to pediatric patients. [redacted]

2. Background

GENVOYA was approved on Nov 5, 2015 in adults with HIV infection. In previous sNDAs, the expansion of indication was granted in pediatric patients 6 years and older and weighing at least 25 kg based on the study Cohort 1 (12 to < 18 years old) and Cohort 2 (6 to < 12 years old) of GS-US-292-0106. Refer to the Clinical Review for full Details on regulatory history, therapeutic context, and prior findings in safety and efficacy of GENVOYA in adults and pediatric patients.

At the time of the approval of the original NDA, a waiver for PREA requirement in pediatric patients less than 6 years old was granted based on that the product will not provide a meanintful benefit and not be used in a significant number of patients because there are other antiretroviral products available for patients in this age group and component drugs in this FDC are expected to be developed for pediatric use. Therefore, the current submission is not intended to fulfill the PREA requirement.

It is noted that the HHS Guideline for the Use of Antiretroviral Agents in Pediatric HIV Infection recommends GENVOYA as an alternative regimen due to the low barrier to resistance to EVG and the potential for significant drug interactions due to COBI. With the recent approval of BIKTARVY in pediatric patients 2 years and older and weighing at least 14 kg, and all currently options for pediatric patients with HIV-1, FDA's assessments on "not provide a meanintful benefit and not be used in a significant number of patients" remains the same.

The study was conducted in response to the Pediatric Writeen Request for GENVOYA. The submission contents were presented to the Pediatric Exclusivity Board on August 11, 2021. Pediatric exclusivity was granted. Since this was conducted in response to the Pediatric

Written Request, GENVOYA USPI will be updated with the findings of GS-US-292-0106 w [redacted (b) (4)]

- Supplement 29 - Treatment of HIV-1 infection in 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 less than 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 of Genvoya (labeling updates with data from Cohort 2 and 3 of GS-US-292-0106

The review team recommends [redacted (b) (4)] approval for S-29, [redacted (b) (4)].

3. Product Quality

The low dose tablet of GENVOYA consists of EVG 90 mg, COBI 90 mg, FTC 120 mg, and TAF 6 mg. [redacted (b) (4)]

Refer to the review of Chemistry, Manufacturing and Control for full details.

4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology studies were reviewed in prior submissions; no new studies were submitted in the current sNDA.

5. Clinical Pharmacology

Refer to clinical pharmacology review by Dr. Kunyi Wu for full details.

Title of study: A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents and Virologically Suppressed Children (Cohort 3, report date: 2/3/2021)

Study design of Cohort 3: This is an open-label, multicenter, multicohort, single-group study of the PK, safety, tolerability, and antiviral activity of E/C/F/TAF, 90/90/120/6 mg in HIV-1

infected, virologically suppressed children ≥ 2 years of age and weighing ≥ 14 to ≤ 25 kg at screening. PK, efficacy, and safety data through Week 48 were included in this supplemental NDA.

Demographics and Baseline Characteristics

The Full Analysis Set included all 27 subjects. The majority of subjects were female (63%) and Black/African American (89%) or Asian (11%). The mean weight at baseline was 19.0 kg with a weight range of 14.6 to 23.5 kg. The mean age of subjects was 6.0 years; subjects ranged from 3 to 9 years of age. There were no 2-year-old subjects enrolled. Most subjects acquired HIV via mother-to-child transmission.

Key Clinical Pharmacology Findings

All pharmacokinetic parameter estimates (AUCtau, Cmax, and Ctau) in pediatric patients in Cohort 3 are considered comparable (similar or no clinically meaningful differences) to those observed in adults or older pediatric patients except the Ctau of EVG based on the intensive PK. Ctau of EVG in pediatric subjects in Cohort 3 were approximately 22% lower as compared to those observed in adults. Moreover, approximately 25% of observed Ctau at steady state were lower than 45 ng/mL, the protein-binding adjusted IC95 of wild-type HIV-1 virus. Similarly, nearly 50% of subjects had observed EVG Ctau that were lower than model-driven in vivo EC90 (126 ng/mL, Ramanathan et al, Clin Pharmacokinet 2011: 50 (4): 229-244). Therefore, the EVG Ctau is unacceptably low in a substantial number of study subjects (b) (4)

Table 1. Statistical Comparisons of Pharmacokinetic Parameter Estimates Between Test and Historical Reference Treatments for TAF, TFV, EVG, COBI, and FTC

	Pediatric Patients in Cohort 3 in Study 106 (Test)				Adult Patients (Reference)			
	Based on simulation results		Based on the intensive PK				Based on simulation results	Based on the intensive PK dataset
TAF PK	n	GLSM	n	GLSM	n	GS-US-292-0104 and 0111*	Test/Reference (90% CI)	Test / Reference (90% CI)
AUCtau (h*ng/mL)	27	206.18	17	343.54	539	178.3	115.64 (110.11, 121.45)	192.68 (165.97,223.67)
Cmax (ng/mL)	27	103.14	27	217.75	539	144.88	71.19 (55.55, 91.23)	150.29 (115.68,195.27)
TFV						GS-US-292-0104 and 0111*		
AUCtau (h*ng/mL)	27	333.8	27	326.7	841	283.86	117.59 (110.15, 125.54)	115.09 (106.96,123.84)
Cmax (ng/mL)	27	18.61	27	19.07	841	14.79	125.88 (114.72, 138.13)	128.95 (119.46,139.20)
Ctau (ng/mL)	27	11.27	27	11.14	841	10.3	109.40 (102.43, 116.83)	108.12 (100.11,116.78)
EVG						GS-US-292-0102**		
AUCtau (h*ng/mL)	27	27168.82	24	29864.03	19	21553.74	126.05 (104.85, 151.54)	138.56 (111.93,171.52)
Cmax (ng/mL)	27	2172.4	27	2850.88	19	1997.55	108.75 (90.79, 130.27)	142.72 (112.94,180.35)
Ctau (ng/mL)	27	266.85	22	195.43	19	247.71	107.73 (78.77, 147.33)	78.90 (53.13,117.17)
COBI						GS-US-292-0102**		
AUCtau (h*ng/mL)	27	11036.81	21	12262.48	19	8975.72	122.96 (101.78, 148.56)	136.62 (103.01,181.20)
Cmax (ng/mL)	27	1371.01	27	1274.56	19	1400.19	97.92 (83.13, 115.34)	91.03 (71.04,116.64)
Ctau (ng/mL)	27	16.99	18	16.61	19	17.01	99.87 (71.00, 140.49)	97.64 (64.57,147.66)
FTC						GS-US-292-102**		
AUCtau (h*ng/mL)			27	18620.48	19	11576.55		160.85 (143.01, 180.90)
Cmax (ng/mL)			27	2808.24	19	2014.35		139.41 (120.28, 161.59)
Ctau (ng/mL)			27	77.4	19	89.11		86.86 (72.30, 104.34)

** PK parameters for the reference group were estimated from PopPK modeling using data from Genvoya-treated, HIV-1 infected adult subjects in Studies GS-US-292-0104 and GS-US-292-0111 who received the E/C/F/TAF 150/150/200/10 mg adult tablet.*

*** Intensive PK parameters for the reference group were derived from Genvoya-treated, HIV-1 infected adult subjects in Study GS-US-292-0102 who received the E/C/F/TAF 150/150/200/10 mg adult tablet.*

GLSM: geometric least square mean

6. Clinical Microbiology

Clinical microbiology studies were reviewed in prior submissions; no new studies were submitted in the current sNDA.

7. Clinical/Statistical- Efficacy

Refer to Clinical Review by Dr. Melisse Baylor for full details. The trial design and the summary of demographics is availabld under Section 5, Clinical Pharmacology.

(b) (4)

8. Safety

Refer to Dr. Melisse Baylor's review for full details.

This submission included safety data up to 48 weeks in Cohorts 2 (b) (4) of Trial GS-US-292-0106. Overall, The types of adverse events observed were similar to conditions or illnesses commonly observed during childhood and with the types of AEs observed in HIV-infected, treatment-experienced children and adults.

One safety issue of GENVOYA in pediatric patients is a decrease in CD4 cell count. This was not observed in adults and adolescents, but noted in Cohort 2 (6 to < 12 years old patients). The mechanism of decreased CD4 cell counts in pediatric patients receiving GENVOYA is currently unknown.

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In Study GS-US-292-0106, no pediatric subjects had CD4 cell counts less than 500 cells/μL at any time, and no illnesses consistent with immunosuppression were reported. However, the study did not enroll subjects with low CD4 cell count at baseline and the risk of a clinically relevant decrease in CD4 cell count cannot be ruled out at this time for pediatric subjects that may have low CD4 cell counts prior to treatment.

9. Advisory Committee Meeting

None.

10. Pediatrics

Refer to Section 2 regarding the regulatory history related to pediatrics.

11. Other Relevant Regulatory Issues

The quality and integrate of the submission were adequate. The division did not consult the Office of Scientific Investigations for clinical inspection as this is a small pediatric trial with PK as the pivotal endpoint.

The Office of Study Integrity and Surveillance (OSIS) determined that inspections for the bioanalytical site are not warranted at this time given that OSIS inspected the site in (b) (4), which falls within the surveillance interval. Refer to the OSIS memo (5/21/2021 under NDA207561) for full details.

12. Labeling

The USPI has been updated to include the summary of efficacy, safety, and PK findings in Section 8. In addition, Section 6 has been updated using Week 48 data from Cohort 2 as follows.
6. Adverse Reactions

6.1 Clinical Trials Experience

Clinical Trials in Pediatric Subjects

Table 4 Mean Change in CD4+ Count and CD4 Percentage from Baseline to Week 48 in Virologically-Suppressed Pediatric Patients from 6 to <12 Years Who Switched to GENVOYA

		Mean Change from Baseline					
	Baseline	**Week 2**	**Week 4**	**Week 12**	**Week 24**	**Week 32**	**Week 48**
CD4+ Cell Count (cells/mm^3)	961 (275.5)[a]	-117	-114	-112	-118	-62	-66
CD4%	38 (6.4)[a]	+0.3%	-0.1%	-0.8%	-0.8%	-1.0%	-0.6%

a. Mean (SD)

8. Use in Specific Populations

8.4 Pediatric Use

A pharmacokinetic evaluation of a reduced strength GENVOYA formulation containing 90 mg of EVG, 90 mg of COBI, 120 mg of FTC, and 6 mg TAF was performed in 27 virologically-suppressed pediatric patients at least 2 years of age and weighing at least 14 to less than 25 kg (cohort 3 of Study 106). Virologic, immunologic, and safety outcomes were similar to those observed in cohort 2 of Study 106. No clinically meaningful differences in drug exposures except EVG were identified between pediatric patients in cohort 3 receiving the reduced strength formulation and adults receiving the GENVOYA tablet containing 150 mg of EVG,150 mg of COBI, 200 mg of FTC, and 10 mg TAF. The median observed EVG Ctrough values in subjects in cohort 3 were significantly lower than the values correlated with efficacy in adults. Therefore, efficacy cannot be extrapolated from adults to pediatric patients weighing 14 to 25 kg.
Safety and effectiveness of GENVOYA in pediatric patients weighing less than 25 kg have not been established.

13. Postmarketing Recommendations

None.

14. Recommended Comments to the Applicant

None.

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