Amsterdam, 26 March 2026
EMADOC-1700519818-2797590
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Genvoya

International non-proprietary name: Elvitegravir / Cobicistat / Emtricitabine / Tenofovir alafenamide

Procedure no.: EMA/PAM/0000320343

Marketing authorisation holder (MAH): Gilead Sciences Ireland Unlimited Company

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	2 March 2026	3 March 2026
☐	CHMP comments	16 March 2026	16 March 2026
☐	Updated CHMP Rapporteur AR	19 March 2026	19 March 2026
☒	CHMP outcome	26 March 2026	26 March 2026

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1. Introduction

On 18 December 2025, the MAH submitted a completed paediatric study for Genvoya, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of a post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that *study GS-US-292-0106: 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* is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation used in the study was tablets.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- *Study GS-US-292-0106: 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*

2.3.2. Clinical study

Study GS-US-292-0106: 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

Description

Study GS-US-292-0106 was a Phase 2/3 open-label, multicentre, multicohort, single-arm study to evaluate the PK, safety, tolerability, and antiviral activity of E/C/F/TAF STR in ARV treatment-naive adolescents and virologically suppressed children with HIV.

Methods

Study participants

Eligible participants were antiretroviral treatment-naive, adolescents with HIV (≥ 12 to < 18 years of age) of either sex with plasma HIV-1 RNA levels ≥ 1000 copies/mL as well as virologically suppressed,

children with HIV (≥ 2 to < 12 years of age and screening weight ≥ 14 kg) of either sex with plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 consecutive months prior to screening on a stable ARV regimen, with no documented history of resistance to any component of E/C/F/TAF STR were enrolled in the study.

Participants were distributed according to body weight and age at screening in the following cohorts:

Cohort 1: Age ≥ 12 to < 18 years and Weight ≥ 35 kg

Cohort 2: Age ≥6 to < 12 years and Weight ≥ 25 kg

Cohort 3: ≥ 2 years of age and Weight ≥ 14 to < 25 kg

Participants should have no laboratory evidence of current active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and an estimated glomerular filtration rate using the Schwartz formula ($eGFR_{Schwartz}$) of ≥ 90 mL/min/1.73 m^2.

Treatments

E/C/F/TAF tablets (either in the dosage 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF or the dosage 90 mg of EVG, 90 mg of COBI, 120 mg of FTC, and 6 mg of TAF) were administered orally once daily with food at approximately the same time each day. For subjects in Cohort 3 unable to swallow the tablet whole, it was acceptable to split the tablet in two and administer both parts sequentially.

Objective(s)

Primary Objectives

Cohort 1

Part A:

- To evaluate the steady state pharmacokinetics (PK) for elvitegravir (EVG) and tenofovir alafenamide (TAF) and confirm the dose of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) single tablet regimen (STR) in HIV-1 infected, antiretroviral (ARV) treatment-naive adolescents.

Part B:

- To evaluate the safety and tolerability of the E/C/F/TAF STR through Week 24 in HIV-1 infected, ARV treatment-naive adolescents.

Cohort 2

Part A:

- To evaluate the PK of EVG and TAF in virologically suppressed HIV-1 infected children 6 to < 12 years of age, weighing ≥ 25 kg, administered E/C/F/TAF STR.

Part B:

- To evaluate the safety and tolerability of E/C/F/TAF STR through Week 24 in HIV-1 infected children 6 to < 12 years of age.

Cohort 3

- To evaluate the PK of EVG and TAF and confirm the dose of the STR in virologically suppressed HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg administered E/C/F/TAF LD STR.
- To evaluate the safety and tolerability of E/C/F/TAF LD STR through Week 24 in virologically suppressed HIV-1 infected children ≥ 2 years of age and weighing ≥ 14 to < 25 kg.

Secondary objectives

Cohort 1

- To evaluate the safety and tolerability of the E/C/F/TAF STR through Week 48 in HIV-1 infected, ARV treatment-naive adolescents.
- To evaluate the antiviral activity of the E/C/F/TAF STR through Week 48 in HIV-1 infected, ARV treatment-naive adolescents.

Cohort 2

- To evaluate the antiviral activity of switching to E/C/F/TAF STR through Week 48 in virologically suppressed HIV-1 infected children 6 to < 12 years of age weighing ≥ 25 kg.
- To evaluate the safety and tolerability of E/C/F/TAF STR through Week 48 in virologically suppressed HIV-1 infected children 6 to < 12 years of age, weighing ≥ 25 kg.

Cohort 3

- To evaluate the antiviral activity of switching to E/C/F/TAF LD STR through Week 48 in virologically suppressed HIV-1 infected children ≥ 2 years of age and weighing ≥ 14 to < 25 kg.
- To evaluate the safety and tolerability of E/C/F/TAF LD STR through Week 48 in virologically suppressed HIV-1 infected children ≥ 2 years of age and weighing ≥ 14 to < 25 kg.

Exploratory objectives

All Cohorts

- To explore the PK of TFV-DP in PBMCs following administration of E/C/F/TAF STR in Cohorts 1 and 2, or E/C/F/TAF LD STR in Cohort 3.

Outcomes/endpoints

Primary Endpoints

Cohort 1

Part A:

- PK parameter of AUC_{tau} for EVG and AUC_{last} for TAF.

Part B:

- incidence of treatment-emergent SAEs and all treatment-emergent adverse events.

Cohort 2

Part A:

- PK parameter of AUC_{tau} for EVG and AUC_{last} for TAF.

Part B:

- incidence of treatment-emergent SAEs and all treatment-emergent adverse events.

Cohort 3

- PK parameter of AUC_{tau} for EVG and TAF, incidence of treatment-emergent SAEs, and all treatment-emergent adverse events.

Secondary Endpoints

Cohort 1

Part A:

- PK parameters of C_{tau}, C_{max}, apparent CL and apparent V_z for EVG, C_{max}, apparent CL and apparent V_z for TAF, AUC_{tau}, C_{max}, and C_{tau} for FTC, TFV and COBI.

Part B:

- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis.
- The percentage of subjects with plasma HIV-1 RNA < 400 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis.
- The change from baseline in plasma log_{10} HIV-1 RNA (copies/mL) and in CD4+ cell count (cells/µL) and percentage at Weeks 24 and 48.

Cohort 2

Part A:

- PK parameters of C_{tau}, C_{max}, apparent CL and apparent V_z for EVG, C_{max}, apparent CL and apparent V_z for TAF, AUC_{tau}, C_{max}, and C_{tau} for FTC, TFV and COBI.

Part B:

- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis.
- The change from baseline in CD4+ cell count (cells/µL) and percentage at Weeks 24 and 48.

Cohort 3

- PK parameters of C_{tau}, C_{max}, apparent CL and apparent V_z for EVG, C_{max}, apparent CL and apparent V_z for TAF, AUC_{tau}, C_{max}, and C_{tau}, for FTC, TFV and COBI.
- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis.
- The change from baseline in CD4+ cell count (cells/µL) and percentage at Weeks 24 and 48

Sample size

A total of 50 adolescents (12 to < 18 years of age) and up to 75 children (2 to < 12 years of age) who meet the eligibility criteria were planned to be enrolled.

Randomisation and blinding (masking)

This is an open-label, non-blinded study.

Statistical Methods

Efficacy:

There was no primary efficacy endpoint in this study. Virologic outcomes were summarized using frequency counts and percentages based on the Full analysis set (all subjects who received at least one dose of study drug).

The changes from baseline in plasma log_{10} HIV-1 RNA (Cohort 1 only) and in CD4+ cell count were summarized using descriptive statistics.

Safety:

All safety analyses were performed using the safety analysis set (all subjects who received at least one dose of study drug).

Pharmacokinetic Analysis

The concentration data of EVG, COBI, FTC, TAF, and TFV over sampling time were listed and summarized. Pharmacokinetic parameters (e.g., AUC_{tau}, AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, Ct_{au}, λ_z, apparent CL, apparent V_z and $T_{½}$) were listed and summarized for analytes EVG, COBI, FTC, TAF, and TFV using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, coefficient of variation %, standard deviation, median, Q1, Q3, minimum, and maximum).

Results

Participant flow

Of 155 participants screened, 129 participants were enrolled and treated.

Overall, 126 of 129 (97.7%) participants completed study drug in the main (48-week treatment) phase (Cohort 1: 48 of 50 participants [96.0%]; Cohort 2: 51 of 52 participants [98.1%]; and Cohort 3: 27 of 27 participants [100.0%]) and 3 participants (2.3%) prematurely discontinued study drug: 1 participant in each of Cohorts 1 and 2 withdrew consent and 1 participant in Cohort 1 was lost to follow-up.

Of the 129 participants treated in the main phase, 125 (96.9%) participants entered the extension phase. One participant in Cohort 2 did not enter the extension phase as they withdrew consent after completing the main phase. Of these 125 participants, 98 participants (78.4%) completed study drug (Cohort 1: 30 of 48 participants [62.5%], Cohort 2: 43 of 50 participants [86.0%], and Cohort 3: 25 of 27 participants [92.6%]). One participant in each of Cohorts 2 and 3 who entered the extension phase did not complete the study drug treatment case report form and were reported as continuing study drug in the extension phase.

Twenty-five of 125 participants (20.0%) prematurely discontinued study drug. The reasons for premature discontinuation were AEs (Cohort 1: 2 of 48 participants [4.2%]), death (Cohort 1: 1 of 48 participants [2.1%]), pregnancy (Cohort 1: 4 of 48 participants [8.3%], Cohort 2: 1 of 50 participants [2.0%]), lack of efficacy (Cohort 2: 1 of 50 participants [2.0%]), investigator's discretion (Cohort 1: 6 of 48 participants [12.5%], Cohort 2:1 of 50 participants [2.0%]), noncompliance with study drug

(Cohort 1:1 of 48 participants [2.1%], Cohort 3: 1 of 27 participants [3.7%]), withdrew consent (Cohort 1:1 of 48 participants [2.1%], Cohort 2: 1 of 50 participants [2.0%]), and lost to follow-up (Cohort 1: 3 of 48 participants [6.3%], Cohort 2: 2 of 50 participants [4.0%]).

Recruitment

Participants were enrolled at a total of 17 study centres: 5 in the United States, 5 in South Africa, 4 in Thailand, 2 in Uganda, and 1 in Zimbabwe.

Baseline data

In the Safety Analysis Set, 129 participants were enrolled across the 3 cohorts and received at least 1 dose of study drug. The median age (range) of participants was as follows: Cohort 1, 15 (12 to 17) years; Cohort 2, 10 (7 to 11) years; and Cohort 3, 6 (3 to 9) years.

For participants in Cohort 1, most participants were assigned female at birth (56.0%), and Black or African American (88.0%). All participants were not Hispanic or Latino. The median (Q1, Q3) baseline body weight and body weight Z-score were 52.0 (41.0, 61.0) kg and −0.31 (−1.08, 0.47), respectively; median (Q1, Q3) baseline height and height Z-score were 157.8 (147.5, 167.0) cm and −0.75 (−1.79, 0.08), respectively. Median (Q1, Q3) baseline body mass index (BMI) and BMI Z-score were 20.0 (18.1, 23.1) kg/m^2 and 0.17 (−0.56, 0.79), respectively. Tanner stages for genitalia at baseline for males were generally evenly distributed through Stages 1 to 4 (6.0% of participants each for Stages 1 to 3 and 4.0% of participants for Stage 4), and 22.0% for Stage 5. For females, Tanner stages for breasts were Stages 1, 2, 3, 4, and 5 (4.0%, 14.0%, 8.0%, 12.0%, and 18.0% of participants, respectively).

For participants in Cohort 2, most participants were assigned female at birth (57.7%), and Black or African American (71.2%). All participants were not Hispanic or Latino. The median (Q1, Q3) baseline body weight and body weight Z-score were 30.9 (28.1, 33.7) kg and −0.48 (−1.01, 0.14), respectively; median (Q1, Q3) baseline height and height Z-score were 136.2 (131.3, 140.0) cm and −0.73 (−1.26, 0.10), respectively. Median (Q1, Q3) baseline BMI and BMI Z-score were 16.7 (15.5, 17.7) kg/m^2 and −0.02 (−0.72, 0.42), respectively. Tanner stages for genitalia at baseline for males were Stages 1, 2, and 3 (32.7%, 7.7%, and 1.9% of participants, respectively). For females, Tanner stages for breasts were Stages 1, 2, and 3 (32.7%, 19.2%, and 5.8% of participants, respectively).

For participants in Cohort 3, most participants were assigned female at birth (63.0%), and Black or African American (88.9%). All participants were not Hispanic or Latino. The median (Q1, Q3) baseline body weight and body weight Z-score were 19.3 (17.0, 20.5) kg and −0.88 (−1.72, −0.32), respectively; median (Q1, Q3) baseline height and height Z-score were 116.0 (106.0, 123.0) cm and −0.28 (−1.42, 0.23), respectively. Median (Q1, Q3) baseline BMI and BMI Z-score were 14.2 (13.7, 15.3) kg/m^2 and −1.24 (−1.79, −0.03), respectively. Tanner stages for genitalia at baseline for males was Stage 1 for 11.1% of participants. For females, Tanner stage for breasts was Stage 1 for 48.1% of participants.

All participants enrolled in Cohort 1 had baseline plasma HIV-1 RNA ≥ 50 copies/mL and all participants enrolled in Cohorts 2 and 3 had baseline plasma HIV-1 RNA < 50 copies/mL.

Number analysed

The number of participants analysed was 129 and their distribution in the three cohorts is represented in the following table:

Analysis Set	Cohort 1 Age ≥ 12 to < 18 years and Weight ≥ 35 kg (N = 50)	Cohort 2 Age ≥6 to < 12 years and Weight ≥ 25 kg (N = 52)	Cohort 3 ≥ 2 years of age and Weight ≥ 14 to < 25 kg (N = 27)	Total (N = 129)
All Enrolled Analysis Set	50 (100.0%)	52 (100.0%)	27 (100.0%)	129 (100.0%)
Safety Analysis Set	50 (100.0%)	52 (100.0%)	27 (100.0%)	129 (100.0%)
Full Analysis Set	50 (100.0%)	52 (100.0%)	27 (100.0%)	129 (100.0%)
Spine DXA Analysis Set	47 (94.0%)	50 (96.2%)	27 (100.0%)	124 (96.1%)
TBLH DXA Analysis Set	45 (90.0%)	52 (100.0%)	27 (100.0%)	124 (96.1%)

DXA = dual-energy x-ray absorptiometry; TBLH = total body less head

Pharmacokinetic results

Pharmacokinetic data from this study has been previously assessed and it is not discussed in this AR.

Efficacy results

Change From Baseline in HIV-1 RNA Values (log_{10} copies/mL) (Cohort 1 Only)

In Cohort 1 (≥ 12 to < 18 years and weight ≥ 35 kg) there was a decrease from baseline in HIV-1 RNA (log_{10} copies/mL) at Week 24 which subsequently remained relatively constant through Week 552. Mean (SD) changes from baseline (log_{10} copies/mL) at Weeks 24 and 552 were −3.25 (0.645) and −3.16 (0.482), respectively.

Mean (SD) Change From Baseline in CD4 Cell Counts (cells/µL)

In Cohort 1, there was an initial increase from baseline that was maintained through Week 552 (Week 24: 191 [175.2] cells/µL and Week 552: 311 [273.2] cells/µL) and in Cohorts 2 and 3 there was an initial decrease from baseline that was maintained after Week 24 through Week 480 and Week 264, respectively (Cohort 2: Week 24: −118 [194.1] cells/µL and Week 480: −236 [252.8] cells/µL; Cohort 3: Week 24: −137 [278.3] cells/µL; Week 264: −255 [289.8] cells/µL).

Mean (SD) Change From Baseline in CD4 Percentages (%)

In Cohort 1, there was an increase from baseline in CD4% that was maintained through Week 552 (12.1% [6.89%]) and in Cohorts 2 and 3 there was a small change from baseline that was maintained through Week 240 and beyond (Cohort 2: 1.2% [6.35%]; Cohort 3: 1.3% [6.57%]).

Percentage of Participants With HIV-1 RNA < 50 copies/mL Using the Missing = Excluded Imputation Method

High virologic suppression was maintained through Week 312, Week 312, and Week 192 for Cohorts 1, 2, and 3, respectively.

Cohort 1: ≥ 12 to < 18 Years of Age and Weight ≥ 35 kg

- Week 96: 97.8% (45 of 46 participants); 95% CI (88.5% to 99.9%)
- Week 192: 100.0% (32 of 32 participants); 95% CI (89.1% to 100.0%)
- Week 312: 100.0% (29 of 29 participants); 95% CI (88.1% to 100.0%)

Cohort 2: ≥ 6 to < 12 Years of Age and Weight ≥ 25 kg

- Week 96: 100.0% (46 of 46 participants); 95% CI (92.3% to 100.0%)
- Week 192: 97.5% (39 of 40 participants); 95% CI (86.8% to 99.9%)
- Week 312: 97.3% (36 of 37 participants); 95% CI (85.8% to 99.9%)

Cohort 3: ≥ 2 Years of Age and Weight 14 kg to < 25 kg

- Week 96: 100.0% (18 of 18 participants); 95% CI (81.5% to 100.0%)
- Week 192: 100.0% (24 of 24 participants); 95% CI (85.8% to 100.0%)

Percentage of Participants With HIV-1 RNA < 400 copies/mL Using the Missing = Excluded Imputation Method (Cohort 1 Only)

The percentage of participants with HIV-1 RNA < 400 copies/mL by visit using the missing = excluded (M = E) imputation method for Cohort 1 was in concordance with percentage of participants with HIV-1 RNA < 50 copies/mL. One participant at Week 96 had HIV-1 RNA > 400 copies/mL using the M = E method.

- Week 96: 97.8% (45 of 46 participants); 95% CI (88.5% to 99.9%)
- Week 192: 100.0% (32 of 32 participants); 95% CI (89.1% to 100.0%)
- Week 312: 100.0% (29 of 29 participants); 95% CI (88.1% to 100.0%)

Clinical virology results

In Cohort 1, 10 of 50 (20.0%) of participants met the criteria for inclusion in the Resistance analysis population (RAP) and had their virus analysed for resistance. Seven of the 10 participants in the RAP resuppressed HIV-1 RNA to < 50 copies/mL after resistance analysis and were excluded from the final RAP. Of the 3 participants that that were included in the final RAP, 1 of 3 (33.3%) participants developed resistance to study drugs. The NRTI-R mutations found were K65R and M184V, and the INSTI-R mutation found was E92Q, with high level phenotypic resistance to TFV, FTC, and EVG.

In Cohort 2, 5 of 52 (9.6%) of participants met criteria for inclusion in the RAP and had their virus analysed for resistance. Two of the 5 participants in the RAP resuppressed HIV-1 RNA to < 50 copies/mL after resistance analysis and were excluded from the final RAP. Of the remaining 3 participants that were included in the final RAP, 1 of 3 (33.3%) participants developed resistance to study drugs. The NRTI-R mutation found was M184V, with high level phenotypic resistance to FTC.

In Cohort 3, 3 of 27 (11.1%) of participants met criteria for inclusion in the RAP and had their virus analysed for resistance. All participants resuppressed HIV-1 RNA to < 50 copies/mL and were excluded from the final RAP. No resistance to study drugs was detected.

Safety results

Adverse Events

Cohort 1: ≥ 12 to < 18 Years of Age and Weight ≥ 35 kg

Among participants in Cohort 1, 48 of 50 participants (96.0%) had at least 1 AE. The most commonly reported AEs were upper respiratory tract infection (20 of 50 participants, 40.0%), respiratory tract infection (19 of 50 participants, 38.0%), and nausea (15 of 50 participants, 30.0%).

Most AEs were Grade 1 or 2. Fourteen Grade 3 AEs were reported for 6 participants (12.0%) and included chorioretinitis, radius fracture, ulna fracture, weight decreased, neuralgia, abortion, abortion spontaneous, suicide attempt, agitation, behavior disorder, bipolar I disorder, drug abuse, substance abuse, and hematuria; all were considered not related to study drug except chorioretinitis. A Grade 4 AE of road traffic accident was reported for 1 participant and Grade 4 AEs of suicidal ideation, suicide attempt, and acute psychosis were reported for a single participant. All these AEs were considered not related to study drug.

Treatment-emergent fracture events (hand, radius, and ulna fractures) were reported in 2 participants. These events were not related to study drug.

Category C AIDS-defining events were reported for 15 participants during the study, none of which was reported as a serious adverse event (SAE). No Category C SAEs were reported during the study.

Adverse events considered related to study drug were reported for 22 of 50 participants (44.0%) and included nausea (11 of 50 participants, 22.0%), abdominal pain (6 of 50 participants, 12.0%), vomiting and product size issue (5 of 50 participants each, 10.0%), diarrhea, somnolence, and abdominal pain upper (3 of 50 participants each, 6.0%), and headache and dizziness (2 of 50 participants each, 4.0%). All other treatment-related AEs were reported in 1 participant (2.0%) each.

Pregnancies were reported for 10 participants.

Cohort 2: ≥ 6 to < 12 Years of Age and Weight ≥ 25 kg

Among participants in Cohort 2, 48 of 52 participants (92.3%) had at least 1 AE. The most commonly reported AEs were upper respiratory tract infection (14 of 52 participants, 26.9%), vomiting (13 of 52 participants, 25.0%), and respiratory tract infection and abdominal pain (11 of 52 participants each, 21.2%).

Most AEs were Grade 1 or 2. Grade 3 AEs were reported for 4 participants (7.7%) (abortion infected, abortion missed, appendicitis, glomerulonephritis acute, and pneumonia); all were considered not related to study drug. No Grade 4 AEs were reported.

Treatment-emergent fracture events (hand, radius, foot, and upper limb fractures) were reported in 4 participants. These events were not related to study drug.

Category C AIDS-defining events were reported for 5 participants during the study, among whom 1 participant reported a Grade 3 SAE of pneumonia.

Adverse events considered related to study drug were reported for 14 of 52 participants (26.9%) and included vomiting (8 of 52 participants, 15.4%), abdominal pain (4 of 52 participants, 7.7%), and headache (2 of 52 participants, 3.8%), No other study drug-related AE was reported for more than a single participant.

Pregnancies were reported for 2 participants.

Cohort 3: ≥ 2 Years of Age and Weight 14 kg to < 25 kg

Among participants in Cohort 3, 25 of 27 participants (92.6%) had at least 1 AE. The most commonly reported AEs were upper respiratory tract infection (14 of 27 participants, 51.9%), cough (9 of 27 participants, 33.3%), and tonsillitis and nasopharyngitis (5 of 27 participants each, 18.5%).

No Grade 3 or 4 AEs were reported during the study.

No fractures were reported during the study.

Category C AIDS-defining events were reported for 4 participants during the study, among whom 1 participant reported a Grade 2 SAE of pneumonia.

Adverse events considered related to study drug were reported in 4 of 27 participants (14.8%) and included vomiting and diarrhea (2 of 27 participants each, 7.4%). All other study drug-related AEs were reported in 1 participant (3.7%) each.

No pregnancies were reported during the study.

Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events

Cohort 1: ≥ 12 to < 18 Years of Age and Weight ≥ 35 kg

SAEs were reported for 10 participants (20.0%). No SAE occurred in more than 1 participant except suicide attempt which was reported for 2 participants, and not considered related to study drug. Visual impairment and uveitis, in 1 participant were reported as SAEs related to study drug.

Adverse events leading to premature study drug discontinuation were reported for 2 participants (lymph node tuberculosis and abortion spontaneous).

One participant died due to a road traffic accident.

Cohort 2: ≥ 6 to < 12 Years of Age and Weight ≥ 25 kg

Serious AEs were reported for 7 participants (13.5%). No SAE occurred in more than 1 participant. None of the SAEs were considered related to study drug.

Adverse events leading to premature study drug discontinuation were reported for 1 participant (abortion infected and abortion missed).

There were no deaths reported during the study.

Cohort 3: ≥ 2 Years of Age and Weight 14 kg to < 25 kg

One SAE, not considered related to study drug, was reported for 1 participant (3.7%).

Adverse events leading to premature study drug discontinuation or death were not reported for any participant.

Bone Safety

Bone Mineral Density (BMD)

Percentage Change From Baseline in Spine and Total Body Less Head (TBLH) BMD

Cohort 1: ≥ 12 to < 18 Years of Age and Weight ≥ 35 kg

Overall, spine and TBLH BMD increased relative to baseline through Week 432. At Weeks 96, 192, and 432, respectively, mean (SD) percentage increases in spine BMD were 9.082% (8.3758%), 22.187% (13.1266%), and 42.872% (24.9781%); and mean (SD) percentage increases in TBLH BMD were 3.552% (4.8549%), 7.180% (7.1606%), and 18.605% (11.0348%).

Cohort 2: ≥ 6 to < 12 Years of Age and Weight ≥ 25 kg

Overall, spine and TBLH BMD increased relative to baseline through Week 336. At Weeks 96, 192, and 336, respectively, mean (SD) percentage increases in spine BMD were 9.532% (10.8790%), 25.603% (15.9208%), and 56.038% (22.2156%); and mean (SD) percentage increases in TBLH BMD were 8.458% (6.6464%), 18.928% (9.3607%), and 29.200% (11.5266%).

Cohort 3: ≥ 2 Years of Age and Weight 14 kg to < 25 kg

Overall, spine and TBLH BMD increased relative to baseline through Week 240. At Weeks 96, 192, and 240, respectively, mean (SD) percentage increases in spine BMD were 10.790% (8.5768%), 20.802% (10.6003%), and 28.699% (13.0372%); and mean (SD) percentage increases in TBLH BMD were 14.252% (5.2464%), 27.390% (7.1833%), and 34.404% (7.4781%).

Change From Baseline in BMD Z-Scores

Overall, spine and TBLH BMD height-age Z-scores remained stable or showed an increase relative to baseline in each cohort. For Cohort 1, the baseline mean (SD) spine and TBLH BMD height-age Z-scores were −0.63 (1.369) and −0.42 (1.014), respectively. The mean (SD) changes from baseline at Week 432 for spine and TBLH BMD height-age Z-scores were 1.07 (0.564) and 0.39 (0.483), respectively. For Cohort 2, the baseline mean (SD) spine and TBLH BMD height-age Z-scores were −0.44 (0.796) and −0.71 (0.857), respectively. The mean (SD) changes from baseline at Week 336 for spine and TBLH BMD height-age Z-scores were 1.38 (0.976) and 0.39 (0.712), respectively. For Cohort 3, the baseline mean (SD) spine and TBLH BMD height-age Z-scores were −1.27 (1.035) and −1.26 (0.823), respectively. The mean (SD) changes from baseline at Week 240 for spine and TBLH BMD height-age Z-scores were 0.26 (0.749) and 0.05 (0.871), respectively.

In Cohort 1, overall, 5 participants had a ≥ 4% decrease from baseline in spine BMD at some time point (4 participants each at 1 time point and 1 participant at 2 time points) and 1 participant had a ≥ 4% decrease from baseline in TBLH BMD at 1 time point. In Cohort 2, overall, 10 participants had a ≥ 4% decrease from baseline in spine BMD at some time point (3 participants at 5 time points, 3 participants at 1 time point, 1 participant at 7 time points, 1 participant at 3 time points, 1 participant at 4 time points, and 1 participant at 2 time points) and 4 participants had a ≥ 4% decrease from baseline in TBLH BMD at some time point (2 participants at 1 time point, 1 participant at 2 time points, and 1 participant at 4 time points). In Cohort 3, overall, 3 participants had a ≥ 4% decrease from baseline in spine BMD at some time point (2 participants at 1 time point and 1 participant at 3 time points) and 1 participant had a ≥ 4% decrease from baseline in TBLH BMD at 1 time point.

Bone Laboratory Parameters

No clinical relevance was derived from the changes from baseline in any of the bone biomarkers (alkaline phosphatase [ALP], N-telopeptide [Cohorts 1 and 2 only], C-telopeptide [Cohorts 1 and 2 only], osteocalcin [Cohorts 1 and 2 only], procollagen Type I N-terminal propeptide [Cohorts 1 and 2 only], parathyroid hormone, 25-hydroxyvitamin D, and 1, 25-dihydroxyvitamin D) and urine bone safety (bicarbonate, N-telopeptide [Cohorts 1 and 2 only]) for any cohort.

Renal Safety

In Cohort 1, median (Q1, Q3) serum creatinine increased from baseline (0.58 [0.50, 0.79] mg/dL) through Week 312 (0.72 [0.64, 0.93] mg/dL) and remained stable thereafter through Week 576 (0.81 [0.62, 0.94] mg/dL).

In Cohort 2, median (Q1, Q3) serum creatinine increased from baseline (0.51 [0.45, 0.55] mg/dL) through Week 360 (0.71 [0.62, 0.81] mg/dL) and remained stable through Week 480 (0.69 [0.63, 0.81] mg/dL).

In Cohort 3, median (Q1, Q3) serum creatinine increased from baseline (0.44 [0.38, 0.49] mg/dL) through Week 264 (0.57 [0.53, 0.64] mg/dL).

In Cohort 1, median (Q1, Q3) estimated glomerular filtration rate using the Schwartz formula ($eGFR_{Schwartz}$) declined from baseline (156.00 [129.00, 185.00] mL/min/1.73m^2) through Week 576 (138.82 [123.78, 161.46] mL/min/1.73m^2).

In Cohort 2, median (Q1, Q3) $eGFR_{Schwartz}$ values declined from baseline (150.26 [137.80, 165.12] mL/min/1.73m^2) through Week 480 (133.92 [126.05, 160.92] mL/min/1.73m^2).

In Cohort 3, there was a modest decline in median (Q1, Q3) $eGFR_{Schwartz}$ from baseline (147.02 [139.10, 159.05] mL/min/1.73m^2) through Week 264 (143.69 [120.80, 160.37] mL/min/1.73m^2).

Clinical Laboratory Abnormalities

There were no clinically relevant changes from baseline in median values for hematology or clinical chemistry parameters in all 3 cohorts. Median values were within normal ranges.

Cohort 1: ≥ 12 to < 18 Years of Age and Weight ≥ 35 kg

All 50 participants had at least 1 graded laboratory abnormality. Grade 3 or 4 laboratory abnormalities were reported for 32.0% (16 of 50) of participants. Grade 3 laboratory abnormalities reported for more than 1 participant included hematuria (11 of 50 participants, 22.0%), neutrophils decreased (4 of 50 participants, 8.0%), and aspartate aminotransferase (AST) increased (2 of 50 participants, 4.0%). The only Grade 4 laboratory abnormality reported was creatine kinase increased (3 of 50 participants, 6.0%).

Cohort 2: ≥ 6 to < 12 Years of Age and Weight ≥ 25 kg

Of the 52 participants, 51 (98.1%) had at least 1 graded laboratory abnormality. Grade 3 or 4 laboratory abnormalities were observed for 48.1% (25 of 52) of participants. Grade 3 laboratory abnormalities reported in more than 1 participant included hematuria (14 of 52 participants, 26.9%) and neutrophils decreased (9 of 52 participants, 17.3%). No Grade 4 laboratory abnormality was reported in more than 1 participant.

Cohort 3: ≥ 2 Years of Age and Weight 14 kg to < 25 kg

Of the 27 participants, 26 (96.3%) had at least 1 graded laboratory abnormality. Grade 3 laboratory abnormalities were observed for 11.1% (3 of 27) of participants and included hematuria (2 of 27 participants, 7.4%) and platelets decreased (1 of 27 participants, 3.7%). No Grade 4 laboratory abnormality was reported during the study.

Liver-Related Laboratory Tests

No participant in any of the 3 cohorts met Hy's Law criteria, defined as concurrent increases in AST or alanine aminotransferase (ALT) > 3 × upper limit of normal (ULN) and total bilirubin > 2 × ULN with ALP < 2 × ULN.

Cohort 1: ≥ 12 to < 18 Years of Age and Weight ≥ 35 kg

In the assessment of liver enzyme elevations in relation to normal ranges, 5 of 50 participants (10.0%) had elevations > 3 × ULN in AST or ALT.

Four of 50 participants (8.0%) had > 1 × ULN elevation in total bilirubin and 16 of 50 participants (32.0%) had > 1.5 × ULN elevation in ALP.

Cohort 2: ≥ 6 to < 12 Years of Age and Weight ≥ 25 kg

In the assessment of liver enzyme elevations in relation to normal ranges, 2 of 52 participants (3.8%) had elevations > 3 × ULN in AST or ALT.

Two of 52 participants (3.8%) had > 1 × ULN elevation in total bilirubin, 1 of 52 participants (1.9%) had > 2 × ULN elevation in total bilirubin, and 16 of 52 participants (30.8%) had > 1.5 × ULN elevation in ALP.

Cohort 3: ≥ 2 Years of Age and Weight 14 kg to < 25 kg

In the assessment of liver enzyme elevations in relation to normal ranges, no participant had elevations > 3 × ULN in AST or ALT and > 1 × ULN elevation in total bilirubin. Four of 27 participants (14.8%) had > 1.5 × ULN elevation in ALP.

Metabolic Laboratory Parameters

There were no clinically relevant changes from baseline in median fasting values for total cholesterol, direct low-density lipoprotein, high-density lipoprotein, total cholesterol to high-density lipoprotein cholesterol ratio, triglycerides, or glucose in any cohort.

Vital Signs and Tanner Stage

There were no clinically relevant changes in any vital signs parameter in any participant during the study. Changes in Tanner stages were consistent with the maturing study population.

2.3.3. Discussion on clinical aspects

The high degree of virologic suppression observed in paediatric participants provides reassurance of the efficacy of E/C/F/TAF in the treatment of HIV-1 infection in this population. The data provided demonstrate a favourable safety profile with no new clinically relevant safety signals being identified following the long-term administration of E/C/F/TAF. Particularly there were no safety concerns in relation to bone and renal parameters.

3. Rapporteur's overall conclusion and recommendation

The applicant reported the findings from the paediatric study GS-US-292-0106, which demonstrated the safety and efficacy of E/C/F/TAF in the treatment of HIV-1 infection in adolescents and children.

The benefit-risk profile for this paediatric population is considered positive, and no changes to the Genvoya EU product information are deemed necessary. The longer-term data from the study continue to support these findings. There were no safety concerns related to bone and renal parameters.

☒ **Fulfilled:**

No regulatory action required.