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Human Medicines Division

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

Descovy

International non-proprietary name: Emtricitabine / Tenofovir alafenamide

Procedure no.: EMA/PAM/0000279692

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	28 July 2025	28 July 2025
☐	CHMP comments	11 August 2025	11 August 2025
☐	Updated CHMP Rapporteur AR	14 August 2025	n/a
☒	CHMP outcome	21 August 2025	21 August 2025

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GS-US-311-1269 - A Phase 2/3, Open-Label, Multi-Cohort Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1 Infected Children and Adolescents Virologically Suppressed on a Tenofovir Disoproxil Fumarate (TDF)-Containing Regimen 4

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1. Introduction

On 10 June 2025, the MAH submitted a completed paediatric study for Descovy, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the GS-US-311-1269 - A Phase 2/3, Open-Label, Multi-Cohort Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1 Infected Children and Adolescents Virologically Suppressed on a Tenofovir Disoproxil Fumarate (TDF)-Containing Regimen is a stand-alone study.

This submission provides safety, pharmacokinetic (PK), and efficacy data from the final analysis of the Phase 2/3 study GS-US-311-1269 on the safety, tolerability, and antiviral activity of F/TAF in virologically suppressed children and adolescents with HIV-1 in fulfilment of the requirements of Article 46 of Regulation (EC) No. 1901/2006.

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:

- GS-US-311-1269 - A Phase 2/3, Open-Label, Multi-Cohort Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1 Infected Children and Adolescents Virologically Suppressed on a Tenofovir Disoproxil Fumarate (TDF)-Containing Regimen.

2.3.2. Clinical study

GS-US-311-1269 - A Phase 2/3, Open-Label, Multi-Cohort Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1 Infected Children and Adolescents Virologically Suppressed on a Tenofovir Disoproxil Fumarate (TDF)-Containing Regimen

Description

The study GS-US-311-1269 was a Phase 2/3, open label, multicohort switch study to evaluate the PK, safety, tolerability, and antiviral activity of F/TAF in adolescents (≥ 12 to < 18 years of age) and children (≥ 1 month to < 12 years of age) with HIV-1 who were virologically suppressed (HIV-1 RNA < 50 copies/mL for at least 6 consecutive months) while on a stable 2-NRTI-containing regimen.

The initial protocol envisaged that 4 cohorts would be included in the study, Cohorts 1 and 2, as detailed below, and Cohorts 3 (participants ≥ 2 to < 6 years of age unable to swallow a tablet) and 4 (participants ≥ 1 month to < 2 years of age). While Cohort 1 was fully enrolled (planned N = 25 participants minimum; participants enrolled N = 29), enrolment was halted prior to full enrolment of Cohort 2 (Group 1: planned N = 16, enrolled N = 9; Group 2: planned N = 17, enrolled N = 3) when F/TAF became the required 2 N(t)RTI backbone in the Tybost® study GS-US-216-0128, to which already enrolled participants in Cohort 2 were allowed to transfer if they wished. Cohorts 3 and 4 were incorporated into Study GS-US-216-0128 and no participant was enrolled in either cohort in Study GS-US-311-1269.

Methods

Study participants

Eligible participants were male or female adolescents and children with HIV-1 on a stable 2-NRTI-containing regimen that included a third ARV agent for ≥ 6 consecutive months prior to screening.

Body weight and age at screening for both cohorts were as follows:

Cohort	Age Range	Weight
1	≥ 12 years to < 18 years	≥ 35 kg
2 (Group 1)	≥ 6 years to < 12 years	≥ 25 kg
2 (Group 2) (participants able to swallow a tablet)	≥ 2 years to < 12 years	≥ 17 kg to < 25 kg

Participants should have had no documented or suspected resistance to TFV or FTC, no laboratory evidence of current active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 consecutive months and an estimated glomerular filtration rate using the Schwartz formula ($eGFR_{Schwartz}$) of ≥ 90 mL/min/1.73 m^2.

Treatments

F/TAF tablets in combination with a third ARV agent, and with or without food (as determined by the third ARV agent), were administered orally once daily for at least 48 weeks as follows:

Cohort	Age and Body Weight	F/TAF Dose (mg) With Third Agent
1	≥ 12 to < 18 years, ≥ 35 kg	200/25 with unboosted third agent 200/10 with boosted third agent
2, Group 1	≥ 6 to < 12 years, ≥ 25 kg	200/25
2, Group 2 (participants able to swallow a tablet)	≥ 2 to < 12 years, ≥ 17 to < 25 kg	120/15

Objective(s)

Primary Objectives

- To evaluate the pharmacokinetics (PK) of tenofovir alafenamide (TAF) and confirm the TAF dose in HIV-1 infected children and adolescents virologically suppressed on a 2-nucleoside reverse transcriptase inhibitor (NRTI)-containing regimen

- To evaluate the safety and tolerability of emtricitabine/tenofovir alafenamide (F/TAF) through Week 24

Secondary Objectives

- To evaluate the PK of TFV and emtricitabine (FTC)
- To evaluate the safety, tolerability, and efficacy of F/TAF through Week 48

Outcomes/endpoints

Primary Endpoints

- The PK parameter AUC_{tau} for TAF and tenofovir (TFV)
- Incidence of treatment-emergent serious adverse events (SAEs) and all treatment-emergent adverse events (AEs) through Week 24

Secondary Endpoints

- PK parameters of C_{max}, C_{last}, CL/F, and V_z/F for TAF; AUC_{tau}, C_{max}, and C_{tau} for FTC and TFV
- Incidence of treatment-emergent SAEs and all treatment-emergent AEs through Week 48
- The percentage of participants with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US Food and Drug Administration (FDA)-defined snapshot algorithm
- The change from baseline in CD4 cell count (cells/µL) and CD4 percentage at Weeks 24 and 48
- The palatability and acceptability of the age-appropriate F/TAF formulation

Sample size

A minimum of 58 participants were planned to be enrolled in Cohorts 1 and 2.

Randomisation and blinding (masking)

In the original protocol participants included in Cohort 2 were to be randomized in a 2:1 ratio to switch their current 2-NRTI (TDF-containing) regimen to either open-label F/TAF or retain open-label emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) while continuing their 3rd ARV agent through 96 weeks. With the F/TAF approval in adolescents, the protocol was amended and all subjects enrolled into Cohort 2 received F/TAF (amendment 2, dated 02 August 2017).

Blinding is not applicable as this is an open-label study.

Statistical Methods

Efficacy:

Analyses of all efficacy endpoints used the Full Analysis Set (FAS), which included all participants enrolled in the study who had received ≥ 1 dose of study drug.

The numbers and percentages of participants with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US FDA-defined snapshot algorithm were summarized by cohort and group. The 95% CIs for the point estimates were constructed using the Clopper-Pearson Exact method. Virologic response was also analysed using the missing = failure (M = F) and missing = excluded (M = E) methods for imputing missing HIV-1 RNA values.

The change from baseline in CD4 cell count (cells/μL) and CD4% was summarized by visit, cohort, and group using descriptive statistics.

Pharmacokinetics:

A by-participant listing for tenofovir diphosphate (TFV-DP) concentrations in available peripheral blood mononuclear cell (PBMC) PK samples was presented. All other analyses related to IPK and sparse PK were completed in Interim Analysis 2.

Safety:

The Safety Analysis Set included all participants who received ≥ 1 dose of study drug. All safety data from the first dose date up to 30 days after permanent discontinuation of study drug were summarized using descriptive statistics. All safety data collected were listed for all enrolled participants.

Adverse event and clinical laboratory data were summarized using descriptive statistics by cohort, group, and overall. Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 27.1.

Bone and renal safety laboratory data were summarized.

Body weight, body weight Z-score, body height, body height Z-score, body mass index (BMI), and BMI Z-score were summarized.

Percentage changes from baseline in spine and total body less head (TBLH) bone mineral density (BMD) was summarized by visit.

Other:

Palatability and acceptability assessments were summarized by visit using frequency count and percentage.

Results

Participant flow

Of 49 participants screened, 41 were enrolled, of whom 40 received study drug; 1 participant was enrolled in error and never received study drug. (The total number of participants screened was reported as 50 in the Interim Analysis 2 CSR; it was later confirmed that 1 screen failure participant had subsequently failed rescreening at a different site but had erroneously been recorded as a separate individual).

Overall, 92.5% (37 of 40) treated participants completed study drug in the main (48-week treatment) phase and entered the extension phase (Cohort 1: 28 of 28 participants; Cohort 2 Group 1: 7 of 9 participants; Cohort 2 Group 2: 2 of 3 participants). Three participants (7.5%) prematurely discontinued study drug in the main phase: 2 participants in Cohort 2 Group 1 due to investigator's discretion and 1 participant in Cohort 2 Group 2 withdrew consent.

Of the 37 participants who entered the extension phase, 17 (45.9%) participants completed study drug (Cohort 1: 10 participants; Cohort 2 Group 1: 5 participants; Cohort 2 Group 2: 2 participants) and 20 participants (54.1%) prematurely discontinued study drug. In Cohort 1, 14 participants prematurely discontinued study drug due to investigator's discretion, 2 due to noncompliance with study drug, 1 was

lost to follow-up, and 1 participant prematurely discontinued due to pregnancy. In Cohort 2 Group 1, 1 participant prematurely discontinued study drug due to investigator's discretion and 1 was lost to follow-up.

Recruitment

Participants were enrolled at 8 study centres: 4 in the United States (US), 3 in South Africa, and 1 in Panama.

Baseline data

For participants in Cohort 1, the median age (range) was 14 (12 to 17) years. Most participants were male (57.1%), and either Black or Other race (42.9% each). Fifty percent of participants were Hispanic or Latino. Median (first quartile [Q1], third quartile [Q3]) baseline body weight and body weight Z-score were 45.3 (40.0, 51.0) kg and -0.91 (-1.57, -0.15), respectively; median (Q1, Q3) baseline height and height Z-score were 152.8 (145.7, 162.0) cm and -1.39 (-1.95, -0.49), respectively. Median (Q1, Q3) baseline BMI and BMI Z-score were 18.6 (17.5, 20.7) kg/m^2 and −0.24 (−0.92, 0.48), respectively. Median (Q1, Q3) body surface area (BSA) was 1.39 (1.29, 1.49) m^2. Tanner stages for genitalia at baseline for males were generally evenly distributed through Stages 1 to 4 (25.0%, 18.8%, 25.0%, and 25.0% participants, respectively). For females, Tanner stages for breasts were Stages 1, 3, 4, and 5 (9.1%, 36.4%, 45.5%, and 9.1% participants, respectively). The Tanner stage evaluation for breasts was missing for 1 female participant.

For participants in Cohort 2 Group 1, the median age (range) was 10 (8 to 11) years. Most participants were female (55.6%), all were either Black or Other race (44.4% and 55.6%, respectively), and most were Hispanic or Latino (55.6%). Median (Q1, Q3) baseline body weight and body weight Z-score were 36.0 (31.0, 44.0) kg and 0.18 (-0.33, 0.59), respectively; median (Q1, Q3) baseline height and height Z-score were 135.0 (132.5, 147.3) cm and -0.78 (-1.37, 0.32), respectively. Median (Q1, Q3) baseline BMI and BMI Z-score were 18.8 (17.7, 20.0) kg/m^2 and 0.59 (0.11, 0.89), respectively. Median (Q1, Q3) BSA was 1.16 (1.08, 1.33) m^2. Tanner stages for genitalia at baseline for males were Stages 1 and 2 (75.0% and 25.0%, respectively). For females, Tanner stages for breasts were Stages 1 and 2 (60.0% and 40.0%, respectively).

For participants in Cohort 2 Group 2, the median age (range) was 8 (6 to 8) years. Most participants were female (66.7%), all were either Black or Other race (66.7% and 33.3%, respectively), and most were not Hispanic or Latino (66.7%). Median (Q1, Q3) baseline body weight and body weight Z-score were 22.0 (17.7, 22.0) kg and -1.49 (-2.12, -1.15), respectively; median (Q1, Q3) baseline height and height Z-score were 125.1 (115.0, 125.5) cm and -1.05 (-1.25, -0.58), respectively. Median (Q1, Q3) baseline BMI and BMI Z-score were 14.0 (13.4, 14.1) kg/m^2 and -1.31 (-2.07, -1.30), respectively. Median (Q1, Q3) BSA was 0.87 (0.75, 0.88) m^2. The Tanner stage for genitalia at baseline for males was Stage 1 (100.0%). For females, the Tanner stage for breasts was Stage 1 (100.0%).

The study enrolled children and adolescents with HIV-1 who were virologically suppressed, thus, all participants, except for 1 participant in Cohort 1, had baseline plasma HIV-1 RNA < 50 copies/mL. The overall median (Q1, Q3) baseline CD4 cell count was 911 (735, 1098) cells/µL (Cohort 1: 908 [735, 988] cells/µL; Cohort 2 Group 1: 910 [689, 1133] cells/µL; Cohort 2 Group 2: 1052 [1013, 1562] cells/µL), with 95.0% of participants overall (Cohort 1: 96.4%; Cohort 2 Group 1: 88.9%; Cohort 2 Group 2: 100.0%) having a baseline CD4 cell count ≥ 500 cells/µL. The overall median (Q1, Q3) baseline CD4% was 37.1% (32.2%, 39.0%) (Cohort 1: 36.7% [31.8%, 39.2%]; Cohort 2 Group 1: 37.2% [33.6%, 38.6%]; Cohort 2 Group 2: 37.2% [32.3%, 38.7%]).

The median (Q1, Q3) number of years since diagnosis of HIV-1 infection was 12.0 (9.0, 13.0) years for participants in Cohort 1; 9.0 (6.0, 10.0) years for participants in Cohort 2 Group 1; and 8.0 (5.0, 8.0) years for participants in Cohort 2 Group 2. The most common mode of infection in all cohorts was vertical transmission (Cohort 1, 85.7%; Cohort 2 Group 1, 100.0%; and Cohort 2 Group 2, 100.0%). At baseline, 100.0% of participants in both cohorts were asymptomatic, and none had a historical diagnosis of AIDS.

No participant tested positive for HBV surface antigen or HCV antibody.

Median (Q1, Q3) values for baseline $eGFR_{Schwartz}$ were as follows: Cohort 1: 157.3 (138.6, 191.5) mL/min/1.73 m^2; Cohort 2 Group 1: 172.7 (144.5, 180.0) mL/min/1.73 m^2; Cohort 2 Group 2: 155.3 (135.3, 169.0) mL/min/1.73 m^2.

In accordance with study eligibility criteria, all participants in Cohorts 1 and 2 received a regimen containing 2 NRTIs in combination with a third agent prior to the screening visit. Among third agents, the majority of participants received lopinavir boosted with ritonavir (57.5%) or EFV (30.0%).

No participants discontinued study drug or the study due to COVID-19 pandemic-related matters. No participant missed study visits or had virtual study visits due to restrictions related to the COVID-19 pandemic.

Number analysed

40 participants were analysed:

Analysis Set	Cohort 1: ≥ 12 to < 18 Years and ≥ 35 kg (N = 29)	Cohort 2 Group 1: ≥ 6 to < 12 Years and ≥ 25 kg (N = 9)	Cohort 2 Group 2: ≥ 2 to < 12 Years and ≥ 17 to < 25 kg (N = 3)	Total (N = 41)
All Enrolled Analysis Set	29	9	3	41
Safety Analysis Set	28 (96.6%)	9 (100.0%)	3 (100.0%)	40 (97.6%)
FAS	28 (96.6%)	9 (100.0%)	3 (100.0%)	40 (97.6%)
PBMC PK Analysis Set	2 (6.9%)	2 (22.2%)	0	4 (9.8%)
Spine DXA Analysis Set	28 (96.6%)	7 (77.8%)	3 (100.0%)	38 (92.7%)
Total Body Less Head DXA Analysis Set	28 (96.6%)	7 (77.8%)	3 (100.0%)	38 (92.7%)

Efficacy results

Percentage of Participants With HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 Using the US FDA-Defined Snapshot Algorithm

Cohort 1: ≥ 12 to < 18 Years of Age and Weight ≥ 35 kg: the percentages of participants in the FAS with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 were 92.9% (26 of 28 participants; 95% CI: 76.5% to 99.1%) and 89.3% (25 of 28 participants; 95% CI: 71.8% to 97.7%), respectively (Interim Analysis 2 CSR).

Cohort 2 Group 1: ≥ 6 to < 12 Years of Age and Weight ≥ 25 kg: the percentages of participants in the FAS with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 were 100.0% (9 of 9 participants; 95% CI: 66.4% to 100.0%) and 77.8% (7 of 9 participants; 95% CI: 40.0% to 97.2%), respectively (Interim Analysis 2 CSR).

Cohort 2 Group 2: ≥ 2 to < 12 Years of Age and Weight ≥ 17 kg to < 25 kg: the percentages of participants in the FAS with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 were each 66.7% (2 of 3 participants; 95% CI: 9.4% to 99.2%) (Interim Analysis 2 CSR).

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

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

• Week 24: 92.9% (26 of 28 participants); 95% CI (76.5% to 99.1%)

• Week 48: 89.3% (25 of 28 participants); 95% CI (71.8% to 97.7%)

Cohort 2 Group 1: ≥ 6 to < 12 Years of Age and Weight ≥ 25 kg:

• Week 24: 100.0% (9 of 9 participants); 95% CI (66.4% to 100.0%)

• Week 48: 77.8% (7 of 9 participants); 95% CI (40.0% to 97.2%)

Cohort 2 Group 2: ≥ 2 to < 12 Years of Age and Weight ≥ 17 kg to < 25 kg

• Week 24: 66.7% (2 of 3 participants); 95% CI (9.4% to 99.2%)

• Week 48: 66.7% (2 of 3 participants); 95% CI (9.4% to 99.2%)

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 96 for Cohort 1, Cohort 2 Group 1, and Cohort 2 Group 2, respectively.

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

• Week 24: 96.3% (26 of 27 participants); 95% CI (81.0% to 99.9%)

• Week 48: 92.6% (25 of 27 participants); 95% CI (75.7% to 99.1%)

• Week 96: 100% (27 of 27 participants); 95% CI (87.2% to 100.0%)

• Week 192: 95.5% (21 of 22 participants); 95% CI (77.2% to 99.9%)

• Week 312: 78.6% (11 of 14 participants); 95% CI (49.2% to 95.3%)

Cohort 2 Group 1: ≥ 6 to < 12 Years of Age and Weight ≥ 25 kg:

• Week 24: 100.0% (9 of 9 participants); 95% CI (66.4% to 100.0%)

• Week 48: 100.0% (7 of 7 participants); 95% CI (59.0% to 100.0%)

• Week 96: 100.0% (6 of 6 participants); 95% CI (54.1% to 100.0%)

• Week 192: 100% (4 of 4 participants); 95% CI (39.8% to 100.0%)

• Week 312: 100% (3 of 3 participants); 95% CI (29.2% to 100.0%)

Cohort 2 Group 2: ≥ 2 to < 12 Years of Age and Weight ≥ 17 kg to < 25 kg

• Week 24: 100.0% (2 of 2 participants); 95% CI (15.8% to 100.0%)

• Week 48: 100.0% (2 of 2 participants); 95% CI (15.8% to 100.0%)

• Week 96: 100.0% (1 of 1 participant); 95% CI (2.5% to 100.0%)

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

Consistent with the high degree of virologic suppression, there was little change in CD4 cell count and CD4% from baseline through Week 312, Week 312, and Week 96 for Cohort 1, Cohort 2 Group 1, and Cohort 2 Group 2, respectively.

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

• Week 24: −130 (272.6)

• Week 48: −105 (162.9)

• Week 96: −162 (241.3)

• Week 192: −75 (334.9)

• Week 312: −119 (239.0)

Cohort 2 Group 1: ≥ 6 to < 12 Years of Age and Weight ≥ 25 kg:

• Week 24: 68 (352.5)

• Week 48: 210 (406.5)

• Week 96: 248 (268.1)

• Week 192: 120 (316.3)

• Week 312: −163 (80.9)

Cohort 2 Group 2: ≥ 2 to < 12 Years of Age and Weight ≥ 17 kg to < 25 kg

• Week 24: −299 (48.8)

• Week 48: −124 (37.5)

• Week 96: −247

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

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

• Week 24: −0.21 (3.840)

• Week 48: −0.20 (3.407)

• Week 96: −0.69 (3.804)

• Week 192: −0.68 (6.182)

• Week 312: −3.01 (9.962)

Cohort 2 Group 1: ≥ 6 to < 12 Years of Age and Weight ≥ 25 kg:

• Week 24: 1.29 (2.395)

• Week 48: 0.70 (3.520)

• Week 96: −1.30 (4.215)

• Week 192: 1.05 (4.075)

• Week 312: 2.23 (2.438)

Cohort 2 Group 2: ≥ 2 to < 12 Years of Age and Weight ≥ 17 kg to < 25 kg

• Week 24: 0.60 (5.798)

• Week 48: 3.65 (7.283)

• Week 96: 9.50

Clinical virology data for Study GS-US-311-1269 (Cohort 1 and Cohort 2 Groups 1 and 2) was also presented. Virology analyses were conducted, inclusive of all data through the end of the study for participants in Cohort 1 (median exposure 306.5 weeks), Cohort 2 Group 1 (median exposure 145.1 weeks), and Cohort 2 Group 2 (median exposure 100.7 weeks).

Cohort 1

Of the 28 participants enrolled and treated in Cohort 1, 6 participants (21.4%) met the criteria for inclusion in the Resistance Analysis Population (RAP) and had their virus analysed for resistance. At the time of virologic failure (VF), 4 participants (66.7%) were receiving efavirenz (EFV) as their third agent; 1 participant (16.7% was receiving dolutegravir (DTG); and 1 participant (16.7%) was receiving ritonavir-boosted atazanavir (ATV/r). Of the 4 participants who had VF while receiving EFV, 3 participants switched their third agent (2 to ATV/r; 1 to DTG) and had VF on their new regimen.

The following nonnucleoside reverse transcriptase inhibitor (NNRTI) and NRTI resistance mutations were found:

NNRTI

- K103N (4 participants [66.7%])
- Y181C (1 participant [16.7%])
- Y188C/L (2 participants [33.3%])
- V106M (1 participant [16.7%])
- K101E (1 participant [16.7%])

NRTI

- K65R (2 participants [33.3%])
- M184V (1 participant [16.7%])
- K219K/N (1 participant [16.7%])

- D67N (1 participant [16.7%])

The K219K/N and D67N mutations are presumed to be transmitted drug resistance as these mutations do not emerge due to tenofovir (TFV) treatment, but no participant in Cohort 1 had a baseline sample or historical genotype available for analysis.

Cohort 2

For the purposes of the virology study report, participants in Cohort 2 Groups 1 and 2 were combined.

Of the 12 participants enrolled in Cohort 2, 1 participant (8.3%) met the criteria for inclusion in the RAP and had their virus analysed for resistance. At the time of VF, this participant was receiving ritonavir-boosted lopinavir as their third agent and had no resistance mutation to any study drug. No preexisting protease (PR)/reverse transcriptase (RT), or integrase (IN) substitution was detected in the baseline sample for this participant.

Altogether, baseline samples were available for 9 of 12 participants (75%) in Cohort 2, and the following preexisting primary NNRTI, NRTI, and IN resistance mutations were found:

- NNRTI

— K103K/N/R/S (1 participant [8.3%])

— Y181Y/C (2 participants [16.7%])

— Y188Y/C (1 participant [8.3%])

- NRTI

— M184M/V (1 participant [8.3%])

- Integrase strand transfer inhibitor (INSTI)

— G140G/R (1 participant [8.3%])

Safety results

The safety data presented in this report are cumulative. All AEs and laboratory abnormalities were treatment-emergent and are referred to as AEs and laboratory abnormalities. Additionally, the relationship of AEs to study drug is investigator-assigned.

Cohort 1 (≥ 12 to < 18 Years of Age and Weighing ≥ 35 kg)

F/TAF was well tolerated by adolescents (≥ 12 to < 18 years of age, weighing ≥ 35 kg) through a median (Q1, Q3) duration of exposure of 306.5 (212.4, 343.9) weeks.

Adverse Events

For participants in Cohort 1, all 28 participants (100.0%) had at least 1 AE.

The most commonly reported AEs were nasopharyngitis and headache (46.4%, 13 participants each), acne and influenza (28.6%, 8 participants each), and vomiting, upper respiratory tract infection, and vitamin D deficiency (25.0%, 7 participants each).

Of the 28 participants in Cohort 1, Grade 2 or higher AEs were reported in 25 participants (89.3%). Nine Grade 3 AEs were reported in 6 participants (21.4%) (syncope, diarrhoea, abdominal pain, vomiting, extrapulmonary tuberculosis, lymph node tuberculosis, forearm fracture, joint dislocation, and stab wound; all were considered not related to study drug). No Grade 4 AEs were reported.

Forearm fracture was reported in 1 participant. It was Grade 3 in severity and was considered serious due to hospitalization. The event was not related to study drug.

Adverse events considered related to study drug were reported for 8 participants (28.6%).

Among study drug-related AEs, only headache (10.7%, 3 participants) was reported in more than 1 participant.

Six SAEs were reported in 4 participants (14.3%) (diarrhoea and electrolyte imbalance in 1 participant, forearm fracture and joint dislocation in 1 participant, stab wound in 1 participant, and syncope in 1 participant; no SAE was considered related to study drug).

No AE led to premature study drug discontinuation. There were no deaths due to AEs.

Clinical Laboratory Abnormalities

There were no clinically relevant changes from baseline in median values for haematology and clinical chemistry parameters. Median values were within normal ranges.

All the participants had at least 1 graded laboratory abnormality. Grade 3 or 4 laboratory abnormalities were observed for 53.6% (15 of 28) of participants. Grade 3 laboratory abnormalities reported in more than 1 participant included increased amylase and urine red blood cells (4 participants [14.3% each]) and increased total bilirubin and increased fasting low-density lipoprotein (2 participants [7.1% each]). Grade 4 laboratory abnormality reported in more than 1 participant included decreased neutrophils (2 participants [7.1%]).

Liver-Related Laboratory Tests

In the assessment of liver enzyme elevations in relation to normal ranges, no participant had elevations > 3 × upper limit of normal (ULN) in aspartate aminotransferase (AST) or alanine aminotransferase (ALT). Six of 28 participants (21.4%) had > 1 × ULN elevation in total bilirubin, 3 of 28 participants (10.7%) had > 2 × ULN elevation in total bilirubin, and 4 of 28 participants (14.3%) had > 1.5 × ULN elevation in alkaline phosphatase (ALP). No Hy's Law cases were identified.

Cohort 2 Group 1 (≥ 6 to < 12 Years of Age and Weighing ≥ 25 kg)

F/TAF was well tolerated by children (≥ 6 to < 12 years of age, weighing ≥ 25 kg) through a median (Q1, Q3) duration of exposure of 145.1 (60.3, 315.0) weeks.

Adverse Events

For participants in Cohort 2 Group 1, 88.9% (8 of 9) participants had at least 1 AE. All AEs were Grade 2 except 1 AE that was Grade 3 in severity.

The most commonly reported AEs were nasopharyngitis (55.6%, 5 participants), dental caries, gastroenteritis, rhinitis allergic, sinus bradycardia, COVID-19, dermatitis allergic, and pharyngotonsillitis (22.2%, 2 participants each).

One participant had a Grade 3 AE of appendicitis that was considered serious due to hospitalization.

No participant had an AE that was considered related to study drug, or an AE leading to study drug discontinuation. No deaths were reported in Cohort 2 Group 1.

Clinical Laboratory Abnormalities

There were no clinically relevant changes from baseline in median values for haematology and clinical chemistry parameters. Median values were within normal ranges.

All the participants had at least 1 graded laboratory abnormality. Grade 3 or 4 laboratory abnormalities were observed for 55.6% (5 of 9) of participants. No Grade 3 laboratory abnormalities were reported in more than 1 participant. The only Grade 4 laboratory abnormality reported was increased creatine kinase in 1 participant.

Liver-Related Laboratory Tests

In the assessment of liver enzyme elevations in relation to normal ranges, 1 of 9 participants had elevations > 3 × ULN in AST and ALT and no participant had elevations > 2 × ULN in total bilirubin and 1 of 9 participant had elevations > 1.5 × ULN in ALP. No Hy's Law cases were identified.

Cohort 2 Group 2 (≥ 2 to < 12 Years of Age and Weighing ≥ 17 to < 25 kg)

F/TAF was well tolerated by children (≥ 2 to < 12 years of age, weighing ≥ 17 to < 25 kg) through a median (Q1, Q3) duration of exposure of 100.7 (9.0, 103.1) weeks.

Adverse Events

For participants in Cohort 2 Group 2, 66.7% (2 of 3) of participants had at least 1 AE, all of which were Grade 2 in severity.

The most commonly reported AE was viral upper respiratory tract infection (66.7%, 2 of 3 participants). All other AEs reported in Cohort 2 Group 1 occurred in 1 participant.

One participant had an AE of neutropenia that was considered related to study drug.

No participant had an SAE, a Grade 3 or 4 AE, or an AE leading to study drug discontinuation. No deaths were reported in Cohort 2 Group 2.

Clinical Laboratory Abnormalities

There were no clinically relevant changes from baseline in median values for haematology and clinical chemistry parameters. Median values were within normal ranges. All 3 participants had at least 1 graded laboratory abnormality. No Grade 3 or 4 laboratory abnormalities were observed in Cohort 2 Group 2.

Liver-Related Laboratory Tests

In the assessment of liver enzyme elevations in relation to normal ranges, no participant had elevations > 3 × ULN in AST or ALT or > 2 × ULN in total bilirubin. One of 3 participants had elevation of > 1.5 × ULN in ALP. No Hy's Law cases were identified.

Bone safety

Fracture Events

Forearm fracture was reported in Cohort 1 in 1 participant. It was Grade 3 in severity and considered serious due to hospitalization. The event was not related to study drug.

Bone Mineral Density

Percentage Change From Baseline in Spine and TBLH BMD

Cohort 1

Overall, spine and TBLH BMD increased relative to baseline through Week 312. At Weeks 96, 192, and 312, respectively, mean (SD) percentage increases in spine BMD were 13.449% (9.0927%), 22.860% (16.328%), and 24.795% (21.444%) and mean (SD) percentage increases in TBLH BMD were 12.041% (9.5905%), 23.387% (15.362%), and 22.710% (15.399%).

Cohort 2 Group 1

Overall, spine and TBLH BMD increased relative to baseline through Week 312. At Weeks 48, 96, and 312, respectively, mean (SD) percentage increases in spine BMD were 5.642% (5.6027%), 22.931% (8.2986%), and 54.014% (11.975%) and mean (SD) percentage increases in TBLH BMD were 6.942% (5.7007%), 15.773% (13.143%), and 48.232% (2.4142%).

Cohort 2 Group 2

Overall, spine and TBLH BMD increased relative to baseline through Week 96. At Weeks 48 and 96, respectively, mean (SD) percentage increases in spine BMD were 4.285% (1.1264%), and 6.116% (0.8884%), and mean (SD) percentage increases in TBLH BMD were 7.060% (0.5988%) and 8.097% (3.1125%).

No participant in either cohort had a ≥ 4% decrease from baseline in spine or TBLH BMD.

Change From Baseline in BMD Z-Scores

Overall, spine and TBLH BMD 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 −0.24 (0.913) and −0.78 (1.232), respectively. Mean (SD) changes from baseline at Week 312 for spine and TBLH BMD height-age Z-scores were 0.35 (0.490) and 1.14 (0.880), respectively.

For Cohort 2 Group 1, the baseline mean (SD) spine and TBLH BMD height-age Z-scores were −0.06 (1.042) and −0.16 (1.141), respectively. Mean (SD) changes from baseline at Week 312 for spine and TBLH BMD height-age Z-scores were −0.35 (0.699) and 0.55 (0.516), respectively.

For Cohort 2 Group 2, the baseline mean (SD) spine and TBLH BMD height-age Z-scores were −1.08 (1.055) and −2.37 (0.939), respectively. Mean (SD) changes from baseline at Week 96 for spine and TBLH BMD height-age Z-scores were −0.05 (0.042) and −0.20 (0.375), respectively.

A shift in spine BMD height-age Z-score from > −2 at baseline to ≤ −2 postbaseline was observed for 1 participant in Cohort 1.

A shift in TBLH BMD height-age Z-score from > −2 at baseline to ≤ −2 at some time point postbaseline was observed for 3 participants (2 in Cohort 1 and 1 in Cohort 2 Group 1).

Bone Laboratory Parameters

No clinical relevance was derived from the changes in any of the bone biomarkers from baseline (serum levels of parameters of bone resorption (type I collagen crosslinked [CTX]; C-telopeptide) and bone formation (bone-specific alkaline phosphatase, procollagen type I N-terminal propeptide [P1NP]), parathyroid hormone (PTH), and 25-OH vitamin D, and 1,25-(OH)2 vitamin D) for either cohort.

Renal Safety

There were no AEs of renal tubulopathy (including Fanconi syndrome) in any cohort. There were no renal AEs that led to discontinuation of study drug and no renal SAEs.

Serum Creatinine

Cohort 1 (≥ 12 to < 18 Years of Age, Weighing ≥ 35 kg)

Median (Q1, Q3) baseline serum creatinine was 0.58 (0.51, 0.68) mg/dL. A gradual increase from baseline was observed at most time points after Week 1 that continued through Week 432. Median (Q1, Q3) changes from baseline were as follows:

- Week 48 (N = 28): 0.02 (−0.02, 0.07) mg/dL
- Week 96 (N = 27): 0.09 (0.02, 0.13) mg/dL
- Week 192 (N = 21): 0.12 (0.04, 0.21) mg/dL
- Week 384 (N = 5): 0.19 (0.15, 0.21) mg/dL
- Week 432 (N = 2): 0.27 (0.18, 0.36) mg/dL

No Grade 3 or 4 serum creatinine abnormalities were reported.

Cohort 2 Group 1 (≥ 6 to < 12 Years of Age, Weighing ≥ 25 kg)

Median (Q1, Q3) baseline serum creatinine was 0.45 (0.43, 0.53) mg/dL. Median (Q1, Q3) changes from baseline remained stable as follows:

- Week 48 (N = 7): 0.01 (−0.02, 0.02) mg/dL
- Week 96 (N = 5): 0.00 (0.00, 0.06) mg/dL
- Week 192 (N = 4): 0.17 (0.10, 0.29) mg/dL

No Grade 3 or 4 serum creatinine abnormalities were reported.

Cohort 2 Group 2 (≥ 2 to < 12 Years of Age, Weighing ≥ 17 to < 25 kg)

Median (Q1, Q3) baseline serum creatinine was 0.41 (0.41, 0.51) mg/dL. There were only 2 participants in the group after Week 8, so no conclusions can be made about trends. Absolute serum creatinine values remained within normal reference ranges.

No Grade 3 or 4 serum creatinine abnormalities were reported.

Estimated Glomerular Filtration Rate (eGFR)

Cohort 1 (≥ 12 to < 18 Years of Age, Weighing ≥ 35 kg)

Median (Q1, Q3) baseline $eGFR_{Schwartz}$ was 157.3 (138.6, 191.5) mL/min/1.73 m^2. A decrease from baseline was observed from Week 2. Median (Q1, Q3) changes from baseline were as follows:

• Week 48 (N = 28): −0.4 (−13.8, 7.2) mL/min/1.73 m^2

• Week 96 (N = 27): −15.4 (−26.4, 4.4) mL/min/1.73 m^2

• Week 192 (N = 21): −14.9 (−36.2, −4.7) mL/min/1.73 m^2

• Week 384 (N = 5): −37.5 (−44.8, −37.4) mL/min/1.73 m^2

• Week 432 (N = 2): −60.8 (−80.9, −40.6) mL/min/1.73 m^2

No clinical relevance was associated with this decrease over a period of years given the high median (Q1, Q3) $eGFR_{Schwartz}$ at both baseline (157.3 [138.6, 191.5] mL/min/1.73 m^2) and Week 432 (153.58 [151.59, 155.56] mL/min/1.73 m^2) for participants in this cohort during the transition from adolescence to early adulthood.

Cohort 2 Group 1 (≥ 6 to < 12 Years of Age, Weighing ≥ 25 kg)

Median (Q1, Q3) baseline $eGFR_{Schwartz}$ was 172.7 (144.5, 180.0) mL/min/1.73 m^2. An increase from baseline was observed at Week 48 that remained at Week 96. Median (Q1, Q3) changes from baseline were as follows:

• Week 48 (N = 7): 19.2 (−1.2, 52.0) mL/min/1.73 m^2

• Week 96 (N = 5): 17.1 (5.1, 21.1) mL/min/1.73 m^2

• Week 192 (N = 4): −1.6 (−22.2, 11.7) mL/min/1.73 m^2

Due to the small number of participants, interpretation of the results is not conclusive.

Cohort 2 Group 2 (≥ 2 to < 12 Years of Age, Weighing ≥ 17 to < 25 kg)

Median (Q1, Q3) baseline $eGFR_{Schwartz}$ was 155.3 (135.3, 169.0) mL/min/1.73 m^2. A decrease from baseline was observed at Week 48 that remained at Week 84. Median (Q1, Q3) changes from baseline were as follows:

• Week 48 (N = 2): −11.1 (−22.7, 0.6) mL/min/1.73 m^2

• Week 84 (N = 2): −13.1 (−13.9, −12.4) mL/min/1.73 m^2

Due to the small number of participants, interpretation of the results is not conclusive.

Urine Retinol Binding Protein (RBP) to Creatinine Ratio and Beta-2 Microglobulin to Creatinine Ratio

Cohort 1 (≥ 12 to < 18 Years of Age, Weighing ≥ 35 kg)

The median (Q1, Q3) baseline urine RBP to creatinine ratio was 88.6 (59.4, 146.4) µg/g. There was a decrease from baseline in the urine RBP to creatinine ratio from Week 2. Median (Q1, Q3) percentage changes from baseline were as follows:

• Week 48 (N = 27): −21.8% (−46.8%, 9.7%)

• Week 96 (N = 27): −8.8% (−32.2%, 54.3%)

• Week 384 (N = 5): −2.0%(−36.3%, 41.3%)

• Week 432 (N = 2): −47.3% (−56.5%, −38.1%)

Median (Q1, Q3) baseline urine beta-2 microglobulin to creatinine ratio was 109.3 (72.5, 320.3) µg/g (Table 15.11.6.3.5). There was a decrease from baseline in the urine beta-2 microglobulin to creatinine ratio from Week 2. Median (Q1, Q3) percentage changes from baseline were as follows:

• Week 48 (N = 27): −44.0% (−67.6%, −2.6%)

• Week 96 (N = 27): −22.3% (−74.6%, 17.8%)

• Week 384 (N = 5): −48.8% (−66.9%, −13.2%)

• Week 432 (N = 2): −28.7% (−29.9%, −27.5%)

Cohort 2 Group 1 (≥ 6 to < 12 Years of Age, Weighing ≥ 25 kg)

There was a decrease from baseline in the urine RBP to creatinine ratio at most of the visits. Median (Q1, Q3) baseline urine RBP to creatinine ratio was 132.6 (92.8, 141.6) µg/g. Median (Q1, Q3) percentage changes from baseline were as follows:

• Week 48 (N = 7): 53.4% (−49.9%, 83.1%)

• Week 96 (N = 5): −12.1% (−38.4%, 12.8%)

• Week 192 (N = 4): −14.1% (−48.0%, 26.8%)

There was a decrease from baseline in the urine beta-2 microglobulin to creatinine ratio at most of the visits. Median (Q1, Q3) baseline urine beta-2 microglobulin to creatinine ratio was 111.6 (110.3, 113.1) µg/g. Median (Q1, Q3) percentage changes from baseline were as follows:

• Week 48 (N = 7): 4.4% (−13.3%, 137.1%)

• Week 96 (N = 5): −16.0% (−40.5%, −12.3%)

• Week 192 (N = 4): −22.7% (−84.3%, 33.0%)

Cohort 2 Group 2 (≥ 2 to < 12 Years of Age, Weighing ≥ 17 to < 25 kg)

Median (Q1, Q3) baseline urine RBP to creatinine ratio was 99.3 (83.6, 100.2) µg/g. Median (Q1, Q3) percentage changes from baseline at Weeks 48 and 96 were as follows:

• Week 48 (N = 2): −3.4% (−20.5%, 13.7%)

• Week 96 (N = 2): −58.2% (−74.3%, −42.1%)

Median (Q1, Q3) baseline urine beta-2 microglobulin to creatinine ratio was 111.7 (96.8, 223.7) µg/g. Median (Q1, Q3) percentage changes from baseline at Weeks 48 and 96 were as follows:

• Week 48 (N = 2): −10.3% (−14.8%, −5.9%)

• Week 96 (N = 2): 52.7% (15.0%, 90.4%)

Due to the small number of participants, interpretation of the results is not conclusive.

Metabolic Laboratory Parameters

There were no clinically relevant changes from baseline in median fasting values for total cholesterol, direct low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol: HDL cholesterol ratio, triglycerides, or glucose for either cohort.

Graded abnormalities were reported for the following:

• Increased fasting total cholesterol: 28.2%, 11 of 39 participants (9 in Cohort 1 and 2 in Cohort 2 Group 1)

• Increased fasting LDL cholesterol: 28.2%, 11 of 39 participants (9 in Cohort 1 and 2 in Cohort 2 Group 1)

• Increased fasting triglycerides: 5.1%, 2 of 39 participants (1 in Cohort 1 and 1 in Cohort 2 Group 1)

• Increased glucose (fasting hyperglycaemia): 15.0%, 6 of 40 participants (all in Cohort 1)

• Decreased glucose (fasting hypoglycaemia); 10.0%, 4 of 40 participants (3 in Cohort 1 and 1 in Cohort 2 Group 2)

All graded fasting lipid and glucose abnormalities were Grade 1 and 2 with the exception of 1 abnormality of Grade 3 increased triglycerides (Cohort 1) and 3 abnormalities of Grade 3 increased LDL (2 in Cohort 1 and 1 in Cohort 2 Group 1).

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 stage was consistent with the maturing study population.

Pregnancy

One participant in Cohort 1 became pregnant during the study.

Other Results:

Palatability and Acceptability Assessments

No participant in either cohort reported dissatisfaction with the palatability of F/TAF tablets at Week 2 or during the IPK visit. No participant in either cohort reported dissatisfaction with the acceptability of F/TAF tablets in terms of shape and size and swallowing.

2.3.3. Discussion on clinical aspects

The high degree of virologic suppression maintained in paediatric participants who switched their previous ARV regimen to include F/TAF provides reassurance of the efficacy of F/TAF as a 2 NRTI “backbone” in combination with a third ARV agent in the treatment of HIV1 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 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-311-1269, which demonstrated the safety and efficacy of 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 Descovy 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.