21 July 2022
EMA/682126/2022
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on group of an extension of marketing authorisation and an extension of indication variation

Genvoya

International non-proprietary name: elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide

Procedure No. EMEA/H/C/004042/X/0079/G

Note

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

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List of abbreviations

AE	adverse event
ART	antiretroviral therapy
BCS	Biopharmaceutics Classification System
BMD	bone mineral density
C	cobicistat
CDC	(US) Centers for Disease Control and Prevention
CHMP	(EMA) Committee for Medicinal Products for Human Use
CLCRSW	creatinine clearance calculated using the Schwartz formula
COBI	cobicistat
CSR	clinical study report
E	elvitegravir
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
eGFR	estimated glomerular filtration rate
eGFRSchwartz	eGFR calculated using the Schwartz formula
EMA	European Medicines Agency
EVG	elvitegravir
EVG/COBI/FTC/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
F	emtricitabine
FAS	Full Analysis Set
FDA	(US) Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine
GEN	Genvoya
HA	height-age (adjusted)
HIV-1	human immunodeficiency virus type 1
LD	low-dose
LPV	lopinavir
M= E	missing = excluded
M = F	missing = failure
PBPK	physiologically based pharmacokinetic

PD	pharmacodynamic
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic
Q1, Q3	first quartile, third quartile
QSP	quantitative systems pharmacology
RBC	red blood cell
RNA	ribonucleic acid
RTV	ritonavir
SAE	serious adverse event
SD	standard deviation
SmPC	summary of product characteristics
TAF	tenofovir alafenamide
TBLH	total-body-less-head
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
US	United States
WT	body weight

1. Background information on the procedure

1.1. Submission of the dossier

Gilead Sciences Ireland UC submitted on 28 May 2021 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension application to introduce a new strength (90 mg/90 mg/120 mg/6 mg film-coated tablets). The extension application is grouped with a type II variation (C.I.6.a) to include treatment of human immunodeficiency virus 1 (HIV 1) infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir in paediatric patients aged from 2 years and with body weight at least 14 kg. Sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the Package Leaflet are updated to support the extended indication. The RMP (version 5.1) is updated in accordance.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0435/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0435/2020 was completed.

The PDCO issued an opinion on compliance for the PIP P/0435/2020.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH received Scientific advice from the CHMP on the development for the indication from the CHMP on 27 June 2019 (EMA/CHMP/SAWP/344146/2019) and 12 December 2019 (EMA/CHMP/SAWP/650387/2019). The Scientific advice pertained to quality and clinical aspects.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	28 May 2021
The procedure started on	15 July 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	5 October 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	12 October 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 October 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	11 November 2021
The MAH submitted the responses to the CHMP consolidated List of Questions on	21 January 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 February 2022
The PRAC Rapporteur's circulated the PRAC Report to all PRAC and CHMP members on	28 February 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 March 2022
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	24 March 2022
The MAH submitted the responses to the CHMP List of Outstanding Issues on	21 June 2022
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	06 July 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Genvoya on	21 July 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The human immunodeficiency virus (HIV) targets the immune system and weakens people's defence against many infections and some types of cancer that people with healthy immune systems can fight off. As the virus destroys and impairs the function of immune cells, infected individuals gradually become immunodeficient. Immune function is typically measured by CD4 cell count. The most advanced stage of HIV infection is acquired immunodeficiency syndrome (AIDS), which can take many years to develop if not treated, depending on the individual. AIDS is defined by the development of certain cancers, infections or other severe long-term clinical manifestations.

2.1.2. Epidemiology

There were approximately 37.6 million people across the globe with HIV in 2020. Of these, 35.9 million were adults and 1.7 million were children (<15 years old). In 2020, 680 000 [480 000–1.0 million] people died from HIV-related causes and 1.5 million [1.0–2.0 million] people acquired HIV.

As of the end of 2020, 27.4 million people with HIV (73%) were accessing antiretroviral therapy (ART) globally. That means 10.2 million people are still waiting. People with HIV who are aware of their status, take ART daily as prescribed, and get and keep an undetectable viral load can live long, healthy lives and have effectively no risk of sexually transmitting HIV to their HIV-negative partner. UNAIDS reports that in 2020, of all people with HIV worldwide: 84% knew their HIV status, 73% were accessing ART, and 66% were virally suppressed.

2.1.3. Clinical presentation, diagnosis

The symptoms of HIV vary depending on the stage of infection. Though people living with HIV tend to be most infectious in the first few months after being infected, many are unaware of their status until the later stages. In the first few weeks after initial infection people may experience no symptoms or an influenza-like illness including fever, headache, rash or sore throat. As the infection progressively weakens the immune system, they can develop other signs and symptoms, such as swollen lymph nodes, weight loss, fever, diarrhoea and cough. Without treatment, they could also develop severe illnesses such as tuberculosis (TB), cryptococcal meningitis, severe bacterial infections, and cancers such as lymphomas and Kaposi's sarcoma.

2.1.4. Management

Standard of care for the treatment of HIV-1 infection uses combination antiretroviral therapy (ART) to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression. For ART-naive HIV infected patients, current treatment guidelines suggest that initial therapy consist of two nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either a non- nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI) or an integrase strand-transfer inhibitor (INSTI).

Virologically suppressed, HIV infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once daily fixed dose combination (FDC) regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes.

The success of ART means that morbidity and mortality in the HIV infected population is increasingly driven by non-AIDS–associated comorbidities. Clinical attention has become more focused on the optimization of tolerability, long term safety, and adherence to potent ART regimens. There remains a significant medical need for new, effective therapies that take into consideration the non-HIV comorbidities, demographics of the aging HIV infected population, antiretroviral (ARV) resistance and regimen simplification.

Chronic kidney disease is important, since observational studies have demonstrated a relationship between kidney disease and progression to AIDS and death. Moreover, HIV associated nephropathy presents in up to 30% of patients and this is a common cause of end-stage renal disease (ESRD) requiring dialysis.

ART with proven efficacy and safety in both the elderly and young patients is important; limited data and treatment options are available in both populations. The elderly have increased risks for comorbidities, including those related to renal and bone. There are specific and complex challenges for the treatment of adolescents, who also represent the population that will require ART for the longest time.

Tenofovir (TFV) is a nucleotide analogue with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF), an oral prodrug of TFV, has improved bioavailability, and delivers high systemic exposures of TFV with favourable efficacy and safety data. TDF is a preferred NtRTI for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

While TDF is used broadly in the treatment of HIV-1 infection, an important identified risk with its use is nephrotoxicity, which is associated with increased creatinine in some patients, increased protein loss (particularly tubular), and occasional cases of proximal renal tubulopathy (PRT) (including Fanconi syndrome). These risks necessitate increased renal monitoring with use of TDF-containing products, placing burden on the patient and healthcare provider. Reductions in bone mineral density (BMD) have also been seen after the initiation of ART, with larger decreases in BMD observed with TDF than with other NRTIs.

Tenofovir alafenamide (TAF) is an oral prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and approximately 90% lower circulating levels of TFV relative to TDF. The distinct metabolism of TAF offers the potential for an improved safety profile compared with TDF.

2.2. About the product

Genvoya (GEN; elvitegravir [E, EVG]/cobicistat [C, COBI]/emtricitabine [F, FTC]/tenofovir alafenamide [TAF]; E/C/F/TAF) is an oral, once daily fixed dose combination (FDC) that provides a potent, convenient, tolerable, and practical regimen for the long-term treatment of patients with HIV-1. At a so-called "adult strength" (E/C/F/TAF 150/150/200/10 mg), GEN is approved for the treatment of HIV-1 infection in patients ≥ 6 years of age weighing ≥ 25 kg by regulatory authorities including the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) under the trade name Genvoya.

Within the European Union (EU), Genvoya (E/C/F/TAF 150/150/200/10 mg) is indicated for the treatment of HIV-1 infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine, or tenofovir in adults and adolescents aged from 12 years and with body weight ≥ 35 kg, and in

children aged from 6 years and with body weight ≥ 25 kg for whom alternative regimens are unsuitable due to toxicities.

2.3. Type of Application and aspects on development

This submission provides safety, pharmacokinetic (PK), and efficacy data generated through 48 weeks (median [Q1, Q3] exposure 48.3 [48.0, 60.1] weeks) of once daily administration of a low-dose (LD) GEN tablet (E/C/F/TAF 90/90/120/6 mg) to HIV-1 infected, virologically suppressed subjects ≥ 2 years of age, weighing ≥ 14 to < 25 kg at screening, comprising Cohort 3 in Study GS-US-292-0106, to support extension of the current indication to include patients down to ≥ 2 years of age weighing ≥ 14 kg.

The ongoing Study GS-US-292-0106 is conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for Good Clinical Practice (GCP), and the original principles embodied in the Declaration of Helsinki.

2.4. Quality aspects

2.4.1. Introduction

The finished product subject of this line extension is presented as immediate release film-coated tablets containing a fixed dose combination (FDC) of four active pharmaceutical ingredients, elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide fumarate (TAF), also referred to as E/C/F/TAF, as 90 mg/90 mg/120 mg/6 mg film-coated tablets.

This is a line extension of a marketed formulation containing 150/150/200/10 mg; in the market, since 2015 (EU/1/15/1061/001-002).

The other ingredients in the tablet core are: lactose (as monohydrate), microcrystalline cellulose (E460), croscarmellose sodium, hydroxypropylcellulose (E463), silicon dioxide (E551), sodium laurilsulfate and magnesium stearate. The film-coating contains: poly(vinyl alcohol) (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b), iron oxide yellow (E172), iron oxide black (E172).

The product is available in high density polyethylene (HDPE) bottle with a polypropylene continuous-thread, child-resistant cap, lined with an induction activated aluminium foil liner containing 30 film-coated tablets. Each bottle contains silica gel desiccant and polyester coil.

2.4.2. Active substances

As the finished product is a line extension of the marketed formulation Genvoya 150/150/200/10 mg tablets all information concerning the active substances was already approved within the initial marketing authorisation (EU/1/15/1061/001-002).

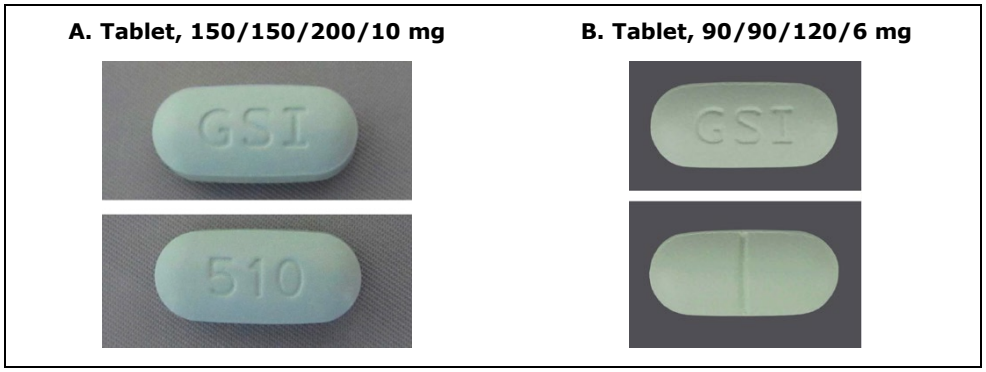
2.4.3. Finished Medicinal Product

2.4.3.1. *Description of the product and Pharmaceutical Development*

The finished product is presented as green, capsule-shaped, film-coated tablets of dimensions 16 mm x 7 mm, debossed with "GSI" on one side of the tablet and scored on the other side of the tablet.

The 150/150/200/10 mg tablets are green, capsule-shaped, film-coated tablets with "GSI" debossed on one side and "510" on the other side. Tablet dimensions are 19 mm x 8.5 mm. The aspect of Genvoya tablets is shown in Figure 1.

Figure 1 - Images of Genvoya E/C/F/TAF tablets



The composition of Genvoya tablets (current approved strength 150/150/200/10 mg and proposed strength 90/90/120/6 mg of E/C/F/TAF) is presented in the dossier.

Both strengths (the already authorised and the new one) of E/C/F/TAF tablets are prepared from a common powder blend and are dose-proportional. Tablet cores are compressed to a different core weight to achieve the target strength. The film coating material used for 90/90/120/6 mg tablets, is similar to that of 150/150/200/10 mg tablets but contains different colour pigments.

E/C/F/TAF tablets, 90/90/120/6 mg, are packaged in white, high density polyethylene bottles containing three (3) grams of silica gel desiccant and polyester coil. Each bottle contains 30 tablets and is capped using a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed, aluminium-faced liner. The container closure systems are identical (in terms of materials used) for both strengths.

Genvoya should be taken orally, once daily with food (see section 5.2). The score on the proposed 90/90/120/6 mg tablets was introduced for ease of administration. Subjects unable to swallow the whole tablet, can split it into halves and swallow each piece one after the other. The score line is not intended for dividing the tablets into equal doses. Patients are instructed to take tablets immediately after splitting and not store split tablets. This information is duly provided in the SmPC. Minimal loss of tablet mass during splitting was demonstrated, ensuring that full dose is taken when subjects split tablet and take both halves as instructed.

During the procedure the applicant was asked about acceptability/palatability for the younger paediatric population. In response, it was clarified that it is not recommended to chew or crush and mix the film-coated tablet with food/liquids, mainly due to the poor palatability profile of tenofovir alafenamide fumarate (TAF) and also an anticipated lower TAF exposure following crushing of tablets.

The pharmaceutical development, manufacture and control of finished product is based on those of the already approved commercial 150/150/200/10 mg tablets. The pharmaceutically and clinically relevant physicochemical properties of the active substance were duly identified, being adequately specified and adequately controlled.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of the film-coating components which are tested against an in-house standard. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. Their functions and amounts used are well justified. No novel excipients or materials of animal are used in the finished product. The safety of the amount of sodium dodecyl sulfate (SLS) in each tablet, in long-term treatment for the paediatric population, was sufficiently addressed and no adverse reactions has been associated with SLS included in oral formulations.

The dissolution testing method has been previously approved for the already approved commercial formulation (Tablet strength 150/150/200/10 mg). Its discriminatory power concerning crucial parameters, such as tablet hardness, and particle size have been addressed.

2.4.3.2. ***Manufacture of the product and process controls***

The manufacturing process consists of several main steps: blending of the active substance with intragranular/extragranular excipients, fluid-bed granulation/dry granulation and milling, compression, tablet film-coating and packaging.

The finished product is produced using a standard manufacturing process. No design space has been proposed. The manufacturing process for 150/150/200/10 mg tablets and 90/90/120/6 mg tablets, is identical through to the final blending step. A portion of the final blend is used for manufacturing the 90/90/120/6 mg tablets. The compression and coating steps are fundamentally equivalent between the two strengths except for the differences introduced by tablet size, shape, film-coating material and the scale of the compression and coating processing equipment.

In–process controls during the manufacture have been established based on data and manufacturing experience from development, clinical, primary stability and scale-up batches. Manufacturing process and control strategy used to produce E/C/F/TAF final powder blend for 90/90/120/6 mg tablets is identical to that developed and validated for 150/150/200/10 mg strength tablets.

The material output at each process step is controlled by the equipment operating parameters and by testing intermediates during the manufacturing process. Manufacturing process validation data for the 90/90/120/6 mg tablets comply with acceptance criteria for content uniformity and the process is considered fully validated.

The validation plan for the manufacturing process of E/C/F/TAF tablets, 90/90/120/6 mg has been provided and found to be acceptable.

2.4.3.3. ***Product specification, analytical procedures, batch analysis***

The release and shelf-life specifications for the finished product Genvoya 90/90/120/6 mg tablets, include tests for appearance, identification (HPLC, UPLC/UV), water content (Ph. Eur.), assay (UPLC/UV), degradation products (UPLC/UV), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.) and microbial examination (Ph. Eur.).

The justification of the tests and acceptance criteria are provided. Specifications are well justified and aligned with the recommendations of ICH guidelines Q6A and Q3B(R2). The 90/90/120/6 mg tablets, have the same formulation composition as the 150/150/200/10 mg tablets, apart from the slight difference in the film-coating and tablet core weight. A common powder blend is used in the manufacture of both tablet strengths. Therefore, except for appearance, the tests, test methods, and acceptance criteria for 90/90/120/6 mg tablets, are equivalent to those for the approved 150/150/200/10 mg tablets.

No information is provided in section 3.2.P.5.5. characterisation of impurities. As this section is applicable to both the approved strength and for the new strength and no changes have been made within the current extension of indication, this is acceptable.

The specified degradation products for the active substances COBI on silicon dioxide, FTC, TAF fumarate, in the specification for 90/90/120/6 mg tablets, have been toxicologically qualified and the qualification levels are supportive of the acceptance limits in for the administration of E/C/F/TAF tablets to the paediatric population of age 2 to <12 years old, body weight of 14 to <25 kg.

Elemental Impurities and nitrosamine impurities were considered for inclusion in the finished product specification, according to ICH guidelines Q3C, Q6A and Q3D. After evaluation of the control strategy for these attributes and relevant data, it is considered that a test for these attributes was not necessary.

The elemental impurities risk assessment provided for 150/150/200/10 mg tablets, applies also 90/90/120/6 mg tablets. Therefore, testing for elemental impurities in the latter is considered unnecessary. Likewise, the nitrosamines risk assessment provided for 150/150/200/10 mg tablets applies also to 90/90/120/6 mg tablets. This is because the formulation compositions, manufacturing processes, manufacturing equipment and packaging components are similar. Therefore, no risk is identified on the formation and contamination of nitrosamines 90/90/120/6 mg tablets, at the end of product shelf-life.

The methods of analysis and the reference standards are the same as those used for the authorised strength; the information is sufficient.

The manufacturing history on the batches 90/90/120/6 mg tablets, manufactured for clinical and stability studies, is presented and batch analysis results are provided. All results comply with the specifications.

2.4.3.4. ***Stability of the product***

Stability data from several commercial scale batches of the 90/90/120/6 mg tablets stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Stability studies included all quality attributes: appearance, strength, degradation product content, water content, dissolution, and microbiological purity. All parameters met the proposed shelf-life specifications.

No significant change on any of the test attributes monitored at the accelerated storage condition of 40 °C / 75% RH.

Stress and photostability studies were not conducted on low dose FDC, because studies have already been conducted, and approved, on 150/150/200/10 mg tablets, which have the same formulation composition, apart from the film-coating material. The 150/150/200/10 mg tablets are stable when stored for up to 4 days at -20

°C, 50 °C and 60 ºC, and are not photolabile. Considering that in-use stability data has been obtained for the higher strength which is manufactured from the same final powder blend, and therefore the composition of the tablet core is the same, it is acceptable that the in-use study is not repeated for the lower strength.

Based on stability studies, the proposed shelf-life of 3 years for the finished product packaged in the proposed container closure system without any special storage conditions as stated in the SmPC (sections 6.3 and 6.4) is acceptable. The post-approval stability protocol and stability commitment is also acceptable.

2.4.3.5. *Post approval change management protocol(s)*

N/A

2.4.3.6. *Adventitious agents*

N/A

2.4.3.7. *GMO*

N/A

2.4.4. Discussion on chemical, and pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure the safety of the formulation for the proposed paediatric population has been demonstrated. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Pharmacology

The pharmacologic basis to recommend the E/C/F/TAF 90/90/120/6 mg for the treatment of HIV infection in children ≥ 2 years old and weighing ≥14 kg to < 25kg is scientifically sound based on the nonclinical in vitro and in vivo efficacy data available for the individual components and the combination of the agents.

The E/C/F/TAF FDC is not anticipated to produce any new human metabolites. Because significant pharmacokinetic interactions are unlikely (other than the intended pharmacokinetic boosting of EVG by COBI) and that the target organ profiles are different, administration of the combination product is unlikely to exacerbate known toxicities of the individual agents. The increase in TAF exposure due to inhibition of intestinal efflux by COBI has been taken into account during the TAF clinical dose selection for E/C/F/TAF FDC.

No new pharmacology data was presented as part of this submission. This is acceptable given the existing data and previously assessed data.

2.5.2. Pharmacokinetics

The pharmacokinetic profile of EVG, COBI, FTC, TAF, and TFV are well characterized in multiple animal species and the findings are pertinent in consideration of the use of these agents in combination. Additional data from clinical studies of the E/C/F/TAF FDC demonstrated acceptable tolerability and safety profiles to support use in patients ≥ 2 years old.

The E/C/F/TAF FDC is not anticipated to produce any new human metabolites. Because significant pharmacokinetic interactions are unlikely (other than the intended pharmacokinetic boosting of EVG by COBI) and that the target organ profiles are different, administration of the combination product is unlikely to exacerbate known toxicities of the individual agents. The increase in TAF exposure due to inhibition of intestinal efflux by COBI has been taken into account during the TAF clinical dose selection for E/C/F/TAF FDC.

No new pharmacokinetic data was presented as part of this submission. This is acceptable given the existing data and previously assessed data.

2.5.3. Toxicology

The toxicologic profile of EVG, COBI, FTC, TAF, and TFV are well characterized in multiple animal species and the findings are pertinent in consideration of the use of these agents in combination. Data from clinical studies of the E/C/F/TAF FDC demonstrated acceptable tolerability and safety profiles to support use in patients ≥ 2 years old.

The toxicity profiles of the 4 agents differ substantially with no clinically significant overlapping toxicity. Nonclinical studies with EVG have not identified any specific target organ toxicities or cause for concern. Potential toxicities related to COBI observed in nonclinical toxicology studies (hematology, clinical chemistry, and urinalysis changes; lower IgG antibody titers; and adaptive liver and thyroid changes) have not been observed in clinical studies with the E/C/F/TAF FDC tablet. The only toxicity observed in chronic animal studies with FTC was mild, reversible anemia at large multiples of clinical exposure; therefore, these hematological findings are not considered relevant to clinical use. Emtricitabine has an established clinical safety profile in children with no significant toxicities observed. The principal target organs of toxicity in animals following oral administration of TAF were the kidney (karyomegaly, tubular degeneration) and bone.

Available non-clinical data, along with clinical data, suggest that COBI reversibly blocks secretion of creatinine in humans. With no apparent pathological change in the kidney due to COBI, the routes of excretion differ for TFV and COBI, and that COBI would not be expected to inhibit the major renal transporters of TFV at clinically relevant concentrations, it is not anticipated that the combination of E/C/F/TAF could exacerbate the renal toxicity of TAF. The small increase in serum creatinine levels may be associated with inhibition of MATE1

mediated creatinine secretion by COBI. In fact, in the Phase 3 pivotal trials, the E/C/F/TAF FDC produces a smaller increase in serum creatinine than the E/C/F/TDF FDC.

The mild hematological changes with FTC should not cause an overlapping toxicity with COBI which was associated with minimal decreases in RBC parameters in rats.

Cobicistat, EVG, and FTC have not shown any potential for bone toxicity in chronic rat and dog toxicity studies; thus, exacerbation of any TAF effects on bone is not expected.

None of the 4 compounds had positive findings in genotoxicity studies. The E/C/F/TAF FDC is not anticipated to alter the genotoxicity profiles of the individual agents.

EVG, COBI, FTC, and TDF/TFV have all demonstrated low carcinogenic potential in conventional 2-year bioassays. Combination dosing would not be expected to change these profiles, and no exacerbation of toxicity is expected.

EVG, FTC, TAF, and COBI have not shown significant adverse effects in reproductive and developmental toxicity studies. In the EVG juvenile toxicity phase of the pre/postnatal study in rats, daily oral gavage administration of EVG to F1 generation pups from postnatal day (PND) 22 to 49 was well tolerated at doses up to 2000 mg/kg/day. The NOAEL for toxicity of EVG is 2000 mg/kg/day for juvenile rats where the mean exposure on PND 28 (169 µg.h/mL) was 5-fold higher than therapeutic human exposures at the 90 mg dose in HIV-1 infected subjects ≥2 years old administered E/C/F/TAF 90/90/120/6 mg (GS-US-292-0106 Interim 5 CSR). In the COBI juvenile toxicity phase of the pre/postnatal study in rats, daily oral gavage administration of COBI to F1 generation pups from PND 22 to 49 was well tolerated at doses up to 75 mg/kg/day. The NOAEL for toxicity of COBI is 75 mg/kg/day for juvenile rats where exposures on PND 49 (20.9 µg.h/mL) was 1.4-fold higher than therapeutic human exposures at the 90 mg dose in HIV-1 infected subjects ≥ 2 years old administered E/C/F/TAF 90/90/120/6 mg (GS US 292 0106 Interim 5 CSR).

Identified impurities and degradants have been assessed as part of the routine toxicology or qualification studies with the individual agents and with the EVG/COBI and FTC/TDF combinations. No unexpected toxicity was observed.

The absence of nonclinical safety studies with the E/C/F/TAF combination is in accordance with the CHMP Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005, January 2008). There are no anticipated clinically relevant pharmacokinetic or toxicological interactions expected in the E/C/F/TAF FDC beyond the anticipated pharmacokinetic boosting of EVG by COBI. EVG, COBI, FTC and TAF have been assessed individually in comprehensive nonclinical programs. Information from all nonclinical studies with EVG, COBI, FTC and TAF are, therefore, considered in the context of the substantial clinical experience with E/C/F/TAF for the treatment of HIV 1 infection. No new adverse drug reactions have been identified from the post marketing cases of ≥ 6 year olds prescribed E/C/F/TAF for treatment of HIV-1 infection. The E/C/F/TAF FDC is considered to have low potential for toxicity in the pediatric patient population ≥ 2 years of age and the existing nonclinical and clinical data supports the proposed use.

2.5.4. Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) was performed separately for each active substance, elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF) fumarate, based on the CHMP guideline on the Environmental Risk Assessment of Medicinal Products for Human Use EU guideline

(EMEA/CHMP/SWP/4447/00 corr 2, EMA 2006) and according to EMA/CHMP/SWP/44609/2010 Rev. 1 (EMA-Questions and answers on "Guideline on the environmental risk assessment of medicinal products for human use" -CHMP 2016).

ERA report's structure and requirements fulfilled the relevant EU guidelines. The studies were conducted according to appropriate OECD test guidelines and under GLP conditions. Protocols of the ecotoxicological studies were sufficiently detailed to confirm compliance and references made to OECD tests were appropriate.

A comprehensible, concise, and detailed ERA report for the 4 active substances was provided, comprising Phase I, Phase II Tier A, and Phase II Tier B. GLP compliant fate and effects studies were reported. All the relevant information required was given and based on the scientific discussion of the results obtained, the potential environmental impact related to their use was assessed.

The main results for Phase I and II assessment and the analysis of the results are reported in the following tables (Tables 3-6).

Tables for the assessment report providing relevant endpoints of the environmental risk assessment of human pharmaceuticals.

Table 1 ***- Summary of main study results for Elvitegravir (EVG)***

Substance (INN/Invented Name): Elvitegravir (EVG)			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	4.33, 4.26 and 3.39 at pH, 5, 7 and 9 respectively	Potential PBT N < 4.5 the Phase I trigger value
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	4.33, 4.26 and 3.39 at pH, 5, 7 and 9 respectively	B > the phase II trigger of 3 EVG has potential to bioaccumulate in biota. A fish bioconcentration study is required in Phase IIB
Persistence	DT50 or ready	Not readily biodegradable	P

	biodegradability		
Toxicity	NOEC or CMR		not T
PBT-statement:	**The compound is not considered as PBT**		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	FA	Worst case-PECsw 0.75 μg/L Refined based on the highest prevalence of disease -PECsw 0.24 μg/L	> 0.01 threshold (Y) Therefore, a Phase II environmental fate and effects analysis is required.
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption With 3 soils and 2 sludges	OECD 106	K_{oc} soil 25,500 – 104,000 L·kg^{-1} K_d sludge 10,400 L·kg^{-1}	The substance strongly binds to sewage sludge. The mean sewage sludge K_F > the trigger value of 3700 for an assessment of fate and effects in the terrestrial environment in Phase II tier B.
Ready Biodegradability Test	OECD 301	0-25% - 28 days	Not readily biodegradable. Evaluate P criterion: An OECD 308 study should be performed.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	> 10% AR associated with sediment from Day 7; System DT_{50} (dissipation) 6 - 53 days; Water DT_{50} (dissipation) 2 - 3 days; Sediment DT_{50} (degradation) >100 days; No significant metabolites formed.	EVG distributes to the sediment with more than 10% of the applied dose associated with the sediment at or after D14. A sediment dweller assessment (Chironomus sediment water toxicity) test must be performed in Phase IIB. No significant degradation products were detected in the sediment/water.

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	162	□g/L	*Pseudokirchneriella subcapitata*. NOEC was 162 □g/L for both growth rate and yield.
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥ 389	□g/L	No statistically significant effect on *Daphnia magna* reproduction at any of the measured concentrations, over a 21day period under test conditions.
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC (growth ; weight)	206	□g/L	*Pimephales promelas* A statistically significant reduction in dry weight among larvae exposed to the 468 □g/L level. No significant effects to fish early life stages.
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥ 500	□g/L	EVG is not considered inhibitory to activated sludge microorganisms.
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	5 □g/Kg: 6.83, 1.83 and 12.33 50 □g/Kg: 6.33, 1.82 and 11.7, for whole fish, edible;inedible tissue, respectively.	L/Kg	BCF values and depuration half-lives suggests that EVG does not significantly bioconcentrate to levels that would pose a risk to aquatic organisms, nor pose a risk to secondary poisoning in predators. Not bioaccumulate.
Aerobic and anaerobic transformation in soil	OECD 307	DT50	DT50 > 1000	Days	EVG is highly persistent in soil. One significant transformation product

Soil Microorganisms: Nitrogen Transformation Test	OECD 216	%effect	1000	mg/kg dry soil	Over 28 day of exposure period EVG had no significant impact on the nitrate/nitrogen production at any conc tested.
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	≥ 5	mg/kg	Low toxicity to 6 species of terrestrial plants
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	LC_{50} = >1000 $mg \cdot kg_{dwt}^{-1}$	mg/kg	*Eisenia fetida* No significant mortality was observed in any treatment group at 1000 mg/Kg_{dwt} Low toxicity to earthworms
Collembola, Reproduction Test	OECD232	NOEC	≥1000	mg/Kg_{d} wt	*Folsomia candida* No significant mortality or reduction of reproduction was observed in any treatment.
Sediment dwelling organism	OECD 225	NOEC	*Lumbriculus* (OECD 225) NOEC ≥1000 $mg.kg_{dwt}^{-1}$ (normalised for 10% OC 4167 $mg.kg_{dwt}^{-1}$)	mg/Kg_{d} wt	No significant degradation occurred. The calculated RQ was < 1. EVG poses an acceptable risk to sediment dwelling organisms.

Table 2 - ***Summary of main study results for Cobicistat (COBI)***

Substance (INN/Invented Name): Cobicistat (COBI)			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.05, 4.00 and 4.10 at pH, 5, 7 and 9 respectively	Potential PBT N < 4.5 the Phase I trigger value
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**

Bioaccumulation	log K_{ow}	3.05, 4.00 and 4.10 at pH, 5, 7 and 9 respectively	B > the phase II trigger of 3 COBI has potential to bioaccumulate in biota. A fish bioconcentration is required in Phase IIB
Persistence	DT50 or ready biodegradability	Not readily biodegradable	P
Toxicity	NOEC or CMR		not T
PBT-statement:	**The compound is not considered as PBT**		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	FA	Worst case PECsw 0.75 μg/L Refined based on the highest prevalence of disease PECsw 0.24 μg/L	> 0.01 threshold (Y) Therefore, a Phase II environmental fate and effects analysis is required.
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption With 3 soils and 2 sludges	OECD 106	K_{oc} soil 3,624 – 9,012 L.kg^{-1} K_d sludge 830 – 1,287 L.kg^{-1}	The mean sewage sludge K_F <3700, the trigger value for an assessment of fate and effects in the terrestrial soil environment in Phase II tier B.
Ready Biodegradability Test	OECD 301	< 56% - 28 days	Not readily biodegradable. Evaluate P criterion: An OECD 308 study should be performed.

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	> 10% AR associated with sediment from Day 7; System DT_{50} (dis.) 171-241 days; Water DT_{50} (dis.) 5.6-12 days; Sediment DT_{50} (deg.) >100 days; No significant metabolites formed.			COBI distributes to the sediment with more than 10% of the applied dose associated with the sediment at or after 14 days. A sediment dweller assessment test must be performed in Phase IIB. No significant degradation products were detected either in sediment or water.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	29.3	mg/L	*Pseudokirchneriella subcapitata*. NOEC was concluded to be 29.28 mg/L for growth rate and yield.
Daphnia sp. Reproduction Test	OECD 211	NOEC	17.48	mg/L	No statistically significant effect on *D magna* survival and reproduction at a geometric mean measured concentration of 17.48 mg/L, over a 21day period under test conditions.
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC (growth; weight)	4.84	mg/L	*Pimephales promelas* A statistically significant reduction for both larval length and dry weight among larvae exposed to any treatment level.
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥ 1000	mg/L	COBI is not considered inhibitory to activated sludge microorganisms.
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	5 □g/Kg: 6.83, 1.83 and 12.33	L/Kg	BCF values and depuration half-lives suggests that EVG does not significantly

			50 □g/Kg: 6.33, 1.82 and 11.7 for whole fish, edible and inedible tissue		bioconcentrate to levels that would pose a risk to aquatic organisms, nor pose a risk to secondary poisoning in predators. Not bioaccumulate.
Aerobic and anaerobic transformation in soil	OECD 307	DT50	Not required		
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	%effect	Not required		
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	Not required		
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	Not required		
Collembola, Reproduction Test	OECD232	NOEC	Not required		
Sediment dwelling organism	OECD 218	NOEC	1000	$mg/Kg_{d\ wt}$	*Chironomus riparius* Results are within the minimum criteria established, i.e., ≥70% emergence and emergence between days 12 and 23. Calculated RQ for sediment dweller was < 1. COBI poses an acceptable risk to sediment dwelling organisms.

Table 3 ***- Summary of main study results for Emtricitabine***

Substance (INN/Invented Name): Emtricitabine (FTC)			
CAS-number (if available):			
PBT screening		Result	**Conclusion**

Bioaccumulation potential- log K_{ow}	OECD107	-0.70 pH 4,7,and 10	Potential PBT (N) < 4.5 the Phase I trigger value
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-0.70	Not B: < the phase II trigger of 3. FTC is not lipophilic and is unlikely to bioaccumulate. No further assessment of bioconcentration and second poisoning is required in Phase IIB.
Persistence	DT50 or ready biodegradability	Not readily biodegradability	P
Toxicity	NOEC or CMR		not T
PBT-statement:	**The compound is not considered as PBT substance**		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)		Worst case: PECsw □□□□μg/L Refined based on the highest prevalence of disease PECsw 0.32 μg/L	> 0.01 threshold (Y) Therefore, a Phase II environmental fate and effects analysis is required.
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**

Adsorption-Desorption	OECD 106	K_d^{ads} sludge 12.9 L·kg^{-1} (AD-162-2001) K_{Foc}^{ads} soil 18.6 – 27.6 L·kg^{-1} K_{Foc}^{des} soil 114 - 319 L·kg^{-1} K_F^{ads} sludge 1.09 L·kg^{-1} K_F^{des} sludge 55.7 L·kg^{-1}			Low adsorption, K_d and K_{oc} values are below the guideline trigger values The sludge K_F value was low, 1.09 L/kg, indicating that minimal sorption of FTC will occur in STPs. FTC is likely to be discharged to surface waters. No further soil assessment is required.
Ready Biodegradability Test	OECD 301	3.7% 14 days -5.0% 28 days			Not readily biodegradability. Evaluate P criterion An OECD 308 study should be performed.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Significant shift to sediment observed (> 10% AR in sediment at or after Day 14); System DT_{50} (deg.) 35.9 -151 days; Sediment DT_{50} (deg.) > 100 days; No significant metabolites formed.			Results demonstrate significant shifting of FTC to the sediment, effects on sediment organisms should be investigated. A sediment dweller study must be performed. FTC is considered to be very persistent in the environment.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC EC50	≥110 >110	mg/L	*Pseudokirchneriella subcapitata*. Statistical analysis using Williams's test revealed no significant reduction in growth rate or yield in any treatment group compared to the control

					72hour- NOEC for growth rate and yield was ≥110 mg/L
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥110	mg/L	No statistically significant difference was identified between the parental survival or mean body length, of any treatment group compared to the control. The 21day FTC NOEC for each endpoint observed during this study was ≥110 mg/L
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	6.10	mg/L	*Pimephales promelas* Statistical analysis (Williams's test) demonstrated no statistically significant reductions in larval length among larvae exposed to any treatment level tested as compared to the control
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	56	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	Not required	L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	Not required		
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	%effect	Not required		

Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	Not required		
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	Not required	mg/kg	
Collembola, Reproduction Test	OECD232	NOEC EC50	Not required		
Sediment dwelling organism	OECD 218	NOEC EC50	38 >38	mg/Kg_{dwt}	*Chironomus riparius* No biological effect on emergence and development rate was observed at the highest concentration of 38 mg/Kg tested. Since there was ≤ 50% inhibition of emergence or development rate, the 28-day EC50 was estimated to be > 38 mg/ Kg_{dwt}

Table 4 - Summary of main study results for TAF as environmentally relevant TFV

Substance (INN/Invented Name):TAF as environmentally relevant TFV			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-3.8 and -4.3 pH 2 and 7	Potential PBT (N) < 4.5 the Phase I trigger value
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**

Bioaccumulation	log K_{ow}	-3.8 and -4.3 pH 2 and 7	Not B. Log Kow was below the Phase II A trigger of 3. TFV is not lipophilic and is unlikely to bioaccumulate. No further assessment of bioconcentration and second poisoning is required in Phase IIB
Persistence	DT50 or ready biodegradability	Not ready biodegradability	P
Toxicity	NOEC or CMR		not T
PBT-statement:	**TFV is not considered a PBT substance**		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)		Worst case PECsw 0.14μg/L Refined based on the highest prevalence of disease PECsw 0.045 μg/L	> 0.01 threshold (Y) Therefore, a Phase II environmental fate and effects analysis is required.
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{Foc}^{ads} soil 351 - 1091 $L \cdot kg^{-1}$ K_{Foc}^{des} soil 968 - 2791 $L \cdot kg^{-1}$ K_F^{ads} sludge 6.0 - 21 $L \cdot kg^{-1}$ K_F^{des} sludge 16 - 62 $L \cdot kg^{-1}$	TFV as environmental relevant residue of TAF, exhibit low adsorption with K_d and $>K_{oc}$ values below the guideline trigger values (K_d sludge > 3700).Will mostly be discharged to receiving waters. No further terrestrial soil environment risk assessment is required.

Ready Biodegradability Test	OECD 301	Not ready biodegradability 5-12% degradation observed over 28 days			Minimal biodegradation based on the results
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Significant shift to sediment observed (> 10% AR in sediment at or after Day 14); System DT_{50} (deg.) 10.4-32.7 days; Water DT_{50} (dis.) 2.0-3.5 days; Three significant metabolites formed.			Greater than 10% of the applied dose was associated with sediment at or after D14, triggering a sediment dweller assessment in Phase II B. The whole system half-life was approximately 10-33 days Three significant transformation products formed, identified as 9-(2-methoxypropyl)-9H-purin-6-amine (M1), ({[1-(9H-purin-9-yl)propan-2- yl]oxy}methyl)phosphonic acid (M3) and 9-(2-methoxypropyl)-9H-purin-6-ol or 9- (2-methoxypropyl)-9H-purin-6-ol (M6).
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC EC50	32 32	mg/L	*Pseudokirchneriella subcapitata* Inhibition of growth rate (preferred endpoint according EMA, 2016) over 0-72 h test period was just 3% for the highest test concentration of 100 mg·L-1. However, examination for statistically significant differences did indicate an effect at 56 mg·L-1, this

					is the only statistical effect noted
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥100	mg/L	TFV residues had no effect on any parameter at the highest exposure concentration of 100 mg/L
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	≥10	mg/L	*Pimephales promelas* TFV residues had no effect on any parameter at the limit conc of 10 mg/L. It is noteworthy that 10 mg/L is the highest recommended test concentration for this species following OECD guidelines. Therefore, it can be concluded that TFV is non-toxic to fish.
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	mg/L	TFV is not considered inhibitory to activated sludge microorganisms at the concentration of 1000 mg/L
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	Not required	L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	Not required		for all 4 soils
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	%effect	Not required	mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	Not required	mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	Not required	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC	Not required	mg/kg	

Sediment dwelling organism	OECD 218	NOEC	NOEC = 290 $mg \cdot kg_{dwt}^{-1}$ (normalised for 10% OC 1,261 $mg \cdot kg_{dwt}^{-1}$)	mg/Kg $_{dwt-1}$	*Chironomus.sp N*o effects were noted in a mean measured sediment concentration 290 $mg \cdot kg_{dwt-1}$. *Since there was ≤ 50% inhibition of emergence or development rate, the 28-day EC50 was estimated to be > 290 mg/Kg* $_{dwt-1}$.PNEC from a sediment dweller test was compared with a PECsediment value derived using partitioning equilibrium algorithms, the resultant RQ was significantly below 1, indicating low risk

2.5.5. Discussion on non-clinical aspects

The MAH did not conduct the usual nonclinical studies to specifically support the use of Genvoya in children ≥ 2 years of age weighing ≥ 14 to < 25 kg and consequently, no module 2.6 data were provided with this application. According to the MAH, the summary of the pharmacology, pharmacokinetics, and toxicology studies of EVG, COBI, FTC and TAF provided in module 2.4 Nonclinical Overview included in the submission to support the extension of the indication for E/C/F/TAF in children 6 to <12 years old and weighing at least 25 kg with HIV-1 infection is relevant to the current assessment of E/C/F/TAF in children ≥ 2 years of age, and this is endorsed. The MAH made an updated Integrated Assessment, to support the use of E/C/F/TAF in children ≥ 2 years of age weighing ≥ 14 to < 25 kg considering the available data. This is acceptable given the existing and previously assessed data.

Environmental Risk Assessment

The n-octanol/water partition coefficient experimental values for EVG, COBI, FTC and TAF were determined experimentally in accordance with OECD guideline 107 Partition Coefficient (n-octanol/water): Shake Flask Method. For each active ingredient the result was < 4.5, the guideline Phase I action limit for PBT(Persistence, Bioaccumulation, Toxicity) assessment. Therefore, no further assessment of PBT was required. All 4 active substances were not considered to have met the persistent, bioaccumulation and toxic (PBT) criteria.

The predicted environmental concentrations PECsurfacewater, both the worst-case and refined values for prevalence of HIV, for the 4 active substances were higher than the trigger value of 0.01 µg/L and therefore a full Phase II assessment is required.

Phase II: The most relevant methods were used, and the results obtained were discussed. Scientific evidence is summarised for each active substance in tables 1 to 4.

All the 4 active substances are classified as not readily biodegradable according to OECD 301 and are considered potentially persistent. Therefore, an OECD 308 test was performed to evaluate P criterion, and FTC was considered to be persistent in the environment.

The log Pow of FTC and TFV at both pH 7 and 9 were below the Phase II A trigger of 3, as such, no further assessment of bioconcentration and secondary poisoning was required in Phase II B. Nevertheless, both EVG, COBI have a Kow value that triggered an assessment of the potential for bioconcentration. Neither EVG nor COBI bioconcentrate in fish tissues.

EVG strongly adsorbed to sewage solids (Kd > 3,700) requiring an assessment in the terrestrial environment in Phase II tier B. However, RQ value for the most sensitive endpoint is less than 1, indicating that EVG poses an acceptable risk to the terrestrial environment.

All four active substances partition to sediment to an extent that triggered assessment of the risk to sediment dwellers. The calculated RQs for sediment dweller was < 1 demonstrate that EVG, COBI, FTC and TFV poses an acceptable risk to sediment dwelling organisms.

EVG, COBI, FTC and TFV risk quotient (RQ) values less than 1 were obtained for sewage microbes, fish, aquatic invertebrates and algae. Similarly, an RQ below the trigger value of 1 was obtained for groundwater. The data indicate that the environmentally relevant residues of EVG, COBI, FTC and TFV are of low risk for all compartments. Therefore, no risk for the environment is to be expected.

From the results of ERA studies, no significant environmental safety issues were identified.

Since no environmental concerns are apparent, it is assumed that EVG, COBI, FTC and TAF (as TFV) are unlikely to represent a risk for the environment following its prescribed usage in patients, including the children and adolescents (aged ≥ 2 years weighing at least 14 Kg>), the purpose of the current line extension.

Based on the data obtained for the Phase II-A and B assessments, the proposed use of Genvoya as a treatment for HIV poses an acceptable risk to the environment.

The approval of the current line extension will not lead to any unacceptable risks to aquatic or terrestrial environments.

As a general rule for all pharmaceutical products, in order to reduce environmental exposure, it is recommended not to dispose them via wastewater or the municipal drainage system and to return them to the pharmacy for appropriate disposal. The precautionary and safety measures taken to reduce any risk to the environment by including the general statement on the SmPC and PL have been applied, which is agreed on and appreciated.

2.5.6. Conclusion on the non-clinical aspects

The overall existing non-clinical programme to date, including data from the combination and individual drug studies, supports the efficacy and safety of E/C/F/TAF 90/90/120/6 mg tablet in the sought indication.

Based on the available data, the use of Genvoya, a fixed dose combination product, containing elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF), 90/90/120/6 mg tablet, in the sought indication, poses an acceptable risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Number	Study Design	Treatment Regimen	Subject Population
GS-US-292-0106	Phase 2/3, open-label, multicohort, multicenter, 2-part, single-group study to evaluate the PK, safety, tolerability, and antiviral activity of GEN	Cohort 3 Single GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) taken orally once daily with food	Cohort 3 HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg

2.6.2. Clinical pharmacology

2.6.2.1. ***Pharmacokinetics***

A primary objective in relation to subjects enrolled in Cohort 3 in Study GS-US-292-0106 was to evaluate the PK of EVG and TAF and confirm the dose of a GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) in virologically suppressed HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg. The safety, tolerability, and antiviral activity of GEN LD tablets were also evaluated in Cohort 3. Dose selection for the GEN LD tablet targeted systemic exposures similar to those observed in adults, and took into consideration WT/body surface area and potential ontogenic changes in transporters and metabolic enzymes that govern the disposition of EVG, COBI, FTC, TAF, and TFV (TAF major metabolite).

Intensive PK data were available for 27 HIV-1 infected children who received the GEN LD tablet (E/C/F/TAF 90/90/120/6 mg). No clinically relevant differences in exposures of EVG, COBI, FTC, TAF, and TFV were observed between pediatric subjects who received the GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) and adults who received the adult-strength GEN tablet (E/C/F/TAF 150/150/200/10 mg).

Population PK models were developed to characterize the exposures of EVG, COBI, TAF, and TFV in HIV-1 infected adolescents and children, including the use of all available intensive and sparse plasma concentration data. Population PK parameters for EVG, COBI, TAF, and TFV were predicted and are presented in the following sections. For FTC, PK parameters estimated from the intensive PK samples from Cohort 3 subjects were used.

To confirm the appropriateness of the E/C/F/TAF dose in virologically suppressed, HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg:

1) PopPK parameters AUCtau, Cmax, and Ctau for EVG, and AUCtau and Cmax for TAF (Ctau was not included due to the short t1/2 of TAF) were compared to historical PopPK data in HIV-1 infected adults treated with E/C/F/TAF using a PK equivalence boundary of 70% to 143% for AUCtau;

2) Pop PK parameters AUCtau, Cmax, and Ctau for COBI and TFV were compared to historical PopPK data in HIV-1 infected adults treated with E/C/F/TAF;

3) PK parameters AUCtau, Cmax, and Ctau for FTC estimated from intensive PK samples from Cohort 3 were compared to historical PopPK data in HIV-1 infected adults treated with E/C/F/TAF.

Pharmacokinetics of TAF in HIV-1 Infected Paediatric Subjects

Predicted systemic exposures of TAF in children weighing ≥ 14 to < 25 kg (Cohort 3, Study GS-US-292-0106) receiving the GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) were compared with those from HIV-1 infected adult subjects receiving the GEN adult-strength tablet (E/C/F/TAF 150/150/200/10 mg) in Phase 2 Studies GS-US-292-0104 and GS-US-292-0111 (N = 539).

TAF AUCtau in children weighing ≥ 14 to < 25 kg receiving the GEN LD tablet was similar to that in adults (Table 7). The 90% CIs of the associated geometric least squares mean (GLSM) ratio for AUCtau were within the predefined PK equivalence boundary of 70% to 143%. The modestly lower (29%) TAF Cmax in children weighing ≥ 14 to < 25 kg was not deemed clinically relevant based on the favourable efficacy profile of the GEN LD tablet, and was within the safe and efficacious range of historical data in adult and paediatric subjects in the EVG/COBI/FTC/TDF and E/C/F/TAF development programs.

Table 5 - GS-US-292-0106: Statistical comparisons of TAF exposures between paediatric subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg and adults (PopPK analysis set)

TAF PK Parameter	GS-US-292-0106 (Test)		GS-US-292-0104, GS-US-292-0111 (Reference)[a]		%GLSM Ratio (90% CI) Test/Reference
	n	GLSM	n	GLSM	
AUC_{tau} (h•ng/mL)	27	206.18	539	178.30	115.64 (110.11, 121.45)
C_{max} (ng/mL)	27	103.14	539	144.88	71.19 (55.55, 91.23)

GLSM = geometric least-squares mean
a Population PK parameters for the reference group were from GEN-treated adults in Studies GS-US-292-0104 and GS-US-292-0111

Pharmacokinetics of TFV in HIV-1 Infected Paediatric Subjects

Predicted systemic exposures of TFV in children weighing ≥ 14 to < 25 kg (Cohort 3, Study GS-US-292-0106) receiving the GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) were compared with those from HIV-1 infected adult subjects receiving the adult-strength tablet (E/C/F/TAF 150/150/200/10 mg) in the Phase 3 studies GS-US-292-0104 and GS-US-292-0111 (N = 841).

TFV AUCtau, Cmax, and Ctau in children weighing ≥ 14 to < 25 kg receiving the GEN LD tablet were similar to those in adults receiving the adult-strength tablet (Table 8).

Table 6 - GS-US-292-0106: Statistical comparisons of TFV exposures between paediatric subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg and adults (PopPK analysis set)

TFV PK Parameter	GS-US-292-0106 (Test)		GS-US-292-0104, GS-US-292-0111 (Reference)[a]		%GLSM Ratio (90% CI) Test/Reference
	n	GLSM	n	GLSM	
AUC_{tau} (h•ng/mL)	27	333.80	841	283.86	117.59 (110.15, 125.54)
C_{max} (ng/mL)	27	18.61	841	14.79	125.88 (114.72, 138.13)
C_{tau} (ng/mL)	27	11.27	841	10.30	109.40 (102.43, 116.83)

GLSM = geometric least-squares mean
a Population PK parameters for the reference group were from GEN-treated adults in Studies GS-US-292-0104 and GS-US-292-0111

Pharmacokinetics of EVG in HIV-1 Infected Paediatric Subjects

Predicted systemic exposures of EVG in children weighing ≥ 14 to < 25 kg (Cohort 3, Study GS-US-292-0106) receiving the GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) were compared with those from HIV-1 infected adult subjects receiving the adult-strength tablet (E/C/F/TAF 150/150/200/10 mg) in the Phase 2 Study GS-US-292-0102 (N = 19).

The geometric mean of EVG AUCtau in children weighing ≥ 14 to < 25 kg was 26% higher than in adult subjects. The upper limit of the 90% CIs of the GLSM ratios for AUCtau exceeded the 143% equivalence boundary (Table 9). EVG Cmax and Ctau in children weighing ≥ 14 to < 25 kg receiving the LD E/C/F/TAF were similar to those in adults.

The modestly higher EVG AUCtau in children weighing ≥ 14 to < 25 kg is not deemed clinically relevant based on the favourable safety profile of the GEN LD tablet, and is within the safe and efficacious range of historical data in adult and paediatric subjects in the EVG/COBI/FTC/TDF and E/C/F/TAF development programs.

Table 7 - GS-US-292-0106: Statistical comparisons of EVG exposures between paediatric subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg and adults (PopPK analysis set)

EVG PK Parameter	GS-US-292-0106 (Test)		GS-US-292-0102 (Reference)[a]		%GLSM Ratio (90% CI) Test/Reference
	n	GLSM	n	GLSM	
AUC_{tau} (h•ng/mL)	27	27168.82	19	21553.74	126.05 (104.85, 151.54)
C_{max} (ng/mL)	27	2172.40	19	1997.55	108.75 (90.79, 130.27)
C_{tau} (ng/mL)	27	266.85	19	247.71	107.73 (78.77, 147.33)

GLSM = geometric least-squares mean
a PK parameters for the reference group were intensive PK parameters from GEN-treated adults who participated in the GS-US-292-0102 PK substudy.

Pharmacokinetics of COBI in HIV-1 Infected Paediatric Subjects

Predicted systemic exposures of COBI in children weighing ≥ 14 to < 25 kg (Cohort 3, Study GS-US-292-0106) receiving the GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) were compared with those from HIV-1 infected adult

subjects receiving the adult-strength tablet (E/C/F/TAF 150/150/200/10 mg) in the Phase 2 Study GS-US-292-0102 (N = 19).

COBI Cmax and Ctau in children weighing ≥ 14 to < 25 kg were similar to those in adults (Table 10). The modestly higher (23%) COBI AUCtau in children weighing ≥ 14 to < 25 kg was not deemed clinically relevant based on the favourable safety profile of the GEN LD tablet, and is within the safe and efficacious range of historical data in adult and paediatric subjects in the EVG/COBI/FTC/TDF and E/C/F/TAF development programs.

Table 8 - GS-US-292-0106: Statistical comparisons of COBI exposures between paediatric subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg and adults (PopPK analysis set)

COBI PK Parameter	GS-US-292-0106 (Test)		GS-US-292-0102 (Reference)[a]		%GLSM Ratio (90% CI) Test/Reference
	n	GLSM	n	GLSM	
AUC_{tau} (h•ng/mL)	27	11036.81	19	8975.72	122.96 (101.78, 148.56)
C_{max} (ng/mL)	27	1371.01	19	1400.19	97.92 (83.13, 115.34)
C_{tau} (ng/mL)	27	16.99	18	17.01	99.87 (71.00, 140.49)

GLSM = geometric least-squares mean
a PK parameters for the reference group were intensive PK parameters from GEN-treated adults who participated in the GS-US-292-0102 PK substudy.

Pharmacokinetics of FTC in HIV-1 Infected Paediatric Subjects

Observed systemic exposures of FTC derived from intensive PK data in children weighing ≥ 14 to < 25 kg (Cohort 3, Study GS-US-292-0106; Table 11) receiving the GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) were compared with those from HIV-1 infected adult subjects receiving the adult-strength GEN tablet (E/C/F/TAF 150/150/200/10 mg) in the Phase 2 Study GS-US-292-0102 (N = 19).

The geometric means of FTC Ctau were similar in children weighing ≥ 14 to < 25 kg in Cohort 3 and adult subjects in the Phase 2 Study GS-US-292-0102. The geometric means of FTC AUCtau and Cmax in children in Cohort 3 were, respectively, 61% and 39% higher than in adult subjects. These differences are not deemed clinically relevant based on the favourable safety profile of the GEN LD tablet, and FTC exposure parameters were within the safe and efficacious range of historical data in adult and paediatric subjects in the E/C/F/TAF development program.

Table 9 - GS-US-292-0106: Statistical comparisons of FTC exposures between paediatric subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg and adults (Intensive PK analysis set)

FTC PK Parameter	GS-US-292-0106 (Test)		GS-US-292-0102 (Reference)[a]		%GLSM Ratio (90% CI) Test/Reference
	n	GLSM	n	GLSM	
AUC_{tau} (h•ng/mL)	27	18620.48	19	11576.55	160.85 (143.01, 180.90)
C_{max} (ng/mL)	27	2808.24	19	2014.35	139.41 (120.28, 161.59)
C_{tau} (ng/mL)	27	77.40	19	89.11	86.86 (72.30, 104.34)

GLSM = geometric least squares mean
a Intensive PK parameters for the reference group were derived from GEN-treated, HIV-1 infected adult subjects with body weights ranging from 58 to 117.5 kg in the Study GS-US-292-0102 PK substudy who received the E/C/F/TAF 150/150/200/10 mg adult tablet.

Impaired renal function

EVG, COBI, and TAF

Baseline CL_{CRSW} (i.e. the estimated glomerular filtration rate) was not identified as a statistically significant covariate for EVG, COBI, or TAF PK in their respective final PopPK models. The impact of baseline CL_{CRSW} on EVG, COBI, and TAF exposures for Cohort 3 subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg in Study GS-US-292-0106 were presented. In paediatric subjects, EVG, COBI, and TAF exposures were generally similar across the range of baseline CL_{CRSW} values.

TFV

Baseline CL_{CRSW} was identified as a statistically significant covariate for TFV PK in the final PopPK model. This was as expected since TFV is renally eliminated. The impact of baseline CL_{CRSW} on TFV exposure in Cohort 3 subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg receiving the GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) in Study GS-US-292-0106 is presented in Table 12. Among these paediatric subjects, TFV exposures were generally similar across the range of baseline CL_{CRSW} values.

Table 10 - GS-US-292-0106: Impact of baseline CL_{CRSW} on mean (%CV) steady-state TFV exposure in paediatric subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg (PopPK analysis set)

Characteristic	Baseline CL_{CRSW} Quartile				Median Q1 – Q4 %Difference[a]
	Q1	Q2	Q3	Q4	
Baseline CL_{CRSW} (mL/min/1.73 m^2) (min, median, max)	115, 134, 139	139, 143, 147	148, 155, 159	160, 165, 179	—
Number of subjects	7	7	7	6	—
AUC_{tau} (h•ng/mL)	362.4 (17.8)	315.3 (15.5)	360.6 (27.6)	321.2 (20.5)	20.7
C_{max} (ng/mL)	21.7 (28.1)	16.6 (18.4)	21.9 (36.8)	17.2 (24.0)	27.3
C_{tau} (ng/mL)	12.1 (16.9)	11.0 (18.5)	11.8 (26.9)	11.1 (24.3)	24.9

%CV = percentage coefficient of variation; Baseline CL_{CRSW} = creatinine clearance derived by the Schwartz formula; Q = quartile

a Median Q1 – Q4 %Difference = (Median Q1 – Median Q4)/Median Q4 × 100%.

Impaired hepatic function

No new information was submitted.

Gender

Sex was not identified as a statistically significant covariate for EVG, COBI, TAF, or TFV in their respective final PopPK model. In paediatric subjects, EVG, COBI, TAF, and TFV exposures were generally similar between males and females.

Race

EVG, COBI, and FTC

Race was not identified as a statistically significant covariate for EVG, COBI, or TFV in the respective final PopPK model. In paediatric subjects, EVG, COBI, and TFV exposures were generally similar between race groups. However, the comparisons may not be robust due to the limited sample sizes within each race category.

TAF

Race was identified as a statistically significant covariate for TAF PK in its final PopPK model once body size was accounted for, with a lower apparent VC/F estimated in Asian subjects, but this did not result in significant changes in PK exposure parameters. The impact of race on TAF exposures in Cohort 3 subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg receiving GEN LD tablets (E/C/F/TAF 90/90/120/6 mg) in Study GS-US-292-0106 are presented in Table 13. It should be noted that the comparisons may not be robust due to the limited sample sizes within each race category.

Table 11 - GS-US-292-0106: Impact of race on steady-state TAF exposure in paediatric subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg (PopPK analysis set)

PK Parameter	%GLSM Ratio (90% CI) N = 24 for Black Subjects
	Asian Subjects Compared with Black Subjects
Number of subjects	3
AUC_{tau} (h•ng/mL)	100.96 (96.42, 105.72)
C_{max} (ng/mL)	45.29 (16.30, 125.89)

CI = confidence interval; GLSM = geometric least-squares means

Weight

EVG

The relationship between baseline WT and EVG exposure for Cohort 3 subjects in Study GS-US-292-106 (HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg receiving the GEN LD tablet [E/C/F/TAF 90/90/120/6 mg]) is presented in Table 14.

Table 12 - GS-US-292-0106: Impact of weight on mean (%CV) steady-state EVG exposure in paediatric subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg (PopPK analysis set)

Characteristic	WT Quartile				Median Q1 – Q4 %Difference[a]
	Q1	Q2	Q3	Q4	
WT (kg) (min, median, max)	14.6, 15.6, 17.0	17.4, 18.7, 19.3	19.4, 20.1, 20.5	21.8, 22.7, 23.5	—
Number of subjects	7	8	6	6	—
AUC_{tau} (h•ng/mL)	41354.0 (33.9)	26324.0 (32.6)	21947.7 (34.3)	26340.3 (24.2)	74.5
C_{max} (ng/mL)	3168.7 (26.9)	2189.6 (35.6)	1929.5 (30.2)	1870.3 (18.2)	68.4
C_{tau} (ng/mL)	527.2 (39.9)	203.9 (37.7)	175.9 (46.0)	489.2 (96.3)	54.0

%CV = percentage coefficient of variation; Q = quartile; WT = baseline body weight

a Median Q1 – Q4 %Difference = (Median Q1 – Median Q4)/Median Q4 × 100%.

COBI

The relationship between baseline WT and COBI exposure for Cohort 3 subjects in Study GS-US-292-106 (HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg receiving the GEN LD tablet [E/C/F/TAF 90/90/120/6 mg]) is presented in Table 15.

Table 13 - GS-US-292-0106: Impact of weight on mean (%CV) steady-state COBI exposure in paediatric subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg (PopPK analysis set)

Characteristic	WT Quartile				Median Q1 – Q4 %Difference[a]
	Q1	Q2	Q3	Q4	
WT (kg) (min, median, max)	14.6, 15.6, 17.0	17.4, 18.7, 19.3	19.4, 20.1, 20.5	21.8, 22.7, 23.5	—
Number of subjects	7	8	6	6	—
AUC_{tau} (h•ng/mL)	17741.1 (30.9)	9209.4 (29.0)	9977.2 (34.7)	11366.3 (44.8)	69.7
C_{max} (ng/mL)	2073.7 (20.3)	1172.0 (35.5)	1317.0 (23.0)	1308.5 (33.2)	66.3
C_{tau} (ng/mL)	32.2 (58.1)	14.6 (36.0)	13.2 (61.1)	23.8 (84.6)	59.8

%CV = percentage coefficient of variation; Q = quartile; WT = baseline body weight
a Median Q1 − Q4 %Difference = (Median Q1 − Median Q4)/Median Q4 × 100%.

TAF

The relationship between baseline WT and TAF exposure for Cohort 3 subjects in Study GS-US-292-106 (HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg receiving the GEN LD tablet [E/C/F/TAF 90/90/120/6 mg]) is presented in Table 16.

Table 14 - GS-US-292-0106: Impact of weight on mean (%CV) steady-state TAF exposure in paediatric subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg (PopPK analysis set)

Characteristic	WT Quartile				Median Q1 – Q4 %Difference[a]
	Q1	Q2	Q3	Q4	
WT (kg) (min, median, max)	14.6, 15.6, 17.0	17.4, 18.7, 19.3	19.4, 20.1, 20.5	21.8, 22.7, 23.5	—
Number of subjects	7	8	6	6	—
AUC_{tau} (h•ng/mL)	236.4 (3.7)	209.4 (3.0)	197.2 (1.6)	180.3 (2.1)	32.2
C_{max} (ng/mL)	172.3 (47.4)	117.0 (43.4)	118.8 (63.7)	98.5 (53.7)	145.4

%CV = percentage coefficient of variation; Q = quartile; WT = baseline body weight
a Median Q1 − Q4 %Difference = (Median Q1 − Median Q4)/Median Q4 × 100%.

TFV

The relationship between baseline body weight and TFV exposure for Cohort 3 subjects in Study GS-US-292-106 (HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg receiving the GEN LD tablet [E/C/F/TAF 90/90/120/6 mg]) is presented in Table 17.

Table 15 - GS-US-292-0106: Impact of weight on mean (%CV) steady-state TFV exposure in paediatric subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg (PopPK analysis set)

Characteristic	WT Quartile				Median Q1 – Q4 %Difference[a]
	Q1	Q2	Q3	Q4	
WT (kg) (min, median, max)	14.6, 15.6, 17.0	17.4, 18.7, 19.3	19.4, 20.1, 20.5	21.8, 22.7, 23.5	—
Number of subjects	7	8	6	6	—
AUC_{tau} (h•ng/mL)	425.3 (15.0)	323.4 (12.9)	318.7 (13.7)	286.5 (18.6)	55.1
C_{max} (ng/mL)	25.3 (29.1)	18.6 (17.4)	18.0 (17.6)	15.0 (28.9)	107.7
C_{tau} (ng/mL)	14.4 (14.0)	10.6 (12.3)	10.8 (18.6)	10.0 (16.8)	45.5

%CV = percentage coefficient of variation; Q = quartile; WT = baseline body weight
a Median Q1 – Q4 %Difference = (Median Q1 – Median Q4)/Median Q4 × 100%.

2.6.2.2. ***Pharmacodynamics***

No exposure-response (safety) analysis was provided by the applicant.

2.6.3. Discussion on clinical pharmacology

Study GS-US-292-0106 is an open-label, multicentre, multicohort, single-group study of the PK, safety, tolerability, and antiviral activity of GEN (E/C/F/TAF) in HIV-1 infected, ART-naive adolescents and virologically suppressed children. Subjects received 1 GEN LD tablet (90/90/120/6 mg) daily, orally with food, at approximately the same time each day. Intensive PK assessments were made at the Week 2 visit for 27 patients and a non-compartmental PK analysis was made. The primary PK endpoint was AUCtau for TAF and EVG. Geometric mean AUCtau values for TAF and EVG, respectively, were 93% and 39% higher than in E/C/F/TAF-treated, HIV-1 infected adults in historical studies. For TFV, the exposure parameter AUCtau was similar to those observed in adult subjects. For COBI, the geometric mean AUCtau was 37% higher in Cohort 3 subjects than in adult subjects. For FTC, the geometric mean of AUCtau was 61% higher than in adult subjects. Generally, the exposures are higher than the ones observed with adult patients, although inside the expected values of that population. The GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) was well tolerated and High rates of virologic suppression (HIV-1 RNA < 50 copies/mL) were maintained.

Validation methods for tenofovir alafenamide (GS-7340), tenofovir (TFV) emtricitabine (FTC), elvitegravir (GS-9137) and cobicistat (GS-9350) were provided. The analytical methods used in the clinical studies for the determination of the studied drugs were well developed and sufficiently validated (both pre- and within study) and have been already used (and assessed) in previous applications. All samples were analysed within the time frame supported by long-term storage stability data. ISR analysis was performed for all the analytes.

Pharmacokinetic parameters were estimated using Phoenix WinNonlin software by application of standard noncompartmental methods. The linear/log trapezoidal rule was used in conjunction with the appropriate non-compartmental model with input values for dose, time of dose, plasma concentration, and corresponding real-time values based on drug dosing times whenever possible. This is standard and acceptable. Population PK modelling was conducted using NONMEM and models were established to describe the plasma PK for COBI, EVG, TAF, and TFV in HIV-1 infected adolescents and children using data collected across several studies, and estimate typical values and between-subject variability of PK parameters. No PopPK study was presented for

emtricitabine. The applicant justified the reason for not presenting a PopPK analysis by the fact that the original dose selection of emtricitabine at the registration of Emtriva was made based on rich sampling and noncompartmental analysis. However, the applicant has already made a commitment with the PDCO for developing a PopPK model for FCT.

Two PopPK studies were presented.

The first considered a population pharmacokinetic analysis of Cobicistat and Cobicistat-Boosted Elvitegravir in HIV-1 Infected Adolescents and Children and included data from Studies GS-US-292-0106, GS-US-292-1515, GS-US-236-0112, and GS-US-216-0128. The base model for pediatric EVG was developed based on previously developed models and the addition of covariates was made by forward addition and backward deletion. The final pediatric EVG model was described by a 2-compartment model with sequential zero and first-order absorption and first-order elimination. Between-subject variability was included on CL/F, Vp/F, Q/F, and D1. A combined error model was used to characterize residual variability (RV). Baseline WT effects were included on clearance (ie, CL/F, Q/F) and distribution-related parameters (ie, Vc/F, Vp/F) using fixed allometric exponents of 0.75 and 1, respectively. In addition, ka was estimated separately for each FDC (E/C/F/TAF and EVG/COBI/FTC/TDF [Stribild]) to improve the fit of the absorption phase. No additional covariates were included. The final model parameters were estimated with good confidence (the percentage of RSE was < 30% for fixed-effects parameters and < 40% for random-effects parameters), presented reasonable to high shrinkage (<72% for Q/F) and were confirmed by bootstrapping. GOF plots were acceptable as well as the presented pcVPC (stratified by weight). The base model for paediatric COBI was developed also based on previously developed models and the addition of covariates was again made by forward addition and backward deletion. The final paediatric COBI model was described by a 1-compartment model with sequential zero-order and first-order absorption with a lag time and first-order elimination. Between-subject variability was included on CL/F, D1, and lag time (ALAG), with an OMEGA block to estimate the correlation between CL/F and D1. A proportional error model with between-subject variability was used to characterize RV. Effects of WT were included on CL/F and Vc/F using fixed allometric exponents of 0.75 and 1, respectively. No additional covariates were found to significantly affect COBI exposure. The final model parameters were estimated with good confidence (percentage of RSE for fixed-effect parameters were generally < 30% and < 55% for ETA [variability] terms) and were confirmed by bootstrapping. Bayesian shrinkage values were low for CL/F and proportional error (< 10%), but higher shrinkage values were observed for D1 and ALAG (42% for each). GOF plots were acceptable as well as the presented pcVPC (stratified by weight) although the 95th percentile showed a tendency toward overprediction.

The second considered a population pharmacokinetic analysis of tenofovir alafenamide and tenofovir following administration of tenofovir alafenamide-containing–fixed-dose combinations in HIV-1-infected adolescents and children. Data was collected across various TAF-based regimens (Studies GS-US-292-0106, GS-US-292-1515, GS-US-311-1269, and GS-US-380-1474) and was used to develop sequential PK model(s) of TAF and TFV in HIV-1-infected adolescents and children. Addition of covariates was again made by forward addition and backward deletion. The final paediatric TAF model, simplified from previous TAF PopPK analysis due to various reproducibility and robustness issues, was described by a 1-compartment model with sequential zero- and first-order absorption and first-order elimination. Between-subject variability was included on the duration of zero-order absorption only and resulted in a high value of 108%. A combined error model was used to characterize residual variability, with the inclusion of between-subject variability on the proportional error term. Baseline WT effects were included on CL/F and Vc/F using fixed allometric exponents of 0.75 and 1, respectively. Cobicistat was found to affect relative bioavailability of TAF (163.6% increase), whereas lopinavir/ritonavir-boosted TAF was found to yield comparable exposure to unboosted TAF. In addition, TAF Vc/F was found to be lower in Asian subjects (-78.8% reduction). No additional covariates were found to significantly affect TAF

exposure. The final model parameters were estimated with good confidence (%RSE <10%), presented low shrinkage (<25%) and were confirmed by bootstrapping. GOF plots were acceptable as well as the presented pcVPC (stratified by weight and by booster groups) although missing on the higher observed values and not entirely able to predict the values around Tmax. This was the result of several model simplifications that were made in order to achieve stability. The final paediatric sequential TAF-TFV model was described by the previous sequential 1-compartment TAF model and a 2-compartment TFV model with first-order elimination was found to best describe the TFV paediatric data. A parallel absorption compartment with first-order process was introduced in the model to describe TFV data in the presence of the LPV/RTV booster. Between-subject variability was included on apparent oral clearance of TFV (CLM/F), apparent inter-compartmental clearance of TFV (QM/F), VcM/F, and apparent peripheral volume of distribution of TFV (VpM/F); and a combined proportional and additive error model was used to characterize the Residual Variability. The estimated LPV/RTV effect on TFV relative bioavailability (F) was 209.5% increase. Effects of WT were included on CLM/F, QM/F, VcM/F, and VpM/F using fixed allometric exponents of 0.75 and 1, for clearances and volumes of distribution, respectively. In addition, baseline creatinine clearance derived by Schwartz equation was found to significantly affect CLM/F. No additional covariates were found to significantly affect TAF exposure. Most of the final model parameters were estimated with good precision (%RSE <25%) and presented low shrinkage (<20%). Parameter were also confirmed by bootstrapping. GOF plots were acceptable as well as the presented pcVPC (stratified by weight and by booster groups).

Taking into account that the experimental data to build the model are the same in modeling reports QP-2018-1027 TAF TFV HIV Pediatric Pop PK and CTRA-2020-1048 TAF-TFV Peds Pop PK, it is unclear how the TAF structural model may differ between both reports. Similarly, the discrepancies in terms of parameter estimates of TAF and TFV between the two reports are not reassuring. Based also on these concerns, a new PopPK analysis was performed by the applicant with updated models for TAF and COBI. These updated models included a better description of the absorption process (inclusion of lag time for TAF and removal of the lag time for COBI) and better description of the IIV, as well as some addition of new available data. A comparison of results from the different versions of the models was presented and the current version parameter estimates now are better related to the initial version model developed in 2018. Overall, these changes improved also considerable the model performance for both drugs when compared to the previous 2020 version.

Besides the typical summary statistics, comparison of the rich data PK in children in Cohort 3 against adults from historical studies for TAF EVG, COBI, FTC, and TFV was made by one-way analysis of variance model fitted to the natural logarithmic-transformed PK values. This is acceptable.

Pharmacokinetics in the target population

The new proposed low dosage (LD) strength was not directly compared in a bioequivalence study with the original dosage strength already approved. However, this new LD was used in the clinical Study GS-US-292-0106 in the target population. The two dosage strengths are fully dose proportional and the applicant provided the in vitro dissolution profiles at pH 1.2, 4.5, 6.8 dissolution medium and at the QC medium. These were similar in all the conditions and for all the drugs.

Regarding the pharmacokinetics in target population, a primary objective in relation to subjects enrolled in Cohort 3 in Study GS-US-292-0106 was to evaluate the PK of EVG and TAF and confirm the dose of the GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) in HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg (Cohort 3). Dose selection for the GEN LD tablet targeted systemic exposures similar to those observed in adults and took into account WT and body surface area and potential ontogenic changes in transporters and

metabolic enzymes that govern the disposition of EVG, COBI, FTC, TAF, and the TAF metabolite TFV (a prior work performed based on PBPK simulations).

Intensive PK data were available from 27 virologically suppressed HIV-1 infected Cohort 3 subjects who received the GEN LD tablet. Based on this PK parameters AUCtau, Cmax, and Ctau for EVG, COBI FTC and TFV and AUCtau and Cmax for TAF (Ctau was not included due to the short t1/2 of TAF) were compared to historical PopPK data in HIV-1 infected adults treated with E/C/F/TAF using a PK equivalence boundary of 70% to 143% for AUCtau; Although not always with the 90% CI inside the acceptance criteria (in particular TAF with a AUCtau 90%CI of 166% to 224% and FTC with a AUCtau 90% CI of 143% to 180%), most of the GLSM ratios were included in the equivalence boundaries, not only for AUCtau but also for the remaining parameters. The same was generally observed when the PK parameters were determined by PopPK analysis for TAF, TFV, EVG and COBI. It seems that, where there were differences, these exposures are falling within safe and efficacious ranges of historical data in adult subjects variously in the EVG/COBI/FTC/TDF and E/C/F/TAF development programs.

Intrinsic Factors

The impact of renal function was tested by the PopPK model considering ClCr as a covariate. Baseline CLCRSW was not identified as a statistically significant covariate for EVG, COBI, and TAF PK in their respective final PopPK models. In addition, EVG, COBI, and TAF exposures were generally similar across the range of baseline CLCRSW values In paediatric subjects. On the contrary, baseline CLCRSW was identified as a statistically significant covariate for TFV PK in the final PopPK model. This is as expected since TFV is renally eliminated. In paediatric subjects, TFV exposures were generally similar across the range of baseline CLCRSW values (115 – 179 ml/min/1.73m^2 for the Cohort 3 population). These findings go in line with the adult population, although all paediatric HIV-1 Infected Subjects presented normal renal function.

Gender was not considered a relevant covariate on the EVG, COBI, TAF or TFV popPK models and goes in line with previous findings in the adult population.

Race was identified as a statistically significant covariate for TAF PK in its final PopPK model once body size was accounted for. However, the limited sample sizes within each race category would prevent a robust quantification of the effects of race on BIC exposures. For the adult population, Race seems not to influence the PK of EVG, COBI, TAF or TFV.

Baseline WT was included as a covariate on apparent clearance and volume of distribution in the final PopPK models for EVG, COBI, TAF, and TFV. Consistent with the identified WT effect, exposures for EVG, COBI, TAF, and TFV were found to increase at decreasing WT. The applicant was asked to discuss if the subjects in Q1 are in increased risk due to higher exposure. The applicant performed the required analysis, focusing in particular on the lower bound of the weight classes. This analysis was preceded by the update of the poppk models for TAF and COBI, by including additional subjects and improved description of the absorption phase and IIV on the models. These changes improved significantly the performance of the models when compared to the previous versions (as seen by the parameters estimates, GOF and VPCs).

In general, and as expected, patients from the lower weight bounds result in higher exposures (AUC) and especially higher Cmax for all drugs. However, these results are usually inside the range of values observed for adults. Reducing the dose in these weight bands appears not to be possible as it could result in an increased number of patients with C_{tau} bellow the observed in adults, resulting in a potential loss of efficacy.

Age and weight are confounding factors. Age was not identified as a statistically significant covariate for EVG, COBI, TAF, or TFV in their respective final PopPK model.

Due to the inability for presenting a QSP approach able to serve as a useful predictor of bone remodelling effects and of BMD changes when considered for both TAF 25 mg QD and TDF 300 mg QD administration, empirical regression models were alternatively explored concluding for the safety profile for TAF (boosted and unboosted) versus TDF in the paediatric population and supported the weight-band-based dosing regimen for both boosted- and unboosted-TAF in the paediatric population.

2.6.4. Conclusions on clinical pharmacology

The pharmacology data supported the authorisation of the new strength.

2.6.5. Clinical efficacy

2.6.5.1. *Main 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-Naïve Adolescents and Virologically Suppressed Children

Methods

Study GS-US-292-0106 is a Phase 2/3 study initially designed to characterize the PK and confirm the dose of the adult GEN tablet (E/C/F/TAF 150/150/200/10 mg) in ART-naïve, HIV-1 infected adolescents ≥ 12 to < 18 years of age (Cohort 1) and virologically suppressed, HIV-1 infected children ≥ 6 to < 12 years of age weighing ≥ 25 kg (Cohort 2). The study was extended in Protocol Amendment 4 to characterize the PK and confirm the dose of a low-dose (LD) GEN tablet (E/C/F/TAF 90/90/120/6 mg) in virologically suppressed, HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg enrolled in an additional cohort, Cohort 3. The safety, tolerability, and antiviral activity of the adult and LD GEN tablets were also evaluated in the cohorts to which they were administered.

The submitted data described the results of the study for subjects in Cohort 3 as determined by an interim analysis performed when all subjects in this cohort had completed their Week 48 visit.

Study Participants

Cohort 3 included virologically suppressed, HIV-1 infected children ≥ 2 years of age, with a screening weight ≥ 14 to < 25 kg, with plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 consecutive months prior to screening, on a stable antiretroviral regimen (ie, stable for ≥ 6 months, or newly initiated within 6 months prior to screening for a reason other than virologic failure) without documented history of resistance to any component of GEN.

Subjects were enrolled at 9 sites in 5 countries: 3 in South Africa, 1 in Thailand, 1 in Uganda, 3 in the US, and 1 in Zimbabwe.

A total enrolment of up to 25 subjects was planned for Cohort 3, all of whom were to participate in an intensive PK evaluation at Week 2, following which subjects would continue to receive study drug and return for scheduled study visits through Week 48.

Treatments

Subjects received one low-dose FDC tablet daily, orally with food, at approximately the same time each day. Subjects were instructed to take their tablet with food at the same time each morning (with breakfast) during the days leading up to intensive PK assessments at the Week 2 visit. On the day of the intensive PK visit, subjects were administered the study drug dose, with food, in the clinic, after an overnight fast of at least 8 hours.

Objectives

The primary objectives for cohort 3 were:

- 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 low dose (LD) (90/90/120/6 mg) 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

The secondary objectives for cohort 3 were:

- 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

The exploratory objective of this study for all cohorts (1, 2 and 3) was to explore the PK of TFV-DP in PBMCs following administration of E/C/F/TAF STR in Cohort 1 and 2, or E/C/F/TAF LD STR in Cohort 3.

Outcomes/endpoints

The primary endpoints for cohort 3 were:

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

The secondary endpoints for cohort 3 were:

- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4 cell count (cells/µL) and percentage at Weeks 24 and 48
- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 (missing = failure [M = F] and missing = excluded [M = E] analyses)
- The incidence of treatment-emergent SAEs and all treatment-emergent AEs through Week 48
- The PK parameters C_{tau}, C_{max}, apparent CL/F, and apparent V_z/F for EVG; C_{max}, apparent CL/F, and apparent V_z/F for TAF; and AUC_{tau}, C_{max}, and C_{tau} for FTC, tenofovir (TFV), and COBI

Sample size

The 25 subjects planned for intensive PK evaluation in Cohort 3 is deemed sufficient for the evaluation of safety due to the large number of subjects in Cohorts 1 and 2 combined who have contributed to the safety profile of GEN at exposures predicted to be similar to those of Cohort 3. The number of included subjects was calculated to provide adequate power to conclude exposure equivalence between children and adults when compared to historical adult data.

Randomisation and Blinding (masking)

Study GS-US-292-0106 is a non-randomized open-label study.

Statistical methods

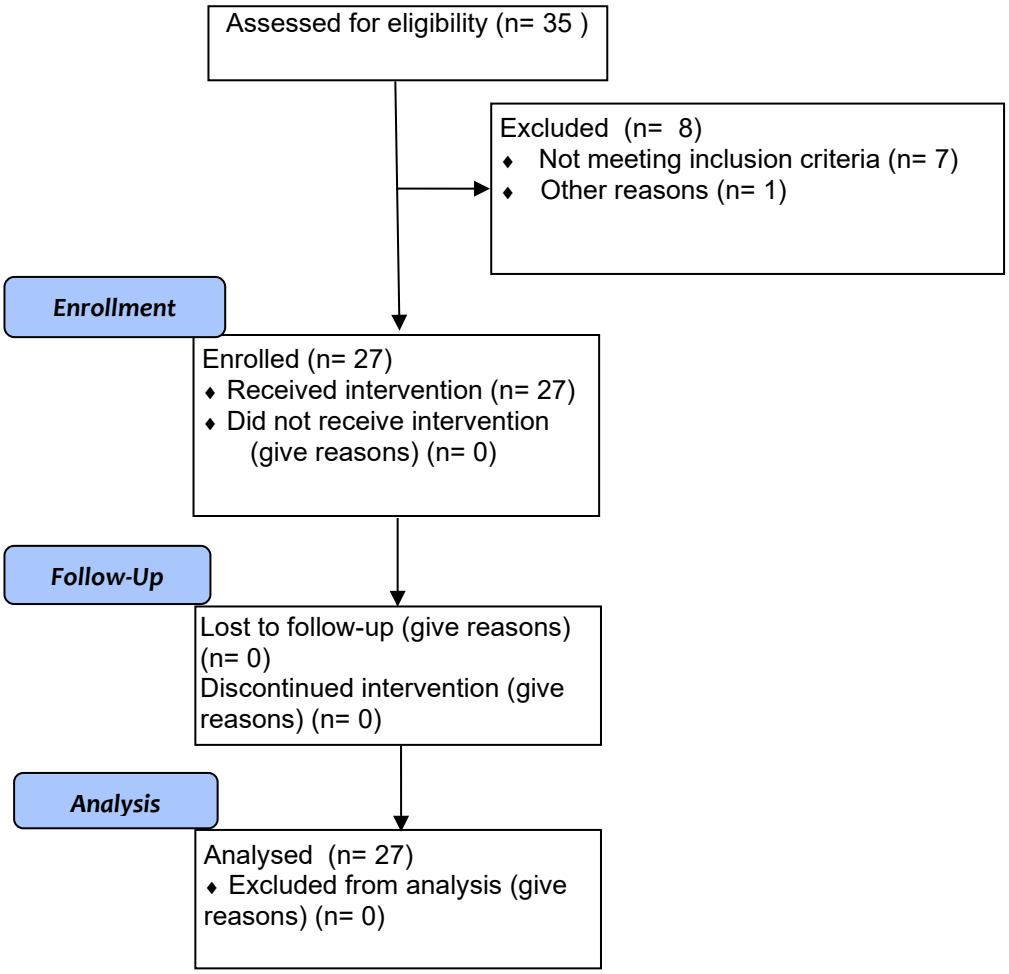
Efficacy analyses used the FAS, which included all subjects who were enrolled into the study and received at least 1 dose of study drug.

The proportions of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 were evaluated using both the US FDA defined snapshot algorithm and M = F and M = E analyses. The 95% CIs for these percentages were constructed using the Clopper-Pearson Exact method.

All safety analyses were performed using the safety analysis set.

Results

Participant flow



The Interim Analysis 6 data-cut date occurred when all subjects had completed their Week 48 visit. Immediately prior to that point, 33.3% (9 of 27) of treated subjects were receiving study drug in the main phase of the study (i.e. 48 weeks), and 66.7% (18 of 27) of subjects were receiving study drug in the extension phase of the study. No subject in either the main or the extension phase of the study prematurely discontinued either study drug or the study.

Recruitment

The first subject was screened for cohort 3 on 12 December 2018. The Last Subject Last Visit for the primary endpoint occurred on 11 May 2020. The evaluation of subjects continued through 6 October 2020 (Last Subject Last Visit for the fifth Interim Report).

Conduct of the study

The original protocol (4 February 2013) was amended 6 times (22 March 2013, 09 January 2015, 11 August 2016, 11 June 2018, 17 August 2018, and 21 February 2020). Cohort 3 was introduced into the protocol at Protocol Amendment 4, dated 11 June 2018. All subjects in Cohort 3 were enrolled under Protocol Amendment 5 or the South Africa-specific Protocol Amendment 5.1, both dated 17 August 2018; the two amendments are identical, and a South Africa-specific protocol was required only because the study is considered to be Phase 1/2 in that country, rather than Phase 2/3 as in the other participating countries. In Protocol Amendment 5, the inclusion criteria were updated to require a CD4 cell count ≥ 400 cells/μL for potential subjects (previously > 100 cells/μL).

Sensitivity analyses were performed in respect of the main efficacy endpoint (percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US FDA-defined snapshot algorithm) and palatability/acceptability assessments, in which subjects who switched from the LD tablet to the adult GEN tablet (E/C/F/TAF 150/150/200/10 mg) by virtue of having attained a weight ≥ 25 kg during the main phase of the study were excluded from the FAS and Safety Analysis Set, respectively, at the appropriate time points.

A total of 35 important protocol deviations were reported for 19 subjects in Cohort 3 during the study through the data-cut date. Of the 19 subjects, 9 subjects had a single important deviation, 4 subjects had 2 important deviations, and 6 subjects had 3 important deviations. The most common important protocol deviations (30 of 35) were in connection with missing data at the Week 24 and/or Week 48 visits.

A total of 25 important protocol deviations related to COVID-19 were reported for 17 subjects. The most common important protocol deviations (24 of 25) were in connection with missing data at the Week 24 and/or Week 48 visits.

According to the MAH, none of these important protocol deviations affected the overall quality or interpretation of the study data.

Adherence to study drug was based on pill count.

The median rates of adherence to study drug up to the Week 24 and Week 48 visits, and up to the data-cut date, were 98.2%, 98.5%, and 98.6%, respectively. The percentage of subjects with an adherence rate ≥ 95% was 85.2% up to the Week 24 visit, 88.9% up to the Week 48 visit, and 92.6% up to the data-cut date.

Adherence to LD E/C/F/TAF was good, with more than 23 out of the 27 subjects with adherence ≥ 95% and no subject with adherence <80%.

Baseline data

The demographic and baseline characteristics are summarised in Table 18 and Table 19 below.

Table 16 - Demographic and baseline characteristics – cohort 3

Characteristic[a]	E/C/F/TAF Cohort 3: Age ≥ 2 Years and Weight ≥ 14 to < 25 kg (N = 27)
Age (years)	
N	27
Mean (SD)	6 (1.9)
Median	6
Q1, Q3	4, 8
Min, Max	3, 9
Age Group	
2-5 Years Old	11 (40.7%)
6-12 Years Old	16 (59.3%)
Sex at Birth	
Male	10 (37.0%)
Female	17 (63.0%)
Race	
Asian	3 (11.1%)
Black	24 (88.9%)
Ethnicity	
Not Hispanic or Latino	27 (100.0%)
Baseline Weight (kg)	
N	27
Mean (SD)	19.0 (2.55)
Median	19.3
Q1, Q3	17.0, 20.5
Min, Max	14.6, 23.5
Baseline Weight Z-score	
N	27
Mean (SD)	−0.93 (1.029)
Median	−0.88
Q1, Q3	−1.72, −0.32
Min, Max	−2.93, 0.98
Baseline Height (cm)	
N	27
Mean (SD)	114.8 (10.00)
Median	116.0
Q1, Q3	106.0, 123.0
Min, Max	95.8, 130.0

Characteristic[a]	E/C/F/TAF Cohort 3: Age ≥ 2 Years and Weight ≥ 14 to < 25 kg (N = 27)
Baseline Height Z-score	
N	27
Mean (SD)	−0.52 (1.098)
Median	−0.28
Q1, Q3	−1.42, 0.23
Min, Max	−2.65, 1.61
Baseline Body Mass Index (kg/m^2)	
N	27
Mean (SD)	14.5 (1.14)
Median	14.2
Q1, Q3	13.7, 15.3
Min, Max	12.4, 17.1
Body Surface Area (m^2)[b]	
N	27
Mean (SD)	0.78 (0.084)
Median	0.79
Q1, Q3	0.69, 0.84
Min, Max	0.64, 0.92
Tanner Stage Evaluation (Subjects ≥ 6 Years of Age)[c]	
Male	
Pubic Hair	
Stage 1	4 (100.0%)
Genitalia	
Stage 1	4 (100.0%)
Male	
Maximum Stage of Pubic Hair or Genitalia	
Stage 1-3	4 (100.0%)
Stage 4-5	0
Female	
Pubic Hair	
Stage 1	14 (100.0%)
Breasts	
Stage 1	14 (100.0%)
Maximum Stage of Pubic Hair or Breasts	
Stage 1-3	14 (100.0%)
Stage 4-5	0

a The denominator for percentages is the number of subjects in the Safety Analysis Set.
b Body surface area (m^2) = √([Height (cm) x Weight (kg)]/3600).
c Baseline Tanner Stage evaluations were erroneously performed in 1 male and 1 female subject < 6 years of age.
Source: Section 15.1, Table 5.1

Table 17 - Baseline disease characteristics – cohort 3

Characteristic[a]	E/C/F/TAF Cohort 3: Age ≥ 2 Years and Weight ≥ 14 to < 25 kg (N = 27)
HIV-1 RNA Categories (copies/mL)	
< 50	27 (100.0%)
≥ 50	0
CD4 Cell Count (cells/µL)	
N	27
Mean (SD)	1153 (459.9)
Median	1061
Q1, Q3	895, 1315
Min, Max	383, 2401
CD4 Cell Count Categories (cells/µL)	
≤ 199	0
200 to ≤ 349	0
350 to ≤ 499	2 (7.4%)
≥ 500	25 (92.6%)
CD4 Percentage (%)	
N	27
Mean (SD)	35.9 (6.73)
Median	37.4
Q1, Q3	30.6, 40.3
Min, Max	24.0, 52.9
HIV Disease Status	
Asymptomatic	26 (96.3%)
Symptomatic HIV Infection	1 (3.7%)

Characteristic[a]	E/C/F/TAF Cohort 3: Age ≥ 2 Years and Weight ≥ 14 to < 25 kg (N = 27)
Mode of Infection (HIV Risk Factors)[b]	
Heterosexual Sex	0
Homosexual Sex	0
IV Drug Use	0
Transfusion	0
Vertical Transmission	25 (92.6%)
Other	2 (7.4%)
Unknown	0
Years Since Subject Diagnosed with HIV	
N	27
Mean (SD)	5.1 (1.75)
Median	5.0
Q1, Q3	4.0, 7.0
Min, Max	2.0, 8.0
HBV Surface Antigen	
Negative	27 (100.0%)
HCV Antibody	
Negative	26 (96.3%)
Positive	1 (3.7%)
Estimated Glomerular Filtration Rate by Schwartz Formula (mL/min/1.73 m^2)	
N	27
Mean (SD)	148.3 (14.35)
Median	147.0
Q1, Q3	139.1, 159.1
Min, Max	115.1, 179.3
Proteinuria by Urinalysis (Dipstick)[c]	
Grade 0	25 (92.6%)
Grade 1	2 (7.4%)
Grade 2	0
Grade 3	0

a The denominator for percentages is the number of subjects in the Safety Analysis Set.
b A subject may fit in more than 1 HIV risk factor category; therefore, percentages may add to more than 100.
c The highest grade for proteinuria is Grade 3.
Source: Section 15.1, Table 5.2

The entry criteria described in the protocol were followed to include virologically suppressed children without advanced disease. The relevance of the efficacy results to other populations (ARV-naïve with advanced disease) is still unknown.

Numbers analysed

All 27 enrolled subjects, who each received at least 1 dose of study drug, were included in each of the specified analysis sets (Safety, Full, DXA [Spine and TBLH], Intensive PK [all analytes], and PK [all analytes]). Even if limited, all subjects enrolled were included in the analyses that were made.

Outcomes and estimation

Percentage of Subjects with Plasma HIV-1 RNA < 50 Copies/mL at Weeks 24 and 48 Using the US FDA-Defined Snapshot Algorithm

At baseline, all Cohort 3 subjects (27 of 27) had HIV-1 RNA < 50 copies/mL.

At both Week 24 and Week 48, 96.3% (26 of 27) of subjects in the FAS had HIV-1 RNA < 50 copies/mL, using the US FDA-defined snapshot algorithm.

Sensitivity analyses in which subjects who had switched from the LD to the adult GEN tablet by virtue of having attained a weight ≥ 25 kg as the study progressed were excluded from the FAS demonstrated a similarly high maintenance of virological suppression. Percentages of subjects receiving the GEN LD tablet at the Week 24 and 48 time points with HIV-1 RNA < 50 copies/mL were as follows: Week 24: 96.2% (25 of 26 subjects); Week 48, 95.8% (23 of 24 subjects).

One subject who remained on the LD tablet through the data-cut date, had HIV-1 RNA ≥ 50 copies/mL at both Week 24 and Week 48. This subject had previously had HIV-1 RNA levels < 20 copies/mL through Week 16, and again at Weeks 32 and 60. Values were > 50 copies/mL at Weeks 20, 40, and 48 in a rather erratic fashion, possibly reflecting inconsistent study drug adherence.

Change from Baseline in CD4 Cell Count (Cells/μL) at Weeks 24 and 48

Twenty-five of the 27 enrolled subjects in Cohort 3 had a CD4 cell count ≥ 500 cells/μL at baseline; 2 subjects had a CD4 cell count in the category 350 to ≤ 499 cells/μL).

A change from baseline in mean CD4 cell count was observed at Week 2 (the first available time point) following which the mean value appeared stable through Week 48.

Mean (SD) and median (Q1, Q3) values for baseline CD4 cell count (FAS; based on observed data) were 1153 (459.9) and 1061 (895, 1315) cells/μL, respectively (Section 15.1, Table 12). Mean and median changes from baseline in CD4 cell count were as follows:

- At Week 24: Mean (SD) −137 (278.3) cells/μL; median (Q1, Q3) −63 (−190, −3) cells/μL
- At Week 48: Mean (SD) −179 (319.2) cells/μL; median (Q1, Q3) −187 (−370, 44) cells/μL

The 2 subjects with baseline CD4 cell counts in this category, aged 7 and 9 years, with baseline CD4 cell count values of 446 and 383 cells/μL, respectively, both had a CD4 cell count ≥ 500 at both Week 24 and Week 48.

Change from Baseline in CD4 Percentage

Mean CD4% values for subjects in Cohort 3 remained stable through Week 48.

Mean (SD) and median (Q1, Q3) values for baseline CD4% (FAS) were 35.9% (6.73%) and 37.4% (30.6%, 40.3%), respectively.

Mean and median changes from baseline in CD4 cell count were as follows:

- At Week 24: Mean (SD) 0.0% (4.40%); median (Q1, Q3) −0.1% (−3.1%, 3.5%)
- At Week 48: Mean (SD) 0.2% (3.78%); median (Q1, Q3) 0.4% (−2.0%, 2.8%)

Percentage of Subjects with HIV-1 RNA < 50 Copies/mL (M = F and M = E) Analyses

Percentages of subjects in Cohort 3 with HIV-1 RNA < 50 copies/mL at Week 24 and Week 48 as determined using M = F and M = E methods were as follows:

- M = F: Week 24, 96.3% (26 of 27 subjects); Week 48, 96.3% (26 of 27 subjects)
- M = E: Week 24, 96.3% (26 of 27 subjects); Week 48, 96.3% (26 of 27 subjects)

The subject with HIV-1 RNA > 50 copies/mL at Weeks 24 and 48 had levels < 20 copies/mL through Week 16 and at Weeks 32 and 60.

Based on efficacy analyses at Week 24 and Week 48 using the USFDA defined snapshot algorithm, the rates of virologic suppression (HIV-1 RNA < 50 copies/mL) were maintained in the analysed population of virologically suppressed children. There were no clinically relevant changes in CD4 cell counts and CD4%.

Virology Resistance Analyses

Of the 27 subjects in Cohort 3 receiving the GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) through Week 48, 1 subject (3.7%) met the virologic failure criteria and qualified for viral resistance testing. No resistance to study drug was detected and the subject remained on study drug, subsequently resuppressing HIV-1 RNA to < 50 copies/mL.

No subjects developed treatment-emergent drug resistance substitutions in integrase or reverse transcriptase.

Ancillary analyses

No subgroup analysis were performed.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18 - Summary of Efficacy for trial GS-US-292-0106

Title: 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-Naïve Adolescents and Virologically Suppressed Children			
Study identifier	**Study No.:** GS-US-292-0106 **EudraCT No.:** 2013-002780-26		
Design	Phase 2/3, open-label, multicohort, multicenter, 2-part, single-group study to evaluate the PK, safety, tolerability, and antiviral activity of GEN		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	48 weeks not applicable until: a) the subject turns 18 and the E/C/F/TAF STR is commercially available for use in adults in the country in which the subject is enrolled or b) the E/C/F/TAF STR becomes commercially available for use in adolescents in the country in which the subject is enrolled or c) Gilead Sciences elects to terminate development of the E/C/F/TAF STR in the applicable country.	
Hypothesis	GEN will be safe, well tolerated, will have pharmacokinetics comparable to adults and will demonstrate antiviral activity when used in HIV-1-infected, virologically suppressed infants and children.		
Treatments groups	Cohort 1: ≥ 12 years to < 18 years of age	See section 4.6 in this AR	
	Cohort 2: ≥ 6 years to < 12 years of age	See section 4.6 in this AR	
	Cohort 3: ≥ 2 years of age	LD EVG/C/F/TAF. 48 weeks, 27 subjects	
Endpoints and definitions	efficacy endpoint	HIV-1 RNA < 50 c/ml	percentage of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24 and 48 (snapshot approach).
	efficacy endpoint	HIV-1 RNA < 50 c/ml	percentage of subjects with plasma HIV-1 RNA <400 c/mL at Weeks 12, 24 and 48, and every 12 weeks after Week 48 (M=F analysis and M=E analysis).
	efficacy endpoint	CD4+	change from baseline in CD4 cell count (cells/µL) and percentage at Weeks 24 and 48
Database lock	06 October 2020		
Results and Analysis			
Analysis description	**Interim Analysis**		
Analysis population and time point description	The Full Analysis Set (FAS) included all subjects enrolled in the study who received at least 1 dose of study drug. 48 weeks		
Descriptive statistics and estimate variability	Treatment group		**Cohort 3**
	Number of subject		27
	HIV-1 RNA < 50 c/ml week 24 and week 48 (FAS) (snapshot approach)		26/27 (96,3%)
	95% CI		81.0% to 99.9%
	HIV-1 RNA < 50 c/ml week 24 and week 48 (FAS) (M=F, M=E approach)		26/27 (96,3%)
	95% CI		81.0% to 99.9%

Title: 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-Naïve Adolescents and Virologically Suppressed Children		
Study identifier	**Study No.:** GS-US-292-0106 **EudraCT No.:** 2013-002780-26	
	CD4+ (cells/uL) Mean change from baseline week 48 (FAS)	-179
	SD	319.2
	CD4+ (%) Mean change from baseline week 48 (FAS)	0.2%
	SD	3.78%

2.6.5.2. ***In vitro biomarker test for patient selection for efficacy***

Not applicable

2.6.5.3. ***Analysis performed across trials (pooled analyses and meta-analysis)***

Not applicable

2.6.5.4. ***Supportive study(ies)***

Not applicable

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

To support the current line extension/variation, the applicant has submitted, as interim report, the data obtained from one ongoing study (GS-US-292-0106) that evaluated PK, safety, and efficacy data of LD E/C/F/TAF in paediatric patients aged ≥ 2 years weighing ≥ 14 to < 25 kg.

A total of 27 subjects were included. Eligible subjects were virologically suppressed HIV-1 subjects aged ≥ 2 years weighing ≥ 14 to < 25 kg on a stable antiretroviral regimen for ≥ 6 months prior to screening; HIV-1 RNA < 50 copies/mL at screening; estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m^2 (as calculated using the Schwartz formula; $eGFR_{Schwartz}$); and adequate hematologic and hepatic function.

The CHMP considered the design and conduct of the study GS-US-292-0106 appropriate.

Efficacy data and additional analyses

The virologic response rate, defined as the number and percentage of subjects with plasma viral load < 50 HIV-1 RNA copies/mL at Week 48 (per FDA Snapshot approach, FAS population) was 96.3% (26/27) in Cohort 3. The results were consistent with M=F and M=E analysis.

Sensitivity analyses in which subjects who had switched from the LD to the adult GEN tablet by virtue of having attained a weight ≥ 25 kg as the study progressed were excluded from the FAS demonstrated a similarly high maintenance of virological suppression. Percentages of subjects receiving the GEN LD tablet at the Week 24

and 48 time points with HIV-1 RNA < 50 copies/mL were as follows: Week 24: 96.2% (25 of 26 subjects); Week 48, 95.8% (23 of 24 subjects).

One subject (3.7%) met the virologic failure criteria and qualified for viral resistance testing. No resistance to study drug was detected and the subject remained on study drug, subsequently resuppressing HIV-1 RNA to < 50 copies/mL.

In this virologically suppressed paediatric study population with high baseline mean CD4 cell count and CD4%, there were no clinically relevant changes from Baseline in CD4 cell counts and CD4% for Cohort 3.

The efficacy data were not the primary endpoints, but they were considered supportive by the CHMP. The study design and the limited population of virologically suppressed children could limit the extrapolation of these results to other populations (e.g. ARV-naïve subjects or with high viral load).

Almost all (26) of the 27 subjects maintained virological suppression at Week 48. One subject had detectable HIV-1 RNA at Weeks 24 and 48, but he had undetectable viral load between these weeks and at Week 60. No Genvoya-related resistance associated mutations were identified.

2.6.7. Conclusions on the clinical efficacy

The CHMP considered that the efficacy data support the lower dose of Genvoya in the extended paediatric population (patients aged ≥ 2 years weighing ≥ 14 kg).

2.6.8. Clinical safety

The MAH submitted the safety data of LD EVG/C/F/TAF in HIV-1-infected, virologically suppressed paediatric subjects ≥ 2 years weighing ≥ 14 kg and < 25 kg participating in Cohort 3 of Study GS-US-292-0106.

The safety data from Cohort 3 provides additional data on the safety profile of Genvoya in a new low-dose tablet.

2.6.8.1. ***Patient exposure***

All 27 paediatric subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg received at least 1 dose of study drug. At the data-cut date, the median (Q1, Q3) exposure to the GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) was 48.3 (48.0, 60.1) weeks, and 77.8% (21 of 27) subjects had received E/C/F/TAF for ≥ 48 weeks.

2.6.8.2. ***Adverse events***

Safety is reported on a cumulative basis and the Safety Analysis Set includes 3 subjects who switched to the adult GEN tablet (E/C/F/TAF 150/150/200/10 mg) having attained a weight > 25 kg during the main phase of the study, 1 at Week 12, 2 at Week 32). The overall summary of adverse events is presented in tables 21 and 22.

74.1% (20 of 27) of subjects had at least 1 AE, the majority of which were Grade 1 (mild) in severity and not considered related to study drug. No subject had a Grade 3 or 4 AE, or an AE leading to premature

discontinuation of study drug. One subject had an SAE, which was not considered related to study drug. There was no treatment emergent death.

Two subjects had a Stage 3, HIV-1 related opportunistic illness, neither of which was considered related to study drug.

No subject experienced an AE for COVID-19 or a suspected COVID-19 infection.

The most commonly reported AEs were as follows:

- Upper respiratory tract infection (29.6%, 8 subjects)
- Cough (18.5%, 5 subjects)
- Decreased appetite and vomiting (each 14.8%, 4 subjects)

Table 19 - GS-US-292-0106 Overall summary of adverse events (safety analysis set, cohort 3)

Adverse Event Category, n (%)	E/C/F/TAF Cohort 3: Age ≥ 2 Years and Weight ≥ 14 to < 25 kg (N = 27)
Subjects Experiencing Any Treatment-Emergent Adverse Event	20 (74.1%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event	2 (7.4%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	0
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	4 (14.8%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study Drug-Related Adverse Event	0
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study Drug-Related Adverse Event	0
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	1 (3.7%)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Serious Adverse Event	0
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	0
Subjects who had Treatment-Emergent Death	0

Table 20 - GS-US-292-0106: Adverse events reported for at least 2 subjects (safety analysis set, cohort 3)

Adverse Events by Preferred Term[a,b]	E/C/F/TAF Cohort 3: Age ≥ 2 Years and Weight ≥ 14 to < 25 kg (N = 27)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event	20 (74.1%)
Upper respiratory tract infection	8 (29.6%)
Cough	5 (18.5%)
Decreased appetite	4 (14.8%)
Vomiting	4 (14.8%)
Nasopharyngitis	3 (11.1%)
Constipation	2 (7.4%)
Diarrhoea	2 (7.4%)
Epistaxis	2 (7.4%)
Tonsillitis	2 (7.4%)

a Adverse events were coded using MedDRA 23.0
b Multiple AEs were counted only once per subject for each preferred term; preferred terms are presented in descending order of total frequencies.

The most commonly reported AEs were consistent with the adverse events that could be expected in this paediatric population.

2.6.8.3. ***Serious adverse event/deaths/other significant events***

Deaths

No treatment-emergent death was reported through the data cut date.

Serious adverse events

Pneumonia, considered not related to study drug, and not leading to premature discontinuation of study drug, was reported as an SAE for 1 subject through the data-cut date.

Treatment-Related Adverse Events

Adverse events related to study drug were reported for 4 subjects (14.8%). Study drug-related AEs that occurred in > 1 subject were diarrhoea and vomiting, each of which was reported for 2 subjects.

Other events

As for other trials assessing cobicistat and tenofovir-containing FDCs particular attention was paid to bone safety and renal safety.

Bone safety

Fracture Events

Fracture events were assessed in this study because of the importance of bone safety in a paediatric population accruing bone mass. No fractures were reported.

Bone Mineral Density

Percentage Change from Baseline in Spine and Total-Body-Less-Head Bone Mineral Density

Spine

Mean (SD) increases from baseline of 3.094% (4.7951%) and 5.275% (5.7970%) in spine BMD were observed at Weeks 24 and 48, respectively.

Total Body Less Head

Mean (SD) increases from baseline of 3.816% (3.3616%) and 7.160% (4.1588%) in TBLH BMD were observed at Weeks 24 and 48, respectively.

The percentages of subjects with ≥ 4% decrease from baseline at Week 24 or Week 48 in spine or TBLH BMD were:

- Spine: Week 24, 2 of 27 subjects (7.4%); Week 48, 1 of 27 subjects (3.7%)
- TBLH: Week 24, 1 of 27 subjects (3.7%); Week 48, 0 of 27 subjects (0.0%)

One subject had percentage decreases ≥ 4% from baseline in both spine (Week 24, −7.544%; Week 48, −6.805%) and TBLH BMD (Week 24, −4.354%). Height-age spine BMD Z-scores at baseline, Week 24, and Week 48 for this subject were 1.54, 0.72, and 0.71, respectively; the corresponding height-age TBLH BMD Z-scores were 0.84, 0.06, and 0.18. A second subject had a percentage decrease ≥ 4% from baseline in spine BMD at Week 24 (−5.451%). Height-age spine BMD Z-scores at baseline, Week 24, and Week 48 for this subject were −0.97, −1.39, and −1.19, respectively; the corresponding height-age TBLH BMD Z-scores were −0.83, −1.19, and −0.98.

Change from Baseline in Bone Mineral Density Z-Scores

BMD status was also assessed using BMD Z-scores. Z-scores are the measurement of choice to interpret BMD outcomes in paediatric populations. The Z-score for any BMD value is the number of SDs that value lies below or above the mean BMD of an age, sex, and race matched control group, and is therefore more informative than an absolute BMD value or percentage change from baseline in BMD. A Z-score ≤ −2.0 is "below the expected range for age" and is considered to reflect a low bone mineral mass or BMD, while a Z-score > −2.0 is within the expected range for age.

Spine

Baseline spine standard and height-age BMD Z-scores and changes from baseline in each at Weeks 24 and 48 are shown in the below Table 23.

Table 21 - GS-US-292-0106: Spine standard and height-age BMD Z-scores at baseline and change form baseline at Weeks 24 and 48 (Spine DXA analysis set, cohort 3)

	Spine BMD Z-Score (Standard) (N = 27)		Spine BMD Z-Score (Height-Age) (N = 27)	
	Mean (SD)	Median (Q1, Q3)	Mean (SD)	Median (Q1, Q3)
Baseline	−1.44 (0.955)	−1.63 (−2.06, −1.06)	−1.27 (1.035)	−1.60 (−2.02, −0.85)
Change from Baseline at Week 24	0.05 (0.360)	0.16 (−0.20, 0.33)	0.10 (0.384)	0.21 (−0.16, 0.36)
Change from Baseline at Week 48	0.05 (0.429)	0.05 (−0.17, 0.40)	0.11 (0.377)	0.14 (−0.14, 0.36)

Total Body Less Head

Baseline TBLH standard and height-age BMD Z-scores and changes from baseline in each at Weeks 24 and 48 are shown in the below Table 24.

Table 22 - GS-US-292-0106: TBLH standard and height-age BMD Z-scores at baseline and change form baseline at Weeks 24 and 48 (TBLH DXA analysis set, cohort 3)

	TBLH BMD Z-Score (Standard) (N = 27)		TBLH BMD Z-Score (Height-Age) (N = 27)	
	Mean (SD)	Median (Q1, Q3)	Mean (SD)	Median (Q1, Q3)
Baseline	−1.58 (0.864)	−1.64 (−2.05, −1.37)	−1.26 (0.823)	−1.39 (−1.81, −0.78)
Change from Baseline at Week 24	−0.03 (0.277)	−0.05 (−0.21, 0.16)	0.06 (0.386)	0.08 (−0.24, 0.35)
Change from Baseline at Week 48	−0.03 (0.348)	−0.09 (−0.23, 0.15)	0.01 (0.456)	−0.06 (−0.33, 0.27)

Spine and Total-Body-Less-Head Clinical Status

Clinical BMD status was assessed using height-age BMD Z-scores. A height-age BMD Z-score that changes from > −2 at baseline to ≤ 2 has been used as a means to identify possible significant bone loss as this is considered a "low-for-age" outcome. The diagnosis of osteoporosis in children is appropriate only when both low bone mass (BMD Z-score ≤ −2) and a clinically significant fracture history are present.

No subject showed a worsening (change from > −2 to ≤ −2) from baseline in spine height-age BMD Z-score at Week 24 or 48.

Two subjects showed a worsening from baseline in TBLH height-age BMD Z-score at Week 48. Neither subject had a clinically significant fracture history.

Median (Q1, Q3) baseline values and percentage changes from baseline at Weeks 24 and 48 for serum levels of bone-specific alkaline phosphatase, PTH, 25-OH-vitamin D, and 1,25-$(OH)_2$ vitamin D are presented in the below table 25. Changes in levels of each between baseline and Week 48 are not considered clinically relevant.

Table 23 - GS-US-292-0106: Median (Q1, Q3) percentage change from baseline in serum bone laboratory parameters at weeks 24 and 48 (Safety analysis set, cohort 3)

Laboratory Parameter	LD E/C/F/TAF		
	N	Median	Q1, Q3
Bone-Specific Alkaline Phosphatase (µg/L)			
Baseline	27	82.75	61.22, 105.76
% Change at Week 24	26	−6.61	−22.45, 10.84
% Change at Week 48	27	11.89	−7.22, 28.73
PTH (pg/mL)			
Baseline	27	35.3	28.1, 57.6
% Change at Week 24	27	−0.7	−28.0, 34.8
% Change at Week 48	27	11.5	−19.9, 27.1
25-OH Vitamin D (ng/mL)			
Baseline	27	28.0	22.4, 34.0
% Change at Week 24	26	−16.6	−32.5, 0.3
% Change at Week 48	27	−18.3	−30.0, 0.0
$1,25\text{-}(OH)_2$ Vitamin D (pg/mL)			
Baseline	27	82.5	70.5, 113.0
% Change at Week 24	18	6.7	−7.0, 35.5
% Change at Week 48	27	16.3	−12.6, 27.9

The bone safety parameters assessed did not show any new safety concern with only two subjects showing a worsening from baseline in TBLH height-age BMD Z-score at Week 48.

Renal Safety

Renal Events

Renal safety was of interest for this study because renal toxicity has been associated with TFV, and because COBI inhibits tubular secretion of creatinine, leading to an increase in serum creatinine and a decrease in eGFR, without an effect on actual glomerular filtration in adults. There were no AEs of renal tubulopathy (including Fanconi syndrome), and no renal AEs that led to discontinuation of study drug.

Renal Laboratory Parameters

Serum Creatinine

Median (Q1, Q3) baseline serum creatinine was 0.44 (0.38, 0.49) mg/dL. Values remained stable through Week 48. Median (Q1, Q3) changes from baseline at Weeks 24 and 48 were as follows:

- Week 24: 0.00 (−0.05, 0.04) mg/dL
- Week 48: −0.01 (−0.04, 0.04) mg/dL

No graded serum creatinine abnormality was reported.

Estimated Glomerular Filtration Rate

Median (Q1, Q3) baseline eGFR using the Schwartz formula was 147.0 (139.1, 159.1) mL/min/1.73 m^2. An increase from baseline was observed at Week 1 that remained relatively stable through Week 48. Median (Q1, Q3) changes from baseline at Weeks 24 and 48 were as follows:

- Week 24: 4.1 (−13.8, 26.8) mL/min/1.73 m^2
- Week 48: 9.6 (−11.2, 19.3) mL/min/1.73 m^2

Phosphorus

Median serum phosphorus values were within the normal reference range throughout the study. No graded abnormalities of serum phosphorus were reported.

Glycosuria

No graded abnormalities in urine glucose were reported.

Treatment-Emergent Proteinuria by Urinalysis (Dipstick)

At baseline, 2 subjects (7.4%) had Grade 1 proteinuria as assessed by dipstick analysis. Postbaseline, treatment-emergent proteinuria (Grade 1) was reported for 6 subjects (22.2%). No obvious correlation was observed between these instances of proteinuria and any other renal laboratory abnormality.

Proteinuria by Quantitative Assessment

The UPCR was ≤ 200 mg/g (and urinary protein < 4.0 mg/dL) for all subjects at baseline and at all subsequent time points (Weeks 8, 12, 24, and 48).

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

The median (Q1, Q3) baseline urine RBP to creatinine ratio was 122.1 (68.4, 138.3) µg/g. A variable decrease in the urine RBP to creatinine ratio was observed at Week 8 (the first time point) and maintained through Week 48. Median (Q1, Q3) percentage changes from baseline at Weeks 24 and 48 were as follows:

- Week 24: −15.7% (−31.0%, 9.6%)
- Week 48: −21.9% (−41.3%, 41.7%)

The median (Q1, Q3) baseline urine beta-2 microglobulin to creatinine ratio was 158.8 (106.3, 190.3). A variable decrease in the urine beta-2 microglobulin to creatinine ratio was observed at Week 8 (the first time point) and maintained through Week 48. Median (Q1, Q3) percentage changes from baseline at Weeks 24 and 48 were as follows:

- Week 24: −24.4% (−68.1%, 34.3%)
- Week 48: −26.6% (−43.4%, −0.9%)

No notable change in renal safety parameters was noted through week 48 in this virologically suppressed paediatric population.

2.6.8.4. ***Laboratory findings***

There were no clinically relevant changes from baseline for median values of haematology or clinical chemistry at Weeks 24 or 48. Median values were within the relevant reference ranges.

Most subjects (92.6%; 25 of 27) had at least 1 graded laboratory abnormality during the study through the data-cut date; for 24 of these 25 subjects the maximum toxicity was Grade 1 or 2. One subject, with a platelet count within the normal reference range at baseline, had a Grade 3 decrease in platelets at Week 24, which persisted at a lesser toxicity grade through Week 60. This was reported as a Grade 1 AE (thrombocytopenia) considered not related to study drug, ongoing at the data-cut date.

No subject met Hy's Law criteria, defined as concurrent increases in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN with alkaline phosphatase < 2 × ULN and no alternative aetiology.

Median (Q1, Q3) change from baseline in fasting glucose and lipid parameters at Weeks 24 and 48 are presented in the below Table 26.

Table 24 - GS-US-292-0106: Median (Q1, Q3) change from baseline in in fasting glucose and lipid parameters at weeks 24 and 48 (Safety analysis set, cohort 3)

	LD E/C/F/TAF (N = 27)		
Metabolic Assessment[a]	**n**	**Median**	**Q1, Q3**
Total Cholesterol (mg/dL)			
Baseline	25	166	155, 179
Change at Week 24	17	−3	−16, 8
Change at Week 48	23	−2	−15, 21
LDL Cholesterol (mg/dL)[b]			
Baseline	25	102	92, 125
Change at Week 24	17	−5	−21, 7
Change at Week 48	23	−9	−21, 2
HDL Cholesterol (mg/dL)			
Baseline	25	55	48, 64
Change at Week 24	15	1	−7, 10
Change at Week 48	23	1	−8, 10
Total Cholesterol to HDL Cholesterol Ratio			
Baseline	25	2.9	2.4, 3.4
Change at Week 24	15	−0.2	−0.5, −0.1
Change at Week 48	23	−0.2	−0.5, 0.4
Triglycerides (mg/dL)			
Baseline	25	91	64, 116
Change at Week 24	17	−26	−41, −11
Change at Week 48	23	−7	−41, 34
Glucose (mg/dL)			
Baseline	26	84	80, 88
Change at Week 24	21	−3	−11, 0
Change at Week 48	26	0	−8, 6

HDL = high-density lipoprotein; LDL = low-density lipoprotein
a Only measurements made under fasting status are summarized
b Samples analyzed by third generation assay were converted to second generation assay and pooled with samples analyzed by second generation assay. For conversion between second and third generation LDL assays: second generation (mmol/L) = (third generation − 0.0626)/0.882.

Graded abnormalities were reported for fasting total cholesterol (hypercholesterolemia, 36%, 9 of 25 subjects), fasting low-density lipoprotein (LDL)-cholesterol (increased, 12%, 3 of 25 subjects), and fasting glucose

(hyperglycaemia, 3.7%, 1 of 27 subjects). All graded fasting lipid and glucose abnormalities were Grade 1 (the majority) or Grade 2.

Vital signs

There have been no clinically relevant changes in any vital signs parameter reported in any subject in Cohort 3.

Tanner Stage

Tanner stages for genitalia in males and breasts in females at baseline and Weeks 24 and 48 were consistent with the paediatric study population ≥ 2 years of age weighing ≥ 14 to < 25 kg.

Body Weight

At baseline, the median (Q1, Q3) body weight was 19.3 (17.0, 20.5) kg, and the median (Q1, Q3) Z-score for weight was −0.88 (−1.72, −0.32).

There were no notable changes in body weight Z-score during the study. Changes in body weight Z-scores at Weeks 24 and 48 were as follows:

- Week 24: Mean (SD) 0.05 (0.269); median (Q1, Q3) 0.04 (−0.17, 0.28)
- Week 48: Mean (SD) 0.21 (0.313); median (Q1, Q3) 0.24 (0.01, 0.46)

Height

At baseline, the median (Q1, Q3) body height was 116.1 (106.0, 123.0) cm, and the median (Q1, Q3) Z-score for height was −0.28, (−1.42, 0.23).

There were no notable changes in body height Z-score during the study. Changes in body height Z-scores at Weeks 24 and 48 were as follows:

- Week 24: Mean (SD) −0.06 (0.379); median (Q1, Q3) −0.10 (−0.32, 0.23)
- Week 48: Mean (SD) 0.03 (0.558); median (Q1, Q3) 0.00 (−0.41, 0.33)

2.6.8.5. *Safety in special populations*

Palatability and Acceptability Assessments

Palatability and acceptability were assessed to confirm the appropriateness of the LD Genvoya tablets. Responses from subjects who had switched to the adult GEN tablet (E/C/F/TAF 150/150/200/10 mg) having attained a weight ≥ 25 kg (1 subject at Week 12; 2 subjects at Week 32) are excluded from assessments at Week 24 and/or Week 48, as applicable.

The majority of Cohort 3 subjects (≥ 2 years of age and weighing ≥ 14 to < 25 kg) had a neutral ("maybe good or maybe bad/could not taste it") or positive ("good" or "super good") palatability response to the GEN LD tablet (E/C/F/TAF 90/90/120/6 mg) at baseline (92.6%, 25 of 27 subjects), Week 24 (93.8%, 15 of 16 subjects), and Week 48 (91.7%, 22 of 24 subjects).

The majority of Cohort 3 subjects had a neutral or positive acceptability response at baseline and Weeks 24 and 48 for ease of swallowing, shape, and size of the GEN LD tablet when the tablet was swallowed whole.

There were some concerns on the acceptability of the tablet considering its size.

Overall the tablet was well taken and tolerated by all patients, irrespective of the age (some with the splitting of the tablet). Interestingly, with time, patients (even the younger ones) developed skills to take the whole tablet.

Data regarding acceptability of a similar size tablet of Biktarvy (B/F/TAF) also pointed to its tolerability in children ≥ 2 years of age and weighing ≥ 14 to < 25 kg.

A score line was added to the tablet to facilitate the process of splitting. On all occasions when the LDT was taken split, both halves were taken within 10 minutes. The information regarding the possibility to split the tablet is already included in section 4.2 of the SmPC. The SmPC has been updated to provide guidance that if the tablet is split both halves should be taken immediately.

Palatability was also assessed with a good or at least neutral response being reported by the vast majority of the patients. The data presented by the MAH regarding the acceptability/palatability studies for the younger paediatric population (new indication is for ≥ 2 years old, ≥ 14 kg) is acknowledged. The MAH does not recommend tablet chewing or crushing and mixing with food/liquids, mainly due to the poor palatability profile of TAF, as well as an anticipated lower TAF exposure following crushing of Genvoya LDT. Therefore, splitting the tablet in half is recommended as reflected in section 4.2 of the proposed SmPC.

Summary of long-term safety and efficacy in HIV-1 infected children and adolescents

Previous interim clinical study reports (CSRs) describing results for adolescents and children in Cohorts 1 and 2 receiving the adult-strength GEN tablet have included safety, efficacy, and PK data for all subjects in Cohort 1 through at least 96 weeks of treatment, and for Cohort 2 subjects through at least 96 weeks (subjects in Cohort 2 Part A) or 48 weeks (subjects in Cohort 2 Part B) of treatment.

The MAH submitted a long-term safety report that describes safety (with a particular focus on bone and renal safety) and efficacy results for adolescent and child subjects in Cohorts 1 and 2 receiving the adult-strength GEN tablet through median (Q1, Q3) exposures of 312.1 (132.7, 336.0) and 168.1 (156.4, 251.9) weeks, respectively.

Safety evaluation

Adverse events

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

Most subjects (96.0%, 48 of 50 subjects) had at least 1 AE. The majority of AEs were Grade 1 or 2 in severity; Grade 3 or 4 AEs were reported for 7 subjects (14.0%). Twenty-two subjects (44.0%) had an AE considered related to study drug. Nine subjects (18.0%) had an SAE and 1 subject (2.0%) had a study drug-related SAE. No subject had an AE that led to study drug discontinuation. One subject (2.0%) died during the study (road traffic accident).

The most commonly reported AEs in cohort 1 were as follows:

- Respiratory tract infection and upper respiratory tract infection (each 38.0%, 19 subjects)
- Nausea (30.0%, 15 subjects)

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

Most subjects (86.5%, 45 of 52 subjects) had at least 1 AE (Table 11). The majority of AEs were Grade 1 or 2 in severity; Grade 3 or 4 AEs were reported for 2 subjects (3.8%). Fourteen subjects (26.9%) had an AE considered related to study drug. Four subjects (7.7%) had SAEs, none of which was considered treatment-related. No subject had an AE that led to study drug discontinuation, and there were no deaths.

The most commonly reported AEs in cohort 2 were as follows:

- Upper respiratory tract infection (26.9%, 14 subjects)
- Vomiting (25.0%, 13 subjects)
- Abdominal pain (19.2%, 10 subjects)

Bone safety and Growth parameters

Fracture Events

In cohort 1, traumatic fracture events were reported for 2 subjects: a Grade 2 AE of hand fracture in 1 subject and Grade 3 SAEs of radius fracture and ulna fracture in 1 subject. No fracture was considered related to study drug.

In cohort 2 traumatic fracture events were reported for 3 subjects. Individual events of radius fracture, foot fracture, and hand fracture were reported. All were reported as Grade 1 AEs unrelated to study drug.

Bone Mineral Density

Percentage Change from Baseline in Spine and Total-Body-Less-Head Bone Mineral Density

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

Overall, spine and TBLH BMD increased relative to baseline through Week 336. At Weeks 96 and 288, respectively, mean (SD) percentage increases in spine BMD were 9.082% (8.3758%) and 31.823% (20.532%), and mean (SD) percentage increases in TBLH BMD were 3.552% (4.8549%) and 11.717% (8.9851%).

Spine

Overall, 5 of 47 subjects had a ≥ 4% decrease from baseline in spine BMD at some time point, 4 subjects at one time point and one at 2 time points (Section 8.1, Listing req13011.14). In only 1 subject was the ≥ 4% decrease in spine BMD accompanied by a shift in HA BMD Z-score from > −2 to ≤ −2.

TBLH

One subject had a ≥ 4% decrease in TBLH BMD, at Week 144, which was not accompanied by a shift in HA BMD Z-score from > −2 to ≤ −2.

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

Overall, spine and TBLH BMD increased relative to baseline through Week 240. At Weeks 96 and 192, respectively, mean (SD) percentage increases in spine BMD were 9.532% (10.8790%) and 28.041% (15.6760%), and mean (SD) percentage increases in TBLH BMD were 8.458% (6.6464%) and 18.073% (9.3998%).

Spine

Overall, 10 of 50 subjects (20%) had a ≥ 4% decrease from baseline in spine BMD at some time point. For 2 subjects such a decrease was noted only at Week 24. For the remaining 8 subjects, all enrolled at a single site, decreases ≥ 4% were generally observed at more than one time point. With 2 isolated and transient exceptions (HA BMD Z-scores of −2.01 and −2.48), these ≥ 4% decreases in spine BMD were not accompanied by a shift from > −2 to ≤ −2 in spine HA-BMD Z-score.

TBLH

Overall, 4 of 52 subjects (7.7%), all from the single site referred to above, had a ≥ 4% decrease from baseline in TBLH BMD at some time point. For 2 subjects the ≥ 4% decrease was noted only at Week 24, while for the remaining 2 subjects, decreases ≥ 4% were observed at more than one time point. With a single transient exception (HA BMD Z-score of −2.06) the ≥ 4% decreases in TBLH BMD were not accompanied by a shift from > −2 to ≤ −2 in TBLH HA BMD Z-score.

Change from Baseline in Bone Mineral Density Z-Scores

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

Spine

Baseline spine standard and HA BMD Z-scores and changes from baseline in each through Week 336 are shown in the below Table 27.

Table 25 - GS-US-292-0106: Spine standard and HA BMD Z-scores at baseline and change from Baseline – Cohort 1 (Spine DXA Analysis set)

	Spine BMD Z-Score (Standard)			Spine BMD Z-Score (HA)[a]		
	N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)
Baseline	47	−1.50 (1.719)	−1.30 (−2.21, −0.07)	41	−0.73 (1.369)	−0.54 (−1.86, 0.15)
Change from Baseline at Week 24	47	−0.08 (0.292)	−0.07 (−0.26, 0.15)	39	−0.05 (0.348)	−0.02 (−0.22, 0.13)
Change from Baseline at Week 48	47	−0.07 (0.370)	−0.02 (−0.30, 0.11)	36	0.00 (0.403)	−0.03 (−0.16, 0.20)
Change from Baseline at Week 96	46	0.01 (0.652)	0.10 (−0.43, 0.44)	33	0.12 (0.661)	0.14 (−0.22, 0.51)
Change from Baseline at Week 144	36	0.22 (0.897)	0.13 (−0.36, 0.67)	26	0.33 (0.721)	0.31 (−0.07, 0.93)
Change from Baseline at Week 192	33	0.37 (0.999)	0.40 (−0.36, 0.83)	25	0.39 (0.808)	0.50 (0.01, 0.92)
Change from Baseline at Week 240	32	0.56 (1.099)	0.49 (−0.32, 0.99)	22	0.71 (0.981)	0.63 (0.13, 1.33)
Change from Baseline at Week 288	30	0.74 (1.208)	0.51 (−0.17, 1.17)	16	1.02 (0.966)	0.81 (0.39, 1.47)
Change from Baseline at Week 336	13	0.96 (1.274)	0.65 (−0.03, 1.31)	6	1.18 (1.168)	0.74 (0.70, 1.05)

BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; HA = height-age; Q1 = first quartile; Q3 = third quartile
a Some subjects had missing HA Z-scores because their heights were outside the median height in the CDC growth chart, or their height-ages were outside the BMD reference data for Z-scores.

Total Body Less Head

Baseline TBLH standard and HA BMD Z-scores and changes from baseline in each through Week 336 are shown in Table 28.

Table 26 - GS-US-292-0106: TBLH standard and HA BMD Z-scores at baseline and change from Baseline – Cohort 1 (Spine DXA Analysis set)

	TBLH BMD Z-Score (Standard)			TBLH BMD Z-Score (HA)[a]		
	N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)
Baseline	45	−1.19 (1.154)	−1.07 (−1.79, −0.30)	39	−0.33 (1.021)	−0.50 (−1.12, 0.60)
Change from Baseline at Week 24	45	−0.11 (0.269)	−0.16 (−0.25, 0.02)	39	−0.11 (0.289)	−0.13 (−0.31, 0.11)
Change from Baseline at Week 48	44	−0.20 (0.276)	−0.24 (−0.38, −0.01)	36	−0.16 (0.300)	−0.09 (−0.33, 0.02)
Change from Baseline at Week 96	43	−0.20 (0.499)	−0.23 (−0.57, 0.12)	32	−0.12 (0.599)	−0.07 (−0.52, 0.17)
Change from Baseline at Week 144	33	−0.20 (0.687)	−0.28 (−0.59, 0.19)	25	−0.14 (0.654)	0.03 (−0.63, 0.21)
Change from Baseline at Week 192	30	−0.29 (0.772)	−0.38 (−0.73, 0.19)	24	−0.26 (0.728)	−0.02 (−0.71, 0.18)
Change from Baseline at Week 240	29	−0.19 (0.814)	−0.16 (−0.65, 0.34)	21	−0.17 (0.745)	0.06 (−0.62, 0.24)
Change from Baseline at Week 288	27	0.01 (0.849)	−0.05 (−0.38, 0.24)	15	0.00 (0.757)	0.05 (−0.41, 0.47)
Change from Baseline at Week 336	13	0.25 (1.049)	0.04 (−0.24, 0.73)	6	0.02 (0.736)	0.32 (0.13, 0.36)

BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; HA = height-age; Q1 = first quartile; Q3 = third quartile; TBLH = total body less head

a Some subjects had missing HA Z-scores because their heights were outside the median height in the CDC growth chart, or their height-ages were outside the BMD reference data for Z-scores.

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

Spine

Baseline spine standard and HA BMD Z-scores and changes from baseline in each through Week 240 are shown in the below Table 29.

Table 27 - GS-US-292-0106: Spine standard and HA BMD Z-scores at baseline and change from Baseline – Cohort 2 (Spine DXA Analysis set)

	Spine BMD Z-Score (Standard)			Spine BMD Z-Score (HA)[a]		
	N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)
Baseline	50	−0.70 (0.871)	−0.96 (−1.27, −0.26)	50	−0.44 (0.796)	−0.62 (−1.00, 0.22)
Change from Baseline at Week 24	50	−0.14 (0.402)	−0.16 (−0.49, 0.21)	50	−0.07 (0.410)	−0.15 (−0.44, 0.26)
Change from Baseline at Week 48	49	−0.24 (0.470)	−0.21 (−0.58, 0.01)	49	−0.13 (0.452)	−0.12 (−0.47, 0.16)
Change from Baseline at Week 96	43	−0.42 (0.686)	−0.41 (−0.93, 0.00)	42	−0.19 (0.729)	−0.20 (−0.71, 0.29)
Change from Baseline at Week 144	39	−0.57 (0.791)	−0.47 (−1.20, −0.15)	39	−0.17 (0.836)	−0.21 (−0.82, 0.29)
Change from Baseline at Week 192	17	−0.32 (0.724)	−0.38 (−0.72, 0.23)	17	0.31 (1.058)	0.35 (−0.21, 1.09)
Change from Baseline at Week 240	9	0.03 (0.696)	−0.27 (−0.57, 0.77)	6	0.95 (1.093)	1.02 (0.28, 1.58)

BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; HA = height-age; Q1 = first quartile; Q3 = third quartile
a Some subjects had missing HA Z-scores because their heights were outside the median height in the CDC growth chart, or their height-ages were outside the BMD reference data for Z-scores.

Total Body Less Head

Baseline TBLH standard and HA BMD Z-scores and changes from baseline in each through Week 240 are shown in the below Table 30.

Table 28 - GS-US-292-0106: TBLH standard and HA BMD Z-scores at baseline and change from Baseline – Cohort 2 (Spine DXA Analysis set)

	TBLH BMD Z-Score (Standard)			TBLH BMD Z-Score (HA)[a]		
	N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)
Baseline	52	−1.11 (0.890)	−1.27 (−1.74, −0.62)	52	−0.71 (0.857)	−0.83 (−1.19, −0.33)
Change from Baseline at Week 24	52	−0.15 (0.313)	−0.13 (−0.36, 0.02)	52	−0.09 (0.323)	−0.08 (−0.31, 0.03)
Change from Baseline at Week 48	51	−0.18 (0.386)	−0.19 (−0.41, 0.09)	51	−0.11 (0.344)	−0.08 (−0.41, 0.08)
Change from Baseline at Week 96	45	−0.34 (0.599)	−0.36 (−0.76, −0.03)	44	−0.24 (0.593)	−0.32 (−0.67, 0.11)
Change from Baseline at Week 144	41	−0.49 (0.646)	−0.47 (−1.01, −0.12)	41	−0.33 (0.634)	−0.42 (−0.77, 0.07)
Change from Baseline at Week 192	19	−0.63 (0.644)	−0.72 (−1.18, −0.27)	19	−0.38 (0.809)	−0.56 (−0.96, 0.14)
Change from Baseline at Week 240	10	−0.36 (0.671)	−0.59 (−0.77, 0.12)	10	0.21 (0.880)	0.39 (−0.29, 0.95)

BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; HA = height-age; Q1 = first quartile; Q3 = third quartile; TBLH = total body less head
a Some subjects had missing HA Z-scores because their heights were outside the median height in the CDC growth chart, or their height-ages were outside the BMD reference data for Z-scores.

From the provided long term bone safety data in 50 children aged 6-12 followed for up to 240 weeks there seems to be some loss of bone mineral density compared to baseline, which may be interpreted as progressive.

The MAH was asked to discuss the post baseline Z score development for bone mineral density in the 6-12 years old along with the methodological strength on evidence that there is a loss of BMD secondary to starting Genvoya, as well as what would be the clinical implications of the measured value:

Bone Safety

Exposure to TAF regimen in children aged 6 to 12 years resulted in a ≥ 4% decrease in spine BMD at one or more timepoints in 10 of 50 exposed patients but this was reversed throughout the subsequent timepoint assessments up to Week 240 in most of them. The applicant argues that this early BMD decrease results from the fact that patients have rich in metabolically active trabecular bone that would mostly be affected in the first weeks of exposure. Nine (9) participants experienced a shift (5 in spine and 7 in TBLH) in HA BMD Z-score from > −2 to ≤ −2 at any visit; 3 of these 9 participants shifted back to a Z-score > −2 at subsequent visits. Among the other 6, 5 increased their BMD values in spine and TBLH, and increased or maintained a stable HA BMD Z-score compared with baseline, although failing to increase BMD as it would be expected with growth. One participant experienced a bone fracture (following traumatic event) that the applicant considers unrelated to the study drug but for which we cannot for sure exclude causality (how would the bone behave if with normal mineralization?). PK assessments did not correlate TAF exposure to impact on BMD (maximum peak exposure does not correlate to higher impact on MBD).

For children aged 2 to 6 years old, despite the smaller sample size (n = 27) and shorter follow-up (only up to Week 48) the rate of mineralization was as expected for this age group, with spine HA BMD Z-scores improving from baseline (as expected with growth). Two participants (1 in spine and 1 in both spine and TBLH) showed a ≥ 4% decrease in BMD without a shift in spine HA BMD Z-score from > −2 to ≤ −2. Two further participants showed a shift in TBLH HA BMD Z-score from > −2 to ≤ −2 at Week 48 without a decrease in their absolute TBLH BMD. Height and weight Z-scores were stable or improved, and no participant experienced a bone-related AE. Longer exposure times are not expected to further affect bone mineral density as per results of patients treated with TDF-containing regimens, and considering also the stability/improvement seen in older cohorts following exposure to TAF-regiments.

The changes in BMD did not correlate with clinical outcomes (for fractures, apart from the above described case) nor biomarkers of bone formation or resorption.

Compared to TDF-containing regimens, patients exposed to TAF had lower impact on Bone mineralization as measured by DXA. A discussion on the lower PK exposures to TFV following TAF Vs TDF (where long terms outcomes are available), is also used to point to the long term safety profile of TAF containing regimens.

The MAH also presented data pointing to the benefit on BMD of the change from TDF-to TAF-containing regimens in adults that he believes would be similar for the paediatric population.

In conclusion, the concerns about the impact of TAF containing regiments on bone mineralization are considered to be addressed in children aged 6-<12 years old. The lack of longer follow-up period for the younger subset (2-<6 years of age) seems to be the most challenging aspect when looking at the available data. The MAH has addressed this topic by discussing the impact on bone mineralization with time for the older patients that overall showed a normalization of even improvement of BMD with longer periods of exposure to TAF containing regimens.

Spine and Total-Body-Less-Head Clinical Status

Clinical BMD status was assessed using HA BMD Z-scores.

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

No subject had a concurrent fracture history.

A shift in spine BMD HA Z-score from > −2 at baseline to ≤ −2 at some time point post-baseline was observed for 3 subjects. A shift in TBLH BMD HA Z-score from > −2 at baseline to ≤ −2 at some time point post-baseline was observed for 3 subjects.

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

No subject had a concurrent fracture history.

A shift in spine BMD HA Z-score from > −2 at baseline to ≤ −2 post-baseline was observed for 5 subjects. A shift in TBLH BMD HA Z-score from > −2 at baseline to ≤ −2 post-baseline was observed for 7 subjects.

Bone Laboratory Parameters

No clinical relevance was derived from the changes in any of the bone biomarkers (serum levels of parameters of bone resorption (collagen type I N-and C-terminal telopeptides) and bone formation (osteocalcin, bone-specific alkaline phosphatase, procollagen type I N-terminal propeptide), parathyroid hormone, 25-OH vitamin D, and 1,25-(OH)2 vitamin D) from baseline to 336 weeks.

Renal Safety

Renal Events

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

There were no AEs of renal tubulopathy (including Fanconi syndrome). As previously reported on the Interim 4 CSR, one subject with a prior history of urinary retention reported a Grade 2 SAE of urinary retention that resulted in hospitalization. The event was unrelated to study drug and resolved 6 days later.

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

There were no AEs of renal tubulopathy (including Fanconi syndrome). One subject reported a Grade 3 SAE of acute glomerulonephritis that resulted in hospitalization; the event was unrelated to study drug and resolved 30 days later. This event was preceded by an AE of pyrexia and was reported concurrently with an SAE of hypertension.

Renal Laboratory Parameters

Serum Creatinine

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

Median (Q1, Q3) baseline serum creatinine was 0.58 (0.50, 0.79) mg/dL. A gradual increase from baseline was observed from Week 1 that continued through at least Week 336. Median (Q1, Q3) changes from baseline at Weeks 48, 96, 192, 288, and 336 were as follows:

- Week 48 (N = 48): 0.07 (0.02, 0.15) mg/dL
- Week 96 (N = 46): 0.10 (0.05, 0.15) mg/dL

- Week 192 (N = 33): 0.13 (0.05, 0.24) mg/dL
- Week 288 (N = 31): 0.16 (0.11, 0.30) mg/dL
- Week 336 (N = 4): 0.28 (0.18, 0.33) mg/dL

Absolute serum creatinine values remained within normal reference ranges, and the gradual increase seen over several years is consistent with the physiological changes accompanying growth in adolescents.

No Grade 3 or 4 serum creatinine abnormalities were reported.

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

Median (Q1, Q3) baseline serum creatinine was 0.51 (0.45, 0.55) mg/dL. A gradual increase from baseline was observed at Week 4 that continued through Week 228. Median (Q1, Q3) changes from baseline at Weeks 48, 96, 192, and 228 were as follows:

- Week 48 (N = 51): 0.03 (−0.01, 0.07) mg/dL
- Week 96 (N = 45): 0.08 (0.01, 0.13) mg/dL
- Week 192 (N = 19): 0.10 (0.05, 0.21) mg/dL
- Week 228 (N = 19): 0.10 (0.05, 0.22) mg/dL

Absolute serum creatinine values remained within normal reference ranges, and the gradual increase seen over several years is consistent with the physiological changes accompanying growth in children.

No Grade 3 or 4 serum creatinine abnormalities were reported.

Estimated Glomerular Filtration Rate

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

Median (Q1, Q3) baseline eGFR calculated using the Schwartz formula was 156.0 (129.0, 185.0) mL/min/1.73 m^2. A decrease from baseline was observed from Week 1. Median (Q1, Q3) changes from baseline at Weeks 48, 96, 192, 288, and 336 were as follows:

- Week 48 (N = 48): −12.2 (−31.5, −1.0) mL/min/1.73 m^2
- Week 96 (N = 46): −19.5 (−34.6, −4.4) mL/min/1.73 m^2
- Week 192 (N = 33): −19.8 (−46.4, −6.0) mL/min/1.73 m^2
- Week 288 (N = 31): −31.0 (−59.0, −9.1) mL/min/1.73 m^2
- Week 336 (N = 4): −38.9 (−57.3, −26.3) mL/min/1.73 m^2

No clinical relevance was attached to this gradual decrease over a period of years given the high median (Q1, Q3) eGFR at both baseline (156.0 [129.0, 185.0] mL/min/1.73 m^2) and Week 288 (138.7 [120.1, 150.2] mL/min/1.73 m^2) for subjects in this cohort during a transition from adolescence to early adulthood.

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

Median (Q1, Q3) baseline eGFR calculated using the Schwartz formula was 150.3 (137.8, 165.1) mL/min/1.73 m^2. A decrease from baseline was observed at Week 1 that remained stable through Week 228. Median (Q1, Q3) changes from baseline at Weeks 48, 96, 192, and 228 were as follows:

- Week 48 (N = 51): 0.2 (−14.3, 14.9) mL/min/1.73 m^2
- Week 96 (N = 45): −2.2 (−20.8, 16.7) mL/min/1.73 m^2
- Week 192 (N = 19): −2.4 (−17.2, 21.1) mL/min/1.73 m^2
- Week 228 (N = 19): −2.9 (−13.9, 14.9) mL/min/1.73 m^2

Laboratory Evaluations

Clinical Laboratory Abnormalities

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

Grade 3 or 4 laboratory abnormalities were observed for 30.0% (15 of 50) of subjects. Grade 3 laboratory abnormalities reported with greater than single subject incidence were as follows:

- Urine red blood cells (RBCs) (20.0%, 10 of 50 subjects; all female)
- Neutrophils decreased (8.0%, 4 of 50 subjects)
- Aspartate aminotransferase (AST) increased (4.0%, 2 of 50 subjects)

Grade 4 laboratory abnormalities reported were as follows:

- Creatine kinase increased (6.0%, 3 of 50 subjects)

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

Grade 3 or 4 laboratory abnormalities were observed for 34.6% (18 of 52) of subjects. Grade 3 laboratory abnormalities reported with greater than single subject incidence were as follows:

- Neutrophils decreased (15.4%, 8 of 52 subjects)
- Urine RBCs (13.5%, 7 of 52 subjects; all female)

The reported Grade 4 laboratory abnormalities were as follows:

- Serum potassium (hyperkalemia; 1.9%, 1 of 52 subjects)
- Neutrophils decreased (1.9%, 1 of 52 subjects)

No notable change to the safety profile of Genvoya was identified in the continued evaluation of safety in the extension phase in both cohorts (median duration of exposure for cohort 1: 312.1 weeks; median duration of exposure for cohort 2: 168.1 weeks).

Regarding bone safety only a few subjects experienced a clinically relevant shift from baseline in BMD while spine and TBLH HA BMD Z-scores were not significantly changed from baseline through the data-cut date.

After initial changes from baseline in serum creatinine and eGFR, the following changes were consistent with physiological changes associated with growth. Changes over the long-term in eGFR were within normal ranges of variability and not considered clinically relevant.

Impact of TFV on kidneys/renal function

There were no renal AEs nor documented impact on serum creatinine nor eGFR in children 6years and older. Again considering adult data the impact of TAF vs TDF containing regimens in renal function is significantly lower.

Data for children 2-<6 years is scarce and only up to W48 of exposure but in line with what is reported for older patients. Considering that the impact on renal function is mostly in the first weeks of exposure, this is considered to be adequately covered with no need for age or weight base restrictions.

Clarifications have been provided on the number of patients having eGFR falling below 70 mL/min/1.73 m^2 and below 90 mL/min/1.73 m^2 throughout the study. All those patients had transient decreases of eGFR and the only case of eGFR value < 70 mL/min/1.73 m^2 (single value at Week 96) was not considered related to study drug, and fully recovered without suspension of the study treatment.

Clarification has been made confirming that no cases of infraclinical renal tubulopathy were identified in any participant in any cohort of Study GS-US-292-0106.

Ocular toxicity of TAF-containing products

Clarifications have been provided on the reported AE with a discussion on the possible causality to TAF-containing products exposure which seems of low probability. A discussion on the ocular substudy is also made which results led to a removal of this concern as an important potential risk from the EU-RMPs for TAF-containing products as agreed with the CHMP.

Potential risk "increased cholesterol and triglycerides with associated cardiovascular events" linked to exposure to TAF-containing medicines and long-term exposure of paediatric patients to these medicines

Considerations have been made regarding the possible impact of this treatment regimen on lipid profile. The conclusions seem reassuring of the safety profile. It is acknowledged that, again, the time of exposure/follow-up period regarding paediatric patients age 2-<6years of age is still significantly lower but this is not seen at this point as problematic considering the time of exposure – effect seen in older patients.

The MAH has conducted a review of BMD data for children ≥ 2 to < 6 years of age receiving TAF-based treatment in Study GS-US-292-0106 and compared the data with BMD information available in the literature for children 2 to 6 years of age. Mean TBLH and spine BMD values obtained at baseline in Cohort 3 participants (≥ 2 years of age weighing ≥ 14 to < 25 kg) were similar to those in other populations of children with HIV of the same age band, and similar or less than the values reported for different groups of healthy children in age groups that reflect the range of ages of children enrolled in Cohort 3. However, skeletal gains shown by increases in BMD after 1 year on E/C/F/TAF in Cohort 3 were comparable to the difference in BMD observed in healthy children in the same age group in a 1-year interval.

2.6.8.6. ***Safety related to drug-drug interactions and other interactions***

No relevant data on this topic could be retrieved from the currently evaluated trial.

2.6.8.7. ***Discontinuation due to adverse events***

No subject discontinued study drug or the study due to an AE through the data cut-off date.

2.6.8.8. ***Post marketing experience***

No post-marketing data are included in this submission.

2.6.9. Discussion on clinical safety

In Cohort 3, i.e. in children aged ≥2 years to <6 years weighting ≥14 kg to <25 kg (n=27), the most commonly reported AEs were upper respiratory tract infection, cough and decreased appetite and vomiting. The overall types of common AEs were consistent with those expected in the study population. Most AEs reported were grade 1 in severity. No Grade 3 or 4 AE and deaths have been reported. No subjects discontinued the study due to AE in this cohort. An SAE (pneumonia, not related to study drug) was reported for 1 subject. There were no AEs of renal tubulopathy (including Fanconi syndrome) or traumatic bone fracture.

AEs related to study drug were reported for 4 subjects, among which only diarrhoea and vomiting, reported for 2 subjects each, occurred with greater than single subject incidence.

No safety issue was identified regarding laboratory abnormalities. Serum creatinine values remained stable through Week 48; Median (Q1, Q3) changes from baseline at Weeks 24 and 48 were 0.00 (−0.05, 0.04) mg/dL and −0.01 (−0.04, 0.04) mg/dL, respectively. Regarding eGFR Schwartz, an increase from baseline was observed at Week 1 that remained relatively stable through Week 48. Median (Q1, Q3) changes from baseline at Weeks 24 and 48 were 4.1 (−13.8, 26.8) mL/min/1.73 m^2 and 9.6 (−11.2, 19.3) mL/min/1.73 m^2.

There were mean increases in both spine and TBLH BMD through Week 48 (spine: Week 24, 3.094%; Week 48, 5.275%; TBLH: Week 24, 3.816%; Week 48, 7.160%). Two subjects had a ≥ 4% decrease in spine and/or TBLH BMD during the study, neither of whom had a clinical shift in their height-age BMD Z-score from > −2 to ≤ −2. Overall, no subject showed a worsening (change from > −2 to ≤ −2) from baseline in spine height-age BMD Z-score at Weeks 24 and 48, while 2 subjects showed such a worsening in TBLH height-age BMD Z-score at Week 48.

Switching to E/C/F/TAF appeared to be well tolerated by virologically suppressed paediatric subjects ≥ 2 years of age (weighing ≥ 14 kg to < 25 kg). However, safety data have been gathered in a very limited number of patients (n=27) and for a median duration of exposure of 48.3 weeks.

All issues raised during the assessment were adequately discussed and are generally considered resolved.

Following a request for further data the MAH has has provided additional data to accommodate for the concerns raised on the comparability of BMD in the youngest age group cohort of children aged 2 to 6 years, to BMD in healthy children aged 2 to 6 years. Apart from the recognized decreased reproducibility of BMD assessment in children younger than 3 years, which is already acknowledged in paediatric guidelines, some methodological limitations were reported that could interfere with interpretability of the data, namely a) the cross-sectional design of the studies in healthy children; b) the fact that studies in healthy children assessed populations of different ethnicities and different ages and c) the fact that different DXA machines and software differ among studies.

The MAH conclusions on the gathered data points to the similarity of mean TBLH and spine BMD values obtained at baseline in Cohort 3 participants to those in children with HIV of the same age band, and similar or less than those of different groups of healthy children in age groups that reflect the range of ages of children enrolled in Cohort 3. Skeletal gains shown by increases in BMD after 1 year on E/C/F/TAF in Cohort 3 were comparable to the difference in BMD observed in healthy children in the same age group in a 1-year interval.

The MAH was asked to address the fact that some uncertainties remain in children concerning the impact of long-term exposure to tenofovir delivered by TAF on the growing bone in terms of fracture risk associated with renal toxicity even if the impact is lower than with TDF-containing products. Also the fact that renal and bone safety data are very limited quantitatively in the 2-6-years-old children was also asked to be discussed.

A new set of data has been provided by the MAH namely from study GS-US-311-1269 were participants received Descovy (F/TAF) were grouped into 2 cohorts (Cohort 1: virologically suppressed adolescents 12 to < 18 years of age weighing ≥ 35 kg; Cohort 2 Group 1: virologically suppressed children 6 to < 12 years of age weighing ≥ 25 kg; Cohort 2 Group 2: virologically suppressed children 2 to < 6 years weighing 17 to < 25 kg). Comparing the results the CHMP considered that:

a) BMD at baseline was similar to children with HIV but lower compared to healthy children which is as expected considering the impact of chronic HIV infection on bone health

b) Changes in BMD did occur in children treated with TAF containing regimens. These changes were more significant in the 2-6 years old cohort. Other possible causes of poor bone health were not possible to be controlled and might have affected the results.

c) Bone mineralization in the spine and TBLH was comparable in TAF treated with impaired BMD compared to healthy children.

d) When occurring, the negative changes in BMD occur early with treatment with a trend for normalization with time.

e) No fractures were described within the study timeframe and, as the negative consequences on BMD seem to improve with time.

Comparing the results of Cohort 2 of the study GS-US-292-0106 and Cohort 2 Group 1 of the study GS-US-311-1269, both concerning virologically suppressed children 6 to < 12 years of age weighing ≥ 25 kg, several aspects have not been fully addressed by the MAH:

a) TBLH BMD (g/cm^2) and Percentage Change from Baseline by Visit; Spine BMD (g/cm^2) and Percentage Change from Baseline by Visit - having the similar baseline values there are significant differences in subsequent visits assessment;

b) Spine BMD Height-age Adjusted Z-score and Change from Baseline by Visit - the trend in the evolution is different with much earlier improvement in study study GS-US-311-1269 compared to GS-US-292-0106.

c) The Percentage of Participants with at ≥ 4% Decline from Baseline in TBLH/Spine BMD by Visit is also different among the cohorts.

Overall, the CHMP was of the opinion that existing uncertainties should be managed with appropriate wording in the SmPC:

Section 4.4

Paediatric population

Reductions in BMD (≥4%) of the spine and total-body-less-head (TBLH) have been reported in patients aged between 3 to <12 years receiving Genvoya for 48 weeks in study GS-US- 292-0106 (see sections 4.8 and 5.1). The long-term effects of changes in BMD on the growing bone, including the risk of fracture, are uncertain. A multidisciplinary approach is recommended to decide the appropriate monitoring during treatment.

Section 4.8

Paediatric population

The safety of Genvoya was evaluated through 48 weeks in HIV 1 infected adolescent patients aged 12 to < 18 years weighing ≥ 35 kg (n=100), in children aged 7 to < 12 years weighing ≥ 25 kg (n = 52), and in children aged 3 to 9 years and weighing ≥ 14 to < 25 kg (n = 27). The safety profile in paediatric patients who received treatment with Genvoya was similar to that in adults. After 48 weeks of treatment with Genvoya, reductions in BMD of the spine and of the TBLH ≥ 4% have been reported in 2.1% (1/47) and 0.0% of adolescents, in 12.2% (6/49) and 3.9% (2/51) of children weighing at least 25 kg, and in 3.7% (1/27) and 0.0% of children aged at least 2 years and weighing 14 kg respectively.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The overall safety profile of LD Genvoya in children ≥ 2 years of age (weighing ≥ 14 kg to < 25 kg) was not significantly different from the already known safety profile of standard dose Genvoya. However, safety data have been gathered in a very limited number of patients (n=27) and for a median duration of exposure of 48.3 weeks.

No notable change to the safety profile of Genvoya was identified in the continued evaluation of safety in the extension phase in both cohorts (median duration of exposure for cohort 1: 312.1 weeks; median duration of exposure for cohort 2: 168.1 weeks).

Regarding bone safety only a few subjects experienced a clinically relevant shift from baseline in BMD while spine and TBLH HA BMD Z-scores were not significantly changed from baseline through the data-cut date.

After initial changes from baseline in serum creatinine and eGFR, the following changes were consistent with physiological changes associated with growth. Changes over the long-term in eGFR were within normal ranges of variability and not considered clinically relevant.

In light of the limitations in long-term data on the effects of tenofovir on bone and renal health in paediatric patients, and furthermore the scarcity of data in the 2–6-year-olds, a warning in section 4.4 of the SmPC was added along with a description of the decrease in BMD observed with Genvoya in section 4.8.

In addition to the precautionary statement concerning the bone and renal safety in children 2- < 6 years of age, these events shall be monitored in upcoming PSURs. Furthermore, as treatment with INSTIs or TAF may be associated with weight increase, it is considered critical to closely monitor this also for the paediatric population.

In terms of renal toxicity, and considering the assessment performed during this procedure, it is currently difficult to identify, in the renal function parameters as presented for Cohort 3, changes over time that are of concern. However, for some of the normative ranges of reference for these parameters (e.g. RBP) are not available in the paediatric population and the interpretation of the ratios to urine creatinine is not always straightforward, adding more uncertainty. The discussion on whether TFV levels after the proposed doses of TAF for each age/weight band cohort are associated to renal toxicity cannot be based on a simple discussion (as provided by the MAH) of data of each of these parameters in isolation and for each of the paediatric cohorts per each study.

In what refers to renal and bone toxicity, the SmPC of Genvoya (and of the other medicinal products containing tenofovir alafenamide) will be subject to further revisions/amendments when more data becomes available (including, but not limited to, data from study -0128, Cohort 3, Cohort 4 and any other cohort as available, from study -1474, Cohort 4 and also including paediatric subjects treated with TAF for chronic hepatitis B in study -1092).

The MAH committed to submitting an updated popPK-PD (renal and bone endpoints) report at the time of the next paediatric regulatory submission which considers the above. The next anticipated submission is the final CSR for GS-US-292-0106 in Q2 2024. Final CSRs for all paediatric studies where TAF-containing products have been evaluated presenting and discussing the totality of the PK, safety, and efficacy data for all age cohorts/weight bands will be submitted when all studies are completed will be submitted to the respective MAs when available.

Current expected final CSR dates for the paediatric studies of Gilead's TAF-containing products are listed below:

Study GS-US-380-1474, LPLV Dec-24, Submission of CSR Jun-25

Study GS-US-216-0128, LPLV Mar-26, Submission of CSR Sep-26

Study GS-US-292-0106, LPLV Dec-23, Submission of CSR Jun-24

Study GS-US-311-1269, LPLV Dec-23, Submission of CSR Jun-24

Study GS-US-320-1092, LPLV Oct-29, Submission of CSR Apr-30

Study GS-US-292-0106 is currently in the extension phase and will continue to enable paediatric participants to receive Genvoya until such a point as an access program is available. The final CSR is therefore expected to be available for submission Q2 2024.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important Identified Risks	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness (EVG)
Important Potential Risks	Concurrent Use of Drugs whose Coadministration with Genvoya is Contraindicated (EVG, COBI)
Missing Information	Long-term safety information in children between the ages of ≥ 2 and < 6 years (GEN)
	Safety in pregnancy and lactation (EVG, COBI, FTC, TAF)
	Safety in patients with cardiac conduction disorders (COBI)

2.7.2. Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Antiretroviral Pregnancy Registry (APR) Non-interventional study Ongoing	To collect information on the risk of birth defects in patients exposed to GEN during pregnancy	*Missing information:* Safety in pregnancy	Submission of interim reports	In the GEN PSUR (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)

2.7.3. Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Routine risk minimization activities	Pharmacovigilance Activities
Important Identified Risks		
Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness (EVG)	Routine risk communication: SmPC Section 4.8 PL Section 4	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Important Potential Risks		
Concurrent use of drugs whose coadministration with Genvoya is contraindicated (EVG, COBI)	Routine risk communication: SmPC Section 4.3 and 4.5 PL Section 2	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Missing Information		
Long-term safety information in children between the ages of ≥ 2 and < 6 years (GEN)	Routine risk communication: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Safety in pregnancy and lactation (EVG, COBI, FTC, TDF)	Routine risk communication: SmPC Section 4.6 PL Section 2	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry
Safety in patients with cardiac conduction disorders (COBI)	No routine risk minimization measures are considered necessary for this population.	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None

2.7.4. Conclusion

The CHMP considered that the risk management plan version 6.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on the new indication in patients aged ⩾ 2 years weighing ⩾ 14 kg and considering that efficacy and safety data in this age group were collected in a very limited number of patients and for a short median duration of exposure, the PRAC is of the opinion that the already existing entry in the EURD list for cobicistat / elvitegravir / emtricitabine / tenofovir alafenamide needs to be amended as follows: the PSUR cycle for the medicinal product should follow a half-yearly cycle. The next data lock point will be 4 November 2022.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Genvoya 150 mg/150 mg/200 mg/10 mg film-coated tablets. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

HIV-1 infection continues to have a significant global burden with approximately 38 million people infected worldwide, including an estimated 1.8 million children under 15 years of age. There were an estimated 1.7 million newly acquired cases of HIV infection worldwide in 2019, of which 150,000 (9% of the total) were in children under 15 years of age, principally (84%) in sub-Saharan Africa. There were, additionally, an estimated 95,000 AIDS-related deaths worldwide in children under 15 years of age.

3.1.2. Available therapies and unmet medical need

Other INSTI-based ARV indicated in paediatric subjects are as follows:

- Dolutegravir (Tivicay): available as dispersible tablets and film-coated tablets, indicated in children ≥ 4 weeks of age and weighing ≥ 3 kg.

- Raltegravir (Isentress): available as granules for oral suspension and chewable tablets, indicated in children weighing ≥ 3 kg.

Four other single-tablet regimens (STRs) are currently approved in the EU for once daily administration in the treatment of HIV-1 infection in adolescents (≥12 years old): EVG/COBI/FTC/ TDF (Stribild),

abacavir/dolutegravir/lamivudine (Triumeq), FTC/ RPV/TAF (Odefsey), and DRV/COBI/FTC/TAF (Symtuza). Genvoya is the only once daily STR approved in children.

3.1.3. Main clinical studies

Study GS-US-292-0106 is a Phase 2/3 study initially designed to characterize the PK and confirm the dose of the adult GEN tablet (E/C/F/TAF 150/150/200/10 mg) in ART-naive, HIV-1 infected adolescents ≥ 12 to < 18 years of age (Cohort 1) and virologically suppressed, HIV-1 infected children ≥ 6 to < 12 years of age weighing ≥ 25 kg (Cohort 2). The study was extended in Protocol Amendment 4 to characterize the PK and confirm the dose of a low-dose (LD) GEN tablet (E/C/F/TAF 90/90/120/6 mg) in virologically suppressed, HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg enrolled in an additional cohort, Cohort 3. The safety, tolerability, and antiviral activity of the adult and LD GEN tablets were also evaluated in the cohorts to which they were administered.

3.2. Favourable effects

For Cohort 3, at Week 48, high rates of virologic suppression (>90%) were maintained in these virologically-suppressed paediatric subjects, and CD4 cell counts remained stable. No subject had treatment-emergent resistance to study drug. Although the efficacy data from this paediatric study were not primary endpoints, these data could be considered supportive.

Week 48 data for cohorts 1 and 2 were previously submitted. The MAH submitted additional long term results from the extension phase of study GS-US-292-0106. Virologic suppression and an accompanying immunologic response were maintained in both cohorts through the data-cut date (336 weeks for cohort 1 and 240 weeks for cohort 2).

3.3. Uncertainties and limitations about favourable effects

The interpretation of the efficacy results is limited by the design of the study (non-comparative, limited sample size).

Cohort 1 included ARV-naïve subjects while cohorts 2 and 3 included only virologically suppressed subjects. All subjects had stable disease and the relevance of the efficacy results to patient with more advanced disease is unknown.

3.4. Unfavourable effects

The analysis of safety data (GS-US-292-0106) has shown that the overall safety profile of Genvoya (adult dose and low dose) in the paediatric population seems comparable to the safety of Genvoya in adults.

Safety data have been gathered in 50 children ≥ 12 to < 18 years of age weighing ≥ 35 kg, 52 children ≥ 6 to < 12 years of age weighing ≥ 25 kg and 27 children ≥ 2 years of age weighing ≥ 14 to < 25 kg). The most commonly reported AEs were respiratory tract infection and upper respiratory tract infection, cough, abdominal pain, decreased appetite and vomiting consistent with those expected in the study population. Most AE were grade 1 and 2. One death was reported in cohort 1 (road traffic accident). One subject in cohort 1 had a study drug-related SAE. No grade 3 / 4 AE have been considered as related to E/C/F/TAF. Initial increases in serum creatinine and decreases in eGFR Schwartz were observed in cohorts 1 and 2, consistent with the known effect

of cobicistat on renal tubular secretion. Both renal safety parameters subsequently stabilize as observed in the provided results from the analysis of the extension phase. Among Cohort 3 subjects receiving the GEN LD (E/C/F/TAF 90/90/120/6 mg) tablet, however, the effects on serum creatinine and eGFR were not observed, the possibility being that they were masked by the increase in eGFR that occurs with kidney maturation in childhood. Regarding bone safety only a few subjects experienced a clinically relevant shift from baseline in BMD while spine and TBLH HA BMD Z-scores were not significantly changed from baseline through the data-cut date. Overall no new safety issue has been identified.

3.5. Uncertainties and limitations about unfavourable effects

Safety data have been gathered in a limited number of children. Safety data is available for a longer exposure in cohorts 1 and 2 than for cohort 3 (median duration of exposure for cohort 1: 312.1 weeks; median duration of exposure for cohort 2: 168.1 weeks; median duration of exposure for cohort 3: 48.3 weeks).

The MAH has provided long term bone safety data in 50 children aged 6-12 followed for up to 240 weeks. There seems to be some loss of bone mineral density compared to baseline, which may be interpreted as progressive. The MAH was asked to discuss the post baseline Z score development for bone mineral density in the 6-12 years old and the methodological strength on evidence that there is a loss of BMD secondary to starting Genvoya, as well as what would be the clinical implications of the measured values.

- **Bone Safety and growth**

Exposure to TAF regimen in children aged 6 to 12 years resulted in a ≥ 4% decrease in spine BMD at one or more timepoints in 10 of 50 exposed patients but this was reversed throughout the subsequent timepoint assessments up to Week 240 in most of them. The applicant argues that this early BMD decrease results from the fact that patients have rich in metabolically active trabecular bone that would mostly be affected in the first weeks of exposure. Nine (9) participants experienced a shift (5 in spine and 7 in TBLH) in HA BMD Z score from > −2 to ≤ −2 at any visit; 3 of these 9 participants shifted back to a Z-score > −2 at subsequent visits. Among the other 6, 5 increased their BMD values in spine and TBLH, and increased or maintained a stable HA BMD Z-score compared with baseline, although failing to increase BMD as it would be expected with growth. One participant experienced a bone fracture (following traumatic event) that the applicant considers unrelated to the study drug but for which causality could not be excluded. PK assessments did not correlate TAF exposure to impact on BMD (maximum peak exposure does not correlate to higher impact on MBD).

For children aged 2 to 6years old, despite the smaller sample size (n = 27) and shorter follow-up (only up to Week 48) the rate of mineralization was as expected for this age group, with spine HA BMD Z-scores improving from baseline (as expected with growth). Two participants (1 in spine and 1 in both spine and TBLH) showed a ≥ 4% decrease in BMD without a shift in spine HA BMD Z-score from > −2 to ≤ −2. Two further participants showed a shift in TBLH HA BMD Z-score from > −2 to ≤ −2 at Week 48 without a decrease in their absolute TBLH BMD. Height and weight Z-scores were stable or improved, and no participant experienced a bone-related AE. Longer exposure times are not expected to further affect bone mineral density as per results of patients treated with TDF-containing regimens, and considering also the stability/improvement seen in older cohorts following exposure to TAF-regiments.

The changes in BMD did not correlate with clinical outcomes (for fractures, apart from the above described case) nor biomarkers of bone formation or resorption.

Compared to TDF-containing regimens, patients exposed to TAF had lower impact on Bone mineralization as measured by DXA. A discussion on the lower PK exposures to TFV following TAF Vs TDF (where long terms outcomes are available), is also used to point to the long term safety profile of TAF containing regimens.

The MAH also presented data pointing to the benefit on BMD of the change from TDF-to TAF-containing regimens in adults that he believes would be similar for the paediatric population.

The concerns about the impact of TAF containing regiments on bone mineralization seem to be well addressed in children aged 6-<12 years old. The lack of longer follow-up period for the younger subset (2-<6 years of age) seems to be the most challenging aspect when looking at the available data. The MAH has addressed this topic by discussing the impact on bone mineralization with time for the older patients, that overall showed a normalization of even improvement of BMD with longer periods of exposure to TAF containing regimens.

- **Impact of TFV on kidneys/renal function**

There were no renal AEs nor documented impact on serum creatinine nor eGFR in children 6years and older. Again, considering adult data the impact of TAF vs TDF containing regimens in renal function is significantly lower. Data for children 2-<6 years is scarce and only up to W48 of exposure but in line with what is reported for older patients.

Clarifications have been provided on the number of patients having eGFR falling below 70 mL/min/1.73 m2 and below 90 mL/min/1.73 m^2 throughout the study. All those patients had transient decreases of eGFR and the only case of eGFR value < 70 mL/min/1.73 m^2 (single value at Week 96) was not considered related to study drug, and fully recovered without suspension of the study treatment.

No cases of infraclinical renal tubulopathy were identified in any participant in any cohort of Study GS-US-292-0106. Despite the clarifications provided, the available data, though scarce and fraught with uncertainty, do seem to indicate an impact of BMD after initiating TAF, and therefore a certain level of risk cannot be excluded. Whether the potential magnitude of this, is acceptable or not, may be considered in relation to the benefits of the drug in the paediatric population, and may be determined by the prescriber on a case-by-case basis.

In light of the limitations in long-term data on the effects of tenofovir on bone and renal health in paediatric patients, and furthermore the scarcity of data in the 2–6-year-olds, a warning in section 4.4 of the SmPC was added along with a description of the decrease in BMD observed with Genvoya in section 4.8.

In addition to the precautionary statement concerning the bone and renal safety in children 2- < 6 years of age, these events shall be monitored in upcoming PSURs. Furthermore, as treatment with INSTIs or TAF may be associated with weight increase, it is considered critical to closely monitor this also for the paediatric population.

In terms of renal toxicity, and considering the assessment performed during this procedure, it is currently difficult to identify, in the renal function parameters as presented for Cohort 3, changes over time that are of concern. However, for some of the normative ranges of reference for these parameters (e.g. RBP) are not available in the paediatric population and the interpretation of the ratios to urine creatinine is not always straightforward, adding more uncertainty. The discussion on whether TFV levels after the proposed doses of TAF for each age/weight band cohort are associated to renal toxicity cannot be based on a simple discussion

(as provided by the MAH) of data of each of these parameters in isolation and for each of the paediatric cohorts per each study.

In what refers to renal and bone toxicity, the SmPC of Genvoya (and of the other medicinal products containing tenofovir alafenamide) will be subject to further revisions/amendments when more data becomes available (including, but not limited to, data from study -0128, Cohort 3, Cohort 4 and any other cohort as available, from study -1474, Cohort 4 and also including paediatric subjects treated with TAF for chronic hepatitis B in study -1092).

The MAH committed to submitting an updated popPK-PD (renal and bone endpoints) report at the time of the next paediatric regulatory submission which considers the above. An updated popPK-PD (renal and bone endpoints) report will be submitted at the next appropriate paediatric regulatory submission for Gilead's TAF-containing products. The next anticipated submission is the final CSR for GS-US-292-0106 in Q2 2024. Final CSRs for all paediatric studies where TAF-containing products have been evaluated presenting and discussing the totality of the PK, safety, and efficacy data for all age cohorts/weight bands will be submitted when all studies are completed will be submitted to the respective MAs when available.

Current expected final CSR dates for the paediatric studies of Gilead's TAF-containing products are listed below:

Study GS-US-380-1474, LPLV Dec-24, Submission of CSR Jun-25

Study GS-US-216-0128, LPLV Mar-26, Submission of CSR Sep-26

Study GS-US-292-0106, LPLV Dec-23, Submission of CSR Jun-24

Study GS-US-311-1269, LPLV Dec-23, Submission of CSR Jun-24

Study GS-US-320-1092, LPLV Oct-29, Submission of CSR Apr-30

Study GS-US-292-0106 is currently in the extension phase and will continue to enable paediatric participants to receive Genvoya until such a point as an access program is available. The final CSR is therefore expected to be available for submission Q2 2024.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The efficacy data observed in either cohort of study GS-US-292-0106 and the efficacy data from adult populations is reassuring of a similar antiviral activity and virological suppression with the proposed weight-doses of Genvoya.

3.6.2. Balance of benefits and risks

The proposed doses of the combination of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in paediatric subjects are expected to be as effective as in adults. Regarding safety, the analysis of the continued evaluation of subjects in cohorts 1 and 2 did not show any clinically relevant change from the previously known safety profile, specifically in what regards bone and renal safety.

The existing restriction of the indication in 6-12 years old is due to the impact of tenofovir on bone turnover secondary to its effect on renal calcium and phosphate handling. Exposure to tenofovir in this age stratum is higher than in adults, where the safety of tenofovir alafenamide was established.

The available data, though scarce and limited with uncertainty, indicate an impact of BMD after initiating TAF, and therefore a certain level of risk cannot be excluded. Whether the potential magnitude of this, is acceptable or not, may be considered in relation to the benefits of the product in the paediatric population, and may be determined by the prescriber on a multidisciplinary approach basis.

These data and concerns were therefore reflected in the product information. In light of the limitations in long-term data on the effects of tenofovir on bone and renal health in paediatric patients, and furthermore the scarcity of data in the 2–6-year-olds group, a warning in section 4.4 of the SmPC was added along with a description of the decrease in BMD observed with Genvoya in section 4.8. These events should be monitored in upcoming PSURS. Further, as treatment with INSTIs or TAF may be associated with weight increase, it is considered key to closely monitor this also for the paediatric population.

The CHMP also considered that the PSUR cycle will be changed to a 6-monthly interval to allow for increased monitoring.

3.7. Conclusions

The overall benefit/risk balance of Genvoya is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP by consensus that the benefit-risk balance of, Genvoya 90 mg/ 90 mg/ 120 mg/ 6 mg is favourable in the following indication:

- Genvoya is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir in adults and paediatric patients aged from 2 years and with body weight at least 14 kg.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Genvoya subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0435/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of human immunodeficiency virus 1 (HIV 1) infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir in paediatric patients aged from 2 years and with body weight at least 14 kg. Sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the Package Leaflet are updated to support the extended indication. The RMP (version 6.0) is updated in accordance.