9 November 2017
EMA/776917/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Genvoya

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

Procedure No. EMEA/H/C/004042/II/0026

Note

Variation 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
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ART	antiretroviral therapy
ARV	antiretroviral
AUC	area under the plasma/serum concentration versus time curve
AUCtau	area under serum concentration versus time curve over the dosing interval
BMD	bone mineral density
Cmax	maximum observed plasma/serum concentration of drug
Ctau	observed drug concentration at the end of the dosing interval
CD	cluster determinant
CDC	Centers for Disease Control and Prevention
COBI; C	cobicistat
CSR	clinical study report
DHHS	Department for Health and Human Services
eGFR	estimated glomerular filtration rate
EVG; E	elvitegravir (Vitekta)
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC; F	emtricitabine (Emtriva)
GEN	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF; co-formulated; Genvoya)
Gilead	Gilead Sciences
HIV-1	human immunodeficiency virus type 1
IC95	95% inhibitory concentration
INSTI	integrase strand-transfer inhibitor
m	Module
M = E	missing = excluded
M = F	missing = failure
N or n	number of subjects in a population (N) or subset (n)
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
P1NP	procollagen type 1 N terminal propeptide

PI/r	ritonavir-boosted protease inhibitor
PK	pharmacokinetic(s)
Q1, Q3	first quartile, third quartile
RBP	retinol binding protein
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
TAF	tenofovir alafenamide
TBLH	total-body-less-head
TDF	tenofovir disoproxil fumarate (TDF, Viread®)
TFV	tenofovir
UPCR	urine protein to creatinine ratio
US, USA	United States, United States of America

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences International Ltd submitted to the European Medicines Agency on 7 December 2016 an application for a variation.

The following variation was requested:

Variation 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 paediatric patients from 6 years of age to less than 12 years of age, with body weight of at least 25kg, infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir, for Genvoya. As a consequence, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated based on the analysis of the paediatric study GS-US-292-0106 (Cohort 2). This is a Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment Naive Adolescents and Virologically Suppressed Children.

The Package Leaflet and the Risk Management Plan (v. 3) are updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0195/2015 on the agreement of a paediatric investigation plan (PIP) the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0195/2015 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Robert James Hemmings

Timetable	Actual dates
Submission date	7 December 2016
Start of procedure:	24 December 2016
CHMP Rapporteur Assessment Report	27 January 2017
PRAC Rapporteur Assessment Report	24 February 2017
PRAC members comments	1 March 2017
Updated PRAC Rapporteur Assessment Report	2 March 2017
PRAC Outcome	9 March 2017
CHMP members comments	13 March 2017
Updated CHMP Assessment Report	15 March 2017
Request for supplementary information	23 March 2017
Submission date	19 May 2017
Start of procedure:	22 May 2017
CHMP Rapporteur Assessment Report	15 June 2017
PRAC Rapporteur Assessment Report	19 June 2017
PRAC members comments	28 June 2017
Updated PRAC Rapporteur Assessment Report	29 June 2017
PRAC Outcome	6 July 2017
CHMP members comments	12 July 2017
Updated CHMP Assessment Report	13 July 2017
2nd Request for supplementary information	20 July 2017
Submission date	10 October
Re-start of procedure:	11 October 2017
PRAC Rapporteur Assessment Report	n/a
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	25 October 2017
PRAC Outcome	n/a
CHMP members comments	30 October 2017
Updated CHMP Assessment Report	3 November 2017
Opinion	9 November 2017

2. Scientific discussion

2.1. Introduction

Genvoya (and hence TAF, EVG and COBI when presented as components of this FDC) is currently approved for use in adults and adolescents from 12 years and 35 kg.

The new data in this dossier concern the clinical safety, efficacy and PK of Genvoya when given to children aged from 8-<12 years. The initial dossier did not include an overview or summary of existing nonclinical data of possible relevance to the use of Genvoya in children aged 6-<12 years. A summary of relevant nonclinical information has been subsequently provided to support the use of E/C/F/TAF to treat HIV-1 infection in 6 year olds weighing more than 25 kg.

2.2. Non-clinical aspects

2.2.1. Introduction

In the original marketing application for Genvoya any juvenile toxicity and reproductive toxicity data that were available of potential relevance to children aged 6-<12 years would not have been considered since the application was for use in adults. This was extended during the procedure to adolescents based on available clinical data. Initially, the MAH has not provided a comprehensive review and integrated nonclinical risk assessment for use of Genvoya in children aged 6-<12 years at the proposed dose. Relevant nonclinical findings in adult and juvenile animals were provided during the evaluation.

2.2.2. Toxicology

Toxicological findings of TFV in SIV efficacy models

Investigators from the California Regional Primate Research Centre have reported results of antiviral efficacy studies of TFV in simian immunodeficiency virus (SIV)-infected and non-infected rhesus monkeys.

Table 1. Nonclinical Pharmacology/Toxicology Studies with TFV

API / route	Age at start of treatment[a]	Dose (mg/kg/day)	Duration of daily treatment	Reference
Tenofovir/SC/n=12	Gestation Day 80; Infants Day 2	30	Gestation Days 80-157 (n=12); Infants: up to 9 months (n=9)	[1787]
Tenofovir/SC/n=54	1 day to 20 months	4, 10, 30	Up to 12 weeks (n=39) At least 8 months (n=13) At least 5 years (n=2)	[7311]
Tenofovir/SC/n=32[b]	1 day to 33 months	1.25 to 30	1 year to 13 years	[12968]

SC = subcutaneous

a A general comparison of growth phases between human and rhesus monkeys is as follows [17656]: Infant: Human = 1-24 months; Rhesus = 1-12 months Child/Juvenile: Human = 2-11 years; Rhesus = 1-2 years; Adolescent: Human = 12-16/18 years Rhesus = 2-4 years

b 15 animals previously reported in Van Rompay 2004, but observations extended.

[1787] Tarantal A, Marthas ML, Shaw J-P, Cundy KC, Bischofberger N. Administration of 9-[2-(R)(phosphonomethoxy)propyl]adenine (PMPA) to gravid and infant rhesus macaques (*Macaca mulatta*): safety and efficacy studies. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999;20 (4):323-33

[7311] Van Rompay KKA, Brignolo LL, Meyer DJ, Jerome C, Tarara R, Spinner A, et al. Biological effects of short-term or prolonged administration of 9-[2- (phosphonomethoxy)propyl]adenine (tenofovir) to newborn and infant rhesus macaques. *Antimicrob Agents Chemother* 2004;48 (5):1469-87

[12968] Van Rompay KKA D-GL, Brignolo LL, et al. Chronic administration of tenofovir to rhesus macaques from infancy through adulthood and pregnancy: summary of pharmacokinetics and biological and virological effects. *Antimicrob Agents Chemother* 2008;52 (9):3144-60

Study 1787 included administration of TFV to 12 gravid rhesus macaques and to more than 85 infant and juvenile rhesus macaques from 1 day to 7.5 years of age at initiation of dosing. This age range covers the human equivalent of prenatal, infant, juvenile and adolescent phases of growth. The duration of treatment ranged from 12 weeks to 13 years. Clinically relevant renal and bone pathology occurred only in rhesus monkeys in which TFV was chronically administered at 30 mg/kg/day by daily subcutaneous injection. Exposure levels (AUC_{ss} 140 µg·h/mL) at this dose were more than 30-fold higher than those in adults (4.4 µg·h/mL) after 300 mg/day TDF. Effects in rhesus monkeys were reversible by decreasing or stopping exposure. Administration of lower doses of TFV did not cause renal dysfunction or abnormal bone density or growth.

Studies were conducted to assess the safety, efficacy and placental transfer of TFV when administered once daily subcutaneously to gravid rhesus monkeys during the second and third trimesters and to their offspring (30 mg/kg/day). Foetuses (SIV-infected, N = 6; non-infected; N = 6) were monitored sonographically and maternal/fetal blood samples were collected at selected time points for haematology, clinical chemistry, virology, immunology and pharmacology assessments. Newborns were delivered by caesarean section at term and nursery reared for postnatal studies. Infants were administered TFV once daily beginning on Day 2 of life until 9 months postnatal age. Results showed significant placental transport of TFV, with peak fetal levels at 1 to 3 hours post-maternal administration, significant and sustained reductions in viral load in SIV-infected foetuses and infants and marked improvements in outcome (survival, growth, health) in SIV-infected offspring.

However, decreased infant body weights and alterations of select serum biochemical parameters (e.g. decreased phosphorus levels, elevated ALP) have been shown to occur in 67% of TFV-treated infants, with severe growth restriction and bone-related toxicity in approximately 25% of animals studied. These data suggest that there is the potential for bone-related toxicity at chronic high dosages, particularly in infants.

In Study 12968, daily subcutaneous doses of TFV at 10 mg/kg/day were given to 2 newborn rhesus monkeys for more than 5 years. No observed adverse effect on their bone density or growth was seen. The steady state AUC for these 2 rhesus monkeys was approximately 19 µg·h/mL (~4.3-fold exposure in adult human populations). Although data were variable, no drug-related changes occurred in the urinary excretion of phosphorus, calcium, potassium, protein, magnesium or chloride. Radiographs and DXA scans of the animals were collected regularly from birth to 5 years of age. There was no radiological evidence of decreased bone opacity, changes in growth plates, bone formation, or bone resorption compared to controls. Bone biopsies at 3.5 years of age showed no significant differences in bone structure measurements.

In study 7311, subcutaneous administration of TFV from 4 to 30 mg/kg/day to 39 infant rhesus monkeys for up to 3 months had no observed adverse effect on health or growth. No proximal renal tubular dysfunction (PRTD) or growth restriction or bone abnormalities were observed after 12 weeks of dosing or at 3.5 months to 14 months after the end of treatment.

However, in another study subcutaneous administration of TFV at 30 mg/kg/day to 13 rhesus monkeys for at least 8 months resulted in PRTD with glycosuria, aminoaciduria, hypophosphataemia, growth restriction, osteomalacia and reduced clearance of TFV. Bone lesions were only observed in animals that also had PRTD.

The long bone metaphyses and the physes and metaphyses of the vertebral bodies were incompletely ossified and there was overall decreased bone opacity. In 4 of the more severely affected animals, there were bone deformations and/or pathological fractures in the long bones or ribs. Serum phosphorus levels were markedly decreased and bone-ALP isoenzyme levels were increased. Urine samples collected by cystocentesis generally showed increased glucose and amino acid levels.

Pharmacokinetic data collected after 11 to 24 months of TFV administration from 4 of the rhesus monkeys with moderate to severe bone disease had a mean AUC of 140 µg·h/mL (range 101 to 222 µg·h/mL), more than 30-fold that in adult subjects. The adverse effects were partially or totally reversible following either complete withdrawal of TFV or reduction of the daily regimen from 30 mg/kg/day to 2.5 or 10 mg/kg/day.

In another study (26057) 13 rhesus monkeys chronically treated with TFV at 30 mg/kg/day. Six animals were killed. A reduction in TFV dose (n = 6), or discontinuation of dosing (n = 1) occurred as a result. In the animals killed there were severe skeletal lesions. Bone histology revealed irregular hyperplastic growth plates and trabecular hyperplasia with widened osteoid seams. In the animal with severe bone disease and in which administration of TFV was discontinued, the serum phosphorus and ALP concentrations returned to normal in about 6 and 8 months, and the metaphyseal osteopenia resolved by 18 months. For the other 6 animals whose TFV dosage was decreased to either 30 mg/kg twice weekly (n = 1) or 10 mg/kg once daily (n = 5), there was improvement in serum phosphorus levels and radiological bone opacity, and a resumption of growth within approximately 6 months.

Van Rompay *et al*. (study 7311) extended their observations and reported on the longer-term safety and pharmacokinetics of TFV in 32 infant and juvenile rhesus monkeys. As reported earlier, the primary toxicity of prolonged subcutaneous TFV administration was PRTD, characterised by glycosuria, decreased serum phosphorus and increased serum ALP levels. The effect of daily subcutaneous administration of TFV at 10 to 30 mg/kg/day for 7 weeks to 25 months was described for 29 animals.

Seven animals given 10 to 30 mg/kg/day TFV had minimal to no evidence of persistent PRTD which was associated with a relatively high TFV clearance. Twenty two animals with relatively reduced TFV clearance had evidence of PRTD based on urine and serum markers. Five of these animals dosed at 10 to 30 mg/kg/day with PRTD had DXA scans performed. DXA confirmed low BMD in 3/5 with growth retardation and severe bone lesions. Two animals with PRTD that had their doses reduced and dietary supplements provided had normal BMD or reduced BMD. Animals that received low-dose regimens of TFV and had no persistent PRTD had relatively normal BMD.

Juvenile Toxicity

Elvitegravir

In a GLP-compliant developmental perinatal/postnatal reproduction toxicity study that included a postnatal behavioural evaluation and a 28-day juvenile toxicity evaluation, EVG was orally administered to parental generation (F0) female Crl:CD(SD) rats (25 rats per group) at 0 (0.5% MC), 300, 1000, and 2000 mg/kg/day from GD7 through Day 20 of lactation (LD 20) or GD 24 (rats that did not deliver a litter) at a dose volume of 10 mL/kg. F1 generation rats (10 rats/sex/group) assigned to the juvenile toxicity evaluation study were orally administered EVG from Day 1 of study, (DS 1, Day 22 postpartum)

through DS 28 (Day 49 postpartum) at dosages of 0 (0.5% MC), 300, 1000, and 2000 mg/kg/day in a dose volume of 10 mL/kg.

Male and female rats assigned to the main portion of the juvenile toxicity evaluation were killed on DS 29 (Day 50 postpartum). Assessment of toxicity was based on mortality, clinical signs, body weight, food consumption, clinical and anatomic pathology.

There were no test article-related effects on body weights, body weight gains and absolute and relative feed consumption. There were no effects on haematology, coagulation and clinical chemistry parameters in both sexes. Weights of the caecum (with contents) and ratios of this weight to terminal body weight and brain weight were increased in males at 2000 mg/kg/day and in females at 1000 and 2000 mg/kg/day; however, these increases were not statistically significant. No microscopic lesions observed in either sex.

There was an overall dose-related exposure on DS 1 and 28 for the F1 generation male and female juvenile rats to EVG and metabolite GS-9200. Low levels of the metabolite GS-9202 were observed. In general, exposure increased with dose, in a less than dose-proportional manner for EVG and GS-9200 on both study days. Female rats tended to have higher EVG exposure on DS 28 than on DS 1. There did not appear to be any accumulation of EVG in male rats on DS 28. Based on the DS 1 and DS 28 exposures, there did not appear to be any accumulation of GS-9200 and GS-9202 in males and females.

The NOAEL was considered to be 2000 mg/kg/day for juvenile male and female rats (Day 28 AUC0-t:169 µg·h/mL).

Table 2. Mean Toxicokinetic Parameters of EVG in Juvenile Rats Following Mean Toxicokinetic Parameters of EVG in Juvenile Rats Following Daily Oral Gavage Administration of EVG for 28 Days

EVG (mg/kg/day)	Day	AUC_{0-t} (µg·h/mL)		C_{max} (µg/mL)	
		Male	Female	Male	Female
300	1	52.6	57.5	12.8	11.0
	28	37.4	51.7	10.9	22.6
1000	1	99.4	130	19.0	21.7
	28	79.1	122	19.3	28.3
2000	1	128	134	19.1	19.1
	28	144	194	31.5	31.4

Table 3. Mean Toxicokinetic Parameters of GS-9200 in Juvenile Rats Following Daily Oral Gavage Administration of EVG for 28 Days

EVG (mg/kg/day)	Day	AUC_{0-t} (µg·h/mL)		C_{max} (µg/mL)	
		Male	Female	Male	Female
300	1	212	191	43.8	39.5
	28	7.60	6.05	2.08	2.52
1000	1	224	317	45.7	66.3
	28	13.5	15.7	2.77	3.41
2000	1	845	699	157	1551
	28	20.8	19.4	4.61	3.25

Table 4. Mean Toxicokinetic Parameters of GS-9202 in Juvenile Rats Following Daily Oral Gavage Administration of EVG for 28 Days

EVG (mg/kg/day)	Day	AUC_{0-t} (µg·h/mL)		C_{max} (µg/mL)	
		Male	Female	Male	Female
300	1	0.879	0.838	0.268	0.241
	28	BLQ	BLQ	BLQ	BLQ
1000	1	1.37	2.43	0.637	0.797
	28	0.0223	BLQ	0.089	BLQ
2000	1	2.09	1.37	0.396	0.211
	28	0.174	0.0737	0.0743	0.0377

COBI

In the development and peri-natal/postnatal reproduction phase of the study (Study number: TX-216-2033), including a postnatal behavioural/functional evaluation, daily oral gavage administration of COBI resulted in lower body weights and food consumption at 75 mg/kg/day during gestation and lactation**,** however there were no effects on maternal performance. In the untreated offspring (F1 generation), there were no effects on survival, growth, physical and behavioural development, reflex responses, visual function, gross pathology or reproductive parameters. Based on these results, the NOAEL for maternal toxicity for the F0 generation was considered to be 30 mg/kg/day, and the NOAEL for the reproduction in the dams and viability, growth, and development of the offspring was considered to be 75 mg/kg/day (Maternal PND 10: Cmax and AUC0-t: 1.9 µg/mL and 9.9 µg.h/mL, respectively).

In the juvenile toxicity phase of the study, daily oral gavage administration of COBI to F1 generation pups from PND 22 to 49 resulted in slight decreases in body weight and food consumption, non-adverse clinical chemistry changes, and adaptive changes in liver and thyroid. Based on these results, the NOAEL for the juvenile males and females was considered to be 75 mg/kg/day (PND 49 Cmax and AUC0-t: 3.2 and 3.1 µg/mL, and 20.6 and 21.2 µg.h/mL, in males and females, respectively).

Table 5. Mean toxicokinetic parameters of COBI in juvenile rats following daily oral doses of COBI

Dose Level (mg/kg/day)	Sex	AUC_{0-t} (µg.h/mL)		C_{max} (µg/mL)	
		PND 22	PND 49	PND 22	PND 49
10	Male	0.3	0.3	0.1	0.1
	Female	0.5	1.8	0.2	0.3
30	Male	9.1	5.0	1.7	1.1
	Female	6.5	8.5	1.7	1.9
75	Male	32.1	20.6	3.7	3.2
	Female	18.6	21.2	3.1	3.1

PND: post-natal dose

TAF / TFV

No specific juvenile toxicity studies have been conducted with TAF or TDF, however data are available from efficacy studies of TFV in SIV-infected and non-infected rhesus macaques (Tarantal 1999, Van

Rompay 2004, Van Rompay 2008). These studies included 12 gravid rhesus macaques, and more than 85 infant and juvenile rhesus macaques treated from ages ranging from 1 day to 7.5 years at initiation of dosing. This age range covers the human equivalent of prenatal, infant, juvenile and adolescent phases of growth. The duration of treatment ranged from 12 weeks to 13 years.

Clinically relevant renal and bone pathology (including reduced bone mineral density, joint swellings, and bone fractures) occurred in animals in which TFV was chronically administered at 30 mg/kg/day by daily subcutaneous injection. Exposure levels (TFV AUC 150 µg·h/ml) at this dose were more than 564-fold higher than those of adults after a 25 mg dose of TAF (30-fold higher than those of adults subjects after a 300 mg/day dose of TDF). Effects in rhesus monkeys were reversible by decreasing or stopping exposure. Administration of lower doses of TFV (10 mg/kg/day, ~15 µg·h/ml) did not cause renal dysfunction or abnormal bone density or growth.

When administered to newborn or infant rhesus monkeys at 4 to 30 mg/kg/day TFV did not cause adverse effects in short term studies (up to 12 weeks). However, prolonged TFV treatment (generally more than 4 months of daily treatment at 30 mg/kg/day administered subcutaneously) resulted in a Fanconi-like syndrome with glycosuria, aminoaciduria, hypophosphatemia, growth restriction, and bone pathology (osteomalacia) {Van Rompay 2004}. Clinical, biochemical, and radiographic resolution/improvement occurred with dose reduction (from 30 to ≤ 10 mg/kg/day) or discontinuation of treatment.

Three animals (1 SIV-infected) were dosed chronically, beginning as neonates, at 10 mg/kg/day subcutaneously. After more than 5 years of treatment, there were no clinical, radiographic, or dual-emission X-ray absorptiometry scan {Van Rompay 2004} findings of an adverse effect on bone. The mean AUC associated with this dosage (18 µg·h/mL) 68-fold greater than the human AUCss following a 25 mg/day dose of TAF.

E/C/F/TAF

There were no notable findings in the juvenile toxicity studies with EVG or with COBI. Although TDF and COBI have produced effects in reproductive toxicity studies, effects on rat fetuses have been observed at doses associated with significant maternal toxicity. Neither compound has shown an effect on rabbit fetuses. For all four agents, EVG, COBI, FTC and TDF, NOELs and NOAELs have been clearly identified and were at exposures above human exposures. No additive effects are anticipated with the four drug combination. No specific studies were conducted with the E/C/F/TAF FDC.

Exposure Margins at NOAEL

Exposure margins were calculated based upon PK derived from administration of GEN (E/C/F/TAF 150/150/200/10 mg) to 23 HIV-infected paediatric subjects (8 to < 12 years of age and weighing ≥ 25 kg in Study GS-US-292-0106 (Cohort 2 Part A)), 24 weeks of treatment. For Study GS-US-292-0106, EVG, COBI, FTC, TAF, and TFV exposures in subjects 6 to < 12 years of age were compared with exposures in adult subjects in Phase 2 and/or Phase 3 populations. Exposures (AUC, Cmax, and/or Ctau) of EVG, COBI, FTC, TAF, and TFV, except EVG Ctau, upon administration of GEN to HIV-infected children were modestly higher (20%-80%) as compared with exposures achieved in adults. The mean EVG Ctau, although lower in this paediatric population versus adult reference comparator values, was > 8-fold above the IC95 for wild-type virus (44.5 ng/mL). TFV AUCtau (440.2 ng•hr/mL) was markedly lower as compared to adult exposures derived from administration of TDF 300 mg (Gilead Sciences Inc 2016a, Gilead Sciences Inc 2016b). The exposures of all analytes were within the efficacious and safe exposure ranges established in the GEN and Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) adult programs.

COBI

Table 6. Estimated Exposure Margins for COBI 150 mg Based on AUC at Animal No-Adverse-Effect-Level (NOAEL)

Species Gender	Study Type	NOAEL Dose (mg/kg/day)	AUC_{0-t} (µg•h/mL)	Exposure Margin[a]
Mouse				
Male - Female	13-week Toxicity	5 - 50	0.93 – 60.1	0.06 – 3.8
Rat				
Male - Female	26-week Toxicity	30	9.9 – 13.3	0.62 – 0.84
Rat + 1000 mg/kg EVG				
Male - Female	13-week Combination Toxicity	30	5.2 – 7.5	0.33 – 0.47
Rat + 50 mg/kg ATV				
Male - Female	13-week Combination Toxicity	30	6.1 – 6.3	0.38 – 0.40
Dog				
Male - Female	39-week Toxicity	10	19.6 – 16.8	1.2 – 1.1

ATV, atazanavir; COBI, cobicistat; EVG, elvitegravir; NOAEL, no observed adverse effect level a Human AUCtau 15.9 µg•h/mL (GEN MAA, 0041, m5.3.5.2, GS-US-292-0106 Interim 3 CSR. n = 20

The MAH states that while the exposure margins are not large, effects above the NOAELs were minimal and some effects were species-specific. At doses above the NOAEL in male mice, liver changes (transaminase elevations and minimal hepatocellular hypertrophy) were observed; female mice were notably less sensitive. In rats, notable effects were limited to decreased body weight gain and food consumption, with slight changes in hematology, clinical chemistry, and urinalysis parameters, and adaptive liver and thyroid changes. In dogs, salivation and emesis, decreased body weight gain and food consumption, slight changes in some clinical chemistry parameters, and minimal adaptive changes in the liver were noted above the NOAEL.

FTC

Table 7. Estimated Exposure Margins of Emtricitabine Based on AUCss When Comparing Animal No-Effect-Level (NOEL)

Target Organ Effect	Species	Study Duration	NOEL (mg/kg/day) FTC	AUC_{ss} (µg·h/mL) NOEL	Margin Relative to Human AUC_{ss}[a]
Anemia	Mouse	6 months	500	350	17
	Rat	3 months	600	346	17
	Monkey	1 year	200	98	5

a Human AUCtau (20.6 µg·h/mL) following a 200 mg/day dose of FTC (GEN MAA, 0041, m5.3.5.2, GS-US-292-0106 Interim 3 CSR

TAF / TFV

Table 8. Estimated Exposure Margins of TAF Based on AUCss When Comparing Animal No-Adverse-Effect-Level (NOAEL)

Target Organ Effect	Species	Study/Dose Duration	TAF NOAEL (mg/kg/day)	AUC_{ss} (µg·h/mL) NOAEL	Margin Relative to Human AUC_{ss}
				TFV/TAF	TFV[a]/TAF[b]
Nasal Turbinate Toxicity	Mouse	13 Weeks	< 10	< 0.213/NC	< 0.5/NC
Renal Toxicity	Rat	26 weeks	25	3.8/NC	9/NC
	Dog	39 weeks	2	1.2/0.08	3/0.2
	Monkey	4-weeks	≥ 30	≥ 5.9/1.0	≥ 13/3
Bone Mineral Loss	Rat	26 weeks	25	3.8/NC	9/NC
	Dog	39 weeks	2	1.2/0.08	3/0.2
	Monkey	4-weeks	≥ 30	≥ 5.9/1.0	≥ 13/3
Fertility[c]	Rat	Up to 10 weeks	160	NA	NA
Embryo fetal development[c]	Rat	12 days	84	17.4/0.2	40/0.6
	Rabbit	14 days	100	27.3/11	62/33
Perinatal/postnatal[c]	Rat	27 days (Gestation day 7 to Lactation day 20)	150 (TDF)	7.84/NA	18/NA

NA = not applicable; NC = insufficient data to calculate. a Predicted exposure margin for TFV human exposure is based on GEN MAA, 0041, m5.3.5.2, GS-US-292-0106 Interim 3 CSR, AUCss = 0.440 µg.h/mL; n= 23
b Predicted exposure margin for TAF human exposure is based on GEN MAA, 0041, m5.3.5.2, GS-US-292-0106 Interim 3 CSR. AUCss = 0.333 µg.h/mL; n= 23
c NOAEL for reproductive endpoints provided; AUC data is for maternal exposure; the peri/postnatal study was conducted with TDF not TAF.

Dog was the most sensitive species to renal and bone effects of TAF. The NOEL for renal effects in monkeys is greater than 30 mg/kg/day. The rat and dog showed some loss of bone mineral density at relatively high doses. Clinically relevant bone pathology (osteomalacia) was documented in rhesus monkeys (only) in which TFV was chronically administered at 30 mg/kg by daily subcutaneous injection to infant and juvenile monkeys at exposure levels (AUCss 150 µg•h/mL) that were more than 650-fold higher than those of adult subjects administered E/C/F/TAF (0.230 µg•h/mL) and 340-fold higher than HIV-1 infected subjects 6 to < 12 years old administered E/C/F/TAF (0.440 µg•h/mL).

MAH conclusions

Elvitegravir and FTC have established clinical safety profiles with no significant toxicities observed. No clinically relevant changes have been observed in PR interval and liver toxicity, potential toxicities related to COBI. Minor anaemia changes related to FTC and COBI administration were identified at doses with large multiples of clinical exposure; therefore, these haematological findings were not considered relevant to clinical use and should not cause overlapping toxicity.

Tenofovir disoproxil fumarate (TDF), also a prodrug of TFV, bone and kidney are target organs for TFV, TDF, and TAF, and although the mechanisms of action are not known, the activity is likely related to TFV exposure. At the FDC TAF dose of 10 mg, TFV levels are reduced by 90% in subjects receiving E/C/F/TAF compared to E/C/F/TDF. The lower systemic levels of TFV and the higher intracellular levels of TFV-DP translate into less risk of nephrotoxicity and reduced bone mineral density loss, which are known risks with TDF administration.

In Phase 3 studies with E/C/F/TAF (GEN MAA, 0000, m5.3.5.1, GS-US-292-0102), compared to E/C/F/TDF, the mean percent decrease in BMD was lower in the E/C/F/TAF group and there was no evidence of nephrotoxicity.

Data are available from efficacy studies of TFV in SIV-infected and non-infected rhesus Macaques have previously been discussed – see above.

With respect to signs of mitochondrial toxicity, it is noted that the related clinical manifestation of lipodystrophy has been frequently observed with the thymidine analogs d4T and AZT, however is not typically associated with the cytosine analogue FTC. TAF is unlikely to cause any mitochondrial toxicity. TAF did not affect the amount of mitochondrial DNA levels up to 1 µM (approximately 3-fold higher than Cmax in 6 to < 12 year olds), the highest concentration tested, in HepG2 cells in a 10-day assay (GEN MAA, 0000, m4.2.1.1, PC-120-2006). The active form of TAF, TFV-DP is highly discriminated as a substrate by mitochondrial DNA polymerase γ relative to the natural substrate, ATP (> 10,000-fold). Therefore, TAF is unlikely to inhibit mitochondrial DNA polymerase γ under clinically relevant conditions.

EVG, FTC, TAF and COBI have not shown significant adverse effects in reproductive and developmental toxicity studies. 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, with adaptive liver and thyroid changes observed at similar dose levels and exposures to adult animals. The NOAEL for toxicity of COBI is 75 mg/kg/day for juvenile rats where exposure on PND 49 (20.9 µg.h/mL) was 1.3-fold higher than therapeutic human exposures at the 150 mg dose in HIV-1 infected subjects 6 to < 12 years old administered E/C/F/TAF.

No specific cause for concern has been identified in genotoxicity and carcinogenicity studies with the individual agents. The combination of the 4 components is not expected to have an altered genotoxicity profile as compared with that of the individual agents. Because of the non-genotoxic nature of TAF, and the lack of pre-neoplastic lesions in chronic studies performed in rats and dogs with TAF, and achievable TFV exposure in mice and rats less than previously tested in chronic and carcinogenicity studies with TDF, the CHMP agreed that additional carcinogenicity studies in mice and rats with TAF were not warranted as they would not add to the overall risk evaluation or risk management of TAF. The CHMP confirmed that the 'overall evidence suggests that carcinogenicity of GS-7340 is not expected to be a major risk, in particular since human exposure will also be low. It was agreed that the conduct of rodent carcinogenicity studies will not add knowledge to the already existing evidence and are therefore not needed (EMA/CHMP/SAWP/629722/2012, Procedure No: EMEA/H/SA/2410/1/2012/I).

While the immune system in humans is not considered to be fully developed until 12 years of age (Doc. Ref. EMEA/CHMP/SWP/169215/2005), there have been no findings in nonclinical (including adolescent animals) or clinical studies to suggest any adverse effects on the immune system of children below 12. Additional testing in animals would be unlikely to provide clinically relevant insights regarding immunotoxicity.

2.2.3. Ecotoxicity/environmental risk assessment

The EMA guideline on the ERA states that "the evaluation of the environmental impact should be made if there is an increase in the environmental exposure, e.g. a new indication may result in a significant increase in the extent of the use." The MAH provided a justification for not providing an updated ERA within this application. The potential use of Genvoya in children aged 6-12 years of age is not considered to significantly impact the sales volume. The predicted increase in sales volume for children ages 6-12 would be less than 0.5%.

The Phase II calculations presented in these ERAs used predicted sales figures that took into consideration the forecasted use of FTC, COBI, EVG and TAF for the treatment of HIV-1 infection across the European Union (EU) economic area. As detailed in the ERAs, the highest Risk Quotient (RQ) is for EVG in fish (0.0004), therefore an increase in sales for Genvoya of 2500 times would be needed to pose an unacceptable risk.

Given the predicted increase in sales volume (less than 0.5%) for this age group and the forecasted numbers use for FTC, COBI, EVG and TAF in the original submissions, the CHMP considered that the current ERAs remain applicable for this variation. The current ERAs are therefore considered applicable to the current Type II variation application.

2.2.4. Discussion on non-clinical aspects

Suitable margins of exposure fold cover exist for the findings seen in the chronic non-human primate studies. The conclusions of the MAH are agreed. There is now a large clinical (both adult and paediatric) safety data set on which the safety of Genvoya is based for the proposed patient population. In addition the toxicology data support the proposed patient population.

Sections 4.6 and 5.3 of the SmPC are acceptable.

2.2.5. Conclusion on the non-clinical aspects

There are no objections from a non-clinical point of view in regard to this extension of the indication in children form 6-12 years of age. Sections 4.6 and 5.3 of the SmPC are acceptable.

Based on the predicted increase in sales volume (less than 0.5%) for this age group, the extended indication does not lead to a significant increase in environmental exposure further to the use of FTC, COBI, EVG and TAF. Considering the above data, FTC, COBI, EVG and TAF is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

GS-US-292-0106 was 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.

Table 9. Tabular overview of clinical studies

Study number	Objectives	Study design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects
GS-US-292-0106	Cohort 2 Part A: To evaluate PK of EVG, COBI, FTC, TFV, and TAF To evaluate safety and tolerability of GEN	Phase 2/3, open-label, multicenter, multicohort, 2-part, single-group study to	Single tablet of GEN (E/C/F/TAF, 150/150/200/10 mg) taken orally once daily with food	48 weeks Extension phase will be offered to participants until subject turns 18 and GEN is	23 subjects

Study number	Objectives	Study design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects
	through Weeks 24 and 48 To evaluate antiviral activity of switching to GEN in virologically suppressed HIV-infected pediatric subjects	evaluate the PK, safety, tolerability, and antiviral activity of GEN		commercially available	

2.3.2. Pharmacokinetics

GS-US-292-0106

Study 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-Naive Adolescents and Virologically Suppressed Children

Please refer to section 2.4.for a complete description of study GS-US-292-0106, including the dose regimen and dosing conditions.

This section reports the PK data from Cohort 2 Part A only.

An intensive PK evaluation was performed at Week 4 for patients enrolled in Cohort 2 Part A. Blood samples were collected pre-dose (0 hours), 5 minutes post-dose, and 0.25, 0.5, 1, 1.5, 2, 4, 5, 8, and 24 hours post-dose. In addition, a single PK blood samples were collected at Weeks 8 and 16. See previous reports regarding the bioanalytical methods, which may be summarised as shown below.

Table 10. GS-US-292-0106: Bioanalytical Assay Validation for EVG, TAF, TFV, COBI, and FTC in Human Plasma

	EVG	TAF	TFV	COBI	FTC
Linear Range (ng/mL)	20 to 10,000	1 to 1000	0.3 to 300	5 to 2500	5 to 3000
Lower Limit of Quantitation (ng/mL)	20	1	0.3	5	5
Interassay Precision Range (%CV)	4.0 to 6.7	1.8 to 7.3	1.8 to 4.8	3.4 to 5.7	1.4 to 5.7
Interassay Accuracy Range (%RE)	–0.6 to 9.3	–3.7 to 6.5	-2.7 to 2.7	–3.0 to 2.0	–7.8 to 2.4
Stability in Frozen Matrix (day)	585 at –70ºC	520 at –70°C	366 at –20°C 1092 at –70°C	121 at –10°C to –30°C 365 at –60ºC to –80°C	190 at –20°C 340 at –70°C 1426 at –80°C

%RE = percentage of relative error

To determine whether GEN (E/C/F/TAF 150/150/200/10 mg) in children aged 8 to < 12 years weighing ≥ 25 kg achieved similar systemic exposure to those in adults, statistical comparisons were performed using combined adult data from other GEN studies, as described in the following:

- For TAF and TFV, PK parameters from POPPK modelling in GEN-treated adults in GS-US-292-0104 and GS-US-292-0111 (N = 539 for TAF and N = 841 for TFV) were used as the reference for comparison
- For EVG, COBI and FTC, the statistical comparison was the GEN-treated adults in the PK sub-study of GS-US-292-0102 (N = 19)

For TAF, a 1-way ANOVA model was fitted to the natural logarithmic transformed values of AUC_{last} and Cmax with treatment group as a fixed effect. Treatment groups were defined as the test treatment (children in this study) and reference treatment (adults from historical studies). For EVG, COBI, FTC and TFV, the PK parameters of AUC_{tau}, Cmax, and C_{tau} were analysed similarly.

For each analyte, 90% CIs for the ratio of GLSMs were calculated for each parameter, consistent with the two 1-sided tests each performed at an alpha level of 0.05. The 90% CI were constructed and assessed with a boundary of 70% to 143%.

Geometric mean estimates of CL/F and Vz/F were also calculated for each analyte and the ratios of the lower and upper bounds of the 95% CIs versus the point estimate of the geometric means were compared to the interval of 60% and 140% of each parameter.

In Cohort 2 Part A of GS-US-292-0106, intensive PK data were available for 23 children aged 8 to < 12 years weighing ≥ 25 kg who received GEN.

EVG AUC_{tau} and Cmax were 34.1% and 41.3% higher, respectively, in children vs. adults and the upper bound of the 90% CI of the GLSM ratio for each parameter extended beyond 143%. EVG C_{tau} was 14.5% lower in children with a lower bound of the 90% CI of the GLSM ratio below 70%, but mean EVG C_{tau} was > 8-fold above the IC_{95} for wild-type virus (44.5 ng/mL).

Table 11. GS-US-292-0106: Statistical Comparisons of EVG Plasma PK Parameter Estimates Between Children Aged 6 to < 12 Years and Adults (EVG Substudy Analysis Set)

	GS-US-292-0106 (Test)		GS-US-292-0102 (Reference)[a]		%GLSM Ratio (90% CI) Test/Reference
Parameters	n	GLSM	n	GLSM	
AUC_{tau} (h•ng/mL)	22	28892.09	19	21553.74	134.05 (103.86, 173.00)
C_{max} (ng/mL)	23	2822.28	19	1997.55	141.29 (115.31, 173.12)
C_{tau} (ng/mL)	23	211.82	19	247.71	85.51 (55.01, 132.92)

GLSM = geometric least-squares mean; rMSE = square root of mean square error.

a PK parameters for the reference group were estimated from Genvoya-treated subjects who participated in the GS-US-292-0102 PK substudy.

Regarding variability of exposure as assessed by CL/F (n = 22) and Vz/F (n = 14), the lower and upper 95% CIs of CL/F and Vz/F relative to the GM were within FDA-specified bounds of 60% to 140%.

Table 12. GS-US-292-0106: EVG CL/F and Vz/F (EVG PK Substudy Analysis Set)

Parameters	n	Mean (%CV)	Geometric Mean	%Ratio: 95% CI/Geometric Mean
CL/F (L/h)	22	6.3 (80.5)	5.2	76.5-130.8
V_z/F (L)	14	46.8 (77.0)	40.1	74.5-134.2

TAF AUC_{last} and Cmax were 70.7% and 81.6% higher, respectively, in children vs. adults and the upper bound of the 90% CI of the GLSM ratio for each parameter extended beyond 143%.

Table 13. GS-US-292-0106: Statistical Comparisons of TAF Plasma PK Parameter Estimates Between Children Aged 6 to < 12 Years and Adults (TAF PK Substudy Analysis Set)

Parameters	GS-US-292-0106 (Test)		GS-US-292-0104 and GS-US-292-0111 (Reference)[a]		%GLSM Ratio (90% CI) Test/Reference
	n	GLSM	n	GLSM	
AUC_{last} (h•ng/mL)	23	304.29	539	178.30	170.66 (146.50, 198.81)
C_{max} (ng/mL)	23	263.13	539	144.88	181.61 (146.42, 225.26)

GLSM = geometric least-squares mean

a PK parameters for the reference group were estimated from the population PK modeling in Genvoya-treated subjects in Studies GS-US-292-0104 and GS-US-292-0111.

The lower and upper 95% CI of CL/F and lower 95% of Vz/F relative to the geometric mean were within the FDA-specified bounds of 60% to 140%.

Table 14. GS-US-292-0106: Geometric Mean (95% CI) TAF CL/F and Vz/F (TAF PK Substudy Analysis Set)

Parameters	n	Mean (%CV)	Geometric Mean	%Ratio: 95% CI/Geometric Mean
CL/F (L/h)	11	31.9 (35.2)	30.3	80.6-124.1
V_z/F (L)	11	28.6 (90.2)	22.9	65.4-152.9

TFV AUC_{tau}, Cmax and C_{tau} were 52.2%, 73.0%, and 43.3% higher, respectively, in children and the upper bound of the 90% CI of the GLSM ratio for each parameter extended beyond 143%. The TFV AUC_{tau} (440.2 h•ng/mL) was approximately 5-fold lower vs. adult exposures from TDF 300 mg.

Table 15. GS-US-292-0106: Statistical Comparisons of TFV Plasma PK Parameter Estimates Between Children Aged 6 to < 12 Years and Adults (TFV PK Substudy Analysis Set)

Parameters	GS-US-292-0106 (Test)		GS-US--292-0104 and GS-US-292-0111 (Reference)		%GLSM Ratio (90% CI) Test/Reference
	n	GLSM	n	GLSM	
AUC_{tau} (h•ng/mL)	23	432.05	841	283.86	152.21 (142.26, 162.84)
C_{max} (ng/mL)	23	25.58	841	14.79	172.99 (161.08, 185.79)
C_{tau} (ng/mL)	23	14.76	841	10.30	143.25 (132.30, 155.10)

GLSM = geometric least-squares mean

a PK parameters for the reference group were estimated from the population PK modeling in Genvoya-treated subjects in Studies GS-US-292-0104 and GS-US-292-0111.

COBI AUC_{tau}, Cmax and C_{tau} were 57.7%, 27.0%, and 71.2% higher, respectively, in children and the upper bound of the 90% CI of the GLSM ratio for each parameter extended beyond 143%.

Table 16. GS-US-292-0106: Statistical Comparisons of COBI Plasma PK Parameter Estimates Between Children Aged 6 to < 12 Years and Adults (COBI Substudy Analysis Set)

Parameters	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)	20	14155.75	19	8975.72	157.71 (125.79, 197.73)
C_{max} (ng/mL)	23	1778.41	19	1400.19	127.01 (97.64, 165.21)
C_{tau} (ng/mL)	23	29.12	18	17.01	171.21 (94.71, 309.51)

GLSM = geometric least-squares mean

a PK parameters for the reference group were estimated from Genvoya-treated subjects who participated in the GS-US-292-0102 PK substudy

The lower and upper 95% CIs of CL/F and Vz/F relative to the GM were within the FDA-specified bounds of 60% to 140%.

Table 17. GS-US-292-0106: Geometric Mean (95% CI) COBI CL/F and Vz/F (COBI PK Substudy Analysis Set)

Parameters	n	Mean (%CV)	Geometric Mean	%Ratio: 95% CI/Geometric Mean
CL/F (L/h)	20	11.9 (51.5)	10.6	79.4-126.0
V_z/F (L)	15	41.0 (30.9)	39.1	83.5-119.8

FTC AUC_{tau}, Cmax and C_{tau} were 75.0%, 63.6%, and 25.4% higher, respectively, in children and the upper bound of the 90% CI of the GLSM ratio for each parameter extended beyond 143%.

Table 18. GS-US-292-0106: Statistical Comparisons of FTC Plasma PK Parameter Estimates Between Children Aged 6 to < 12 Years and Adults (FTC Substudy Analysis Set)

Parameters	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)	22	20261.93	19	11576.55	175.03 (159.57, 191.98)
C_{max} (ng/mL)	23	3294.50	19	2014.35	163.55 (145.11, 184.34)
C_{tau} (ng/mL)	23	111.77	19	89.11	125.42 (107.40, 146.47)

GLSM = geometric least-squares mean

a PK parameters for the reference group were estimated from Genvoya-treated subjects who participated in the GS-US-292-0102 PK substudy.

The lower and upper 95% CIs of CL/F and Vz/F relative to the geometric mean were within the FDA-specified bounds of 60% to 140%.

Table 19. GS-US-292-0106: Geometric Mean (95% CI) FTC CL/F and Vz/F (FTC PK Substudy Analysis Set)

Parameters	n	Mean (%CV)	Geometric Mean	%Ratio: 95% CI/Geometric Mean
CL/F (L/h)	22	10.1 (20.3)	9.9	91.7-109.1
V_z/F (L)	21	71.3 (24.8)	69.3	89.6-111.6

2.3.3. Discussion on clinical pharmacology

According to the CHMP guidance (as revised and published 2016) on development of anti-HIV agents:

A specific demonstration of antiviral efficacy in paediatric patients is not required. As it is assumed that the PK/PD relation for a direct acting antiviral is roughly similar regardless of the age of the patient, the efficacy of a dose that yields sufficiently similar exposure in children, compared to adults, would be inferred. The parameters that would be applied to conclude on similarity should be based on available data from the entire development programme, including PK and efficacy data in adults. Therefore non-comparative data in children on the tolerability and safety of the proposed dose regimens as well as documentation of adherence should be generated over appropriate time-spans. Data collected over 24 weeks would form a reasonable basis for the evaluation of a paediatric indication.

Large inter-individual variability in pharmacokinetics is common for antiretroviral agents, and particularly in children, making population PK an important objective of these studies.

The number of treatment naïve children is low in the EU, and mostly limited to the very young. Older children and adolescents are to a great extent suppressed on successful therapies and those failing in many cases do so for reasons of poor adherence, making them less suitable for clinical trials (and particularly where PK evaluation is crucial). Therefore, switch studies in suppressed children, if deemed feasible for the new agent with respect to the drug qualities, is one possible way forward.

GS-US-292-0106 is in compliance with this guidance (see also sections 4 and 5). The MAH proposes that in children aged 6-<12 years and weighing at least 25 kg no age-specific formulation is needed.

In the treatment-naïve adolescents (Cohort 1) in GS-US-292-0106, the plasma exposures to the relevant analytes at steady state were very similar to those in adults. The tables show the mean POPPK-predicted values for TAF and TFV in adolescents and adults.

Table 20. Multiple-Dose TAF exposure in ARV-naive adolescents and adults

Age Group	AUC_{last} (ng•h/mL)	C_{max} (ng/mL)
Adolescent Subjects (N = 23)[a]	242.8 (57.8)	121.7 (46.2)
Adult Subjects (N=539)[b]	206.4 (71.8)	162.2 (51.1)

Table 21. Multiple-Dose TFV exposure in ARV-naive adolescents and adults

Age Group	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
Adolescent Subjects (N = 23)[a]	275.8 (18.4)	14.6 (20.0)	10.0 (19.6)
Adult Subjects (N=841) [b]	292.6 (27.4)	15.2 (26.1)	10.6 (28.5)

a Adolescents from Study GS-US-292-0106 b Adults from Studies GS-US-292-0104 and GS-US-292-0111

As reported in the Genvoya application dossier, COBI exposures were lower in adolescents (Cohort 1) vs. adults in studies 0102 and 0103 (based on ratio and 90% CI within 80, 125%) but the EVG Cmax and AUC were comparable and only the EVG C_{trough} was lower (69.3%; CI 52.8, 91). FTC exposures were also comparable between age groups. See Table 5 in section 5.1 of the SmPC.

In Cohort 2 Part A it is clear that plasma exposures (AUC, Cmax and C_{tau}) are higher for all analytes except for EVG C_{tau}, which still considerably exceeds (>8-fold) the in-vitro IC_{95} value. See Table 6 in section 5.1 of the SmPC. Use of the adult dose of Genvoya in children aged from 6 years and 25 kg does not raise any concerns regarding efficacy. The potential concern is with regard to safety, taking into account that at this time only 50 patients aged 12-<17 years have been followed and there are only 23 treated in the age range 8-<12 years, with current complete follow-up limited to 6 months.

The MAH effectively dismiss any concerns based on the PK comparisons, describing the GM increases in AUC (TAF 70.7%, TFV 52.2%, EVG 34.1%, COBI 57.7% and FTC 75.0%) as modest and within the safe and efficacious ranges of the adult exposures in the GEN and STB programmes. In this regard, note that the CV% for AUCs were ~50% for TAF, EVG and COBI but ~20% for TFV and FTC. There is no discussion of the actual range of plasma exposures or the potential that the adult dose of Genvoya, when administered to children with other intrinsic or extrinsic factors that are known to increase plasma exposures to one or more of the 5 compounds of interest, could result in very much higher plasma concentrations than are covered by the adult safety data. For example, there are several recognised DDIs leading to increased plasma TAF and TFV for which no dose modification is considered necessary in adults. However, against a background of already higher exposures in children aged 6-<12 years, it is not possible to predict the resulting safety profile. Furthermore, the actual lowest age of children in Cohort 2 was 8 years and the Q1 for the body weight range was 27.5 kg.

The greatest concern has to be the plasma levels of TFV that could occur and the unknown effect of very chronic exposure to plasma levels much lower than those observed with TDF yet with unknown long-term effects on bone and renal targets in children. In this regard, the MAH points out that the mean TFV AUC_{tau} (440.2 ng•hr/mL) was ~5-fold lower as compared to adult exposures from TDF 300 mg. It should be noted that this is ~1.6 x the mean AUC in adolescents and adults (POPPK-predicted; see above) dosed with Genvoya. As already pointed out in the SmPCs for TAF-containing products, the long term effects of exposure to such levels of plasma TFV cannot be determined at this time. Whilst the risk in adults and adolescents was deemed to be low, the higher exposures in the younger children, especially if there are other factors serving to further increase plasma TFV, pose risks that cannot be assessed at this time.

2.3.4. Conclusions on clinical pharmacology

There was concern regarding the lack of safety data to support acceptance of the higher plasma exposures associated with use of the adult dose of Genvoya in children aged 8-<12 years and from 25 kg. In particular, there is concern that even higher exposures could occur chronically in the presence of other factors (intrinsic and extrinsic) that could further increase plasma levels of one or more of the 5 compounds of interest. A warning has been introduced in section 4.4 of the SmPC to reflect this.

2.4. Clinical efficacy

GS-US-292-0106

This study was confined to paediatric HIV-infected patients and commenced in May 2013.

The design of the study overall and the safety, efficacy and PK data obtained from adolescents up to 48 weeks on study has been previously assessed in a series of application dossiers as data were collected from this cohort (**Cohort 1**; **Part A and B**). These data have supported approvals for use of the adult dose regimens of Genvoya, Descovy, Odefsey (HIV) and Vemlidy (HBV) in patients from 12 years of age and body weight 35 kg.

The most recent interim report submitted in the current application covers data collected from patients aged 6 to < 12 years who weighed ≥ 25 kg (**Cohort 2; Part A**). These patients were enrolled at 5 study centres (1 in Thailand, 1 in Uganda and 3 in the US). Data are reported up to April 2016, at which time all patients in Cohort 2 Part A had completed the Week 24 visit or previously discontinued. The interim report submitted was completed in August 2016.

Methods

This is an open label uncontrolled study in age-defined cohorts.

Part A: An initial group of patients was enrolled in Part A to evaluate the steady-state PK and confirm the dose of GEN, in particular, to evaluate the EVG and TAF plasma PK to confirm the doses of these agents. All patients participated in an intensive PK evaluation at Week 4 and may continue to receive GEN through Week 48.

Part B: Following confirmation of EVG and TAF exposures in Part A and an IDMC review of preliminary safety and efficacy data, additional patients were to be enrolled in Part B to evaluate the safety and antiviral activity of GEN through Week 48. No data are currently reported from Cohort 2 Part B.

Study visits were at Weeks 1, 2, 4, 8, 12, 16, and 24, then every 8 weeks through Week 48. Patients who complete 48 weeks of study treatment are given the option to continue to receive GEN in an extension phase of the study.

Study participants

Patients eligible for Cohort 2 were to meet the following criteria:

- 6 to < 12 years of age at baseline and weight ≥ 25 kg (55 lbs) at screening
- Plasma HIV-1 RNA < 50 copies/mL (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection was > 50 copies/mL) for ≥ 180 consecutive days (6 months) prior to screening on a stable ARV regimen, without documented history of resistance to any component of GEN; an unconfirmed HIV-1 RNA ≥ 50 copies/mL after previously reaching virologic suppression (transient detectable viraemia, or "blip") prior to screening was acceptable
- Currently receiving an ARV regimen that had been stable for ≥ 180 consecutive days (6 months) or had been newly initiated within 6 months for reasons other than virologic failure.
- eGFR ≥ 90 mL/min/1.73 m2 (using the Schwartz formula)
- Clinically normal ECG
- Negative screening for active pulmonary tuberculosis per local standard of care within prior 6 months
- AST and ALT ≤ 5 ULN and total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin
- ANC ≥ 500/mm^3, platelets ≥ 50,000/mm^3, haemoglobin ≥ 8.5 g/dL

Exclusions included (but were not limited to):

- A new AIDS-defining condition diagnosed within the 30 days prior to screening
- HCV or HBV infection
- Decompensated cirrhosis (e.g. ascites, encephalopathy)
- Treatment with immunosuppressant therapies or chemotherapeutic agents within 3 months of study screening or expected to receive these agents during the study
- Concomitant treatment with a list of forbidden medications (see previous ARs) with significant DDI potential

Treatments

All patients receive 1 GEN tablet daily with food. In Part A, GEN was to be taken at breakfast. On the day of the intensive PK evaluation, patients received GEN in the clinic with food and after an overnight fast of at least 8 hours.

Objectives

For Cohort 2 Part A, the primary objectives are:

- To evaluate the PK of EVG and TAF in virologically suppressed HIV-infected children 6 to < 12 years of age weighing ≥ 25 kg when administered GEN
- To evaluate the safety of GEN through Week 24 in virologically suppressed HIV-infected children 6 to < 12 years of age weighing ≥ 25 kg

For Cohort 2 Part A, the secondary objectives are:

- To evaluate the effect on viral load of switching virologically suppressed HIV-infected children 6 to < 12 years of age weighing ≥ 25 kg to GEN
- To evaluate the PK of COBI, FTC and TFV in virologically suppressed HIV-infected children 6 to < 12 years of age administered GEN
- To evaluate the safety of GEN through Week 48 in virologically suppressed HIV-infected children 6 to < 12 years of age weighing ≥ 25 kg

Outcomes / endpoints

The on-study assessments of plasma viral load (HIV RNA) were conducted in a central laboratory using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, Version 2.0.

The resistance analysis population (RAP) was to include any treated patient with:

- Virologic Rebound (VR): a rebound in HIV-1 RNA ≥ 50 copies/mL, which was subsequently confirmed and with ≥ 400 copies/mL at the next visit
- Viraemic at the Final Time point: HIV-1 RNA ≥ 400 copies/mL at the study endpoint or study discontinuation who did not meet any of the criteria above

Resistance testing included genotyping and phenotyping of protease (PR), reverse transcriptase (RT) and IN at the virologic failure (VF) time point. Monogram Biosciences, Inc. (South San Francisco, CA) was the designated reference laboratory for all resistance analyses at VF. Resistance testing was only conducted when HIV-1 RNA was ≥ 400 copies/mL, which is close to the validated LLOD of the assays (500 copies/mL). The PhenoSense® GT assay, GenoSure® IN assay, and PhenoSense® IN assay (Monogram Biosciences, South San Francisco, CA) were used to determine virus genotypes and phenotypes for PR/RT and IN at the time of confirmed VF. The PhenoSense GT assay tests for genotypic and phenotypic resistance to all currently approved antiretroviral drugs in the NRTI, NNRTI, and PI classes. The GenoSure IN assay tests for IN genotype, while the PhenoSense IN assay tests for IN phenotype. These data were made available to study investigators in real time for cases of VR.

Historical baseline PR and RT sequences were analysed for the presence of previously identified resistance-associated mutations (RAMs) to antiretroviral agents.

Sample size

For Cohort 2 Part A it was planned to enrol 18-24 patients. Using adult data as historical control for comparison (see under Pharmacokinetics) 23 patients in Cohort 2 Part A would provide 90% power for EVG AUC_{tau} and 88% power for TAF AUC_{last} to conclude exposure equivalence between adults and children. In this power analysis, it was assumed that the geometric mean ratios were equal to 1, that the inter-subject standard deviation (natural log scale) of EVG AUC_{tau} and TAF AUC_{last} were 0.34 ng•hr/mL and 0.52 ng•hr/mL, respectively, that the 2 one-sided statistical tests were done at an alpha level of 0.05, and that the equivalency boundary was 70% to 143%.

A total of 23 patients in Cohort 2 Part A would also provide > 86% power to target a 95% CI within 60% and 140% of the geometric mean estimate of CL and Vz of TAF respectively, assuming a CV of 53% for CL and 76% for Vz (based on POPPK data from GS-US-292-0104 and GS-US-292-0111 combined).

Statistical methods

See under Pharmacokinetics regarding the analysis of the PK data. The efficacy data were analysed descriptively. The efficacy endpoints for Cohort 2 are as follows:

- The percentage 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 percentages with HIV-1 RNA < 50 at Weeks 24 and 48 (M = F and M = E)

The Week 24 analysis window was defined as from Study Day 140 to Study Day 195 (inclusive). All HIV-1 RNA data collected on treatment were used in the US FDA-defined snapshot algorithm.

Results

All 23 patients enrolled into Cohort 2 Part A were still on study at the time of the data cut-off for the current report.

There had been three important protocol deviations through 20 April 2016 that involved protocol-specified assessments or procedures. Two were deviations related to DXA scan procedures and one was due to a laboratory sample received outside of the specified window.

Baseline data

Among the 23 children, 14 were female and 9 male and 18/23 were Black. The median age was 10 years (range 8 to 11 years). The median (Q1, Q3) body weight at baseline was 30.5 (27.5, 33.0) kg and the median (Q1, Q3) baseline Z-score for weight was −0.25 (−1.16, 0.39) with a median (Q1, Q3) baseline Z-score for height of −0.43 (−1.04, 0.37). The median (Q1, Q3) value for BMI at baseline was 15.9 (15.2, 18.1) kg/m^2. Median eGFR was 150.0 (134.7, 165.6) mL/min/1.73 m^2 (Schwarz formula) and 110.5 (104.8, 122.9) mL/min/1.73 m^2 (modified Schwarz formula). The pubertal stage at baseline was Tanner stages 1-3 for all patients. Baseline disease characteristics are shown below. All patients had acquired HIV by vertical transmission and none had concurrent HCV or HBV.

Table 22. GS-US-292-0106: Baseline Disease Characteristics of Cohort 2 Subjects (Safety Analysis Set)

Characteristic[a]	GEN (N = 23)
HIV-1 RNA Categories (copies/mL)	
< 50	23 (100.0%)
≥ 50	0
CD4 Cell Count (/μL)	
N	23
Mean (SD)	966 (201.7)
Median	969
Q1, Q3	843, 1087
Min, Max	603, 1421
CD4 Cell Count Categories (/μL)	
≤ 199	0
≥ 200 and ≤ 349	0
≥ 350 and ≤ 499	0
≥ 500	23 (100.0%)
CD4 Percentage (%)	
N	23
Mean (SD)	39.6 (5.32)
Median	38.8
Q1, Q3	36.1, 44.3
Min, Max	30.4, 50.9
Years Since Subject Diagnosed with HIV	
N	23
Mean (SD)	8.8 (1.38)
Median	8.0
Q1, Q3	8.0, 10.0
Min, Max	6.0, 11.0

All patients were receiving a NRTI at study entry (82.6%, 60.9% and 52.2% for 3TC, ABV and ZDV, respectively), 11 were receiving a NNRTI (efavirenz or nevirapine), 5 were receiving PIs (4 LPV/r and one ATV/r), 2 were taking RAL and 2 TDF.

Mean adherence to Genvoya up to Week 24 (pill count) was 96.8% and all had an adherence rate ≥ 95%.

Outcomes and estimation

At Week 24, all patients remained suppressed at < 50 copies/mL (US FDA-defined snapshot algorithm).

The mean (SD) baseline CD_4 cell count was 966 (201.7) cells/μL and no patient had < 500 cells/μL.

A mean (SD) decrease from baseline in CD_4 cell count was observed at Week 2 (162 [144.6] cells/μL), which was stable through Week 24 (150 [164.6] cells/μL). For 19/23 who had reached Week 32, the mean (SD) CD_4 cell count had returned to near baseline value (900 [237.7] cells/μL).

Four patients had CD_4 cell declines to < 500 cells/μL at a single visit and all had resolved by the next visit. Two had concurrent AEs of acute respiratory tract infection with a CD_4 count of 468 cells/μL and one had tonsillar hypertrophy with pyrexia and thrombocytopenia with a CD4 count of 359 cells/μL.

The mean (SD) baseline CD_4% was 39.6% and the mean (SD) changes from baseline in CD4% at Week 2 and Week 24 were 0.5% (3.01%) and −1.5% (3.67%), respectively. For 19/23 who had reached Week 32, the mean (SD) change from baseline in CD4% was −1.2% (4.25%).

Only one of the 23 patients had historical genotype data available, showing HIV-1 subtype B without any primary RT or PR RAMs. The CSR indicates that HIV-1 subtype was not determined under the protocol.

2.4.1. Discussion on clinical efficacy

Design and conduct of clinical studies

See section 2.3.3 regarding the study design, which is compliant with current CHMP guidance.

Efficacy data and additional analyses

All the children have maintained virologic suppression for at least 24 weeks after switching to GEN. They all had relatively high CD4 counts at baseline. Although an initial decline in CD4 count was noted at Week 2, the mean count at Week 32 for 19/23 who had reached that visit was near baseline, with little change in CD4% over the course of treatment. The finding may reflect variability in CD4 counts in small numbers of patients. It cannot be ruled out that very high intracellular TFV-PP levels might have impacted on CD4 counts but the slow return to baseline provides some reassurance. Therefore this is an issue that needs to be monitored but it does not preclude approval from 6 years of age and 25 kg.

Treatment adherence was high and no patient discontinued study drug. In terms of tablet palatability and size, one patient reported the tablet to have abnormal taste at baseline but not at Week 4 and one had a tablet size issue at baseline and Week 4. Both continued taking Genvoya.

CHMP requested to investigate other possibilities to administer the current formulation to children in the target age and weight range who may have difficulties swallowing whole tablets. The MAH proposed the tablet to be split and the two halves taken in rapid sequence. This strategy will assist in swallowing and is less likely to cause palatability issues compared to crushing. Given that by splitting the tablet in half the surface area of the tablet is reduced and thus there is less exposure to the bitter taste. Stability data following tablets split was provided. In addition, the MAH provided a plan to address the formulation of a lower dose tablet that could be more appropriate for children from 6 years and 17 kg. Furthermore, a subset of patients from 6 to less than 12 years is to be switched to the age appropriate STR formulation before the end of the study.

The CHMP considered the proposal of cutting the tablets in half and taking them in swift succession as acceptable. This alternative is reflected in section 4.2 of the SmPC and in the PL.

2.4.2. Conclusions on the clinical efficacy

There are no concerns so far regarding efficacy of the adult dose of Genvoya in virologically suppressed children aged from 8 years and 25.5 kg (the actual minima included). As discussed in section 2.3.3, provided that children take the medication as recommended, the PK data raise no concerns over the potential longer-term efficacy of once daily dosing of Genvoya with food in this paediatric subset. Genvoya has not been studied in ART-naïve children in the age range 6-<12 years but the CHMP guidance acknowledges the scarcity of such children for study and that the efficacy already shown in treatment-naïve adults and adolescents can be assumed to apply to the children based on comparisons of plasma levels. It is noted that HIV-1 subtype is apparently not known for 22 children. However, all have maintained virologic suppression so that no analysis of response by type is anyway possible. In addition, it may be assumed that the data in adults on responses by subtype would be applicable.

2.5. Clinical safety

Introduction

See section 2.4. for details of the design of GS-US-292-0106 and the baseline characteristics of the patient population.

Patient exposure

The median (Q1, Q3) duration of exposure to GEN was 32.1 weeks (31.7, 32.1). At the time of the interim Week 24 analysis, 15 children (65.2%) had received ≥32 weeks.

Adverse events

Most patients (17/23) had at least 1 AE, all of which were Grade 1 or Grade 2 in severity, including 9 with AEs considered related to Genvoya by the investigator. Adverse events reported in ≥ 5% (≥ 2 patients) are shown in Table 23.

Table 23. GS-US-292-0106: Adverse Events Occurring in at Least 5% of Subjects (Safety Analysis Set)

Adverse Event by System Organ Class and Preferred Term[a,b]	GEN (N = 23)
Subjects Experiencing Any Treatment-Emergent Adverse Event	17 (73.9%)
Gastrointestinal disorders	11 (47.8%)
Abdominal pain	6 (26.1%)
Vomiting	5 (21.7%)
Infections and infestations	9 (39.1%)
Respiratory tract infection	7 (30.4%)
Injury, poisoning and procedural complications	5 (21.7%)
Contusion	2 (8.7%)
Metabolism and nutrition disorders	3 (13.0%)
Vitamin D deficiency	3 (13.0%)
Nervous system disorders	4 (17.4%)
Headache	3 (13.0%)
Respiratory, thoracic and mediastinal disorders	5 (21.7%)
Rhinitis allergic	2 (8.7%)

MedDRA = Medical Dictionary for Regulatory Activities

a Adverse events were coded using MedDRA 19.0.

b Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively. System organ class was presented alphabetically and preferred term was presented by descending order of the total frequencies.

The AEs considered to be related to study drug are shown in Table 24.

Table 24. GS-US-292-0106: Study Drug-Related Adverse Events (Safety Analysis Set)

Adverse Event by System Organ Class and Preferred Term[a,b]	GEN (N = 23)
Subjects Experiencing Any Treatment-Emergent Adverse Event Related to Study Drug	9 (39.1%)
Gastrointestinal disorders	6 (26.1%)
Abdominal pain	4 (17.4%)
Vomiting	4 (17.4%)
Constipation	1 (4.3%)
Metabolism and nutrition disorders	1 (4.3%)
Vitamin D deficiency	1 (4.3%)
Nervous system disorders	2 (8.7%)
Dizziness	1 (4.3%)
Headache	1 (4.3%)
Product issues	1 (4.3%)
Product shape issue	1 (4.3%)
Product size issue	1 (4.3%)

MedDRA = Medical Dictionary for Regulatory Activities

a Adverse events were coded using MedDRA 19.0.

b Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively. System organ class was presented alphabetically and preferred term was presented by descending order of the total frequencies

No AEs of fractures were reported. Mean increases from baseline of 2.9% and 1.7% in spine and TBLH BMD, respectively, were observed at Week 24.

Table 25. GS-US-292-0106: Baseline Value and Percentage Change from Baseline in Spine and Total-Body-Less-Head BMD at Week 24 (Spine and TBLH DXA Analysis Sets)

	Spine BMD (N = 21)		TBLH BMD (N = 23)	
Time Point	Mean (SD)	Median (Q1, Q3)	Mean (SD)	Median (Q1, Q3)
Baseline (g/cm^2)	0.619 (0.1237)	0.577 (0.534, 0.657)	0.685 (0.0759)	0.659 (0.639, 0.709)
% Change at Week 24	2.937 (4.9459)	4.154 (−2.417, 7.246)	1.731 (2.5231)	1.156 (0.000, 3.756)

Two patients had ≥4% decrease in spine BMD at week 24 (values were -5.276% and -6.555%) but none had such a change in TBLH BMD.

The Z-score for any BMD value is the number of SDs that the value lies below or above the mean BMD of an age, sex and race-matched control group. A Z-score ≤ −2.0 is "below the expected range for age" and is considered to reflect a low bone mass or BMD, while a Z-score > −2.0 is "within the expected range for age". BMD Z-scores were also calculated adjusted for height-age. A height-age adjusted BMD Z score at baseline that changes from > −2 to ≤ −2 has been used as 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 scores < −2) and a clinically significant fracture history are present, which was not observed in this cohort.

Table 26. GS-US-292-0106: Spine Standard and Height-Age BMD Z-Scores at Baseline and Change from Baseline at Week 24 (Spine DXA Analysis Set)

	Spine BMD Z-Score (Standard) (N = 21)		Spine BMD Z-Score (Height-Age) (N = 21)	
	Mean (SD)	Median (Q1, Q3)	Mean (SD)	Median (Q1, Q3)
Baseline	−0.82 (0.864)	−1.09 (−1.34, −0.75)	−0.56 (0.829)	−0.81 (−1.07, −0.28)
Change from Baseline at Week 24	−0.06 (0.375)	−0.01 (−0.38, 0.26)	0.05 (0.414)	0.10 (−0.29, 0.48)

Table 27. GS-US-292-0106: Total-Body-Less-Head Standard and Height-Age BMD Z-Scores at Baseline, and Change from Baseline at Week 24 (TBLH DXA Analysis Set)

	TBLH BMD Z-Score (Standard) (N = 23)		TBLH BMD Z-Score (Height-Age) (N = 21)[a]	
	Mean (SD)	Median (Q1, Q3)	Mean (SD)	Median (Q1, Q3)
Baseline	−1.00 (1.014)	−1.25 (−1.64, −0.34)	−0.74 (0.978)	−0.83 (−1.17, −0.32)
Change from Baseline at Week 24	−0.18 (0.228)	−0.22 (−0.29, −0.03)	−0.10 (0.207)	−0.12 (−0.25, −0.02)

For spine BMD height-age Z scores there was no change in clinical status for the 20 patients with baseline Z score > −2 or in the patient with baseline Z score ≤ −2. For TBLD BMD height-age Z scores there was no change in clinical status for the 19 patients with baseline Z score > −2 or in the patient with baseline Z score ≤ −2.

Fluctuation in the bone biomarkers measured through Week 24 was consistent with the effects of growth, skeletal size and pubertal maturation expected in children in this age range. No clinical relevance was derived from the changes in any of the bone biomarkers from baseline to 24 weeks.

Table 28. GS-US-292-0106: Median (Q1, Q3) Percentage Change from Baseline in Serum Bone Laboratory Parameters at Week 24 (Safety Analysis Set)

	GEN		
	N	Median	Q1, Q3
N-Telopeptide (nmol BCE/L)			
Baseline	23	67.2	57.7, 84.9
% Change at Week 24	23	9.3	−17.0, 37.7
C-Telopeptide (µg/L)			
Baseline	22	14.0	12.3, 15.9
% Change at Week 24	22	24.2	13.8, 42.1
Osteocalcin (ng/mL)			
Baseline	22	100.57	84.62, 157.80
% Change at Week 24	22	40.23	18.31, 58.06
Bone-Specific Alkaline Phosphatase (µg/L)			
Baseline	22	91.65	82.01, 103.52
% Change at Week 24	22	−10.67	−18.69, 2.89
P1NP (ng/mL)			
Baseline	23	683.5	537.8, 814.0
% Change at Week 24	23	13.7	4.3, 25.1
PTH (pg/mL)			
Baseline	22	42.6	31.7, 60.8
% Change at Week 24	21	8.4	−16.6, 51.2
25-OH Vitamin D (ng/mL)			
Baseline	22	20.0	15.2, 26.4
% Change at Week 24	22	8.3	−12.8, 28.2
$1,25\text{-}(OH)_2$ Vitamin D (pg/mL)			
Baseline	22	103.1	81.9, 125.8
% Change at Week 24	21	−7.8	−22.8, 4.2

% Change = Change from baseline at a post-baseline visit/baseline * 100%

There were no renal AEs (including tubulopathy/Fanconi syndrome). For serum creatinine there was an increase from baseline observed at Week 4 that remained stable through Week 24 (ascribed to COBI).

The median (Q1, Q3) changes from baseline were Week 4: 0.04 (−0.02, 0.08) mg/dL and Week 24: 0.04 (0.01, 0.07) mg/dL. No graded serum creatinine abnormalities were reported.

For eGFR using the Schwartz formula there was a decrease from baseline observed at Weeks 4 and 24. The median (Q1, Q3) changes from baseline were Week 4: −9.9 (−18.9, 4.3) mL/min/1.73 m^2 and Week 24: −6.5 (−18.7, 5.9) mL/min/1.73 m^2. For eGFR using the modified Schwartz formula the corresponding changes were −6.7 (−14.0, −2.5) mL/min/1.73 m^2 and −9.0 (−15.4, 0.0) mL/min/1.73 m^2.

No graded abnormalities in serum phosphorus or urine glucose were reported. Transient Grade 1 proteinuria was reported for 3 patients. A decrease in UPCR from baseline was observed at Week 1 (−26.53%), which persisted through Week 24 (−30.33%). For both urine RBP and urine beta-2 microglobulin to creatinine ratios there were declining trends from baseline to Weeks 8, 12 and 24. The urine RBP to creatinine ratio percentage change from baseline to Week 24 was −31.13% and the change for the urine beta-2 microglobulin to creatinine ratio was −6.2%.

No patient had a SAE or an AE that led to study drug discontinuation.

There were no clinically relevant changes from baseline in median values for haematology or chemistry parameters through Week 24. Generally, median values were within normal ranges. However, 21/23 had at least 1 laboratory abnormality reported. Grade 3 laboratory abnormalities were reported for 5 patients but most were isolated and none was reported as an AE. Grade 3 low neutrophil count was reported for 4 patients. Single patients had Grade 3 hypocalcaemia plus Grade 3 hypomagnesaemia at Week 4 and one had Grade 3 haematuria by quantitative assessment at Week 16. No Grade 4 abnormalities were reported.

No patients had elevations > 3 × ULN in AST or ALT in addition to > 2 × ULN in total bilirubin and ALP < 2 × ULN.

One patient had Grade 1 fasting hyperglycaemia and 2 had Grade 1 fasting hypoglycaemia. There were small increases in median cholesterol (total and LDL).

Table 29. GS-US-292-0106: Median (Q1, Q3) Change from Baseline in Fasting Glucose and Lipid Parameters at Week 24 (Safety Analysis Set)

	GEN (N = 50)		
	N	Median	Q1, Q3
Total Cholesterol (mg/dL)			
Baseline	22	171	153, 186
Change at Week 24	22	4	−5, 25
LDL Cholesterol (mg/dL)			
Baseline	22	103	84, 125
Change at Week 24	22	10	−1, 28
HDL Cholesterol (mg/dL)			
Baseline	22	57	47, 67
Change at Week 24	22	−2	−12, 6
Total Cholesterol to HDL Cholesterol Ratio			
Baseline	22	2.96	2.60, 3.35
Change at Week 24	22	0.34	0.01, 0.62
Triglycerides (mg/dL)			
Baseline	22	91	70, 128
Change at Week 24	22	−8	−29, 26
Glucose (mg/dL)			
Baseline	21	81	76, 84
Change at Week 24	21	1	−5, 4

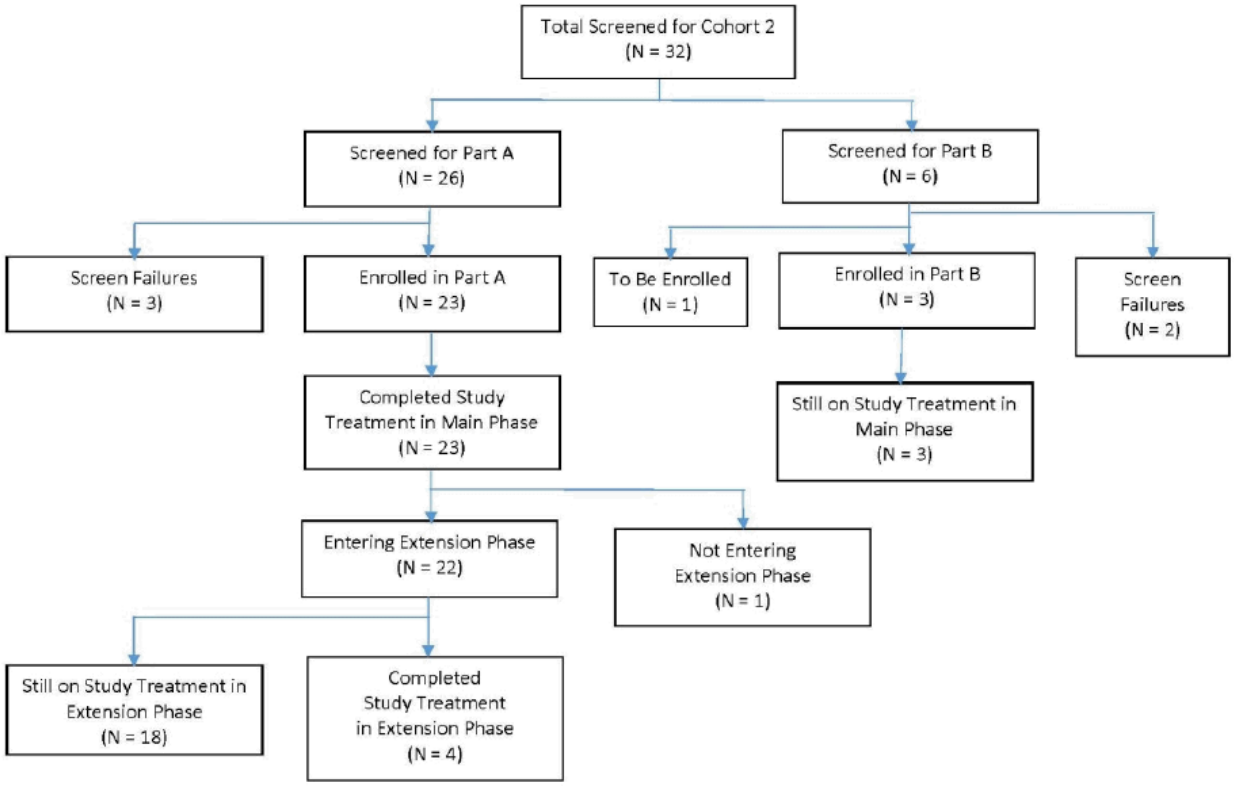
Changes from baseline to Week 24 of Tanner stage in the 9 male patients were as follows: 2 males with baseline Tanner stage 1 for pubic hair and 4 with baseline Tanner stage 1 for genitalia had progressed to Tanner stage 2 at Week 24. Changes from baseline to Week 24 in Tanner stage in the 14 females were as follows: 4 with baseline Tanner stage 1 for pubic hair and 3 with baseline Tanner stage 1 for breasts had progressed to Tanner stage 2 at Week 24. Two females with baseline Tanner stage 2 for breasts had progressed to Tanner stage 3 at Week 24.

Body weight Z-scores increased during the study. Change from baseline at Week 24 were median (Q1, Q3) 0.13 (−0.12, 0.37). For height there were no clinically relevant changes in Z-scores during the study.

Additional safety data form Study GS-US-292-0106

The updated interim report covers the 23 subjects enrolled in Part A, all of whom completed the 48-week main treatment phase with 22 entering the extension phase. As of 27 February 2017, 3 subjects had been enrolled into Part B and all were on study treatment.

Figure 1. Subject disposition



Disposition as of 27 February 2017

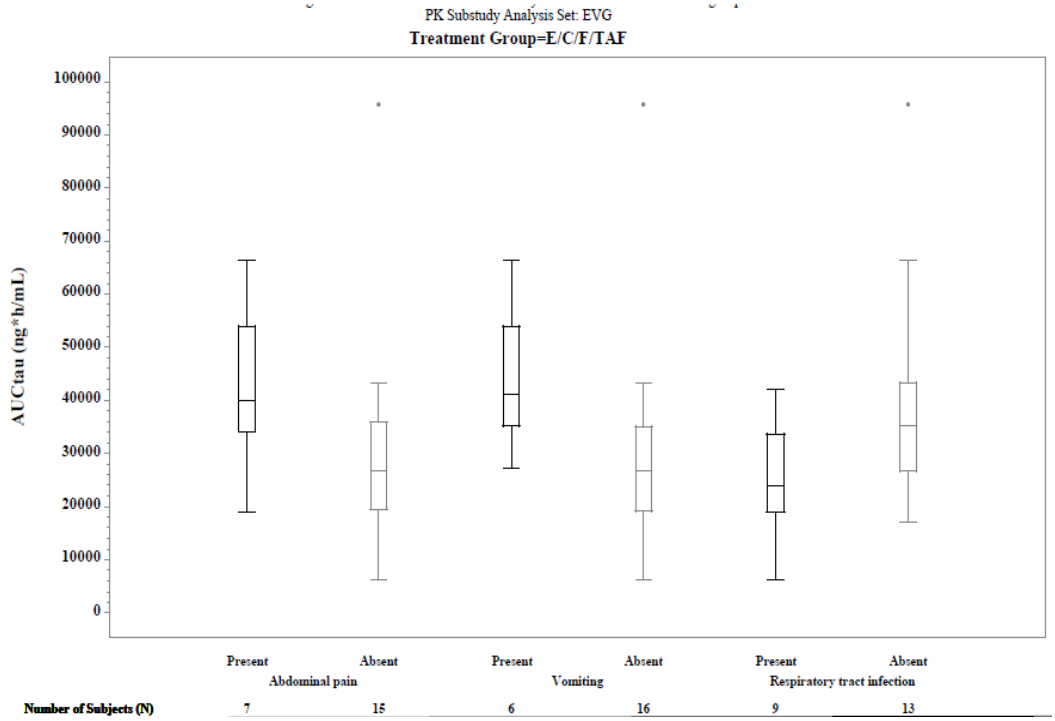
At Week 48, all of the 23 subjects in the Part A FAS had HIV-1 RNA < 50 copies/mL (US FDA-defined snapshot algorithm) as did the 3 subjects in Part B at Week 4 (M = E analysis).

For Part A subjects the mean baseline CD4 cell count was 966 cells/μL, falling to 816 cells/μL at Week 24 but increasing to 875 cells/μL at Week 48 (mean change from baseline −90 cells/μL). The median change (Q1, Q3) from baseline of CD4 cell counts was −130 (−299, −44) and −67 (−256, 53) cells/μL at Weeks 24 and 48, respectively. Mean CD4% was 39.6% at baseline and 38.1% and 38.3% at Weeks 24 and 48, respectively. The median (Q1, Q3) change from baseline CD4% was −2.1% (−3.8%, 1.9%) and −0.2% (−3.7%, 1.9%) at Weeks 24 and 48, respectively.

For Part B the mean baseline CD4 cell count was 669 cells/μL, increasing at Week 8 to reach 843 cells/μL. Mean CD4% was 39.2% at baseline and 39.7% at Week 8.

One subject in Part A had historical genotype data available showing HIV-1 subtype B without any primary RT or PR RAMs. One subject was included in the resistance analysis population due to confirmed virologic rebound at the Week 40 retest visit with an HIV-1 RNA level of 1330 copies/mL. No emergent resistance to the actives in Genvoya was observed. Low adherence to drug was suspected, but confirmation was not possible as the subject failed to return a bottle of pills at Week 40. The subject re-suppressed HIV-1 RNA to < 50 copies/mL at the Week 48 retest visit with continued treatment.

No additional PK analyses have been generated since the prior interim CSR. Pharmacokinetic-pharmacodynamic (PK-PD) analyses for each analyte and the most commonly reported AEs (abdominal pain, vomiting or respiratory tract infection) were conducted. These AEs were the 3 most frequently reported AEs as of this interim analysis (occurred in > 20% of subjects). Using logistic regression analysis, the MAH concluded there was no association between these AEs and AUC or Cmax of EVG, COBI, FTC, TAF or TFV. The assessor concludes (as before) that there may be a relationship between EVG exposures and GI events (abdominal pain and vomiting; see plot for EVG AUC_{tau}).



Subjects had a median (Q1, Q3) exposure to treatment of 72.1 (71.7, 72.1) weeks in Part A and 8.1 (7.6, 12.1) weeks in Part B.

As of 27 February 2017 most subjects (84.6% [22 of 26]) experienced an AE. No AEs ≥ Grade 3 and no SAEs were reported. No AEs resulted in discontinuation from study drug. No deaths have occurred.

The most frequently reported AEs were respiratory tract infection (34.6%, 9 subjects), abdominal pain (30.8%, 8 subjects), vomiting (26.9%, 7 subjects) and diarrhoea (19.2%, 5 subjects). All of these AEs were Grade 1 and most resolved within 4 days. Subjects generally experienced these AEs only once during the study.

Table 30. GS-US-292-0106: Adverse Events in ≥ 5% of Subjects in Cohort 2 Part A or Part B by System Organ Class and Preferred Term (Safety Analysis Set)

	Part A (N=23)	Part B (N=3)	Total (N=26)
Subjects Experiencing Any Treatment-Emergent AE	19 (82.6%)	3 (100.0%)	22 (84.6%)
Blood and lymphatic system disorders	2 (8.7%)	1 (33.3%)	3 (11.5%)
Leukopenia	0	1 (33.3%)	1 (3.8%)
Neutropenia	0	1 (33.3%)	1 (3.8%)
Gastrointestinal disorders	11 (47.8%)	3 (100.0%)	14 (53.8%)
Abdominal pain	7 (30.4%)	1 (33.3%)	8 (30.8%)
Vomiting	6 (26.1%)	1 (33.3%)	7 (26.9%)
Diarrhoea	2 (8.7%)	3 (100.0%)	5 (19.2%)
Constipation	2 (8.7%)	0	2 (7.7%)
Dental caries	2 (8.7%)	0	2 (7.7%)
General disorders and administration site conditions	2 (8.7%)	0	2 (7.7%)
Pyrexia	2 (8.7%)	0	2 (7.7%)
Infections and infestations	13 (56.5%)	1 (33.3%)	14 (53.8%)
Respiratory tract infection	9 (39.1%)	0	9 (34.6%)
Gingivitis	2 (8.7%)	0	2 (7.7%)
Nasopharyngitis	1 (4.3%)	1 (33.3%)	2 (7.7%)
Urinary tract infection	1 (4.3%)	1 (33.3%)	2 (7.7%)
Injury, poisoning and procedural complications	6 (26.1%)	0	6 (23.1%)
Contusion	2 (8.7%)	0	2 (7.7%)
Investigations	0	1 (33.3%)	1 (3.8%)
Blood creatinine increased	0	1 (33.3%)	1 (3.8%)
Metabolism and nutrition disorders	3 (13.0%)	0	3 (11.5%)
Vitamin D deficiency	3 (13.0%)	0	3 (11.5%)
Nervous system disorders	4 (17.4%)	1 (33.3%)	5 (19.2%)
Headache	3 (13.0%)	1 (33.3%)	4 (15.4%)
Dizziness	1 (4.3%)	1 (33.3%)	2 (7.7%)
Respiratory, thoracic and mediastinal disorders	7 (30.4%)	1 (33.3%)	8 (30.8%)
Rhinitis allergic	3 (13.0%)	0	3 (11.5%)
Rhinorrhoea	2 (8.7%)	1 (33.3%)	3 (11.5%)
Cough	2 (8.7%)	0	2 (7.7%)

None of the AEs of respiratory tract infection were considered related to study drug. Four subjects had abdominal pain considered related to study drug on Day 1 that resolved within 4 days. Three of these subjects also experienced vomiting of 1-day duration on Day 1 or 2. Vomiting was considered related to study drug for 4 subjects. None of the AEs of diarrhoea were considered related to study drug.

Laboratory data are available up to 21 March 2017. Grade 3 laboratory abnormalities were observed in 7 of 26 (26.9%) subjects but no Grade 4 laboratory abnormalities were reported. Consistent with the Week 24 analysis, Grade 3 low neutrophils was observed in 5 (19.2%) while Grade 3 albumin corrected calcium (hypocalcaemia) and Grade 3 magnesium (hypomagnesaemia) was each observed in one subject (3.8%).

Only subjects in Part A were included in the bone analyses because they were expected to have completed their Week 48 visit. BMD status was assessed using BMD Z-scores (Z-score ≤ −2.0 is "below the expected range for age" and is considered to reflect a low bone mass or BMD, while a Z-score > −2.0 is "within the expected range for age" based on ISCD 2013).

Mean (SD) increases from baseline of approximately 2.9% (4.9%) and 5.1% (6.6%) in spine BMD were observed at Weeks 24 and 48, respectively. Mean (SD) increases from baseline of approximately 1.7% (2.5%) and 4.3% (4.4%) in TBLH BMD were observed at Weeks 24 and 48, respectively.

However, mean spine and TBLH standard Z-scores decreased during the study. The mean (SD) spine standard Z-score was −0.82 (0.864), −0.88 (0.860) and −0.98 (0.941) at baseline, Week 24 and Week 48, respectively.

Table 31. Spine BMD Standard Z-Score and Change from Baseline by Visit Part A Spine DXA Analysis Set

	E/C/F/TAF (N=21)							
	N	Mean	SD	Min	Q1	Median	Q3	Max
baseline	21	-0.82	0.864	-1.77	-1.34	-1.09	-0.75	1.02
Week 24	21	-0.88	0.860	-2.27	-1.44	-1.04	-0.54	1.37
Week 48	21	-0.98	0.941	-2.30	-1.70	-1.04	-0.70	1.71
Change at W24	21	-0.06	0.375	-0.88	-0.38	-0.01	0.26	0.44
Change at W48	21	-0.16	0.467	-1.04	-058	-0.06	0.18	0.69

The mean (SD) TBLH standard Z-score was −1.00 (1.014), −1.17 (0.916) and −1.19 (1.020) at baseline, Week 24, and Week 48, respectively.

Table 32. Total Body Less Head BMD Standard Z-Score and Change from Baseline by Visit Part A Total Body Less Head DXA Analysis Set

	E/C/F/TAF (N=23)							
	N	Mean	SD	Min	Q1	Median	Q3	Max
baseline	23	-1.00	1.014	-2.66	-1.64	-1.25	-0.34	1.49
Week 24	23	-1.17	0.916	-2.45	-1.76	-1.39	-0.47	1.24
Week 48	23	-0.1.19	1.020	-2.63	-1.79	-1.41	-0.75	1.44
Change at W24	23	-0.18	0.228	-0.63	-0.29	-0.22	-0.03	0.25
Change at W48	23	-0.19	0.376	-0.94	-0.41	-0.29	0.13	0.51

Mean spine and TBLH BMD height-age Z-scores were almost unchanged from baseline at Week 48, with a mean (SD) change of 0.01 (0.487) and −0.06 (0.351), respectively.

One subject had a traumatic (due to a fall) Grade 1 radius fracture on Day 304 that was not considered related to study drug. At Week 48, this subject's spine BMD value was 0.525 g/cm^2, with a percent change from baseline of 8.696; the standard Z-score was −1.38 and the height-age Z-score was −0.31. At Week 48, this subject's TBLH BMD value was 0.644 g/cm^2, with a percent change from baseline of 3.074; the standard Z-score was −1.43 (no height-age Z-score was available because this subject's height was outside of the BMD reference data for Z-score).

Three subjects had a ≥ 4% decrease from baseline in spine (n = 2) or TBLH (n = 1) BMD during the study. None of the 3 subjects had an adverse bone outcome such as a fracture.

Table 33. GS-US-292-0106: Part A Subjects with ≥ 4% change from baseline in Spine or TBLH BMD

Baseline Age (years)	Body Weight (kg): Baseline, Week 24, Week 48	Prior ARV Regimen	Height-Age Spine Z-score: Baseline, Week 24, Week 48	Height-Age TBLH Z-score: Baseline, Week 24, Week 48	TFV AUC (h*ng/mL)	TFV C_{max} (ng/mL)
11	30.5, 34.2, 35.7	3TC, AZT, NVP	0.46, −0.07, −0.19	1.33, 1.31, 0.88	349.7	19.4
8	29, 32, 36.5	3TC, ABC, NVP	0.42, −0.29, −0.39	−0.63, −1.03, −0.88	422.8	27.3
9	25.5, 26, 27	3TC, AZT, D4T, NVP	0.36, −0.99, −1.01	−0.83, −1.08, −1.29	343.6	17.5

Two of the three had a ≥ 4% decrease from baseline in spine BMD at Week 24. One of these continued to have a ≥ 4% decrease in spine BMD at week 48 while the other (7547-2072) had a percent change in spine BMD of −3.894 at Week 48. The height-age adjusted spine and TBLH Z-scores were > −2.0 at Weeks 24 and 48 for these subjects. The TFV AUC and Cmax were similar to the mean values (mean [CV%] AUC: 440.2 h*ng/mL [20.9]; mean Cmax: 26.1 ng/mL [20.8]) for Cohort 2 Part A.

The third subject had a 4.173% decline in TBLH BMD from baseline at Week 48. This subject did not have a baseline spine BMD value but spine BMD was 0.538 g/cm^2 at Week 24 and 0.541 g/cm^2 at Week 48.

For subjects in Part A, the median (Q1, Q3) baseline serum creatinine was 0.52 (0.45, 0.55) mg/dL and an increase of 0.04 mg/dL from baseline was observed at Week 4 that remained stable through Week 48. For subjects in Part B (n = 3), the median (Q1, Q3) baseline serum creatinine was 0.51 (0.44, 0.53) mg/dL and a decrease of 0.02 mg/dL was observed at Week 8. No Grade 3 or 4 serum creatinine abnormalities were reported. One subject in Part B had an AE of Grade 1 increase of blood creatinine and Grade 1 AEs of leukopenia and neutropenia; all 3 AEs had an onset on Day 8 (17 January 2017) and were continuing at the data cut-off date. None of the AEs was considered related to study drug and none required treatment.

For subjects in Part A (n = 23), the median (Q1, Q3) baseline eGFR using the Schwartz formula was 150.0 (134.7, 165.6) mL/min/1.73 m^2. A decrease from baseline was observed from Week 4 with median (Q1, Q3) changes from baseline as follows:

- Week 4: −9.9 (−18.9, 4.3) mL/min/1.73 m^2
- Week 24: −6.5 (−18.7, 5.9) mL/min/1.73 m^2
- Week 48: −1.5 (−17.4, 16.0) mL/min/1.73 m^2

For subjects in Part B (n = 3), the median (Q1, Q3) baseline eGFR using the Schwartz formula was 139.6 (138.3, 177.3) mL/min/1.73 m^2. An increase of 5.7 (−35.9, 29.7) mL/min/1.73 m^2 was observed at Week 8.

2.5.1. Discussion on clinical safety

The safety data currently comprise 23 children aged from 8 years and 25.5 kg who have been followed for at least 24 weeks, including 15 who had been followed for 32 weeks or more at the time of the report. In this uncontrolled study in which GEN was commenced in children who were already taking antiretroviral therapy, albeit mainly NRTIs and frequently only NRTI-containing regimens, it is not possible to draw any clear conclusions regarding the safety of using the adult dose of Genvoya in this paediatric subset.

This fact alone would not preclude an approval for use at least from 8 years and ~30 kg (near to the mean/median baseline body weight) if the plasma exposures were very comparable to those observed in adults. However, as discussed in section 2.3.3, plasma exposures are substantially higher in children aged 8-<12 years and with CV% values ~50% for AUCs of TAF, EVG and COBI and ~20% for AUCs of TFV and FTC. Graphical representations of AUCs by actual baseline body weight are not found in the application, nor is there any discussion of the nonclinical safety margins that would apply to the paediatric exposures. Furthermore, these children were treated under a protocol in which a large number of potentially interacting concomitant medications were forbidden and in which the actual concomitant medications were almost all antibacterial agents, analgesics and vaccines.

The actual safety data appear to be as expected based on prior data in older patients. No Grade 3 or 4 clinical AEs were reported so far and the range of events is not unexpected for the population treated.

The effects on serum creatinine and eGFR most likely reflect initiation of COBI, with stable values after ~ Week 4. There was a decrease from baseline in proteinuria assessed by UPCR. Thus far the data do not suggest renal toxicity in the population studied.

The safety profile over 48 weeks is similar to that reported at 24 weeks. Mean spine and TBLH standard Z-scores decreased during the study but mean spine and TBLH BMD height-age Z-scores were almost unchanged from baseline at Week 48. Three of 23 subjects had a $\geq$ 4% decrease from baseline in spine (2) or TBLH (1) BMD at Week 24 and/or Week 48. For two the height-age adjusted spine and TBLH Z-scores were > −2.0 at Weeks 24 and 48. The third subject (9983-2061) had a 4.173% decline in TBLH BMD from baseline at Week 48. With a safety dataset of 23 exposed for 48 weeks and 3 others for 8 weeks the data are very limited.

2.5.2. Conclusions on clinical safety

The actual safety data reported do not raise any very major concerns but they are very limited in terms of number of patients and duration of treatment. In light of the potential concerns raised by the plasma concentrations, especially those of TFV, it is not possible to conclude that the long-term safety profile of the adult dose of Genvoya in children aged 6-12 years and from 25 kg is acceptable. Furthermore, the actual minimum age treated was 8 years and it appears that very few children weighed < 30 kg.

The safety profile over 48 weeks is similar to that reported at 24 weeks. With a safety dataset of 23 exposed for 48 weeks and 3 others for 8 weeks the data are very limited.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The PRAC considered that the risk management plan version 3.1 is acceptable. The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 3.1 with the following content:

Safety concerns

Table 34. Summary of Safety Concerns

	Safety Concerns for Genvoya	Attributable Component(s) of Genvoya
Important Identified Risks	Post-treatment hepatic flares in HIV/HBV coinfected patients	FTC, TAF
Important Potential Risks	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness	EVG
	Renal toxicity	TAF
	Bone events due to potential proximal renal tubulopathy/loss of BMD	TAF
	Ocular effects (posterior uveitis)	TAF
	Concurrent use of drugs whose coadministration with Genvoya is contraindicated	EVG, COBI
	Overdose of tenofovir occurring through accidental concurrent use of Genvoya with a TDF-containing product	TAF
Missing Information	Long-term safety information in adults and children	Genvoya
	Safety in pregnancy and lactation	EVG, COBI, FTC, TAF
	Safety in patients with severe renal impairment	COBI, FTC, TAF
	Safety in patients with severe hepatic impairment (CPT score C)	EVG, COBI, TAF
	Safety in patients with cardiac conduction disorders	COBI
	Safety in patients with HCV coinfection	TAF
	Development of drug resistance in long term use	Genvoya
	Drug-drug interactions	COBI, TAF

Key: BMD – bone mineral density, COBI – cobicistat, CPT – Child-Pugh-Turcotte, EVG – elvitegravir, FTC – emtricitabine, HBV – hepatitis B virus, HCV hepatitis C virus, HIV – human immunodeficiency virus, STR – single tablet regimen, TAF – tenofovir alafenamide.

Pharmacovigilance plan

Table 35. Ongoing and Planned Studies/Activities in the Post-Authorization Pharmacovigilance Development Plan

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Interventional clinical studies (Category 3)				
Study GS-US-292-0104 A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/ Cobicistat/Emtricitabine/ Tenofovir Alafenamide Versus Elvitegravir/ Cobicistat/Emtricitabine/ Tenofovir Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment-Naïve Adults	To evaluate the long-term safety of Genvoya versus Stribild® in HIV-1 infected, ARV treatment-naive adults	*Important potential risk:* Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness *Missing information:* Long-term safety information Development of drug resistance in long term use	Started	Week 144 report: Q3 2017
Study GS-US-292-0111 A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/ Cobicistat/Emtricitabine/ Tenofovir Alafenamide Versus Elvitegravir/ Cobicistat/Emtricitabine/ Tenofovir Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment-Naïve Adults	To evaluate the long-term safety of Genvoya versus Stribild® in HIV-1 infected, ARV treatment-naive adults	*Important potential risk:* Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness *Missing information:* Long-term safety information Development of drug resistance in long term use	Started	Week 144 report: Q3 2017
Noninterventional studies (Category 3)				
Antiretroviral Pregnancy Registry	To collect information on the risk of birth defects in patients exposed to ARVs, including the components of Genvoya, during pregnancy	*Missing information*: Safety in pregnancy	Started	Interim reports to be included in Genvoya PSURs (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)
Nonclinical studies (Category 3)				
In vitro study on the potential for significant effects on plasma TFV concentrations upon coadministration of TAF and xanthine oxidase inhibitors	The provide information on the potential for a drug-drug interaction between TAF and xanthine oxidase inhibitors	*Missing information*: Drug-drug interactions	Started	Final report: Q2 2017

Risk minimisation measures

Table 36. Summary of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important identified risk(s)		
Post-treatment hepatic flares in HIV/HBV coinfected patients	Section 4.4 of the SmPC informs about the risk of exacerbation of hepatitis in HIV-1/HBV coinfected patients following discontinuation of Genvoya.	None
Important potential risk(s)		
Suicidal ideation / suicide attempt in patients with a pre-existing history of depression or psychiatric illness	None	None
Renal toxicity	Section 4.4 of the SmPC informs that a potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded.	None
Bone events due to potential proximal renal tubulopathy / loss of BMD	None	None
Ocular effects (posterior uveitis)	None	None
Concurrent use of drugs whose coadministration with Genvoya is contraindicated	Sections 4.3 and 4.5 of the SmPC provide information on drugs whose coadministration with Genvoya is contraindicated. The Package Leaflet lists medications that should never be taken with Genvoya.	None
Overdose of tenofovir occurring through accidental concurrent use of Genvoya with a TDF-containing product	Section 4.4 (and 4.5) of the SmPC warns that Genvoya should not be administered concomitantly with medicinal products containing TDF used for the treatment of HBV infection. The Package Leaflet includes TDF in a list of medicines used in treating hepatitis B infection which should not be taken with Genvoya.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Missing information		
Long-term safety information in adults and children	None	None
Safety in pregnancy and lactation	Section 4.6 of the SmPC provides information on pregnancy in humans for the emtricitabine component and in animals for all components of Genvoya, and notes that Genvoya should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Section 4.6 of the SmPC also provides information on excretion of emtricitabine in human milk, that it is unknown whether elvitegravir, cobicistat and tenofovir alafenamide are excreted in human milk, and informs that Genvoya should not be used during breastfeeding.	None
Safety in patients with severe renal impairment	Section 4.2 of the SmPC states that Genvoya should not be initiated in patients with estimated creatinine clearance < 30 mL/min as there are no data available regarding the use of Genvoya in this population, and that Genvoya should be discontinued in patients with estimated creatinine clearance that declines below 30 mL/min during treatment. In addition, no data are available to make dose recommendations in children aged less than 12 years with renal impairment.	None
Safety in patient with severe hepatic impairment (CPT score C)	Section 4.2 of the SmPC informs that Genvoya is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C). Section 5.2 of the SmPC states that the effect of severe hepatic impairment on the pharmacokinetics of EVG, COBI or TAF has not been studied, and that the impact of liver impairment on the pharmacokinetics of FTC should be limited.	None
Safety in patients with cardiac conduction disorders	None	None
Safety in patients with HCV coinfection	Section 4.4 of the SmPC states that the safety and efficacy of Genvoya have not been established in patients coinfected with HIV-1 and HCV.	None
Development of drug resistance in long term use	None	None
Drug-drug interactions	Section 4.3 of the SmPC provides a list of drugs for which coadministration with Genvoya is contraindicated. Section 4.5 of the SmPC provides information on interactions that have not been studied, potential effects on drug levels, and recommendations concerning coadministration with Genvoya.	None

Key: BMD – bone mineral density, COBI- cobicistat, CPT – Child-Pugh-Turcotte, EVG- elvitegravir, HBV – hepatitis B virus, HCV – hepatitis C virus, HIV – human immunodeficiency virus, SmPC – Summary of Product Characteristics, TAF tenofovir alafenamide.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification (as follows) for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable.

3. Benefit-Risk Balance

3.1.1. Main clinical study

The MAH has an ongoing study (GS-US-292-0106) in paediatric patients. An updated clinical study report on Cohort 2 was provided with the responses during this procedure. This reports data to at least week 48 (median 72 weeks) for 23 subjects in Cohort 2 Part A (aged from 8 years and 25.5kg) and short term data (median 8 weeks) for 3 subjects enrolled into Part B. The approach that has been taken by the MAH to evaluate the use of Genvoya in HIV-infected children is compliant with current CHMP guidance.

3.2. Favourable effects

All the children in Cohort 2 Part A of the study have maintained their pre-study virologic suppression for at least 48 weeks after switching to GEN. They all had relatively high CD4 counts at baseline. Although an initial decline in CD4 count was noted at Week 2, the mean count then increased to near baseline by week 48, with little change in CD4% over the course of treatment. The finding may reflect variability in CD4 counts in small numbers of patients. It cannot be ruled out that very high intracellular TFV-PP levels might have impacted on CD4 counts but the slow return to baseline provides some reassurance. Therefore this is an issue that needs to be monitored but it does not preclude approval from 6 years of age and 25 kg.

Treatment adherence was high and no patient discontinued study drug. In terms of tablet palatability and size, one patient reported the tablet to have abnormal taste at baseline but not at Week 4 and one had a tablet size issue at baseline and Week 4. Both continued taking Genvoya. Therefore it seems that the adult dose form is acceptable in children from 8 years of age (the minimum age studied).In addition, the MAH committed to develop an age appropriate formulation and a subset of patients from 6 to less than 12 years are to be switched to the age appropriate STR formulation before the end of the study.

Comparisons of PK data obtained from these children at Week 4 and prior data obtained from adolescents and adults (as reflected tables 5 and 6 in section 5.2 of the SmPC) show that plasma exposures (AUC, C_{max} and C_{tau}) are higher for all analytes in Cohort 2 Part A children except for EVG C_{tau}, which is still >8-fold the in-vitro IC95 value.

Thus, based on 48-Week data and the PK comparisons, the use of the adult dose of Genvoya in children aged from 8 years and 25 kg does not raise any concerns regarding efficacy. Furthermore, use from 6 years is acceptable.

3.3. Uncertainties and limitations about favourable effects

There are only 23 children in Cohort 2 Part A (with 3 so far in Part B) and the data extend to completion of 48 weeks dosing. Nevertheless, if adherence remains high as they enter adolescence there is no a priori reason to expect that virologic suppression will not be maintained. Similarly, although all children were already virologically suppressed when they commenced Genvoya, the plasma exposures support expectation that responses in treatment–naïve children in this age group would be similar to those in adults assuming a similar level of adherence prevails.

3.4. Unfavourable effects

The actual safety profile appears to be as expected based on prior data in older patients. No Grade 3 or 4 clinical AEs were reported so far (27 February 2017 cut-off date) and the range of events is not

unexpected for the population treated. The effects on serum creatinine and eGFR most likely reflect initiation of COBI, with stable values after ~ Week 4. There was a decrease from baseline in proteinuria assessed by UPCR. Thus far the data do not suggest renal toxicity in the population studied.

3.5. Uncertainties and limitations about unfavourable effects

The safety data currently comprise 23 children in Cohort 2 Part A aged from 8 years and 25.5 kg who have been followed for a median of 72 weeks and data to week 8 (median) for another 3 children. Since this is an uncontrolled study, and since all children were already taking antiretroviral therapy, albeit mainly NRTIs and frequently only NRTI-containing regimens, it is not possible to draw firm conclusions regarding the safety of using the adult dose of Genvoya in this paediatric subset.

This fact alone would not preclude an approval for use at from 6 years and 25 kg body weight if the plasma exposures were very comparable to those observed in adults. However, plasma exposures are substantially higher in children aged 8-<12 years, with CV% values ~50% for AUCs of TAF, EVG and COBI and ~20% for AUCs of TFV and FTC. Furthermore, these children were treated under a protocol in which a large number of potentially interacting concomitant medications were forbidden and in which the actual concomitant medications were almost all antibacterial agents, analgesics and vaccines.

The MAH describes the GM increases in AUC (TAF 70.7%, TFV 52.2%, EVG 34.1%, COBI 57.7% and FTC 75.0%) as *modest and within the safe and efficacious ranges of the adult exposures in the GEN and STB programmes*. In this regard, note that the CV% for AUCs were ~50% for TAF, EVG and COBI but ~20% for TFV and FTC. There remains a potential that when the adult dose of Genvoya is administered to children with other intrinsic or extrinsic factors known to increase plasma exposures to one or more of the analytes of interest could result in higher plasma concentrations than are covered by the adult safety data. For example, there are several recognised DDIs leading to increased plasma TAF and TFV for which no dose modification is considered necessary in adults. However, against a background of already higher exposures in children aged 6-<12 years, it is not possible to predict the resulting safety profile.

The greatest concern has to be the plasma levels of TFV that could occur and the unknown effect of very chronic exposure to plasma levels much lower than those observed with TDF yet with unknown long-term effects on bone and renal targets in children. In Cohort 2 Part A the mean TFV AUC_{tau} (440.2 ng•hr/mL) was ~5-fold lower as compared to adult exposures from TDF 300 mg. It should be noted that this is ~1.6 x the mean AUC in adolescents and adults (POPPK-predicted) dosed with Genvoya.

Furthermore, the MAH compares TFV exposures in children aged 6-<12 years dosed with Genvoya to those in children aged 6-<12 years and adolescents dosed with regimens containing TDF. For TDF there are alternative formulations available for use in children aged < 12 years. The recommended daily doses of TDF for HIV-1 infected paediatric patients aged 6 to < 12 years are 123, 163 or 204 mg using reduced dose tablets for weights 17-22, 22 kg to < 28 kg and 28 kg to < 35 kg, respectively. Alternatively, equivalent doses can be administered using 33 mg/g granules with further dose adjustments for patients aged 2 to < 12 years who weigh < 17 kg. Importantly, the use of TDF in paediatric patients from 2 years and Truvada from 12 years is restricted to patients *with resistance or toxicities that preclude the use of alternative first line agents*. In contrast, use of Genvoya in adolescents and adults is restricted to patients with *HIV-1 that does not have mutations associated with resistance to EVG, FTC or TFV*.

It is accepted that the higher exposures observed to TAF, FTC, EVG and COBI may not be a major concern based on what is known about their safety profiles. It is also accepted that TFV exposures in the paediatric subjects dosed with Genvoya in study 106 are much lower than those documented in small numbers of children aged 6 to < 12 years treated with TDF and adolescents aged 12 to < 18 years treated with Stribild. However, it must be remembered that in the review of the TAF-containing products

the concerns regarding the unknown effect of long-term exposure to TFV levels typically associated with TAF was reflected in all the SmPCs as follows:

Nephrotoxicity

A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded (see section 5.3).

The comparisons made between TFV exposures in children aged 6-<12 years and adults with moderate renal impairment (eGFR: 30 to 60 mL/min) after daily dosing with Genvoya do not take into account the fact that use in the latter was mainly based on considerations of the relative effects of TAF vs. TDF on renal function markers. It is not agreed with the MAH that *safety has been established* for the range of exposures in these adults, only that the data available suggested there were *lesser safety issues* with TAF vs. TDF. Therefore the comparison made does not address the concerns regarding long-term exposure of children aged 6-<12 years to TFV at the levels observed with the adult dose of Genvoya.

Taking into account the TFV levels, mean increases from baseline of 2.9% and 5.1% in spine BMD were observed at Weeks 24 and 48, respectively, while corresponding mean increases from baseline in TBLH BMD were 1.7% and 4.3%. Mean spine and TBLH standard Z-scores decreased during the study but mean spine and TBLH BMD height-age Z-scores were almost unchanged from baseline at Week 48. Three subjects had a ≥ 4% decrease from baseline in spine (n = 2) or TBLH (n = 1) BMD during the study. Two had a ≥ 4% decrease from baseline in spine BMD at Week 24. One continued to have a ≥ 4% decrease in spine BMD at week 48 while the other had a percent change in spine BMD of −3.894 at Week 48. The height-age adjusted spine and TBLH Z-scores were > −2.0 at Weeks 24 and 48 for these subjects and they had TFV AUC and Cmax values similar to the mean values. The third subject had a 4.173% decline in TBLH BMD from baseline at Week 48.

3.6. Effects Table

Table 37. Effects Table for use of Genvoya in children from 6 years and 25 kg (data cut-off: April 2016)

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
HIV-RNA	FDA snapshot algorithm	< 50 c/mL	Genvoya 23/23	N/A	48 weeks data N=23; 8-11 years Virologically suppressed at baseline	GS-US-292-0106 Cohort 2 Part A
CD_4	Change in count and CD_4% from baseline	Cells/ mm^3 or %	Genvoya Mean drop in CD_4 count followed by rise toward baseline and CD_4% not affected	N/A	48 weeks data N=23; 8-11 years High counts at baseline	GS-US-292-0106 Cohort 2 Part A
Unfavourable Effects						
Plasma exposure	AUCs	ng.h/ mL	Higher AUCs for EVG, COBI, FTC, TAF and TFV vs. adolescents and adults	N/A	N=23 Potential for long-term safety issues related to chronic raised exposure vs. older subjects is unknown	GS-US-292-0106 Cohort 2 Part A
Safety profile	AEs, laboratory data		Grade 1-2 clinical AEs 7 Grade 3	N/A	N=23 Median follow-up 72 months	GS-US-292-0106 Cohort 2 Part A

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			laboratory abnormal, of which 5 neutropenia			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There is a need for better and simple HIV treatment regimens for children. There are no concerns so far regarding efficacy of the adult dose of Genvoya in virologically suppressed children aged from 8 years and 25.5 kg (the actual minima included). Provided that children take the medication as recommended, the PK data raise no concerns over the potential longer-term efficacy of once daily dosing of Genvoya with food in this paediatric subset.

Genvoya has not been studied in ART-naïve children in the age range 6-<12 years but the CHMP guidance acknowledges the scarcity of such children for study and that the efficacy already shown in treatment-naïve adults and adolescents can be assumed to apply to ART-naïve children based on comparisons of plasma levels.

There is an important potential concern with regard to safety due to the plasma exposures reported and the potential effects, especially for TFV in growing children. This concern takes into account that that at this time only 50 patients aged 12-<17 years have been followed and there are only 23 treated in the age range 8-<12 years for whom there is a median follow-up of 72 weeks.

While the actual safety data reported do not raise any very major concerns, they are very limited in number of patients and duration of treatment. In light of the potential concerns raised by the plasma concentrations, especially those of TFV, it is not possible to conclude that the long-term safety profile of the adult dose of Genvoya in children aged 6-12 years and from 25 kg will resemble that in older subjects.

3.7.2. Balance of benefits and risks

The concerns regarding the safety of long-term use of the adult dose of Genvoya in children aged from 6-< 12 years and from 25 kg body weight cannot be resolved by the data available from study 106 and based on comparisons of plasma levels across age groups, studies and formulations. Nevertheless, taking into account that use of Genvoya is anyway restricted to treatment of HIV-1 without mutations associated with resistance to EVG, FTC TFV it is proposed that use could be allowed in this age and weight range if it is additionally restricted to children with toxicities precluding the use of alternative first-line regimens.

3.8. Conclusions

There are potential safety concerns raised by the PK data that cannot be addressed by the data currently available. However, recognising the efficacy of Genvoya and the need for simple treatment regimens, it is proposed that the benefit-risk could be favourable if use in children aged from 6-<12 years and from 25 kg is restricted such that section 4.1 of the SmPC reads as follows:

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 as follows:

- In adults and adolescents aged from 12 years and with body weight at least 35 kg

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

See sections 4.2, 4.4 and 5.1.

4. Recommendations

Final outcome

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**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, II and IIIB

Extension of Indication for Genvoya to include children aged from 6 t years and with body weight at least 25kg for whom alternative regimens are unsuitable due to toxicities, infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir.

As a consequence, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on the analysis of the paediatric study GS-US-292-0106 (Cohort 2). This is a Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment Naive Adolescents and Virologically Suppressed Children.

In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0.

The Package Leaflet and the Risk Management Plan (v. 3.2) are updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Package Leaflet and to the Risk Management Plan (RMP).

This CHMP recommendation is subject to the following conditions:

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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.

- In addition, an updated RMP should be submitted:
- At the request of the European Medicines Agency

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication for Genvoya to include children aged from 6 tyears and with body weight at least 25kg for whom alternative regimens are unsuitable due to toxicities, infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir.
As a consequence, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on the analysis of the paediatric study GS-US-292-0106 (Cohort 2). This is a Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment Naive Adolescents and Virologically Suppressed Children.
In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0.
The Package Leaflet is updated in accordance. Furthermore, the updated RMP version 3.2 has been agreed.

Summary

Please refer to the scientific discussion Genvoya EMEA/H/C/004042/II/0026.