Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide

Proprietary Product Name: Genvoya

Sponsor: Gilead Sciences Pty Ltd

Date of first round report: 30 June 2017
Date of second round report: 27 October 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
l z	Terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log plasma/serum concentration of drug versus time curve of the drug
ABC	Abacavir
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
anti-HBe	Antibody against hepatitis B e-antigen
Anti-HBs	Antibody against hepatitis B surface antigen
ANOVA	Analysis of variance
ART	Antiretroviral therapy
ARV	Antiretroviral
ARV/r+TVD	Ritonavir booted antiretroviral
AST	Aspartate aminotransferase
ATR	Atazanavir
ATV/co	Cobicistat booted atazanavir
AUC	Area under the plasma/serum concentration versus time curve
AUC_{∞}	Area under the plasma/serum concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-last}} + (C_{last}/l\ z)$
AUC_{last}	Area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	Area under the plasma/serum concentration versus time curve over the dosing interval
β2MG	β-2-microglobulin
BMD	Bone mineral density
CD4	Cluster determinant 4
CD4%	Percentage of CD4 cells

Abbreviation	Meaning
CG	Cockcroft-Gault
CI	Confidence interval
CL/F	Apparent oral clearance after administration of the drug: CL/F = Dose/AUC_{∞}. Where 'Dose' is the dose of the drug
CMH	Cochran-Mantel-Haenszel
C_{last}	Last observed quantifiable plasma/serum concentration of the drug
C_{max}	Maximum observed plasma/serum concentration of the drug
C_{tau}	Observed drug concentration at the end of the dosing interval
COBI/C	Cobicistat
CPT	Child-Pugh-Trucotte
CSR	Clinical study report
CV	Coefficient of variation
DNA	Deoxyribonucleic acid
DXA	Dual energy X-ray absorptiometry
E/C/F/TAF	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated) = Genvoya = Genvoya
EFV	Efavirenz
EMA	European Medicines Agency
EVG/E	Elviregravir (Vitekta)
eGFR	Estimated glomerular filtration rate
$eGFR_{CG}$	Estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
$eGFR_{CKD\text{-}EPI,\ creatinine}$	Estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration serum creatinine equation
$eGFR_{CKD\text{-}EPI,\ cyst}$	Estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration cystatin C equation
FAS	Full analysis set

Abbreviation	Meaning
FDA	Food and Drug Administration (USA)
FDC	Fixed dose combination
$FEPO_4$	Fractional excretion of phosphate
FEUA	Fractional excretion of uric acid
F/FTC	Emtricitabine (Emtriva)
F/TAF	Emtricitabine/tenofovir alafenamide, co-formulated (Descovy)
F/TDF	Emtricitabine/tenofovir disoproxil fumarate (co-formulated) = Truvada
GEN	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated) = E/C/F/TAF = Genvoya
GFR	Glomerular filtration rate
GLSM	Geometric least square mean
HBcAg	Hepatitis B core antigen
HBcIgM	Hepatitis B core antigen IgM
HBeAg	Hepatitis B e-antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV/HIV-1	Human immunodeficiency virus, type 1
HDL	High density lipoprotein
IC_{95}	95% inhibitory concentration
ICH	International Council for Harmonisation (of Technical Requirements of Pharmaceuticals for Human Use)
INSTI	Integrase strand transfer inhibitor
LDL	Low density lipoprotein
LOCF	Last observation carried forward
LSM	Least squares mean

Abbreviation	Meaning
M=E	Missing = excluded
M=F	Missing = failure
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
N or n	Number of subjects in a population
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI/ NtRTI	Nucleoside reverse transcriptase inhibitor
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamics
PEP	Pre-exposure prophylaxis
PI	Protease inhibitor
PI	Product Information (Australia)
PI	Prescribing information/package insert (USA)
P1NP	Procollagen type 1 N-terminal propeptide
PK	Pharmacokinetics
PrEP	Pre exposure prophylaxis
PTH	Parathyroid hormone
Q1, Q3	First, third quartile
r	Ritonavir
RAP	Resistance analysis population
RBP	Retinol binding protein
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Standard deviation
STB	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild)

Abbreviation	Meaning
T½	Estimate of the terminal elimination half-life of the drug in plasma/serum, calculated by dividing the natural log of 2 by the terminal elimination rate constant (l z)
TAF	Tenofovir alafenamide
TBLH	Total body less head
T_{max}	Time (observed time point) of C_{max}
TDF	Tenofovir disoproxil fumerate (Viread)
TDF-DP	Tenofovir disphosphate
TFV	Tenofovir
TmP/GFR	Renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate
TVD	Emtricitabine/tenofovir disoproxil fumerate (co-formulated; Truvada^{Ò}
UACR	Urine albumin to creatinine ratio
ULN	Upper limit of normal
UACR	Urine albumin to creatinine ratio
UPCR	Urine protein to creatinine ratio
VF	Virologic failure
Vz	Volume of distribution of the drug after intravenous administration
Vz/F	Apparent volume of distribution of the drug

1. Submission details

1.1. Identifying information

Submission number	PM-2016-04632-1-2
Sponsor	Gilead Sciences Pty Ltd
Trade name	Genvoya
Active substance	Elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide

1.2. Submission type

This is an abridged submission. The submission seeks to make the following amendments to the current registration:

- An extension to the indication to include treatment of chronic hepatitis B infection in adults co-infected with HIV and hepatitis B virus (HBV).
- To extend the indication to include treatment of paediatric patients weighing at least 25 kg.
- To remove the class warnings in the Precautions section of the PI that are related to lactic acidosis, severe hepatomegaly with steatosis and lipodystrophy.

Genvoya is a fixed dose combination product containing 150 mg elvitegravir and 150 mg cobicistat and 200 mg emtricitabine and 10 mg tenofovir alafenamide.

1.3. Drug class and therapeutic indication

Genvoya is a fixed dose combination (FDC) product which contains elvitegravir (E/EVG), an integrase inhibitor; cobicistat (C/COBI), a CYP3A inhibitor which acts as a pharmacokinetic enhancer; emtricitabine (F/FTC) and tenofovir alafenamide (TAF) which are nucleoside reverse transcriptase inhibitors.

The current approved indication is:

> *Genvoya is indicated as a single tablet regimen for the treatment of HIV-1 infection in adults and adolescents aged 12 years of age and older with body weight at least 35 kg who are either treatment–naïve; or virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see CLINICAL TRIALS). Patients must not have a history of treatment failure or known mutations associated with resistance to the antiretroviral components of Genvoya.*
>
> *Genvoya is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV 1 reverse transcriptase inhibitors.*

The proposed revised indication (the changes to the indication are underlined) is:

> *Genvoya is indicated as a single tablet regimen for the treatment of HIV-1 infection in adults and <u>paediatric patients</u> weighing <u>at least 25 kg</u> who are either treatment–naïve; or virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see*

CLINICAL TRIALS). Patients must not have a history of treatment failure or known mutations associated with resistance to the antiretroviral components of Genvoya.

Genvoya is also indicated for the treatment of chronic hepatitis B in adults co-infected with HIV-1 and hepatitis B (HBV).

Genvoya is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors.

1.4. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

- Tablet containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg emtricitabine and tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide. Bottle of 30 tablets.

No new dosage forms or strengths are proposed.

1.5. Dosage and administration

The current approved dose regimen is: one tablet daily taken with food.

No change to the current dose regimen is proposed.

The proposed revised Dosage and Administration section of the PI (the revised sections of the wording are underlined) is:

Adults: The recommended dose of Genvoya is one tablet once daily taken with food.

Children and Adolescents up to 18 Years of Age: In paediatric patients weighing ≥ 25 kg, the recommended dose of Genvoya is one tablet once daily taken with food.

No data are available on which to make a dose recommendation for paediatric patients weighing less than 25 kg.

No data are available on which to make a dose recommendation for paediatric patients younger than 18 years who are co-infected with HIV-1 and chronic hepatitis B.

Elderly: No dose adjustment is required for elderly patients. Clinical trials of Genvoya included 97 patients (80 receiving Genvoya) aged 65 years and over. No differences in safety or efficacy have been observed between elderly patients and those between 8 and less than 65 years of age.

Renal impairment: No dose adjustment of Genvoya is required in adult patients with estimated creatinine clearance greater than or equal to 30 mL/min. The safety of Genvoya has not been established in patients with estimated creatinine clearance that declines below 30 mL/min.

Genvoya should not be initiated in patients with estimated creatinine clearance below 30 mL/min as there are insufficient data available regarding the use of Genvoya in this population.

No data are available to make dose recommendations in paediatric patients with renal impairment.

Hepatic Impairment: No dose adjustment of Genvoya is required in patients with mild (Child Pugh Class A), or moderate (Child-Pugh Class B) hepatic impairment. Genvoya has not been studied in patients with severe hepatic impairment (Child-Pugh Class C); therefore, Genvoya is not recommended for use in patients with severe hepatic impairment (see Pharmacological Properties: Pharmacokinetics in Special Populations).

1.6. Proposed changes to the product documentation

The submission proposes changes to the following sections of the PI: Indications, Precautions, Pharmacology (Drug Resistance), Drug Interactions, Clinical Trials, Adverse Effects and Dosage and Administration,

These describe the pivotal trials supporting the proposed new indications, amend the precautions, and update the table of adverse reactions in clinical trials to include the studies in the submission. Detailed comments on the changes are provided later in this report.

2. Background

2.1. Information on the condition being treated

No new information on HIV infection is included in the submission.

2.2. Current treatment options

Morbidity and mortality in the HIV-infected population is increasingly driven by non-acquired immune deficiency syndrome-associated co-morbidities, and the development of novel therapeutics has become more focused on the optimisation of tolerability, long-term safety, and adherence of potent antiretroviral (ARV) therapy (ART) regimens. In addition, new therapies must take into consideration HIV genetic variability, the aging HIV-infected population, ARV resistance, regimen simplification, and durable efficacy.

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

The pathogenesis of HIV-1 infection and the general virologic and immunologic principles underlying the use of ART are similar in HIV-infected adult and paediatric patients. Adult guidelines for ART are usually appropriate for post pubertal adolescents. However, there are important and unique issues for HIV infected infants, children, and adolescents that are relevant to ART, including the following:

- In utero, intrapartum, and/or postpartum neonatal exposure to antiretrovirals (ARVs) in most perinatally infected children.
- Higher viral loads in perinatally infected infants than in adolescents and adults.
- Age-specific interpretation of CD4 cell counts.
- Changes in PK parameters with age caused by the continuing development and maturation of organ systems involved in drug absorption, distribution, metabolism, and clearance.
- Special considerations associated with adherence to ART.

2.3. Clinical rationale

There are few ARVs available for young children compared with those available for adults. In particular, there is no once-daily FDC as a complete regimen available for patients < 12 years of age. This is an important unmet medical need in this patient population, as FDCs improve adherence by reducing pill burden, leading to improved clinical and virologic outcomes. The

benefit of a FDC tablet as a complete regimen is particularly relevant for children, as inadequate social support, peer-pressure, and a complex social environment may negatively impact their adherence. In addition, with multi-tablet regimens, they may selectively avoid certain ARVs that are not acceptable (eg, big pill size) or palatable (eg, bitter taste), which can result in adverse clinical outcomes such as development of resistance and virologic failure.

Genvoya fulfils the unmet medical need in HIV-1 infected paediatric patients < 12 years of age weighing ≥ 25 kg as the first FDC for this population (versus multi tablet regimens) to comprise a complete once daily single tablet regimen.

2.4. Formulation

2.4.1. Formulation development

The formulation used in the clinical studies is the same as that currently marketed.

2.4.2. Excipients

The registered formulation contains the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hyprolose, silicon dioxide, sodium lauryl sulfate, and magnesium stearate. Film-coating: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, indigo carmine aluminum lake, and iron oxide yellow.

No change to the formulation is proposed in this application.

2.5. Guidance

The TGA has adopted the following guidelines which are relevant to this application:

- Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection EMEA/CPMP/EWP/633/02 Revision 2, which came into effect in June 2009 and was adopted by TGA in July 2009.
- Guideline on the Clinical Evaluation of Direct Acting Antiviral Agents Intended for Treatment of Chronic Hepatitis C. EMEA/CHMP/EWP/30039/2008. Effective from May 2010.

2.6. Evaluator's commentary on the background information

The background information is adequate.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The dossier documented a development program of and other clinical trials relating to the proposed extension of indications.

- 2 x Pivotal efficacy/safety studies
- 4 x Other efficacy/safety studies
- 1 x ISE (tables)
- 1 x SAP and 1 x ISS (tables)
- 5 x Virology reports + Virology analysis plan.

3.2. Paediatric data

The submission included paediatric efficacy and safety data.

3.3. Good clinical practice

The study reports state that all studies were conducted in accordance with the ICH GCP and the original principles embodied in the Declaration of Helsinki. Studies conducted in the USA also complied with the requirement of the US Code of Federal Regulations Title 21, Part 312 and the studies conducted in Europe complied with the European Community Directive 2001/20/EC. All studies conducted in other countries complied with local regulatory requirements. All subjects completed written informed consent prior to any study procedures and all necessary documents were submitted to appropriate independent ethics committees.

3.4. Evaluator's commentary on the clinical dossier

The dossier submitted has been compiled from the multiple submissions made in the EU, leading to the submission including multiple summaries and therefore comprises:

Table 1: Summaries submitted

Indication	Summaries
Co-infection HIV / HBV (24 weeks) and long term treatment virologically suppressed subjects switching therapy (96 weeks)	Clinical Overview Summary of Biopharmaceuticals Studies Summary of Clinical Pharmacology Summary of Clinical Efficacy Summary of Clinical Safety
Paediatric use > 25 kg (24 weeks)	Clinical Overview Summary of Biopharmaceuticals Studies Summary of Clinical Pharmacology Summary of Clinical Efficacy Summary of Clinical Safety
Long Term efficacy and safety data in treatment naïve adults (144 weeks)	Clinical Overview Summary of Clinical Pharmacology Summary of Clinical Efficacy Summary of Clinical Safety
Renal Impairment	Clinical Overview Summary of Clinical Pharmacology Summary of Clinical Efficacy Summary of Clinical Safety
Class warnings (remove lactic	Clinical Overview

Indication	Summaries
acidosis/severe hepatomegaly)	

The dossier makes reference to a number of studies evaluated in previous submissions to TGA. These studies have not been evaluated again and reference is given for the previous submissions, where possible.

The *Clinical Overview* for the renal impairment indication relates only to the data to Week 96 and not to the data from Week 144 and therefore does not discuss the data in the CSR included in this submission. The *Summary of Clinical Efficacy* and *Summary of Clinical Safety* discuss the data to Week 144.

The Note to Reviewer included in Module 1 contains one study (GS-US-320-0108) included twice and omits study GS-US-320-0110. The listing of studies outlined in the cover letter is correct.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

The only new pharmacokinetic data included in this submission relates to the use in children aged > 6 to < 12 years weighing ≥ 25 kg.

Table 2: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary aim
PK in special populations	Children/adolescents	GS-US-292-0106	Efficacy and Safety

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

4.2.1. Physicochemical characteristics of the active substance

No new data submitted.

4.2.2. Pharmacokinetics in healthy subjects

No new data was submitted in this application.

4.2.3. Pharmacokinetics in the target population

Study GS-US-292-0106 was a study designed to characterise the PK and confirm the dose of Genvoya, was well as to evaluate the safety, tolerability and antiviral activity in ART naïve male and female HIV infected adolescents (Cohort 1) and virologically suppressed HIV infected children 6 to < 12 years of age (Cohort 2). The results for Cohort 1 were evaluated in previous submissions.

The results for Cohort 2 were provided for evaluation in this submission.

Cohort 2 Part A consisted of 23 subjects whose weights range from 25.5 kg to 58.2 kg, with a median weight of 30.5 kg, and with ages ranging from 8 years to 11 years. This study did not

enrol any Cohort 2 Part A subjects < 8 years of age who met the weight cut-off of ≥ 25 kg. However, exposure and safety assessed across the weight spectrum for this cohort, as in this study, are expected to apply to any child who is 6 to 12 years of age and ≥ 25 kg, as exposures in this age group are expected to be dictated by weight alone.

Exposures of EVG, COBI, FTC, TAF, and tenofovir (TFV, major metabolite of TAF) in subjects 6 to < 12 years of age weighing ≥ 25 kg were compared with exposures in adult subjects in Phase II/III populations. Exposures (AUC, C_{max}, and/or C_{tau}) of TAF, TFV, EVG, COBI, and FTC, except EVG C_{tau}, upon administration of Genvoya to these paediatric subjects were modestly higher (20%-80%) as compared with exposures achieved in adults. Increases in AUC were as follows: TAF (70.7%), TFV (52.2%), EVG (34.1%), COBI (57.7%), and FTC (75.0%).

The mean EVG C_{tau}, although slightly lower versus adult reference comparator values, was > 8-fold above the IC_{95} for wild-type virus (44.5 ng/mL). TFV AUC_{tau} (440.2 ng*hr/mL) was approximately 5-fold lower as compared with adult exposures from TDF 300 mg.

4.3. Evaluator's overall conclusions on pharmacokinetics

The exposures of all the drug components in children aged 6 to 12 years were within the safe and efficacious range of the adult exposures in the Genvoya and/or Stribild (elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate) programs confirming the appropriateness of Genvoya for use in HIV-infected children weighing ≥ 25 kg.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

No new pharmacodynamic (PD) information was included in this submission.

5.2. Evaluator's overall conclusions on pharmacodynamics

Not applicable as no new information on PD was included in this submission.

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics dose finding studies

Not applicable.

6.2. Phase II dose finding studies

Not applicable.

6.3. Phase III pivotal studies investigating more than one dose regimen

Not applicable.

6.4. Evaluator's conclusions on dose finding for the pivotal studies

The dose of Genvoya used in the study of patients co-infected with HIV and HBV is the same as the currently approved dose for the adult approved indications.

The dose of Genvoya used in the paediatric study was the same as the currently approved dose which for children aged > 12 years (which is same as the adult dose).

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

The following clinical efficacy studies were submitted:

Indication 1: Treatment of patients co-infected with HIV and Hep B.

- Pivotal studies
  - Study GS-US-292-1249: A Phase IIIb Open-label Study of the Efficacy and Safety of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen in HIV-1/Hepatitis B Co-infected Adults
- Other studies – not applicable
- Analyses performed across trials – not applicable
- Evaluator's conclusions.

Indication 2: Treatment in children ≥ 25 kg

- Pivotal studies
  - Study GS-US-292-0106: A Phase II/III, 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.
- Other studies – not applicable
- Analyses performed across trials – not applicable
- Evaluator's conclusions.

Indication 3: Amendments to PI update Clinical trials and Renal impairment

- Pivotal studies
  - Study GS-US-292-0109: A Phase III, Open-Label Study to Evaluate Switching from a TDF-Containing Combination Regimen to a TAF-Containing Combination Single Tablet Regimen (STR) in Virologically-Suppressed, HIV-1 Positive Subjects
  - Study GS-US-292-0104: A Phase III, Randomised, 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-Naive Adults
  - Study GS-US-292-0111: A Phase III, Randomised, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Versus Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1Positive, Antiretroviral Treatment-Naive Adults

  - Study GS-US-292-0112: A Phase III Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment.

- Other studies – not applicable
- Analyses performed across trials = pooled analysis of Studies GS-US-292-0104 and GS-US-292-0111
- Evaluators conclusions

Indication 4: Removal of Class Statements

- Pivotal studies – not applicable
- Other studies – not applicable
- Analysis performed across trials
- Evaluators conclusions.

7.2. Indication 1: Treatment of patients co-infected with HIV and HBV

7.2.1. Pivotal or main efficacy studies

7.2.1.1. Study GS-US-292-1249

A Phase IIIb Open-label Study of the Efficacy and Safety of Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen in HIV-1/Hepatitis B Co-infected Adults.

Study design, objectives, locations and dates

An open label, single arm, dual cohort, multicentre study conducted at 24 sites: USA (21), Canada (2) and Japan (1) from February 2014 to June 2015.

The study population consisted of two cohorts:

- Cohort 1: HIV/HBV co-infected adults who were HIV and HBV treatment naïve, n = up to 50
- Cohort 2: HIV/HBV co-infected adults who were HIV suppressed (with or without suppression of HBV DNA), n = up to 75

Inclusion and exclusion criteria

Inclusion: HIV and HBV (chronic) co-infected males and females (non-childbearing potential) ≥ 18 years of age, with a CD4 count > 200 cells/µL, ALT ≤ 10 x ULN, total bilirubin ≤ 2.5 mg/dL, INR ≤ 1.5, albumin ≥ 3 g/dL, and Screening creatinine clearance by Cockcroft-Gault of ≥ 50 mL/min, no evidence of cirrhosis or hepatocellular carcinoma, and hepatitis C (HCV) and hepatitis D (HDV) negative.

Cohort 1: No current or prior anti-HIV treatment, included ARV medication received for prevention or post exposure prophylaxis; plasma HIV-1 RNA level ≥ 500 copies/mL; HBV DNA ≥ 3 $\log_{10}$ IU/mL

Cohort 2: Receiving current ARV regimen for at least 4 consecutive months but could not be on TDF/FTC/entecavir or TDF/lamivudine (3TC)/entrecavir; maintained plasma HIV-1 RNA <50 copies/mL for 6 consecutive months; HBV DNA < 9 $\log_{10}$ IU/mL. No current or prior regimen containing 3 active anti-HBV agents (that is, patients could not be on TDF/FTC/entecavir or TDF/lamivudine [3TC]/entecavir). Current regimens containing two active anti-HBV agents that included entecavir must have been discontinued and switched to study drug only.

Chronic HBV was defined as HBsAg positive for ≥ 6 months or HBsAg positive at screening and either HBeAg or HBV DNA positive for ≥ 6 months or positive Total anti-HBc and negative HBcIgM antibody and HBsAg positive or HBe Ag positive or HBV DNA positive.

Study treatments

All patients received Genvoya (E/C/F/TAF 150/150/200/10 mg) administered in an open label manner orally once daily with food.

Efficacy variables and outcomes

The *co-primary endpoints* were:

- Percentage of patients that achieved HIV-1 RNA < 50 copies/mL at Week 24 [as defined by the US FDA snapshot algorithm]
- Percentage of patients with HBV DNA < 29 IU/mL at Week 24 (missing = failure [M = F])

For the snapshot algorithm for the Week 24 HIV virologic outcome, the analysis window was defined as from Study Day 126 to Study Day 209 (inclusive).

For HIV

Virologic Success: included subjects who had the last available HIV-1 RNA < 50 copies/mL in the Week 24 analysis window while on treatment.

HIV Virologic Failure: included the following:

- subjects with HIV-1 RNA was ≥ 50 copies/mL in the Week 24 analysis window
- subjects who did not have an on-treatment HIV-1 RNA in the Week 24 analysis window and:
  - subjects who discontinued prior to Week 24 due to lack of efficacy
  - subjects who discontinued prior to Week 24 for other reason than lack of efficacy and last available HIV-1 RNA ≥ 50 copies/mL
- subjects who had non-study ARV added between the first dose of study drug and last HIV-1 collection date in the Week 24 analysis window
- *No Virologic Data:* defined as subjects who did not have HIV-1 RNA data in the Week 24 analysis window due to discontinuation of study drug prior to Week 24 due to AE, death or other reason and the last available HIV-1 RNA was < 50 copies/mL or missing data wile on study drug.

For HBV

Virologic response: defined as achieving HBV DNA < 29 IU/mL at Week 24 (analysed using an M = F approach in which all missing data were treated as HBV DNA ≥ 29 IU/mL).

Secondary outcomes included:

- HIV efficacy endpoints:
  - The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot algorithm
  - The percentage of subjects with HIV-1 RNA < 50 copies/mL and < 20 copies/mL at Weeks 24 and 48 as defined by 2 different missing data imputation methods (M = F and M = E)
  - The change from baseline in CD4 cell count at Week 24 and 48
  - The change from baseline in CD4% at Week 24 and 48
- HBV efficacy, serological, biochemical and FibroTest score endpoints:

- The percentage of subjects with HBV DNA < 29 IU/mL at Week 48 as defined by 2 different missing data imputation methods (M = F and M = E [missing = excluded])
- The percentage of subjects with HBV DNA < 20 IU/mL at Weeks 24 and 48 as defined by 2 different missing data imputation methods (M = F and M = E)
- The percentage of subjects with HBsAg loss at Weeks 24 and 48
  - § This was defined as having a positive HBsAg and negative anti-HBs at baseline and a negative HBsAg by the given post baseline visit.
- The percentage of subjects with HBsAg seroconversion to anti-HBs at Weeks 24 and 48
  - § This was defined as having both of the following 2 criteria met: (1) anti-HBs negative at baseline and anti-HBs positive post baseline and (2) HBsAg positive at baseline and HBsAg negative by the given post baseline visit or HBsAg negative at baseline with anti-HBs negative at baseline.
- The percentage of subjects with HBeAg loss at Weeks 24 and 48 (defined as above for HBsAg)
- The percentage of subjects with HBeAg seroconversion to anti-HBe at Weeks 24 and 48 (defined as above for HBsAg)
- The percentage of subjects with ALT normalization at Weeks 24 and 48
  - § This was defined as having an ALT value above the normal range at baseline and within the normal range at the given post baseline visit.
- Change from baseline in FibroTest score at Weeks 24 and 48
- Shifts from baseline in FibroTest categories at Weeks 24 and 48

Randomisation and blinding methods

Not applicable – study was open label.

Analysis populations

Full analysis set (FAS): defined as all subjects who were enrolled, received at least one dose of study drug, had at least one post Day 1 plasma HBV DNA or HIV-1 RNA result while on study drug and had no major protocol violations or eligibility criteria.

Safety analysis set: defined as all subjects who were enrolled and received at least one dose of study drug.

Sample size

The sample size limits for the study, 50 in Cohort 1 and 75 in Cohort 2, were chosen based on the feasibility of conducting such a study and not based on statistical considerations. The table below summarises the extent of the half-width of 2-sided 95% confidence intervals (CIs) for a range of observed single proportions (precision), using normal approximation.

Table 3: Half-width of 2-sided 95% confidence intervals (CIs) for observed single proportions (precision) using normal approximation

Observed Proportion	Half-Width of 95% CI When N = 50	Half-Width of 95% CI When N = 75
0.8	0.111	0.091
0.9	0.083	0.068

Statistical methods

Descriptive statistics were used to characterise the efficacy and safety profile of each cohort in the study, including count, mean standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous measures and count and percentage for categorical/ordinal data.

For the primary HIV efficacy endpoint, virologic outcomes were summarised using frequency counts and percentages. A 2-sided exact 95% CI for the proportion of virologic success was constructed.

For the primary HBV efficacy endpoint, outcomes were summarised using frequency counts and percentages. A 2-sided exact 95% CI for the percentage of responders was constructed. A p-value from McNemar's test comparing the joint distribution of baseline and Week 24 HBV DNA categories (< 29 IU/mL versus ≥ 29 IU/mL) was provided for Cohort 2 subjects.

In a secondary analysis of the primary HBV efficacy endpoint, a Missing = Excluded (M = E) approach was taken. In this approach, all missing data were excluded in the computation of virologic response (that is, missing data points were excluded from both the numerator and denominator in response rate computation).

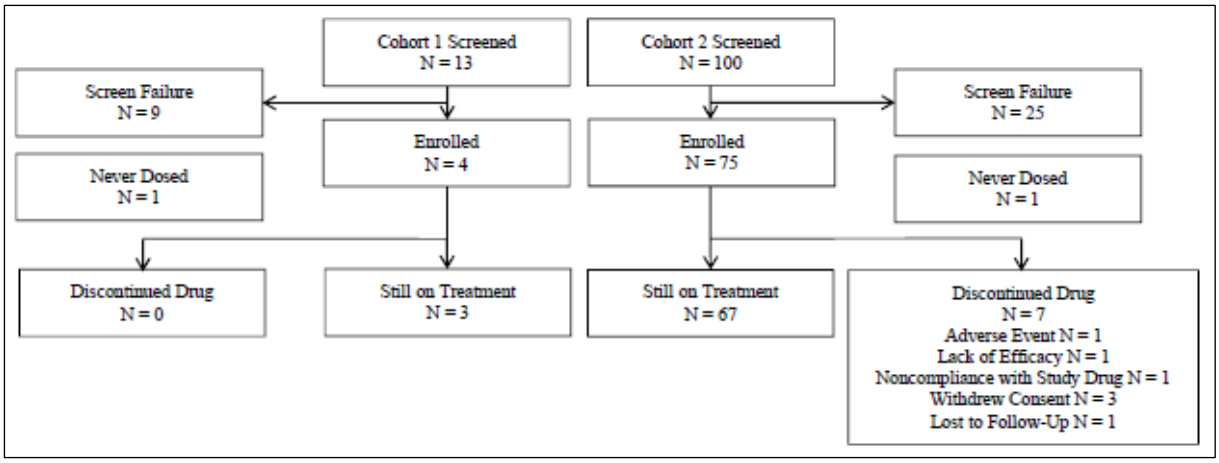
Participant flow

Screened: 113 subjects

Enrolled 79 subjects: Cohort 1 = 4 HIV/HBV treatment naïve subjects and Cohort 2 = 75 HIV suppressed subjects.

Completed study (Week 48) = 70 subjects; 2 subjects did not receive study drug and 7 subjects were discontinued.

Figure 1: Study GS-US-292-1249: Disposition of study subjects



Major protocol violations/deviations

Two subjects did not meet the inclusion criteria of chronic HBV infection and were excluded from the FAS. A total of 24 important protocol deviations occurred in 21 subjects during the study. The majority of deviations were violations of inclusion criteria but none were considered to affect the overall quality or interpretation of the study data.

Baseline data

Cohort 1: HIV/HBV Treatment naïve subjects: The 3 subjects treated in Cohort 1 were all male and under 50 years of age. Two subjects were Asian and 1 subject was White (not Hispanic/Latino).

Cohort 2: HIV-Suppressed Subjects: The majority of the 74 subjects in Cohort 2 were male (91.9%) and < 65 years of age (97.3%; median: 51 years, range: 28 to 67). The most common races were White (67.6%), Black (18.9%), and Asian (9.5%). Most subjects (83.8%) were not Hispanic/Latino. The median (Q1, Q3) baseline BMI was 25.4 (23.1, 28.3) kg/m^2.

Results for the primary efficacy outcome

HIV Response

Cohort 1 Treatment naïve subjects

As only 3 subjects were treated in this cohort, limited summaries are provided and interpretation is not possible due to small numbers. At Week 24 all 3 subjects had virologic success (HIV-1 RNA < 50 copies/mL using the FDA snapshot algorithm).

Cohort 2 HIV suppressed subjects

At Week 24, 94.4% of subjects (95% CI: 86.4% to 98.5%) had virologic success (HIV-1 RNA < 50 copies/mL using the FDA snapshot algorithm).

One subject (1.4%) was classified as a virologic failure (HIV-1 RNA ≥ 50 copies/mL). This subject, a [information redacted] year-old White man, was virologically suppressed on darunavir, RTV, and FTC/TDF (Truvada) prior to switching to Genvoya. The subject's reported overall adherence was ≥ 95%). His HIV-1 RNA was < 50 copies/mL until Day 188 when his HIV-1 RNA value was 61 copies/mL. Upon repeat testing 14 days later (Day 202; Week 24 assessment), his HIV-1 RNA value was 66 copies/mL. Study drug was discontinued on Day 210 due to lack of efficacy. Three subjects had no virologic data in the Week 24 window due to having discontinued study drug.

Table 4: Study GS-US-292-1249: Virologic outcome at Week 24 using FDA snapshot algorithm and HIV-1 RNA < 50 copies/mL (full analysis set)

	E/C/F/TAF Cohort 1 (N = 3)	E/C/F/TAF Cohort 2 (N = 72)
Virologic Success at Week 24		
HIV-1 RNA < 50 copies/mL	3/3 (100.0%)	68/72 (94.4%)
95% CI	29.2% to 100.0%	86.4% to 98.5%
Virologic Failure at Week 24	0	1 (1.4%)
HIV-1 RNA ≥ 50 copies/mL	0	1 (1.4%)
Discontinued Study Drug Due to Lack of Efficacy	0	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL	0	0
Added New ARV	0	0
No Virologic Data in Week 24 Window	0	3 (4.2%)
Discontinued Study Drug Due to AE/Death	0	1 (1.4%)

	E/C/F/TAF Cohort 1 (N = 3)	E/C/F/TAF Cohort 2 (N = 72)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	0	2 (2.8%)
Missing Data During Window but on Study Drug	0	0

Week 24 window was between Days 126 and 209 (inclusive). Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor. 95% CI is the 2-sided exact 95% confidence interval (CI) for binomial proportions.

HBV Response

Cohort 1 Treatment naïve subjects

At Week 24, 1 subject had HBV DNA < 29 IU/mL.

Cohort 2 HIV suppressed subjects

At Week 24, the overall percentage of subjects with HBV DNA < 29 IU/mL (M = F) was 86.1% (62 subjects; 95% CI: 75.9% to 93.1%). Using the M = E method, the overall percentage at Week 24 was 89.9% (62 of 69 subjects; 95% CI: 80.2% to 95.8%).

Table 5: Study GS-US-292-1249: Percentage of subjects with HBV DNA < 29 IU/mL at Week 24 using M = F and M = E approaches (full analysis set)

	E/C/F/TAF Cohort 1 (N = 3)	E/C/F/TAF Cohort 2 (N = 72)
Missing = Failure (m=F)		
HBV DNA at Baseline		
< 29 IU/mL	0/3	62/72 (86.1%)
95% CI	0.0% to 70.8%	75.9% to 93.1%
≥ 29 IU/mL	3/3 (100.0%)	10/72 (13.9%)
HBV DNA at Week 24		
< 29 IU/mL	1/3 (33.3%)	62/72 (86.1%)
95% CI	0.8% to 90.6%	75.9% to 93.1%
≥ 29 IU/mL	2/3 (66.7%)	7/72 (9.7%)
Missing	0/3	3/72 (4.2%)
P value[b]	-	1.00

	E/C/F/TAF Cohort 1 (N = 3)	E/C/F/TAF Cohort 2 (N = 72)
Missing = Excluded (M = E)c		
HBV DNA at Baseline		
< 29 IU/mL	0/3	62/72 (86.1%)
95% CI	0.0% to 70.8%	75.9% to 93.1%
≥ 29 IU/mL	3/3 (100.0%)	10/72 (13.9%)
HBV DNA at Week 24		
< 29 IU/mL	1/3 (33.3%)	62/69 (89.9%)
95% CI	0.8% to 90.6%	80.2% to 95.8%
≥ 29 IU/mL	2/3 (66.7%)	7/69 (10.1%)
P-value[d]	-	0.73

95% CI is the 2-sided exact 95% CI for binomial proportions. [a] The denominator for percentages is based on the number of subjects in the full analysis set. [b] P-value is from McNemar's test comparing baseline and post baseline. Subjects with missing data were counted as ≥ 29 IU/mL for the test. [c] The denominator for percentages is based on the number of subjects in the full analysis set with non-missing HBV DNA value at each visit. [d] P-value is from McNemar's test comparing baseline and post baseline for subjects with non-missing paired data.

Results for other efficacy outcomes

Cohort 1 - treatment naïve

HIV Efficacy

At Week 48, 2 subjects had virologic success and 1 subject had missing data (HIV-1 RNA was 39 copies/mL at the last assessed time point [Week 36]).

CD4 cell counts increased from baseline during treatment with Genvoya.

HBV Efficacy

At Week 48, 2/3 subjects and 2/2 subjects had HBV DNA < 29 IU/mL as assessed using the M = F and M = E methods, respectively.

No subjects experienced HBsAg loss or seroconversion to anti-HBs at Week 24 or 48.

One subject experienced HBeAg loss with seroconversion to anti-HBe at Week 24, which was maintained at Week 48.

All 3 subjects achieved ALT normalisation at Week 24. Two subjects maintained ALT normalisation and 1 subject was missing ALT data at Week 48.

All 3 subjects continued in the no/minimal fibrosis FibroTest category at Week 24. Two subjects continued in the no/minimal fibrosis FibroTest category and 1 subject was missing FibroTest data at Week 48.

Cohort 2 – HIV suppressed subjects

HIV Efficacy

At Week 48, 91.7% of subjects (95% CI: 82.7% to 96.9%) had virologic success. Two subjects (2.8%) were classified as virologic failures. Of those 2 subjects, 1 subject was a virologic failure at Week 24 and discontinued study drug due to lack of efficacy, and 1 subject had an HIV-1 RNA level of 127 copies/mL. Four subjects (5.6%) had no virologic data in the Week 48 analysis window: 3 subjects had discontinued before Week 24; and 1 subject had missing data, but was still on study drug (HIV-1 RNA was < 50 copies/mL at all prior visits and at Week 60).

High percentages of virologic suppression were maintained through Week 48, as assessed using the M = F and M = E methods. The percentages of subjects with virologic suppression (HIV-1 RNA < 50 copies/mL) at Week 24 were 94.4% and 98.6% using the M = F and M =E methods, respectively. The percentages of subjects with virologic suppression at Week 48 were 91.7% and 97.1% using the M = F and M =E methods, respectively.

CD4 cell counts remained stable during treatment with Genvoya. The mean (SD) baseline CD4 cell count was 636 (258.6) cells/µL. The mean (SD) change from baseline in CD4 cell counts at Week 24 (observed data) was 21 (166.0) cells/µL. The mean (SD) change in CD4 cell counts through Week 48 (observed data) was -2 (131.2) cells/µL.

HBV Efficacy

At Week 48, 66/72 subjects (91.7%) had HBV DNA < 29 IU/mL and 66/68 subjects (97.1%) had HBV DNA < 29 IU/mL using the M = F and M = E methods, respectively. Two subjects had detectable levels of HBV DNA at baseline and did not achieve suppression to < 29 IU/mL by Week 48. The Week 48 HBV DNA level was 51 IU/mL for 1 subject and 170 IU/mL for the other subject. Four subjects were missing data at Week 48: 2 subjects withdrew consent; 1 subject discontinued due to AEs; and 1 subject was missing Week 48 data, but had HBV DNA < 20 IU/mL at all prior visits and at Week 60.

Of the 70 subjects who were HBsAg positive and anti-HBs negative at baseline, 1 subject (1.4%) experienced HBsAg loss with seroconversion to anti-HBs at Week 24. At Week 48, 2 other subjects (2.9%) experienced HBsAg loss and 1 of these subjects (1.4%) also achieved seroconversion to anti-HBs.

Of the 30 subjects who were HBeAg positive and anti-HBe negative at baseline, 1 subject (3.3%) experienced HBeAg loss with seroconversion to anti-HBe at Week 24. At Week 48, 1 other subject (3.3%) experienced HBeAg loss.

Ten subjects (13.9%) had ALT values > ULN at baseline; of those subjects, 5 (50.0%) achieved ALT normalisation at Week 24 and 4 subjects (40.0%) achieved ALT normalisation at Week 48. Using the M = E approach, 5 of 9 subjects (55.6%) at Week 24 and 4 of 8 subjects (50.0%) at Week 48 achieved ALT normalisation.

Excluding the 8 subjects who were receiving ATV at baseline, the median (Q1, Q3) FibroTest score was 0.35 (0.21, 0.51) at baseline, and the median (Q1, Q3) change from baseline was -0.02 (-0.11, 0.05; p = 0.064) at Week 24 and −0.04 (−0.11, 0.03; p = 0.018) at Week 48.

Subgroup analysis

Cohort 1 (naïve): no meaningful comparisons were possible due to the small number treated.

Cohort 2 (suppressed): the majority of the patients were male (91.7%), White (69.4%) and had high overall drug compliance ≥ 95% (83.3% at Week 24 and 87.5% at Week 48), precluding any meaningful comparison between sex, race and study drug compliance subgroups. The results for both efficacy endpoints were similar between age subgroups (< and ≥ 50 years).

Virology resistance

Resistance testing was performed for any subject meeting the criteria of the resistance analysis population (RAP). The RAP included any subject who received at least 1 dose of study drug, maintained their study drug regimen (or within 72 hours after interruption or discontinuation of study drugs), and met one of the virologic failure (VF) criteria.

A VF subject was only included in the RAP if the HIV-1 RNA level at VF was ≥ 400 copies/mL.

HIV-1 Analysis: After 48 weeks of Genvoya treatment no subjects in the FAS population (0%, 0/75) met the criteria for inclusion in the resistance analysis population (RAP).

HBV Analysis: At baseline there were 10 HBV viraemic (HBV DNA ≥ 69 IU/mL) subjects; of these, 5 had primary lamivudine resistance mutations detected at baseline. After 48 weeks of Genvoya treatment, 2 subjects in the FAS population (2.8%, 2 of 72) qualified for resistance testing and were analysed by sequence analysis of the HBV polymerase/reverse transcriptase (pol/RT) gene. None of the amino acid substitutions observed in HBV pol/RT were associated with resistance to TAF.

Resistance conclusion

No subject had both persistent HIV-1 and HBV viraemia observed through 48 weeks of Genvoya treatment. None of the HIV-1/HBV co-infected subjects in the study were found to have emergent resistance to any of the components of Genvoya.

7.2.1.2. Evaluator commentary

This was an ongoing, open label, single arm study in treatment naïve and HIV suppressed HIV/HBV co-infected subjects treated for 48 weeks. In the treatment naïve group only 3 patients were enrolled which means that there were insufficient data to make any conclusions about the subgroup.

In the HIV virologically suppressed subjects who switched treatment to Genvoya the response rates indicated that the patients maintained their virologic control both at 24 weeks (primary efficacy endpoint) and at 48 weeks:

Table 5: Study GS-US-292-1249 Summary of results

	Week 24	Week 48
HIV-1 RNA < 50 copies/mL (FDA snapshot algorithm)	94.4%	91.7%
HBV DNA < 29 IU/mL (M=F)	86.1%	91.7%

The mean (SD) changes from baseline in CD4 cell counts at Weeks 24 and 48 were 21 (166.0) cells/µL and −2 (131.2) cells/µL, respectively. In subjects who primarily switched from TDF, 2.9% achieved anti-HBs seroconversion, 3.3% achieved anti-HBe seroconversion, and 40% achieved ALT normalisation. Improvements in FibroTest scores were observed at Weeks 24 and 48.

7.2.2. Other efficacy studies

The sponsor makes reference to two other studies which have been previously evaluated by the TGA. Studies GS-US-320-0108 and GS-US-320-0110 are stated to have demonstrated the non-inferior efficacy of TAF versus TDF in treatment naïve and treatment experienced adults with

HBeAg negative (GS-US-320-0108 interim Week 48 CSR) and HBeAg positive (GS-US-320-0110[1] interim Week 48 CSR) chronic HBV infection. In both studies, similar rates of HBV suppression were achieved in the two treatment groups when assessed using the M = F method at Week 48. The percentages of subjects with HBV DNA < 29 IU/mL at Week 48 were as follows:

- Study GS-US-320-0108: TAF 94.0%, TDF 92.9%; difference in proportions (baseline stratum-adjusted): 1.8%, 95% CI: -3.6% to 7.2%
- Study GS-US-320-0110: TAF 63.9%, TDF 66.8%; difference in proportions (baseline stratum-adjusted): -3.6%, 95% CI: −9.8% to 2.6%

In both studies, the lower bound of the two sided 95% CI of the difference (TAF - TDF) in the response rate was greater than the prespecified -10% margin; therefore, TAF met the primary endpoint of non-inferiority to TDF.

7.3. Analyses performed across trials: pooled and meta analyses

Not applicable.

7.4. Evaluator's conclusions on clinical efficacy for indication 1

Only one new study was submitted and in the study only the subset of patients switching from primarily TDF containing regimens provided adequate numbers for evaluation. In this group the patients maintained both HIV and HBV virologic suppression for up to 48 weeks.

At Week 24 for virologically suppressed subjects the virological success for HIV was 94.4% and for HBV was 86.1%. At Week 48 the virological success for HIV was 91.7% and for HBV was 91.7%.

7.5. Indication 2: Treatment of children ≥ 25 kg

7.5.1. Pivotal or main efficacy study

7.5.1.1. Study ID GS-US-292-0106

Study design, objectives, locations and dates

An open label, multi-cohort, single group study conducted at 5 sites (3 in USA, 1 in Thailand and 1 in Uganda) from May 2013 to April 2016.

Subjects were enrolled in two cohorts:

- Cohort 1: ART naïve adolescents (aged 12 to < 18 years)
- Cohort 2: virologically suppressed children (aged 6 to <12 years)

Comment: The efficacy and safety for Cohort 1 was evaluated previously (PM-2014-04011-1-2). This report only provides the results for Cohort 2 up to Week 24, which is the basis for this application. The trial is ongoing to Week 48.

Objectives

Cohort 2

Primary objectives:

[1] This is stated to be Study GS-US-320-0108 in the *Clinical Overview* but in the context this appears to be an error and the correct study should be Study GS-US-320-0110.

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

Secondary objectives:

- To evaluate the antiviral activity of switching to Genvoya in virologically suppressed HIV-infected children 6 to < 12 years of age weighing ≥ 25 kg

Inclusion and exclusion criteria

Inclusion: (Cohort 2) HIV-infected children, 6 to < 12 years of age, weight ≥ 25 kg, with plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 consecutive months prior to screening, on a stable (that is, ≥ 6 consecutive months or newly initiated within 6 months for reasons other than virologic failure) ART regimen, CD4 cell counts > 100 cells/µL, and without history of resistance to any component of Genvoya and adequate renal function (eGFR ≥ 90 mL/min/1.73 m^2), hepatic function (AST and ALT ≤ 5 x ULN) and haematologic function (ANC ≥ 500 /mm^3, platelets ≥ 50,000 /mm^3 and Hb ≥ 8.5 g/dL)

Exclusion: new AIDS defining condition diagnosed within 30 days prior to screening; positive HCV or HBV antigens; decompensated cirrhosis or active TB.

Study treatments

All subjects received one Genvoya tablet, administered orally with food at approximately the same time each day. Each tablet contained 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF (as 11.2 mg of TAF fumarate).

Efficacy variables and outcomes

The efficacy endpoints for Cohort 2 were:

- Percentage of subjects with plasma HIV-1 RNA < 50 copies/ml at Week 24 as determined by the US FDA-defined snapshot algorithm
- Percentages of subjects with HIV-1 RNA < 50 copies/ml at Week 24 (M = F and M = E methods)
- Change from baseline in CD4 cell count (cells/µL) and percentage at Week 24

Randomisation and blinding methods

The study was not randomised or blinded as it was an open label study.

Analysis populations

Full analysis set (FAS): defined as all subjects who were enrolled in the study and received at least one dose of study drug.

Safety analysis set: defined as all subjects who received at least one dose of study drug.

All enrolled analysis set: defined as all subjects who were enrolled in the study.

Sample size

Adult data was used as historical control for comparison. A total of 23 subjects in Cohort 2 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 intersubject 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 subjects from 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 population PK data).

Statistical methods

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 (eg, data collected from Day 1 up to 1 day after the last dose date of study drug) were used in the US FDA defined snapshot algorithm.

The numbers and percentages of subjects with HIV-1 RNA < 50 copies/mL based on the US FDA-defined snapshot algorithm, missing = failure (M = F) analysis, and missing = excluded (M = E) analysis, were summarised. The 95% CI for the percentage estimate in the M = F and M = E analyses was constructed using an exact method. For the US FDA-defined snapshot algorithm, the numbers and percentages of subjects with HIV-1 RNA < 50 copies/mL (including subcategories), and no virological data (including reasons) were summarised. For the M = F analysis, results were summarised for all visits up to Week 24. For the M = E analysis, results were summarised at all visits through the data-cut date.

The CD4 cell count and CD4% data were summarised using observed, on-treatment data (that is, up to 1 day after the last dose date of study drug). Baseline and change-from-baseline values in CD4 cell count (cells/µL), and CD4% at each visit were summarised descriptively (sample size, mean, SD, 95% CI, median, Q1, Q3, minimum, and maximum).

Participant flow

Table 6: Study GS-US-292-0106: Disposition of Cohort 2 subjects (all screened subjects)

Subject Disposition	GEN
Subjects Screened[a,b]	26
Screened Subjects Who Were Not Enrolled	3
Screen Failure Subjects Who Were Not Enrolled	3
Subjects Enrolled	23
Subjects in Safety Analysis Set	23
Subjects in FAS	23
MAIN PHASE	
Subjects Still on Study Treatment	23 (100.0%)
Subjects Completing Study Treatment	0
Subjects Still on Study	23 (100.0%)
Subjects Completing Study	0
Subjects Prematurely Discontinuing from Study	0

[a] The number of screen failures is counted by unique subject based on the date of birth, race, ethnicity, sex, country, and initials. [b] eCRF data collected up to 20 April 2016 and laboratory data collected up to 01 June 2016 were included in the Week 24 analysis data cut, including data collected after the Week 24 visit.

Major protocol violations/deviations

A total of 3 important protocol violations occurred in 3/23 subjects, all involving deviations in relation to protocol specified assessments or procedures. None were considered to affect the overall quality or interpretation of the study data.

Baseline data

In the Safety Analysis Set, 60.9% of subjects were female. The median age of subjects was 10 years (range: 8 to 11 years); most of the subjects were Black (78.3%), or Asian (13.0%), and none were Hispanic or Latino.

The median (Q1, Q3) body weight of subjects 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). The median (Q1, Q3) baseline height was 136.3 (130.5, 140.0) cm; and the median (Q1, Q3) baseline Z-score for height was −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, and the median (Q1, Q3) baseline eGFR calculated using the Schwartz and modified Schwartz formulas were 150.0 (134.7, 165.6) mL/min/1.73 m^2 and 110.5 (104.8, 122.9) mL/min/1.73 m^2, respectively. Pubertal stage at baseline was Tanner stages 1-3 for all subjects.

All 23 subjects had plasma HIV-1 RNA < 50 copies/mL at baseline. Median (Q1, Q3) baseline CD4 cell count was 969 (843, 1087) cells/μL; 100% of subjects had CD4 cell counts ≥ 500 cells/μL. The median (Q1, Q3) CD4% was 38.8% (36.1, 44.3). The median (Q1, Q3) number of years since diagnosis of HIV infection was 8.0 years (8.0, 10.0). The risk factor for HIV infection was vertical transmission for all 23 subjects. All 23 subjects had asymptomatic HIV-1 infection, and no subject was HBsAg positive.

All Cohort 2 subjects were receiving at least 1 ARV drug in accordance with study entry criteria. All 23 subjects were receiving a NRTI; 82.6%, 60.9%, and 52.2% of subjects were being treated with lamivudine, abacavir, and zidovudine, respectively. Eleven of 23 (47.8%) subjects were receiving a NNRTI; 30.4% and 17.4% were being treated with efavirenz and nevirapine, respectively. Five (21.7%) of 23 subjects were receiving protease inhibitors (4 of whom received Kaletra [lopinavir/ritonavir] and 1 subject received atazanavir boosted with ritonavir). Two (8.7%) subjects received the IN inhibitor raltegravir, and 2 (8.7%) subjects received TDF. The most recent ARV drug regimen for 6 (26.1%) subjects consisted of lamivudine, abacavir, and zidovudine only.

Results for the primary efficacy outcome

Percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24 using the US FDA-defined snapshot algorithm

At Week 24, 100.0% of subjects (23) in the FAS had HIV-1 RNA < 50 copies/mL (US FDA-defined snapshot algorithm)

Percentage of subjects with HIV-1 RNA < 50 at Week 24 (M = F and M = E analyses)

All (100.0%) subjects had HIV-1 RNA < 50 copies/mL at Week 24 for both analytical methods.

Change from Baseline in CD4 Cell Count at Week 24

The mean (SD) baseline CD4 cell count (FAS) was 966 (201.7) cells/μL. No subjects had < 500 cells/ μL at baseline. A mean (SD) decrease from baseline in CD4 cell count was observed at Week 2 (the first available time point) (162 [144.6] cells/μL), which was stable through Week 24 (150 [164.6] cells/μL). For 19 of the 23 subjects who had reached Week 32, the mean (SD) CD4 cell count had returned to near baseline value (900 [237.7] cells/μL).

Table 7: Study GS-US-292-0106: Change from baseline in CD4 cell count (cells/µL) by visit while on treatment full analysis set

	E/C/F/TAF (N=23)							
	N	Mean	SD	Min	Q1	Median	Q3	Max
Baseline	23	966	201.7	603	843	969	1087	1421
Week 2	23	804	160.7	468	671	818	859	1138
Week 4	22	845	265.6	359	711	831	923	1622
Week 8	22	848	146.7	577	746	843	984	1101
Week 12	23	803	172.6	575	620	822	928	1153
Week 16	23	833	197.7	485	626	829	1026	1163
Week 24	23	816	175.2	473	690	805	934	1143
Week 32	19	900	237.7	545	739	849	1036	1433
Week 40	2	685	102.5	612	612	685	757	757
Change at Week 2	23	-162	144.6	-363	-283	-199	-63	161
Change at Week 4	22	-125	232.7	-728	-254	-146	16	426
Change at Week 8	22	-134	172.6	-426	-257	-166	-50	321
Change at Week 12	23	-162	204.3	-543	-256	-145	-41	247
Change at Week 16	23	-133	191.3	-489	-279	-94	-5	200
Change at Week 24	23	-150	164.6	-472	-299	-130	-44	266
Change at Week 32	19	-79	176.0	-382	-197	-97	7	322
Change at Week 40	2	-119	180.3	-246	-246	-119	9	9

On-treatment values include data after the first dose date up to the database finalisation date for ongoing subjects or up to the last dose date + 1 day for subjects who prematurely discontinued study drug.

Results for the other efficacy outcomes

Change from baseline in CD4 percentage at Week 24

The mean (SD) baseline CD4% (FAS) was 39.6% (5.32%). 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 of the 23 subjects who had reached Week 32, the mean (SD) change from baseline in CD4% was −1.2% (4.25%).

Table 8: Study GS-US-292-0106: Change from Baseline in CD4 percentage (%) by visit while on treatment full analysis set

	E/C/F/TAF (N=23)							
	N	Mean	SD	Min	Q1	Median	Q3	Max
Baseline	23	39.6	5.32	30.4	36.1	38.8	44.3	50.9
Week 2	23	40.1	5.40	30.9	35.8	39.4	44.9	52.1
Week 4	22	39.0	5.84	29.8	34.9	38.7	42.4	51.3
Week 8	22	40.2	5.48	30.5	35.4	40.6	43.9	50.8
Week 12	23	38.8	5.64	28.9	33.5	40.2	42.2	50.6
Week 16	23	39.0	4.73	28.7	36.0	38.9	42.3	47.1
Week 24	23	38.1	5.71	27.5	33.3	37.5	41.6	51.6
Week 32	19	38.7	5.22	28.7	34.9	37.2	43.5	50.0
Week 40	2	43.4	10.61	35.9	35.9	43.4	50.9	50.9
Change at Week 2	23	0.5	3.01	-8.1	-0.4	1.0	1.9	6.3
Change at Week 4	22	-0.1	3.25	-5.9	-3.0	-0.4	3.1	6.0
Change at Week 8	22	0.3	4.01	-9.3	-2.2	0.6	3.4	7.2
Change at Week 12	23	-0.8	4.43	-10.5	-3.4	0.9	2.6	4.4
Change at Week 16	23	-0.5	4.29	-12.5	-1.7	-0.3	2.8	4.5
Change at Week 24	23	-1.5	3.67	-8.4	-3.8	-2.1	1.9	5.9
Change at Week 32	19	-1.2	4.25	-9.4	-3.1	-1.8	1.0	7.6
Change	2	2.9	0.85	2.3	2.3	2.9	3.5	3.5

	E/C/F/TAF (N=23)							
	N	Mean	SD	Min	Q1	Median	Q3	Max
at Week 40								

On-treatment values include data after the first dose date up to the database finalisation date for ongoing subjects or up to the last dose date + 1 day for subjects who prematurely discontinued study drug.

Resistance analysis

Of the 23 subjects enrolled in Cohort 2 through Week 24, 1 subject had historical genotype data available (HIV-1 subtype B without any primary RT or PR RAMs). No subjects qualified for resistance analysis.

7.5.1.2. Evaluator commentary

This CSR only presented the results for the Cohort 2 patients which comprised HIV infected children aged 6 to < 12 years weighting ≥ 25 kg. The Cohort 1 patients (ART naïve, HIV infected adolescents 12 to < 18 years and weighting ≥ 35 kg) had been previously evaluated resulting in approval in this group. The results for Cohort 1 demonstrated virologic suppression in 92.0% (46 of 50 subjects).

Cohort 2 comprised 23 subjects whose weight ranged from 25.2 kg to 58.2 kg with a median weight of 30.5 kg. There were no subjects who were < 8 years who met the weight cut off of ≥ 25 kg. However, the Sponsor proposed that exposure and safety assessed across the weight spectrum for this cohort, as in the study, are expected to apply to any child who is 6 to 12 years of age and ≥ 25 kg, as exposures in this age group are expected to be dictated by weight alone.

In Cohort 2 100% (23 of 23 subjects) maintained virologic suppression (HIV-1RNA < 50 copies/mL) after switching to Genvoya at Week 24. All subjects were virologically suppressed for at least 6 months and therefore had relatively high CD4 counts at baseline and remained relatively stable over the course of treatment. No subject qualified for resistance analysis.

Results were also provided for the resistance analysis for Cohort 1 through Week 48. Of the 50 subjects enrolled in Cohort 1 through Week 48, 4% of subjects (2 of 50) met the criteria for inclusion in the resistance analysis population (RAP) and had their virus analysed for resistance. No subjects developed resistance to study drugs.

7.5.2. Other efficacy studies

Not applicable.

7.6. Analysis performed across trials

Not applicable.

7.7. Evaluator's commentary on indication 2

The single study submitted provides evidence of efficacy in virologically suppressed HIV infected subjects aged 6 to < 12 years weighing ≥ 25 kg. The submission did not contain data for treatment naïve subjects in this age group. The wording of the proposed indication is acceptable to cover the data but there should be a statement somewhere in the PI to indicate that there is currently insufficient data on treatment naïve children aged 6 to < 12 years and weighing ≥ 25 kg.

It is noted that the full dose of Genvoya was used with no adjustment for the younger children. No subject discontinued study drug.

7.8. Indication 3 Amendments to PI update clinical trials and renal impairment

7.9. Pivotal or main efficacy studies

7.9.1. Study ID GS-US-292-0112 – renal impairment

A Phase III, Open-Label Study to Evaluate Switching from a TDF-Containing Combination Regimen to a TAF-Containing Combination Single Tablet Regimen (STR) in Virologically-Suppressed, HIV-1 Positive Subjects

Comment: The CSR submitted for this study was the fourth CSR submitted which extends the previously evaluated data to Week 144. This study was primarily a safety study with efficacy as a secondary outcome.

Study GS-US-292-0112 was an open label, multiple cohort study to evaluate the safety, efficacy and tolerability of Genvoya in HIV-infected adult subjects with stable, mild to moderate renal impairment (subjects with baseline eGFR 30 to 69 mL/min, inclusive). Stable renal function was defined as follows:

1. Serum creatinine measurement(s) must have been stable for 3 months and assessed at least once (within 3 months of screening) and
2. Differences between the measured values and screening value must have been < 25% of the screening value.

Subjects were enrolled in 1 of the following 2 cohorts:

- Cohort 1: switched to Genvoya from their existing antiretroviral (ARV) regimen ('switch' subjects), HIV-infected adults with stable virologic suppression (HIV-1 RNA < 50 copies/mL for at least 6 months prior to screening), and stable $eGFR_{CG}$ 30 to 69 mL/min for 3 months prior to screening
- Cohort 2: ART-naive, HIV-infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL and stable $eGFR_{CG}$ 30 to 69 mL/min for 3 months prior to screening

Cohort 2 only enrolled 6 patients and so the number is too small to make any meaningful conclusions about efficacy.

Cohort 1 enrolled 246 patients of whom 153 completed treatment to Week 144. The efficacy results for this cohort are summarised below.

The percentage of Cohort 1 switch subjects with virologic suppression at Week 144 was 83.1% when assessed using the US FDA-defined snapshot algorithm, with HIV-1 RNA < 50 copies/mL (baseline $eGFR_{CG}$ < 50 mL/min, 84.2%; baseline $eGFR_{CG}$ ≥ 50 mL/min, 82.6%). A total of 14.8% of Cohort 1 switch subjects had no virologic data in the Week 144 window.

Of the 5 (of 237, 2.1%) Cohort 1 switch subjects with HIV-1 RNA ≥ 50 copies/mL at Week 144, 3 subjects had HIV-1 RNA ≥ 50 copies/mL in the Week 144 window, 1 subject discontinued due to lack of efficacy, and 1 subject added new ARV treatment.

The percentage of Cohort 1 switch subjects with virologic suppression at Week 144 was 80.2% when assessed using the US FDA-defined snapshot algorithm, with HIV-1 RNA < 20 copies/mL based on the Week 144 FAS (baseline $eGFR_{CG}$ < 50 mL/min, 82.9%; baseline $eGFR_{CG}$ ≥ 50 mL/min, 78.9%).

High rates of virologic suppression were maintained in Cohort 1 switch subjects at Week 144 using the M = F and M = E methods. Among Cohort 1 switch subjects, rates of virologic suppression (HIV-1 RNA levels < 50 copies/mL) at Week 144 were 86.5% and 98.1% using the M = F and M = E methods, respectively.

CD4 cell counts in Cohort 1 switch subjects remained stable during treatment with Genvoya through Week 144. The mean (SD) baseline CD4 cell count for Cohort 1 switch subjects overall was 662 cells/µL (288.0). The mean (SD) change from baseline in CD4 cell counts (observed data) for Cohort 1 switch subjects overall was 13 cells/µL (177.9) at Week 144; the mean (SD) change from baseline in percentage CD4 was 0.3% (4.47%).

There were no clinically significant differences between subgroups (age, sex, race, region, or study drug adherence rate) in the percentages of subjects with virologic suppression (HIV-1 RNA < 50 copies/mL) at Week 144 using the US FDA-defined snapshot algorithm.

The results at Week 144 are consistent with those previously reported

7.9.2. Study GS-US-292-0109 long term use (virologically suppressed 96 Weeks)

A Phase III, Open-Label Study to Evaluate Switching from a TDF-Containing Combination Regimen to a TAF-Containing Combination Single Tablet Regimen (STR) in Virologically-Suppressed, HIV-1 Positive Subjects.

The CSR submitted for this study was the third CSR submitted which extends the previously evaluated data to Week 96.

Study GS-US-292-0109 was a randomised, open label, multicentre, active controlled study to evaluate the efficacy, safety and tolerability of switching to Genvoya from regimens containing FTC/TDF in virologically suppressed, HIV infected subjects. All subjects enrolled had participated in previous Sponsor clinical studies. All subjects were virologically suppressed on one of the following regimens:

- EVF/COBI/FTC/TDF (Stribild)
- Efavirenz (EVF)/FTC/TDF (Atripla)
- COBI boosted atazanavir (ATV/co) + FTC/TDF (Truvada)
- Ritonavir (RTV)-boosted atazanavir (ATV/r) + TVD.

Subjects were randomised to switch to open label Genvoya or remain on their previous FTC/TDF containing regimen. Randomisation was stratified by prior treatment regimen. Treatment was for 96 weeks, after which all subjects were given the opportunity to receive open label Genvoya.

A total of 1,436 subjects were enrolled and randomised: 959 Genvoya and 477 FTC/TDF + 3rd agent.

The results at Week 96 were consistent with those previously reported and evaluated through to Week 48. Virologic success (HIV-1 RNA < 50 copies/mL, using the FDA defined snapshot algorithm) was maintained through Week 96 in both treatment groups (using FAS): Gen 92.8% versus FTC/TDF+3rd agent 89.1%. Switching to Genvoya was determined to be non-inferior and statistically superior to maintaining FTC/TDF+3rd agent at Week 96. The lower bound of the 2 sided CI of the difference in response (GEN-FTC/TDF+3rd agent) was greater than the prespecified -12% margin and greater than zero (differences in percentages: 3.7%, 95%CI: 0.4 to 7.0%).

The percentages of subjects with virologic failure at Week 96 were balanced between the treatment groups (Genvoya: 2.4%; FTC/TDF+3rd agent: 1.7%). In the Genvoya group, 4.8% of the subjects had no virologic data at Week 96 compared with 9.2% of subjects in the

FTC/TDF+3rd agent group. The difference between treatment groups was primarily driven by study drug discontinuation due to 'other' reasons (Genvoya 2.7%; FTC/TDF+3rd agent: 6.5%).

Table 9: Study GS-US-292-0109: Virologic outcome at Week 96 using FDA snapshot algorithm and HIV-1 RNA < 50 copies/mL (FAS)

	GEN (N = 959)	FTC/TDF + 3rd Agent (N = 477)	GEN vs. FTC/TDF+3rd Agent	
			p-value[a]	Difference in Percentages (95% CI)[b]
Virologic Success at Week 96				
HIV-1 RNA < 50 copies/mL	890 (92.8%)	425 (89.1%)	0.017	3.7% (0.4% to 7.0%)
Virologic Failure at Week 96	23 (2.4%)	8 (1.7%)		
HIV-1 RNA ≥ 50 copies/mL	14 (1.5%)	6 (1.3%)		
Discontinued Study Drug Due to Lack of Efficacy	2 (0.2%)	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[c]	5 (0.5%)	0		
Added New ARV	2 (0.2%)	2 (0.4%)		
No Virologic Data in Week 96 Window	46 (4.8%)	44 (9.2%)		
Discontinued Study Drug Due to AE/Death	13 (1.4%)	12 (2.5%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	26 (2.7%)	31 (6.5%)		
Missing Data During Window but on Study Drug	7 (0.7%)	1 (0.2%)		

Week 96 window is between Day 630 and 713 (inclusive). [a] P-value for the superiority test comparing the percentages of virologic success was from the Cochran-Mantel-Haenszel test stratified by the prior treatment regimen (STB, ATR, ATV/boosted+TVD). [b] Difference in percentages of virologic success and its 95% CI were calculated based on the Mantel-Haenszel proportion adjusted by the prior treatment regimen. [c] Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

In both treatment groups, CD4 cell counts were similar and continued to improve through Week 96, with both groups having modest increases from baseline (mean GEN: 60 cells/µL); FTC/TDF+3rd agent: 42 cells/µL).

The emergence of resistance mutations was rare across both the Genvoya and FTC/TDF+3rd agent groups, and similar for the Genvoya group (0.3% 3/959 subjects) compared with the FTC/TDF+3rd agent group (0.2%, 1/477).

The results at Week 96 were consistent with those previously reported.

7.9.3. Study GS-US-292-0104 – long term use (treatment naïve 144 weeks)

A Phase III, Randomised, 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.

Comment: The CSR submitted for this study was the third CSR submitted which extends the previously evaluated data to Week 144.

Study GS-US-292-0104 was a randomised, double blind, multicentre, active controlled study that evaluated the efficacy and safety of Genvoya versus STB (E/C/F/tenofovir disoproxil fumarate) in HIV infected ART naïve adult subjects. Randomisation was stratified by HIV-1 RNA level (≤ 100,000 copies/mL, > 100,000 to ≤ 400,000 copies/mL, or > 400,000 copies/mL), CD4 count (< 50 cells/µL, 50 to 199 cells/µL, or ≥ 200 cells/µL), and region (US versus ex-US) at screening.

A total of 872 subjects were randomised (Genvoya: 438 subjects; STB: 434 subjects) and 738 subjects remained on study at the Week 144 cut-off date. Demographic and baseline characteristics were similar between the two treatment groups.

The percentage of subjects with HIV-1 RNA < 50 copies/mL was higher in the Genvoya group compared with the STB group at Week 144: Genvoya 86.9%, 378/435 subjects; STB 83.1%, 359/432 subjects. The difference in percentages: 4.0%, 95% CI: -0.8% - 8.8%. Treatment with Genvoya was non-inferior to treatment with STB as the lower bound of the 2 sided 95% CI for the difference in the response (Genvoya - STB) was greater than the prespecified -12% margin.

The percentage of subjects with HIV-1 RNA < 20 copies/mL as assessed using the US FDA-defined snapshot algorithm was also higher in the Genvoya group compared with the STB group at Week 144: Genvoya 84.6%, 368/435 subjects; STB 80.1%, 346/432 subjects; difference in percentages: 4.8%, 95% CI: -0.3% - 9.8%. Treatment with Genvoya was non-inferior to treatment with STB as the lower bound of the 2-sided 95% CI of the difference in the response (Genvoya - STB) rate was greater than the prespecified -12% margin.

HIV-1 RNA levels decreased rapidly by Week 2 following initiation of study drugs and remained stable from Week 8 through Week 144 in both treatment groups. Mean (SD) changes from baseline in HIV-1 RNA levels at Week 144 were: Genvoya -3.25 (0.702) $\log_{10}$ copies/mL; STB -3.27 (0.677) $\log_{10}$ copies/mL; differences in least-squares mean (LSM) of 0.03 $\log_{10}$ copies/mL, 95% CI: -0.05 to 0.10 $\log_{10}$ copies/mL.

Following initiation of study drugs, CD4 cell counts increased in both treatment groups. Mean (SD) increases from baseline in CD4 cell counts through Week 144 (observed data) using the FAS were as follows: Genvoya 323 (213.1) cells/µL; STB 310 (207.2) cells/µL; difference in LSM: 12 cells/µL, 95% CI: -18 to 42 cells/µL. Using LOCF to impute missing values, mean (SD) increases from baseline at Week 144 were as follows: Genvoya 307 (213.8) cells/µL; STB 297 (210.6) cells/µL; difference in LSM: 9 cells/µL, 95% CI: -19 - 37 cells/µL.

The results for Week 144 are consistent with those previously reported.

7.9.4. Study GS-US-292-0111 – long term use (treatment naïve 144 Weeks)

A Phase III, Randomised, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Alafenamide Versus Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir Disoproxil Fumarate in HIV-1Positive, Antiretroviral Treatment-Naïve Adults.

Comment: The CSR submitted for this study was the third CSR submitted which extends the previously evaluated data to Week 144.

Study GS-US-292-0111 was a randomised, double blind, multicentre, active controlled study to evaluate the efficacy and safety of a regimen containing Genvoya versus STB in HIV infected ART naïve adult subjects. Randomisation was stratified the same as for Study GS-US-292-0104 (≤ 100,000 copies/mL, > 100,000 to ≤ 400,000 copies/mL, or > 400,000 copies/mL), CD4 count (< 50 cell/µL, 50 to 199 cells/µL, or ≥ 200 cells/µL), and region (US versus ex US) at screening. Subjects were treated for 144 weeks of randomised, double blind treatment, followed by open label rollover extension in which all subjects received Genvoya.

A total of 866 subjects were randomised of which 702 remained on treatment at the Week 144 cut-off date (Genvoya: 356 subjects; STB: 346 subjects). Demographic and baseline characteristics were similar between the two treatment groups.

The percentage of subjects with HIV-1 RNA < 50 copies/mL was higher in the Genvoya group compared with the STB group at Week 144 based on the FAS, as follows: Genvoya 81.4%, 351/431 subjects; STB 77.0%, 335/435 subjects; difference in percentages: 4.5%, 95% CI: -0.9% - 9.9%. Treatment with Genvoya was non-inferior to treatment with STB as the lower bound of the 2-sided 95% CI for the difference in the response (Genvoya - STB) was greater than the prespecified -12% margin.

The percentage of subjects with HIV-1 RNA < 20 copies/mL as assessed using the US FDA defined snapshot algorithm was also higher in the Genvoya group compared with the STB group at Week 144: Genvoya 77.5%, 334/431 subjects; STB 71.5%, 311/435 subjects; difference in percentages: 5.9%, 95% CI: 0.1% - 11.8%. Treatment with Genvoya was non-inferior and statistically superior to treatment with STB as the lower bound of the 2-sided 95% CI for the difference in the response [Genvoya - STB] was greater than the prespecified -12% margin and also greater than zero (p=0.045).

HIV-1 RNA levels decreased rapidly by Week 2 following initiation of study drugs and remained stable from Week 8 through Week 144 in both treatment groups. Mean (SD) changes from baseline in HIV-1 RNA levels at Week 144 were as follows: Genvoya -3.21 (0.682) $\log_{10}$ copies/mL; STB -3.18 (0.729) $\log_{10}$ copies/mL; difference in least-squares mean (LSM) of -0.05 $\log_{10}$ copies/mL, 95% CI: -0.13 - 0.03 $\log_{10}$ copies/mL.

Following initiation of study drugs, CD4 cell counts increased in both treatment groups. Mean (SD) increases from baseline in CD4 cell counts through Week 144 (observed data) using the FAS were as follows: Genvoya 329 (217.8) cells/µL; STB 300 (201.7) cells/µL; difference in LSM: 29 cells/µL, 95% CI: -2 to 60 cells/µL. Using LOCF to impute missing values, mean (SD) increases in CD4 cell counts at Week 144 were as follows: Genvoya 311 (215.3) cells/µL; STB 279 (202.8) cells/µL; difference in LSM: 32 cells/µL, 95% CI: 5 - 60 cells/µL; p=0.022.

The results for Week 144 are consistent with those previously reported.

7.9.5. **Other studies**

Not applicable.

7.10. Analysis performed across trials: pooled and meta-analyses

7.10.1. **Renal impairment**

Not applicable.

7.10.2. **Virologically suppressed subjects to Week 96**

Not applicable.

7.10.3. **Treatment naïve subjects to Week 144**

The sponsor has provided pooled results of studies GS-US-292-0104 and GS-US-292-0111 for the Week 144 results.

7.10.3.1. Percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 144 using the US FDA defined snapshot algorithm:

Table 10: Pooled data (Studies GS-US-292-0104 and GS-US-292-0111) Virologic outcome at Week 144 using the US FDA-defined snapshot algorithm and HIV-1 RNA < 50 copies/mL – (FAS)

	E/C/F/TAF (N = 866)	STB (N = 867)	E/C/F/TAF vs. STB	
			p-value[a]	Difference in percentages (95% CI)[a]
HIV-1 RNA < 50 copies/mL	729 (84.2%)	694 (80.0%)	0.021	4.2% (0.6% to 7.8%)
HIV-1 RNA ≥ 50 copies/mL	40 (4.6%)	34 (3.9%)		
HIV-1 RNA ≥ 50 copies/mL in Week 144 Window	10 (1.2%)	9 (1.0%)		
Discontinued Study Drug Due to Lack of Efficacy	7 (0.8%)	8 (0.9%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[b]	21 (2.4%)	15 (1.7%)		
Added New ARV	2 (0.2%)	2 (0.2%)		
No Virologic Data in Week 144 Window	97 (11.2%)	139 (16.0%)		
Discontinued Study Drug Due to AE/Death	13 (1.5%)	29 (3.3%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[b]	79 (9.1%)	99 (11.4%)		

	E/C/F/TAF (N = 866)	STB (N = 867)	E/C/F/TAF vs. STB	
			p-value[a]	Difference in percentages (95% CI)[a]
Missing Data During Window but on Study Drug	5 (0.6%)	11 (1.3%)		

Week 144 window is between Day 966 and 1049 (inclusive). a Difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel (MH) proportions adjusted by baseline (BL) HIV-1 RNA, region, and study stratum. P-value for the superiority test comparing the percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups was from the Cochran-Mantel-Haenszel (CMH) test stratified by BL HIV-1 RNA, region and study stratum. BL HIV-1 RNA stratum: ≤ 100,000 or > 100,000 copies/mL; region stratum: US or ex-US; study stratum: GS-US-292-0104 or GS-US-292-0111. b Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.

7.10.3.2. Percentage of subjects with HIV-1 RNA < 20 copies/mL at Week 144 using the US FDA defined snapshot algorithm:

Table 11: Pooled data (Studies GS-US-292-0104 and GS-US-292-0111): Virologic outcome at Week 144 using the US FDA defined snapshot algorithm and HIV-1 RNA < 20 copies/mL – (FAS)

	E/C/F/TAF (N = 866)	STB (N = 867)	E/C/F/TAF vs. STB	
			p-value[a]	Difference in Percentages (95% CI)[a]
HIV-1 RNA < 50 copies/mL	702 (81.1%)	657 (75.8%)	0.006	5.4% (1.5% to 9.2%)
HIV-1 RNA ≥ 50 copies/mL	76 (8.8%)	80 (9.2%)		
HIV-1 RNA ≥ 50 copies/mL in Week 144 Window	37 (4.3%)	46 (5.3%)		
Discontinued Study Drug Due to Lack of Efficacy	7 (0.8%)	8 (0.9%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[b]	30 (3.5%)	24 (2.8%)		
Added New ARV	2 (0.2%)	2 (0.2%)		
No Virologic Data in Week 144 Window	88 (10.2%)	130 (15.0%)		
Discontinued Study Drug Due to AE/Death	13 (1.5%)	29 (3.3%)		

	E/C/F/TAF (N = 866)	STB (N = 867)	E/C/F/TAF vs. STB	
			p-value[a]	Difference in Percentages (95% CI)[a]
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[b]	70 (8.1%)	90 (10.4%)		
Missing Data During Window but on Study Drug	5 (0.6%)	11 (1.3%)		

Week 144 window is between Day 966 and 1049 (inclusive). [a] Difference in percentages of subjects with HIV-1 RNA < 20 copies/mL between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel (MH) proportions adjusted by baseline (BL) HIV-1 RNA, region, and study stratum. P-value for the superiority test comparing the percentages of subjects with HIV-1 RNA < 20 copies/mL between treatment groups was from the Cochran-Mantel-Haenszel (CMH) test stratified by BL HIV-1 RNA, region and study stratum. BL HIV-1 RNA stratum: ≤ 100,000 or > 100,000 copies/mL; region stratum: US or ex-US; study stratum: GS-US-292-0104 or GS-US-292-0111. [b] Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.

7.10.3.3. Percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 144 using missing data imputation methods

Based on the pooled data, high rates of virologic suppression at Week 144 were maintained in the two treatment groups, as assessed using the M = F and M = E methods for the FAS. Rates of virologic suppression at Week 144 were as follows: M = F: Genvoya 85.0%, 736 of 866 subjects; STB 83.0%, 720 of 867 subjects; difference in percentages: 2.0%, 95% CI: -1.4% - 5.5%); M = E: Genvoya 98.4%, (736/748 subjects); STB 98.5%, (720/731 subjects). The difference in percentages was -0.1%, 95% CI: -1.6% - 1.4%.

7.10.3.4. Change from baseline in plasma HIV-1 RNA

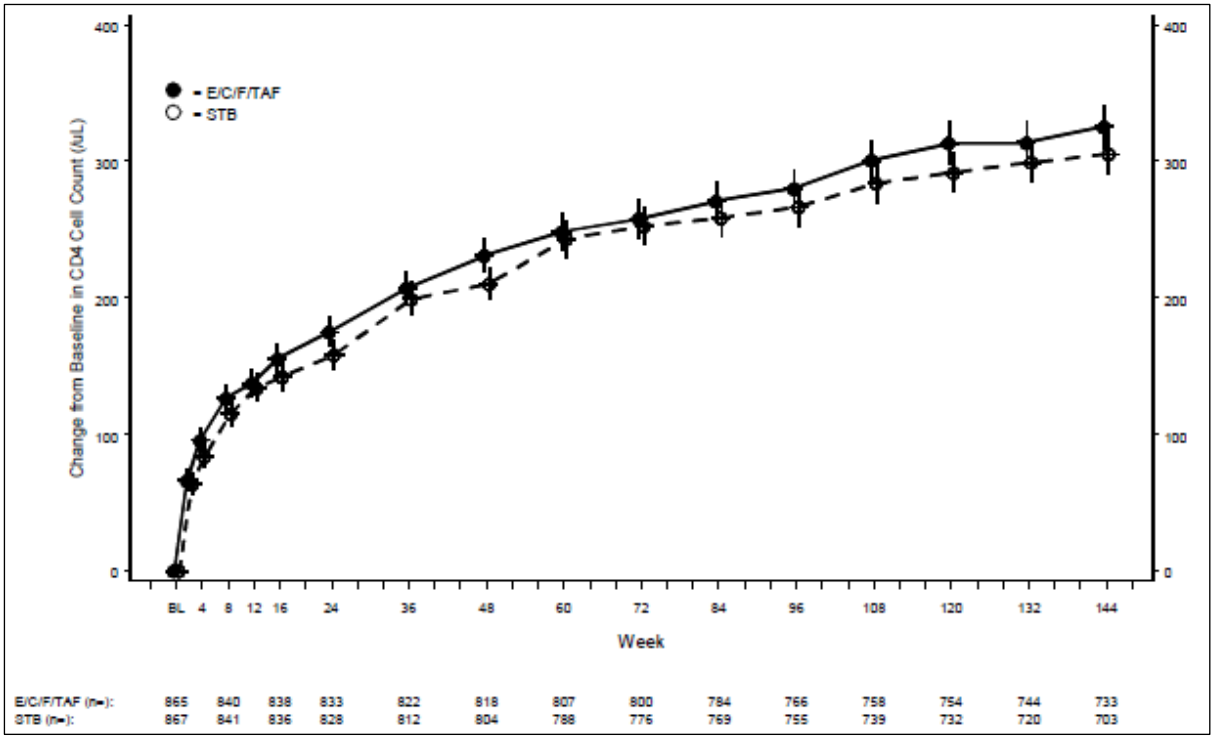
For the pooled data, mean (SD) baseline HIV-1 RNA levels were as follows: Genvoya 4.54 (0.665) $\log_{10}$ copies/mL; STB 4.53 (0.682) $\log_{10}$ copies/mL. As expected with an integrase strand-transfer inhibitor-containing regimen, HIV-1 RNA levels decreased rapidly by Week 2 following initiation of study drugs and remained stable from Week 8 through Week 144; mean (SD) decreases at Week 144 were as follows: Genvoya 3.23 (0.693) $\log_{10}$ copies/mL; STB 3.23 (0.704) $\log_{10}$ copies/mL; difference in least-squares mean -0.01 $\log_{10}$ copies/mL, 95% CI: -0.06 - 0.04 $\log_{10}$ copies/mL.

7.10.3.5. Change from baseline in CD4 cell counts

Based on the pooled observed data (M = E), CD4 cell counts increased following initiation of study drug for each treatment group in the FAS. Mean (SD) baseline CD4 cell counts were as follows: Genvoya 426 (215.6) cells/µL; STB 429 (219.6) cells/µL. The mean (SD) increases for each treatment group through Week 144 (observed data) were as follows: Genvoya 326 (215.3) cells/µL; STB 305 (204.5) cells/µL; difference in LSM: 20 cells/µL, 95% CI: -1 - 42 cells/µL.

The change from baseline in CD4 cell counts using last observation carried forward (LOCF) to impute missing values showed similar trends compared with the observed data. Mean (SD) increases from baseline at Week 144 were as follows: Genvoya 309 (214.4) cells/µL; STB 288 (206.8) cells/µL; difference in LSM; 21 cells/µL, 95% CI: 1 - 40 cells/µL.

Figure 2: Pooled Data (Studies GS-US-292-0104 and GS-US-292-0111): Mean and 95% CIs of change from Baseline in CD4 cell count (cells/µL) by visit while on treatment (observed pooled data, FAS)



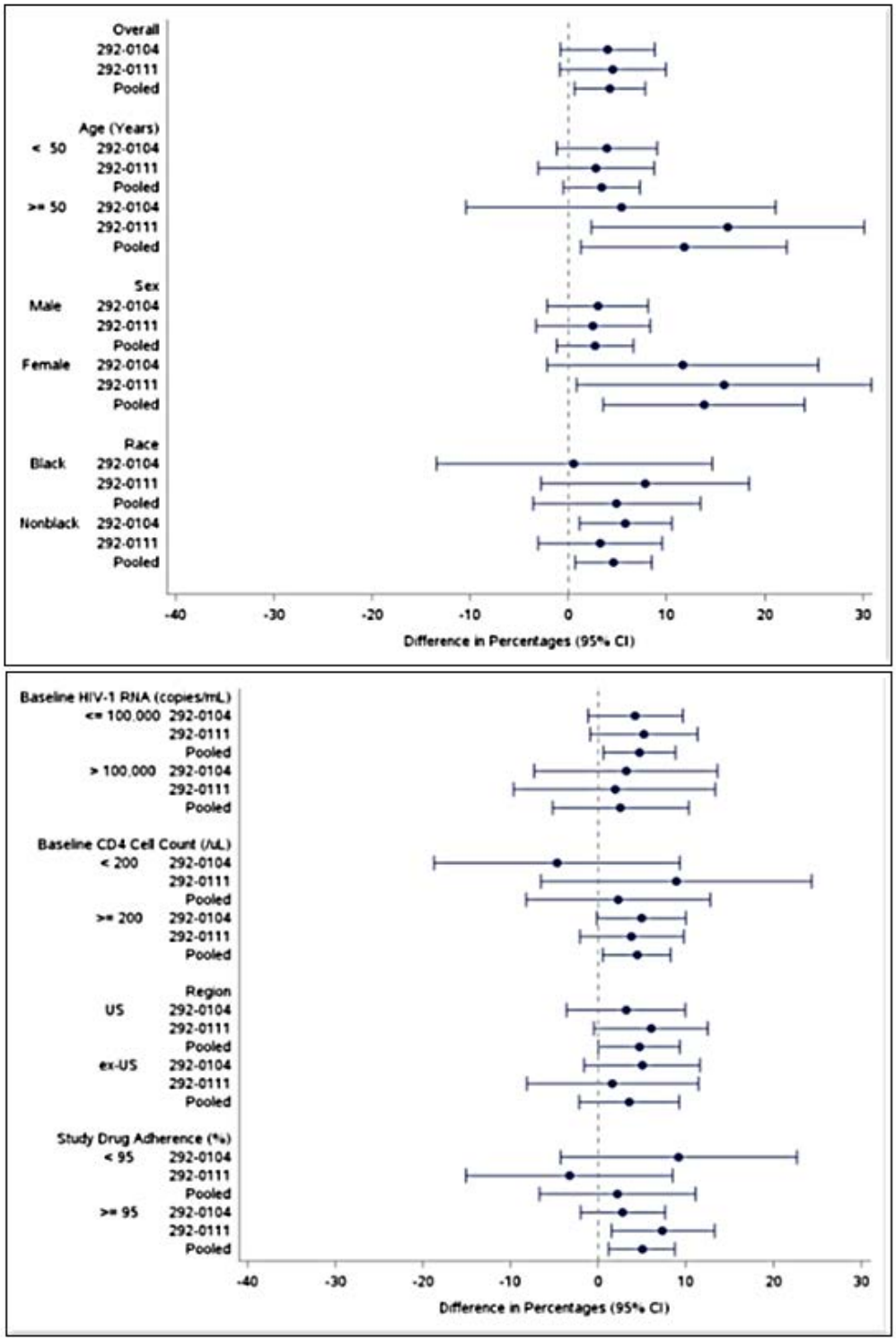
BL = baseline; On-treatment values include data after the first dose date up to the database finalization date for ongoing subjects or up to the last dose date + 1 day for subjects who prematurely discontinued study drug.

7.10.3.6. Subgroup analysis

Using pooled data at Week 144, analyses comparing the rates of virologic suppression (HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm) between treatments within prespecified subgroups according to age, sex, race, baseline HIV-1 RNA, baseline CD4 cell count, region (US versus ex-US), and study drug adherence favoured treatment with Genvoya over treatment with STB in the age ≥ 50 years, female sex, nonblack race, baseline HIV-1 RNA ≤ 100,000 copies/mL, baseline CD4 cell count ≥ 200 cells/µL, and study drug adherence ≥ 95% subgroups.

Homogeneity tests of the treatment effects between subgroups were performed for individual and pooled study data at Week 144 using the FAS. The tests did not show a significant difference in treatment effects between subgroups.

Figure 3: Pooled data (Studies GS-US-292-0104 and GS-US-292-0111): Forest plot of treatment difference in HIV-1 RNA < 50 copies/ml at week 144 (US FDA-defined snapshot algorithm) by subgroup (FAS)



Difference in response rates and its 95% CI were calculated based on the MH proportions adjusted by baseline (BL) HIV-1 RNA and region (if not the subgroup factor), and study (for pooled analysis) stratum. Relative to the vertical line at 0, differences on the right favour the Genvoya group and differences on the left favour the STB group. BL HIV-1 RNA stratum: ≤ 100,000 or > 100,000 copies/mL; region stratum: US or ex-US; study stratum: GS-US-292-0104 or GS-US-292-0111.

7.11. Evaluators conclusions on clinical efficacy for indication 3

7.11.1. Renal impairment

The data presented in this submission provides additional long term (to Week 144) efficacy and safety data from a single study (GS-US-292-0112) for virologically suppressed HIV infected adults with stable, mild to moderate renal impairment ($eGFR_{CG}$ of 30 to 69 mL/min). The primary outcome of the study was safety. The efficacy results were consistent with those previously reported and evaluated for this study. In Cohort 1 (switch subjects) virological suppression (using the FDA-defined snapshot algorithm, with HIV-1 RNA < 50 copies/mL) was maintained in 83.1% of subjects overall at Week 144. In Cohort 2 (ART naïve subjects) the numbers are too low to make any conclusions but it is noted that all 6 subjects had HIV-1 RNA < 50 copies/mL at Week 144.

7.11.2. Virologically suppressed to Week 96

The data presented consisted of additional long term data (Week 96) from a single study (GS-US-292-0109) in virologically suppressed HIV infected adults switching to Genvoya from a stable TDF containing regimen. In these subjects switching to Genvoya was statistically superior to continuing FTC/TDF+3rd Agent (STB, [ATR; efavirenz/FTC/TDF], atazanavir [ATV]/boosted+Truvada [TVD; FTC/TDF]) at Weeks 48 and 96 (virologic success at Week 96: Genvoya 92.8%; FTC/TDF+3rd Agent 89.1%), demonstrating durable virologic efficacy in subjects switching from standard-of-care regimens.

7.11.3. Treatment naïve to Week 144

The data presented consisted of additional long term data (Week 144) from two studies (GS-US-292-0104 and GS-US-292-0111) plus pooled data from the two studies. Treatment with Genvoya was non-inferior and statistically superior to treatment with STB in the Week 144 pooled analysis based on the percentage of subjects with virologic suppression, defined as HIV-1 RNA < 50 copies/mL using the US FDA defined snapshot algorithm (difference in percentages: 4.2%, 95% CI: 0.6% - 7.8%; p=0.021. Superiority of Genvoya over STB at 144 weeks was primarily driven by fewer subjects in the Genvoya group having no virology data in the Week 144 window than subjects in the STB group. The main reason for the difference was due to a better safety profile (See Section 8.8).

7.12. Indication 4: Class statements

7.12.1. Pivotal studies

Not applicable

7.12.2. Other studies

Not applicable

7.13. Analysis preformed across trials: pooled and meta-analyses

The sponsor has provided a *Clinical Overview* that argues for the removal of the class warnings related to lactic acidosis/severe hepatomegaly with steatosis and fat distribution.

The currently approved Australian PI contains the following class statements in the Precautions section:

> *Lactic Acidosis/Severe Hepatomegaly with Steatosis*
>
> *Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of antiretroviral nucleoside analogues in combination with other antiretrovirals, in the treatment of HIV infection. A majority of these cases have been in*

women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Genvoya should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Lipodystrophy

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

The data supporting the removal of the class warnings are based on the cumulative safety review and updated TAF addendum of the relevant clinical study and post marketing safety data from all sponsor (Gilead) FTC, TDF and TAF containing products. The products included in the review are listed in the Table 12 below.

Table 12: Products included in the safety review; products containing FTC, TDF and F/TAF

Product (Trade Name)	Components
Genvoya Ò	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
VireadÒ	Tenofovir disoproxil fumarate
EmtrivaÒ	Emtricitabine
TruvadaÒ	Emtricitabine/tenofovir disoproxil fumarate
AtriplaÒ	Efavirenz/emtricitabine/tenofovir disoproxil fumarate
ComplieraÒ/ EviplieraÒ	Emtricitabine/rilpivirine/tenofovir disoproxil fumarate
StribildÒ	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
DescovyÒ	Emtricitabine/tenofovir alafenamide
OdefseyÒ	Emtricitabine/rilpivirine/tenofovir alafenamide

Table 13: Estimated cumulative subject exposure in clinical trials involving FTC, TDF and TAF containing products[a]

Product	Period	Cumulative Clinical Trial Exposure (subjects)
Emtriva (FTC)	Cumulative to 02 July 2015	1281
Viread[b] (TDF)	Cumulative to 31 October 2015	4211
Truvada[b] (FTC/TDF)	Cumulative to 02 August 2015	1601
Atripla (EFV/FTC/TDF)	Cumulative to 12 July 2015	655
Complera/Eviplera (FTC/RPV/TDF)	Cumulative to 10 August 2015	912
Stribild (EVG/COBI/FTC/TDF)	Cumulative to 26 August 2015	1807
Genvoya (EVG/COBI/FTC/TAF)	Cumulative to 17 March 2016	3345
Descovy (F/TAF)	Cumulative to 15 June 2015	806
Odefsey (FTC/RPV/TAF)	Cumulative to 16 October 2015	751

[a] exposure based on product as investigational drug. [b] Includes exposure for both the HIV or HBV indications.

Table 14: Estimated cumulative post marketing exposure for all FTC, TDF and TAF-containing products

Product	Period	Cumulative Post-marketing
Emtriva (FTC)	Cumulative to 30 June 2015	161,329
Viread[a] (TDF)	Cumulative to 31 October 2015	3,393,649
Truvada[b] (FTC/TDF)	Cumulative to 31 July 2015	3,677,086
Atripla (EFV/FTC/TDF)	Cumulative to 31 December 2015	2,364,782
Complera/Eviplera (FTC/RPV/TDF)	Cumulative to 31 January 2016	320,059
Stribild (EVG/COBI/FTC/TDF)	Cumulative to 31 August 2015	166,119
Genvoya (EVG/COBI/FTC/TAF)	Cumulative to 31 January 2016	3382
Estimated exposure to all TDF-containing products[a,b,c]		9,921,694
Estimated exposure to all FTC-containing products[b,c]		6,689,374

Product	Period	Cumulative Post-marketing
Estimated exposure to all TAF-containing products[c]		3382

[a] Includes exposure to Viread tablets for both the HIV or HBV indications as it is not possible to separate post marketing exposure by indication, since post marketing exposure is based on sales data and the same tablets are used for both indications. Excludes exposure to Viread oral powder. [b] Includes exposure to Truvada tablets for both the HIV or the PrEP indications as it is not possible to separate post marketing exposure by indication, since post marketing exposure is based on sales data and the same tablets are used for both indications. [c] Total number of patient-years may not match the sum of the patient-years for the individual products due to the effect of rounding to the nearest patient-year.

Treatment emergent AEs and treatment emergent related AEs potentially associated with lactic acidosis reported in HIV and HBV clinical studies of TDF and FTC containing products and TAF containing products are shown in the tables below.

Table 15: Lactic acidosis related TEAEs from Gilead sponsored clinical trials of TDF and FTC containing products

Preferred Term, n (%)	TDF HBV[a]	TDF-containing HIV products[b]	FTC-containing HIV products[c]
	(N=706)	(N=2750)	(N=2451)
Hepatomegaly	12 (1.7%)	7 (0.3%)	4 (0.2%)
Hepatosplenomegaly	0	2 (0.1%)	2 (0.1%)
Hepatic steatosis	5 (0.7%)	12 (0.5%)[d]	11 (0.4%)
Lactic acidosis	0	0	0

[a] Week 48 and Week 384 (TDF→TDF group) data from Studies GS-US-174-0102 and GS-US-174-0103, Week 96 data from Study GS-US-174-0121. [b] Week 144 data from Studies GS-99-903, GS-01-934, GS-US-236-0102, GS-US-236-0103; Week 96 data from Study GS-US-264-0110. [c] Week 144 data from Studies GS-01-934, GS-US-236-0102, GS-US-236-0103; Week 96 data from Study GS-US-264-0110. [d] Includes one AE of liver fatty deposit from the COSTART dictionary which codes to the MedDRA PT of hepatic steatosis.

Table 16: Lactic acidosis related TEAEs considered related to study drug by the investigator from Gilead sponsored clinical trials of TDF and FTC containing products

Preferred Term, n (%)	TDF HBV[a]	TDF-containing HIV products[b]	FTC-containing HIV products[c]
	(N=706)	(N=2750)	(N=2451)
Hepatomegaly	1 (0.1%)	0	0
Hepatosplenomegaly	0	0	0
Hepatic steatosis	1 (0.1%)	3 (0.1%)[d]	3 (0.1%)[d]

Preferred Term, n (%)	TDF HBV[a]	TDF-containing HIV products[b]	FTC-containing HIV products[c]
	(N=706)	(N=2750)	(N=2451)
Lactic acidosis	0	0	0

[a] Week 48 and Week 384 (TDF→TDF group) data from Studies GS-US-174-0102 and GS-US-174-0103, Week 96 data from Study GS-US-174-0121. [b] Week 144 data from Studies GS-99-903, GS-01-934, GS-US-236-0102, GS-US-236-0103; Week 96 data from Study GS-US-264-0110. [c] Week 144 data from Studies GS-01-934, GS-US-236-0102, GS-US-236-0103; Week 96 data from Study GS-US-264-0110. [d] All 3 AEs were reported from the ATV+RTV+TVD treatment group in Study GS-US-236-0103.

Table 17: Lactic acidosis related TEAEs from Gilead sponsored clinical trials of TAF containing products

Preferred Term n (%)	HBV Studies		HIV Studies		
	Randomised comparative data[a]		Randomised comparative data[b]	All data[c]	
	TAF N = 866	TDF N = 432	F/TAF-containing product N = 3024	FTC/TDF-containing regimen N = 2483	F/TAF-containing product N = 3704
Hepatomegaly	0	0	2 (0.1%)	2 (0.1%)	2 (0.1%)
Hepatosplenomegaly	0	0	0	1 (0.04%)	0
Hepatic steatosis	6 (0.7%)	3 (0.7%)	17 (0.6%)	14 (0.6%)	23 (0.6%)
Lactic acidosis	0	0	1 (0.03%)	1 (0.04%)	2 (0.1%)

a Week 72 data from Studies GS-US-320-0108 and GS-US-320-0110. b Studies GS-US-292-0102, GS-US-292-0104, GS-US-292-0109, GS-US-292-0111, GS-US-311-1089, GS-US-366-1216 and GS-US-366-1160 which include a comparator group comprising a FTC/TDF-containing regimen. c Studies GS-US-292-0102, GS-US-292-0104, GS-US-292-0111, GS-US-292-0112, GS-US-292-0106, GS-US-292-0109, GS-US-292-0119, GS-US-292-1249, GS-US-311-1089, GS-US-366-1216 and GS-US-366-1160.

Table 18: Lactic acidosis related TEAEs considered related to the study drug by the investigator from Gilead-sponsored clinical trials of TAF containing products

Preferred Term n (%)	HBV Studies	HIV Studies	
	Randomised comparative	Randomised comparative data[b]	All data[c]

	TAF (N = 866)	TDF (N = 432)	F/TAF-containing product (N = 3024)	FTC/TDF-containing regimen (N = 2483)	F/TAF-containing product (N = 3704)
Hepatomegaly	0	0	0	0	0
Hepatosplenomegaly	0	0	0	0	0
Hepatic steatosis	0	0	3 (0.1%)	1 (0.04%)	4 (0.1%)
Lactic acidosis	0	0	0	0	0

[a] Week 72 data from Studies GS-US-320-0108 and GS-US-320-0110. [b] Studies GS-US-292-0102, GS-US-292-0104, GS-US-292-0109, GS-US-292-0111, GS-US-311-1089, GS-US-366-1216 and GS-US-366-1160 which include a comparator group comprising a FTC/TDF-containing regimen. [c] Studies GS-US-292-0102, GS-US-292-0104, GS-US-292-0111, GS-US-292-0112, GS-US-292-0106, GS-US-292-0109, GS-US-292-0119, GS-US-292-1249, GS-US-311-1089, GS-US-366-1216 and GS-US-366-1160.

7.14. Evaluators conclusions on clinical efficacy for indication 4

Review of the extensive pooled data indicates that the risk of FTC, TDF and TAF containing products causing lactic acidosis and fat redistribution is very low. The main aim of the US submission appears to have been to remove the boxed warning from the US PI. A boxed warning has not been included in the currently approved Australian PI. The US FDA has agreed to remove the boxed warning but have retained a warning in the US PI. It is not appropriate to remove all warnings from the Australian PI. The replacement wording on lactic acidosis/severe hepatomegaly as included in the US PI would be appropriate to replace the current wording in the Precautions section.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.1.2. Pivotal and/or main efficacy studies

- General adverse events (AEs): collected at each study visit, spontaneously reported by observation by the investigator, spontaneously reported by the patient or volunteered during open ended questioning of the patient.
- AEs of particular interest: bone safety (fractures, osteoporosis/osteopenia) and renal AEs.
- Laboratory tests: collected at each study visit included a complete blood count with differential and platelet count, chemistry profile and urine chemistry, cystatin C, eGFR calculated using the Cockcroft-Gault equation (eGFRCG).
- Metabolic assessments: Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides) collected at baseline and at Week 24 and 48.
- Blood and urine collected for analysis of bone (C-type collagen sequence [CTX], procollagen type 1 N-terminal propeptide [P1NP]) and renal (retinol binding protein [RBP] and beta-2-microglobulin) biomarkers.

- Blood collected for analysis of AFP at baseline and at Week 24 and 48. If AFP was > 50 ng/mL, an ultrasonogram was required (after Day 1 only).
- Other safety variables: complete physical examination including weight, 12 lead ECG, vital signs (blood pressure, pulse, respiration rate and temperature).

8.1.3. Other studies

8.1.3.1. Other efficacy studies

The safety assessment was the same as for the pivotal studies.

8.1.3.2. Studies with evaluable safety data: dose finding and pharmacology

Not applicable.

8.1.3.3. Studies evaluable for safety only

Not applicable.

8.1.4. Studies that assessed safety as the sole primary outcome

Not applicable.

8.2. Patient exposure

8.2.1. HIV/HBV co-infection

Data on use of Genvoya in patients co-infected with HIV and HBV relies on a single, open label study (GS-US-292-1249). The median (Q1, Q3) duration of exposure to study drug was 49.1 (48.1, 59.4) weeks.

Table 19: Exposure to Genvoya in clinical Study GS-US-292-1249 (Cohort 2)

	GEN Cohort 2 (N = 74)
Total Exposure to Study Drug (Weeks)	
Mean (SD)	50.5 (10.99)
Median	49.1
Q1, Q3	48.1, 59.4
Min, Max	4.1, 61.1
Total Exposure to Study Drug	
≥ 4 Weeks (28 Days)	74 (100.0%)
≥ 8 Weeks (56 Days)	72 (97.3%)
≥ 12 Weeks (84 Days)	71 (95.9%)
≥ 24 Weeks (168 Days)	71 (95.9%)
≥ 36 Weeks (252 Days)	70 (94.6%)

	GEN Cohort 2 (N = 74)
≥ 48 Weeks (336 Days)	60 (81.1%)
≥ 60 Weeks (420 Days)	14 (18.9%)

Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug. If the last dose date was completely missing, or only the year was known, or a subject was still on study drug, either study drug start and end dates or clinic and laboratory visit dates (excluding the 30-day follow-up visit date), whichever gave the latest date, was used to impute the last dose date.

8.2.2. Paediatric use

Data on paediatric use is based on a single open label, non-comparative study (GD-US-292-0106).

Table 20: Study GS-US-292-0106: Duration of exposure to study drug (Cohort 2 Part A safety analysis set)

Total Exposure to Study Drug (weeks)[a,b]	GEN (N = 23)
N	23
Mean (SD)	31.6 (3.83)
Median	32.1
Q1, Q3	31.7, 32.1
Min, Max	24.3, 40.3
Total Exposure to Study Drug	
≥ 1 Week (7 days)	23 (100.0%)
≥ 2 Weeks (14 days)	23 (100.0%)
≥ 4 Weeks (28 days)	23 (100.0%)
≥ 8 Weeks (56 days)	23 (100.0%)
≥ 12 Weeks (84 days)	23 (100.0%)
≥ 16 Weeks (112 days)	23 (100.0%)
≥ 24 Weeks (168 days)	23 (100.0%)

Total Exposure to Study Drug (weeks)[a,b]	GEN (N = 23)
≥ 32 Weeks (224 days)	15 (65.2%)

[a] Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug. b If the last dose date was completely missing, or only the year was known, either study drug start and end dates or clinic and laboratory visit dates (excluding the 30-day follow-up visit date), whichever gave the latest date, was used to impute the last dose date; in case of the last study drug end date was non-missing, then it was used to impute the last dose date.

8.2.3. Renal impairment

Data on patients with mild to moderate renal impairment is from a single open label study (GS-US-292-0112). Median duration of exposure to study drug was 144.1 weeks for Cohort 1 switch subjects.

Table 21: Study GS-US-292-0112: Duration of exposure to study drug (Cohort 1, safety analysis set)

	Cohort 1: Switch		
	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)
Total Exposure to Study Drug (Weeks)			
N	80	162	242
Mean (SD)	129.9 (37.34)	136.4 (33.84)	134.3 (35.10)
Median	143.8	144.1	144.1
Q1, Q3	138.3, 144.9	143.9, 149.1	143.0, 146.3
Min, Max	7.0, 157.4	4.9, 168.7	4.9, 168.7
Total Exposure to Study Drug			
≥ 24 Weeks (168 days)	75 (93.8%)	157 (96.9%)	232 (95.9%)
≥ 48 Weeks (336 days)	74 (92.5%)	152 (93.8%)	226 (93.4%)
≥ 60 Weeks (420 days)	73 (91.3%)	151 (93.2%)	224 (92.6%)
≥ 72 Weeks (504 days)	72 (90.0%)	149 (92.0%)	221 (91.3%)
≥ 84 Weeks (588 days)	71 (88.8%)	148 (91.4%)	219 (90.5%)
≥ 96 Weeks (672 days)	70 (87.5%)	147 (90.7%)	217 (89.7%)
≥ 108 Weeks (756 days)	69 (86.3%)	147 (90.7%)	216 (89.3%)
≥ 120 Weeks (840 days)	69 (86.3%)	145 (89.5%)	214 (88.4%)

	Cohort 1: Switch		
	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)
≥ 132 Weeks (924 days)	66 (82.5%)	144 (88.9%)	210 (86.8%)
≥ 144 Weeks (1008 days)	35 (43.8%)	114 (70.4%)	149 (61.6%)
≥ 156 Weeks (1092 days)	5 (6.3%)	20 (12.3%)	25 (10.3%)
≥ 168 Weeks (1176 days)	0	1 (0.6%)	1 (0.4%)

Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug. If the last dose date was completely missing, or only the year was known, or for subjects still on study drug, the latest of study drug start and end dates or clinic and laboratory visit dates (excluding the 30-day follow-up visit date) was used to impute the last dose date; in case of the last study drug end date was non-missing, then it was used to impute the last dose date.

8.2.4. Long term treatment

8.2.4.1. Virologically suppressed to Week 96

Data on virologically suppressed subjects switched to Genvoya was presented in a single, open label, randomised study (GS-US-292-0109). The median duration of exposure to study drug was 96.0 weeks for both treatment groups.

Table 22: Study GS-US-292-0109: Duration of exposure to study drug (safety analysis set)

	GEN (N = 959)	FTC/TDF+3rd Agent (N = 477)
Total Exposure to Randomised Study Drug (Weeks)		
N	959	477
Mean (SD)	93.9 (11.34)	90.7 (18.26)
Median	96.0	96.0
Q1, Q3	95.7, 96.3	95.4, 96.3
Min, Max	1.7, 107.1	0.3, 101.6
Total Exposure to Randomised Study Drug		
≥ 24 Weeks (168 days)	949 (99.0%)	462 (96.9%)
≥ 48 Weeks (336 days)	940 (98.0%)	449 (94.1%)
≥ 60 Weeks (420 days)	932 (97.2%)	445 (93.3%)
≥ 72 Weeks (504 days)	926 (96.6%)	438 (91.8%)
≥ 84 Weeks (588 days)	916 (95.5%)	434 (91.0%)

	GEN (N = 959)	FTC/TDF+3rd Agent (N = 477)
≥ 96 Weeks (672 days)	575 (60.0%)	271 (56.8%)

Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug. For subjects in the Genvoya group, the randomized phase last dose date was defined as Week 96 visit date − 1 day. For subjects in the FTC/TDF+3rd Agent group, if the last randomized study drug end date was non-missing, it was used to impute the randomised phase last dose date. Otherwise, either randomised study drug start and end dates or clinic and laboratory visit dates (excluding the 30-day follow-up visit date), whichever gave the latest date was used to impute the randomized phase last dose date.

8.2.5. Treatment naïve to Week 144

Data on treatment naïve patients is presented as pooled data from two studies (GS-US-292-0104 and GS-US-292-0111). The median exposure was similar in the two treatment groups (Genvoya: 144.9 weeks and STB: 144.4 weeks).

Table 23: Pooled data (Studies GS-US-292-0104 and GS-US-292-0111): Duration of exposure to study drug (safety analysis set)

Exposure[a,b]	GEN (N = 866)	STB (N = 867)
Total Exposure to Study Drug (Weeks)		
N	866	867
Mean (SD)	140.8 (34.31)	137.0 (38.67)
Median	144.9	144.4
Q1, Q3	143.0, 156.6	140.9, 156.4
Min, Max	0.1, 181.1	0.1, 180.6
Duration of Exposure to Study Drug		
≥ 4 weeks (28 days)	859 (99.2%)	857 (98.8%)
≥ 8 weeks (56 days)	855 (98.7%)	854 (98.5%)
≥ 12 weeks (84 days)	853 (98.5%)	849 (97.9%)
≥ 16 weeks (112 days)	850 (98.2%)	844 (97.3%)
≥ 24 weeks (168 days)	842 (97.2%)	833 (96.1%)
≥ 36 weeks (252 days)	831 (96.0%)	821 (94.7%)
≥ 48 weeks (336 days)	827 (95.5%)	808 (93.2%)
≥ 60 weeks (420 days)	818 (94.5%)	795 (91.7%)
≥ 72 weeks (504 days)	808 (93.3%)	784 (90.4%)
≥ 84 weeks (588 days)	790 (91.2%)	770 (88.8%)

Exposure[a,b]	GEN (N = 866)	STB (N = 867)
≥ 96 weeks (672 days)	779 (90.0%)	756 (87.2%)
≥ 108 weeks (756 days)	771 (89.0%)	749 (86.4%)
≥ 120 weeks (840 days)	763 (88.1%)	740 (85.4%)
≥ 132 weeks (924 days)	757 (87.4%)	727 (83.9%)
≥ 144 weeks (1008 days)	578 (66.7%)	551 (63.6%)
≥ 156 weeks (1092 days)	327 (37.8%)	299 (34.5%)
≥ 168 weeks (1176 days)	105 (12.1%)	115 (13.3%)
≥ 180 weeks (1260 days)	5 (0.6%)	4 (0.5%)

[a] Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug. [b] If the last dose date was completely missing, or only the year was known, or a subject was still on study drug, the latest of study drug start and end dates or clinic and laboratory visit dates (excluding the 30-day Follow-up Visit date) was used to impute the last dose date; if the last study drug end date was non-missing, then it was used to impute the last dose date.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Integrated safety analyses

Not applicable.

8.3.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.3.1.3. Pivotal and/or main efficacy studies

HIV/HBV Co-infection Study GS-US-292-1249

Cohort 1 (naïve): 2/3 subjects reported at least one AE during the study. No AE was reported by ≥ 1 patient. The AEs reported were diarrhoea and upper respiratory tract infection.

Cohort 2 (suppressed): 61 (82.4%) reported at least one AE during the study. The AEs were consistent with those expected in the subject population and the known safety profiles of the study drug.

Table 24: Study GS-US-292-1249: Overall summary of AEs (Cohort 2, safety analysis set)

	GEN
Subjects Experiencing Any AE	61 (82.4%)
Subjects Experiencing Any Grade 3 or 4 AE	4 (5.4%)
Subjects Experiencing Any Grade 2, 3, or 4 AE	24 (32.4%)
Subjects Experiencing Any Study Drug-Related AE	12 (16.2%)

	GEN
Subjects Experiencing Grade 3 or 4 Study Drug-Related AE	0
Subjects Experiencing Grade 2, 3, or 4 Study Drug-Related AE	3 (4.1%)
Subjects Experiencing Any SAE	6 (8.1%)
Subjects Experiencing Study Drug-Related SAE	0
Subjects Experiencing Any AE Leading to Permanent Study Drug Discontinuation	1 (1.4%)
Subjects Who Died	0

TEAE = treatment emergent adverse event; AE = adverse event; SAE = serious adverse event

Table 25: Study GS-US-292-1249: AE reported for ≥ 5% of subjects in Cohort 2 (Cohort 2, safety analysis set)

Adverse Events by System Organ Class and Preferred Term[a]	GEN Cohort 2 (N = 74)
Subjects Experiencing Any AE	61 (82.4%)
Gastrointestinal Disorders	
Diarrhoea	5 (6.8%)
Gastroesophageal Reflux Disease	5 (6.8%)
General Disorders and Administration Site Conditions	
Pyrexia	4 (5.4%)
Infections and Infestations	
Upper Respiratory Tract Infection	12 (16.2%)
Nasopharyngitis	6 (8.1%)
Musculoskeletal and Connective Tissues Disorders	
Back Pain	5 (6.8%)
Respiratory, Thoracic and Mediastinal Disorders	
Rhinitis Allergic	4 (5.4%)

[a] Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.

8.3.1.4. Paediatric use 6 – < 12 years

Most subjects (73.9%, 17/23 subjects) had at least 1 AE. The most common AEs were respiratory tract infection, abdominal pain, vomiting, headache, Vitamin D deficiency, contusion and allergic rhinitis.

Table 26: Study GS-US-292-0106: Overall summary of AE (Cohort 2 Part A safety analysis set)

	GEN (N = 23)
Subjects Experiencing Any TEAE	17 (73.9%)
Subjects Experiencing Any Grade 2, 3 or 4 TEAE	5 (21.7%)
Subjects Experiencing Any Grade 3 or 4 TEAE	0
Subjects Experiencing Any Treatment-Emergent AE Related to Study Drug	9 (39.1%)
Subjects Experiencing Any Grade 2, 3 or 4 TEAE Related to Study Drug	0
Subjects Experiencing Any Treatment-Emergent SAE	0
Subjects Experiencing Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation	0
Subjects who had Treatment-Emergent Death	0

TEAE = treatment emergent adverse event; AE = adverse event; SAE = serious adverse event

Table 27: Study GS-US-292-0106: AE occurring in at least 5% of subjects (Cohort 2 Part A safety analysis set)

Adverse Event by System Organ Class and Preferred Term[a,b]	GEN (N = 23)
Subjects Experiencing Any Treatment-Emergent AE	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%)

Adverse Event by System Organ Class and Preferred Term[a,b]	GEN (N = 23)
Respiratory, thoracic and mediastinal disorders	5 (21.7%)
Rhinitis allergic	2 (8.7%)

[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.

8.3.1.5. Other studies

Other efficacy studies

Renal impairment

At least 1 AE was reported in 95.5% of Cohort 1 switch subjects (n = 231; baseline eGFRCG < 50 mL/min 95.0% [76 subjects]; baseline eGFRCG ≥ 50 mL/min 95.7% [155 subjects]. The most commonly reported AEs in Cohort 1 were bronchitis, upper respiratory tract infection, arthralgia and diarrhoea. Osteoporosis was the only AE reported for notably more subjects with baseline eGFRCG < 50 mL/min than with baseline $eGFR_{CG}$ ≥ 50 mL/min.

Table 28: Study GS-US-292-0112: Overall summary of TEAE (Cohort 1, safety analysis set)

	Cohort 1: Switch		
	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)
Subjects Experiencing Any TEAE	76 (95.0%)	155 (95.7%)	231 (95.5%)
Subjects Experiencing Any Grade 2, 3, or 4 TEAE	59 (73.8%)	112 (69.1%)	171 (70.7%)
Subjects Experiencing Any Grade 3 or 4 TEAE	21 (26.3%)	30 (18.5%)	51 (21.1%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related AE	27 (33.8%)	46 (28.4%)	73 (30.2%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study-Drug-Related AE	14 (17.5%)	20 (12.3%)	34 (14.0%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related AE	3 (3.8%)	2 (1.2%)	5 (2.1%)
Subjects Experiencing Any Treatment-Emergent SAE	19 (23.8%)	33 (20.4%)	52 (21.5%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related SAE	0	0	0
Subjects Experiencing Any TEAE Leading to Premature Study Drug Discontinuation	8 (10.0%)	4 (2.5%)	12 (5.0%)

	Cohort 1: Switch		
	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)
Subjects who had Treatment-Emergent Death	1 (1.3%)	1 (0.6%)	2 (0.8%)

TEAE = treatment emergent adverse event; AE = adverse event; SAE = serious adverse event

Table 29: Study GS-US-292-0112: AE reported for at least 5% of subjects (Cohort 1, safety analysis set)

	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)
Number of Subjects Experiencing Any TEAE	76 (95.0%)	155 (95.7%)	231 (95.5%)
GASTROINTESTINAL DISORDERS	38 (47.5%)	71 (43.8%)	109 (45.0%)
Diarrhoea	11 (13.8%)	21 (13.0%)	32 (13.2%)
Nausea	6 (7.5%)	16 (9.9%)	22 (9.1%)
Constipation	4 (5.0%)	11 (6.8%)	15 (6.2%)
Abdominal pain	5 (6.3%)	8 (4.9%)	13 (5.4%)
Vomiting	4 (5.0%)	9 (5.6%)	13 (5.4%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	14 (17.5%)	45 (27.8%)	59 (24.4%)
Fatigue	6 (7.5%)	13 (8.0%)	19 (7.9%)
INFECTIONS AND INFESTATIONS	42 (52.5%)	114 (70.4%)	156 (64.5%)
Bronchitis	13 (16.3%)	26 (16.0%)	39 (16.1%)
Upper respiratory tract infection	3 (3.8%)	33 (20.4%)	36 (14.9%)
Nasopharyngitis	4 (5.0%)	19 (11.7%)	23 (9.5%)
Urinary tract infection	3 (3.8%)	19 (11.7%)	22 (9.1%)
Sinusitis	3 (3.8%)	15 (9.3%)	18 (7.4%)

	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	41 (51.3%)	89 (54.9%)	130 (53.7%)
Arthralgia	8 (10.0%)	26 (16.0%)	34 (14.0%)
Back pain	5 (6.3%)	22 (13.6%)	27 (11.2%)
Osteopenia	12 (15.0%)	14 (8.6%)	26 (10.7%)
Pain in extremity	4 (5.0%)	20 (12.3%)	24 (9.9%)
Osteoporosis	7 (8.8%)	6 (3.7%)	13 (5.4%)
Muscle Spasms	3 (3.8%)	9 (5.6%)	12 (5.0%)
Myalgia	4 (5.0%)	8 (4.9%)	12 (5.0%)
NERVOUS SYSTEM DISORDERS	25 (31.3%)	54 (33.3%)	79 (32.6%)
Headache	3 (3.8%)	17 (10.5%)	20 (8.3%)
Dizziness	8 (10.0%)	9 (5.6%)	17 (7.0%)
Paraesthesia	3 (3.8%)	9 (5.6%)	12 (5.0%)
PSYCHIATRIC DISORDERS	11 (13.8%)	27 (16.7%)	38 (15.7%)
Depression	3 (3.8%)	9 (5.6%)	12 (5.0%)
Insomnia	1 (1.3%)	11 (6.8%)	12 (5.0%)
RENAL AND URINARY DISORDERS	20 (25.0%)	32 (19.8%)	52 (21.5%)
Renal cyst	5 (6.3%)	9 (5.6%)	14 (5.8%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	15 (18.8%)	51 (31.5%)	66 (27.3%)
Cough	6 (7.5%)	18 (11.1%)	24 (9.9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	19 (23.8%)	51 (31.5%)	70 (28.9%)
Rash	2 (2.5%)	11 (6.8%)	13 (5.4%)
VASCULAR DISORDERS	15 (18.8%)	23 (14.2%)	38 (15.7%)
Hypertension	9 (11.3%)	14 (8.6%)	23 (9.5%)

Multiple AEs were counted only once per subject for each system organ class, high level term, and preferred term, respectively.

Virologically suppressed long term (96 week)

Similar percentages of subjects in each group had an AE (Genvoya 89.6%, 859/959 subjects; FTC/TDF+3rd Agent 88.1%, 420/477 subjects). The most commonly reported AEs were the same for each treatment group: upper respiratory tract infection, diarrhoea, and nasopharyngitis. No AE by preferred term (PT) was reported with a difference in percentages of ≥ 5% between groups.

Table 30: Study GS-US-292-0109: Overall summary of AEs during the randomised phase (safety analysis set)

	GEN (N = 959)	FTC/TDF+ 3rd Agent (N = 477)
Subjects Experiencing Any AE	859 (89.6%)	420 (88.1%)
Subjects Experiencing Any Grade 2, 3, or 4 AE	529 (55.2%)	259 (54.3%)
Subjects Experiencing Any Grade 3 or 4 AE	101 (10.5%)	58 (12.2%)
Subjects Experiencing Any Study Drug-Related AE	218 (22.7%)	91 (19.1%)
Subjects Experiencing Any Grade 2, 3, or 4 Study Drug-Related AE	68 (7.1%)	40 (8.4%)
Subjects Experiencing Any Grade 3 or 4 Study Drug-Related AE	6 (0.6%)	9 (1.9%)
Subjects Experiencing Any SAE	79 (8.2%)	39 (8.2%)
Subjects Experiencing Any Study-Drug-Related SAE	1 (0.1%)	2 (0.4%)
Subjects Experiencing Any AE Leading to Premature Study Drug Discontinuation	9 (0.9%)	12 (2.5%)
Subjects Who Died	4 (0.4%)	0

TEAE = treatment emergent adverse event; AE = adverse event; SAE = serious adverse event

Table 31: Study GS-US-292-0109: AEs reported for ≥ 5% of subjects in any treatment group (safety analysis set

Adverse Events by System Organ Class and Preferred Term[a]	GEN (N = 959)	FTC/TDF+3rd Agent (N = 477)
Subjects Experiencing Any AE	859 (89.6%)	420 (88.1%)
GASTROINTESTINAL DISORDERS		
Diarrhoea	110 (11.5%)	52 (10.9%)
Nausea	56 (5.8%)	18 (3.8%)
GENERAL DISORDERS AND ADMINISTRATION SITE	48 (5.0%)	21 (4.4%)

Adverse Events by System Organ Class and Preferred Term[a]	GEN (N = 959)	FTC/TDF+3rd Agent (N = 477)
CONDITIONS		
Pyrexia		
INFECTIONS AND INFESTATIONS		
Influenza	43 (4.5%)	25 (5.2%)
Bronchitis	70 (7.3%)	27 (5.7%)
Syphilis	63 (6.6%)	38 (8.0%)
Upper Respiratory Tract Infection	168 (17.5%)	64 (13.4%)
Nasopharyngitis	96 (10.0%)	48 (10.1%)
Sinusitis	59 (6.2%)	31 (6.5%)
Pharyngitis	56 (5.8%)	14 (2.9%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Arthralgia	78 (8.1%)	31 (6.5%)
Osteopenia	67 (7.0%)	25 (5.2%)
Back Pain	70 (7.3%)	33 (6.9%)
NERVOUS SYSTEM DISORDERS		
Headache	84 (8.8%)	25 (5.2%)
PSYCHIATRIC DISORDERS		
Depression	48 (5.0%)	32 (6.7%)
Insomnia	58 (6.0%)	36 (7.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Cough	73 (7.6%)	31 (6.5%)
Oropharyngeal Pain	57 (5.9%)	12 (2.5%)

[a] Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.

Treatment naïve long term (144 weeks)

Using the pooled data from Studies GS-US-292-0104 and GS-US-292-0111 there were similar percentages of subjects reporting AEs in each treatment group (Genvoya: 94.3%; STB: 96.1%). The most common AEs reported for Genvoya were: diarrhoea, upper respiratory tract infection

and headache. The most common AEs reported for STB were: diarrhoea, upper respiratory tract infection and nausea.

Table 32: Pooled Studies GS-US-292-0104 and GS-US-292-0111: Overall summary of TEAEs (safety analysis set)

	GEN (N=866)	STB (N=867)
Subjects Experiencing Any Treatment-Emergent AE	817 (94.3%)	833 (96.1%)
Subjects Experiencing Any Grade 2, 3, or 4 TEAE	559 (64.5%)	552 (63.7%)
Subjects Experiencing Any Grade 3 or 4 TEAE	140 (16.2%)	137 (15.8%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related AE	382 (44.1%)	424 (48.9%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study-Drug-Related AE	109 (12.6%)	113 (13.0%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related AE	15 (1.7%)	15 (1.7%)
Subjects Experiencing Any Treatment-Emergent SAE	121 (14.0%)	124 (14.3%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related SAE	5 (0.6%)	6 (0.7%)
Subjects Experiencing Any TEAE Leading to Premature Study Drug Discontinuation	11 (1.3%)	29 (3.3%)
Subjects who had Treatment-Emergent Death	4 (0.5%)	5 (0.6%)

TEAE = treatment emergent adverse event; AE = adverse event; SAE = serious adverse event

Table 33: Pooled Studies GS-US-292-0104 and GS-US-292-0111: AEs reported for ≥ 10% of subjects in either treatment group (safety analysis set)

Adverse Events by System Organ Class and Preferred Term	GEN (N=866)	STB (N=867)
Number of Subjects Experiencing Any TEAE	817 (94.3%)	833 (96.1%)
Gastrointestinal disorders	508 (58.7%)	521 (60.1%)
Diarrhoea	203 (23.4%)	212 (24.5%)
Nausea	150 (17.3%)	167 (19.3%)
General disorders and administration site conditions	256 (29.6%)	231 (26.6%)
Fatigue	101 (11.7%)	97 (11.2%)
Infections and infestations	661 (76.3%)	650 (75.0%)
Upper respiratory tract infection	176 (20.3%)	170 (19.6%)

Adverse Events by System Organ Class and Preferred Term	GEN (N=866)	STB (N=867)
Nasopharyngitis	125 (14.4%)	123 (14.2%)
Syphilis	86 (9.9%)	97 (11.2%)
Musculoskeletal and connective tissue disorders	364 (42.0%)	365 (42.1%)
Back pain	104 (12.0%)	104 (12.0%)
Arthralgia	104 (12.0%)	82 (9.5%)
Osteopenia	69 (8.0%)	87 (10.0%)
Nervous system disorders	286 (33.0%)	270 (31.1%)
Headache	166 (19.2%)	135 (15.6%)
Psychiatric disorders	260 (30.0%)	262 (30.2%)
Insomnia	94 (10.9%)	68 (7.8%)
Respiratory, thoracic and mediastinal disorders	266 (30.7%))	264 (30.4%)
Cough	117 (13.5%)	102 (11.8%)

Adverse events were coded using MedDRA 19.0. System organ class (SOC) and high level term (within each SOC) were presented alphabetically, and preferred term was presented by decreasing order of the total frequencies. Multiple AEs were counted only once per subject for each system organ class, high level term, and preferred term, respectively.

Studies with evaluable safety data: dose finding and pharmacology

Not applicable.

Studies evaluable for safety only

Not applicable.

8.3.2. Treatment related adverse events (adverse drug reactions)

8.3.2.1. Pivotal and/or main efficacy studies

HIV/HBV Co-infection Study GS-US-292-1249

Cohort 1 (naïve): There were no AEs considered related to study drug reported during the study.

Cohort 2 (suppressed): There were 12 (16.2%) subjects who reported AEs considered to be related to study drug. The most common AEs were diarrhoea (3 subjects [4.1%]) and increased appetite (2 subjects [2.7%]). Each of the other AEs was reported in 1 subject (1.4%).

Paediatric use 6 to 12 years

AEs considered related to study drug were reported by 9 subjects (39.1%), all study related AEs reported for ≥ 2 subjects were in the gastrointestinal system: abdominal pain (4 subjects, 17.4%) and vomiting (4 subjects, 17.4%).

8.3.2.2. Other studies

Other efficacy studies

Renal impairment

AEs considered related to study drug were reported in 30.2% of subjects (n = 73; baseline $eGFR_{CG}$ < 50 mL/min 33.8% [27 subjects]; baseline $eGFR_{CG}$ ≥ 50 mL/min 28.4% [46 subjects]). The most commonly reported AEs considered related to study drug in Cohort 1 switch subjects were diarrhoea, dizziness, headache, hypercholesterolaemia, nausea, constipation, and osteopenia.

Table 34: Study GS-US-292-0112: Study drug-related, TEAE reported for at least 1% of subjects (Cohort 1, safety analysis set)

	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)
Number of Subjects Experiencing Any Treatment-Emergent Study-Drug-Related AE	27 (33.8%)	46 (28.4%)	73 (30.2%)
GASTROINTESTINAL DISORDERS	10 (12.5%)	24 (14.8%)	34 (14.0%)
Diarrhoea	2 (2.5%)	6 (3.7%)	8 (3.3%)
Constipation	1 (1.3%)	4 (2.5%)	5 (2.1%)
Nausea	2 (2.5%)	3 (1.9%)	5 (2.1%)
Flatulence	2 (2.5%)	2 (1.2%)	4 (1.7%)
Abdominal Discomfort	2 (2.5%)	1 (0.6%)	3 (1.2%)
Dyspepsia	0	3 (1.9%)	3 (1.2%)
METABOLISM AND NUTRITION DISORDERS	6 (7.5%)	8 (4.9%)	14 (5.8%)
Hypercholesterolaemia	1 (1.3%)	4 (2.5%)	5 (2.1%)
Dyslipidaemia	3 (3.8%)	1 (0.6%)	4 (1.7%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5 (6.3%)	6 (3.7%)	11 (4.5%)
Osteopenia	3 (3.8%)	2 (1.2%)	5 (2.1%)
NERVOUS SYSTEM DISORDERS	5 (6.3%)	9 (5.6%)	14 (5.8%)
Dizziness	4 (5.0%)	4 (2.5%)	8 (3.3%)
Headache	1 (1.3%)	4 (2.5%)	5 (2.1%)
PSYCHIATRIC DISORDERS	4 (5.0%)	4 (2.5%)	8 (3.3%)
Abnormal Dreams	2 (2.5%)	1 (0.6%)	3 (1.2%)

	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)
Insomnia	1 (1.3%)	2 (1.2%)	3 (1.2%)

Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.

Virologically suppressed long term (96 week)

Subjects who switched to Genvoya had a slightly higher incidence of any AE considered by the investigator as related to study drug (Genvoya 22.7%, 218 subjects; FTC/TDF+3rd Agent 19.1%, 91 subjects). The most commonly reported AEs considered related to Genvoya were diarrhoea, nausea and flatulence. The most commonly reported AEs considered related to FTC/TDF+3rd agent were osteopenia, jaundice and ocular icterus.

Table 35: Study GS-US-292-0109: Study drug-related AE reported for at least 1% of subjects in either treatment group (safety analysis set)

Adverse Events by System Organ Class and Preferred Term[a]	GEN (N = 959)	FTC/TDF+3rd Agent (N = 477)
Subjects Experiencing Any Study Drug-Related AE	218 (22.7%)	91 (19.1%)
Eye Disorders		
Ocular Icterus	0	8 (1.7%)
Gastrointestinal Disorders		
Diarrhoea	25 (2.6%)	6 (1.3%)
Flatulence	18 (1.9%)	2 (0.4%)
Nausea	22 (2.3%)	3 (0.6%)
General Disorders and Administration Site Conditions		
Fatigue	10 (1.0%)	5 (1.0%)
Hepatobiliary Disorders		
Jaundice	0	8 (1.7%)
Metabolism and Nutrition Disorders		
Hypercholesterolaemia	12 (1.3%)	0
Musculoskeletal and Connective Tissue Disorders		
Osteopenia	17 (1.8%)	10 (2.1%)
Osteoporosis	3 (0.3%)	6 (1.3%)

Adverse Events by System Organ Class and Preferred Term[a]	GEN (N = 959)	FTC/TDF+3rd Agent (N = 477)
Nervous System Disorders		
Headache	17 (1.8%)	1 (0.2%)
Dizziness	12 (1.3%)	6 (1.3%)
Psychiatric Disorders		
Depression	4 (0.4%)	5 (1.0%)
Insomnia	10 (1.0%)	7 (1.5%)
Abnormal Dreams	12 (1.3%)	6 (1.3%)

a Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.

Treatment naïve long term (144 weeks)

The percentage of subjects that had any AE considered related to study drugs by the investigator was slightly lower in the Genvoya group compared with the STB group, as follows: Genvoya 44.1%, 382 of 866 subjects; STB 48.9%, 424 of 867 subjects. The most commonly reported AEs considered related to study drug were the same in both groups: nausea, diarrhoea and headache.

Table 36: Pooled Study GS-US-292-0104 and GS-US-292-0111: AEs related to study drug reported for ≥ 1% of subjects in either treatment group (safety analysis set)

Adverse Events by System Organ Class and Preferred Term	GEN (N=866)	STB (N=867)
Number of Subjects Experiencing Any Treatment-Emergent Study-Drug-Related AE	382 (44.1%)	424 (48.9%)
Nausea	91 (10.5%)	115 (13.3%)
Diarrhoea	63 (7.3%)	77 (8.9%)
Flatulence	23 (2.7%)	29 (3.3%)
Vomiting	16 (1.8%)	29 (3.3%)
Abdominal pain	12 (1.4%)	11 (1.3%)
Abdominal pain upper	11 (1.3%)	12 (1.4%)
Abdominal distension	12 (1.4%)	9 (1.0%)
Fatigue	44 (5.1%)	38 (4.4%)

Adverse Events by System Organ Class and Preferred Term	GEN (N=866)	STB (N=867)
Bone density decreased	8 (0.9%)	11 (1.3%)
Decreased appetite	13 (1.5%)	8 (0.9%)
Osteopenia	32 (3.7%)	40 (4.6%)
Osteoporosis	8 (0.9%)	12 (1.4%)
Headache	53 (6.1%)	47 (5.4%)
Dizziness	26 (3.0%)	20 (2.3%)
Somnolence	9 (1.0%)	10 (1.2%)
Abnormal dreams	13 (1.5%)	29 (3.3%)
Insomnia	18 (2.1%)	15 (1.7%)
Proteinuria	8 (0.9%)	22 (2.5%)
Rash	15 (1.7%)	9 (1.0%)

Adverse events were coded using MedDRA 19.0. System organ class was presented alphabetically and preferred term was presented by descending order of the total frequencies. Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Pivotal and/or main efficacy studies

HIV/HBV Co-infection Study GS-US-292-1249

Cohort 1 (naïve): There were no deaths or SAEs reported.

Cohort 2 (suppressed): There were no deaths and six subjects (8.1%) had SAEs, none of which were considered related to study drug. Six subjects (8.1%) had at least 1 SAE during this study: acute myocardial infarction; appendicitis; benign prostatic hyperplasia and prostatitis; diabetes mellitus and limb abscess; pneumonia; pneumococcal bacteraemia, pneumococcal meningitis and pneumococcal pneumonia. None were considered related to study drug.

Paediatric use – 6 - < 12 years

There were no deaths or other SAEs reported during the study.

8.3.3.2. Other studies

Other efficacy studies

Renal impairment

Two deaths were reported during the study (cardiopulmonary arrest and cardiac arrest). Both events were considered unrelated to study drug.

At least 1 SAE was reported in 21.5% of subjects (n = 52; baseline $eGFR_{CG}$ < 50 mL/min 23.8% [19 subjects] baseline $eGFR_{CG}$ ≥ 50 mL/min 20.4% [33 subjects]). The following SAEs were reported for > 1 subject through Week 144: acute myocardial infarction (4 subjects), pneumonia (4 subjects), dehydration (3 subjects), abdominal pain, gastroenteritis, congestive cardiac

failure, acute kidney injury, type 2 diabetes mellitus, arthralgia, chronic obstructive pulmonary disease, and syncope (all in 2 subjects). All SAEs were considered unrelated to study drug by the investigator.

Virologically suppressed long term (96 week)

Four subjects in the Genvoya group died during the randomised phase of the study and 1 subject died during the extension phase. None of the events leading to death were considered related to study drug. The causes of death were: septic shock, stage 4 adenocarcinoma, sudden death/undetermined cause, methamphetamine related myocarditis and coronary artery disease, and non-small cell lung cancer. No subject in the FTC-TDF+3rd agent died during the study.

Serious AEs were reported for similar percentages of subjects in both treatment groups during the randomised phase of the study (Genvoya 8.2%, 79 subjects; FTC/TDF+3rd Agent 8.2%, 39 subjects).

The following SAEs were reported for > 2 subjects in either treatment group: sepsis (Genvoya 0.4%, 4 subjects; FTC/TDF+3rd Agent 0.2%, 1 subject); pneumonia (Genvoya 0.5%, 5 subjects; FTC/TDF+3rd Agent 0%); suicide attempt (Genvoya 0.4%, 4 subjects; FTC/TDF+3rd Agent 0%); appendicitis (Genvoya 0.3%, 3 subjects; FTC/TDF+3rd Agent 0.2%, 1 subject); aseptic meningitis (Genvoya 0.3%, 3 subjects; FTC/TDF+3rd Agent 0%); and abdominal pain (Genvoya 0.3%, 3 subjects; FTC/TDF+3rd Agent 0%).

One SAE in the Genvoya group (metrorrhagia) was considered related to study drug. In the FTC/TDF+3rd Agent group, 2 subjects had SAEs considered related to study drug by the investigator: Fanconi Syndrome in 1 subject and acute cholecystitis, cholelithiasis, and hydropic gallbladder in 1 subject. None of the SAEs reported during the extension phase were considered related to study drug.

Treatment naïve long term (144 weeks)

Nine treatment emergent deaths were reported through Week 144 (Genvoya 4 subjects: completed suicide, cerebral infarction, cerebrovascular accident, and alcohol poisoning [1 subject each]; STB 5 subjects: cardiac arrest [2 subjects], unknown cause and acute myocardial infarction [1 subject each]; recreational drug and alcohol overdose [both in 1 subject]). Two additional deaths were reported through Week 144 that were not treatment emergent as they occurred more than 30 days after the last dose of study drugs (Genvoya 1 subject: myocardial infarction; STB 1 subject: non-small cell lung cancer). All SAEs that resulted in death were considered not related to study drug by the investigator.

SAEs were reported for similar percentages of subjects in each treatment group (Genvoya 14.0%, 121 of 866 subjects; STB 14.3%, 124 of 867 subjects).

Appendicitis was the only SAE that occurred in ≥ 1% of subjects in either treatment group (Genvoya 1.0%, 9 subjects; STB 0.8%, 7 subjects). None of the appendicitis SAEs was considered related to study drugs by the investigator. No SAE considered related to study drugs by the investigator was reported for > 1 subject in either treatment group.

Six subjects had SAEs due to renal and urinary disorder or associated investigation (Genvoya 3 subjects: ureterolithiasis, nephrotic syndrome, and post infectious glomerulonephritis; STB 3 subjects: ureterolithiasis, acute kidney infection, and renal haematoma).

8.3.4. Discontinuations due to adverse events

8.3.4.1. Pivotal and/or main efficacy studies

HIV/HBV Co-infection – Study GS-US-292-1249

Cohort 1 (naïve): There were no discontinuations due to AEs.

Cohort 2 (suppressed): One subject had two AEs that led to discontinuation of study drug – weight increased and increased appetite. Neither was considered serious but both were considered drug related.

Paediatric use – 6-12 years

There were no discontinuations due to AEs.

8.3.4.2. Other studies

Other efficacy studies

Renal impairment

AEs leading to premature study drug discontinuation were reported in 5.0% of subjects (n = 12) with a higher percentage reported in subjects with baseline $eGFR_{CG}$ < 50 mL/min (10.0% [8 subjects]) compared with subjects with baseline $eGFR_{CG}$ ≥ 50 mL/min (2.5% [4 subjects]).

The only AE leading to study drug discontinuation reported in > 1 subject was nephropathy (3 subjects). All AEs leading to discontinuation of study drug were considered unrelated to study drug, with the exception of AEs in 4 subjects (2 with baseline $eGFR_{CG}$ < 50 mL/min and 2 with baseline $eGFR_{CG}$ ≥ 50 mL/min) who each had a single AE leading to premature study drug discontinuation considered related to study drug (sleep disorder, renal failure, nephropathy, and choking, respectively). Five subjects discontinued study drug due to renal AEs. There were no new discontinuations of study drug due to AEs reported after the Week 96 data cut-off date.

Virologically suppressed long term (96 week)

Few subjects in either group discontinued study drug due to AEs (Genvoya 0.9%, 9 subjects; FTC/TDF+3rd Agent 2.5%, 12 subjects). None of the AEs leading to study drug discontinuation in the Genvoya group were reported for > 1 subject.

The following were the AEs leading to study drug discontinuation reported for > 1 subject in the FTC/TDF+3rd Agent group: jaundice (3 subjects, all of whom were taking boosted-ATV+FTC/TDF); and depression, increased blood creatinine, and insomnia (2 subjects for each AE). Most of the AEs leading to study drug discontinuation were non serious and considered related to study drug.

Treatment naïve long term (144 weeks)

The incidence of AEs leading to discontinuation of study drugs was lower in the Genvoya group compared with the STB group, as follows: Genvoya 1.3%, 11 of 866 subjects; STB 3.3%, 29 of 867 subjects. The difference was driven primarily by study drugs discontinuation due to bone and renal events in the STB group. In the Genvoya group, no subjects had bone or renal events that resulted in discontinuation of study drugs; however, in the STB group, 6 subjects had bone events and 12 subjects had renal events that resulted in discontinuation of study drugs. One subject in the STB group had both bone and renal events.

Most AEs leading to discontinuation of study drug were non serious and considered related to study drugs by the investigator. No AE leading to discontinuation was reported for > 1 subject in the Genvoya group. Six AEs leading to discontinuation were reported for > 1 subject in the STB group (bone density decreased and renal tubular disorder [0.3%, 3 subjects each]; vomiting, blood creatinine increased, glomerular filtration rate decreased, headache, and renal failure [0.2%, 2 subjects each]).

8.4. Evaluation of issues with possible regulatory impact

8.4.1. Liver function and liver toxicity

8.4.1.1. Co-infection with HIV and HBV

No hepatic AEs were reported for subjects in either cohort. The only AE reported in the hepatobiliary disorders SOC was cholelithiasis for a single subject in Cohort 2 (HIV suppressed subjects). No subject in either cohort has a confirmed on treatment HBV flare during the study. A HBV flare was defined as a confirmed (within 3 days of initial results) serum ALT > 2 x Day 1 ALT value and > 10 x ULN, with or without symptoms.

Two subjects (2.7%) had elevated AST or ALT levels > 3 × ULN during this study; 1 subject (1.4%) had AST and ALT levels > 5 × ULN. The liver enzyme abnormalities for this subject were due to a non-serious, Grade 1 AE of HCV infection. The HCV infection was not considered related to study drug by the investigator, and was continuing as of the data cut-off date. Neither of these subjects had an elevation in total bilirubin > 1 × ULN. Three subjects (4.1%) had elevations in total bilirubin > 1 × ULN, but ≤ 2 × ULN. No subject had an elevation in ALP > 1.5 × ULN.

The *Summary of Clinical Safety* provides and analysis of safety comparing the results of Study GS-US-292-1249 (co-infection) and HIV infected subject without HBV co-infection (Study GS-US-292-0109 Week 48 Interim CSR[2]). The incidence of AEs and the nature and incidence of commonly reported AEs were similar between HIV/HBV co-infected subjects (82.4%, 61 of 74 subjects) and HIV-infected subjects without HBV co-infection (79.7%, 764 of 959 subjects). The incidence of SAEs was slightly higher in HIV/HBV co-infected subjects (8.1%, 6 subjects) than in HIV-infected subjects without HBV co-infection (4.4%, 42 subjects). There were no deaths reported in HIV/HBV co-infected subjects and 2 deaths reported in HIV-infected subjects without HBV co-infection.

8.4.1.2. Paediatric patients

In the assessment of liver enzyme elevations in relation to normal ranges, no subjects had elevations > 3 × ULN in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) in addition to > 2 × ULN in total bilirubin and ALP < 2 × ULN. No Hy's law cases were identified.

8.4.1.3. Long term use

Virologically suppressed (96 weeks): Not discussed in the CSR or the summaries.

Treatment naïve (144 weeks): not discussed in CSR or summaries.

Renal impairment

There were no clinically significant changes from baseline in median values for clinical chemistry parameters in either cohort through Week 144. Laboratory abnormalities associated with FTC use (such as increased creatine kinase, serum glucose, triglycerides, cholesterol, AST, ALT, bilirubin, and decreased neutrophils) were reported; these were generally balanced between the baseline $eGFR_{CG}$ < 50 mL/min group and the baseline $eGFR_{CG}$ ≥ 50 mL/min group, despite higher FTC exposures in subjects with baseline $eGFR_{CG}$ < 50 mL/min compared with historical data from HIV-infected subjects with normal renal function.

Overall, 5.0% and 5.8% of subjects in Cohort 1(switch) had AST or ALT elevations > 3 x ULN through Week 144, respectively, with elevations of > 5 x ULN occurring infrequently. There were no Hy's Law cases identified in either cohort.

Table 37: Study GS-US-292-0112: Summary of treatment-emergent liver-related laboratory tests (safety analysis set)

[2] Study GS-US-292-0109 Week 48 CSR not included in this submission, as it was previously evaluated.

	Cohort 1: Switch		Cohort 2: ART-Naïve	
	Baseline $eGFR_{CG}$ < 50 mL / min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL / min (N = 162)	Total (N = 242)	Total (N = 6)
AST				
> 3 × ULN	4/80 (5.0%)	8/162 (4.9%)	12/242 (5.0%)	1/6 (16.7%)
> 5 × ULN	1/80 (1.3%)	3/162 (1.9%)	4/242 (1.7%)	0/6
> 10 × ULN	0/80	2/162 (1.2%)	2/242 (0.8%)	0/6
> 20 × ULN	0/80	0/162	0/242	0/6
ALT				
> 3 × ULN	8/80 (10.0%)	6/162 (3.7%)	14/242 (5.8%)	0/6
> 5 × ULN	1/80 (1.3%)	5/162 (3.1%)	6/242 (2.5%)	0/6
> 10 × ULN	0/80	3/162 (1.9%)	3/242 (1.2%)	0/6
> 20 × ULN	0/80	2/162 (1.2%)	2/242 (0.8%)	0/6
AST or ALT[a]				
> 3 × ULN	10/80 (12.5%)	8/162 (4.9%)	18/242 (7.4%)	1/6 (16.7%)
> 5 × ULN	2/80 (2.5%)	5/162 (3.1%)	7/242 (2.9%)	0/6
> 10 × ULN	0/80	3/162 (1.9%)	3/242 (1.2%)	0/6
> 20 × ULN	0/80	2/162 (1.2%)	2/242 (0.8%)	0/6
Total Bilirubin				
> 1 × ULN	5/80 (6.3%)	8/162 (4.9%)	13/242 (5.4%)	0/6
> 2 × ULN	1/80 (1.3%)	0/162	1/242 (0.4%)	0/6
Alkaline Phosphatase (ALP)				
> 1.5 × ULN	9/80 (11.3%)	6/162 (3.7%)	15/242 (6.2%)	0/6
AST or ALT > 3 × ULN	10/80 (12.5%)	8/162 (4.9%)	18/242 (7.4%)	1/6 (16.7%)

	Cohort 1: Switch		Cohort 2: ART-Naïve	
	Baseline $eGFR_{CG}$ < 50 mL / min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL / min (N = 162)	Total (N = 242)	Total (N = 6)
Total Bilirubin > 1.5 × ULN	1/80 (1.3%)	1/162 (0.6%)	2/242 (0.8%)	0/6
Total Bilirubin > 2 × ULN	1/80 (1.3%)	0/162	1/242 (0.4%)	0/6
Total Bilirubin > 2 × ULN and ALP < 2 × ULN	1/80 (1.3%)	0/162	1/242 (0.4%)	0/6

Denominator for percentage for individual test is the number of subjects in the safety analysis set with at least 1 post baseline laboratory value. The most severe post baseline value per subject was summarised for each laboratory test. For AST, ALT, AST or ALT, and total bilirubin, subjects may be counted in multiple categories, eg, subject would be counted in > 3 ULN, > 5 ULN and > 10 ULN if the worst value was > 10 ULN. [a] For the composite endpoint of AST or ALT, and total bilirubin with or without alkaline phosphatase (ALP), subjects were counted once when the criteria were met at the same post baseline visit date. The denominator is the number of subjects in the safety analysis set with non-missing post baseline values of the tests in evaluation at the same post baseline visit date.

8.4.2. Metabolic (Lipid) parameters

8.4.2.1. Co-infection with HIV and HBV

For HIV-suppressed subjects, there were increases from baseline to Week 48 in median fasting total cholesterol and direct LDL cholesterol, but not in median fasting total cholesterol to HDL ratio. In addition, no change from baseline was observed through Week 48 in fasting glucose. There was no change from baseline in total cholesterol to HDL ratio, and the observed changes were not clinically significant.

8.4.2.2. Paediatric patients 6 to <12 years

One subject had Grade 1 high fasting glucose (hyperglycaemia) and 2 subjects had Grade 1 low fasting glucose (hypoglycaemia) levels during the study. No Grade ≥ 2 fasting serum glucose levels were observed.

8.4.2.3. Long term use

Virologically suppressed subjects 96 weeks

There were increases from baseline in fasting values of total cholesterol, LDL cholesterol, and triglycerides in the Genvoya group, while these parameters remained unchanged or were changed to a relatively smaller extent in the FTC/TDF+3rd Agent group at both Week 48 and Week 96 ($p \leq 0.002$ for the differences between groups in changes from baseline). Findings were similar when the analysis excluded subjects who were taking lipid-modifying medications.

Increases from baseline in median fasting values for total cholesterol, LDL cholesterol, and triglycerides at Weeks 48 and 96 were consistently observed in the Genvoya group, regardless of prior treatment regimen.

ART naïve subjects 144 weeks

In ART naïve subjects the data through 144 weeks showed greater increases in the fasting lipid parameters total cholesterol, direct LDL, high-density lipoprotein (HDL), total cholesterol to HDL ratio, and triglycerides in subjects treated with Genvoya compared with those treated with STB ($p<0.001$ for the difference between treatment groups for fasting total cholesterol, direct LDL, HDL, and triglycerides). The median (Q1, Q3) change from baseline at Week 144 in the

total cholesterol to HDL cholesterol ratio was 0.2 (-0.3, 0.7) in the Genvoya group and 0.1 (−0.4, 0.6) in the STB group (p=0.028 for the difference between groups).

Similar percentages of subjects in each treatment group initiated lipid-modifying medications during the studies (Genvoya 5.5%, 48 subjects; STB 5.8%, 50 subjects).

Renal impairment

For Cohort 1 (switch subjects) statistically significant median increases from baseline to Week 144 were observed in fasting triglycerides and fasting glucose, but not in fasting total cholesterol, fasting low-density lipoprotein (LDL) cholesterol, or fasting total cholesterol to HDL ratio. Generally, median changes from baseline at Week 144 increased in subjects with pre-switch TDF use and decreased for subjects without pre-switch TDF use. The percentage of Cohort 1 switch subjects initiating lipid-modifying medications during the study was similar between subjects with pre-switch TDF use (26.6%, 42 subjects) and those without pre-switch TDF use (31.0%, 26 subjects).

8.4.3. Renal safety

8.4.3.1. Co-infection with HIV and HBV

In HIV/HBV co-infected adults who were HIV-suppressed there were no subjects with reported proximal tubulopathy (or Fanconi Syndrome). No subjects had renal SAEs or discontinued study drug due to a renal AE. There were minimal changes from baseline, considered not clinically meaningful, in serum creatinine and eGFR through 48 weeks. Decreases from baseline in proteinuria (UPCR), albuminuria (UACR), and tubular proteinuria (urine RBP to creatinine ratio and urine B2MG to creatinine ratio) were observed at Week 48.

8.4.3.2. Paediatric patients – 6 to < 12 years

No safety concerns regarding renal parameters were observed during this study. Specifically, no renal AEs were reported. Changes from baseline in serum creatinine and estimated glomerular filtration rate (eGFR) were consistent with the inhibitory effect of COBI on renal tubular secretion of creatinine, and are not considered reflective of changes in actual glomerular filtration. No graded serum creatinine, phosphorus, or urine glucose abnormalities were reported. There was no obvious correlation in the 3 subjects with transient Grade 1 proteinuria and any other renal abnormality. A median decrease from baseline urine protein to creatinine ratio (UPCR) observed at Week 1 persisted through Week 24. For both baseline urine retinol binding protein (RBP) and urine β-2 micro globulin to creatinine ratios, a declining trend from baseline was observed at Weeks 8, 12, and 24, although the mean and median values were highly variable.

8.4.3.3. Long term use

Virologically suppressed subjects

In the analysis of renal effects, subjects with Atripla as the prior treatment regimen were excluded from treatment group comparisons because these subjects had not previously received COBI or RTV, known inhibitors of creatinine secretion: serum creatinine, eGFR (calculated using CG or either CKD-EPI method), TmP/GFR, urine FEPO4, and urine FEUA.

In the Genvoya group, 1 subject had a renal SAE (acute kidney injury) that was considered unrelated to study drug. Two subjects in the Genvoya group discontinued study drug due to renal AEs (tubulointerstitial nephritis and acute kidney injury, respectively); both events were non-serious and considered unrelated to study drug by the investigator. There were no AEs of proximal renal tubulopathy (or Fanconi syndrome) reported in the Genvoya group.

In the FTC/TDF+3rd Agent group, 3 subjects had renal SAEs (Fanconi syndrome acquired in 1 subject and acute kidney injury [verbatim term: acute renal failure] in 2 subjects). The SAE of Fanconi Syndrome acquired was considered related to the study drug by the investigator and

led to study drug discontinuation. The SAEs of acute kidney injury were considered unrelated to study drug. Additionally in the FTC/TDF+3rd Agent group, 2 subjects discontinued study drug due to non-serious AEs of chronic kidney disease and renal colic, respectively, and 2 subjects discontinued study drug due to non-serious AEs of blood creatinine increased; all of these AEs were considered related to study drug.

At Weeks 48 and 96, there were decreases or no changes from baseline in mean serum creatinine in the Genvoya group compared with increases or no changes from baseline in the FTC/TDF+3rd Agent group after excluding subjects with Atripla as prior treatment regimen ($p<0.001$ for the difference between groups at Weeks 48 and 96). For subjects who switched to Genvoya from COBI or RTV containing, TDF based regimens (Stribild or boosted-ATV+FTC/TDF), there were decreases from baseline in mean serum creatinine compared with increases from baseline among subjects who remained on their COBI or RTV containing, TDF-based regimen ($p<0.001$ for the differences between groups at Week 96). In contrast, for subjects who switched to Genvoya from Atripla (that is, added COBI), there were increases from baseline in mean serum creatinine compared with minimal changes from baseline among subjects who remained on Atripla ($p<0.001$ for the differences between groups at Weeks 2 through 96). These findings are consistent with the established effect of COBI on serum creatinine.

Increases from baseline in median $eGFR_{CG}$ were observed in the Genvoya group at Week 2 and persisted through Week 96 (excluding subjects with Atripla as prior treatment regimen), compared with decreases from baseline in the FTC/TDF+3rd Agent group ($p<0.001$ for the difference between groups at Week 96).

Most subjects in both treatment groups had no proteinuria (Grade 0 by dipstick) at baseline and through Week 96. Decreases from baseline in median UPCR and UACR were observed in the Genvoya group at Week 96 compared with increases from baseline in the FTC/TDF+3rd Agent group ($p<0.001$ for the differences between groups at Week 96).

Analysis of RBP to creatinine ratio and urine β-2-microglobulin to creatinine ratio were not taken after Week 48. Decreases from baseline in median TmP/GFR at Week 96 were comparable between treatment groups (excluding subjects with Atripla as prior treatment regimen) ($p=0.23$ for the difference between groups at Week 96). There was minimal change from baseline in median urine FEPO4 at Week 96 in the Genvoya group compared with an increase from baseline in the FTC/TDF+3rd Agent group (excluding subjects with Atripla as prior treatment regimen) ($p=0.043$ for the difference between groups at Week 96). A decrease from baseline in median urine FEUA was observed at Week 4 and persisted through Week 96 in the Genvoya group compared with minimal changes from baseline in the FTC/TDF+3rd Agent group (excluding subjects with Atripla as prior treatment regimen) ($p<0.001$ for the difference between groups at Weeks 4 through 96).

ART naïve subjects (pooled Studies GS-US-292-0104 and GS-US-292-0111)

No subjects in either study discontinued Genvoya due to a renal and urinary disorder or associated investigation AE, compared with 12 subjects who discontinued STB (1.4%; $p<0.001$). Discontinuations of study drugs due to renal and urinary disorder or associated investigation AEs that are indicative of proximal renal tubulopathy in the STB group were reported for 4 subjects, as follows: renal tubular disorder, 3 subjects (1 subject had a renal tubular disorder reported as injury level renal tubule, 2 subjects had proteinuria, normoglycaemic glycosuria, and elevated serum creatinine in addition to renal tubular disorder); and acquired Fanconi syndrome, 1 subject (this subject also had proteinuria, elevated serum creatinine, hypophosphatemia, and a concurrent AE of glycosuria). All but 1 of 14 renal and urinary disorders or associated investigation events (blood creatinine increased) that led to discontinuation of STB were considered related to study drug by the investigator. The subject who had an AE of blood creatinine increased that was not considered related to study drugs by

the investigator also had an AE of bone density decreased. SAEs due to renal and urinary disorder or associated investigation were reported as follows: Genvoya 3 subjects (Grade 3: ureterolithiasis and post-infectious glomerulonephritis; Grade 2: nephrotic syndrome [1 subject each]); STB 3 subjects (Grade 3: renal hematoma; Grade 2: ureterolithiasis and acute kidney infection [1 subject each]). None of the renal SAEs were indicative of proximal renal tubulopathy or considered related to study drugs, and none resulted in the discontinuation of study drugs. Each renal SAE resolved without interruption to study drugs. The difference between treatment groups in change from baseline in serum creatinine was statistically significant at all but 1 time point from Weeks 2 through 144 ($p<0.001$ except at Week 108). Overall, increases from baseline in mean values for serum creatinine were smaller in the Genvoya group compared with the STB group. Increases were observed by Week 2 in both treatment groups, and remained evident through Week 144.

The difference between treatment groups in change from baseline in $eGFR_{CG}$ was statistically significant ($p<0.001$) at all time points from Weeks 2 through 144. Overall, decreases from baseline in median $eGFR_{CG}$ values were smaller in the Genvoya group compared with the STB group. Decreases were observed by Week 2 for each treatment group and remained evident through Week 144.

Renal impairment

There were no subjects with treatment emergent proximal tubulopathy (or Fanconi Syndrome) reported through Week 144.

Four Cohort 1 (switch subjects) (1.7%) had renal SAEs through Week 144; two subjects had renal SAEs after the Week 96 data cut-off date (acute kidney injury and chronic kidney disease). None of the renal SAEs were considered related to study drug. Five subjects (2.1%) had renal AEs that resulted in discontinuation of study drug through Week 96; there were no subjects with renal AEs leading to discontinuation of study drug after Week 96. Three of these events were considered unrelated and two were considered related to study drug.

Overall, there were no clinically significant changes from baseline in serum creatinine through Week 144 for Cohort 1 switch subjects and there were statistically significant improvements (increases) in eGFR at Week 144, irrespective of filtration marker or equation.

Subjects with moderate renal impairment ($eGFR_{CG} < 50$ mL/min) showed greater improvements in eGFR compared with subjects with mild renal impairment ($eGFR_{CG} \geq 50$ mL/min) at Week 144, all of which were statistically significant ($p \leq 0.003$) for subjects with moderate renal impairment irrespective of the filtration marker or equation used.

There were no clinically significant changes from baseline in serum cystatin C or serum phosphorus through Week 144. Most Cohort 1 switch subjects had either no change from baseline or an improvement from baseline (toxicity grade decreased at least 1 grade from baseline) in proteinuria toxicity grade at Week 144. Improvements from baseline in proteinuria toxicity grade occurred more frequently in subjects with baseline $eGFR_{CG} \geq 50$ mL/min than those with baseline $eGFR_{CG} < 50$ mL/min.

The difference between treatment groups in percentage change from baseline in urine RBP to creatinine ratio was statistically significant from Week 2 through Week 144 ($p<0.001$ at each time point). The difference between treatment groups in percentage change from baseline in urine β-2-microglobulin to creatinine ratio was statistically significant from Week 2 through Week 144 ($p<0.001$ at each time point). There were decreases from baseline in median FEUA using adjusted serum creatinine through Week 144 in the Genvoya group, compared with an increase in the STB group. There were decreases from baseline in median TmP/GFR using adjusted serum creatinine through Week 144 in both treatment groups; the decreases were generally smaller in the Genvoya group compared with the STB group. There were increases from baseline in median FEPO4 using adjusted serum creatinine through Week 144 in both

treatment groups; the increases were smaller in the Genvoya group compared with the STB group.

8.4.4. Bone safety

8.4.4.1. Co-infection with HIV and HBV

One HIV-suppressed subject (1.4%) had a fracture event (foot fracture). This AE (fractured left calcaneus) was a non-serious traumatic injury that was considered unrelated to study drug.

Median decreases from baseline in C-telopeptide and P1NP were observed at Week 48 for HIV-suppressed subjects (p=0.049 and p<0.001, respectively). The change from baseline in PTH was not statistically significant. Median (Q1, Q3) percentage changes from baseline at Week 48 were as follows:

- C-Telopeptide: -12.5% (-24.2%, 9.6%)
- P1NP: -28.52% (-39.30%, -8.80%)
- PTH: -3.4% (-28.5%, 29.1%)

8.4.4.2. Paediatric patients

Bone safety in children is particularly relevant due to the importance of bone safety in a paediatric population accruing bone mass during their pre- and/or peri-pubertal stage and because of concerns of decreased BMD that have been associated with high TFV exposure from TDF-containing regimens. Bone safety analyses included assessments of fracture events and spine and total-body-less-head (TBLH) BMD. BMD status was assessed using BMD Z-scores, which were also calculated adjusted for height-age. 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'. Additionally, bone laboratory parameters were assessed.

No AEs of fractures were reported for subjects enrolled in Cohort 2 Part A (virologically suppressed children aged 6 - <12 years). No subject experienced worsening of the spine or total body less head (TBLH) clinical status (that is, to a BMD Z-score < -2) using height-age Z-scores.

Fluctuation in the bone biomarkers (collagen type I N and C-terminal telopeptides (bone resorption parameters), osteocalcin, bone-specific alkaline phosphatase (ALP), procollagen type 1 N-terminal propeptide (P1NP) (bone formation parameters), and parathyroid hormone, 25-OH vitamin D, and 1,25-$(OH)_2$ vitamin D) measured in this population through Week 24 was consistent with the effects of growth, skeletal size, and pubertal maturation expected in children in this age range.

No clinically relevant effects of Genvoya treatment on growth were observed, as assessed by changes from baseline in body height, body height Z-scores, body weight, or body weight Z-scores to Week 24. Changes in Tanner stage from baseline to Week 24 were consistent with the young paediatric population.

Table 38: Study GS-US-292-0106: Spine standard and height-age BMD Z-scores at Baseline and change from Baseline at Week 24 (Cohort 2 Part A, 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 39: Study GS-US-292-0106: Total-body-less-head standard and height-age BMD Z-scores at Baseline, and change from Baseline at Week 24 (Cohort 2, Part A, 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)

[a] Some subjects had missing height-age Z-scores because their height-ages were outside the BMD reference data for Z-scores.

8.4.4.3. Long term use

Virologically suppressed subjects 96 weeks

The percentages of subjects with fracture events were comparable between treatment groups (Genvoya 0.8%, 8 subjects; FTC/TDF+3rd Agent 0.8%, 4 subjects; p=1.00). In the Genvoya group, 3 of the fracture events were reported as SAEs: acetabulum fracture, radius fracture, and hip fracture. In the FTC/TDF+3rd Agent group, rib fracture in 1 subject was reported as an SAE. All the other fracture events were non-serious. All fracture AEs were the result of trauma and considered unrelated to study drug; none were indicative of fragility fractures and none resulted in permanent discontinuation of study drug.

There were increases from baseline in mean (SD) hip and spine BMD in the Genvoya group compared with minimal changes from baseline in both parameters in the FTC/TDF+3rd Agent group (p<0.001 for the differences between groups at Weeks 24, 48, and 96).

Analysis by prior treatment regimen showed that increases from baseline in hip and spine BMD were observed for subjects in the Genvoya group at Weeks 24, 48, and 96 regardless of prior treatment regimen (Stribild, Atripla, or boosted-ATV+FTC/TDF). In contrast, there were minimal changes from baseline at both sites for subjects who continued on their baseline regimen.

Analysis of bone laboratory parameters (C-telopeptide and P1NP) was only measured through Week 48. At Week 96, increases from baseline in PTH were observed for both treatment groups, with a smaller increase from baseline in the Genvoya group than in the FTC/TDF+3rd Agent group (p<0.001 for the difference between groups at Week 96).

ART naïve subjects – 144 weeks

At Week 144 the incidence of fracture events was similar in both treatment groups (Genvoya 3.6%, 31 of 866 subjects; STB 4.5%, 39 of 867 subjects. Fracture AEs were reported as serious for 6 subjects in the Genvoya group (ankle fracture [2 subjects]; femur fracture, foot fracture, humerus fracture, and lower limb fracture [1 subject each]) and 6 subjects in the STB group (ankle fracture, thoracic vertebral fracture, cervical vertebral fracture, facial bones fracture, and radius fracture [1 subject each]; and thoracic vertebral fracture, rib fracture, and ulna fracture [all in 1 subject]). No fracture AE was considered related to study drug or resulted in discontinuation of study drug. No subject discontinued Genvoya due to a bone AE; however, 6 subjects discontinued STB due to bone AEs: bone density decreased (3 subjects); and bone loss, osteopenia, and osteoporosis (1 subject each).

The incidences of osteopenia and osteoporosis reported as an AE were: osteopenia: Genvoya 8.0%, 69 subjects; STB 10.0%, 87 subjects; osteoporosis: Genvoya 2.0%, 17 subjects; STB 2.9%, 25 subjects. Osteopenia was considered related to study drugs for 72 subjects: Genvoya 32 subjects (3.7%); STB 40 subjects (4.6%). Osteoporosis was considered related to study drugs for 20 subjects: Genvoya 8 subjects (0.9%); STB 12 subjects (1.4%). All AEs of osteopenia or osteoporosis were non-serious.

For both hip and spine BMD, the difference between treatment groups in the percentage change from baseline was statistically significant ($p < 0.001$) at all visits.

Changes from baseline in parathyroid hormone were smaller in the Genvoya group than the STB group at Weeks 48, 96, and 144 ($p<0.001$ for the differences between the 2 groups in median percentage changes from baseline).

Changes in C-telopeptide (bone resorption) and procollagen type 1 N-terminal propeptide (bone formation) were only assessed through Week 96.

Renal impairment

Overall, 5 Cohort 1 switch subjects (2.1%) experienced 7 fracture events, of whom 3 were subjects with pre-switch TDF use (1.9%) and 2 were subjects without pre-switch TDF use (2.4%). One fracture AE (lumbar vertebral fracture) was considered related to study drug. None of the fracture AEs resulted in discontinuation of study drug. Two fracture events (spinal compression fracture and rib fracture) were considered serious. All fracture events were the result of trauma, and none were reported as fragility fractures.

Overall, hip and spine BMD increased for Cohort 1 switch subjects after switching to Genvoya. Mean (SD) percentage increases from baseline were observed in hip BMD (2.365% [4.8586]) and spine BMD (2.771% [4.9770]) at Week 144. The percentage changes from baseline in hip and spine BMD were statistically significant at each time point through Week 144 for Cohort 1 overall ($p<0.001$). There was evidence for an improvement in hip and spine BMD after switching to GEN, when assessed using a threshold of 3% for changes from baseline at Week 144; higher percentages of subjects had increases versus decreases from baseline in BMD at both hip (38.4% versus 9.0%) and spine (47.4% versus 10.3%).

Overall, there were no clinically significant changes from baseline in PTH through Week 144 for Cohort 1 switch subjects.

8.4.5. Cardiovascular and cerebrovascular safety

8.4.5.1. Co-infection with HIV and HBV

Not discussed in CSR or summaries.

8.4.5.2. Paediatric patients

Not discussed in CSR or summaries.

8.4.5.3. Long term use

In virologically suppressed subjects switching to GEN, there were similar percentages of subjects in each treatment group reporting potential cardiovascular events (Genvoya 1.8%, 17 subjects; FTC/TDF+3rd Agent 2.3%, 11 subjects; p=0.54). The incidence of serious potential cardiovascular events was 0.6% (6 subjects) in the Genvoya group (acute myocardial infarction, 2 subjects; coronary artery disease, 2 subjects; myocardial infarction, 1 subject; and acute coronary syndrome, 1 subject) and was 1.0% (5 subjects) in the FTC/TDF+3rd Agent group (myocardial infarction, 2 subjects; acute myocardial infarction, 1 subject; embolic stroke 1 subject; and transient ischemic attack, 1 subject). None of these events were considered related to study drugs, and none of the events were fatal.

In treatment naïve subjects treated for 144 weeks potential cardiovascular or cerebrovascular events were reported for similar percentages of subjects in the 2 treatment groups (Genvoya 2.8%, 24 of 866 subjects; STB 3.8%, 33 of 867 subjects). One subject in the Genvoya group had a cerebral infarction that led to discontinuation of study drug, but was considered not related to study drug. Serious potential cardiovascular or cerebrovascular events were reported as follows: Genvoya 5 subjects (0.6%; acute myocardial infarction in 2 subjects; cerebral infarction and myocardial infarction, in 1 subject each; and cerebrovascular accident and transient ischemic attack, both in 1 subject; STB 6 subjects (0.7%; acute myocardial infarction in 2 subjects; acute coronary syndrome, cerebrovascular accident, coronary artery disease, and ischemic cardiomyopathy, in 1 subject each). One of these events in the STB group (acute coronary syndrome) was considered by the investigator to be related to study drug. The events of myocardial infarction, cerebrovascular accident, and cerebral infarction in 1 subject each in the Genvoya group and acute myocardial infarction in 1 subject in the STB group were fatal.

Renal impairment

Potential cardiovascular or cerebrovascular events were reported in 5.8% of Cohort 1 (switch subjects) through Week 144 (n = 14; with pre-switch TDF use 3.8% [6 subjects]; without pre-switch TDF use 9.5% [8 subjects]). Of these events, only 1 was considered related to study drug Grade 3, non-serious increased blood creatine phosphokinase (baseline $eGFR_{CG}$ < 50 mL/min, without pre-switch TDF use)

Serious potential cardiovascular or cerebrovascular events were reported in 2.5% of Cohort 1 (switch subjects) through Week 144 (n = 6; with pre-switch TDF use 1.9% [3 subjects]; without pre-switch TDF use 3.6% [3 subjects]). Acute myocardial infarction was reported in 4 subjects, which was reported along with acute coronary syndrome in 1 of these subjects. None of the serious potential cardiovascular or cerebrovascular events were considered related to study drug.

No potential cardiovascular or cerebrovascular events were reported in Cohort 2 (ART-naïve) subjects.

8.4.6. Vital signs and clinical examination findings

No clinically relevant changes due to study drug were found in vital signs, clinical examination of ECG parameters in any of the groups studied, other than the following isolated events.

- AEs of supraventricular extra systoles, palpitations and atrial fibrillation reported for a single subject in the Genvoya group (Study GS-US-292-0109) were assessed as related to study drug but did not lead to drug discontinuation
- Changes in Tanner stage from baseline to Week 24 were consistent with the young paediatric population (Study GS-US-292-0106)

8.4.7. Resistance

Overall the emergence of resistance mutations was rare across the treatment groups.

8.4.7.1. Coinfection with HIV and HBV

After 48 weeks of Genvoya treatment, none of the 75 subjects met the criteria for inclusion in the resistance analysis for HIV-1. At baseline there were 10 HBV viraemic (HBV DNA ≥ 69 IU/mL) subjects; of these, 5 had primary lamivudine resistance mutations detected at baseline. After 48 weeks of Genvoya treatment, 2 subjects (2.8%, 2/72) qualified for resistance testing and were analysed by sequence analysis of the HBV polymerase/reverse transcriptase (pol/RT) gene. None of the amino acid substitutions observed in HBV pol/RT were associated with resistance to TAF.

8.4.7.2. Paediatric patients

No subjects qualified for resistance analysis as 100% of them maintained virological suppression for the 24 week duration of the study.

8.4.7.3. Long term use

Virologically suppressed (96 weeks)

The final resistance analysis population included 6 subjects (0.6%) from the Genvoya group and 2 subjects (0.4%) from the FTC/TDF+3rd Agent group. Three subjects from the Genvoya group developed resistance to study drugs (2 with EVG/FTC resistance, M184I + E92G and M184V + E92Q; and 1 with FTC resistance only, M184M/I). This latter subject resuppressed to HIV-1 RNA < 50 copies/mL while taking GEN, but then switched therapies due to protocol requirements. One subject from the FTC/TDF+3rd Agent group developed resistance to all 3 components of the regimen (multiple TAMs + M184V + T66A/E92Q), likely due in part to the transmission of a TAM-containing drug-resistant HIV-1 at the time of infection in that subject.

Treatment naïve (144 weeks)

After 144 weeks of treatment, the emergence of resistance mutations was rare across the Genvoya and STB groups. There were 24 subjects who developed any treatment emergent genotypic resistance, 12 of 866 subjects (1.4%) in the Genvoya group and 12 of 867 subjects (1.4%) in the STB group.

In the Genvoya group, the NRTI resistance (R) mutation M184V/I was observed in conjunction with primary INSTI-R mutations in 7 of 12 subjects with emergent resistance, including 1 subject also developing K65R. Four subjects developed M184V/I only, and one subject developed K65N and K70R (in conjunction with INSTI-R, N155H) which was associated with phenotypic resistance to both tenofovir (TFV) and FTC. The cross resistance profiles for the virologic failure subjects with emergent resistance to EVG, FTC, and tenofovir (TFV) were consistent with historical data. No novel TAF resistance mutations were observed.

Renal impairment

In Cohort 1 (renally-impaired, ART-experienced, and virologically suppressed subjects switching to GEN), 3 subjects (1.2%, 3 of 242) were analysed and showed resistance to multiple drug classes by Week 96. One subject with HIV-1 subtype C at baseline had detectable resistance to all study drugs as well as non-study drugs at virologic failure with an HIV-1 subtype B variant, possibly due to reinfection. This subject achieved HIV-1 RNA re-suppression to < 20 copies/mL with continued Genvoya treatment prior to switching to a new regimen. The second subject showed persistent low-level viremia and had drug resistance mutations to NRTI and PIs that were documented in a historical genotype prior to initiating Genvoya treatment. The third subject had NRTI resistance to TFV (A62A/V and K65R), FTC (M184V), EVG (E138K, S147G, and Q148R) as well as non-study drugs at virologic failure in the absence of an available historical genotype. This subject achieved HIV-1 RNA reduction to 70 copies/mL with continued Genvoya treatment prior to switching to a new regimen.

In Cohort 2 (ART-naïve), no subject met the criteria for resistance analysis (0%, 0 of 6).

Overall, in all subjects administered Genvoya, the incidence of resistance mutations for subjects experiencing virologic failure was low in the populations studied. The genotypic changes detected in the Genvoya group were comparable to the genotypic changes detected in the control groups or historical data. No novel TAF resistance mutations were observed to develop in any of the Genvoya virologic failure subjects.

8.5. Other safety issues

8.5.1. Safety related to drug-drug interactions and other interactions

No new information submitted.

8.6. Post marketing experience

From both the long term use and co-infection Clinical Overview the only statement from the sponsor is that 'there have been no newly identified adverse reactions for Genvoya based on the post marketing data available to date.'

The Clinical Overview for the paediatric use also states that review of the sponsor's safety database for use in paediatric patients < 18 years found no safety issues specific to paediatric patients. Usage data is only provided for the US for patients aged 12 years and older (cumulative patient exposure for the period 5 November 2015 to 30 April 2016 was estimated to be 13,960 patient years.

8.7. Evaluator's overall conclusions on clinical safety

8.7.1. Patients co-infected with HIV and HBV

The safety profile of Genvoya was consistent across the populations and maintained for the duration of exposure. No new safety signals for TAF or Genvoya were detected. The common AEs found in the study were consistent with those expected in the subject population and the previously documented safety profile of the drugs.

8.7.2. Paediatric use

Treatment with Genvoya was generally well tolerated in virologically suppressed HIV-infected subjects 6 to < 12 years old weighing ≥ 25 kg and no new safety signal was detected. The safety profile in the smaller children appears to be similar to that seen in adolescents and adults.

8.7.3. Long term use

Overall the long term use extension to 96 weeks for virologically suppressed subjects and to 144 weeks for treatment naïve subjects is consistent with that seen in the previous evaluations to 48 and 96 weeks.

For HIV-infected, virologically suppressed adults who switched to Genvoya from a TDF-based regimen, Genvoya was associated with improvements in hip and spine BMD through Week 96, compared with minimal changes from baseline at both sites in the FTC/TDF+3rd Agent group. Compared with the FTC/TDF+3rd Agent group, lower percentages of subjects in the Genvoya group had decreases from baseline in hip and spine BMD, and higher percentages of subjects in the Genvoya group had increases from baseline in hip and spine BMD.

No cases of proximal renal tubulopathy (including Fanconi syndrome) were reported for subjects who received Genvoya throughout the large development program across multiple patient populations. In contrast, 3 cases of clinically evident proximal renal tubulopathy have been reported after similar durations of exposure to comparator, TDF-containing regimens: 2 HIV-infected, ART-naïve subjects on STB (Studies GS-US-292-0104 and GS-US-292-0111) and 1 HIV-infected, virologically suppressed subject on ATV/boosted+TVD (Study GS-US-292-0109).

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
1. Co-infection with HIV and HBV *:* *In HIV/HBV co-infected adults who were HIV suppressed, Genvoya maintained high virologic success (HIV-1 RNA < 50 copies/mL)*	***1. Co-infection with HIV and HBV :*** *Strength is result of 91.7% at Week 48.* *Uncertainty is single study of 72 subjects.*
2. Paediatric use in children > 6 and < 12 years weighing ≥ 25 kg: *Virologically suppressed patients 100 % maintained virologic suppression 24 weeks after switching to Genvoya.*	***2. Paediatric use in children <6 and ≤ 12 years weighing ≥ 25 kg****:* *Uncertainty is no data on treatment naïve patients in this age group.* *Uncertainty is single small study – 23 subjects.*
3. Long term use: *In virologically suppressed adults Genvoya was efficacious and statistically superior to continuing with FTC/TDF+3rd agent to 96 weeks* *In treatment naïve subjects data to 144 weeks superior efficacy of Genvoya over STB.* *In long term study of treatment naïve subjects there were fewer drug discontinuations with Genvoya compared to STB due to bone and renal AEs*	***Long term use:*** *Strength is virologic success at Week 96: Genvoya 92.8%; FTC/TDF+3rd Agent 89.1%*
4. Renal Impairment: *Treatment with Genvoya continued to be well tolerated in ART naïve adults with mild to moderate renal impairment*	***4. Renal Impairment:*** *Strength is data to 96 weeks.*

9.2. First round assessment of risks

Risks	Strengths and Uncertainties
Known side effect profile	*Strength is large overall patient population with treatment in adult to 96 weeks (virologically suppressed) and 144 weeks (treatment naïve).* *Strength is no new safety signals identified in any of the patient populations.* *Risk is small paediatric population especially children aged >6 and < 12 years – only 23 subject treated for 24 weeks.*

9.3. First round assessment of benefit-risk balance

Overall, for the indications and changes requested the benefit-risk balance is positive. The extension of the patient population to children aged >6 and < 12 years and weighing ≥ 25 kg is justified even though the patient population is small. The data presented is for virologically suppressed patients in this age group. There was no data presented in this submission for treatment naïve patients aged >6 and < 12 years.

The proposed wording of the PI includes both treatment naïve and virologically suppressed children aged >6 and < 12 years, however given the concerns about the ability to recruit this population, it is recommended that the indication be approved, with a statement in the PI that the data on treatment naïve children was not available.

The proposed PI removes the specified age range and proposes only to define those eligible for treatment by weight. In the study submitted there were no children less than 8 years who met the weight requirement of at least 25 kg. Therefore it appears that use of weight alone is acceptable.

The data to support the use of Genvoya in patients co-infected with HIV and HBV is based on a single study of both treatment naïve patients and HIV virologically suppressed patients. There were only three patients enrolled and treated in the treatment naïve cohort and while all three had HIV and one had HBV suppression, this is insufficient to make any conclusions. In the HIV suppressed cohort 72 patients were enrolled and available for analysis. The results at Week 24 were 94.4% HIV suppression and 86.4% HBV suppression and at Week 48 the results for both outcomes was 91.7%. These results are consistent with previously approved results for TAF versus TDF regimens.

The sponsor is seeking approval for treatment of co-infected patients irrespective of their HIV status at presentation (that is treatment naïve or virologically suppressed). To be consistent with the patients presented in this submission the indication should be amended to be for HIV virologically suppressed patients who are co-infected with HBV. There should be wording in the Clinical Trial section of the PI to indicate that in the treatment naïve cohort there were only three patients enrolled and that the HIV virologically suppressed patients were generally switching from TDF containing regimens.

The request to remove the Class statements relating to lactic acidosis/severe hepatomegaly from the PI is not consistent with the agreed wording in the approved US PI. The modified wording as it appears in the US PI (April 2017 amendment) should be included in the Australian PI.

10. First round recommendation regarding authorisation

Based on the clinical data submitted, approval of Genvoya is recommended for the indication as requested:

> *Genvoya is indicated as a single tablet regimen for the treatment of HIV-1 infection in adults and paediatric patients weighing at least 25 kg who are either treatment–naïve; or virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see CLINICAL TRIALS). Patients must not have a history of treatment failure or known mutations associated with resistance to the antiretroviral components of Genvoya.*
>
> *Genvoya is also indicated for the treatment of chronic hepatitis B in adults co-infected with HIV-1 and hepatitis B (HBV) who are HIV virologically suppressed (HIV-1 < 50 copies/mL) on a stable antiretroviral regimen at the start of therapy.*

Genvoya is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors.

11. Clinical questions

11.1. Clinical questions

None.

12. Second round evaluation

There were no clinical questions asked in the first round evaluation. However, the Sponsor has provided a response to the Evaluator's conclusions on efficacy and the recommendation for the indication relating to the use in patients co-infected with HIV and HVB.

The sponsor provided the following comment:

The evaluator has raised a concern that there were only three patients enrolled and treated in the treatment-naïve cohort for Study GS-US-292-1249 and that this information is insufficient to make any conclusions. However, Gilead would like to emphasise that within Studies GS-US-320-0108 and GS-US-320-0110, the patient population consisted of both HBV treatment-naïve and treatment-experienced adults.

There appears to be some confusion as to which patients the evaluator was referring.

In Studies GS-US-320-0108 and GS-US-320-0110 the patient population was those with chronic HBV infection (HBsAg positive for more than 6months) but specifically excluded patients who were co-infected with HIV. It is accepted that the patient population included both HBV treatment naïve and treatment experienced patients.

In the first round evaluation the comments about treatment naïve related to HIV status not HBV. In Study GS-US-292-1249 there were only 3 patients who were HIV treatment naïve.

The sponsor has noted that:

'the US Department of Health and Human Service (DHHS), International Antiviral Society - USA (IAS-USA) and European AIDS Clinical Society (ARCS) guidelines are all supportive of the use of TAF in the HIV/HBV coinfection setting.

*The DHHS guideline has specifically referenced Study **GS-US-292-1249** as the supporting study for their recommendation that HBV/HIV-co-infected patients can switch to TAF/FTC containing regimens with a potential reduction in renal and bone toxicity while maintaining HBV suppression. Locally, the Australian Health Minister's Advisory Committee on HIV and STI has endorsed the DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents.'*

This is noted however there is no comment on the FDA status of the product. Despite evaluation of Study GS-US-292-1249 (submitted in April 2016) the FDA has not approved use in chronic HBV or co-infected patients and carries a boxed warning about such use.

The Sponsor's comments are noted but do not change the conclusions and recommendations of the first round evaluation.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

No new clinical information was submitted. Accordingly, the benefits of Genvoya are unchanged from those identified in Section 9.1.

13.2. Second round assessment of risks

No new clinical information was submitted. Accordingly, the risks of Genvoya are unchanged from those identified in Section 9.2.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balanced of Genvoya, given the proposed usage, is favourable. It is unchanged from the first round evaluation.

14. Second round recommendation regarding authorisation

The recommendation regarding authorisation is unchanged from the first round evaluation. It is recommended that Genvoya is approved for the following indication:

> *Genvoya is indicated as a single tablet regimen for the treatment of HIV-1 infection in adults and paediatric patients weighing at least 25 kg who are either treatment–naïve; or virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see CLINICAL TRIALS). Patients must not have a history of treatment failure or known mutations associated with resistance to the antiretroviral components of Genvoya.*
>
> *Genvoya is also indicated for the treatment of chronic hepatitis B in adults co-infected with HIV-1 and hepatitis B (HBV) who are HIV virologically suppressed (HIV-1 < 50 copies/mL) on a stable antiretroviral regimen at the start of therapy.*
>
> *Genvoya is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors.*

15. References

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Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au