Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide (as fumarate)

Proprietary Product Name: Genvoya

Sponsor: Gilead Sciences Pty Ltd

October 2018

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 AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

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; Tradename: Genvoya)
EFV	Efavirenz
EMA	European Medicines Agency
EVG/E	Elviregravir (Trade name: 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 (Tradename: Emtriva)
F/TAF	Emtricitabine/tenofovir alafenamide, co-formulated (Trade name: Descovy)
F/TDF	Emtricitabine/tenofovir disoproxil fumarate (co-formulated; Trade name: Truvada)
GEN	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Trade name: Genvoya); also abbreviated asE/C/F/TAF
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

Abbreviation	Meaning
LSM	Least squares mean
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
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; Tradename: Stribild)
$T_{½}$	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)

Abbreviation	Meaning
TAF	Tenofovir alafenamide
TBLH	Total body less head
T_{max}	Time (observed time point) of C_{max}
TDF	Tenofovir disoproxil fumerate (Trade name: 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; trade name: Truvada)
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

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	20 March 2018
Date of entry onto ARTG:	28 March 2018
ARTG number(s):	233398
Active ingredient(s):	Elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide (as fumarate)
Product name(s):	Genvoya
Sponsor's name and address:	Gilead Sciences Pty Ltd 417 St Kilda Rd, Melbourne 3004 VIC
Dose form(s):	Tablet
Strength(s):	150 mg/150 mg/200 mg/10 mg
Container(s):	Bottle
Pack size(s):	30 tablets.
Approved therapeutic use:	*Treatment of HIV-1 infection in paediatric patients weighing at least 25* kg.
Route(s) of administration:	Oral (PO)
Dosage:	*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. For further details see PI Attachment 1.

Product background

This AusPAR describes the application by the sponsor of Genvoya, a multiple active ingredient combination drug product, containing elvitegravir (EVG; E) 150mg/cobicistat (COBI; C) 150 mg/emtricitabine (FTC; F) 200 mg/tenofovir alafenamide (TAF; T) 10 mg, 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 (FDC) product which contains an integrase inhibitor (elvitegravir); a cytochrome P450 isozyme CYP3A inhibitor which acts as a pharmacokinetic enhancer cobicistat, and two nucleoside reverse transcriptase inhibitors (emtricitabine and tenofovir alafenamide).

The currently approved indication in Australia 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.*

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 ~~adolescents~~ paediatric patients ~~aged 12 years of age and older with body~~ weigh~~t~~ing at least ~~35~~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 coinfected 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*

- No new dosage forms or strengths are proposed. 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 in a bottle of 30 tablets.

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 in Cluster determinant 4 (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 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 pharmacokinetic (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.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 15 January 2016.

At the time the TGA considered this application similar application had been approved or were under consideration in the following countries:

USA

The initial United States (US) approval was in 2015. The approved indication at the time of submission to TGA was:

> *'Genvoya is a four-drug combination of elvitegravir, an HIV-1 integrase strand transfer inhibitor (INSTI), cobicistat, a CYP3A inhibitor, and emtricitabine and tenofovir alafenamide (TAF), both HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older weighing at least 35* kg *who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya. (1).'*

Europe

Genvoya was first approved in Europe on 19 November 2015. The proposed indication at the time of submission to TGA was (proposed indication is underlined):

> *'Genvoya is indicated for the treatment of adults and adolescents and paediatric patients (aged 6 years and older with body weight at least 25* kg*) infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir (see sections 4.2 and 5.1).'*

Canada

The submission is still under review. The proposed indication (new indication is underlined) in Canada is:

> *Genvoya (150 mg elvitegravir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir alafenamide) is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older (and weighing ≥ 35* kg*) and with no known mutations associated with resistance to the individual components of Genvoya.*

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

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Description	Date
Submission dossier accepted and first round evaluation commenced	31 March 2017
First round evaluation completed	31 August 2017
Sponsor provides responses on questions raised in first round evaluation	29 September 2017
Second round evaluation completed	31 October 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	2 January 2018
Sponsor's pre-Advisory Committee response	16 January 2018
Advisory Committee meeting	1-2 February 2018
Registration decision (Outcome)	20 March 2018
Completion of administrative activities and registration on ARTG	28 March 2018
Number of working days from submission dossier acceptance to registration decision*	221

*Statutory timeframe for standard applications is 220 working days

III. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

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 (such as a big pill size) or palatable (for example, 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.

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.

Contents of the clinical dossier

Scope of the clinical dossier

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

- 2 Pivotal efficacy/safety studies
- 4 Other efficacy/safety studies
- 1 Integrated summary of efficacy (ISE; tables)
- 1 Statistical analysis plan (SAP) and 1 Integrated summary of safety (ISS) (tables)
- 5 Virology reports and Virology analysis plan.

Paediatric data

The submission included paediatric efficacy and safety data.

Good clinical practice

The study reports state that all studies were conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (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.

Pharmacokinetics

Studies providing pharmacokinetic data

The only new pharmacokinetic data included in this submission relates to the use in children aged > 6 to < 12 years weighing ≥ 25 kg (see Table 1 for details).

Table 1: 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.

Evaluator's 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.

Pharmacodynamics

Studies providing pharmacodynamic data

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

Evaluator's conclusions on pharmacodynamics

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

Dosage selection for the pivotal studies

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).

Efficacy

Studies providing 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.

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.

Amendments to PI updated 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.
- Analyses performed across trials = pooled analysis of Studies GS-US-292-0104 and GS-US-292-0111.

Evaluator's conclusions on clinical efficacy

Treatment of patients co-infected with HIV and hepatitis B

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%.

Treatment of children ≥ 25 kg

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.

Amendments to Clinical trials and Renal impairment sections in the PI

Renal impairment

The data presented in this submission provides additional long term (to Week 144) efficacy and safety data from a single study (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.

Virologically suppressed to Week 96

The data presented consisted of additional long term data (Week 96) from a single study (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 GEN was statistically superior to continuing FTC/TDF plus a third agent (STB, (ATR; efavirenz/FTC/TDF), atazanavir (ATV)/boosted plus Truvada (TVD; FTC/TDF)) at Weeks 48 and 96 (virologic success at Week 96: Genvoya 92.8%; FTC/TDF plus a third agent 89.1%), demonstrating durable virologic efficacy in subjects switching from standard-of-care regimens.

Treatment naïve to Week 144

The data presented consisted of additional long term data (Week 144) from two studies (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.

Removal of class statements

Review of the extensive pooled data indicates that the risk of FTC, tenofovir disoproxil fumerate (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 Prescribing Information. 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 Prescribing Information would be appropriate to replace the current wording in the Precautions section.

Safety

Studies providing safety data

Pivotal and/or main efficacy studies

The following data were collected in the 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, estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation (eGFRCG).
- Metabolic assessments: fasting glucose and lipid panel (total cholesterol, high density lipoprotein (HDL), direct low density lipoprotein (LDL) and 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 β-2-microglobulin) biomarkers.
- Blood collected for analysis of alpha-fetoprotein (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 electrocardiogram (ECG), vital signs (blood pressure, pulse, respiration rate and temperature).

Patient exposure

HIV/HBV co-infection

Data on use of Genvoya in patients co-infected with HIV and HBV relies on a single, open label study (Study GS-US-292-1249) and are detailed in Table 2 below. The median (Q1, Q3) duration of exposure to study drug was 49.1 (48.1, 59.4) weeks.

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

	Genvoya 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%)
≥ 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.

Paediatric use

Data on paediatric use is based on a single open label, non-comparative study (Study GD-US-292-0106) and are detailed in Table 3, below.

Table 3: 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]	Genvoya (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 (weeks)[a,b]	Genvoya (N = 23)
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%)
≥ 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.

Renal impairment

Data on patients with mild to moderate renal impairment is from a single open label study (Study GS-US-292-0112) and are detailed in Table 4 below. Median duration of exposure to study drug was 144.1 weeks for Cohort 1 switch subjects.

Table 4: 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

	Cohort 1: Switch		
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%)
≥ 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.

Long term treatment

Virologically suppressed to Week 96

Data on virologically suppressed subjects switched to Genvoya was presented in a single, open label, randomised study (Study GS-US-292-0109) and are detailed in Table 5 below. The median duration of exposure to study drug was 96.0 weeks for both treatment groups.

Table 5: Study GS-US-292-0109: Duration of exposure to study drug (safety analysis set)

	Genvoya (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%)
≥ 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.

Treatment naïve to Week 144

Data on treatment naïve patients is presented as pooled data from two studies (Studies GS-US-292-0104 and GS-US-292-0111) in Table 6. The median exposure was similar in the two treatment groups (GEN: 144.9 weeks and E/C/F/TDF (coformulated; STB): 144.4 weeks).

Table 6: Pooled data (Studies GS-US-292-0104 and GS-US-292-0111); Duration of exposure to study drug (safety analysis set)

Exposure[a,b]	Genvoya (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%)
≥ 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.

Safety issues with the potential for major regulatory impact

See Attachment 2 and *Evaluator's conclusions on safety* below.

Postmarketing data

From both the long term use and co-infection Clinical Overviews 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.

Evaluator's conclusions on safety

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.

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.

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 bone mineral density (BMD) through Week 96, compared with minimal changes from baseline at both sites in the FTC/TDF plus a third agent group. Compared with the FTC/TDF plus a third agent group, lower percentages of subjects in the Genvoya group had decreases from Baseline in hip and spine bone mass density (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 E/C/F/TDF (coformulated)(STB) (Studies GS-US-292-0104 and GS-US-292-0111) and 1 HIV-infected, virologically suppressed subject on ATV/boosted plus TVD (Study GS-US-292-0109).

First round benefit-risk assessment

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.	***3. Long term use:*** Strength is virologic success at Week 96: Genvoya 92.8%; FTC/TDF+3rd Agent 89.1%. Strength is virological success at week 144 was non-inferior and statistically superior to STB (difference in percentages 4.2% (95% CI: 0.6%-7.8%, p = 0.021).
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.

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.

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, patients that are 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.

First round recommendation regarding authorisation

Genvoya is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors. Based on the clinical data submitted in 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.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

No new clinical information was submitted. Accordingly, the benefits of Genvoya are unchanged from those identified in the first round evaluation.

Second round assessment of risks

No new clinical information was submitted. Accordingly, the risks of Genvoya are unchanged from those identified in the first round evaluation.

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.

Second round recommendation regarding authorisation

The recommendation regarding authorisation is unchanged from the first round evaluation.

VI. Pharmacovigilance findings

In support of the current application the sponsor submitted European Union (EU) Risk Management Plan (RMP) version 3.0 (dated 29 November 2016) and Australian Specific Annex (ASA) version 2.0 (dated January 2017).

Most recently evaluated EU RMP for Genvoya was version 0.1 (dated 10 November 2014) and ASA version 0.2 (dated August 2015), which were submitted with the first application for approval of Genvoya as a new fixed dose combination.

Since the last evaluated version of the RMP, the following safety concerns have been added to the safety summary:

Important potential risks:

- Renal toxicity
- Bone events due to potential proximal renal tubulopathy/loss of BMD
- Ocular effects (posterior uveitis)
- Overdose of tenofovir occurring through accidental concurrent use of Genvoya with a TDF-containing product.

Missing information:

- Development of drug resistance in long term use
- Drug-drug interactions.

The clinical evaluator concluded that the revised summary of safety concerns was also acceptable.

In the current RMP, the pharmacovigilance plan includes routine and additional pharmacovigilance activities.[1] The additional activities include clinical trials and a pregnancy registry. Routine risk minimisation activities are proposed for all safety concerns.

The sponsor provided an annotated copy of the ASA. It is noted that the current ASA has been revised to align with the EU RMP. There are no significant changes to the pharmacovigilance plan. The pharmacovigilance plan section of the ASA has been updated to remove the studies that have been completed.

During the previous evaluation, routine risk minimisation measures were deemed adequate to address the important safety concerns associated with this product. Routine risk minimisation measures are considered acceptable to minimise the important potential risks and the missing information that have been added to the safety summary since the last evaluation.

There are no differences in the pharmacovigilance and the risk minimisation plans between the EU and Australia.

Conclusion

The proposed changes to the indication were not considered to constitute a significant difference in the target population from an RMP perspective. Although the summary of safety concerns has been updated since the last RMP evaluation, conducting a full evaluation of the current RMP was not expected to result in a significant difference in RMP outcomes.

Therefore, though an RMP was submitted by the sponsor, a full RMP evaluation was not conducted for the current submission.

The wording for conditions of registration, that include the current versions of the EU RMP and the ASA, are provided to the Delegate below:

> *The EU-RMP version 3.0 (dated 29 November 2016, DLP 31 October 2016) with ASA version 2.0 (dated January 2017) included with submission PM-2016-04632-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

[1] [1] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

This overview captures only the Studies GS-US-292-1249 (HIV/HBV co-infection in adults) and Study GS-US-292-0106 (use in children ≥ 25 kg body weight). Please see the accompanying Clinical Evaluation Report in Attachment 2 including the sponsor's response to the report.

The clinical evaluator supports extension of indication to '*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*.' A statement in the PI that there were only 3 patients in the (HIV)-treatment naïve group and that HIV virologically suppressed patients were generally switching from TDF containing regiments is also recommended.

The clinical evaluator supports extension of indication to '*paediatric patients weighing at least 25 kg*' with a statement in the PI that no treatment naïve children in age group 6 to 12 years have been treated with Genvoya.

Clinical efficacy

Hepatitis B Study GS-US-292-1249

This was an open label, single arm study to examine the clinical efficacy/safety of Genvoya once daily orally in the treatment of adults with HIV/HBV co-infection. The study was conducted in USA, Canada and Japan in 2014 to 2015.

The eligible population comprised of HIV/HBV co-infected male or females (non-childbearing) at least 18 years of age, CD4 count >200 cells/μL, alanine transaminase (ALT) ≤ 10 x upper limit of normal (ULN), total bilirubin ≤ 2.5 mg/dL, international normalised ratio (INR)[2] ≤1.5, albumin ≥ 3 g/dL and creatinine clearance ≥ 50 mL/min, and without evidence of cirrhosis or hepatocellular carcinoma who were hepatitis C or D negative. The sample size was chosen based on the feasibility of patient recruitment. Two cohorts to be recruited were as follows:

- Cohort 1: Treatment naïve HIV/HBV co-infected adult patients (planned N = up to 50).
- Cohort 2: HIV suppressed HIV/HBV co-infected adult patients (planned N = up to 75).

In Cohort 1, only 4 patients could be enrolled of which 3 received the study treatment. In Cohort 2, a total of 75 patients were enrolled of which 74 received the study treatment and

[2] INR is a laboratory measurement of how long it takes blood to form a clot. It is used to determine the effects of oral anticoagulants on the clotting system.

72 were included in the Full Analysis Set. The age distribution and years of disease since diagnosis were as follows:

Table 7: Study GS-US-292-1249 Demographic and baseline characteristics (safety analysis set)

Characteristic	E/C/F/TAF Cohort 1 (N = 3)	E/C/F/TAF Cohort 2 (N = 74)	Total (N = 77)
Age (Years)			
N	3	74	77
Mean (SD)	27 (4.0)	49 (7.8)	49 (8.9)
Median	26	51	50
Q1, Q3	23, 31	44, 54	43, 54
Min, Max	23, 31	28, 67	23, 67
Age Category (Years)			
< 50	3 (100.0%)	35 (47.3%)	38 (49.4%)
50 to < 65	0	37 (50.0%)	37 (48.1%)
≥ 65	0	2 (2.7%)	2 (2.6%)
Years Positive for HIV			
N	3	74	77
Mean (SD)	4 (2.9)	17 (8.7)	16 (8.9)
Median	2	18	17
Q1, Q3	2, 7	8, 24	7, 24
Min, Max	2, 7	2, 30	2, 30
Years Positive for HBV			
N	3	71	74
Mean (SD)	2 (0.6)	14 (9.5)	13 (9.6)
Median	2	12	12
Q1, Q3	1, 2	5, 20	5, 20
Min, Max	1, 2	2, 35	1, 35

At Baseline, HIV viral load in the trial population was as follows:

Table 8: Study GS-US-292-1249 Baseline HIV disease characteristics (Safety analysis set)

Disease Characteristic	E/C/F/TAF Cohort 1 (N = 3)	E/C/F/TAF Cohort 2 (N = 74)	Total (N = 77)
HIV-1 RNA (log_{10} copies/mL)			
N	3	74	77
Mean (SD)	4.20 (1.242)	1.29 (0.068)	1.41 (0.606)
Median	4.71	1.28	1.28
Q1, Q3	2.79, 5.11	1.28, 1.28	1.28, 1.28
Min, Max	2.79, 5.11	1.28, 1.77	1.28, 5.11
HIV-1 RNA Categories (copies/mL)			
< 50	0	73 (98.6%)	73 (94.8%)
≥ 50	3 (100.0%)	1 (1.4%)	4 (5.2%)

At Baseline, HBV DNA level, hepatitis B surface antigen, hepatitis B e-antigen and the corresponding antibody status in the trial population were as follows:

Table 9: Study GS-US-292-1249 Baseline HBV and liver disease characteristics (Safety analysis set)

Disease Characteristic	E/C/F/TAF Cohort 1 (N = 3)	E/C/F/TAF Cohort 2 (N = 74)	Total (N = 77)
HBV DNA (log_{10} IU/mL)			
N	3	74	77
Mean (SD)	8.31 (0.416)	1.49 (0.883)	1.75 (1.588)
Median	8.48	1.28	1.28
Q1, Q3	7.84, 8.62	1.28, 1.28	1.28, 1.28
Min, Max	7.84, 8.62	1.28, 8.41	1.28, 8.62
HBV DNA Category (IU/mL)			
< 29	0	64 (86.5%)	64 (83.1%)
≥ 29	3 (100.0%)	10 (13.5%)	13 (16.9%)
Hepatitis B Surface Antigen Status			
Positive[a]	3 (100.0%)	71 (95.9%)	74 (96.1%)
Negative	0	3 (4.1%)	3 (3.9%)
Hepatitis B Surface Antibody Status			
Positive	0	2 (2.7%)	2 (2.6%)
Negative	3 (100.0%)	72 (97.3%)	75 (97.4%)
Hepatitis B e-Antigen Status			
Positive	3 (100.0%)	30 (40.5%)	33 (42.9%)
Negative	0	44 (59.5%)	44 (57.1%)
Hepatitis B e-Antibody Status			
Positive	0	26 (35.1%)	26 (33.8%)
Negative[b]	3 (100.0%)	48 (64.9%)	51 (66.2%)

At Baseline, prior exposure to anti-HBV agents as part of HIV antiretroviral treatment was as follows:

Table 10: GS-US-292-1249 Baseline prior exposure to anti-HBV as part of HIV ANT treatment

Disease Characteristic	E/C/F/TAF Cohort 1 (N = 3)	E/C/F/TAF Cohort 2 (N = 74)	Total (N = 77)
ARV Regimen at Baseline			
TDF-containing	—	71 (95.9%)	—
Non-TDF-containing	—	3 (4.1%)	—
3TC- or FTC-containing	—	72 (97.3%)	—
TDF- and 3TC- or FTC-containing	—	71 (95.9%)	—

The dose of Genvoya examined in the study was same as the currently approved dose that is, (E/C/F/T 150/150/200/10 mg) single tablet once daily with food. The primary efficacy outcomes were examined after 24 weeks of treatment. The results were as follows:

HIV results at Week 24

At Baseline in Cohort 1 (treatment naïve; N = 3), the mean HIV-1 RNA was 4.20 (standard deviation (SD) 1.242) log10 copies/mL with all 3 patients having ≥ 50 copies/mL. At Week 24, all 3 patients achieved virologic success (HIV-1 RNA < 50 copies/mL) using FDA snapshot algorithm (3/3; 100%; 95% CI 29.2% to 100%)

At Baseline, in Cohort 2 (HIV suppressed; N = 74), the mean HIV-1 RNA was 1.29 (SD 0.068) log10 copies/mL with 73/74 (98.6%) patients having < 50 copies/mL. At Week 24, virologic success criterion (HIV-1 RNA < 50 copies/mL) was met by 68/72 (94.4% patients; 95% CI 86.4% to 98.5%) using FDA snapshot algorithm in full analysis set.

One patient was classified as a Virologic Failure. Data was missing for 3 patients in the Week 24 analysis window:

Table 11: 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%)
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.

At Baseline, the mean CD4 cell count was 636 (SD 258.6) cells/μL. At 24 weeks, the mean change from Baseline in CD4 cell count was 21 (SD 166.0) cells/μL.

HIV results at Week 48

In Cohort 1 (treatment naïve) at Week 48, two patients had Virologic Success (2/3; 91.7%; 95% CI 9.4% to 99.2%). Data was missing for one patient.

In Cohort 2 (HIV suppressed) at Week 48, Virologic Success was achieved by 66/72 (91.7% patients; 95% CI 82.7% to 96.9%).

Two patients were classified as virologic failures (VF). Of those two, one patient had VF at Week 24 and discontinued study drug due to lack of efficacy, and 1 patient had HIV-1 RNA 127 copies/mL. Data was missing for 4 patients in the Week 48 analysis window:

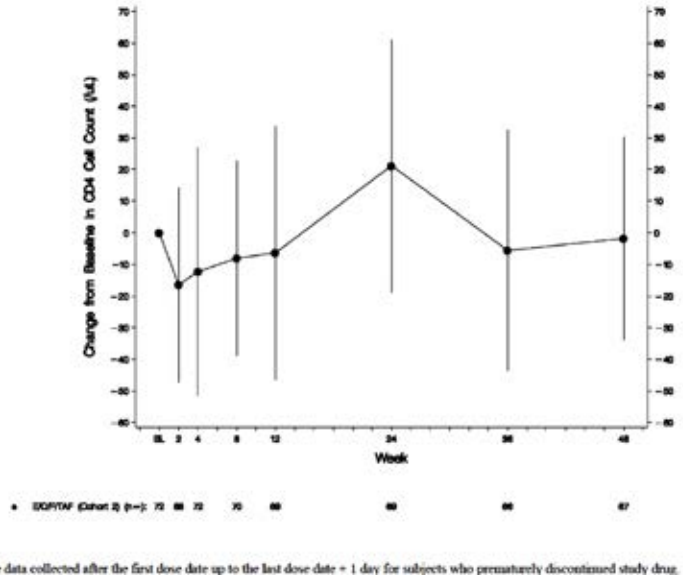
Table 12: GS-US-292-1249 Virologic outcome at Week 48 using FDA snapshot algorithm and HIV-1 RNA < 50 copies/mL (full analysis set)

	E/C/F/TAF Cohort 1 (N = 3)	E/C/F/TAF Cohort 2 (N = 72)
Virologic Success at Week 48		
HIV-1 RNA < 50 copies/mL	2/3 (66.7%)	66/72 (91.7%)
95% CI	9.4% to 99.2%	82.7% to 96.9%
Virologic Failure at Week 48	0	2 (2.8%)
HIV-1 RNA ≥ 50 copies/mL	0	1 (1.4%)
Discontinued Study Drug Due to Lack of Efficacy	0	1 (1.4%)
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 48 Window	1 (33.3%)	4 (5.6%)
Discontinued Study Drug Due to AE/Death	0	1 (1.4%)
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	1 (33.3%)	1 (1.4%)

Week 48 window was between Days 294 and 377 (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.

The CD4 cell count remained stable during treatment. The mean change in CD4 cell count through to Week 48 was - 2 (SD 131.2) cells/µL.

Figure 1: Study GS-US-292-1249 Mean ad 95% Cis of change from Baseline in CD4 cell count (µL) while on treatment (observed data) (full analysis set)



BL = Baseline
On-treatment values include data collected after the first dose date up to the last dose date + 1 day for subjects who prematurely discontinued study drug.

HBV results at Week 24

In Cohort 1 at Baseline, the mean HBV DNA was 8.31 (SD 0.416) log10 IU/mL and all 3 patients had HBV DNA ≥ 29 IU/mL. At Week 24, one patient (1/3; 33.3%; 95%CI 0.8%, 90.6%) met the Virologic Response criteria (HBV DNA < 29 IU/mL) using Missing (M) = Failure (F) or Missing (M) = Excluded (E) approach. Two of the 3 patients remained with HBV DNA ≥ 29 IU/mL.

In Cohort 2 at Baseline, the mean HBV DNA was 1.49 (SD 0.883) log10 IU/mL and 62/72 (86.1%) patients had HBV DNA < 29 IU/mL at Baseline. At Week 24, the percentage of patients meeting the virologic response criteria (HBV DNA < 29 IU/mL) using M = F approach remained stable at 86.1% (62/72 patients; 95% CI 75.9% to 93.1%). Using the M = E approach, the virologic response was achieved by 89.8% (62/69 patients; 95% CI 80.2%, 95.8%) patients.

The results are included in tabular format below:

Table 13: 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)[a]		
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
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% confidence interval (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 postbaseline. 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 postbaseline for subjects with non-missing paired data.

HBV results at Week 48

At Week 48 in Cohort 1, 2 of 3 patients (66.7%; 95%CI 9.4% to 99.2%) had HBV DNA < 29 IU/mL using M = F approach and 2 of 2 patients (100%; 95% CI 15.8% to 100%) had HBV DNA < 29 IU/mL using M = E approach.

At Week 48 in Cohort 2, 66/72 patients (91.7%; 95%CI 82.7% to 96.9%) had HBV DNA < 29 IU/mL using M = F approach, whereas 66/68 patients (97.1%; 95% CI 89.8% to 99.6%) had HBV DNA <29 IU/mL using the M = E approach.

The 48 weeks HBV results are included in the tabular format below:

Table 14: Study GS-US-292-1249 Percentage of subjects with HBV DNA < 29 IU/mL at Week 48 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)[a]		
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 48		
< 29 IU/mL	2/3 (66.7%)	66/72 (91.7%)
95% CI	9.4% to 99.2%	82.7% to 96.9%
≥ 29 IU/mL	0/3	2/72 (2.8%)
Missing	1/3 (33.3%)	4/72 (5.6%)
P-value[b]	—	0.34
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 48		
< 29 IU/mL	2/2 (100.0%)	66/68 (97.1%)
95% CI	15.8% to 100.0%	89.8% to 99.6%
≥ 29 IU/mL	0/2	2/68 (2.9%)
P-value[d]	—	0.016

95% CI is the 2-sided exact 95% confidence interval (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 postbaseline. 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 postbaseline for subjects with non-missing paired data.

Two patients 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 in one patient and 170 IU/mL in the other patient. Four patients were missing data at Week 48.

HBsAg: The results were as follows:

Table 15: Study GS-US-292-1249 Proportion of subjects with HBV surface antigen loss/seroconversion by Visit; M = E (full analysis set)

	E/C/F/TAF Cohort 1 (N = 3)	E/C/F/TAF Cohort 2 (N = 72)
Hepatitis B Surface Antigen Loss (N)[a,b]	3	70
At Week 12	0/3	0/70
At Week 24	0/3	1/70 (1.4%)
At Week 48	0/3	2/70 (2.9%)
Seroconversion to Hepatitis B Surface Antibody (N)[a,c]	3	70
At Week 12	0/3	0/70
At Week 24	0/3	1/70 (1.4%)
At Week 48	0/3	1/70 (1.4%)

a Only subjects with positive antigen and negative antibody at baseline are considered as antigen loss and seroconversion.
b Antigen loss is defined as a negative postbaseline antigen value for those subjects with a positive antigen and a negative antibody at baseline.
c Seroconversion to antibody is defined as (1) antigen loss or negative antigen at baseline, and (2) positive postbaseline antibody value for those subjects with a negative antibody at baseline.

In Cohort 1, no patient experienced HBsAg loss or seroconversion at Week 24 or Week 48.

In Cohort 2, out of the 70 patients who were HBsAg positive at Baseline, 1 patient experienced HBsAg loss with anti-HBsAg seroconversion at Week 24. At Week 48, 2 more

patients experienced HBsAg loss and 1 of these 2 patients also achieved seroconversion to anti-HBsAg at Week 48.

HBeAg: The results were as follows:

Table 16: Study GS-US-292-1249 Proportion of subjects with HBV e antigen loss/seroconversion by Visit; M = E (Full analysis set)

	E/C/F/TAF Cohort 1 (N = 3)	E/C/F/TAF Cohort 2 (N = 72)
Hepatitis B e Antigen Loss (N)[a,b]	3	30
At Week 12	1/3 (33.3%)	0/30
At Week 24	1/3 (33.3%)	1/30 (3.3%)
At Week 48	1/3 (33.3%)	1/30 (3.3%)
Seroconversion to Hepatitis B e Antibody (N)[a,c]	3	30
At Week 12	1/3 (33.3%)	0/30
At Week 24	1/3 (33.3%)	1/30 (3.3%)
At Week 48	1/3 (33.3%)	0/30

a Only subjects with positive antigen and negative antibody at baseline are considered as antigen loss and seroconversion.
b Antigen loss is defined as a negative postbaseline antigen value for those subjects with a positive antigen and a negative antibody at baseline.
c Seroconversion to antibody is defined as (1) antigen loss or negative antigen at baseline, and (2) positive postbaseline antibody value for those subjects with a negative antibody at baseline.

In Cohort 1, one of the 3 patients in Cohort 1 experienced HBeAg loss and anti-HBeAg seroconversion over the course of treatment.

In Cohort 2, out of the 30 patients who were HBeAg positive at Baseline, 1 patient experienced HBeAg loss with seroconversion to anti-HBeAg at Week 24. At Week 48, 1 other patient experienced HBeAg loss.

ALT

In Cohort 1, all 3 patients had ALT values above ULN at Baseline and were within normal range at Weeks 24 and 48 time-points.

In Cohort 2, 10/72 (13.9%) patients had ALT values above ULN at Baseline. Of those, 5 achieved ALT normalisation at Week 24 and 4 achieved ALT normalisation at Week 48.

In Cohort 2, 62/72 (86.1%) patients had ALT values within the normal range at Baseline. Of those, 54/62 (87.1%) were reported with ALT within normal range at Week 24 and 57/62 (91.9%) were reported with ALT within normal range at Week 48.

Virological resistance

Resistance testing was performed for patients meeting the criteria for Resistance Analysis Population (RAP). The RAP included any patient 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 patient 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 patient in the FAS population met the criteria for inclusion in RAP.

HBV Analysis: At Baseline there were 10 HBV viraemic patients. Of these, 5 had primary lamivudine resistance mutations detected at Baseline. After 48 weeks of Genvoya treatment, 2 of 72 patients in the FAS population 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.

Paediatrics Study GS-US-292-0106

This study was designed to investigate the PK and efficacy/safety of Genvoya (E/C/F/T) in treatment-naïve HIV infected adolescents aged 12 to < 18 years (Cohort 1) and virologically-suppressed HIV infected children 6 to <12 years of age (Cohort 2).

The results for Cohort 1 were evaluated in a previous submission leading to the currently approved indication in adolescents. This current submission reports results for Cohort 2 up to Week 24. The trial is ongoing to Week 48.

The study structure was as follows:

Table 17: Study design and structure

Study Number	Study Design	Treatment Regimen	Subject Population
GS-US-292-0106 (Cohort 2 Part A)[a]	Phase 2/3, open-label, multicohort, 2-part study single-group study to evaluate the PK, safety, tolerability, and antiviral activity of GEN	Single tablet of GEN (E/C/F/TAF, 150/150/200/10 mg) taken orally once daily with food	Cohort 2 Part A: Virologically suppressed HIV-infected children 6 to < 12 years of age weighing ≥ 25 kg with plasma HIV-1 RNA < 50 copies/mL and receiving ARV regimen that had been stable for ≥ 6 months or newly initiated for reasons other than virologic failure (n = 23)

a Cohort 1 data for ART-naive subjects have been reported in earlier submissions.

The study did not enrol any children < 8 years of age who met the body weight cut-off of ≥ 25 kg. The dose of Genvoya used in the paediatric study was the same as the currently approved adult dose and the currently approved dose in children aged ≥ 12 years that is, single tablet (E/C/F/T 150/150/200/10) daily by oral route.

For Cohort 2, the eligible patients were 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 (≥ 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). Exclusions included patients with new acquired immunodeficiency syndrome (AIDS) defining condition diagnosed within 30 days prior to screening; positive hepatitis C virus (HCV) or HBV antigens, decompensated cirrhosis or active tuberculosis (TB).

For Cohort 2, the primary objectives were as follows:

- To evaluate pharmacokinetics of individual components of Genvoya in particular EVG (E) and TAF (T).
- To evaluate safety and tolerability of Genvoya at Week 24.

A total of 23 children participated in the study. Adult data was used as historical control for comparison. On-treatment data were available for all 23 participants.

The median age of participating children was 10 years (range 8 to 11 years). The ethnic makeup was Black (18/23), Asian (3/23) and White (2/23). The median body weight at Baseline was 30.5 kg (range 27.5, 33.0 kg). The median body mass index (BMI) at Baseline was 15.9 (range 15.2, 18.1) kg/m2. The median body surface area at Baseline was 1.06 m^2 (range 1.00, 1.14). The median baseline eGFR calculated using the Schwartz and modified Schwartz formulas were 150 mL/min/1.73 m^2 and 110 mL/min/1.73 m^2 respectively.

Pharmacokinetics

Pharmacokinetic data were available for all 23 children in Cohort 2 and were compared with historical data in adult subjects in Phase 2/3 trials. The results were as follows:

Systemic exposures (area under the plasma/serum concentration versus time curve (AUC), maximum observed plasma/serum concentration of the drug (C_{max}) and/or observed drug concentration at the end of the dosing interval (C_{tau})) of TAF, TFV, EVG, COBI, and FTC, except EVG C_{tau}, were higher by 20% to 80% as compared to exposures in adults. Increases in AUC were: TAF (70.7%), TFV (52.2%), EVG (34.1%), COBI (57.7%), and FTC (75.0%). The mean EVG C_{tau} was slightly lower (15%) compared to AUC in adults.

Clinical efficacy

In Cohort 2, all participating children (N=23) had plasma HIV-1 RNA <50 copies/mL at baseline. The median baseline CD4 cell count was 969 cells/μL (range 843, 1087). All children had CD4 cell counts ≥ 500 cells/μL at baseline. The median number of years since diagnosis of HIV was 8 years (range 8 to 10 years). The risk factor for HIV infection was vertical transmission for all children. No child was HBsAg positive. All Cohort 2 children were receiving at least 1 ARV drug in accordance with entry criteria.

All children (N = 23) maintained virologic suppression (HIV-1 RNA < 50 copies/mL) after switching to Genvoya (E/C/F/TAF) and treatment for 24 weeks.

The mean CD4 cell count was 966 (SD 201) at Baseline. Mean decrease in CD4 cell count was seen from Week 2 through to Week 40 (-79 to -162 cells/μL). However, the mean count was maintained above 500 cells/μL at all time-points.

In Cohort 2, no child qualified for resistance analysis. Results were also provided for the resistance analysis for Cohort 1 through to Week 48. Of the 50 children enrolled in Cohort 1, two out of 50 met the criteria for resistance analysis. No child developed resistance to study drugs.

Clinical safety

Safety data have been extensively reviewed for which please see the accompanying Attachment 2.

Use in HIV/HBV co-infection: The adverse effects profile in adult HIV/BHV population was consistent with the known knowledge of the drug. No new safety signal was detected.

Use in Paediatrics: 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.

It is noted that the full adult dose of Genvoya was used with no adjustment for the younger children in the paediatric Study GS-US-292-0106.

Improved renal and bone profile of Genvoya containing TAF compared to regimens containing TDF is noted. In paediatric Study GS-US-292-0106, the TFV exposure (AUC_{tau}) was approximately 5 fold lower as compared with adult exposures with TDF 300 mg. This was consistent with lower systemic TFV exposures reported in adults with TAF versus TDF.

Risk management plan

See *Pharmacovigilance findings* above.

Risk-benefit analysis

Delegate's considerations

HIV/HBV co-infection in adults

Study GS-US-292-1249

In Cohort 1 (Treatment-naïve adult patients), only 3 patients were treated which does not allow any reliable conclusions for regulatory purpose.

In Cohort 2 (HIV suppressed adult patients), who switched to Genvoya from TDF containing regimens (n = 71/74), the responder rates were indicative of successful maintenance of effect at 24 weeks and 48 weeks of treatment as follows:

Table 18: Study GS-US-292-1249: Summary of efficacy (Cohort 2)

	Baseline	Week 24	Week 48
HIV-1 RNA < 50 copies/mL	98.6% (73/74)	94.4% (68/72)	91.7% (66/72)
HBV DNA < 29 IU/mL	86.5% (64/74)	86.1% (62/72)	86.1% (66/72)

The mean CD4 cell count/µL at Baseline was 636 (SD 258.6) cells per µL. The change from Baseline was 21 (SD 166.0) cells per µL at Week 24 and −2 (SD 131.2) cells/µL at Week 48 (Cohort 2 results). The number of participants with ALT within normal range (Cohort 2) was 62/72 (Baseline), 54/62 (Week 24) and 57/62 (Week 48).

At Baseline, 70/72 participants were HBsAg positive. HBsAg loss was reported for one patient at Week 24 and 2 patients at Week 48. One patient at Week 24 and one patient at Week 48 seroconverted (Cohort 2 results). At Baseline, 30/72 participants were HBeAg positive. HBeAg loss was reported for 1 patient at Week 24 and one patient at Week 48. One patient seroconverted at Week 24 (Cohort 2 results).

Development of resistance to the study drugs was not reported in patients who qualified for resistance analysis. The adverse effects/safety profile was acceptable.

Use in paediatric HIV-1 patients (6 to < 12 years of age weighing at least 25 kg)

Study GS-US-292-0106

The data (N = 23) presented was for HIV virologically suppressed (HIV-1 RNA <50 copies/mL) children who had been stable on antiretroviral therapy and who switched to Genvoya in this trial. The approved adult dose (single tablet daily) was used. No children under 8 years of age weighing at least 25 kg could be recruited in the trial.

All children (N = 23) maintained virologic suppression (HIV-1 RNA < 50 copies/mL) to 24 weeks after switching to Genvoya. The mean CD4 cell count was 966 (SD 201) at Baseline. Mean decrease in CD4 cell count was seen from Week 2 through to Week 40 (-79 to -162 cells/µL). However, the mean count was maintained above 500 cells/µL at all time-points. No patient qualified for resistance analysis in Cohort 2. Two patients from earlier Cohort 1 qualified for resistance analysis. No child developed resistance to study drugs. The adverse effects/safety profile was acceptable.

Increases in AUC in children compared to adults (historical data) were: TAF (70.7%), TFV (52.2%), EVG (34.1%), COBI (57.7%), and FTC (75.0%). The mean EVG C_{tau} was slightly lower (15%) compared adults. TFV AUC_{tau} was approximately 5 fold lower as compared with adult TFV exposures with TDF 300 mg.

Other changes to the PI: these are acceptable as recommended by the clinical evaluator. The sponsor's response to the CER is noted.

Delegate's conclusion

HIV/HBV co-infection (adult patients)

The data is limited to adult HIV/HBV patients who were HIV suppressed (HIV-1 < 50 copies/mL) on stable TDF containing antiretroviral regimens and were switched to single tablet Genvoya in this trial.

The indication proposed by the sponsor ('*Genvoya is also indicated for the treatment of chronic hepatitis B in adults co-infected with HIV-1 and hepatitis B'*) or the modified version recommended by the clinical evaluator ('*Genvoya is also indicated for the treatment of chronic hepatitis B in adults co-infected with HIV-1 and hepatitis B who are HIV virologically suppressed (HIV-1 < 50 copies/mL) on a stable antiretroviral regimen at the start of therapy*') both result in extrapolation beyond the observed data. In addition, the proposed indication(s) imply an optimum regime for the treatment of hepatitis B in HIV/HBV coinfection to the exclusion of applicable clinical guidelines.

The proposed standalone indication is not supported. The data is valuable and suitable for addition to the Clinical Trials section of the PI and is so recommended.

The Studies GS-US-320-0108 and GS-US-320-0110 nominated by the sponsor in support of this extension of indication were evaluated in the submission to register tenofovir alafenamide fumarate (TAF) as a 25 mg tablet single agent (Vemlidy) in the treatment of adult patients with chronic hepatitis B. These studies are not relevant to the proposed use of Genvoya (E/C/F/TAF 150/150/200/10 mg) in HIV/HBV co-infection.

Paediatric use (6 to <12 years of age weighing at least 25 kg)

The proposed extension of indication is based on body weight (≥ 25 kg) rather than age as no patients under 8 years of age weighing at least 25 kg could be recruited. This is considered acceptable. There is no data on the use of Genvoya in the treatment-naïve patients in this age group. This is an important limitation and should be reflected in the therapeutic indication.

Adult dose was used in the clinical trial. This is acceptable given the pharmacokinetic results. The differences from adult systemic exposures (AUC) reported in this trial are considered clinically acceptable in view of the concomitant 24 weeks efficacy/safety data generated in the trial.

Delegate's proposed action

The following indication is recommended by the Delegate:

> *'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. Note that no Treatment-naïve children in 6 to <12 years of age (weighing at least 25 kg) were treated in the clinical trial and the experience was limited to virologically suppressed children who switched to Genvoya.*
>
> *Genvoya is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors.'*

As noted above, the HIV/HBV coinfection clinical trials data is supported for inclusion in the Clinical Trials section of the Australian PI for Genvoya.

Summary of issues

Inappropriateness of standalone indication for treatment of hepatitis B in adult HIV/HBV co-infected patients.

Reference to treatment-naïve patients in HIV infected children 6 to <12 years of age in the proposed indication.

Request for ACPM advice

The Advisory Committee on Medicines (ACM) was requested to provide advice on the following specific issues:

1. Does the ACM agree with the Delegate to limit the inclusion of adult HIV/HBV coinfection data to the Clinical Trials section of the PI only rather than a standalone indication as proposed by the sponsor?
2. Does the ACM agree with the Delegate to include reference to the lack of data in treatment-naïve HIV infected children in 6 to < 12 years of age (weighing at least 25 kg) in the indication or will it be appropriate to include this information in the Clinical Trials and/or Dosage and Administration section rather than the therapeutic indication?

The ACM is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Executive summary

Genvoya tablets were originally approved in Australia on 15 January 2016 and are currently indicated as a single tablet regimen for the treatment of HIV-1 infection in adults and adolescents aged 12 years of age and older.

More data has since become available demonstrating the safety and efficacy against both HIV and HBV in adults with HIV/HBV co-infection who switched therapy to Genvoya in Study GS-US-292-1249. Further evidence for efficacy of Genvoya in HBV infected subjects is provided from the pivotal Vemlidy Studies GS-US-320- 0108 and GS-US-320-0110 that demonstrated the non-inferior efficacy of tenofovir alafenamide (TAF) versus tenofovir disoproxil fumarate (TDF) in treatment-naive and treatment-experienced adults with HBeAg negative and HBeAg positive chronic HBV-infection.

New data has also become available in HIV infected children that provides efficacy, PK and safety data through 24 weeks of treatment in virologically suppressed HIV infected patients aged 6 to < 12 years old weighing ≥ 25 kg in Study GS-US-292-0106 (Cohort 2, Part A).

As such, the sponsor proposes to include data from these studies in the Genvoya PI and to extend the HIV indication for Genvoya to include paediatric patients weighing at least 25 kg and for the treatment of chronic hepatitis B in adults co infected with HIV-1 and HBV. The proposed HBV indication represents current clinical guidance and practice seen with TAF and TDF containing fixed dose combinations in treating co-infected patients; in Genvoya's case substantial clinical evidence with Genvoya and TAF confirms this practice is warranted and Genvoya should be indicated as such.

Discussion of delegate's comments

The Delegate's comments are presented first and are followed by the sponsor's response.

ACPM advice sought by the TGA delegate

1. *Does the ACM agree with the Delegate to limit the inclusion of adult HIV/HBV coinfection data to the Clinical Trials section of the PI only rather than a standalone indication as proposed by the sponsor?*

The sponsor is encouraged that the Delegate has stated that the data relating to Study GS-US-292-1249 is valuable and suitable for addition to the Clinical Trials section of the PI and is so recommended.

However, the sponsor respectfully disagrees with the Delegate's comment that '*These studies (Study GS- US-320-0108 and Study GS-US-320-0110) are not relevant to the proposed use of Genvoya (E/C/F/TAF 150/150/200/10 mg) in HIV/HBV co-infection*.' The sponsor would like to reiterate the importance of these studies in relation to this proposed Indication as the efficacy of the TAF component of Genvoya in patients infected with HBV is demonstrated by the two independent confirmatory Phase III studies in treatment naive and treatment experienced adults with HBeAg negative (Study GS-US-320-0108) and HBeAg positive (Study GS-US-320-0110) HBV mono-infection. These studies, cross referenced in this application, were submitted to the TGA to support the application for Vemlidy (tenofovir alafenamide, TAF). The TGA has since evaluated and approved the registration of Vemlidy on 21 March 2017 with the indication for the treatment of chronic hepatitis B (CHB) in adults.

Studies GS-US-320-0108 and GS-US-320-0110 demonstrated the non-inferior efficacy of TAF versus TDF in treatment-naive and treatment-experienced adults with HBeAg negative and HBeAg positive chronic HBV infection. In both studies, similar rates of HBV DNA suppression were achieved in the 2 treatment groups when assessed using the M = F method at Week 48. Genvoya provides the equivalent exposure to TAF as the dosing in Vemlidy and therefore these studies are relevant to confirming the HBV efficacy of Genvoya.

In Study GS-US-292-1249, treatment with Genvoya in HIV/HBV co-infected adults who were HIV-suppressed was associated with continued HIV and HBV virologic control, as evidenced by suppression at Week 48 (HIV-1 RNA < 50 copies/mL using the FDA snapshot method, 91.7%; HBV DNA < 29 IU/mL using the M = F method, 91.7%). These results demonstrate the efficacy of Genvoya in HIV/HBV co-infected adults and highlight there is no reason to consider that the bioequivalence in TAF exposure is impacted by concurrent HIV infection. In all other HIV infected populations studied, there was no difference in efficacy across the different subpopulations evaluated. Overall, these results continue to demonstrate that Genvoya is efficacious in all populations without regard to demographic characteristics, baseline viral load or underlying renal function.

TAF has been shown to be effective against HIV (as part of fixed dose combinations like Genvoya) for both treatment naïve and virologically suppressed HIV infected subjects. TAF has also been shown to be effective against HBV (as a single agent) for both treatment naïve and virologically suppressed HBV infected subjects, thereby demonstrating the principle that TAF is effective against both viruses, irrespectively of previous treatment status.

Additionally, the US Department of Health and Human Service (DHHS)[3], International Antiviral Society USA (IAS-USA)[4] , European AIDS Clinical Society (EACS)[5], European Association for the Study of the Liver (EASL)[6] 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[7] has endorsed the DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents.

The inclusion of this proposed standalone HBV indication will ensure that Australian patients with HIV/HBV coinfection will have access to an effective and safe treatment regimen for both infections. Gilead emphasises that the totality of data provided, including Study GS-US-292-1249 in the present application and the previously submitted data in Study GS-US-320-0108 and Study GS-US-320-0110 are supportive of the additional proposed indication:

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

2. *Does the ACM agree with the Delegate to include reference to the lack of data in treatment naïve HIV infected children in 6 to <12 years of age (weighing at least 25 kg) in the indication or will it be appropriate to include this information in the Clinical Trials and/or Dosage and Administration section rather than the therapeutic indication?*

The sponsor supports the proposed action of the Delegate with regards to inclusion of the paediatric indication but respectfully disagrees with the proposed wording to include a reference to the lack of data within the Indication section, or in any other sections of the Genvoya PI.

The Delegate has expressed concern regarding the lack of data on the use of Genvoya in the treatment-naïve patients in this age group. Enrolling treatment naive patients in this age group in clinical trials is challenging as there have been advances in HIV care and ARV coverage in children, resulting in the likelihood that a majority of children at this age will have accessed ARV therapy. Due to the high similarity between the pathophysiology of HIV-1 infection in adults and children and in treatment response, the efficacy of ARVs can be extrapolated from adult to paediatric patients by targeting adult PK parameters in children. This approach minimises the number of children who are required to be subjected to studies and trial burden while still allowing for acquisition of necessary data which is, ethically, the goal for paediatric research.

As demonstrated in the adult studies of Genvoya, differences in exposures are not expected in treatment naïve patients versus virologically suppressed patients. Thus, extrapolation of efficacy based upon PK data obtained in virologically suppressed paediatric patients applies to treatment naïve paediatric patients as well. This is also supported by the TGA adopted EU guidelines *Guideline on the Clinical Development of*

[3] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC) Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Last Updated 14 July

[4] Gunthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society-USA Panel. JAMA 2016;316 (2):191-210.

[5] E. A. C. S. (2017). European AIDS Clinical Society (EACS) Guidelines Version

[6] European Association for the Study of the Liver (EASL). EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. [Article In Press]. J Hepatol 2017:1-29

[7] Sexually Transmitted Diseases

Medicinal Products for the Treatment of HIV Infection[8] which supports the use of switch studies in virologically suppressed children as a means of evaluation of an ARV for an overall paediatric indication due to the scarcity of treatment-naïve children.

Study GS-US-292-0106 demonstrated the PK data for paediatric patients between the ages of 6 to < 12 years (≥ 25 kg) who received Genvoya were generally higher (20 to 80%) than exposures achieved in adults and met the statistical lower bound of the 90% CI required to extrapolate efficacy using a comparison of the geometric least square mean (GLSM) of adult versus paediatric exposures.

Similar safety outcomes in adult and paediatric subjects strongly support the expectation that treatment naive paediatric patients respond to treatment with Genvoya no differently than do adults. The same expectation applies to the safety outcomes of virologically suppressed versus treatment naïve children. It would be unreasonable to expect clinical research in children in different sub-populations when there is such strong evidence that there is no age-associated difference in humans infected with the same virus treated with Genvoya.

Therefore, the sponsor would like to propose the following indication for Genvoya for consideration by the Delegate:

> *'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.'*

The clinical evaluator has agreed that the wording of the proposed indication is acceptable to cover the data and it is recommended that the indication be approved but there should be a statement in the PI that the data on treatment naïve children was not available. The sponsor maintains that the proposed text within the Australian PI Clinical Trials section already reflects that patients of Study GS-US-292-0106 Cohort 2 were only virologically suppressed children. Also the proposed text in this section is comparable in terms of content to the text within other foreign labels, including the approved Genvoya US PI and EU Summary of Product Characteristic (SmPC).

Genvoya fulfils the unmet medical need in HIV-1 infected paediatric patients 6 to < 12 years of age as the first FDC for this population (versus multi-tablet regimens) as an efficacious, well tolerated, complete, once daily, oral, single tablet regimen. The sponsor believes the inclusion of paediatric patients in the indication is important due to the specific and complex challenges for the treatment of paediatric patients who also represent the population that will require antiretroviral therapy for the longest time.

The clinical evaluator has stated that 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. As such, the sponsor would like the Delegate and ACM to consider an indication statement inclusive of treatment- naïve and virologically suppressed paediatric patients, which is also consistent with the currently approved indications of the Genvoya US PI and EU SmPC.

Summary of other issues raised by the TGA delegate

The sponsor has provided an updated foreign regulatory status in relations to Study GS-US-292-1249 and GS-US-292-0106 in this response.

[8] EMEA/CPMP/EWP/633/02; Rev 3

Advisory Committee Considerations[9]

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Genvoya tablet containing Elvitegravir (EVG;E) 150 mg/Cobicistat (COBI;C) 150 mg/Emtricitabine (FTC;F) 200 mg/Tenofovir alafenamide (TAF;T) 10 mg of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide to have an overall positive benefit-risk profile for the Delegate's amended 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. Note that no treatment-naïve children (6 to <12 years of age (weighing at least 25 kg) were treated in the clinical trial and the experience was limited to virologically suppressed children who switched to Genvoya.*
>
> *Genvoya is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors.*

In making this recommendation the ACM:

- Noted that HBV was not an approved indication by FDA, EMA or Health Canada and reference to HBV in clinical trials was inconsistent across international regulators.
- Expressed concern about the tablet size and the potential that children weighing 25 kg would receive almost triple the adult dose. The ACM was of the view that a specific paediatric dose should be considered.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration.

Proposed PI (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the PI (PI) and Consumer Medicine Information (CMI).

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

The ACM is requested to provide advice on the following specific issues:

1. *Does the ACM agree with the Delegate to limit the inclusion of adult HIV/HBV co-infection data to the Clinical Trials section of the PI only rather than a standalone indication as proposed by the sponsor?*

[9] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

The ACM advised that while it is likely that TAF is effective, the submitted studies only included 3 patients not already on treatment, which is insufficient to support the use of Genvoya in HIV/HIV co-infection. The ACM supported inclusion of the data in the Clinical Trials section of the PI.

2. *Does the ACM agree with the Delegate to include reference to the lack of data in treatment-naïve HIV infected children in 6 to <12 years of age (weighing at least 25 kg) in the indication or will it be appropriate to include this information in the Clinical Trials and/or Dosage and Administration section rather than the therapeutic indication?*

The ACM agreed that there was a lack of data in treatment naïve HIV infected children aged between 6 to < 12 years and hence agreed to a reference of a lack of data in this population in the indication.

The ACM agreed that the proposed wording of the indication should not preclude the use of Genvoya in treatment-naïve HIV infected children aged between 6 to < 12 years, but indicate the limited evidence available for this specific population.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided, would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Genvoya (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg and tenofovir alafenamide (as fumarate) 10 mg) for oral administration, for the following indications:

Treatment of HIV-1 infection in paediatric patients weighing at least 25 kg*.*

Specific conditions of registration applying to these goods

1. The EU-RMP version 3.0 (dated 29 November 2016, Data Lock Point (DLP) 31 October 2016) with ASA version 2.0 (dated January 2017) included with submission PM-2016-04632-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information (PI) for Genvoya approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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