EU Risk Management Plan for Genvoya® (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide)

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RMP version to be assessed as part of this application:

Version number:	Data lock point for this RMP:	Date of final sign off:
6.1	31 Jul 2025	06 Oct 2025

Rationale for submitting an updated RMP:

The Risk Management Plan has been updated to remove the following:

- Important identified risk:
  - Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness
- Important potential risk:
  - Concurrent use of drugs whose coadministration with Genvoya is contraindicated
- Missing information:
  - Safety in patients with cardiac conduction disorders

Summary of significant changes in this RMP:

Part	Module/Annex	Significant changes to RMP
Part I Product Overview	N/A	None
Part II Safety Specification	Part II: Module SI: Epidemiology of the indication and target populations(s)	None
	Part II: Module SII: Non-clinical part of the safety specification	None
	Part II: Module SIII: Clinical trial exposure	None
	Part II: Module SIV: Populations not studied in clinical trials	None
	Part II: Module SV: Post-authorization experience	Post-authorization exposure updated.

Part	Module/Annex	Significant changes to RMP
	Part II: Module SVI: Additional EU requirements for the safety specification	None
	Part II: Module SVII: Identified and potential risks	Updated the list of safety concerns to remove the important identified risk of 'suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness', important potential risk of 'concurrent use of drugs whose coadministration with Genvoya is contraindicated' and missing information of 'safety in patients with cardiac conduction disorders'.
	Part II: Module SVIII: Summary of the safety concerns	List of safety concerns revised to align with Module SVII.
Part III Pharmacovigilance Plan		None
Part IV Plan for post-authorization efficacy studies		None
Part V Risk Minimization Measures		Revised to reflect the updated list of safety concerns to align with Part II Module SVII.
Part VI Summary of RMP		Revised to reflect the updated list of safety concerns to align with Part II Module SVII.
Part VII Annexes		Updated Annex 8 to reflect the removal of safety concerns

Other RMP versions under evaluation:

There are no other EU-RMP versions under evaluation.

Details of the currently approved RMP:

Version number:	Approved with procedure	Date of approval (opinion date)
6.0	EMEA/H/C/004042/X/0079/G	03 October 2022

QPPV name:	Rainer Heissing
QPPV signature:	The RMP has been reviewed and approved by the QPPV and the electronic signature is on file.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral therapy
ARV	Antiretroviral
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical (classification system)
BCRP	breast cancer resistance protein
BIC	bictegravir
BMD	bone mineral density
CD4	cluster of differentiation 4
CHMP	Committee for Medicinal Products for Human Use
CPT	Child-Turcotte-Pugh classification
CYP	cytochrome P450 enzyme
DLP	data-lock point
DNA	deoxyribonucleic acid
DRV	darunavir
DTG	dolutegravir
EACS	European AIDS Clinical Society
ECG	electrocardiogram
ECHO	echocardiogram
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EPAR	European Public Assessment Report
EU	European Union
EVG	elvitegravir
FTC; F	emtricitabine
GEN	Genvoya®
GERS	Groupement pour l'Élaboration et la Réalisation de Statistiques
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IC_{50}	concentration required to produce 50% inhibition
IDU	injection drug users
INN	international Nonproprietary Name
INSTI	integrase strand-transfer inhibitor

m	module
MAH	marketing Authorization Holder
MATE	multidrug and toxin extrusion
MRP	multi-drug resistance protein
MSM	men who have sex with men
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
OAT	organic anion transporter protein
OCT	organic cation transporter
OCTN	organic cation transporter novel
ODE	Odefsey
Pgp	P-glycoprotein
PI	protease inhibitor
PIL	patient information leaflet
PL	package leaflet
PK	pharmacokinetics
PRT	proximal renal tubulopathy
PSUR	periodic safety update report
QPPV	Qualified Person for Pharmacovigilance
RAL	Raltegravir
RMP	risk management plan
RTV	ritonavir
SmPC	Summary of Product Characteristics
TAF	tenofovir alafenamide
TFV	tenofovir
TDF	tenofovir disoproxil fumarate
TVD	Truvada
UGT	uridine glucuronosyltransferase
UNAIDs	Joint United Nations Programme on HIV and AIDS

PART I: PRODUCT OVERVIEW

Table Part I. 1. Product Overview

Active substance(s) (INN or common name)	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide
Pharmaco-therapeutic group(s) (ATC Code)	Antivirals for the treatment of human immunodeficiency virus (HIV) infections, combinations (J05AR18)
Marketing Authorization Holder	Gilead Sciences Ireland UC
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Genvoya®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class Elvitegravir: integrase strand-transfer inhibitor (INSTI) Cobicistat: pharmacokinetic enhancer Emtricitabine: nucleoside reverse transcriptase inhibitor (NRTI) Tenofovir alafenamide: nucleotide reverse transcriptase inhibitor (NtRTI)
	Summary of mode of action Elvitegravir is a strand transfer inhibitor of HIV-1 integrase, an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus. The provirus is required for production of progeny virus, so inhibiting integration prevents propagation of the viral infection. Cobicistat enhances or 'boosts' the systemic exposure of CYP3A substrates, such as EVG, where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism. Emtricitabine is a nucleoside analogue of 2'-deoxycytidine. Intracellularly, FTC is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate, the active metabolite, which competitively inhibits HIV reverse transcriptase, resulting in DNA chain termination. Emtricitabine has activity that is specific to HIV-1 and HIV-2 and hepatitis B virus. Tenofovir alafenamide is an oral prodrug of tenofovir (TFV), a nucleotide analog. TAF is converted to TFV, which is metabolized intracellularly to the active metabolite tenofovir diphosphate (TFV-DP). Tenofovir diphosphate inhibits the activity of HIV reverse transcriptase by competing with the natural substrate, deoxyadenosine 5'-triphosphate, leading to DNA chain termination. Tenofovir has activity that is specific to HIV-1 and HIV-2 and hepatitis B virus.
	Important information about its composition None.
Hyperlink to the Product Information	Genvoya Summary of Product Characteristics (SmPC)

Indication(s) in the EEA	Current: Genvoya is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir in adults and pediatric patients aged from 2 years and with body weight at least 14 kg.
	Proposed: None.
Dosage in the EEA	Current: One tablet to be taken once daily with food.
	Proposed: None.
Pharmaceutical form(s) and strengths	Current: Film-coated tablet containing 150 mg EVG, 150 mg COBI, 200 mg FTC and 10 mg TAF for adults or pediatric patients weighing at least 25 kg. Film-coated tablet containing 90 mg EVG, 90 mg COBI, 120 mg FTC and 6 mg TAF for pediatric patients at least 2 years of age and weighing at least 14 to less than 25 kg.
	Proposed: None.
Is/Will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1. HIV-1 Infection

SI.1.1. Epidemiology of the Disease

Human immunodeficiency virus is a retrovirus that attacks helper T cells, macrophages, and dendritic cells of the immune system, and weakens the body's ability to fight infections and disease. A person with HIV infection is considered to have developed acquired immune deficiency syndrome (AIDS) when the immune system becomes depleted in that it can no longer fight off a range of opportunistic diseases with which it would normally cope. HIV infection is predominantly transmitted through unprotected sexual intercourse and contact with infected blood and certain bodily products (e.g., needle exchanges, maternal blood during childbirth, and breast milk). Along with the development of prevention strategies to decrease transmission rates, the advent of highly active antiretroviral therapy (HAART) in 1996 and subsequent medications have dramatically changed the natural history of HIV/AIDS by improving clinical outcomes, leading to reductions in morbidity and mortality worldwide. However, HIV/AIDS remains a major public health problem worldwide.

SI.1.2. Incidence

The estimated number of people (adults and children) acquiring HIV infection in 2019 was 1.7 million (95% confidence interval [CI]: 1.2 million-2.2 million), which is a 23% decrease in the number of new infections compared to 2010(Table SI 1) {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Among adults (15 years and older), there was a 17% decrease in the overall number of new infections between 2010 and 2019, with the total number of new adult infections in 2019 estimated at 1.5 million (95% CI: 1.1-2.0 million) {UNAIDS AidsInfo 2020b}. Among children (<15 years old), the number of new infections in 2019 (n= 150,000 [95% CI: 94,000-240,000]) decreased by 52% during the same time (2010 to 2019) {UNAIDS AidsInfo 2020c}. However, incidence rates vary by country and region due to differences in structural and societal determinants across the globe. Notable declines in the number of new HIV infections overall have been observed in Eastern and Southern Africa (38%), the Caribbean (29%), Western and Central Africa (25%), Central Europe and North America (15%), and Asia and the Pacific (12%). In contrast, new HIV infections have been on the rise in Eastern Europe and Central Asia, with an increase of 72% between 2010 and 2019, largely due to transmission among injection drug users (IDU) and their sexual partners, as well as political and technical barriers to HIV treatment programs. The Middle East and North Africa and Latin America regions have also seen an increase in the number of new infections since 2010 (by 25% and 21%, respectively), where stigma against those living with HIV and lack of resources for HIV prevention and treatment programs are major barriers to ART access, and to preventing spread of infection. Disparate groups within other regions also experience disproportionately higher rates of HIV incidence, such as adolescent girls and young women in Eastern and Southern Africa,

children in Western and Central Africa, and men who have sex with men (MSM) in certain countries within the Asian and the Pacific region {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

SI.1.3. Prevalence

The distribution of HIV-infected individuals varies enormously across geographical regions. Approximately 36.2 million adults and 1.8 million children were living with HIV globally at the end of 2019 (total: 38.0 million; 95% CI: 31.6-44.5 million) (Table SI 1) {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. An estimated 0.6% (95% CI: 0.5-0.8%) of adults (15 years and above) worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions {UNAIDS 2019a, UNAIDS AidsInfo 2020d}.

The Eastern and Southern Africa region is most severely affected, with an estimated 20.7 million (95% CI: 18.4-23.0 million) people living with HIV infection in 2019 {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Although this region comprises 6.2% of the global population, it accounts for over 50% of people living with HIV worldwide. Western and Central Africa is the second most affected region with 4.9 million (95% CI: 3.9-6.2 million) people living with HIV. In both these African regions, which are referred to collectively as Sub-Saharan Africa, prevalence is high among key populations including MSM, sex workers, IDUs, and sexual partners of these groups. After Sub-Saharan Africa, the regions most heavily affected are the Caribbean, Eastern Europe and Central Asia, and Latin America where 0.5-1.1% of adults were living with HIV in 2019 {UNAIDS 2019a, UNAIDS AidsInfo 2020d}. Eastern Europe and Central Asia is the only region where HIV prevalence remains on the rise, reaching an estimated 1.7 million in 2019 (95% CI: 1.4-1.9 million), resulting largely from a surge of infections among IDU and their sexual partners {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. In contrast, estimated regional prevalence is lower in Western and Central Europe and North America (0.3%[95% CI: 0.2-0.3] in adults) {UNAIDS AidsInfo 2020d}. In this region, although more than 81% of people living with HIV are accessing ART, unprotected sex between men continues to dominate patterns of HIV transmission. In Western and Central Europe, stigma and discrimination within the health-care system persist as significant barriers to accessing HIV treatment among MSM, in addition to sex workers and IDUs {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

Table SI 1. Regional Prevalent and Incident Cases of HIV Infection in 2019

	Incident Cases (n; 95% CI)		Prevalent Cases (n; 95% CI)	
	Overall	**Adults[a]**	**Overall**	**Adults[a]**
Asia and Pacific	300,000 (210,000-390,000)	280,000 (200,000-370,000)	5.8 million (4.3-7.2 million)	5.7 million (4.2-7.1 million)
Caribbean	13,000 (8,700-19,000)	12,000 (8,000-17,000)	330,000 (270,000-400,000)	320,000 (260,000-390,000)
Eastern and Southern Africa	730,000 (580,000-940,000)	660,000 (520,000-850,000)	20.7 million (18.4-23.0 million)	19.6 million (17.5-21.8 million)

	Incident Cases (n; 95% CI)		Prevalent Cases (n; 95% CI)	
	Overall	**Adults[a]**	**Overall**	**Adults[a]**
Eastern Europe and Central Asia	170,000 (140,000-190,000)	160,000 (140,000-190,000)	1.7 million (1.4-1.9 million)	1.6 million (1.4-1.8 million)
Latin America	120,000 (73,000-180,000)	120,000 (71,000-170,000)	2.1 million (1.4-2.8 million)	2.1 million (1.4-2.8 million)
Middle East and North Africa	20,000 (11,000-38,000)	18,000 (9,500-36,000)	240,000 (170,000-400,000)	230,000 (160,000-380,000)
Western and Central Africa	240,000 (150,000-390,000)	190,000 (120,000-310,000)	4.9 million (3.9-6.2 million)	4.5 million (3.6-5.7 million)
Western and Central Europe and North America	65,000 (49,000-87,000)	65,000 (48,000-87,000)	2.2 million (1.7-2.6 million)	2.2 million (1.7-2.6 million)
Total [b]	**1.7 million (1.2-2.2 million)**	**1.5 million (1.1-2.0 million)**	**38.0 million (31.6-44.5 million)**	**36.2 million (30.2-42.5 million)**

a Aged 15 years and older.
b Numbers in the columns may not add up to match the totals exactly due to the effect of rounding.
Source: {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020, UNAIDS AidsInfo 2020d, UNAIDS AidsInfo 2020e}

SI.1.4. Demographics of the HIV Population

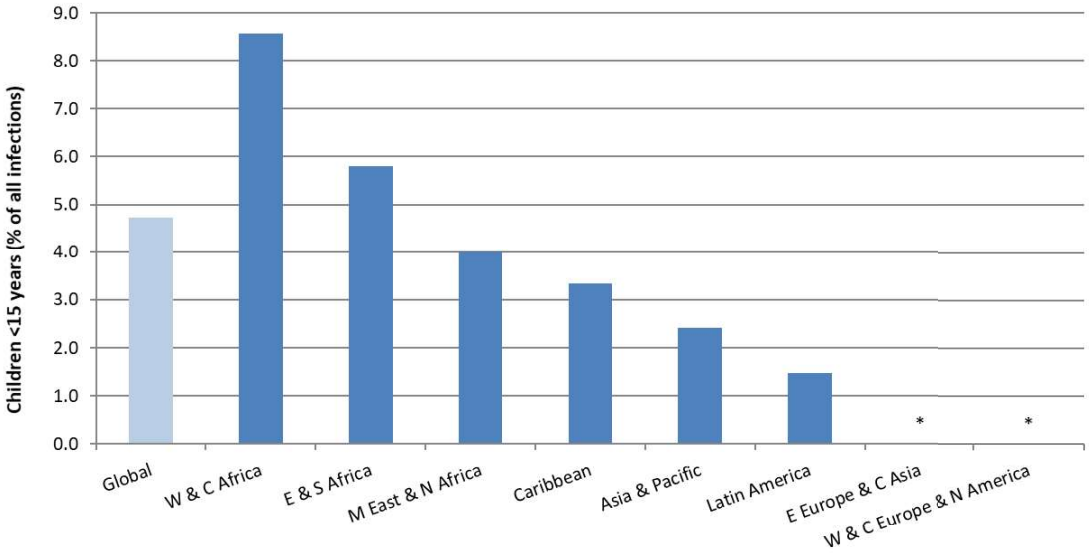
SI.1.4.1. HIV Infection in Children

Worldwide, 1.8 million (95% CI: 1.3-2.2 million) children (<15 years old) were living with HIV in 2019, accounting for a substantial proportion of existing infections in Western and Central Africa (8.6%) and Eastern and Southern Africa (5.8%) (Figure SI 1) {UNAIDS 2019b, UNAIDS AidsInfo 2020g}. Estimates of prevalence among children were unavailable for 2019 in the Eastern Europe and Central Asia and Western and Central Europe and North America regions.

Mother-to-child transmission is the main route of infection among children, by which a woman infected with HIV passes HIV to her child through pregnancy, childbirth, or breast milk. If the mother has access to ART during pregnancy, delivery, and breastfeeding, the risk of mother-to-child transmission reduces to 5% or less {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. Expansions in ART and infant feeding-based prevention services are primarily responsible for the observed declines in the number of newly infected children {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. It is estimated that since 1995, ART and prophylaxis to women living with HIV while pregnant or breastfeeding prevented 1.6 million children from acquiring HIV infection worldwide, with over 80% of those infections prevented between 2010 and 2015. Approximately 49% of all children who acquired HIV infection in 2019 were living in Eastern and Southern Africa, followed by Western and Central Africa (35%), Asia and Pacific (10%), Latin America (2%), and Caribbean (<1%) {UNAIDS AidsInfo 2020c}. The greatest reductions in HIV incidence among children between 2010 and 2019 were observed in Eastern and Southern Africa (63%), followed by Caribbean

(55%), West and Central Africa (37%), Latin America (29%), and Asia and Pacific (21%){UNAIDS AidsInfo 2020c}. However, the Middle East and North Africa region has yet to see a significant reduction in the number of children newly infected. This is likely attributable to the rates of mother-to-child transmission remaining high in the region (30% in 2019) due to low coverage of services for prevention of vertical transmission{Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

Figure SI 1. Proportion of Individuals Infected with HIV Aged <15 years old by Geographical Region



* Data on individuals infected with HIV aged <15 years old not available for Eastern Europe & Central Asia and Western & Central Europe and North America.
Source: {UNAIDS AidsInfo 2020e, UNAIDS AidsInfo 2020f}

SI.1.4.2. HIV Infection by Gender

Worldwide, males comprised approximately 52% of total new infections (all ages) in 2019, while 48% were among females {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Since 2010, the annual number of new HIV infections has declined by 18% among males and 27% among females {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Differences in incidence rates exist globally, particularly in developing regions of the world, where societal gender inequalities, differential access to services, and sexual violence contribute to increased infection risk {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Women account for 63% of prevalent adult infections in Eastern and Southern Africa, 62% in Western and Central Africa, 47% in the Caribbean, 40% in Eastern Europe and Central Asia, 37% in Asia and Pacific, 36% in Middle East and North Africa, 30% in Latin America, and 23% in Western and Central Europe and North America {UNAIDS AidsInfo 2020e, UNAIDS AidsInfo 2020h}. Among young women (aged 15 to 24 years), incident infections reduced by 35% between 2010 and 2019, however, adolescent girls and young women still accounted for 19% of new adult HIV infections in 2019 and are globally twice as likely to become infected

compared to men {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. In sub-Saharan Africa, although women in this age group comprise only 10% of the total population, as high as 30% of new infections in this region are among young women {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

SI.1.4.3. HIV Infection by Age

There is evidence to suggest that the life expectancy of HIV patients is approaching that of HIV-negative persons, if diagnosis and treatment occur at an early enough stage and patients maintain adherence to treatment {Nakagawa 2013}. With increased life expectancy, the mean age of HIV patients continues to increase, and HIV is more prevalent among those who are older, particularly in countries where effective therapies were available earlier {Nakagawa 2013, Wing 2016}. Worldwide, between 1995 and 2013, prevalence rates among those aged 50 years and older have gradually increased over time; and the proportion of those living with HIV who are above the age of 50 ranged from 10% (in low- and middle-income countries) to 30% (in high income countries) {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017, Mahy 2014}. UNAIDS reports that this trend is largely due to the success of ART, decreases in HIV incidence among adults below the age of 50, and those above 50 having similar risk behaviors as those who are younger {UNAIDS 2013}.

SI.1.5. Main Existing Treatment Options

Standard of care for the treatment of HIV-1 infection uses combination ART to suppress viral replication to below detectable limits, allow CD4 cell counts to increase, and stop disease progression. For ART-naive HIV-infected patients, current European treatment guidelines recommend that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) with an unboosted integrase strand transfer inhibitor (INSTI) with a high genetic barrier such as dolutegravir (DTG) or bictegravir (BIC) as the preferred third agent {European AIDS Clinical Society (EACS) 2020}. In the US, recommended initial ART regimens for HIV-infected patients consist 2 NRTIs and an INSTI, a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic enhancer {Panel on Antiretroviral Guidelines for Adults and Adolescents 2019}.

Virologically suppressed HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification.

Highly active antiretroviral therapy (HAART) has led to a significant reduction in HIV-associated morbidity and mortality. However, several factors influence the safety and efficacy of antiretroviral (ARV) therapy to suppress plasma viral load and restore and preserve immune function. These factors include non-adherence, adverse drug reactions, drug-drug interaction and development of resistance. Long-term adherence to ART is required to maintain viral suppression, and can be associated with toxicity. The ongoing chronic inflammation associated with HIV infection, even on HAART, has also been associated with increased risk of non-AIDS defining morbidity and mortality. HAART is active only against replicating virus and has no impact on integrated viral deoxyribonucleic acid (DNA) within latent HIV-1 infected memory CD4+ T cells. These cells persist and serve as the source of viral rebound in the setting of an ART treatment interruption. Eradication of this viral reservoir is a key priority in achieving HIV cure and improving outcomes in HIV-infected individuals. The timely development of a

safe and effective agent that effectively targets the latent reservoir and eliminates viral persistence would address an unmet medical need for an HIV cure.

SI.1.6. Natural History of the Indicated Condition

Untreated HIV compromises the host's immune system, which makes it susceptible to opportunistic infections and malignancies, and is associated with comorbidities that affect all organ systems. When untreated, HIV advances through three stages of infection: acute infection, clinical latency, and acquired immune deficiency syndrome (AIDS). The development of specific comorbidities and adverse events among those with HIV is dependent on a number of factors including stage of infection, the presence of coinfections, and treatment status. It is therefore difficult to provide frequency estimates of adverse events among the undiagnosed and untreated HIV population, which are also likely to differ substantially by geography, reflecting local conditions {Bradley 2014, Hamers 2008}. Although no effective cure currently exists, ART administered at an early enough stage can dramatically improve an HIV patient's prognosis, decreasing morbidity, mortality, and the risk of spreading the infection to others {Schwarcz 2013}. However, as the number of HIV patients with lifelong access to treatment is increasing, HIV-associated complications and chronic diseases related to inflammation, immunodeficiency, and ageing are also emerging, as well as health-related quality of life and depression {Deeks 2013a, Langebeek 2017}.

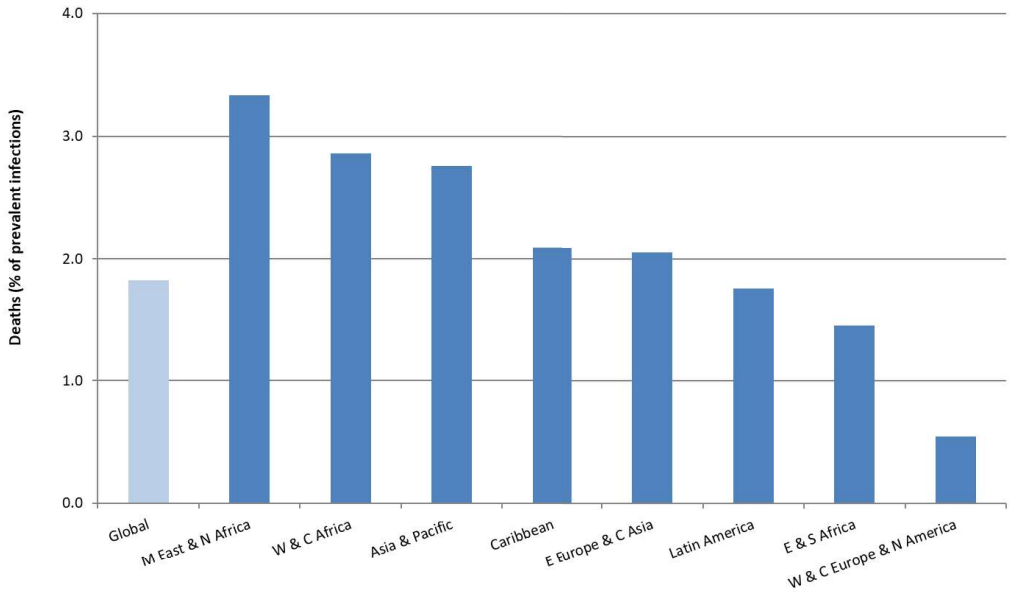
SI.1.6.1. Mortality and Morbidity

Access to effective treatment varies considerably, accounting for different rates of mortality by region. The number of people dying from AIDS-related causes began to decline in the mid-2000s because of scaled up ART and the steady decline in HIV incidence since the peak in 1997. Since its peak in 2004, AIDS-related deaths have reduced by more than 55% {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. In 2019, this decline continued, with evidence that the drop in the number of people dying from AIDS-related causes is accelerating in several countries. In 2019, 690,000 (95% CI: 500,000-970,000) people died from AIDS-related causes worldwide, representing a 39% decline since 2010 {UNAIDS AidsInfo 2020a}. AIDs-related mortality among men tends to be higher than women worldwide, which is likely reflective of women being more likely to test for HIV, receive treatment, and adhere to treatment compared to men {UNAIDS 2018}. The leading cause of death among those living with HIV continues to be tuberculosis, which accounts for around one in three AIDS-related deaths {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

The number of people dying from AIDS-related causes in Eastern and Southern Africa declined by 49% from 2010 to 2019, although the region still accounted for approximately 31% of all the people dying from AIDS in 2019{Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Declines in AIDS-related deaths between 2010 and 2019 also occurred in the Caribbean (37%), Western and Central Europe and North America (37%), Western and Central Africa (37%), Asia and Pacific (28%), Latin America (8%), and Middle East and North Africa (2%). Eastern Europe and Central Asia however, experienced a 24% increase in mortality from AIDS during the same time. Figure SI 2 provides regional variations in HIV related mortality (deaths as a percentage of prevalent HIV infections in 2019) {UNAIDS AidsInfo 2020a}.

Following the introduction of Highly Active Antiretroviral Therapy (HAART), mortality rates declined due to decreases in both non-AIDS and AIDS-related deaths, although the proportion of deaths associated with non-AIDS-related diseases has increased in patients on ART {Ingle 2014, Palella 2013, Weber 2013}. Common causes of non-AIDS-related deaths are non-AIDS-related malignancies, liver failure, non-AIDS-related infections, substance use-related, suicide, and myocardial infarction {Weber 2013}.

Figure SI 2. Regional Variation in HIV-Related Mortality



Source: {UNAIDS AidsInfo 2020a, UNAIDS AidsInfo 2020f}

SI.1.7. Concomitant Medication(s) in the Target Population

In HIV-1 infected patients, particularly those with low CD4 counts, concomitant medications which could be used to treat common comorbidities and coinfections of HIV infection include antibiotics, antifungals, antivirals, and chemotherapeutic agents.

SI.1.8. Important Co-morbidities

Prior to the success of ART for the treatment of HIV/AIDS, the most common co-morbidities were those traditionally defined as AIDS-related illnesses and correlated with CD4 cell count, such as Guillain-Barre Syndrome, Kaposi's sarcoma, and Non-Hodgkin's lymphoma {Hanson 1995}. As HIV patients on ART are living longer with viral suppression, the more prevalent co-morbidities are chronic health conditions in both resource-limited settings and wealthy regions {Deeks 2013b}, {Hirschhorn 2012}, {Balderson 2013}, {Hsue 2016} {Langebeek 2017}. Below is a list of important conditions that have evidence of higher risk among HIV patients and/or those accessing ART:

- Arthritis
- Bone disease (i.e., osteopenia, osteoporosis, and fracture)
- Cardiovascular disease (i.e., hypertension and hyperlipidemia)

- Chronic pain
- Endocrine disease, including diabetes
- Frailty
- Hepatitis
- Mental illness (i.e., depression and suicidal ideation)
- Neurocognitive disorders
- Other sexually transmitted diseases
- Pulmonary disease (i.e., Chronic obstructive pulmonary disease)
- Renal disease
- Some non-HIV-related malignancies (i.e., liver, cervical, anal, and Hodgkin's lymphoma)
- Tuberculosis

PART II: MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

No nonclinical studies of GEN have been conducted. Information on relevant safety findings for the components of GEN are presented in the tables within this section. No additional nonclinical studies are planned for GEN.

SII.1. Elvitegravir

Table SII. 1. Table of Key Safety Findings from Nonclinical Studies

Key Safety Findings from Nonclinical studies	Relevance to Human Usage
No clinically relevant adverse effects were observed in the safety pharmacology, general toxicity, genotoxicity, carcinogenicity, reproductive, juvenile toxicity, local tolerance, and immunotoxicity studies, or in special mechanistic studies to investigate potential quinolone related toxicity.	Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

SII.2. Cobicistat

Table SII. 2. Key Safety Findings from Nonclinical Studies

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
No clinically relevant adverse effects were observed in the genotoxicity, carcinogenicity, reproductive, juvenile toxicity, and local tolerance studies with COBI.	Nonclinical data reveal no special hazard for humans based on conventional studies of single-or repeat dose toxicity, genotoxicity, carcinogenicity and toxicity to reproduction and development.
COBI showed a potential to decrease left ventricular (LV) function and prolong the PR interval in the isolated rabbit heart at concentrations that are approximately 10-fold above the clinical exposures at the 150-mg dose.	*Safety in patients with cardiac conduction disorders is considered to be missing information for COBI.* In a thorough QT clinical study (GS-US-216-0107), COBI demonstrated a lack of prolongation effects on the QTcF interval in healthy adult subjects at therapeutic and supratherapeutic exposures. A small but statistically significant negative association between COBI plasma concentration and QTc interval, and a modest, dose-related increase in PR interval, were observed in the QT/QTc study, which are not considered to be clinically significant. Further, echocardiograms (ECHO) performed in healthy subjects in Study GS-US-216-0116 at baseline and after receiving 150 mg COBI for at least 15 days indicated no clinically significant change in LV function. No cardiac safety concerns were apparent in Phase 2 and 3 studies for COBI-containing product (Tybost, Stribild, Genvoya) with 150 mg dose of COBI

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
COBI is a potent mechanism-based inhibitor of human CYP3A with inactivation kinetics (k_{inact} 0.47 min^{-1}, K_I 1.1 µM), similar to those of RTV (AD-216-2028). COBI does not inhibit human CYP1A2, CYP2C9, or CYP2C19, is a very weak inhibitor of CYP2C8 (IC_{50} 30.1 µM), a weak inhibitor of CYP2D6 (IC_{50} 9.2 µM), and a modest inhibitor of CYP2B6 (IC_{50} 2.8 µM) (AD-216-2029 and AD-216-2070). COBI is a weak inhibitor of human hepatic microsomal UGT1A1 activity (IC_{50} 16.3 µM), being less potent than RTV (IC_{50} 4.7 µM). COBI treatment should thus not raise serum bilirubin concentrations due to inhibition of UGT1A1, a known effect of ATV, which is a considerably more potent inhibitor (IC_{50} 0.8 µM) (AD-216-2075).	COBI is a selective, mechanism-based CYP3A inhibitor and a CYP3A substrate. COBI will likely increase the plasma concentration of drugs metabolized by CYP3A, and coadministration of drugs that inhibit or induce CYP3A may alter the clearance of COBI. Coadministration of COBI with medicinal products with a narrow therapeutic index, which are highly dependent on CYP3A for their clearance and for which increased plasma concentrations result in serious and/or life-threatening reactions, is contraindicated. Coadministration of COBI with potent CYP3A inducers that may significantly decrease the plasma concentrations of COBI and EVG (which may result in loss of therapeutic effect and development of resistance to EVG) is also contraindicated. *Concurrent use of drugs whose coadministration with Genvoya is contraindicated is an important potential risk for the COBI and EVG components of Genvoya.*
COBI is a weak inhibitor of the efflux transporters P-glycoprotein (Pgp), multi-drug resistance protein-1 (MRP1), MRP2, MRP4, breast cancer resistance protein (BCRP), multidrug and toxin extrusion protein 2-K (MATE2-K), and of the renal uptake transporters OAT1, OAT3, organic cation transporter 2 (OCT2). COBI is a more potent inhibitor of the renal efflux transporters MATE1 and organic cation transporter novel, type 1 (OCTN1). OCT2 and MATE1 transporters appear to play a role in the active tubular secretion of creatinine by the kidney {Sato 2008, Tanihara 2007, Urakami 2004}. Inhibitory potencies for COBI were similar to those obtained with RTV, but RTV was a more potent inhibitor of OAT3 and a less potent inhibitor of OCT2.	In clinical studies, COBI has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting glomerular function. These changes are consistent with nonclinical findings of COBI inhibition of the renal transporters, MATE1 and OCT2.

SII.3. Emtricitabine

Table SII. 3. Key Safety Findings from Nonclinical Studies

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
Nonclinical data on FTC reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.	No safety concerns for humans are anticipated based on the non-clinical data for FTC

SII.4. Tenofovir Alafenamide

Table SII. 4. Key Safety Findings from Nonclinical Studies

Key Safety Findings from Nonclinical studies	Relevance to Human Usage
Safety pharmacology, genotoxicity, carcinogenic potential and reproductive toxicity[No specific concerns were identified in the safety pharmacology, genotoxicity and reproductive toxicity studies with TAF.	No safety concerns have been identified for humans based on nonclinical studies of safety pharmacology, genotoxicity, carcinogenic potential, and reproductive toxicity.
Renal toxicity The repeat-dose oral toxicity of TAF has been studied in mice, rats, dogs and monkeys. In chronic studies, kidneys (karyomegaly, tubular degeneration), and bone (atrophy of metaphyseal cancellous bone) were the primary target organs. Renal tubular karyomegaly was observed in rats and dogs orally administered TAF. Focal areas of minimal renal cortical tubular basophilia and associated minimal nuclear karyomegaly were present in rats administered 400 mg/kg/day for 4 weeks and 100 mg/kg/day for 26 weeks. Renal tubular karyomegaly and/or basophilia were observed in dogs administered 3 and 10 mg/kg/day for 4 weeks and dogs administered 6 or 18/12 mg/kg/day for at least 13 weeks. Renal cortical tubular degeneration/regeneration findings were limited to animals administered 6 or 18/12 mg/kg/day for at least 13 weeks in the 39-week dog toxicity study. Similar findings of renal cortical tubular degeneration/regeneration and karyomegaly were present in dogs administered at either 6 or 18/12 mg/kg/day for 39 weeks. These changes were minimal to slight in affected males and females at 6 mg/kg/day. In high-dose males (18/12 mg/kg/day) the severity ranged from mild to moderate. Similar lesions (karyomegaly and tubular degeneration) but of only minimal severity were also present in 2 males administered 2 mg/kg/day of TAF for 39 weeks. After a 13-week recovery period, treatment-related histology changes were still observed in the kidney but were of reduced incidence and severity.	The estimated safety margin for use of 25 mg/day TAF in humans based TFV exposure at the no observed adverse effect level (NOAEL) in the animal studies is 12 for rats, 4 for dogs and > 18 for monkeys when considering renal toxicity.
Loss of bone mineral density (BMD) Atrophy of metaphyseal cancellous bone was observed in rats administered TAF at 100 mg/kg/day for 26 weeks. TAF also increased biochemical markers of bone turnover and decrease serum 1,25-dihydroxy- and 25-hydroxyvitamin D_3 in rats (≥ 25 mg/kg/day) and dogs (≥ 37.5 mg/kg/day for 6 days). In a 39-week dog study, BMD changes at 18/12 mg/kg/day were most likely due to body weight loss, but these changes were accompanied by a slight but significant decrease in serum 1,25-dihydroxyvitamin D_3 in males only and a significant increase in 25-hydroxyvitamin D_3 in females only.	The estimated safety margin for use of 25 mg/day TAF in humans based on TFV exposure at the NOAEL in the animal studies is 12 for rats, 4 for dogs and > 18 for monkeys when considering BMD loss.
Nasal inflammation in mice TAF administered by oral gavage for up to 13 weeks to mice at ≥ 10 mg/kg/day resulted in adverse degenerative (olfactory) and acute inflammatory (infiltrate neutrophil) changes in the nasal mucosa (TX-120-2007). These changes were not observed in rats, dogs or monkeys for longer durations of administration.	Because these changes were not observed in rats, dogs or monkeys for longer durations of administration, the risk of nasal inflammation in humans is considered to be very low.

Key Safety Findings from Nonclinical studies	Relevance to Human Usage
PR and QT prolongation The IC_{50} for the inhibitory effect of TAF on hERG potassium current was estimated to be greater than 10 μM, far above human exposure (PC-120-2005). In the 39-week dog study (TOX-120-002), there was some evidence at 6 and 18/12 mg/kg/day for an effect to slightly prolong PR intervals (approximately 13% to 24%). TAF appeared to reversibly reduce heart rate with an associated mild QT interval prolongation in the high-dose group only. These changes were associated with decreases in serum triiodothyronine {Kienle 1994, Tribulova 2010}. No PR prolongation or any change in ECG results occurred in the safety pharmacology study in dogs that evaluated a TAF dose up to 100 mg/kg (D2000006).	No PR or QT prolongation or any change in ECG results occurred in a thorough QT study of TAF (GS-US-120-0107).
Histiocyte infiltrate in dogs At 18/12 mg/kg/day in dogs, the highest dose tested, a minimal infiltration of histiocytes was present in some organs (eye [choroid plexus, ciliary body], lung, and spleen) in some animals. In-life ophthalmologic examinations of all dogs were normal. The histiocytic infiltration observed in multiple organs was most likely an indirect drug effect due to general debilitation and was not observed in other repeat dose toxicity studies. There were no drug-related effects on ophthalmic exams or microscopic exams of ocular tissue observed in repeat dose toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks), nonhuman primates (4 weeks) or in the 4-week dog toxicology study. The posterior uveitis in dogs administered the highest dose of TAF occurred at 4- and 17-fold higher exposure to TAF and TFV, respectively, than that observed in human subjects administered a 25-mg dose of TAF and does not correlate with the tissue distribution where TAF was found to poorly penetrate across the blood brain and blood retinal barrier in dogs. Because TAF has poor penetration across the blood brain and blood retinal barrier in dogs it is unlikely that TAF directly caused the observed histiocytic infiltration in the posterior uvea.	Based on the evidence from tissue distribution and toxicology studies, the risk of posterior uveitis in humans is considered to be very low.

SII.5. Conclusions on Nonclinical Data

Table SII. 5. Safety Concerns from Nonclinical Data

	Safety Concern	Attributable Component
Important Identified Risks	None	NA
Important Potential Risks	Concurrent use of drugs whose coadministration with Genvoya is contraindicated	COBI, EVG
Missing information	Safety in patients with cardiac conduction disorders	COBI

PART II: MODULE SIII: CLINICAL TRIAL EXPOSURE

SIII.1. Clinical Trial Exposure

The tables in this section present exposure to GEN up to 04 November 2020 in subjects with HIV-1 infection from the following studies:

- Completed studies: GS-US-236-0128, GS-US-292-0102, GS-US-292-0104, GS-US-292-0109, GS-US-292-0111, GS-US-292-0112, GS-US-292-0117, GS-US-292-0119, GS-US-292-1249, GS-US-292-1515, GS-US-292-1823, GS-US-2921-824, GS-US-292-1825, GS-US-292-1826, GS-US-366-1992, and GS-US-380-1961

- Ongoing Study: GS-US-292-0106

Table SIII. 1. Duration of Exposure in Subjects with HIV-1 Infection

Duration Of Exposure	Patients	Person-Years
≥ 1 day	4289	9101
> 30 days	4258	9100
> 90 days	4142	9078
> 180 days	3906	8977
> 1 year	2965	8185
> 2 years	2405	7319
> 3 years	1025	3743
> 4 years	157	789
> 5 years	60	363
> 6 years	30	200

Table SIII. 2. Exposure by Age Group and Gender in Subjects with HIV-1 Infection

	Patients		Person-Years	
Age Group	**Male**	**Female**	**Male**	**Female**
< 12 years	32	47	89	131
12 - 17 years	40	60	139	208
18 - 30 years	717	122	1851	259
31 - 40 years	837	230	1837	419
41 – 50 years	873	248	1853	430
51 – 65 years	741	187	1320	311
66 – 75 years	119	23	196	40
> 75 years	12	1	17	0

Table SIII. 3. Exposure by Ethnic Origin in Subjects with HIV-1 Infection

Ethnic origin	**Patients**	**Person-Years**
White	2503	5191
Black or African American	1166	2440
Asian	350	834
American Indian or Alaska Native	15	37
Native Hawaiian or Other Pacific Islander	19	43
Other	220	534
Not provided	16	23

PART II: MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Program

Table SIV. 1. Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Considered to be Missing Information
Pregnant females and females who are breastfeeding	Limited patient exposure to GEN at the start of the Phase 3 development program. It is not known whether EVG, COBI or TAF are excreted in human milk. Emtricitabine and TFV have been shown to be excreted in human milk after administration of Truvada (TVD; FTC/TDF).	Yes
Hepatitis C antibody positive patients	Limited information on the use in this patient population.	No Rationale: No new safety concerns for GEN are anticipated in hepatitis C antibody positive patients. No new safety concerns were identified in Study GS-US-366-1992 in 74 HIV/HCV coinfected subjects exposed to GEN.
Patients with severe renal impairment	Limited information on the use in this patient population.	No Rationale: No safety concerns for GEN are anticipated in patients with severe renal impairment.
Medicinal products excluded from concurrent use in studies of GEN: alfuzosin, dihydroergotamine, ergotamine, ergometrine, oral administered midazolam, triazolam, cisapride, pimozide, sildenafil for the treatment of pulmonary arterial hypertension, simvastatin and lovastatin. St. John's wort (*Hypericum perforatum*), rifampicin, carbamazepine, phenobarbital, phenytoin	The exposure to medicinal products with a narrow therapeutic index that are highly dependent on CYP3A for their clearance may be increased when coadministered with COBI, which may result in serious and/or life-threatening reactions. Medications that are potent inducers of CYP3A may decrease plasma concentrations of COBI and EVG, which may lead to loss of therapeutic effect and possible development of resistance.	No Rationale: Coadministration is contraindicated in the GEN SmPC. Concurrent use of drugs whose coadministration with GEN is contraindicated is an important potential risk for GEN.
Patients with clinically significant ECG abnormalities or with an implanted defibrillator or pacemaker.	A modest, dose-related increase in PR interval has been observed with COBI, which is not considered to be clinically relevant	Yes

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

Table SIV. 2. Ability of the Clinical Trial Development Program to Detect Adverse Drug Reactions (ADRs)

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are rare	4289 HIV-1 infected patients have been exposed to GEN in the GEN clinical trial program.	The clinical trial population is large enough to detect rare ADRs. ADRs with a frequency greater than 1 in 1430 could potentially be detected if there were no background incidence.
Due to prolonged exposure	2965 HIV-1 infected subjects have been exposed to GEN for more than 1 year and 2405 HIV-1 infected subjects have been exposed to GEN for more than 2 years in the GEN clinical trial program.	No ADRs specifically associated with prolonged exposure to GEN have been identified in the GEN clinical trial program.
Due to cumulative effects	2965 HIV-1 infected subjects have been exposed to GEN for more than 1 year and 2405 HIV-1 infected subjects have been exposed to GEN for more than 2 years in the GEN clinical trial program.	No cumulative effects to GEN have been identified in the GEN clinical trial program.
Which have a long latency	2965 HIV-1 infected subjects have been exposed to Genvoya for more than 1 year and 2405 HIV-1 infected subjects have been exposed to GEN for more than 2 years in the GEN clinical trial program.	No ADRs to GEN with a long latency have been identified in the GEN clinical trial program.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table SIV. 3. Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of special population	Exposure	Considered to be Missing Information
Long-term safety information in children	As of 04 November 2020, 79 subjects aged < 12 years and 100 subjects aged 12 to 17 years were exposed to GEN in clinical studies.	No Rationale: No new safety concerns for GEN were identified in children in Study GS-US-292-0106.
Pregnant women	Pregnant and breastfeeding women were excluded from enrolling in clinical studies. As of 04 November 2020, 30 pregnant subjects were exposed to GEN in clinical studies (Studies GS-US-236-0128, GS-US-292-0102, GS-US-292-0104, GS-US-292-0106, GS-US-292-0109, GS-US-292-1515, GS-US-380-1961).	Yes
Breastfeeding women		

Type of special population	Exposure	Considered to be Missing Information
Elderly	As of 04 November 2020, 155 subjects over 65 years old were exposed to GEN in clinical studies.	No Rationale: No safety concerns for GEN were identified from data in elderly subjects.
Patients with severe renal impairment	Not included in pivotal Phase 3 clinical studies.	No Rationale: No safety concerns for GEN are anticipated in patients with severe renal impairment. No clinically relevant differences in EVG, COBI, TAF, or TFV PK were observed between healthy subjects and subjects with severe renal impairment (Studies GS-US-216-0124 and GS-US-120-0108). Mean systemic FTC exposure was higher in patients with severe renal impairment than in subjects with normal renal function; however, no safety concerns are anticipated based on the safety profile of FTC (Study FTC-107). GEN was well tolerated in patients with mild to moderate renal impairment in Study GS-US-292-0112, with a safety profile similar to that in patients with normal renal function.
Patient with severe hepatic impairment	Not known. Patients had to have hepatic transaminases (AST and ALT) ≤ 5 × upper limit of normal (ULN) and total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin to be enrolled.	No Rationale: No new safety concerns for GEN are anticipated. The PK of FTC have not been studied in subjects with hepatic impairment, however, as FTC is not significantly metabolized by liver enzymes the impact of hepatic impairment should be limited. Clinically relevant changes in the PK of TAF or TFV were not observed in patients with severe hepatic impairment (Study GS-US-320-1615). EVG and COBI have not been studied in subjects with severe hepatic impairment. Safety data for patients with severe hepatic impairment has been monitored through routine PV activities, including PSURs, since marketing approval of EVG and COBI-containing products and no safety concern has been identified.
Coinfection with Hepatitis C	Not included in pivotal Phase 3 clinical studies. Seventy-four HIV/HCV coinfected subjects received GEN in Study GS-US-366-1992.	No Rationale: No new safety concerns for GEN were identified in Study GS-US-366-1992.
Patients with Cardiac Conduction Disorders	Subjects with abnormal ECG results at screening that were determined by the investigator to be clinically significant were not included in the clinical development program. In studies GS-US-292-0102, GS-US-292-0104, GS-US-292-0111, 304 subjects had abnormal ECG results at screening that were determined by the investigator to be not clinically significant.	Yes
Sub-Populations Carrying Known and Relevant Polymorphisms	Not known	No Rationale: A PK study of EVG in subjects with decreased UGT1A1 activity (GS-US-183-1004) indicated that UGT1A1 activity does not influence overall EVG clearance, obviating any utility in screening for UGT1A1 polymorphisms. Based on the findings of this study, no dose modification of EVG is necessary in patients with UGT1A1 polymorphisms receiving GEN.

PART II: MODULE SV: POST-AUTHORIZATION EXPERIENCE

SV.1. Post-Authorization Exposure

SV.1.1. Method Used to Calculate Exposure

Patient exposure to marketed GEN has been estimated from both sales data and from prescription data and is reported in applicable PSURs/PBRERs. The methodology used to calculate patient exposure from these 2 sources is described below:

Sales Data

The number of bottles sold during the reporting period was multiplied by 30 to provide the number of tablets sold. As GEN is taken as a once daily dose, the total number of tablets was divided by 365.25 to provide patient-years of treatment. It should be noted that the use of sales data for patient exposure calculations will generally overestimate patient exposure due to the accumulation of drug stocks at pharmacies/distributors.

Prescription Data

Estimates of the demographics of HIV infected patients exposed to GEN in the EU (in five EU countries: UK, France, Germany, Italy and Spain) was obtained from data from the following sources:

- IVQIA/Groupement pour l'Élaboration et la Réalisation de Statistiques (GERS): IQVIA data in the EU provides details of the number of bottles prescribed (no details are provided on whether a prescription is a repeat or an initial prescription). The data is obtained through a comprehensive panel of pharmacies and wholesalers. GERS data is based on a syndicate of manufacturers and wholesalers who provide their transactions and is available in France only; GERS data is combined with IQVIA data.

- Ipsos Monitor: The Ipsos Healthcare HIV EU Therapy Monitor study is a syndicated, annual diary study involving HIV treating physicians and data has been obtained from April – June 2020. A total of 207 HIV treating physicians are involved across the EU5 and the sample is regionally representative of the prevalence of HIV infection in each country. The physicians are screened to ensure they see at least 15 HIV patients per week and manage the care of at least 50 HIV patients. Each physician completes patient record forms for the next 12 patients they see during the fieldwork period. These patients could be initiating, switching or maintaining, as well as patients who have never been treated or those who are not currently receiving ARV therapy. In the EU5 (20Q2), this dataset consists of 1677 patient records.

SV.1.2. Exposure

SV.1.2.1. Exposure Based on Sales Data

Based on sales data cumulative global patient exposure to GEN since first marketing approval in United States on 05 November 2015 to 30 June 2025 is estimated to be 1,675,115 patient-years, including 377,781patient-years in the EU.

SV.1.2.2. Exposure Based on Prescription Data

Based on 2022 prescription data from UK, France, Germany, Italy and Spain, most patients exposed to GEN were male and aged > 35 years.

PART II: MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

There are no data to suggest that there is potential for GEN to be misused for illegal purposes.

PART II: MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP submission

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an updated RMP

No safety concerns have been identified or reclassified since the submission of the last RMP.

Risks previously classified as important, and missing information, removed from the list of safety concerns, along with the reasons for their removal, are presented in Table SVII.1.

Table SVII.1. Reason for Removing an Important Identified risk, Potential risk or Missing Information From the List of Safety Concerns in the RMP

Safety Concern Removed	Reason for Removal from the List of Safety Concerns
Identified Risks	
Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness	Risk is to be removed from the list of safety concerns and will continue to be monitored by routine PV activities. There are no outstanding additional risk minimization measures or additional PV activities for this risk. No new safety concerns were identified for GEN from long-term data from Studies GS-US-292-0104 and GS-US-292-0111. This risk is considered fully characterized and will continue to be monitored by routine PV activities.
Potential Risk	
Concurrent use of drugs whose coadministration with Genvoya is contraindicated	Risk is to be removed from the list of safety concerns and will continue to be monitored by routine PV activities. There are no outstanding additional risk minimization measures or additional PV activities for this risk. No new safety concerns were identified for GEN from concurrent use of drugs whose administration with GEN is contraindicated. This risk is considered fully characterized and will continue to be monitored by routine PV activities.
Missing information	
Safety in patients with cardiac conduction disorders	Safety data for patients with cardiac conduction disorders has been monitored through routine PV activities, including PSURs, and no safety concern has been identified. There are no outstanding additional pharmacovigilance activities.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

There are no important identified risks for GEN or its components.

SVII.3.1.2. Important Potential Risks

There are no important potential risks for GEN or its components.

SVII.3.2. Presentation of the Missing Information

Table SVII. 2. Missing Information

Missing Information:	Evidence source
Long-term safety information in children between the ages of ≥ 2 and < 6 years (GEN)	Population in need of further characterization: Limited information is available on long-term use of GEN in children between the ages of ≥ 2 and < 6 years.
Safety in pregnancy and lactation (EVG, COBI, FTC, TAF)	Population in need of further characterization: Limited information is available on use in pregnant women and breastfeeding women. Data from the Antiretroviral Pregnancy Registry (APR) suggest no increase in fetal defects associated with the individual components of GEN during pregnancy, although data for EVG and COBI is limited. Emtricitabine has been shown to pass into human breast milk. It is not known whether TAF, EVG and COBI pass into human breast milk.

PART II: MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Table SVIII. 1. Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	Long-term safety information in children between the ages of ≥ 2 and < 6 years (GEN)
	Safety in pregnancy and lactation (EVG, COBI, FTC, TAF)

PART III: PHARMACOVIGILANCE PLAN

III.1. Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond ADRs Reporting and Signal Detection

Specific Adverse Reaction Follow-up Questionnaires

There are no specific adverse reaction follow-up questionnaires for any of the safety concerns.

Other Forms of Routine Pharmacovigilance Activities

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

III.2. Additional Pharmacovigilance activities

Table Part III. 1. Ongoing and Planned Additional Pharmacovigilance Activities

Study Short Name and Title	Rationale and Study Objectives	Study design and Study Populations	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Antiretroviral Pregnancy Registry (APR) Non-interventional study	*Safety concern addressed:* Safety in pregnancy (missing information) *Objectives* : To collect information on the risk of birth defects in patients exposed to ARVs, including GEN, during pregnancy	Prospective, observational, exposure registration, and follow-up study. Pregnant women exposed to antiretroviral drugs.	Submission of interim reports	In the GEN PSUR (data-lock point [DLP] and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)

III.3. Summary Table of additional Pharmacovigilance Activities

Table Part III. 2. Ongoing and Planned Additional Pharmacovigilance Activities

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

PART IV:
PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing post-authorization efficacy studies for GEN.

PART V:
RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1. Routine risk minimization measures

The routine risk minimization measures for GEN in the EU comprise of the SmPC, the package leaflet (PL) and the legal status of the product. Genvoya is subject to restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HIV infection (SmPC Section 4.2).

The routine risk minimization recommendations provided by the SmPC and PL are described further by safety concern in Table Part V. 1.. The legal status can be considered a general measure applicable to all of the individual safety concerns.

Table Part V. 1. Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Important Identified Risks	
None	
Important Potential Risks	
None	
Missing Information	
Long-term safety information in children between the ages of ≥ 2 and < 6 years (GEN)	Routine risk communication: SmPC Sections 4.4 and 4.8
Safety in pregnancy and lactation (EVG, COBI, FTC, TDF)	Routine risk communication: SmPC Section 4.6

V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V Section V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary risk minimization measures

Table Part V. 2. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety concern	Routine risk minimization activities	Pharmacovigilance Activities
Important Identified Risks		
None		
Important Potential Risks		
None		
Missing Information		
Long-term safety information in children between the ages of ≥ 2 and < 6 years (GEN)	Routine risk communication: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Safety in pregnancy and lactation (EVG, COBI, FTC, TDF)	Routine risk communication: SmPC Section 4.6 PL Section 2	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

I. SUMMARY OF RISK MANAGEMENT PLAN FOR GENVOYA (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

This is a summary of the risk management plan (RMP) for Genvoya. The RMP details important risks of Genvoya, how these risks can be minimized, and how more information will be obtained about Genvoya risks and uncertainties (missing information).

The Genvoya summary of product characteristics (SmPC) and package leaflet (PL) give essential information to healthcare professionals and patients on how Genvoya should be used.

This summary of the RMP for Genvoya should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Genvoya RMP.

II. The Medicine and What is it Used for

Genvoya is authorized for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and pediatric patients aged 2 years and above and weighing at least 14 kg (see SmPC for the full indication). It contains elvitegravir (EVG), cobicistat (COBI), FTC and tenofovir alafenamide (TAF) as the active substances and it is given orally.

Further information about the evaluation of Genvoya's benefits can be found in Genvoya's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage*:*
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004042/WC500197864.pdf.

III. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Genvoya, together with measures to minimize such risks and the proposed studies for learning more about Genvoya's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Genvoya is not yet available, it is listed under 'missing information' below.

III.A. List of important risks and missing information

Important risks of Genvoya are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Genvoya. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table Part VI. 1. List of Important Risks and Missing Information

Important Identified Risks	None
Important Potential Risks	None
Missing Information	Long-term safety information in children between the ages of ≥ 2 and < 6 years (GEN)
	Safety in pregnancy and lactation (EVG, COBI, FTC, TDF)

III.B. Summary of Important Risks

There are no important identified or potential risks for Genvoya.

Table Part VI. 2. Summary of Missing Information

Missing Information	**Long-term safety information in children between the ages of ≥ 2 and < 6 years (GEN)**
Risk Minimization Measure(s)	Routine risk communication: SmPC Sections 4.4 and 4.8
Additional Pharmacovigilance activities	None

Missing Information	Safety in pregnancy and lactation (EVG, COBI, FTC, TDF)
Risk Minimization Measure(s)	Routine risk communication: SmPC Section 4.6 PL Section 2
Additional Pharmacovigilance activities	Antiretroviral Pregnancy Registry

III.C. Post-authorization Development Plan

III.C.1. Studies which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Genvoya.

III.C.2. Other Studies in Post-Authorization Development Plan

Table Part VI. 3. Other Studies in Post-Authorization Development Plan

Short Study Name	Purpose of the Study
Antiretroviral Pregnancy Registry (APR)	To collect information on the risk of birth defects in patients exposed to antiretroviral drugs (ARVs), including GEN, during pregnancy.

PART VII: ANNEXES

Table of Contents

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