EU Risk Management Plan for Stribild® (Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Disoproxil Fumarate)

EU Risk Management Plan for Stribild

RMP version to be assessed as part of this application:

Version number:	Data lock point for this RMP:	Date of final sign off:
16.0	08 May 2025	Refer to ELECTRONIC SIGNATURES

Rationale for submitting an updated RMP:

The Risk Management Plan (RMP) has been updated to remove:

- Targeted questionnaires corresponding to the previously removed important identified bone and renal risks.

Summary of significant changes in this RMP:

Part	Module/Annex	Significant changes to RMP
Part II Safety Specification	Section Part II: Module SI: Epidemiology of the indication and target populations(s)	None
	Section Part II: Module SII: Non-clinical part of the safety specification	None
	Section Part II: Module SIII: Clinical study exposure	None
	Section Part II: Module SIV: Populations not studied in clinical studies	None
	Section Part II: Module SV: Post-authorization experience	Information updated with Postmarketing exposure data.
	Section Part II: Module SVI: Additional EU requirements for the safety specification	None
	Section Part II: Module SVII: Identified and potential risks	None
	Section Part II: Module SVIII: Summary of the safety concerns	None
Part III Pharmacovigilance Plan		Revised to remove the targeted questionnaires on identified bone and renal risks.
Part IV Plan for post-authorization efficacy studies		None
Part V Risk Minimization Measures		None
Part VI Summary of RMP		None
Part VII Annexes		Updated Annex 4 to remove the targeted questionnaires on identified bone and renal risks

Other RMP versions under evaluation:

No other RMP versions are under evaluation.

Details of the currently approved RMP:

Version number:	Approved with procedure	Date of approval (opinion date)
15.0	EMEA/H/C/002574/WS2320/0120	12 January 2023

QPPV name:	Rainer Heissing
QPPV signature:	Refer to ELECTRONIC SIGNATURES

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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
aRMM	additional risk minimization measures
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical (classification system)
AUC	area under the concentration versus time curve
BCRP	breast cancer resistance protein
BMD	bone mineral density
BUN	blood urea nitrogen
CD4	cluster determinant 4
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CL_{cr}	creatinine clearance
COBI	Cobicistat
CSR	clinical study report
CYP	cytochrome P450 enzyme
dATP	deoxyadenosine triphosphate
DHHS	Department of Health and Human Services
DLP	data-lock point
DNA	deoxyribonucleic acid
DRV	darunavir
DTG	dolutegravir
EACS	European AIDS Clinical Society
ECDC	European Center for Disease Prevention and Control
ECG	electrocardiogram
ECHO	echocardiogram
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EVG	Elvitegravir
FTC; F	emtricitabine (Emtriva®)
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
PDE	phosphodiesterase
Pgp	P-glycoprotein
PI	protease inhibitor
PIL	Patient Information Leaflet
PL	package leaflet
PLWH	people living with HIV
PK	pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
PRT	proximal renal tubulopathy
PSUR	periodic safety update report
QPPV	Qualified Person for Pharmacovigilance
RAL	raltegravir
RMP	risk management plan
RPV	rilpivirine
RSI	Request for Supplementary Information
RTV	ritonavir
SmPC	Summary of Product Characteristics
STB	Stribild
STR	single tablet regimen
TAF	tenofovir alafenamide
TFV	tenofovir
TDF	tenofovir disoproxil fumarate
TVD	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)

UGT	uridine glucuronosyltransferase
ULN	upper limit of normal
UNAIDs	Joint United Nations Programme on HIV and AIDS
UNODC	United Nations Office on Drugs and Crime

PART I: PRODUCT OVERVIEW

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate
Pharmaco-therapeutic group(s) (ATC Code)	Antivirals for the treatment of human immunodeficiency virus (HIV) infections, combinations (J05AR09)
Marketing Authorization Holder	Gilead Sciences Ireland UC.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Stribild (STB)
Marketing authorization procedure	Centralized
Brief description of the product	*Chemical class* Elvitegravir: integrase strand-transfer inhibitor (INSTI) Cobicistat: selective mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily (primarily CYP3A4 and CYP3A5). Emtricitabine: nucleoside reverse transcriptase inhibitor (NRTI) Tenofovir disoproxil fumarate: nucleotide reverse transcriptase inhibitor (NtRTI) *Summary of mode of action* Elvitegravir (EVG) 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 (COBI) 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 (FTC) 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. Tenofovir disoproxil fumarate (TDF), an oral prodrug of tenofovir, is a NtRTI. Following absorption, TDF is rapidly converted to tenofovir, which is metabolized intracellularly to the active metabolite, tenofovir diphosphate. Tenofovir diphosphate inhibits viral polymerases by direct binding competition with the natural deoxyribonucleotide substrate (deoxyadenosine triphosphate, dATP) and, after incorporation into DNA, by DNA chain termination. Important information about its composition: None.
Hyperlink to the Product Information	Stribild Summary of Product Characteristics (SmPC)

Indication(s) in the EEA	Current: Treatment of HIV-1 infection in adults aged 18 years and over who are antiretroviral treatment-naive or are infected with HIV-1 without known mutations associated with resistance to any of the 3 antiretroviral agents in STB. Treatment of HIV-1 infected adolescents aged 12 to < 18 years weighing ≥ 35 kg who are infected with HIV-1 without known mutations associated with resistance to any of the 3 antiretroviral agents in STB and who have experienced toxicities which preclude the use of other regimens that do not contain TDF. Proposed: Not applicable.
Dosage in the EEA	Current: One tablet once daily with food Proposed: Not applicable
Pharmaceutical form(s) and strengths	Film-coated tablet containing 150 mg EVG, 150 mg COBI, 200 mg FTC and 300 mg TDF.
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 Infection

SI.1.1. 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), resulting in a 23% decline since 2010 (Table SI.1) {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Among adults (15 years and older), there was a 17% decline 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]) declined by 52% during the same time (2010 to 2019) {UNAIDS AidsInfo 2020c}.

However, incidence rates vary considerably and different trends over time exist by region and within 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%), Western and Central Europe and North America (15%), and Asia and the Pacific (12%). 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 prevention and 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 preventing infection and ART access. Disparate groups within these and 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.1.2. 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 {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017b, 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 region's most heavily affected are Eastern Europe and Central Asia and Latin America and the Caribbean where 0.5-1.1% of adults were living with HIV in 2019 {UNAIDS AidsInfo 2020d}. The Eastern Europe and Central Asia region is the only region where HIV prevalence remains on the rise. The number of people living with HIV in this region has more than tripled since 2000 and reached an estimated 1.7 million in 2019 (95% CI: 1.4-1.9 million), resulting largely from a surge of infections among IDUs 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

	Prevalent Cases (n; 95% CI)		Incident 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)
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}

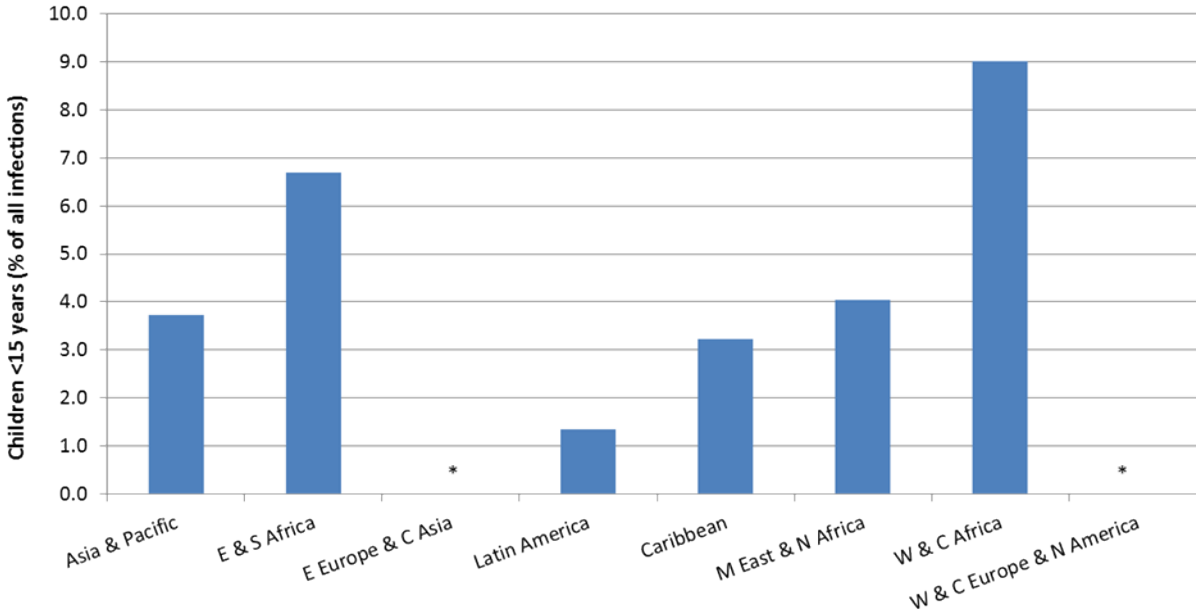
SI.1.3. Demographics of the Population in the Authorized Indication

SI.1.3.1. HIV Infection in Children

Worldwide, 1.8 million (95% CI: 1.3-2.2 million)children (<15 years) 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%) {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018c}. Estimates of prevalence among children were unavailable for 2019 in Western and Central Europe and North America and Eastern Europe and Central Asia (Figure SI.1).

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 antiretroviral therapy (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 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.1.3.2. 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 {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018b, UNAIDS AidsInfo 2020e, UNAIDS AidsInfo 2020g}. 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.1.3.3. 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}C. 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) 2017a, 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.1.4. Main Existing Treatment Options

For ART-naïve HIV-1 infected patients, current treatment guidelines in the EU favour initial therapy with an unboosted integrase strand transfer inhibitor (INSTI) (dolutegravir [DTG] or bictegravir [BIC]) as the 3rd agent; recommended regimens consist of 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) plus an INSTI (preferred regimen), 2 NRTIs plus either an non-nucleoside reverse transcriptase inhibitor (NNRTI) or a boosted protease inhibitor (PI) or 1 NRTI plus an INSTI. Treatment guidelines list emtricitabine/tenofovir alafenamide in combination with an INSTI (such as DTG, BIC, or raltegravir [RAL]), rilpivirine (RPV), ritonavir (RTV)- or cobicistat (COBI)-boosted darunavir (DRV) as one of the recommended regimens for initial therapy {European AIDS Clinical Society (EACS) 2020}.

In the current US treatment guideline, the following are recommended regimens for ART-naive patients {Panel on Antiretroviral Guidelines for Adults and Adolescents 2019}:

- INSTI-Based Regimens:
  - BIC/tenofovir alafenamide (TAF)/emtricitabine (FTC)
  - DTG /abacavir/lamivudine—only for patients who are HLA-B*5701 negative
  - DTG plus tenofovir disoproxil fumarate (TDF)/FTC or TAF/FTC
  - RAL plus TDF/FTC or TAF/FTC
  - DTG plus lamivudine

While current combination antiretroviral (ARV) therapy for the treatment of HIV-1 infection is efficacious and well tolerated, these agents need to be taken every day and require near-perfect adherence to minimize the emergence of drug-resistant variants. As such, there remains a significant medical need for ARVs that can be administered less frequently (ie, long-acting drug products), thereby providing an alternative treatment option for people living with HIV (PLWH). Currently cabotegravir/rilpivirine is the only long-acting ARV regimen approved for the treatment of HIV-1 infection; cabotegravir/rilpivirine is currently only approved in Canada and the United States.

SI.1.5. 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 {Deeks 2013a}.

SI.1.5.1. Mortality and Morbidity

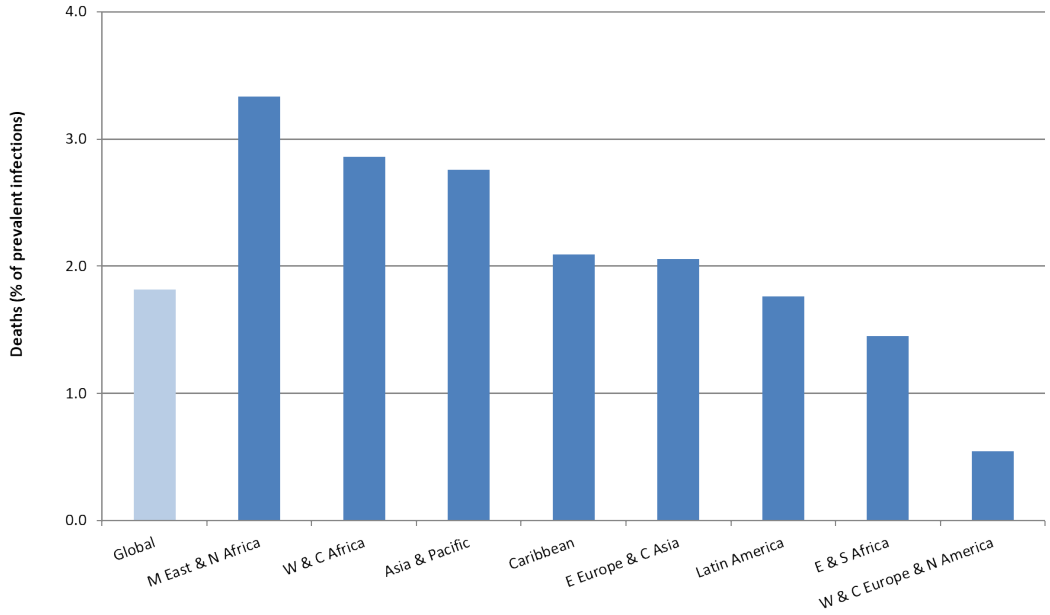
Access to effective treatment varies considerably, accounting for different rates of mortality by region. The number of people dying from AIDS-related causes began to decline in the mid-2000s because of scaled up ART and the steady decline in HIV incidence since the peak in 1997. Since its peak in 2004, 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 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%), Asia and Pacific (28%), Latin America (18%), 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) {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018a}{The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018a}{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: {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018a}

SI.1.6. Important Co-morbidities and Co-infections

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}. 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 suicide 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 additional non-clinical studies are considered warranted for STB or any of its components.

SII.1. Stribild

Table SII.1. Key Safety Findings from Non-Clinical Studies (Stribild)

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Use
The potential effect of STB components on the cytotoxicity of tenofovir (TFV) was investigated in an in vitro model consisting of human embryonic kidney 293T cells co-expressing renal transporters organic anion transporter protein-1 (OAT1) and multi-drug resistance protein-4 (MRP4) that are known to mediate TFV active renal secretion (PC-236-2013). COBI alone or in combination with FTC and EVG at concentrations corresponding to their respective peak plasma levels in treated HIV-infected patients did not affect the cytotoxicity of TFV in this in vitro system.	These data suggest that the COBI, EVG and FTC components of STB are not likely to directly affect the toxicity potential of TFV in renal cells and tissues expressing the relevant renal transporters.

SII.2. Elvitegravir

Table SII.2. Key Safety Findings from Non-Clinical Studies (Elvitegravir)

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Use
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.	Non-clinical 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.
Elvitegravir is largely eliminated by oxidative metabolism by CYP3A (the major route) and by glucuronidation (minor route) by uridine diphosphate glucuronosyltransferase (UGT) 1A1 and 1A3. When administered with a CYP3A inhibitor, such as COBI, oxidative metabolism is blocked and the resulting bioavailability and half-life of EVG are compatible with once-daily dosing. Elvitegravir was demonstrated to be a weak inhibitor of human hepatic microsomal UGT1A1 (concentration required to produce 50% inhibition [IC_{50}] 18.4 µmol/L), a weak inhibitor of human UGT1A3 (IC_{50} 14.0 µmol/L), and not an inhibitor of human hepatic microsomal UGT2B7 (IC_{50} > 250 µmol/L) (Studies AD-183-2036, AD-183-2037, AD-183-2038, respectively).	No adverse pharmacokinetic interactions that would negatively affect safety or pharmacological efficacy of EVG have been observed in nonclinical studies. EVG should not cause any clinically significant pharmacokinetic drug interactions via inhibition of UGT1A1, UGT1A3 or UGT2B7 at therapeutic concentrations, since the unbound mean C_{max} of EVG (0.03 µmol/L) is substantially below the observed IC_{50} values (≥14.0 µmol/L). Medicinal products that induce CYP3A activity would be expected to increase the clearance of EVG and COBI, which may result in decreased plasma concentration of EVG and lead to loss of therapeutic effect and possible resistance to EVG. Since STB contains the CYP3A inhibitor, COBI, the overall effect cannot be predicted.

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Use
	The coadministration of STB with strong CYP3A inducers is contraindicated. *Concurrent use of drugs whose coadministration with STB is contraindicated is an important identified risk for the EVG and COBI components of STB.*

SII.3. Cobicistat

Table SII.3. Key Safety Findings from Nonclinical Studies (Cobicistat)

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Use
No clinically relevant adverse effects were observed in the genotoxicity, carcinogenicity, reproductive, juvenile toxicity, and local tolerance studies with COBI.	Non-clinical 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 (GS-US-216-0105, GS-US-216-0114 and GS-US-216-0130) or STB (GS-US-236-0102, GS-US-236-0103 and GS-US-236-0104) with 150 mg dose of COBI.
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 ritonavir (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	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 the

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Use
considerably more potent inhibitor (IC_{50} 0.8 μM) (AD-216-2075).	COBI-boosted antiretroviral (ARV) agent (which may result in loss of therapeutic effect and development of resistance to the COBI-boosted ARV agent) is also contraindicated. *Concurrent use of drugs whose coadministration with STB is contraindicated is an important identified risk for the COBI and EVG components of STB.*
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.4. Emtricitabine

Table SII.4. Key Safety Findings from Nonclinical Studies (Emtricitabine)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Use
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.5. Tenofovir DF

Table SII.5. Table of Key Safety Findings from Nonclinical Studies (Tenofovir DF)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Use
Nonclinical safety pharmacology studies reveal no special hazard for humans (D990155, R990152, R990153, R990154). Findings in repeated dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Evidence of renal toxicity was noted in four animal species exposed to TFV and TDF in nonclinical studies. Increases in serum creatinine, blood urea nitrogen (BUN), glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. In rats and mice, renal tubular karyomegaly was observed. In dogs and monkeys renal tubular degeneration/regeneration was observed in addition to karyomegaly. The incidence, severity and reversibility of the histopathological changes were related to dose and duration of treatment. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans after a 300 mg daily dose. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in pediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40-fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.	*Renal toxicity is an important identified risk for TDF.* Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal renal tubulopathy (PRT) (including Fanconi syndrome) have been reported with the use of TDF (STB SmPC). *Bone events due to PRT / loss of BMD is an important identified risk for TDF.* Decreases in BMD observed following the initiation of antiretroviral therapy (ART) appear to be greater with regimens containing TDF compared to those without TDF. Osteomalacia (infrequently contributing to fractures) may be associated with PRT (STB SmPC).
Genotoxicity studies revealed positive results in the *in vitro* mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in an unscheduled DNA synthesis (UDS) test in primary rat hepatocytes. However, it was negative in an *in vivo* mouse bone marrow micronucleus assay. Oral carcinogenicity studies in rats and mice only revealed a low incidence of duodenal tumors at an extremely high dose in mice.	These tumors are unlikely to be of relevance to humans.
Reproductive studies in rats and rabbits showed no effects on mating, fertility, pregnancy or fetal parameters. Tenofovir DF reduced the viability index and weight of pups in peri-postnatal toxicity studies at maternally toxic doses.	No safety concerns for humans are anticipated based on the non-clinical reproductive studies for TDF.

SII.6. Conclusions on Nonclinical Data

Table SII.6. Safety Concerns from Nonclinical Data

	Safety Concern	Attributable Component
Important Identified Risks	Renal toxicity	TDF
	Bone events due to PRT/loss of BMD	TDF
	Concurrent use of drugs whose coadministration with STB is contraindicated	COBI, EVG
Important Potential Risks	None	Not applicable
Missing Information	Safety in patients with cardiac conduction disorders	COBI

PART II: MODULE SIII - CLINICAL STUDY REXPOSURE

SIII.1. Clinical Study Exposure

The following tables provide clinical trial exposure to STB up to 26 August 2021 from following completed studies in subjects with HIV-1 infection:

- Completed studies: GS-US-236-0102, GS-US-236-0103, GS-US-236-0104, GS-US-236-0115, GS-US-236-0118 (Cohort 1), GS-US-236-0121, GS-US-236-0123, GS-US-236-0140, GS-US-292-0102, GS-US-236-0112, GS-US-236-0128, GS-US-292-0109, GS-US-380-1961, GS-US-292-0104, GS-US-292-0111

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

Duration of Exposure	Persons[a]	Person-Years
≥ 1 Day	2732	6966
> 1 Month	2684	6964
> 3 Months	2639	6956
> 6 Months	2580	6934
> 1 Year	2459	6844
> 2 Years	1663	5520
> 3 Years	1212	4303
> 4 Years	188	893
> 5 Years	64	327

a Previously, subjects who were rolled over to Study-GS-US-292-0109 from other Gilead studies (GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104) had not been considered the same subject and were counted as unique. Since 2018, the subjects were more appropriately considered the same subject if they were linked to previous studies and were counted only once, thereby reducing the number of subjects on STB as well as the number of total unique subjects.

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

	Persons		Person-Years	
Age Group	**Male**	**Female**	**Male**	**Female**
12 - 17 Years	35	15	85	43
18 - 30 Years	600	154	1607	381
31 - 40 Years	648	180	1651	474
41 - 50 Years	587	151	1453	400
51 - 65 Years	255	87	620	206
66 - 75 Years	16	2	40	4
> 75 Years	2	0	4	0

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

Race	**Persons**	**Person-Years**
White	1726	4349
Black or African American	715	1791
Asian	151	439
American Indian or Alaska Native	21	45
Native Hawaiian or Pacific Islander	10	31
Other	107	306
Not provided	2	4

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL STUDIES

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
Medicinal products excluded from concurrent use: alfuzosin, dihydroergotamine, ergotamine, ergometrine, oral administered midazolam, triazolam, cisapride, pimozide, 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 STB SmPC. Concurrent use of drugs whose coadministration with STB is contraindicated is an important identified risk for STB.
Pregnant females and females who are breastfeeding	Limited information on the use in this patient population.	Yes
Inadequate renal function: Estimated glomerular filtration rate (eGFR) < 70 mL/min according to the Cockcroft-Gault formula	Tenofovir is primarily renally excreted by a combination of glomerular filtration and tubular secretion. Tenofovir PK are substantially altered in subjects with moderate and severe renal impairment.	Yes
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 The safety of COBI in patients with cardiac conduction disorders is considered to be missing information.

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

Table SIV.2. Ability of the Clinical Study 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 uncommon	2732 HIV-1 infected subjects have been exposed to STB in clinical studies	The clinical study population is large enough to detect at least uncommon ADRs. ADRs with a frequency greater than 1 in 938 could potentially be detected if there was no background incidence.
Due to prolonged exposure	1663 HIV-1 infected subjects have been exposed to STB for more than 2 years and 1212 HIV-1 infected subjects have been exposed to STB for more than 3 years in clinical studies.	No ADRs specifically associated with prolonged exposure to STB have been identified in the STB clinical study program.
Due to cumulative effects	1663 HIV-1 infected subjects have been exposed to STB for more than 2 years and 1212 HIV-1 infected subjects have been exposed to STB for more than 3 years in clinical studies.	No cumulative effects to STB have been identified in the STB clinical study program.
Which have a long latency	1663 HIV-1 infected subjects have been exposed to STB for more than 2 years and 1212 HIV-1 infected subjects have been exposed to STB for more than 3 years in clinical studies.	No ADRs to STB with a long latency have been identified in the STB clinical study program.

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

Table SIV.3. Populations Included or Not in Clinical Study Development Programs

Type of Special Population	Exposure	Considered to be Missing Information
Long-term safety in adolescents	50 subjects (128 Person-years) between 12 – 17 years of age were exposed to STB in clinical studies.	No Rationale: Safety data for adolescent patients has been monitored through routine PV activities, including periodic safety update reports (PSURs), and no safety concern has been identified.

Type of Special Population	Exposure	Considered to be Missing Information
Elderly	20 subjects (48 person-years) over 65 years old were exposed to STB in clinical studies.	No Rationale: Case reports involving elderly patients have been monitored through routine PV activities, including PSURs, since marketing approval of STB, no safety concern has been identified.
Pregnant women Breastfeeding women	Pregnant and breastfeeding women were excluded from enrolling in clinical studies. As of 04 May 2022, there were a total of 69 cases of pregnancy during treatment with STB from Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0128.	Yes
Patients with renal impairment	In Study GS-US-236-0118, 33 subjects with creatinine clearance (CLcr) between 50-89 mL/min were enrolled and received STB.	No Rationale: No new safety concerns were identified from completed Study GS-US-236-0118 in people with HIV with mild to moderate renal impairment. Safety data for patients with renal impairment has also been monitored through routine PV activities, including PSURs, and no safety concern has been identified.
Patients with severe hepatic impairment (CPT score C)	Not known. Patients had to have hepatic transaminases (AST and ALT) $\leq 5 \times$ upper limit of normal (ULN) and total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin to be enrolled.	No Rationale: Safety data for patients with severe hepatic impairment has been monitored through routine PV activities, including PSURs, since marketing approval of STB, and no safety concern has been identified
Coinfection with Hepatitis B or Hepatitis C	In Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104, 45 HIV-1 infected subjects in the STB group (6.0%) were coinfected with HBV (10 subjects, 1.3%) or HCV (35 subjects, 4.7%) at screening.	No Rationale: No new safety concerns for STB were identified. As would be expected in this subject population, elevations in AST and ALT occurred more frequently than in the general HIV-1 infected population.

Type of Special Population	Exposure	Considered to be Missing Information
Subpopulations with UGT1A1 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 STB.
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-236-0102, GS-US-236-0103 and GS-US-236-0104, 133 subjects had abnormal ECG results at screening that were determined by the investigator to be not clinically significant.	No Rationale: Safety data for patients with cardiac conduction disorders has been monitored through routine PV activities, including PSURs, and no safety concern has been identified.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1. Post-Authorization Exposure

SV.1.1. Method Used to Calculate Exposure

Patient exposure to marketed STB has been estimated from both sales data and from prescription data (Module 2.5 [Addendum to Clinical Overview] of 5-year renewal submission). The methodology used to calculate patient exposure from these 2 sources is described below:

Sales data

The number of bottles sold cumulatively was multiplied by 30 to provide the number of tablets sold. As STB 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 tend to overestimate exposure, due to the accumulation of drug stocks at pharmacies/distributors.

Prescription Data

Estimates of the demographics of HIV infected patients exposed to STB in the 5 major European markets (UK, France, Germany, Italy and Spain) were obtained from prescription data from the Ipsos Healthcare HIV EU Therapy Monitor study, which is a syndicated, bi-annual diary study involving HIV treating physicians.

SV.1.2. Post-Authorization Exposure

SV.1.2.1. Exposure Based on Sales Data

Based on sales data cumulative global patient exposure to STB since first marketing approval in United States on 27 August 2012 to 30 April 2025 is estimated to be 595,090 patient-years, including 116,807 patient-years in the EU.

SV.1.2.2. Exposure Based on Prescription Data

Based on prescription data from UK, France, Germany, Italy and Spain, most patients exposed to STB were male and aged 26 to 45 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 STB 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

Not applicable.

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

None

SVII.3.1.2. Important Potential Risks

None

SVII.3.2. Presentation of the Missing Information

Table SVII.1. Missing Information

Missing Information	Evidence Source
Safety in pregnancy and lactation (EVG, COBI, FTC, TDF)	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 STB during pregnancy, although data for EVG and COBI is limited. FTC and TDF have been shown to pass into human breast milk. It is not known whether EVG and COBI pass into human breast milk.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1. Summary of Safety Concerns

	Safety Concerns for STB
Important Identified Risks	None
Important Potential Risks	None
Missing Information	Safety in pregnancy and lactation

PART III:
PHARMACOVIGILANCE PLAN

III.1. Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond ADR 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 in Annex 4.

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 Title	Rationale and Study Objectives	Study Design and Study Populations	Milestones	Due Dates
Non-interventional Studies				
Antiretroviral Pregnancy Registry (Category 3)	To collect information on the risk of birth defects in patients exposed to EVG, COBI, FTC and TDF during pregnancy	Prospective, observational, exposure-registration, and follow-up study of pregnant patients exposed to antiretroviral drugs.	Submission of interim reports	In the STB PSUR (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 Ongoing	To collect information on the risk of birth defects in patients exposed to EVG, COBI, FTC and TDF during pregnancy	*Missing information*: Safety in pregnancy (EVG, COBI, FTC, TDF)	Submission of interim reports	In the STB 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

IV.1. PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

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

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

V.1. Routine risk minimization measures

The routine risk minimization measure for STB in the EU comprises of the SmPC, the package leaflet (PL), and the legal status of the product. STB 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 1-1. The legal status can be considered a general measure applicable to all 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	
Safety in pregnancy and lactation (EVG, COBI, FTC, TDF)	Routine risk communication: SmPC Section 4.6 PL Section 2

V.2. Additional Risk minimization measures

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

V.3. Summary of risk minimization measures

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

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risk(s)		
None		
Important Potential Risk(s)		
None		
Missing Information		
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

SUMMARY OF RISK MANAGEMENT PLAN FOR STRIBILD

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

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

This summary of the RMP for Stribild should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 Stribild's RMP.

I. The Medicine and What It Is Used for

Stribild is authorized for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) (see SmPC for the full indication). Stribild is also used to treat HIV-1 infected adolescents aged 12 to < 18 years who weigh at least 35 kg, and who have already been treated with other HIV medicines that have caused side effects. It contains elvitegravir (EVG), cobicistat (COBI) emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) as the active substances and it is given orally.

Further information about the evaluation of Stribild's benefits can be found in Stribild's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002574/WC500144275.pdf.

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

Important risks of Stribild, together with measures to minimize such risks and the proposed studies for learning more about Stribild'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 the case of Stribild, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

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 Stribild is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Stribild 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 Stribild. 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	Safety in pregnancy and lactation

II.B. Summary of Important Risks

There are no important identified or potential risks for Stribild. STB has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby STB therapy should be initiated by a doctor experienced in the management of HIV infection (as described in section 4.2 of the SmPC).

Table Part VI.2. Summary of Missing Information

Missing Information	Safety in Pregnancy and Lactation
Risk Minimization Measure(s)	Routine risk communication: SmPC Section 4.6 PL Section 2
Additional Pharmacovigilance activities	Antiretroviral Pregnancy Registry See Section II.C of this summary for an overview of the post-authorization development plan.

II.C. Post-Authorization Development Plan

II.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 Stribild.

II.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	To collect information on the risk of birth defects in patients exposed to anti-HIV medicines, including the components of Stribild, during pregnancy

PART VII: ANNEXES

Table of Contents

Annex 1. EudraVigilance Interface

This XML file is submitted electronically and can be provided on request.

Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Annex 3. Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

None

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

None

Annex 6. Details of Proposed Additional Risk Minimization Measures (if Applicable)

None

Annex 7. Other Supporting Data (Including Referenced Material)

The following information is included in this annex:

- Referenced material

Annex 8. Summary of Changes to the Risk Management Plan over Time

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2. ELECTRONIC SIGNATURES

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
[redacted]	Patient Safety eSigned	30-Jul-2025 12:25:26
Rainer Heissing	QPPV eSigned	30-Jul-2025 12:31:26