EU Risk Management Plan for Biktarvy® (Bictegravir/Emtricitabine/Tenofovir Alafenamide)

EU Risk Management Plan for Biktarvy (Bictegravir/Emtricitabine/Tenofovir Alafenamide [B/F/TAF])

RMP version to be assessed as part of this application:

Version Number	Data Lock Point for This RMP	Date of Final Sign-off
5.0	19 October 2020	Refer to ELECTRONIC SIGNATURES

Rationale for submitting an updated RMP:

Gilead is requesting a delay in provision of the final Cohort 3 study report from Q1 2025 to Q1 2026 for GS-US-380-1474. This is due to a delay in expected last patient last visit (LPLV) for the Cohort 3 which is now anticipated by June 2025. Gilead proposes to have the report available by Q1 2026.

As described in the protocol for Study GS-US-380-1474, upon completion of Week 48, participants are given the option to receive Biktarvy® in an open label extension phase until the study drug becomes available for use in the country or, accessible through an access program. Currently, the study drug is not commercially available in the countries where Study GS-US-380-1474 is being conducted, and there has been a delay in establishing an access program.

The access program is being implemented (Study GS-US-380-6684) with clinical study approval still pending in certain countries. By June 2025, it is anticipated that all Cohort 3 participants that wish to transition to this program will have completed rollover.

Summary of significant changes in this RMP:

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

Part	Module/Annex	Significant changes to RMP
	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		Updated to reflect new proposed submission date for the GS-US-380-1474 (Cohort 3) final CSR.
Part IV Plan for postauthorization efficacy studies		None
Part V Risk Minimization Measures		None
Part VI Summary of RMP		None
Part VII Annexes		Annex 8 updated to reflect the new proposed date for provision of the final CSR for study GS-US-380-1474 (Cohort 3).

Other RMP versions under evaluation:

Not applicable.

Details of the currently approved RMP:

Version number:	Approved with procedure	Date of approval (opinion date)
4.0	EMEA/H/C/004449/X/0040/G	14 July 2022

QPPV name: Anne-Ruth van Troostenburg de Bruyn

QPPV signature: Refer to ELECTRONIC SIGNATURES

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

3TC	lamivudine
ABC	abacavir
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical (classification system)
AUC_{inf}	area under the plasma concentration versus time curve extrapolated to infinite time
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
BIC; B	bictegravir
BMD	bone mineral density
CD4	cluster determinant 4
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum observed concentration of drug
CYP	cytochrome P450 enzyme
DLP	data-lock point
DNA	deoxyribonucleic acid
DRV	darunavir
DTG	dolutegravir
DVY	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
EACS	European AIDS Clinical Society
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
EPAR	European Public Assessment Report
EU	European Union
F/TAF	emtricitabine/tenofovir alafenamide (Descovy®; DVY)
FTC; F	emtricitabine (Emtriva®)
GEN	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)
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
MAA	Marketing Authorization Application
MATE	multidrug and toxin extrusion
MSM	men who have sex with men
NOEL	no observed effect level
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
OCT	organic cation transporter
ODE	emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®)
PD	pharmacodynamics
PI	protease inhibitor
PL	package leaflet
PK	pharmacokinetics
PRT	proximal renal tubulopathy
PSUR	periodic safety update reports
PT	preferred term
QPPV	Qualified Person for Pharmacovigilance
RMP	risk management plan
SmPC	Summary of Product Characteristics
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TVD	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
UACR	urine albumin to creatinine ratio
UGT	uridine glucuronosyltransferase
ULN	upper limit of normal
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)	Bictegravir (BIC; B), emtricitabine (FTC; F), tenofovir alafenamide (TAF)
Pharmaco-therapeutic group(s) (ATC Code)	Antivirals for the treatment of human immunodeficiency virus (HIV) infections, combinations (J05AR20)
Marketing authorization holder	Gilead Sciences Ireland UC.
Medicinal products to which this RMP refers	Bictegravir/emtricitabine/tenofovir alafenamide film-coated tablet
Invented name(s) in the European Economic Area (EEA):	Biktarvy®
Marketing authorization procedure	Centralized
Brief description of the product	*Chemical class* Bictegravir: integrase strand-transfer inhibitor (INSTI) Emtricitabine: nucleoside reverse transcriptase inhibitor (NRTI) Tenofovir alafenamide: nucleotide reverse transcriptase inhibitor (NtRTI)
	Summary of mode of action Bictegravir binds to the integrase active site and blocks the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Bictegravir has activity that is specific to HIV-1 and HIV-2. 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. Tenofovir alafenamide 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:	Biktarvy Summary of Product Characteristics (SmPC)
Indication(s) in the EEA:	Current: Biktarvy is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and pediatric patients at least 2 years of age and weighing at least 14 kg without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir.
Dosage in the EEA:	Current: One tablet to be taken orally, once daily, with or without food.
Pharmaceutical form(s) and strengths:	Current: Film-coated tablet contains BIC sodium equivalent to 50 mg of BIC, 200 mg of FTC, and TAF fumarate equivalent to 25 mg of TAF for adults and pediatric patients weighing at least 25 kg. Film-coated tablet contains BIC sodium equivalent to 30 mg of BIC, 120 mg of FTC, and TAF fumarate equivalent to 15 mg of TAF for pediatric patients ≥ 2 years of age and weighing ≥ 14 kg to < 25 kg.
Is/Will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

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

SI.1. HIV 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.

SI.1.2. Incidence

Worldwide, the number of new HIV infections continues to decrease over time. In 2019, 1.7 million people (95% CI: 1.2 million-2.2 million) acquired HIV, 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 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 (IDUs) 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 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.1.3. 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 million; 95% confidence interval [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, 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 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

	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)
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

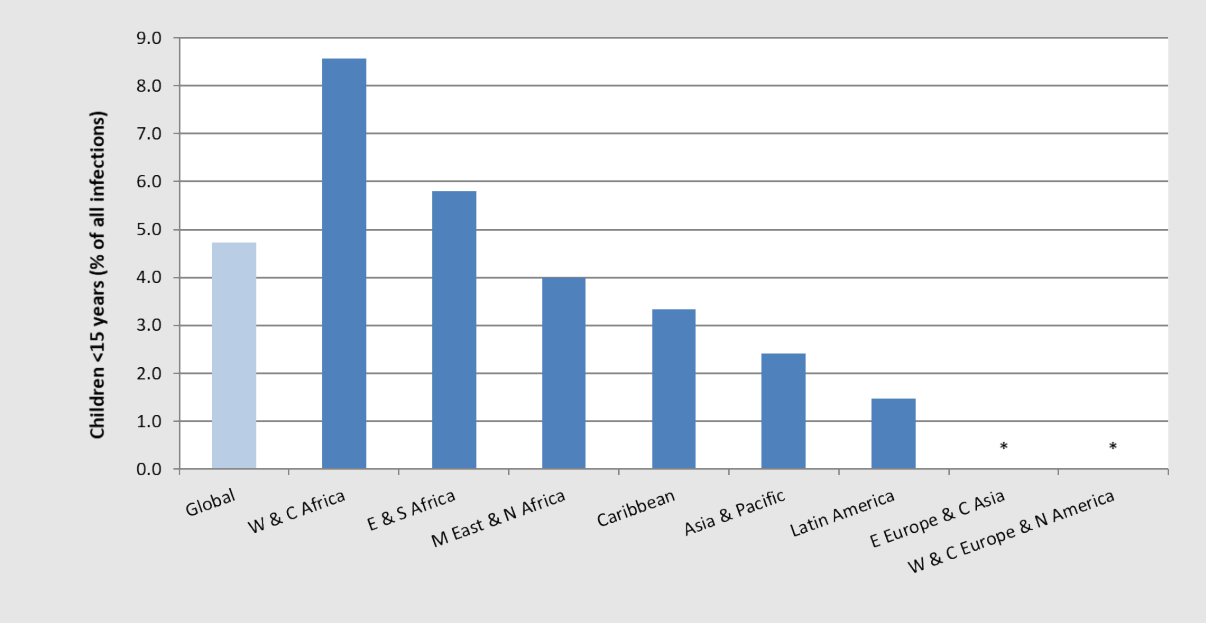
SI.1.4.1. HIV Infection in Children

Worldwide, 1.8 million (95% CI: 1.3-2.2 million) children (<15 years) 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 Western and Central Europe and North America and Eastern Europe and Central Asia.

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.1.4.2. 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 above the age of 50 living with HIV ranged from 10% (low- and middle-income countries) to 30% (high income countries; {Mahy 2014}; {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017}). UNAIDS reports that this trend is largely due to the success of antiretroviral therapy (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 immunodeficiency 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 2013, Langebeek 2017}.

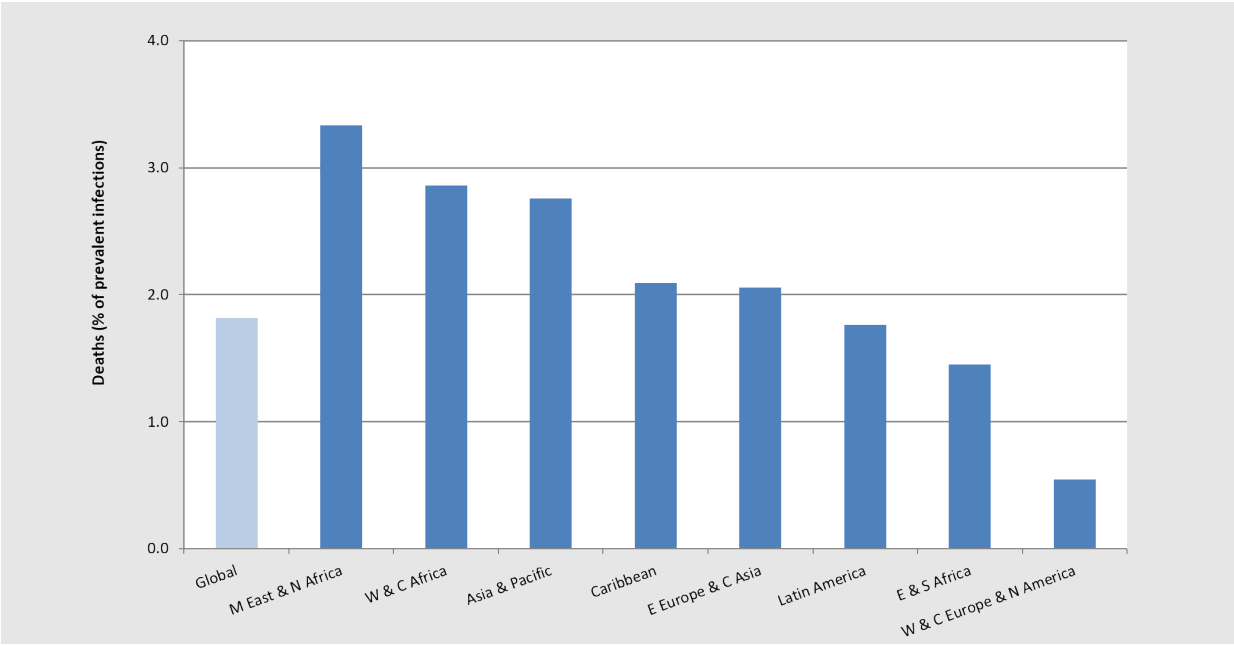
SI.1.6.1. Mortality and Morbidity

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: 500,000-970,00) people died from AIDS-related causes worldwide, representing a 39% decline compared to 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%), 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 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.1.7.1. Important Comorbidities

Prior to the success of ART for the treatment of HIV/AIDS, the most common comorbidities 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 comorbidities are chronic health conditions in both resource-limited settings and wealthy regions {Balderson 2013, Deeks 2013, Hirschhorn 2012, 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 - NONCLINICAL PART OF THE SAFETY SPECIFICATION

Given the lack of significant overlapping toxicities of the individual components (BIC, FTC, TAF), nonclinical studies with B/F/TAF were not considered necessary. Key safety findings from nonclinical studies of the new active substance BIC are summarized in Table SII.1.

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

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Hepatobiliary Findings The only significant effect of BIC in chronic animal studies was hepatobiliary toxicity in monkeys following 39 weeks of administration at 1000 mg/kg/day (Study TX-141-2032, m2.4, Section 4.3.1.1 and Section 4.11.1.1.1). Hepatobiliary observations included bile duct hyperplasia in all monkeys in this high dose group. Minimally to mildly increased mean alanine aminotransferase (ALT) activity (≤3.5-fold versus mean baseline values) was not clearly correlated with the BIC-related microscopic hepatobiliary changes. There were no elevated bilirubin findings or any other adverse findings in the study. The no observed effect level (NOEL) after 39-weeks administration was 200 mg/kg/day, corresponding to an exposure margin of at least 7.0-fold higher than the projected steady state human exposure of BIC following administration of B/F/TAF (50/200/25 mg) once daily under fed conditions.	Similar findings have not been seen in monkeys administered lower doses, or in rats at the highest dose tested (300 mg/kg/day) in a 26-week study. The available cross-species data on in vitro and in vivo metabolism of BIC in humans, rats, and monkeys suggest that the biotransformation pathways for BIC in humans are more consistent with those observed in the rat than in the monkey. No safety concerns associated with hepatotoxicity were identified for BIC in the clinical trial program. No patient treated with B/F/TAF had a non-infectious, non-congenital hepatic serious adverse event, discontinued study drugs due to hepatic adverse events (AEs), or met Hy's Law criteria. Across the 4 Phase 3 B/F/TAF studies, most patients treated with B/F/TAF did not have a hepatic laboratory abnormality. Among the patients who did have a hepatic laboratory abnormality, most were Grade 1 and resolved with continued B/F/TAF administration (m2.7.4, Section 2.1.5.1).
Reproductive Toxicity In rabbits administered 1000 mg/kg/day, abortion and decreased fetal body weights were considered secondary to overt maternal toxicity (adverse clinical observations, body weight loss and low food consumption) and are regarded as species-specific (m2.4, Section 4.6.1, Studies TX-141-2035, TX-141-2038 and TX-141-2037). The NOEL for maternal and embryofetal toxicity in pregnant rabbits is 300 mg/kg/day, at an exposure margin of 0.6-fold over the anticipated clinical exposure in humans.	Findings in rabbits are considered secondary to overt maternal toxicity and are regarded as species-specific; there were no effects on reproductive or developmental effects in rats at exposure margins of at least 30-fold.
Potential Cytochrome P450 (CYP) 3A and Uridine glucuronosyltransferase (UGT) 1A1 Drug-Drug Interactions UGT 1A1 and CYP 3A played a major role in the biotransformation of BIC in vitro (m2.6.4, Section 7.1.2, AD-141-2290 and AD-141-2291).	Coadministration of BIC and medicinal products that potently induce both CYP3A and UGT1A1, such as rifampicin, may significantly decrease plasma concentrations of BIC, which may result in a loss of therapeutic effect of B/F/TAF and development of resistance, therefore coadministration of rifampicin is contraindicated in the SmPC. Coadministration of BIC with medicinal products that potently inhibit both CYP3A and UGT1A1, such as atazanavir, may significantly increase plasma concentrations of BIC, therefore co-administration is not recommended in the SmPC (Study GS-US-141-1485, m2.7.2, Section 3.2.4.2.2.1).
Inhibition of Drug Transporters Bictegravir showed dose-dependent inhibition of multidrug and toxin extrusion (MATE) 1 with an IC_{50} value of 8.0 µM. Bictegravir was an inhibitor of renal uptake transporter organic cation transporter (OCT) 2 in vitro, with an IC_{50} value of 0.42 µM (m2.6.4, Section 7.1.4, AD-141-2285).	A clinical study was conducted with B/F/TAF and metformin (an OCT2 and MATE1 substrate), which showed no clinically relevant changes in the pharmacokinetics (PK) and pharmacodynamics (PD) of metformin (Study GS-US-380-3908, m2.7.2, Section 2.5.1.3). BIC has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine via OCT2 and/or MATE1 without affecting renal glomerular function (m2.7.4, Section 2.1.5.4).

PART II: MODULE SIII - CLINICAL STUDY EXPOSURE

SIII.1. Clinical Study Exposure

The tables in this section present exposure data for B/F/TAF in patients with HIV-1 infection from the following studies (m2.7.4, Section 1.2):

- **Ongoing Blinded:** GS-US-380-4458
- **Ongoing Open Label/Unblinded or Completed Studies:**
  - **Completed Studies:** GS-US-141-1475, GS-US-200-4072, GS-US-292-1825, GS-US-380-1844, GS-US-380-1878, GS-US-380-1961, GS-US-380-4449, GS-US-380-4580
  - **Completed Blinded Phase:** GS-US-380-1489 and GS-US-380-1490 (144 weeks) and GS-US-380-4030 (48 weeks)
  - **Ongoing Open Label Extension Phase:** GS-US-380-1489, GS-US-380-1490 and GS-US-380-4030 (additional 96 weeks follow-up)
  - **Ongoing Open Label:** GS-US-200-4334, GS-US-380-1474 and GS-US-380-5310

Table SIII.1. Duration of Exposure in Patients With HIV-1 Infection

	Ongoing Blinded Studies		Ongoing Open Label/Unblinded or Completed Studies	
Duration of Exposure	**Patients**	**Patient-years**	**Patients**	**Patient-years**
≥ 1 day	179	165	3992	7637
≥ 30 days	169	165	3971	7636
≥ 90 days	147	162	3895	7622
≥ 180 days	126	154	3808	7588
≥ 1 year	89	126	3217	7089
≥ 2 years	2	4	1331	4355
≥ 3 years	0	0	691	2837

Table SIII.2. Exposure by Age Group and Gender in Patients With HIV-1 Infection

	Ongoing Blinded Studies (All Subjects Treated)				Ongoing Open Label/Unblinded or Completed Studies (Subjects exposed to B/F/TAF)			
	Patients		Patient-years		Patients		Patient-years	
Age Group	Male	Female	Male	Female	Male	Female	Male	Female
< 18 years	0	0	0	0	52	70	137	187
18 - 40 years	140	2	128	0	1305	386	2875	610
41 - 64 years	29	6	33	3	1392	559	2583	876
65 - 75 years	2	0	1	0	172	45	286	66
> 75 years	0	0	0	0	11	0	17	0

Table SIII.3. Exposure by Ethnic Origin in Patients With HIV-1 Infection

	Ongoing Blinded Studies (All Subjects Treated)		Ongoing Open Label/Unblinded or Completed Studies (Subjects exposed to B/F/TAF)	
Ethnic origin	Patients	Patient-years	Patients	Patient-years
White	17	20	2004	4064
Black or African American	8	6	1508	2700
Asian	152	136	209	374
American Indian or Alaska Native	0	0	17	37
Native Hawaiian or Other Pacific Islander	0	0	12	25
Other	2	3	231	418
Not Permitted	0	0	11	21

Table SIII.4. Exposure by Baseline Estimated Glomerular Filtration Rate in Patients With HIV-1 Infection

Baseline $eGFR_{CG}$ (mL/min)[a]	Ongoing Blinded Studies (All Subjects Treated)		Ongoing Open Label/Unblinded or Completed Studies (Subjects Exposed to B/F/TAF)	
	Patients	Patient-years	Patients	Patient-years
< 30	0	0	11	14
30 - < 60	1	0	89	137
60 - < 90	34	34	903	1519
≥ 90	144	131	2914	5733
Missing	0	0	75	233

a eGFR_CG was not derived in GS-US-380-1474 study, as such this study was excluded from the exposure by baseline eGFR_CG analysis.

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 B/F/TAF at the start of the Phase 3 development program. It is not known whether BIC 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
Patients with severe renal impairment	Patients had to have estimated glomerular filtration rate (eGFR) of ≥30 ml/min to be included in B/F/TAF Phase 3 studies.	No

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 uncommon	3992 HIV-1 infected patients have been exposed to B/F/TAF in the B/F/TAF clinical trial program (ongoing open-label/unblinded or completed studies).	The clinical trial population is large enough to detect at least some uncommon ADRs. ADRs with a frequency greater than 1 in 1331 could potentially be detected if there were no background incidence.
Due to prolonged exposure	3217 HIV-1 infected patients have been exposed to B/F/TAF for more than 1 year in the B/F/TAF clinical trial program (ongoing open-label/unblinded or completed studies).	No ADRs specifically associated with prolonged exposure to B/F/TAF have been identified in the B/F/TAF clinical trial program.
Due to cumulative effects	3217 HIV-1 infected patients have been exposed to B/F/TAF for more than 1 year in the B/F/TAF clinical trial program (ongoing open-label/unblinded or completed studies).	No cumulative effects to B/F/TAF have been identified in the B/F/TAF clinical trial program.
Which have a long latency	3217 HIV-1 infected patients have been exposed to B/F/TAF for more than 1 year in the B/F/TAF clinical trial program (ongoing open-label/unblinded or completed studies).	No ADRs to B/F/TAF with a long latency have been identified in the B/F/TAF clinical trial program.

SIV.3. Limitations in Respect to Populations Typically Underrepresented 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
Pregnant women Breastfeeding women	Cumulative to 19 October 2020, 42 pregnancies were reported in patients receiving B/F/TAF (Studies GS-US-380-1474, GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878, GS-US-380-1961, GS-US-280-5310). Pregnancy outcomes were as follows: elective abortion (n=5), spontaneous abortion (n=9) and live birth without congenital anomalies (n=23), live birth with a congenital anomaly (n=1 – patent urachus), still birth (n=1), not reported/unknown (n=3).	Yes
Patients with relevant comorbidities		
Patients with severe hepatic impairment	Not known. Patients had to have hepatic transaminases (aspartate aminotransferase [AST] and ALT) ≤ 5 × upper limit of normal (ULN) and total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin to be included in Studies GS-US-380-1474, GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878, GS-US-380-1961, GS-US-380-4030, GS-US-380-4458, GS-US-380-4449 and GS-US-380-4580.	No Rationale: The PK of FTC have not been studied in patients 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, m2.7.2, Section 3.2.3.4). BIC PK has not been studied in patients with severe hepatic impairment and the use of B/F/TAF is not recommended in this patient population.
Patients with severe renal impairment	Not included in the Phase 3 clinical development program.	No Rationale: No safety concerns for B/F/TAF are anticipated in patients with severe renal impairment. No clinically relevant differences in BIC, TAF, or TFV PK were observed between healthy subjects and patients with severe renal impairment (Studies GS-US-141-1479 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, m2.7.2, Section 3.2.3.3). The F/TAF containing-regimen Genvoya (GEN; elvitegravir/ cobicistat/emtricitabine/tenofovir alafenamide, coformulated [E/C/F/TAF]) 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 (m2.7.4, Section 5.1.6).

Type of Special Population	Exposure	Considered to Be Missing Information
Subpopulations with UGT1A1 polymorphisms	Not known.	No Rationale: BIC is primarily eliminated through hepatic metabolism by CYP3A and UGT1A1. As only a weak drug-drug interaction is expected for BIC in the presence of strong inhibition of UGT1A1 only (see Table SII.), a polymorphism of UGT1A1 is not anticipated to alter BIC PK to a clinically meaningful extent (in line with what has been observed in studies for raltegravir {Wenning 2009}, elvitegravir [Study GS-US-183-1004] and dolutegravir [DTG] {Chen 2014}).
Patients coinfected with hepatitis B virus (HBV)	258 coinfected with HBV received B/F/TAF in Studies GS-US-380-1490, GS-US-380-1844, GS-US-380-1878, GS-US-380-1961 and GS-US-380-4030, GS-US-380-4449, GS-US-380-4458, GS-US-380-4580.	No Rationale: Safety of B/F/TAF was similar to that in HIV monoinfected patients (m2.7.4, Section 5.1.8.1). Genvoya was well tolerated in HIV infected patients coinfected with HBV in Study GS-US-292-1249 (m2.7.4, Section 5.1.8.1.2).
Patients coinfected with hepatitis C virus (HCV)	46 coinfected with HCV received B/F/TAF in Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878 and GS-US-380-1961, GS-US-380-4030, GS-US-380-4580.	No Rationale: Safety of B/F/TAF was similar to that in HIV monoinfected patients (m 2.7.4, Section 5.1.8.2).
Elderly patients	230 patients ≥ 65 years old received B/F/TAF in Studies GS-US-141-1475, GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878, GS-US-380-1961, GS-US-380-4030, GS-US-380-4458, GS-US-380-4449, GS-US-380-4580, GS-US-200-4072, GS-US-292-1825, GS-US-200-4334, GS-US-380-1474, GS-US-380-5310	No Rationale: Safety of B/F/TAF in elderly patients was similar to that in younger adults (m2.7.4, Section 5.1.1).

PART II: MODULE SV - POSTAUTHORIZATION EXPERIENCE

SV.1. Postauthorization Exposure

Biktarvy was first approved in the United States on 07 February 2018 and as of the 06 August 2020 was approved in 59 countries for the treatment of HIV-1 infection in adults and in 4 countries for the treatment of HIV-1 infection in pediatric patients. Since first marketing approval, cumulative exposure to 31 July 2020 is estimated to be 598,686 patient-years of treatment.

Cumulative and periodic exposures to Biktarvy are routinely reported in the periodic reports.

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 B/F/TAF to be misused for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

The adverse reactions included in Section 4.8 of the SmPC for B/F/TAF are not associated with undesirable clinical outcomes and are therefore not considered to be risks for B/F/TAF, with the exception of angioedema and anemia, which are adverse reactions identified previously for FTC-containing products and are risks that are not considered important (see Table SVII.1).

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

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table SVII.1. Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reason	List of Risks
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated	Identified risks of angioedema and anemia for FTC-containing products. These risks were added as uncommon ADRs to the SmPCs of FTC-containing products at the request of the Committee for Medicinal Products for Human Use (CHMP) following postmarketing cumulative safety reviews and so have also been included as uncommon ADRs in Section 4.8 of the proposed B/F/TAF SmPC.
Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorized). Minimal impact on the risk-benefit balance of the product	Identified risk of post-treatment hepatic flares in HIV/HBV coinfected patients. There are no additional pharmacovigilance activities associated with this risk and specific clinical measures to address this risk have become fully integrated into standard clinical practice as they are included in the European AIDS Clinical Society (EACS) guidelines {European AIDS Clinical Society (EACS) 2019}. Furthermore, as reported in the periodic safety update reports (PSURs) for GEN, Descovy (DVY) and Odefsey (ODE), no cases of post-treatment hepatic flares in HIV/HBV coinfected patients have been reported for these products in the post-marketing setting, suggesting that post-treatment hepatic flares do not impact the risk-benefit balance of F/TAF-containing products including B/F/TAF.
Other reasons for considering the risks not important: Minimal impact on the risk-benefit balance of the product	Potential risk of renal toxicity. Renal toxicity was added as an important potential risk for TAF-containing products at the request of the CHMP during the review of the Marketing Authorization Application (MAA) for GEN as at that time it could not be ruled out that chronic exposure to low levels of TFV as a result of dosing with TAF could result in renal toxicity in the longer term. Long term data are now available for GEN with no cases of proximal renal tubulopathy (PRT) reported at Week 144, including in patients with mild to moderate renal impairment, a population at greatest risk for renal toxicity.

Reason	List of Risks
	In addition to the extensive clinical trial data for GEN and other TAF-containing products, the B/F/TAF clinical trial program provides the first large scale data comparing a TAF-containing product to a non-TDF containing regimen. In these studies, the renal safety profile of B/F/TAF in both ART-naive and virologically suppressed adults, (Studies GS-US-380-1489 and GS-US-380-1844, respectively), was comparable to that of abacavir/DTG/ lamivudine (ABC/DTG/3TC) which is not associated with renal toxicity, and no renal toxicity risks for lamivudine, abacavir or ABC/3TC containing regimens are included in the product EPARs. No patient treated with B/F/TAF in Phase 2 or Phase 3 studies had PRT (including Fanconi Syndrome) or discontinued study drugs due to a renal and urinary disorder or associated investigation AE. Changes from baseline in serum creatinine and estimated glomerular filtration rate calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) were consistent with the known inhibitory effect of BIC or DTG on renal tubular secretion via OCT 2 and/or MATE 1. These changes were not clinically relevant and are not reflective of changes in actual glomerular filtration rate. Changes from baseline in quantitative measures of albuminuria (urine albumin to creatinine ratio, UACR) and specific markers of proximal tubular proteinuria (urine retinol binding protein and beta-2-microglobulin to creatinine ratios) were comparable between the B/F/TAF and ABC/DTG/3TC treatment groups (m2.7.4, Section 2.1.5.4). Therefore, the renal safety profile for B/F/TAF is similar to that of ABC/DTG/3TC and ABC/3TC. In summary, the clinical trial data demonstrate that the renal safety profile of TAF-containing regimens is consistent with that of regimens that do not contain TAF or TDF and have not been associated with renal toxicity. There have been a small number of cases with events potentially related to PRT in the postmarketing setting; however, there is insufficient evidence to support a causal association from these cases and the reporting rate is far lower than that for TDF-containing products.

SVII.1.1.1. Potential Risks Previously Associated with Descovy (F/TAF) that are No Longer Considered Risks for B/F/TAF

Risk Previously Associated with Descovy (DVY)	Reason it is No Longer Considered a Risk for B/F/TAF
Bone events due to potential proximal renal tubulopathy/loss of bone mineral density (BMD)	Bone events due to potential proximal renal tubulopathy/loss of BMD was added as an important potential risk for TAF-containing products at the request of the CHMP during the review of the MAA for GEN as at that time the CHMP considered that it was not possible to extend the safety profile of non-TDF-containing ART to GEN. The B/F/TAF clinical trial program provides the first large scale data comparing a TAF-containing product to a non-TDF-containing regimen. In addition, longer-term data has become available for GEN. As described above, the renal safety profile of B/F/TAF was similar to ABC/DTG/3TC, with no cases of PRT (including Fanconi Syndrome) reported for B/F/TAF in the clinical study program and no cases of PRT have been reported in long-term (week 144) studies for GEN, including in patients with mild to moderate renal impairment. B/F/TAF or ABC/DTG/3TC treatment resulted in comparable changes from baseline in hip and spine BMD for ART-naive patients (Study GS-US-380-1489) and minimal changes from baseline in virologically suppressed patients who switched to B/F/TAF from a DTG+ABC/3TC regimen (Study GS-US-380-1844) (m2.7.4, Section 2.1.5.3). In the long-term GEN studies, decreases in median hip and spine BMD were not observed from Week 48 to Week 144 (Studies GS-US-292-0104 and GS-US-292-0111). These data demonstrate that the bone safety profile of TAF-containing regimens is consistent with that of regimens that do not contain TAF or TDF, with BMD changes comparable between B/F/TAF and ABC/DTG/3TC, a regimen that has not been associated with bone toxicity. Furthermore, clinical trial data for GEN demonstrate that long-term exposure to TAF has no adverse clinical effect on BMD. These robust data therefore support bone events due to potential PRT/loss of BMD not being a potential risk for F/TAF-containing products (including B/F/TAF).
Ocular effects (posterior uveitis)	Ocular effects (posterior uveitis) was added as an important potential risk for TAF-containing products at the request of the CHMP during the review of the MAA for GEN as at that time the CHMP considered that although the data did not suggest that nonclinical findings translated into a concern regarding the ocular safety of TAF, a clinical effect could not be ruled out. Minimal mononuclear cell infiltration in the posterior uvea, considered secondary to general debilitation, was observed in dogs treated at high dose of TAF, which was at 3.7- and 17-fold higher exposure to TAF and TFV, respectively, than that observed in human patients administered a 25 mg dose. This finding did not occur in animals given lower doses, and it has not occurred in other animal studies (m2.6.6, Section 9.1.3.3, TOX-120-002). Since the marketing authorization of GEN, there has been considerable exposure to TAF-containing products including the following: • Across the Phase 3 randomized clinical trial population, 1206 patients have been treated with B/F/TAF for a median duration of 149.6 weeks (pooled Studies GS-US-380-1489 and GS-US-380-1490), 49.9 weeks (Study GS-US-380-1844), and 46.7 weeks (Study GS-US-380-1878). The incidence of AEs potentially related to uveitis and other eye disorders was low and comparable between treatment groups (m2.7.4, Section 2.1.5.5). Clinically, none of the AEs potentially related to uveitis in the B/F/TAF groups were considered representative of an actual case of posterior uveitis. • Approximately 6000 HIV-1 infected patients have been treated with GEN, DVY or ODE in clinical studies. No safety concerns related to ocular safety have been identified from these studies (including an ophthalmic substudy in Study GS-US-292-0109). • There has been no signal associated with ocular safety from postmarketing experience with TAF-containing HIV products during approximately 400,000 patient-years exposure (as reported in the PSURs for GEN, DVY and ODE). Given that no safety concerns related to ocular safety have been identified during extensive exposure to TAF-containing products, the data do not support ocular effects (posterior uveitis) being a potential risk for F/TAF-containing products (including B/F/TAF).

Risk Previously Associated with Descovy (DVY)	Reason it is No Longer Considered a Risk for B/F/TAF
Overdose of tenofovir occurring through accidental concurrent use of TAF-containing product with a TDF-containing product	Overdose of tenofovir occurring through accidental concurrent use of a TAF-containing product with a TDF-containing product was added as an important potential risk for TAF-containing products following a request from the CHMP during the review of the MAA for GEN. As plasma TFV levels are more than 90% lower with a TAF product such as B/F/TAF compared to a TDF product, coadministration is expected to have a minimal effect on plasma TFV levels compared to use of a TDF product alone and no undesirable clinical outcome is expected. This is supported by postmarketing data for other TAF-containing products, GEN, DVY, and ODE, for which very few cases of accidental concurrent use with a TDF-containing product have been reported (no cases for GEN; 2 cases for DVY, 1 case for ODE) and there were no associated AEs reported in any of the cases. This information has been, reported in the PSURs for GEN, DVY and ODE. Given that coadministration of TAF- and TDF-containing products appears to occur very infrequently and is not associated with an undesirable clinical outcome, the data do not support overdose of tenofovir occurring through accidental concurrent use of a TAF-containing product with a TDF-containing product being a potential risk for F/TAF-containing products (including B/F/TAF).

SVII.1.2. Risk(s) Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.2.1. Important Identified Risks

No important identified risks have been identified for B/F/TAF.

SVII.1.2.2. Important Potential Risks

No important potential risks have been identified for B/F/TAF.

SVII.1.2.3. Missing Information

Table SVII.2. Missing Information

Missing Information (applicable component of B/F/TAF)	Risk-Benefit Impact
Safety in pregnancy and lactation (BIC, FTC, TAF)	No adequate and well-controlled studies of B/F/TAF or its components have been conducted in pregnant women.

SVII.2. New Safety Concerns and Reclassification With a Submission of an Updated RMP

Long term safety in children aged between ≥ 2 and < 6 years has been classified as new missing information.

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

No important identified risks have been identified for B/F/TAF.

SVII.3.1.2. Important Potential Risks

There are no important potential risks for B/F/TAF for inclusion in the RMP.

SVII.3.2. Presentation of the Missing Information

Table SVII.3. Missing Information

Missing Information	Evidence Source
Safety in Pregnancy and Lactation	Population in need of further characterization: No adequate and well-controlled studies of B/F/TAF or its components have been conducted in pregnant women. Data from the Antiretroviral Pregnancy Registry (APR) suggest no increase in fetal defects associated with FTC use during pregnancy (m2.7.4, Section 5.4). There is limited pregnancy data available for TAF in the APR. FTC is excreted in human milk. It is unknown whether BIC or TAF are excreted in human milk.
Long term safety in children aged between ≥ 2 and < 6 years	Population in need of further characterization: Limited information is available on long-term use of B/F/TAF in children between the ages of ≥ 2 and < 6 years.

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	Safety in pregnancy and lactation
	Long term safety in children aged between ≥ 2 and < 6 years

PART III:PHARMACOVIGILANCE PLAN

III.1. Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Drug Reactions 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. Additional Pharmacovigilance Activities for B/F/TAF

Antiretroviral Pregnancy Registry (APR)	
Rationale and Study Objectives	*Safety concern addressed:* Safety in pregnancy (missing information) O*bjectives:* To collect information on the risk of birth defects with antiretroviral drugs, including B/F/TAF, to which pregnant women are exposed.
Study Design	Prospective, observational, exposure registration, and follow-up study.
Study Populations	Pregnant women exposed to antiretroviral drugs.
Milestones/Due Dates	Submission of interim reports. In the B/F/TAF PSUR (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs).
GS-US-380-1474 (Cohort 3)	
Rationale and Study Objectives	*Safety concern addressed:* Long term safety in children aged between ≥ 2 and < 6 years (missing information) O*bjectives:* To evaluate the pharmacokinetics, safety, tolerability and antiviral activity of the low dose B/F/TAF tablet through Week 48 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 kg to < 25 kg.
Study Design	Phase 2/3, open-label, multicenter, multicohort, single-arm study of the pharmacokinetics, safety, tolerability, and antiviral activity of B/F/TAF.
Study Populations	Cohort 3: Virologically suppressed children with HIV-1 infection ≥ 2 years of age and weighing ≥ 14 kg to < 25 kg.
Milestones/Due Dates	Submission of updated analyses including final CSR for Cohort 3 is anticipated by Q1 2026.

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) Ongoing	To collect information on the risk of birth defects with antiretroviral drugs, including B/F/TAF, to which pregnant women are exposed.	Safety in pregnancy (missing information)	Submission of interim reports	In the B/F/TAF PSUR (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs).
GS-US-380-1474 (Cohort 3) Ongoing	To evaluate the pharmacokinetics, safety, tolerability and antiviral activity of the low dose B/F/TAF tablet through Week 48 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 kg to < 25 kg.	Long term safety in children aged between ≥ 2 and < 6 years (missing information)	Submission of updated analyses including final CSR for Cohort 3	Anticipated submission by Q1 2026

PART IV:PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing postauthorization efficacy studies for B/F/TAF.

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

V.1. Routine Risk Minimization Measures

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

Safety Concern	Routine Risk Minimization Activities
Safety in pregnancy and lactation	Routine risk communication: SmPC section 4.6 PL section 2
Long term safety in children aged between ≥ 2 and < 6 years	Routine risk communication: SmPC sections 4.4 and 4.8

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V Section 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 Measures	Pharmacovigilance Activities
Important identified risk(s)		
None	N/A	N/A
Important potential risk(s)		
None	N/A	N/A
Missing information		
Safety in pregnancy and lactation	Routine risk communication: SmPC section 4.6 PL section 2	*Additional pharmacovigilance activities:* Antiretroviral Pregnancy Registry
Long term safety in children aged between ≥ 2 and < 6 years	Routine risk communication: SmPC sections 4.4 and 4.8	*Additional pharmacovigilance activities:* Ongoing study GS-US-380-1474 (Cohort 3) to address long term safety in virologically suppressed children ≥ 2 years of age weighing ≥ 14 kg to < 25 kg.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

I. SUMMARY OF RISK MANAGEMENT PLAN FOR BIKTARVY (Bictegravir/Emtricitabine/Tenofovir Alafenamide)

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

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

This summary of the RMP for Biktarvy 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 Biktarvy's RMP.

II. The Medicine and What Is It Used For

Biktarvy is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and pediatric patients at least 2 years of age and weighing at least 14 kg without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir. (see SmPC for the full indication). It contains bictegravir (BIC; B), emtricitabine (FTC; F) and tenofovir alafenamide (TAF) (B/F/TAF) as the active substances and it is given orally.

Further information about the evaluation of Biktarvy's benefits can be found in Biktarvy's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage*:* https://www.ema.europa.eu/en/medicines/human/EPAR/biktarvy.

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

Important risks of Biktarvy, together with measures to minimize such risks and the proposed studies for learning more about Biktarvy'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 Biktarvy is not yet available, it is listed under 'missing information' below.

III.A. List of Important Risks and Missing Information

Important risks of Biktarvy 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 Biktarvy. 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
	Long term safety in children aged between ≥ 2 and < 6 years

III.B. Summary of Important Risks

Table Part VI.2. Summary of Important Risk(s) and 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 1.2.3 of this summary for an overview of the postauthorization development plan.
Missing information	Long term safety in children aged between ≥ 2 and < 6 years
Risk Minimization Measure(s)	Routine risk communication: SmPC sections 4.4 and 4.8
Additional Pharmacovigilance activities	Ongoing study GS-US-380-1474 (Cohort 3) to address long term safety of B/F/TAF in virologically suppressed children ≥ 2 years of age weighing ≥ 14 kg to < 25 kg.

III.C. Postauthorization 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 Biktarvy.

III.C.2. Other Studies in Postauthorization Development Plan

Table Part VI.3. Other Studies in Postauthorization Development Plan

Short Study Name	Purpose of the Study
Antiretroviral Pregnancy Registry (APR)	To collect information on the risk of birth defects with antiretroviral drugs, including Biktarvy, to which pregnant women are exposed.
GS-US-380-1474 (Cohort 3)	To evaluate the pharmacokinetics, safety, tolerability and antiviral activity of the low dose B/F/TAF tablet through Week 48 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 kg to < 25 kg.

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)

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

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2. ELECTRONIC SIGNATURES

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Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
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[redacted]	Patient Safety eSigned	08-Dec-2024 14:12:20

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

Table 1. Planned and Ongoing Studies

Study	Summary of Objectives	Safety Concern Addressed	Protocol link Milestones
Category 3 - Required additional pharmacovigilance activities			
Ongoing studies			
Antiretroviral Pregnancy Registry (APR)	To collect information on the risk of birth defects with antiretroviral drugs, including B/F/TAF, to which pregnant women are exposed	Safety in pregnancy (missing information)	See Annex 3 for full protocol. Interim reports to be submitted in the B/F/TAF PSUR (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)
GS-US-380-1474 (Cohort 3)	To evaluate the pharmacokinetics, safety, tolerability and antiviral activity of the low dose B/F/TAF tablet through Week 48 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 kg to < 25 kg.	Long term safety in children aged between ≥2 and <6 years (missing information)	See Annex 3 for full protocol. Interim Week 24 study report submitted in Q2 2021*

* Long term data from Cohort 3 (median exposure of 99.5 weeks) was analyzed (Interim Analysis 3) and presented in a summary report that was submitted to EMA in Q4 2021. Updated analyses and final CSR including Cohort 3 is anticipated by Q1 2025.

Table 2. Completed Studies

Study	Summary of Objectives	Safety Concern addressed	Protocol link Milestones
GS-US-380-1489 – Long term safety and efficacy study comparing B/F/TAF to ABC/DTG/3TC	To evaluate the efficacy, safety, and tolerability of B/F/TAF and ABC/DTG/3TC through 144 weeks in HIV-infected, ART-naive adults	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness (important potential risk) Long-term safety (missing information)	Interim Week 144 study report* submitted in Q4 2019
GS-US-380-1490 – Long term safety and efficacy study comparing B/F/TAF to DTG+F/TAF	To evaluate the efficacy, safety, and tolerability of B/F/TAF and DTG+F/TAF through 144 weeks in HIV-infected, ART-naive adults	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness (important potential risk) Long-term safety (missing information)	. Interim Week 144 study report* submitted in Q4 2019

* The provision of the Week 144 clinical study reports CSRs for Studies GS-US-380-1489 and GS-US-380-1490 fulfil additional pharmacovigilance activities (Category 3) in the BVY EU-RMP agreed during the original marketing authorization application. The week 144 CSRs are the final CSRs covering the blinded phase of this study providing long-term comparative safety data. Both studies have a 96 Week open-label phase.

Protocols for Proposed and Ongoing Studies in Categories 1 to 3 in RMP Part III

Protocols for the studies included in Table 1 are provided in this annex.

Table 1. Overview of Included Protocols

Study Number and Title	Version of Protocol	Date of Protocol Version
Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP		
None	N/A	N/A
Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP		
None	N/A	N/A
Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority.		
Approved protocols:		
None	N/A	N/A
Final protocols not reviewed or not approved:		
Antiretroviral Pregnancy Registry (APR)	4	17 September 2013
GS-US-380-1474 - A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Bictegravir/Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination (FDC) in HIV-1 Infected Adolescents and Children.	Amendment 6	29 March 2022

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

Version	Approval date Procedure	Change
2.0	19 February 2019 EMEA/H/C/004449/IAIN/0016	MAH name was changed from Gilead Sciences International Ltd. to Gilead Sciences Ireland UC.
3.0	13 February 2020 EMEA/H/C/004449/II/0027	The following completed Category 3 activities were removed from the pharmacovigilance plan: • GS-US-380-1489 (Week 144 study report) • GS-US-380-1490 (Week 144 study report) Removed suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness (important potential risk) and long term safety (missing information).
4.0	21 November 2022 EMEA/H/C/004449/X/0040/G	To support the extension of the current indication to include children weighing ≥25 kg and the registration of a new strength tablet in children ≥ 14 kg to < 25 kg aged ≥ 2 years. Added long-term safety in children aged between ≥ 2 and < 6 years (missing information).
5.0	To be confirmed	Gilead is requesting a delay in provision of the final Cohort 3 study report from Q1 2025 to Q1 2026 for GS-US-380-1474. This is due to a delay in expected last patient last visit (LPLV) for the Cohort 3 which is now anticipated by June 2025. Gilead proposes to have the report available by Q1 2026.

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