SECTION 2.5—CLINICAL OVERVIEW

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

All studies conducted in the B/F/TAF development program met the requirement for International Council for Harmonisation (ICH) guidelines. Therefore, data should be interchangeable across regions. For studies conducted under a United States investigational new drug (IND) application, investigators were required to ensure that the basic principles of "Good Clinical Practice" (GCP) were adhered to, as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

3TC	lamivudine
ABC	abacavir
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the concentration versus time curve
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BCRP	breast cancer resistance protein
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated)
BIC; B	bictegravir (previously referred to as GS-9883)
BMD	bone mineral density
CatA	cathepsin A
CD4	cluster determinant 4
CES1	carboxylesterase 1
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum observed concentration of drug
COBI	cobicistat (Tybost®)
C_{tau}	observed drug concentration at the end of the dosing interval
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DRV	darunavir
DTG	dolutegravir
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
EOP2	End of Phase 2
EVG	elvitegravir (Vitekta®)
F/TAF	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC; F	emtricitabine (Emtriva®)

FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
FTC-TP	emtricitabine 5′-triphosphate
GEN	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)
Gilead	Gilead Sciences
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV, HIV-1	human immunodeficiency virus, type 1
HLA	human leukocyte antigen
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
INSTI	integrase strand-transfer inhibitor
ISS	Integrated Summary of Safety
IQ	inhibitory quotient
LSM	least-squares mean
M = E	missing = excluded
M = F	missing = failure
MATE1	multidrug and toxin extrusion 1
NDA	new drug application
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
OCT2	unknown description
$paEC_{95}$	protein-adjusted 95% effective concentration
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics(s)
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic(s)
PP	per protocol
Q1, Q3	first quartile, third quartile
RAL	raltegravir
RBP	retinol binding protein
RNA	ribonucleic acid
RTV	ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SBR	stay on baseline regimen
SD	standard deviation
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)

TAF	tenofovir alafenamide (Vemlidy®)
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
TFV-DP	tenofovir-diphosphate
T_{max}	time (observed time point) of C_{max}
UACR	urine albumin to creatinine ratio
UGT	uridine glucuronosyltransferase
ULN	upper limit of normal
US	United States

1. PRODUCT DEVELOPMENT RATIONALE

Gilead Sciences (Gilead) is submitting this dossier in support of a new marketing application for a fixed-dose combination (FDC) tablet of bictegravir (BIC; B) (previously referred to as GS-9883), emtricitabine (FTC, F), and tenofovir alafenamide (TAF): the B/F/TAF FDC tablet (50/200/25 mg). B/F/TAF is proposed for the treatment of adults infected with HIV-1 without any known mutations associated with resistance to the individual components.

This overview presents the clinical rationale for the development of B/F/TAF and reviews the information that is relevant to the benefit/risk assessment for the use of the FDC tablet in the treatment of HIV-1 infection. This overview includes biopharmaceutic, clinical pharmacology, efficacy, and safety data that support the proposed labeling and patient information.

1.1. Scientific Background

1.1.1. HIV-1 Infection and Current Treatment Options

HIV-1 infection is a life-threatening and serious disease of major public health interest, with approximately 37 million people infected worldwide {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. 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 treatment guidelines suggest that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either an integrase strand transfer inhibitor (INSTI), the nonnucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine, or the boosted protease inhibitor (PI), darunavir (DRV) {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. Virologically suppressed HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once-daily FDC regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {Aldir 2014, Sterrantino 2012}.

1.1.2. Rationale for B/F/TAF Development

Given the success of potent and well-tolerated ART, morbidity and mortality in HIV-infected patients is increasingly driven by non-AIDS-associated comorbidities. Clinical attention has become more focused on optimizing ART tolerability, long-term safety, and adherence {Costagliola 2014}. There remains a significant medical need for effective and safe therapies that take into consideration the aging HIV-infected patient population, the many non-AIDS-related comorbidities, drug resistance, and regimen simplification.

Bictegravir is a potent INSTI that is being evaluated for the treatment of HIV-1 infection {Gallant 2016} and that has demonstrated a terminal half-life suitable for once-daily administration without a boosting agent. In a Phase 2 study of ART-naive HIV-infected subjects, BIC was compared with the guideline-recommended INSTI, dolutegravir (DTG) {Sax 2017}. When coadministered with the guideline-recommended N(t)RTI backbone F/TAF, each INSTI

demonstrated high ARV activity, with no virologic failures due to resistance, and both treatments were safe and well tolerated. Gilead has coformulated BIC with FTC and TAF into an FDC tablet.

Emtricitabine and TAF form a guideline-recommended N(t)RTI backbone for ART-naive HIV-infected patients {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. In clinical trials, FTC and TAF have demonstrated potent and sustained efficacy, with excellent tolerability and minimal long-term toxicity in HIV-infected subjects {Descovy 2017, DESCOVY® 2017}. Tenofovir alafenamide is also approved as a single agent for the treatment of chronic hepatitis B infection {Vemlidy 2017, VEMLIDY® 2016}, and F/TAF is a guideline-recommended backbone for patients coinfected with HIV and hepatitis B virus (HBV) {Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}.

B/F/TAF is a potent, convenient, tolerable, and practical regimen for the long-term treatment of patients with HIV infection. The small tablet size of the FDC is expected to provide an additional benefit, especially in patients for whom pill swallowing can be a barrier to treatment compliance, (eg, the elderly). Described herein, clinical data demonstrate the following:

- High rates of virologic suppression with B/F/TAF in studies of ART-naive subjects and those switching therapy
- No subject in the Phase 2 or Phase 3 studies developed treatment-emergent resistance to any component of B/F/TAF
- B/F/TAF is generally safe and well tolerated in HIV-infected subjects
- The bone and renal safety profiles of B/F/TAF are comparable with those of abacavir (ABC)/DTG/lamivudine (3TC)

1.2. Overview of the Clinical Development Program

1.2.1. Clinical Pharmacology Development Program

A comprehensive program of 49 clinical studies characterized the pharmacokinetics (PK) of B/F/TAF and its components BIC, FTC, and TAF (m2.7.2, Section 1.2). Data are provided from studies conducted with BIC, B/F/TAF, TAF, F/TAF, Genvoya® (GEN), FTC, and/or FTC/tenofovir disoproxil fumarate (TDF). Data from the approved products TAF, F/TAF, GEN, FTC, and FTC/TDF are summarized, as needed, to describe their contribution to the clinical pharmacology profile of B/F/TAF.

Clinical pharmacology studies entailed single and/or multiple dosing and clinically relevant exposure of the drug(s) to assess PK, PK/pharmacodynamic (PD) relationships, and/or the effects of intrinsic and extrinsic factors. Drug-drug interaction (DDI) studies were performed using appropriate designs with adequate sample size to provide proper statistical comparisons and allow assessment of the clinical relevance of findings.

1.2.2. Dose Selection

All data for the B/F/TAF FDC in the pivotal Phase 3 studies in HIV-infected subjects were generated using the designated commercial formulation of the B/F/TAF 50/200/25 mg FDC.

FTC and TAF Dose Selection

The 200-mg dose of FTC and the 25-mg dose of TAF are approved doses for the treatment of HIV-1 infection in adults and adolescents. Emtricitabine and TAF are also components of the Descovy® (DVY) FDC, indicated for use in combination with other ARV agents, and of the complete regimens, GEN and Odefsey®. In the Phase 3 B/F/TAF studies, a coformulated FDC of BIC 50 mg, FTC 200 mg, and TAF 25 mg resulted in FTC and TAF exposures consistent with the wide range of safe and efficacious exposures observed historically with F/TAF-containing products.

BIC Dose Selection

The 50-mg dose of BIC was selected for the B/F/TAF FDC based on the totality of data from the BIC first-in-human, single- and multiple-ascending dose, BIC+F/TAF DDI study (GS-US-141-1218), the dose-ranging, proof-of-concept study (GS-US-141-1219), the Phase 2 safety and efficacy study (GS-US-141-1475; single-agent BIC 75 mg coadministered with F/TAF [200/25 mg]), and a relative bioavailability study (GS-US-141-1233), which evaluated 2 FDC tablet formulations (a 50-mg BIC B/F/TAF [50/200/25 mg] FDC and a 75-mg BIC B/F/TAF [75/200/25 mg] FDC) compared with BIC 75 mg + F/TAF (200/25 mg). Further details are provided in m2.7.3, Section 4.

1.2.3. Clinical Efficacy and Safety Development Program

Primary studies that support the safety and efficacy of the B/F/TAF (50/200/25 mg) FDC are 2 Phase 3 studies in HIV-infected, ART-naive adults (Studies GS-US-380-1489 and GS-US-380-1490) and 2 Phase 3 studies in HIV-infected, virologically suppressed adults (Studies GS-US-380-1844 and GS-US-380-1878) (Table 2). These are supported by a Phase 2 study of BIC 75 mg + F/TAF in HIV-infected, ART-naive adults (Study GS-US-141-1475).

The safety and efficacy of B/F/TAF for the treatment of HIV-1 infection in ART-naive adults is supported by data from 2 Phase 3, randomized, double-blind, active-controlled studies, GS-US-380-1489 and GS-US-380-1490. Study GS-US-380-1489 uses ABC/DTG/3TC as the comparator, allowing for comparison of B/F/TAF with a guideline-recommended, INSTI-based, once-daily FDC {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. Study GS-US-380-1490 uses DTG administered with the F/TAF (200/25 mg) FDC (DTG+F/TAF) as the comparator, allowing for direct and exclusive comparison between the INSTIs BIC and DTG, as both were administered with the guideline-recommended N(t)RTI FDC of FTC and TAF {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}.

Data from Studies GS-US-380-1489 and GS-US-380-1490 are supported by data from the Phase 2 study GS-US-141-1475, in which single-agent BIC 75 mg and DTG 50 mg, each administered with the F/TAF (200/25 mg) FDC, were compared. Subjects who participated in the open-label extension phase of Study GS-US-141-1475 received the B/F/TAF (50/200/25 mg) FDC.

The safety and efficacy of B/F/TAF for the treatment of HIV-1 infection in virologically suppressed adults is supported by data from 2 Phase 3 studies, GS-US-380-1844 and GS-US-380-1878. The double-blind study GS-US-380-1844 compares continuing ABC/DTG/3TC with switching to B/F/TAF in subjects who were virologically suppressed on ABC/DTG/3TC or a regimen consisting of those components. In the open-label study GS-US-380-1878, the comparator group stayed on their baseline regimen (SBR) consisting of cobicistat (COBI)- or ritonavir (RTV)-boosted atazanavir (ATV) or DRV plus either FTC/TDF or ABC/3TC. Boosted PIs are recognized for having high barriers to viral resistance {Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. The use of boosted ATV or DRV with 2 N(t)RTIs allows comparison of B/F/TAF with non-INSTI-containing regimens.

A total of 1511 HIV-infected subjects received at least 1 dose of the B/F/TAF FDC at the proposed commercial dose of 50/200/25 mg in the US, Europe, and rest of world (Table 1). This includes 1419 subjects in the Phase 3 studies: 1206 subjects in the randomized phases of the studies and 213 subjects who switched from SBR to receive B/F/TAF in the extension phase of Study GS-US-380-1878. In addition, 92 subjects received B/F/TAF in the extension phase of Study GS-US-141-1475.

Table 1. Number of HIV-Infected Subjects Who Received B/F/TAF in Phase 2 and Phase 3 Studies Included in the Submission by Region

	US	Europe	Rest of World (ROW)	Total Enrolled
Phase 3 Studies[a]	928	341	150	1419
Phase 2 Studies[b]	92	0	0	92
TOTAL	**1020**	**341**	**150**	**1511**

a Phase 3 studies: GS-US-380-1489 (US: 228; Europe: 66; ROW: 20), GS-US-380-1490 (US:193; Europe: 84; ROW: 43); GS-US-380-1844 (US: 203; Europe: 57; ROW: 22); GS-US-380-1878 (randomized phase—US: 166; Europe: 87; ROW: 37) (extension phase—US: 138; Europe: 47; ROW: 28)
b Phase 2 study: GS-US-141-1475 (only includes subjects who received open-label B/F/TAF)
Source: m2.7.3, Tables 1 and 2; GS-US-380-1878 Interim Week 48, Listing 16.2.1.3

Additional supportive data are provided from a Phase 3 study of GEN in adults with estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation ($eGFR_{CG}$) between 30 and 69 mL/min (inclusive; Study GS-US-292-0112), a Phase 3b study of GEN in HIV/HBV-coinfected adults (Study GS-US-292-1249), and 2 Phase 3 studies of TAF in adults with chronic HBV infection (Studies GS-US-380-0108 and GS-US-380-0110), supporting the efficacy and safety of B/F/TAF in adults with mild to moderate renal impairment and in HIV/HBV-coinfected adults.

Table 2. Primary Studies Supporting the Clinical Efficacy and Safety of B/F/TAF

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented	Narrative Location
HIV-Infected, ART-Naive Adult Subjects				
GS-US-380-1489	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs ABC/DTG/3TC	B/F/TAF (N = 314) ABC/DTG/3TC (N = 315)	Week 48 efficacy, PK, and safety	m2.7.3, Section 2.1.1
GS-US-380-1490	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs DTG+F/TAF	B/F/TAF (N = 320) DTG+F/TAF (N = 325)	Week 48 efficacy, PK, and safety	m2.7.3, Section 2.1.2
GS-US-141-1475	Phase 2, randomized, double-blind study to evaluate the safety and efficacy of BIC+F/TAF vs DTG+F/TAF Open-label extension phase allowed crossover to B/F/TAF from DTG+F/TAF or continuation of BIC and F/TAF as the B/F/TAF FDC	Double-blind phase: BIC 75 mg + F/TAF (N = 65) DTG+F/TAF (N = 33) Open-label extension phase: Continue BIC and F/TAF as the B/F/TAF FDC (N = 62) Switch to B/F/TAF from DTG+F/TAF (N = 30)	Double-blind phase: Week 48 efficacy, PK, and safety Open-label extension phase: Week 72 efficacy and safety	m2.7.3, Section 2.1.3
HIV-Infected, Virologically Suppressed Adult Subjects				
GS-US-380-1844	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of switching to B/F/TAF from DTG+ABC/3TC or ABC/DTG/3TC vs continuing DTG and ABC/3TC as the ABC/DTG/3TC FDC	Switch to B/F/TAF (N = 282) Stay on DTG and ABC/3TC as the ABC/DTG/3TC FDC (N = 281)	Week 48 efficacy, PK, and safety	m2.7.3, Section 2.2.1
GS-US-380-1878	Phase 3, randomized, open-label study to evaluate the safety and efficacy of switching to B/F/TAF vs continuing on boosted ATV or DRV plus either FTC/TDF or ABC/3TC	Randomized phase: Switch to B/F/TAF (N = 290) Stay on baseline regimen (SBR; N = 287) Open-label extension phase: Continue B/F/TAF (N = 241) Switch to B/F/TAF from SBR (N = 213)	Randomized phase: Week 48 efficacy, PK, and safety Open-label extension phase: deaths, SAEs, and discontinuations due to AEs	m2.7.3, Section 2.2.2

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).

1.2.4. Regulatory Guidelines and Advice

All B/F/TAF Phase 3 studies were of an adequate design and duration, as recommended in applicable regulatory guidance (International Council for Harmonisation [ICH] E8 and E10; {European Medicines Agency (EMEA) 2016, U. S. Department of Health and Human Services 2015}), with well-established endpoints to characterize the efficacy and safety of B/F/TAF for the treatment of HIV-1 infection {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER) 2002}. Advice was sought from the Committee for Medicinal Products for Human Use (CHMP) on 2 aspects of the nonclinical development plan (m2.4, Section 1.3). Advice on overall development was sought from the United States (US) Food and Drug Administration (FDA).

The overall clinical development plan for the B/F/TAF FDC for the treatment of HIV-1 infection was discussed with the US FDA at the [redacted] meeting on [redacted] 20[redacted]. At the [redacted] meeting, the US FDA [redacted], and that Studies GS-US-380-1844 and GS-US-380-1878 were adequately designed to provide supportive data for an NDA.

The clinical evidence provided from the clinical development described above support the use of B/F/TAF once daily for the treatment of adults infected with HIV-1 without any known mutations associated with resistance to the individual components.

2. OVERVIEW OF BIOPHARMACEUTICS

Biopharmaceutical studies of B/F/TAF are summarized in detail in m2.7.1.

2.1. Formulation

The designated commercial drug product is an immediate-release FDC tablet containing 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 200 mg of FTC, and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate) (m2.7.1, Section 1.1). This tablet formulation was used in all primary and registration stability batches and in all pivotal Phase 3 clinical studies. B/F/TAF tablets are capsule-shaped, film-coated purplish-brown, debossed with "GSI" on one side of the tablet and "9883" on the other side. B/F/TAF tablets are approximately 15 mm in length and 8 mm in width.

The B/F/TAF tablet is a bilayer tablet with one layer containing BIC and the other layer containing FTC and TAF. Bictegravir sodium is dry granulated with intragranular excipients to produce BIC granules, which are subsequently blended with extragranular excipients to produce the BIC final powder blend. FTC and TAF fumarate are co-dry granulated with intragranular excipients and lubricated with extragranular magnesium stearate to produce the F/TAF final powder blend. The BIC final powder blend and the F/TAF final powder blend are compressed into bilayer tablet cores that are then film-coated for appearance.

2.2. Dissolution Profile

The dissolution profile for the proposed commercial B/F/TAF FDC tablet formulation showed that not less than 90% of BIC, FTC, and TAF were dissolved by 30 minutes, consistent with the dissolution profile expected for an immediate-release formulation (m2.7.1, Section 1.2).

2.3. Bioavailability

Upon single-dose administration of the B/F/TAF (50/200/25 mg) FDC or BIC 75 mg + F/TAF (200/25 mg) under fasted conditions, the geometric least-squares mean ratios and their 90% CIs for the BIC primary PK parameters of AUC_{last}, AUC_{inf}, and C_{max} were 78.46% (73.38, 83.89), 78.56% (73.44, 84.04), and 78.07% (73.41, 83.01), respectively, and were within the protocol-defined boundary of PK equivalence (70% to 143%). Based on these data, the B/F/TAF 50/200/25 mg FDC was chosen for further evaluation in Phase 3 studies. Further details are provided in in m2.7.1, Section 3.1.

2.4. Food Effect on Exposure

Administration of B/F/TAF with or without food does not result in clinically meaningful changes in the PK of its components. B/F/TAF was administered without regard to food in Phase 2 and 3 studies. Collectively, safety, efficacy, PK, and PK/PD data support administration of B/F/TAF without regard to food. Further details are provided in m2.7.1, Section 3.2.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

A comprehensive program of nonclinical experiments and clinical studies has characterized the antiviral activity of B/F/TAF and its individual components. Nonclinical virology studies were performed to evaluate the individual and combination activity of BIC, FTC, and TAF in both biochemical and cell-based in vitro systems. Results for these nonclinical and clinical virology analyses for BIC, FTC, TAF, and B/F/TAF are provided in m2.7.2, Sections 4.1 and 4.2, respectively.

3.1. Mechanism of Action and In Vitro Activity

The INSTI BIC and the N(t)RTIs FTC and TAF are potent and selective inhibitors of HIV-1 and HIV-2. Emtricitabine and TAF are also potent and selective inhibitors of HBV. All 3 drugs show potent ARV activity against diverse subtypes of HIV-1 in vitro. Emtricitabine and TAF are phosphorylated intracellularly through nonoverlapping pathways, and in combination show no antagonism for the formation of their active metabolites. Bictegravir does not require metabolic modification for activity. Two- and 3-drug combinations of BIC, FTC, and TAF consistently show synergistic anti-HIV-1 activity in vitro and no evidence of antagonism or cytotoxicity.

The resistance profiles for the individual agents BIC, FTC, and TAF have been well characterized. There is no known cross-resistance between the NRTI and INSTI classes.

Bictegravir, FTC, and TAF have no pharmacologically significant off-target binding affinity to the receptors tested. Bictegravir, FTC, and TAF have low in vitro cytotoxicity in a variety of human cell types. Both FTC and TAF have shown a low potential for mitochondrial toxicity in long-term toxicity studies and there was no evidence of toxicity to mitochondria in vitro and in vivo.

Further details on the primary and secondary PD, and in vitro profiles of BIC, FTC, and TAF are provided in m2.7.2, Section 4.1.

3.2. Clinical Pharmacokinetics

A comprehensive clinical pharmacology program was conducted using BIC, TAF, and FTC as individual agents or as part of an FDC in Phase 1, 2, or 3 studies to support the use of B/F/TAF for the treatment of HIV infection (m2.7.2, Section 1.2). Phase 1 clinical studies evaluated single- and multiple-dose escalations, PK in healthy and HIV-infected subjects, absorption, distribution, metabolism, and elimination (ADME), the potential for B/F/TAF to affect other drugs, and the potential of food, other drugs, organ impairment, or other demographic factors to affect B/F/TAF. The steady-state PK of B/F/TAF was also evaluated in HIV-infected subjects in Phase 3 clinical studies. Population PK analyses evaluated intrinsic and extrinsic factors affecting the PK of BIC and TAF in HIV-infected subjects, and potential relationships were evaluated between BIC and TAF exposure and efficacy and safety outcomes. The PK and PK/PD conclusions based on these data are summarized in the following sections.

3.2.1. Pharmacokinetic Profile

Detailed summaries of clinical and nonclinical studies investigating the ADME of BIC, TAF, and FTC as single agents and as components of BIC+F/TAF or B/F/TAF are provided in m2.7.2, Section 3.1.

3.2.1.1. Absorption

The PK properties of BIC, TAF, and FTC have been evaluated in HIV-infected and healthy subjects. Following oral administration of B/F/TAF with or without food, BIC, TAF, and FTC were absorbed quickly with median peak plasma concentrations (T_{max}) observed from 2.0 to 4.0 hours, 0.5 to 2.0 hours, and 1.5 to 2.0 hours postdose, respectively. There are no clinically relevant differences in BIC, TAF, and FTC exposures (AUC_{tau}, C_{max}, and/or C_{tau}) between HIV-infected and healthy subjects. Bictegravir exposure is dose-proportional over the dose range of 25 to 100 mg; TAF exposure is dose-proportional over the dose range of 8 to 125 mg; and FTC exposure is dose-proportional over the dose range of 25 to 200 mg.

The multiple dose PK parameters of the components of B/F/TAF are provided in Table 3.

Table 3. Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of the B/F/TAF FDC With or Without Food in HIV-Infected Adults

Parameter Mean (%CV)	BIC (N = 1193)[a]	FTC (N = 77)[b]	TAF (N = 486)[c]
C_{max} (ng/mL)	6145.8 (22.9)	2127.0 (34.7)	121.3 (15.4)
AUC_{tau} (ng•h/mL)	102,001.0 (26.9)	12,293.6 (29.2)	142.0 (17.3)
C_{tau} (ng/mL)	2609.9 (35.2)	96.0 (37.4)[d]	NA

NA = not applicable
a From Population PK analysis in Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878
b From Intensive PK analysis in Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878
c From Population PK analysis in Studies GS-US-380-1489 and GS-US-380-1490
d n = 74
Source: m2.7.2, Tables 13 and 14; Table Req8913.3

3.2.1.2. Distribution

Bictegravir is > 99% bound to human plasma proteins. Following a single oral dose of [^{14}C]BIC in healthy subjects, the blood-to-plasma ratio of [^{14}C]-radioactivity ranged between 0.50 and 0.55 through 120 hours postdose. The ex vivo plasma protein binding of TAF was approximately 80% in healthy subjects. Following a single oral dose of [^{14}C]TAF in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity was 0.6 at 0.25 hours and 2.4 at 216 hours postdose. The protein binding of FTC was < 5% in human plasma. Following a single oral dose of [^{14}C]FTC in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity was approximately 1.0.

3.2.1.3. Metabolism

Bictegravir is primarily metabolized by cytochrome P450 (CYP)3A and uridine glucuronosyltransferase (UGT)1A1 with each enzyme playing an approximately equal role in the clearance of BIC. Following a single oral dose of [^{14}C]BIC, the majority (67.9%) of radioactivity in plasma was parent drug. Hydroxy-BIC-sulfate (20.1%) and BIC-glucuronide (8.6%) were the major metabolites identified in human plasma. Unchanged drug accounted for 31% to 34% of the radioactive dose in the feces that likely represents a combination of both unabsorbed drug and deconjugated BIC glucuronide. Desfluoro-hydroxy-BIC-cysteine-conjugate (10% to 13% of dose) and other minor oxidative metabolites were identified in feces. Radioactivity in urine consisted primarily of BIC-glucuronide(s) (21% of dose) and other minor oxidative metabolites and their conjugates.

Tenofovir alafenamide is rapidly metabolized to tenofovir (TFV) primarily via hydrolysis by carboxylesterase 1 (CES1) while cathepsin A (CatA) is the major enzyme hydrolyzing TAF to TFV in peripheral blood mononuclear cells (PBMCs). Tenofovir is then further phosphorylated to the active metabolite, tenofovir-diphosphate (TFV-DP) by cellular nucleotide kinases. [^{14}C]-radioactivity showed TAF as the most abundant species in the initial few hours and uric acid in the later period. The predominant species detected in feces and urine was TFV with other minor metabolites also present including xanthine, hypoxanthine, and adenine (< 2% of the dose).

Emtricitabine is not subject to significant hepatic metabolism and is eliminated primarily as unchanged drug by renal excretion. Emtricitabine is effectively metabolized intracellularly in PBMCs to form its active metabolite, emtricitabine 5′-triphosphate (FTC-TP). Following a single oral dose of [^{14}C]FTC to healthy subjects, FTC was the predominant species present in plasma. Sulfoxide metabolite(s) and direct glucuronide were primarily recovered in low levels in urine (12.9% of dose).

3.2.1.4. Excretion

Following a single oral dose of [^{14}C]BIC, mean total recovery of radioactivity was 95.3%, consisting of approximately 35.0% and 60.3% recovered in urine and feces, respectively. The median plasma BIC $t_{1/2}$ was approximately 17.26 hours. Radioactivity in feces consisted primarily of unchanged BIC (31% to 34% of dose) and other oxidative metabolites and their conjugates. Unchanged BIC likely represents a combination of both unabsorbed drug and deconjugated BIC glucuronide. Radioactivity in urine consisted primarily of BIC-glucuronide(s) (21% of dose) and other minor oxidative metabolites and their conjugates. Renal clearance of the unchanged BIC was minimal (1.3% of dose). The nonclinical and human ADME data indicate that metabolism is the primary clearance pathway for BIC.

Following a single oral dose of [^{14}C]TAF, approximately 84.4% of radioactive dose was recovered, with 47.2% of the dose from feces and 36.2% of the dose from urine. TAF was rapidly metabolized to TFV, with a median TAF plasma $t_{1/2}$ of 0.51 hours and the median TFV T_{max} of 3.25 hours and plasma $t_{1/2}$ of 32.37 hours. The predominant species detected in feces and urine was TFV with other minor metabolites including xanthine, hypoxanthine, and adenine (< 2% of the dose). Renal excretion of TAF as unchanged parent was minimal (1.4% of dose). The nonclinical and human ADME data indicate that TAF is primarily cleared through metabolism via the purine catabolic pathway following conversion to TFV.

Following a single oral dose of [^{14}C]FTC, 99.6% of the total radioactive dose was recovered, with 85.8% of the dose from urine and 13.7% of the dose from feces. The plasma FTC $t_{1/2}$ was approximately 10.2 hours. Approximately 65.4% of dose excreted in urine as parent, indicating FTC is eliminated primarily as unchanged drug by renal excretion.

3.2.2. Effect of Intrinsic Factors

Detailed summaries of the potential effect of intrinsic factors on PK are provided in m2.7.2, Section 3.2.3.

The impact of intrinsic factors on the PK of BIC, TAF, and FTC was evaluated in Phase 1 studies in non-HIV-infected subjects and as covariates in population PK analyses, which included HIV-infected subjects who received B/F/TAF, TAF, or FTC. Intrinsic factors evaluated include HIV infection status, renal and hepatic impairment, and demographic factors. No clinically relevant PK differences due to HIV infection status and demographic factors, such as age, weight, sex, and race, were identified for BIC, TAF, and FTC.

Clinically significant exposure changes of the TAF metabolite, TFV, and FTC were not observed in HIV-infected subjects with mild or moderate renal impairment relative to the subjects with normal renal function in Phase 3 clinical studies. Therefore, F/TAF-containing products are indicated for use in renally impaired, HIV-infected subjects with $eGFR_{CG} \geq 30$ mL/min. Consistent with the known ADME profile of BIC, severe renal impairment did not result in clinically relevant changes in BIC exposure. The recommendation for use of B/F/TAF in subjects with renal impairment is guided by the most conservative dosing recommendation for affected components in the setting of renal impairment (ie, FTC). B/F/TAF may be administered without dose adjustment in subjects with $eGFR_{CG} \geq 30$ mL/min. There are insufficient data available regarding the use of the B/F/TAF in subjects with $eGFR_{CG} < 30$ mL/min.

The PK of TAF was evaluated in non-HIV-infected subjects with mild, moderate, and severe hepatic impairment. Hepatic impairment did not result in clinically relevant changes in TAF exposure. Minimal change in FTC exposure is expected in subjects with hepatic impairment due to its renal clearance pathway. Therefore, F/TAF-containing products can be used in HIV-infected subjects with mild and moderate hepatic impairment without dose adjustment. The PK of BIC was studied in non-HIV-infected subjects with moderate hepatic impairment. Moderate hepatic impairment did not result in clinically relevant changes in BIC exposure. Therefore, B/F/TAF may be administered without dose adjustment in subjects with mild to moderate hepatic impairment. There are insufficient data available regarding the use of the B/F/TAF FDC in subjects with severe hepatic impairment.

3.2.3. Effect of Extrinsic Factors

Detailed summaries of the potential effect of extrinsic factors on PK are provided in m2.7.2, Section 3.2.4.

The impact of extrinsic factors on the PK of BIC, TAF, and FTC was evaluated in Phase 1 food-effect and DDI studies, as well as modeling and simulation analyses. Administration of B/F/TAF with or without food does not result in clinically meaningful changes in the PK of its

components; therefore, BIC+F/TAF and B/F/TAF were administered without regard to food in Phase 2 and Phase 3 clinical studies. The cumulative safety, efficacy, PK, and PK/PD data support administration of B/F/TAF without regard to food.

Bictegravir is a substrate of UGT1A1 and CYP3A. Potent inhibition of both CYP3A and UGT1A1 results in a substantial increase in BIC exposure, and coadministration of BIC with potent dual inhibitors of CYP3A and UGT1A1 is not recommended. Tenofovir alafenamide is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and although coadministration of B/F/TAF with potent inhibitors of P-gp and/or BCRP will result in increases in the plasma concentrations of TAF, these increases are not clinically relevant changes in exposures based on supporting safety data for TAF following administration of B/F/TAF. Drugs that are potent inducers of CYP3A, UGT1A1, and/or P-gp may result in lower plasma exposures of BIC and TAF and lead to reduced therapeutic effect of B/F/TAF; coadministration with potent inducers is not recommended. Coadministration with rifampin is contraindicated.

Coadministration of B/F/TAF with medications or oral supplements containing polyvalent cations (eg, magnesium, aluminum, calcium, and iron) under fasted conditions will result in a decrease of BIC exposure due to chelation of BIC with these cations. Administration of medications (eg, antacid) or oral supplements containing polyvalent cations should be separated from the fasted administration of B/F/TAF by at least 2 hours. Alternatively, these medications or oral supplements can be taken simultaneously with B/F/TAF together with food.

BIC, TAF, and FTC are not clinically relevant inhibitors or inducers of major human drug metabolizing enzymes and transporters. As such, there is low potential for B/F/TAF to be perpetrators of DDIs through human drug metabolizing enzymes or drug transporters, including with the organic cation transporter 2 (OCT2)/multidrug and toxin extrusion 1 (MATE1) substrate metformin. No data are available regarding the use of B/F/TAF with dofetilide, which has a narrow therapeutic index and which is a substrate of OCT2/MATE1. Due to the potential for serious and/or life-threatening events with increased dofetilide plasma concentrations, coadministration of B/F/TAF with dofetilide is contraindicated.

3.3. Clinical Pharmacokinetics/Pharmacodynamics

Detailed summaries PK/PD relationships with efficacy and safety parameters are provided in m2.7.2, Sections 3.3.2 and 3.3.3, respectively.

A 50-mg dose of BIC was selected based on the totality of PK, safety, and efficacy data from Phase 1 and 2 studies in conjunction with the knowledge that trough concentration maintained above the in vitro protein-adjusted 95% effective concentration ($paEC_{95}$: 361 nM or 162 ng/mL) is desired for INSTIs. Bictegravir 50 mg, coformulated as the B/F/TAF 50/200/25 mg FDC, provided near maximal virologic response and an inhibitory quotient (IQ) of 16.1-fold above the $paEC_{95}$ against wild-type HIV-1 virus. The 25-mg dose of TAF and the 200-mg dose of FTC are approved for the treatment of HIV-1 infection in combination with other ARV agents and as a component of the complete regimen, Odefsey. Tenofovir alafenamide and FTC demonstrated a lack of DDIs with BIC and were coformulated as the B/F/TAF 50/200/25 mg FDC for Phase 3 studies.

In the Phase 3 studies, exposure-efficacy relationships at BIC and TAF exposures (AUC_{tau} and C_{max}) above or below population median, as well as across quartiles for individual agents versus the primary efficacy endpoint (HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA defined snapshot algorithm), were examined. All analyses consistently revealed high virologic response rates across all groups (including subjects with the lowest quartile exposure to BIC and TAF) with no trends in exposure-response relationships. Importantly, for BIC in particular, all subjects had trough concentrations (C_{tau}) above the $paEC_{95}$ with no loss of efficacy at lower IQ. Exposure of once-daily FTC 200 mg has consistently demonstrated efficacy in clinical studies and is a standard of care in HIV treatment.

Relationships between BIC and TAF exposure parameters and safety parameters from Phase 3 studies were evaluated. Bictegravir and TAF exposures (AUC_{tau} and C_{max}) were similar regardless of the presence or absence of the most common adverse events (AEs), indicating a lack of association between BIC or TAF and findings of diarrhea, headache, nausea, nasopharyngitis, and fatigue in the Phase 3 studies. Exposure of once-daily FTC 200 mg has consistently demonstrated safety in clinical studies and is a standard of care in HIV treatment.

4. OVERVIEW OF EFFICACY

This section provides an overview of the pooled analysis of efficacy that was conducted for the pivotal Phase 3 studies in ART-naive adults (Studies GS-US-380-1489 and GS-US-380-1490), as well as results from the individual studies as appropriate, and of the efficacy results of the individual studies of B/F/TAF in virologically suppressed adults (Studies GS-US-380-1844 and GS-US-380-1878) and of BIC 75 mg + F/TAF in ART-naive adults (Study GS-US-141-1475) (Table 2; detailed descriptions of efficacy data are provided in m2.7.3, Section 3.2).

Pooling of the efficacy data for Studies GS-US-380-1489 and GS-US-380-1490 is appropriate due to their similar study design, including key eligibility criteria (m2.7.3, Section 1.2). Statistical methods for pooling and analysis of efficacy data are provided in the B/F/TAF Integrated Summary of Efficacy statistical analysis plan (SAP). No other data were pooled due to differences in the subject populations and study designs. The clinical virology analyses conducted for the B/F/TAF development program are described in m2.7.2, Section 4.2.

Demographic and general baseline characteristics were similar between treatment groups within each study (m2.7.3, Section 3.1.2.1); characteristics of the overall population are summarized below:

- Mean age was 35 years in ART-naive subjects (both in the pooled analysis of Studies GS-US-380-1489 and GS-US-380-1490, and in Study GS-US-141-1475) and 45 and 46 years, respectively, in the 2 studies of virologically suppressed subjects (Studies GS-US-380-1844 and GS-US-380-1878).

- Most subjects were male (ranging from 83% to 96% across the individual studies and pooled analysis). The proportion of female subjects (approximately 12% across all studies combined) was similar to the Phase 3 studies for GEN (Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0109, and GS-US-292-0112).

- The most common races were white (ranging from 57% to 73% across the individual studies and pooled analysis) and black (ranging from 22% to 37% across the individual studies and pooled analysis), and approximately 15% to 24% of subjects across the individual studies and pooled analysis were Hispanic or Latino.

Generally, baseline disease characteristics were similar between treatment groups within each study (m2.7.3, Section 3.1.2.2); characteristics of the overall population are summarized below:

- Median baseline HIV-1 RNA in ART-naive subjects was approximately 4.4 $\log_{10}$ copies/mL and approximately 17.5% of subjects had baseline HIV-1 RNA above 100,000 copies/mL.

- Median baseline CD4 cell count was approximately 440 cells/µL in ART-naive subjects and ranged from 617 to 732 cells/µL across treatment groups in the studies of virologically suppressed subjects.

- Most subjects in each study had asymptomatic HIV infection.

Subjects with HIV/HBV coinfection were enrolled as follows: 14 ART-naive subjects (B/F/TAF 8 subjects; DTG+F/TAF 6 subjects) in Study GS-US-380-1490 and 14 virologically suppressed subjects (B/F/TAF 8 subjects; SBR 6 subjects) in Study GS-US-380-1878.

Across the Phase 3 studies, 25 subjects (B/F/TAF group 10 subjects; comparator groups 15 subjects) were coinfected with hepatitis C virus (HCV) at baseline and 16 subjects (B/F/TAF group 8 subjects; comparator groups 8 subjects) had incident HCV infection.

Overall, the studied populations are representative of both ART-naive and virologically suppressed HIV-infected subjects in the general population. In addition, clinical data were collected from a broad range of countries to support applicability across different geographical regions (Table 1).

4.1. Rationale for Primary Efficacy Endpoint

In accordance with US FDA guidance on developing ARV drugs for the treatment of HIV-1 infection and the CHMP Guideline on the clinical development of medicinal products for the treatment of HIV infection (EMEA/CPMP/EWP/633/02 Rev. 3), the primary efficacy endpoint for the studies of ART-naive HIV-infected subjects was the proportion of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm (at Week 48 for the Phase 3 Studies GS-US-380-1489 and GS-US-380-1490, and at Week 24 for the double-blind phase of the Phase 2 Study GS-US-141-1475), whereas the primary efficacy endpoint for the studies of virologically suppressed HIV-infected subjects (Studies GS-US-380-1844 and GS-US-380-1878) was the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL using the US FDA-defined snapshot algorithm at Week 48 {U. S. Department of Health and Human Services 2015}. The assay utilized to assess HIV-1 RNA levels was the sensitive, US FDA-approved, COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, Version 2.0 (Roche).

Noninferiority of treatment with B/F/TAF versus active comparators was assessed using a 2-sided 95% CI with a noninferiority margin of −12% for the studies of ART-naive HIV-infected subjects and a noninferiority margin of 4% for the studies of virologically suppressed HIV-infected subjects. These margins are appropriate for the establishment of noninferiority of B/F/TAF against active comparators with well-defined efficacy in accordance with US FDA guidance on developing ARV drugs for the treatment of HIV-1 infection. Noninferiority was assessed using the Full Analysis Set (FAS) and the Per Protocol (PP) Analysis Set (a detailed description of the analysis populations is provided in m2.7.3, Section 3.1.3).

4.2. Efficacy in ART-Naive Adult Subjects

Detailed descriptions of the efficacy results from the pooled analysis of the Phase 3 ART-naive Studies GS-US-380-1489 and GS-US-380-1490 are provided in m2.7.3, Section 3.2.1, along with the results from those studies individually and of the double-blind phase of the Phase 2 Study GS-US-141-1475. A detailed description of the efficacy results from the open-label extension phase of the Phase 2 Study GS-US-141-1475 is provided in m2.7.3, Section 5.

The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were as follows (Table 4):

- Pooled B/F/TAF 90.9%
- ABC/DTG/3TC 93.0%
- DTG+F/TAF 92.9%

Because the lower bounds of the 2-sided 95% CIs of the differences between treatment groups (pooled B/F/TAF – ABC/DTG/3TC and pooled B/F/TAF – DTG+F/TAF) were greater than the prespecified −12% margin, B/F/TAF was determined to be noninferior to both ABC/DTG/3TC (difference in percentages [95% CI]: −2.1% [−5.9% to 1.6%]) and DTG+F/TAF (difference in percentages [95% CI]: −1.9% [−5.6% to 1.8%]).

These pooled results confirm those from the individual studies GS-US-380-1489 and GS-US-380-1490, where noninferiority of B/F/TAF versus ABC/DTG/3TC and DTG+F/TAF, respectively, was determined using the FAS (GS-US-380-1489: difference in percentages [95.002% CI]: −0.6% [−4.8% to 3.6%]; GS-US-380-1490: difference in percentages [95.002% CI]: −3.5% [−7.9% to 1.0%]) and confirmed using the PP Analysis Set.

Table 4. GS-US-380-1489 and GS-US-380-1490: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 copies/mL – Pooled Data (Full Analysis Set)

	Pooled B/F/TAF 380-1489,1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)
HIV-1 RNA < 50 copies/mL	576 (90.9%)	293 (93.0%)	302 (92.9%)
Difference in Percentages (95% CI)	—	-2.1% (-5.9% to 1.6%)	-1.9% (-5.6% to 1.8%)
p-value	—	0.26	0.32
HIV-1 RNA ≥ 50 copies/mL	17 (2.7%)	8 (2.5%)	4 (1.2%)
HIV-1 RNA ≥ 50 copies/mL in Week 48 Window	5 (0.8%)	6 (1.9%)	1 (0.3%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	0
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA ≥ 50 copies/mL	12 (1.9%)	2 (0.6%)	3 (0.9%)
No Virologic Data in Week 48 Window	41 (6.5%)	14 (4.4%)	19 (5.8%)
Discontinued Study Drug Due to AE/Death	3 (0.5%)	4 (1.3%)	3 (0.9%)
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA < 50 copies/mL	27 (4.3%)	9 (2.9%)	14 (4.3%)
Missing Data During Window but on Study Drug	11 (1.7%)	1 (0.3%)	2 (0.6%)

Week 48 window is between Day 295 and 378 (inclusive).
* Other reasons include subjects who discontinued study drug due to investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
P-value for the superiority test comparing the percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups was from the Cochran-Mantel-Haenszel test stratified by baseline HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. Ex-US).
The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportion adjusted by baseline HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. Ex-US).
Source: m2.7.3, Table 22

Results from the pooled analysis of Studies GS-US-380-1489 and GS-US-380-1490 and from those studies individually for other key efficacy endpoints and subgroup analyses were similar between treatment groups, as summarized below:

- The percentages of subjects with HIV-1 RNA < 20 copies/mL at Week 48 using the US FDA-defined snapshot algorithm for the pooled data were as follows: Pooled B/F/TAF 84.9%; ABC/DTG/3TC 87.3%; DTG+F/TAF 87.1%. The differences in percentages (95% CIs) were as follows:

  — Pooled B/F/TAF vs ABC/DTG/3TC −2.2% (−6.8% to 2.4%)

  — Pooled B/F/TAF vs DTG+F/TAF −1.6% (−6.2% to 3.0%)

- In the pooled subgroup analysis (ie, pooled B/F/TAF group vs pooled active control [ABC/DTG/3TC and DTG+F/TAF]), the percentages of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm were similar between treatment groups for each of the subgroups analyzed (age, sex, race, baseline HIV-1 RNA, baseline CD4 cell count, region, and study drug adherence) (m2.7.3, Section 3.3.1). The 95% CIs for differences between treatment groups included zero for all subgroups evaluated.

- The percentages of subjects in the individual studies with HIV-1 RNA < 50 copies/mL at Week 48 using the missing = failure (M = F) method were as follows:

  — Study GS-US-380-1489: B/F/TAF 92.4%; ABC/DTG/3TC 93.3%; difference in percentages (95% CI) −0.9% (−5.1% to 3.2%)

  — Study GS-US-380-1490: B/F/TAF 90.0%; DTG+F/TAF 93.5%; difference in percentages (95% CI) −3.4% (−7.7% to 0.9%)

- No subject in the Phase 2 or Phase 3 studies of ART-naive subjects developed treatment-emergent resistance to any component of B/F/TAF (m2.7.2, Section 4.2.1).

- Mean (SD) increases from baseline in CD4 cell counts at Week 48 (observed data) were similar between treatment groups for the pooled analysis, as follows: Pooled B/F/TAF 207 (178.0) cells/µL; ABC/DTG/3TC 229 (188.8) cells/µL; DTG+F/TAF 201 (166.4) cells/µL (results were generally consistent for the last observation carried forward [LOCF] method).

Efficacy data from the Phase 2 ART-naive study GS-US-141-1475 supported those from the Phase 3 ART-naive studies and demonstrated evidence of durable efficacy; 100.0% (61 of 61 subjects) of subjects treated with BIC 75 mg + F/TAF during the double-blind phase (and switching to B/F/TAF for the extension phase) achieved and maintained HIV-1 RNA < 50 copies/mL at Week 72 (missing = excluded [M = E]).

4.3. Efficacy in Virologically Suppressed Adult Subjects

Key treatment outcomes for Studies GS-US-380-1844 and GS-US-380-1878 are described below; full details are provided in m2.7.3, Section 3.2.2.

The percentages of subjects in the FAS with HIV-1 RNA ≥ 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were as follows (Table 5):

- Study GS-US-380-1844: B/F/TAF 1.1%; ABC/DTG/3TC 0.4%

- Study GS-US-380-1878: B/F/TAF 1.7%; SBR 1.7%

Because the upper bound of the 2-sided 95.002% CI of the difference between treatment groups (B/F/TAF − ABC/DTG/3TC and B/F/TAF − SBR) was less than the prespecified 4% margin, switching to B/F/TAF was determined to be noninferior to both maintaining ABC/DTG/3TC (difference in percentages [95.002% CI]: 0.7% [−1.0% to 2.8%]) and staying on a baseline

regimen consisting of boosted ATV or DRV plus either FTC/TDF or ABC/3TC (difference in percentages [95.002% CI]: −0.0% [−2.5% to 2.5%]). Noninferiority of B/F/TAF versus ABC/DTG/3TC and B/F/TAF versus SBR was confirmed by analyses using the PP Analysis Sets in each study.

Table 5. GS-US-380-1844 and GS-US-380-1878: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 copies/mL (FAS)

	GS-US-380-1844		GS-US-380-1878	
	B/F/TAF (N = 282)	**ABC/DTG/3TC (N = 281)**	**B/F/TAF (N = 290)**	**SBR (N = 287)**
HIV-1 RNA < 50 copies/mL	264 (93.6%)	267 (95.0%)	267 (92.1%)	255 (88.9%)
Difference in Percentages (95.002% CI)	-1.4% (−5.5% to 2.6%)		3.2% (-1.6% to 8.2%)	
p-value	0.59		0.20	
HIV-1 RNA ≥ 50 copies/mL	3 (1.1%)	1 (0.4%)	5 (1.7%)	5 (1.7%)
Difference in Percentages (95.002% CI)	0.7% (-1.0% to 2.8%)		-0.0% (-2.5% to 2.5%)	
p-value	0.62		1.00	
HIV-1 RNA ≥ 50 copies/mL in Week 48 Window	1 (0.4%)	0	2 (0.7%)	2 (0.7%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	1 (0.3%)	0
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA ≥ 50 copies/mL	1 (0.4%)	0	0	0
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA ≥ 50 copies/mL	1 (0.4%)	1 (0.4%)	2 (0.7%)	3 (1.0%)
No Virologic Data in Week 48 Window	15 (5.3%)	13 (4.6%)	18 (6.2%)	27 (9.4%)
Discontinued Study Drug Due to AE/Death and the Last Available HIV-1 RNA < 50 copies/mL	5 (1.8%)	2 (0.7%)	3 (1.0%)	2 (0.7%)
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA < 50 copies/mL	5 (1.8%)	9 (3.2%)	10 (3.4%)	19 (6.6%)
Missing Data During Window but on Study Drug	5 (1.8%)	2 (0.7%)	5 (1.7%)	6 (2.1%)

Week 48 window was between Day 295 and 378 (inclusive).
* Other reasons included subjects who discontinued study drug due to investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
P-values for the superiority tests comparing the percentages between treatment groups were from the Fisher exact test.
The differences in percentages of subjects between treatment groups and their 95.002% CIs were calculated based on an unconditional exact method using 2 inverted 1-sided tests.
Source: m2.7.3, Tables 24 and 25

Results for other key efficacy endpoints and subgroup analyses from Studies GS-US-380-1844 and GS-US-380-1878 were similar between treatment groups, as summarized below:

- The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were as follows:
  - Study GS-US-380-1844: B/F/TAF 93.6%; ABC/DTG/3TC 95.0%; difference in percentages (95.002% CI) −1.4% (−5.5% to 2.6%)
  - Study GS-US-380-1878: B/F/TAF 92.1%; SBR 88.9%; difference in percentages (95.002% CI) 3.2% (−1.6% to 8.2%)
- The percentages of subjects in the FAS with HIV-1 RNA < 20 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were as follows:
  - Study GS-US-380-1844: B/F/TAF 90.1%; ABC/DTG/3TC 91.5%; difference in percentages (95% CI): −1.4% (−6.4% to 3.5%)
  - Study GS-US-380-1878: B/F/TAF 85.9%; SBR 84.7%; difference in percentages (95% CI) 1.2% (−4.7% to 7.1%)
- The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the M = F method were as follows:
  - Study GS-US-380-1844: B/F/TAF 95.0%; ABC/DTG/3TC 95.4%; difference in percentages (95% CI) −0.3% (−4.1% to 3.4%)
  - Study GS-US-380-1878: B/F/TAF 92.8%; SBR 90.9%; difference in percentages (95% CI) 1.8% (−2.8% to 6.5%)
- In the subgroup analyses for Studies GS-US-380-1844 and GS-US-380-1878, the percentages of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm were similar between treatment groups for each of the subgroups analyzed (age, sex, race, region, and study drug adherence [analysis by adherence subgroup performed in Study GS-US-380-1844 only]) (m2.7.3, Section 3.3.2). The 95% CIs for differences between treatment groups included zero for all subgroups evaluated.
- No subject in either study developed treatment-emergent resistance to any component of B/F/TAF (m2.7.2, Section 4.2.1).
- The mean (SD) changes from baseline in CD4 cell counts at Week 48 (observed data) were as follows:
  - Study GS-US-380-1844: B/F/TAF −31 (181.3) cells/μL; ABC/DTG/3TC 4 (191.0) cells/μL
  - Study GS-US-380-1878: B/F/TAF 25 (151.2) cells/μL; SBR 0 (159.4) cells/μL

4.4. Efficacy in Special Populations

Efficacy results from Studies GS-US-380-1490 and GS-US-380-1878 support the efficacy of TAF-containing regimens for the treatment of HBV in the context of HIV/HBV-coinfection.

HBV DNA suppression (HBV DNA < 29 IU/mL) was achieved by Week 48 in 84.6% (11 of 13 subjects with available data) of ART-naive HIV/HBV-coinfected adults treated with B/F/TAF or DTG+F/TAF in Study GS-US-380-1490. The 2 subjects who did not have HBV DNA < 29 IU/mL at Week 48 had baseline values > 170,000,000 IU/mL and Week 48 values of 303 and 80 IU/mL, respectively. Among virologically suppressed HIV/HBV-coinfected adults who switched to B/F/TAF from an FTC/TDF-based regimen (Study GS-US-380-1878), HBV DNA suppression (HBV DNA < 29 IU/mL) was maintained through Week 48 in 100% (8 of 8 subjects with available data).

Additional supportive studies demonstrating the efficacy of TAF for the treatment of HBV monoinfection (Studies GS-US-320-0108 and GS-US-320-0110) and for the treatment of HBV in HIV/HBV-coinfected subjects in the context of the TAF-containing product GEN (Study GS-US-292-1249) are summarized in m2.7.3, Section 3.3.3.

4.5. Efficacy Conclusions

The efficacy of B/F/TAF was noninferior to guideline-recommended ART regimens in the Phase 3 studies, as follows:

- In ART-naive adults, B/F/TAF was noninferior to both ABC/DTG/3TC and DTG+F/TAF for the Week 48 primary endpoint (HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm) as the lower bounds of the 2-sided 95% CIs of the differences between treatment groups were greater than the prespecified −12% margin (−5.9% for pooled B/F/TAF – ABC/DTG/3TC; −5.6% for pooled B/F/TAF – DTG+F/TAF).

- In virologically suppressed adults, switching to B/F/TAF was noninferior to either continuing ABC/DTG/3TC or staying on a baseline regimen consisting of boosted ATV or DRV plus either FTC/TDF or ABC/3TC for the Week 48 primary endpoint (HIV-1 RNA ≥ 50 copies/mL using the US FDA-defined snapshot algorithm) as the upper bounds of the 2-sided 95.002% CI of the difference between treatment groups were less than the prespecified 4% margin (2.8% for B/F/TAF − ABC/DTG/3TC; 2.5% for B/F/TAF – SBR).

High rates of virologic suppression were achieved and/or maintained through 48 weeks of treatment in the Phase 3 studies:

- In ART-naive adults, subjects achieved high rates of virologic suppression as assessed by HIV-1 RNA < 50 copies/mL in the FAS using the US FDA-defined snapshot algorithm (Pooled B/F/TAF 90.9%; ABC/DTG/3TC 93.0%; DTG+F/TAF 92.9%).

- In virologically suppressed adults switching to B/F/TAF, subjects maintained high rates of virologic suppression through 48 weeks of treatment as assessed by HIV-1 RNA < 50 copies/mL in the FAS using the US FDA-defined snapshot algorithm (Study GS-US-380-1844: B/F/TAF 93.6% and ABC/DTG/3TC 95.0%; Study GS-US-380-1878: B/F/TAF 92.1% and SBR 88.9%).

In the Phase 2 Study GS-US-141-1475, 100% of subjects treated with BIC 75 mg + F/TAF during the double-blinded phase (and switching to B/F/TAF for the extension phase) achieved and maintained HIV-1 RNA < 50 copies/mL through 72 weeks of treatment (M = E), providing evidence for durable efficacy.

Among subjects with HIV/HBV coinfection, 84.6% of ART-naive subjects (11 of 13 subjects with available data) with an F/TAF-containing regimen (B/F/TAF or DTG+F/TAF) and 100% of virologically suppressed subjects (8 of 8 subjects with available data) treated with B/F/TAF had HBV DNA < 29 IU/mL at Week 48.

Across all studies, analyses of secondary HIV-1 RNA endpoints supported the primary efficacy analyses. Generally, there was no difference in efficacy across the different subpopulations evaluated. In addition, the immunologic benefits of treatment with B/F/TAF were demonstrated by improvements in CD4 cell counts in ART-naive subjects and maintenance of CD4 cell counts in virologically suppressed subjects. Overall, these results indicate that B/F/TAF is efficacious in all populations without regard to demographic or HIV disease characteristics.

Across the Phase 2 and Phase 3 studies, no subject developed treatment-emergent resistance to any component of B/F/TAF.

Overall, these data demonstrate potent and durable efficacy of B/F/TAF for the treatment of HIV-1 infection in ART-naive and virologically suppressed adults.

5. OVERVIEW OF SAFETY

This section provides an overview of the pooled analysis of safety that was conducted for the pivotal Phase 3 studies in ART-naive subjects (GS-US-380-1489 and GS-US-380-1490), along with safety results of the individual studies, as appropriate, and of the safety results of the individual Phase 3 studies in virologically suppressed adults (GS-US-380-1844 and GS-US-380-1878) (Table 2). For the open-label Study GS-US-380-1878, 454 subjects switched from randomized treatment to open-label B/F/TAF at the Week 48 visit (241 subjects initially randomized to B/F/TAF; 213 subjects initially randomized to SBR); extension-phase deaths, serious adverse events (SAEs), and discontinuations due to AEs for these subjects are included in addition to all randomized-phase data. Additionally, an overview of the safety results from the Phase 2 study in ART-naive subjects (GS-US-141-1475) is presented in Section 5.4.

Pooling of the safety data for Studies GS-US-380-1489 and GS-US-380-1490 is appropriate due to their similar study design, including key eligibility criteria (m2.7.4, Section 1.1). Statistical methods for pooling and analysis of safety data are provided in the B/F/TAF Integrated Summary of Safety (ISS) SAP. No other data were pooled due to differences in the subject populations and study designs.

A comprehensive nonclinical pharmacology and virology, PK, and toxicology program for BIC, TAF, and FTC as single agents was undertaken to support the clinical evaluation of B/F/TAF for the treatment of HIV-1 infection. No specific findings from the nonclinical program were confirmed as safety concerns in the clinical development program (m2.4, Section 1).

5.1. Extent of Exposure

In the randomized phases of the 4 Phase 3 studies, 1206 subjects were treated with B/F/TAF, with median (Q1, Q3) exposure of 49.2 (45.6, 56.1) weeks in ART-naive adults (pooled data from Studies GS-US-380-1489 and GS-US-380-1490) and 49.9 (45.1, 56.3) weeks and 46.7 (44.0, 48.0) weeks, respectively, in virologically suppressed adults (Studies GS-US-380-1844 and GS-US-380-1878) (m2.7.4, Section 1.2). This population exposure to B/F/TAF exceeds the requirements of the ICH E1 guideline for the safety evaluation of drugs. The duration of exposure was similar between groups within each study.

Duration of exposure in the Phase 2 Study GS-US-141-1475 is described in Section 5.4.

5.2. Adverse Events

The adverse event (AE) profile was generally similar in ART-naive and virologically suppressed adults (Table 6; m2.7.4, Section 2). All of the treatments evaluated (B/F/TAF, ABC/DTG/3TC, DTG+F/TAF, and boosted ATV or DRV plus FTC/TDF or ABC/3TC) were well tolerated, with comparable rates of Grade 3 or 4 AEs, SAEs, SAEs considered related to study drugs, and AEs leading to study drug discontinuation. Across the Phase 3 studies, 7 deaths were reported.

The percentages of subjects reporting any AE were as expected for the respective study populations. In ART-naive adults, the most commonly reported AEs following treatment with B/F/TAF were diarrhea, headache, and nausea. The most commonly reported AEs in

virologically suppressed subjects switching to B/F/TAF were upper respiratory tract infection, diarrhea, and nasopharyngitis in Study GS-US-380-1844 and headache, diarrhea, nasopharyngitis, and upper respiratory tract infection in Study GS-US-380-1878. These events were generally consistent with those from prior studies of GEN and other TAF-based regimens {Genvoya 2017, GENVOYA® 2017}.

Across the Phase 3 studies, most of the AEs considered related to study drug were Grade 1 or 2 in severity. The incidence of study drug-related AEs was similar between the B/F/TAF and DTG+F/TAF treatment groups in Study GS-US-380-1490. When compared with ABC/DTG/3TC, the incidence of study drug-related AEs for B/F/TAF was lower both in ART-naive (Study GS-US-380-1489) and virologically suppressed subjects (Study GS-US-380-1844). The difference between treatment groups was mainly in the gastrointestinal disorders system organ class (SOC) for Study GS-US-380-1489, and in the gastrointestinal disorders and psychiatric disorders SOCs for Study GS-US-380-1844. As expected, among virologically suppressed subjects who were stable on their treatment regimen before participating in Study GS-US-380-1878, the incidence of AEs considered related to study drug was higher among subjects who switched to B/F/TAF than among subjects who stayed on their baseline boosted-PI regimen, likely due to the open-label study design.

Table 6. GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

	ART-Naive Adult Subjects			Virologically Suppressed Adult Subjects			
	380-1489, 1490	380-1489	380-1490	GS-US-380-1844		GS-US-380-1878	
	Pooled B/F/TAF (N = 634)	ABC/DTG/ 3TC (N = 315)	DTG +F/TAF (N = 325)	B/F/TAF (N = 282)	ABC/DTG/ 3TC (N = 281)	B/F/TAF (N = 290)	SBR (N = 287)
Any AE	529 (83.4%)	283 (89.8%)	272 (83.7%)	225(79.8%)	225 (80.1%)	233 (80.3%)	226 (78.7%)
Grade 3 or 4 AE	56 (8.8%)	24 (7.6%)	25 (7.7%)	16 (5.7%)	10 (3.6%)	13 (4.5%)	18 (6.3%)
Study Drug-Related AE	139 (21.9%)	127 (40.3%)	83 (25.5%)	23 (8.2%)	44 (15.7%)	54 (18.6%)	6 (2.1%)
Grade 3 or 4 Study Drug-Related AE	5 (0.8%)	4 (1.3%)	0	2 (0.7%)	0	2 (0.7%)	0
Any SAE	58 (9.1%)	25 (7.9%)	23 (7.1%)	15 (5.3%)	22 (7.8%)	17 (5.9%)	20 (7.0%)
Study Drug-Related SAE	3 (0.5%)	1 (0.3%)	0	1 (0.4%)	0	1 (0.3%)	0
AE Leading to Premature Study Drug Discontinuation	5 (0.8%)	4 (1.3%)	1 (0.3%)	6 (2.1%)	2 (0.7%)	2 (0.7%)	1 (0.3%)
Death	1 (0.2%)	0	2 (0.6%)	2 (0.7%)	0	1 (0.3%)	1 (0.3%)

The denominator for percentages was based on the number of subjects in the Safety Analysis Set
Severity grades were defined by Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities.
Relatedness to study drug is assessed by the investigator.
Source: m2.7.4, Tables 5, 7, and 8

5.2.1. Deaths, Serious Adverse Events, and Discontinuations due to Adverse Events

Across the Phase 3 studies, 7 deaths were reported: 4 in subjects receiving B/F/TAF (Studies GS-US-380-1490, GS-US-380-1844, or GS-US-380-1878), 2 in subjects receiving DTG+F/TAF (Study GS-US-380-1490), and 1 in a subject receiving boosted ATV + FTC/TDF (Study GS-US-380-1878). None of the deaths was considered related to study drug (m2.7.4, Section 2.1.2).

Across the Phase 3 studies, 7.5% of subjects (90 of 1206 subjects) who were randomized to B/F/TAF and received at least 1 dose of study drug had any SAEs (m2.7.4, Section 2.1.3). An additional 4 of 454 subjects (0.9%) in the extension phase of Study GS-US-380-1878 had an SAE. The incidence of SAEs during the randomized phases for the studies was comparable between treatment groups within each study. Five SAEs considered related to study drug were reported in subjects treated with B/F/TAF and 1 was reported in a subject treated with ABC/DTG/3TC. There was no consistency in the nature of B/F/TAF-related SAEs across studies.

Across the Phase 3 studies, 1.1% of subjects (13 of 1206 subjects) who were randomized to B/F/TAF and received at least 1 dose of study drug discontinued study drug due to AEs (m2.7.4, Section 2.1.4). One additional subject (0.2%; 1 of 454 subjects) who switched from SBR to B/F/TAF in the extension phase of Study GS-US-380-1878 discontinued study drug due to AEs. The nature of the AEs leading to discontinuation in the B/F/TAF group were generally similar to those in the comparator groups consisting of DTG coadministered with 2 N(t)RTIs. The incidence of AEs leading to discontinuation of study drug was comparable between treatment groups within each study.

5.2.2. Analysis of Adverse Events by Organ System or Syndrome

In nonclinical studies with BIC, the only notable adverse finding was partially reversible microscopic hepatobiliary toxicity in monkeys following 39 weeks of dosing at 1000 mg/kg/day, corresponding to BIC AUC plasma values that were 16-fold higher than clinical BIC AUC plasma values when administered as B/F/TAF (50/200/25 mg). Reversible alanine aminotransferase (ALT) elevations at 1000 mg/kg/day were not clearly associated with the hepatobiliary changes. The no observed effect level (NOEL) was 200 mg/kg/day, corresponding to BIC AUC plasma values that were at least 7.0-fold higher than clinical BIC AUC observed in the Phase 3 studies. Hepatic safety was assessed in the Phase 3 studies through analyses of clinical laboratory results and a standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ)-based analysis of non-infectious and non-congenital hepatic AEs.

Both TAF and TDF are oral prodrugs of TFV, a nucleotide analog that inhibits HIV-1 reverse transcription. Although TDF is a preferred NtRTI for initial therapy, nephrotoxicity is an identified risk, and reductions in bone mineral density (BMD) have been shown that are larger than those seen with other NRTIs. Both TAF-containing regimens and ABC-containing regimens have preferential bone and renal safety profiles relative to TDF-containing regimens {Genvoya 2017, GENVOYA® 2017, McComsey 2011}, and ABC/DTG/3TC is not associated with bone or renal toxicity. To compare the bone and renal safety profiles of a TAF-containing regimen to those of an ABC-containing regimen, BMD was assessed in Studies GS-US-380-1489 and GS-US-380-1844, and urine albumin to creatinine ratio (UACR),

urine retinol binding protein (RBP) to creatinine ratio, and urine beta-2-microglobulin to creatinine ratio were assessed in Studies GS-US-380-1489, GS-US-380-1844, and GS-US-380-1878.

Serum creatinine and $eGFR_{CG}$ were assessed in all of the Phase 3 studies to evaluate the known in vitro inhibitory effects of BIC and DTG on the renal transporters OCT2 and MATE1.

In a 39-week toxicology study in dogs, some animals administered the highest dose of TAF (12 to 18 mg/kg/day) had minimal mononuclear cell infiltration in the posterior uvea, considered secondary to general debilitation. This did not occur in animals given lower TAF doses or in other animal studies. This nonclinical finding has not been observed in humans administered a much lower dose of TAF. Analyses of eye disorders SOC AEs and potential uveitis AEs were performed across the 4 Phase 3 B/F/TAF studies.

Analyses of AEs based on the suicide/self injury SMQ were performed across the 4 Phase 3 B/F/TAF studies.

5.2.2.1. Hepatic Safety

B/F/TAF demonstrated a hepatic safety profile similar to that of the comparator regimens in the Phase 3 studies (m2.7.4, Section 2.1.5.1).

The incidence of non-infectious, non-congenital hepatic AEs was comparable between the B/F/TAF and comparator group within each Phase 3 study and within the pooled analysis, as follows:

- In ART-naive adults,
  - Studies GS-US-380-1489 and GS-US-380-1490: Pooled B/F/TAF 1.4%; ABC/DTG/3TC 1.9%; DTG+F/TAF 3.1%
- In virologically suppressed adults,
  - Study GS-US-380-1844: B/F/TAF 1.8%; ABC/DTG/3TC 0.4%
  - Study GS-US-380-1878: B/F/TAF 1.4%; SBR 3.5%

No subject treated with B/F/TAF had a non-infectious, non-congenital hepatic SAE or discontinued study drugs due to hepatic AEs.

No subject treated with B/F/TAF or a comparator met Hy's Law criteria, defined as concurrent increases in aspartate aminotransferase (AST) or ALT > 3 × upper limit of normal (ULN) and total bilirubin > 2 × ULN, with alkaline phosphatase < 2 × ULN and no alternate etiology.

No clinically relevant median changes from baseline were observed in alkaline phosphatase, ALT, AST, or total bilirubin for the B/F/TAF or comparator group in any of the Phase 3 studies.

Graded total bilirubin increases occurred in a higher percentage of subjects treated with B/F/TAF than the comparator in Studies GS-US-380-1489, GS-US-380-1490, and GS-US-380-1844; however, the increases were primarily Grade 1 or Grade 2 in severity and were not associated with hepatic AEs or other liver-related laboratory abnormalities.

The incidence of Grade 3 or 4 treatment-emergent liver-related laboratory abnormalities was comparable between treatment groups within each Phase 3 study and within the pooled analysis (with the exception of total bilirubin in Study GS-US-380-1878) (Table 7). In Study GS-US-380-1878, Grade 3 or 4 total bilirubin abnormalities were less common among subjects who switched to B/F/TAF than among subjects who stayed on their baseline boosted-PI regimen (B/F/TAF 0.7%, 2 of 290 subjects; SBR 15.4%, 44 of 287 subjects). Most of the subjects with Grade 3 or 4 total bilirubin abnormalities in the SBR group (43 of 44 subjects) were receiving ATV, which is associated with reversible hyperbilirubinemia {Reyataz 2016}. All Grade 3 or 4 ALT or AST abnormalities in the B/F/TAF groups of the Phase 3 studies either resolved on therapy or were attributable to alternate etiologies.

Table 7. GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878: Grade 3 and 4 Liver-Related Laboratory Abnormalities (Safety Analysis Set)

	ART-Naive Adult Subjects			Virologically Suppressed Adult Subjects			
	380-1489, 1490	380-1489	380-1490	GS-US-380-1844		GS-US-380-1878	
	Pooled B/F/TAF (N = 634)	ABC/DTG/ 3TC (N = 315)	DTG +F/TAF (N = 325)	B/F/TAF (N = 282)	ABC/DTG/ 3TC (N = 281)	B/F/TAF (N = 290)	SBR (N = 287)
Alkaline Phosphatase	1 (0.2%)	0	0	0	0	0	0
ALT	9 (1.4%)	4 (1.3%)	3 (0.9%)	6 (2.1%)	0	6 (2.1%)	4 (1.4%)
AST	10 (1.6%)	4 (1.3%)	8 (2.5%)	4 (1.4%)	1 (0.4%)	5 (1.7%)	4 (1.4%)
Total Bilirubin	2 (0.3%)	1 (0.3%)	0	2 (0.7%)	0	2 (0.7%)	44 (15.4%)

The denominator for percentages was the number of subjects in the Safety Analysis Set with at least 1 postbaseline laboratory value for the test under evaluation.
Subjects were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Source: m2.7.4, Tables 27, 31, and 33

5.2.2.2. Bone Safety

B/F/TAF demonstrated a bone safety profile comparable with that of ABC/DTG/3TC, a regimen that is not associated with bone toxicity (m2.7.4, Section 2.1.5.3). In both ART-naive and virologically suppressed subjects, mean (SD) percentage changes from baseline in hip and spine BMD were comparable between the B/F/TAF and ABC/DTG/3TC treatment groups, as follows:

ART-naive subjects (Study GS-US-380-1489):

- Hip: B/F/TAF −0.783% (2.2207%); ABC/DTG/3TC −1.021% (2.3128%); difference in least-squares means (LSMs) (95% CI) 0.238% (−0.151%, 0.626%)

- Spine: B/F/TAF −0.831% (3.1901%); ABC/DTG/3TC −0.596% (3.1009%); difference in LSMs (95% CI) −0.235% (−0.766%, 0.297%)

Virologically suppressed subjects (Study GS-US-380-1844):

- Hip: B/F/TAF 0.156% (2.2138%); ABC/DTG/3TC 0.299% (2.1077%); difference in LSMs (95% CI) −0.143% (−0.534%, 0.248%)

- Spine: B/F/TAF 0.692% (3.1296%); ABC/DTG/3TC 0.416% (2.9973%); difference in LSMs (95% CI) 0.276% (−0.275%, 0.827%)

5.2.2.3. Renal Safety

B/F/TAF demonstrated a renal safety profile comparable with that of ABC/DTG/3TC, a regimen that is not associated with renal toxicity, and an improved renal safety profile compared with a regimen consisting of boosted ATV or DRV plus FTC/TDF or ABC/3TC (m2.7.4, Section 2.1.5.4).

Of the 1734 subjects (B/F/TAF 1419; DTG+F/TAF 325) who received an F/TAF-based regimen in the Phase 3 studies, none had proximal tubulopathy (including Fanconi Syndrome) or discontinued study drugs due to a renal and urinary disorder or associated investigation AE.

Across the Phase 3 studies, changes from baseline in serum creatinine and $eGFR_{CG}$ were consistent with the known inhibitory effect of BIC or DTG on renal tubular secretion via OCT2 and/or MATE1. These changes were not clinically relevant and are not reflective of changes in actual glomerular filtration rate (Study GS-US-141-1487; {Koteff 2013}). Changes in serum creatinine and $eGFR_{CG}$ were observed by Week 4 and remained stable thereafter through Week 48.

In ART-naive subjects (Studies GS-US-380-1489 and GS-US-380-1490), comparable increases in serum creatinine and corresponding decreases in $eGFR_{CG}$ were observed upon initiation of therapy with B/F/TAF, ABC/DTG/3TC, or DTG+F/TAF. Median (Q1, Q3) changes from baseline at Week 48 were as follows:

- Serum creatinine: Pooled B/F/TAF 0.10 (0.03, 0.17) mg/dL; ABC/DTG/3TC 0.11 (0.03, 0.18) mg/dL; DTG+F/TAF 0.11 (0.04, 0.19) mg/dL

- $eGFR_{CG}$: Pooled B/F/TAF −8.8 (−18.4, 0.1) mL/min; ABC/DTG/3TC −10.8 (−21.6, −2.4) mL/min; DTG+F/TAF −10.8 (−20.0, −1.7) mL/min.

In virologically suppressed subjects (Study GS-US-380-1844), minimal changes in serum creatinine or $eGFR_{CG}$ were observed whether subjects switched to B/F/TAF or continued on ABC/DTG/3TC. Median (Q1, Q3) changes from baseline at Week 48 were as follows:

- Serum creatinine: B/F/TAF 0.00 (−0.07, 0.06) mg/dL, ABC/DTG/3TC 0.02 (−0.05, 0.09) mg/dL

- $eGFR_{CG}$: B/F/TAF 1.0 (−5.2, 9.4) mL/min; ABC/DTG/3TC −1.8 (−9.0, 4.8) mL/min

In Study GS-US-380-1878, increases in serum creatinine and corresponding decreases in $eGFR_{CG}$ were observed upon switching to B/F/TAF from a RTV- or COBI-boosted PI-based regimen, likely due to the overall net decrease in serum creatinine transport at the level of the renal tubule when changing from a MATE1 inhibitor (ie, RTV or COBI) to an OCT2 and MATE1 inhibitor (ie, BIC), whereas no change from baseline was observed in the SBR group. Median (Q1, Q3) changes from baseline at Week 48 were as follows:

- Serum creatinine: B/F/TAF 0.06 (−0.03, 0.13) mg/dL; SBR 0.00 (−0.07, 0.07) mg/dL
- $eGFR_{CG}$: B/F/TAF −4.3 (−12.6, 4.8) mL/min; SBR 0.2 (−6.6, 7.6) mL/min

In ART-naive and virologically suppressed adults (Studies GS-US-380-1489 and GS-US-380-1844, respectively), changes from baseline in quantitative measures of albuminuria (UACR) and specific markers of proximal tubular proteinuria (urine RBP and beta-2-microglobulin to creatinine ratios) were comparable between the B/F/TAF and ABC/DTG/3TC treatment groups (Table 8 for Study GS-US-380-1489 and m2.7.4, Table 24 for Study GS-US-380-1844).

Results from Study GS-US-380-1878 demonstrate that switching to B/F/TAF from a regimen consisting of boosted ATV or DRV plus FTC/TDF or ABC/3TC resulted in a decrease in tubular proteinuria (m2.7.4, Table 26). Improvements in urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio were primarily experienced by subjects who switched to B/F/TAF from FTC/TDF-containing regimens. Subjects who switched to B/F/TAF from ABC/3TC-containing regimens also showed an improved tubular proteinuria profile relative to subjects who remained on their baseline regimen.

Table 8. GS-US-380-1489: Percentage Changes from Baseline in Renal Biomarkers at Week 48 (Safety Analysis Set)

	B/F/TAF (N = 314)		ABC/DTG/3TC (N = 315)		
Parameter	**n**	**Median (Q1, Q3)**	**n**	**Median (Q1, Q3)**	**p-value**
UACR (mg/g)	287	0.6% (−32.0%, 48.9%)	293	6.2% (−23.6%, 57.7%)	0.11
Urine RBP to creatinine ratio (µg/g)	287	13.6% (−20.9%, 63.6%)	292	19.9% (−16.0%, 58.9%)	0.34
Urine Beta-2-microglobulin to creatinine ratio (µg/g)	286	−23.0% (−57.2%, 19.8%)	291	−18.1% (−54.2%, 17.4%)	0.40

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
For urine creatinine, value of < 1 was handled as a missing value in its summary and the calculation of related ratios.
Source: m2.7.4, Table 23

5.2.2.4. Ocular Safety

Overall, the incidence of AEs in the eye disorders SOC and the incidence of AEs potentially related to uveitis were low and similar between treatment groups (m2.7.4, Section 2.1.5.5). Clinically, none of the AEs potentially related to uveitis were considered representative of an actual case of posterior uveitis.

5.2.2.5. Suicidal Ideation and Suicide Attempt

Adverse events based on the suicide/self-injury SMQ were infrequent in the 4 Phase 3 B/F/TAF studies through 48 weeks of treatment (m2.7.4, Section 2.1.5.6). Most subjects who experienced a suicide-related AE when receiving B/F/TAF had a pre-existing history of depression or mental illness.

5.3. Clinical Laboratory Abnormalities

B/F/TAF demonstrated a clinical laboratory safety profile similar to that of comparator regimens (m2.7.4, Section 3).

In the Phase 3 studies, there were no clinically relevant changes from baseline in the B/F/TAF group or differences between the B/F/TAF and comparator groups in median values for hematology or clinical chemistry parameters (including metabolic parameters), and median values were generally within reference ranges.

Across the Phase 3 studies, between 14% and 17% of subjects who received B/F/TAF had at least 1 Grade 3 or 4 laboratory abnormality, with similar incidence between treatment groups within each Phase 3 study, except in Study GS-US-380-1878. In Study GS-US-380-1878, Grade 3 or 4 laboratory abnormalities were less common for subjects who switched to B/F/TAF than for subjects who stayed on their baseline boosted-PI regimen (B/F/TAF 15.5%, 45 of 290 subjects; SBR 29.1%, 83 of 287 subjects), mostly due to increases in total bilirubin associated with continued use of ATV (Section 5.2.2.1).

5.4. Phase 2 Safety Summary

During the double-blind phase of Study GS-US-141-1475, median exposure to randomized study drug was 59.9 weeks in the BIC+F/TAF group and 60.0 weeks in the DTG+F/TAF group. Both BIC+F/TAF and DTG+F/TAF were generally well tolerated through 60 weeks of treatment as demonstrated by the low percentages of subjects who had Grade 3 or 4 AEs, SAEs or discontinued study drug due to AEs (Table 9). No Grade 4 AEs, study drug-related SAE, pregnancies, or deaths were reported.

Among the 65 subjects who received BIC 75 mg + F/TAF in the double-blind phase of the study (62 of whom received B/F/TAF in the open-label extension phase), median (Q1, Q3) exposure to BIC 75 mg + F/TAF followed by B/F/TAF was 75.9 (74.7, 77.1) weeks. The AE profile in the open-label extension phase was similar to that reported in the double-blinded phase. There were no reports during the open-label extension phase of Grade 3 or 4 AEs, SAEs, deaths, or AEs leading to study drug discontinuation.

Table 9. GS-US-141-1475: Overall Summary of Adverse Events Occurring During the Double-Blinded Phase (Safety Analysis Set)

	BIC+F/TAF (N = 65)	DTG+F/TAF (N = 33)
Any AE	57 (87.7%)	24 (72.7%)
Grade 3 or 4 AE	4 (6.2%)	0
Study drug-related AE	13 (20.0%)	7 (21.2%)
Grade 3 or 4 study drug-related AE	1 (1.5%)	0
Any SAE	3 (4.6%)	0
Study drug-related SAE	0	0
AE leading to premature study drug discontinuation	1 (1.5%)	0
Death	0	0

Source: m2.7.4, Table 6

No subject met criteria for Hy's Law criteria. There were no clinically relevant changes from baseline within either treatment group or differences between the 2 groups in median values for alkaline phosphatase, ALT, AST, or total bilirubin; median values were within reference ranges. Grade 3 or 4 ALT and AST abnormalities were reported in 3.1% (2 subjects) and 4.7% (3 subjects), respectively, in the BIC+F/TAF group; alternate etiologies were available for all cases. Through 72 weeks of treatment with BIC+F/TAF or B/F/TAF, the hepatic safety profile was similar to that observed during the double-blinded phase.

Increases from baseline in serum creatinine and corresponding decreases from baseline in $eGFR_{CG}$ were observed by Week 4 in both treatment groups. After Week 4, median (Q1, Q3) serum creatinine levels remained stable through Week 60.

There were no clinically relevant changes from baseline within either treatment group or differences between the 2 treatment groups in median values for hematology or clinical chemistry parameters (including metabolic parameters), and median values were within reference ranges. The incidence of Grade 3 or 4 laboratory abnormalities was similar in the 2 treatment groups.

5.5. Analysis of Adverse Drug Reactions

Based on an assessment of safety data from the Phase 2 and Phase 3 studies of BIC+F/TAF or B/F/TAF (Studies GS-US-141-1475, GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878), no adverse drug reactions (ADRs) for B/F/TAF were identified beyond those included in the DVY Summary of Product Characteristics (SmPC). Therefore, it is proposed that the ADRs included in the B/F/TAF SmPC be aligned with those in the DVY SmPC, which includes ADRs identified from clinical studies of F/TAF-containing products.

Consistent with the approach taken for the DVY SmPC, the frequencies of these ADRs in the proposed B/F/TAF SmPC are based on the incidence of treatment-emergent AEs considered related to study drug by the investigator from the B/F/TAF Phase 3 studies in ART-naive subjects (Studies GS-US-380-1489 and GS-US-380-1490) (Table 10).

Table 10. GS-US-380-1489 and GS-US-380-1490: Treatment-Emergent Adverse Events Related to Study Drug (All Grades) for ADRs Identified from Clinical Studies of F/TAF-Containing Products Proposed for Inclusion in the B/F/TAF Prescribing Information

Adverse Events by System Organ Class and Preferred Term	Pooled B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)
Gastrointestinal disorders			
Nausea	26 (4.1%)	55 (17.5%)	17 (5.2%)
Diarrhoea	29 (4.6%)	13 (4.1%)	11 (3.4%)
Vomiting	6 (0.9%)	5 (1.6%)	2 (0.6%)
Abdominal pain	3 (0.5%)	6 (1.9%)	2 (0.6%)
Dyspepsia	4 (0.6%)	4 (1.3%)	3 (0.9%)
Flatulence	6 (0.9%)	2 (0.6%)	7 (2.2%)
General disorders and administration site conditions			
Fatigue	16 (2.5%)	10 (3.2%)	7 (2.2%)
Musculoskeletal and connective tissue disorders			
Arthralgia	3 (0.5%)	0	0
Nervous system disorders			
Headache	29 (4.6%)	15 (4.8%)	10 (3.1%)
Dizziness	13 (2.1%)	9 (2.9%)	2 (0.6%)
Psychiatric disorders			
Abnormal dreams	9 (1.4%)	8 (2.5%)	2 (0.6%)
Skin and subcutaneous tissue disorders			
Rash	1 (0.2%)	1 (0.3%)	1 (0.3%)
Pruritus	1 (0.2%)	0	1 (0.3%)

Source: B/F/TAF ISS, Table 11.1

The DVY SmPC also includes the ADRs of angioedema and anemia, which were added as uncommon ADRs to the SmPCs of FTC-containing products at the request of the CHMP following postmarketing cumulative reviews (EMEA/H/C/00533/II/0074, dated [redacted] 20[redacted], and EMEA/H/C/00533/II/0044, dated [redacted] 20[redacted], respectively). These ADRs have therefore also been included as uncommon ADRs in Section 4.8 of the proposed B/F/TAF SmPC.

Information on changes in serum creatinine and bilirubin is also proposed for inclusion in the B/F/TAF SmPC:

- Bictegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function (Section 5.2.2.3). Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 48. In Studies GS-US-380-1489 and GS-US-380-1490, median (Q1, Q3) serum creatinine increases from baseline at Week 48 were as follows: Pooled B/F/TAF 0.10 (0.03, 0.17) mg/dL; ABC/DTG/3TC 0.11 (0.03, 0.18) mg/dL; DTG+F/TAF 0.11 (0.04, 0.19) mg/dL. There were no discontinuations due to renal AEs through Week 48 in B/F/TAF clinical studies.

- In Studies GS-US-380-1489 and GS-US-380-1490, graded total bilirubin increases were observed in 11.6% of subjects administered B/F/TAF through Week 48. Increases were primarily Grade 1 (8.6%) or Grade 2 (2.7%) in severity and were not associated with hepatic AEs or other liver-related laboratory abnormalities. There were no discontinuations due to hepatic AEs through Week 48 in B/F/TAF clinical studies (Section 5.2.2.1).

5.6. Safety in Special Populations

Safety information pertinent to the use of B/F/TAF in special groups and situations is described in m2.7.4, Section 5, with appropriate information included in the proposed prescribing information. Key findings are as follows:

- The AE profile for subjects receiving B/F/TAF was not affected by sex, age, race, region, HIV-1 RNA level, or CD4 count.

- Pharmacokinetic and relevant safety data support administration of B/F/TAF once daily without dose adjustment in HIV-infected subjects with $eGFR_{CG} \geq 30$ mL/min. Bictegravir is not renally eliminated, and no clinically meaningful changes in BIC PK were observed in subjects with $eGFR_{CG}$ between 15 and 29 mL/min (inclusive) compared with subjects with $eGFR_{CG} \geq 90$ mL/min (Section 3.2.2). In Study GS-US-292-0112, the safety profile of the TAF- and FTC-containing compound GEN in subjects with $eGFR_{CG}$ 30 to < 50 mL/min was similar to that in subjects with $eGFR_{CG} \geq 50$ mL/min.

- Based on available PK data (Section 3.2.2), no dose adjustment of B/F/TAF is necessary for patients with mild to moderate hepatic impairment (Child Pugh Class A or B). B/F/TAF has not been evaluated in subjects with severe hepatic impairment (Child Pugh Class C).

- In HIV/HBV-coinfected subjects, the safety profile of B/F/TAF was similar to that in patients with HIV monoinfection. The safety of TAF for the treatment of HBV infection (Studies GS-US-320-0108 and GS-US-320-0110), along with data from HIV/HBV-coinfected subjects treated with the TAF-containing product GEN (Study GS-US-292-1249) is summarized in m2.7.4, Section 5.1.8.1.

- In HIV/HCV-coinfected subjects, the safety profile of B/F/TAF was similar to that in subjects with HIV monoinfection. The hepatic AE profile in these subjects was consistent with underlying HCV infection. As expected in this subject population, elevations in AST and ALT occurred more frequently than in the subjects without HCV infection.

- No adequate and well-controlled studies of B/F/TAF or its components have been conducted in pregnant women. Animal studies do not indicate direct or indirect harmful effects of BIC, FTC, or TAF with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development. B/F/TAF should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. No clinically relevant concerns are apparent from review of available pregnancy data in clinical studies or from Antiretroviral Pregnancy Registry (APR) data for FTC and from the limited data for TAF.

- Because of the potential for HIV transmission, the potential for adverse reactions similar to those seen in adults, and the risk for developing viral resistance to FTC in nursing infants, mothers should be instructed not to breastfeed if they are receiving B/F/TAF.

- No safety issues have been identified regarding overdose.

5.7. Conclusions on Safety Experience

The B/F/TAF clinical development program has allowed extensive characterization of the safety of the regimen in HIV-infected subjects. A similar proportion of subjects who received B/F/TAF had AEs compared with subjects who received ABC/DTG/3TC, DTG+F/TAF, or a PI-boosted treatment regimen. There was no pattern of clinically relevant B/F/TAF-associated clinical laboratory abnormalities or median changes from baseline in laboratory parameters (including metabolic parameters).

In summary, the cumulative safety results from the Phase 2 and Phase 3 studies of ART-naive and virologically suppressed adults demonstrated the following:

- Treatment with B/F/TAF for up to 72 weeks was generally safe and well tolerated, with a low incidence of related SAEs and AEs leading to discontinuation.

- No subject treated with B/F/TAF had a non-infectious, non-congenital hepatic SAE, discontinued study drugs due to hepatic AEs, or met Hy's Law criteria. The incidence of Grade 3 or 4 treatment-emergent liver-related laboratory abnormalities was comparable between B/F/TAF, ABC/DTG/3TC, and DTG+F/TAF within each double-blind Phase 3 study and within the pooled analysis.

- Bone and renal safety profiles of B/F/TAF were comparable with those of ABC/DTG/3TC, a regimen that is not associated with bone or renal toxicity {TRIUMEQ 2017a, Triumeq 2017b}.

- No subject treated with B/F/TAF had proximal tubulopathy (including Fanconi Syndrome) or discontinued study drugs due to a renal or urinary disorder or associated investigation AE.

In conclusion, B/F/TAF was generally safe and well tolerated in HIV-infected subjects.

6. BENEFITS AND RISKS CONCLUSIONS

The B/F/TAF FDC combines the potent INSTI BIC with the guideline-recommended N(t)RTI backbone F/TAF in an FDC tablet suitable for once-daily administration without regard to food. The following considerations support a favorable benefit:risk profile for B/F/TAF for the treatment of HIV-1 infection.

6.1. Therapeutic Context

6.1.1. HIV Infection

HIV-1 infection is a life-threatening and serious disease that is of major public health interest around the world. There are approximately 37 million people living with HIV-1 worldwide, including approximately 2.4 million people in North America and Western and Central Europe {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. The infection, if left untreated or suboptimally treated, is characterized by deterioration in immune function, ultimately resulting in death. Therapeutic strategies for the treatment of HIV-1 disease have been significantly advanced by the availability of highly active antiretroviral therapy (HAART); the introduction of HAART was associated with a dramatic decrease in AIDS-related morbidity and mortality {Antiretroviral Therapy Cohort Collaboration 2017, Mocroft 1998, Palella 1998, Sterne 2005}.

The success of potent and well-tolerated ART means that morbidity and mortality in the HIV-infected population is increasingly driven by non-AIDS-associated comorbidities. Clinical attention has become more focused on the optimization of tolerability, long-term safety, and adherence of potent ART regimens {Costagliola 2014}. In addition, there remains a significant medical need for new, effective therapies that take into consideration HIV genetic variability, the aging HIV-infected population, ARV resistance, non-HIV comorbidities, and regimen simplification.

6.1.2. Current Therapies

For ART-naive HIV-infected patients, current treatment guidelines recommend that initial therapy consist of 2 N(t)RTIs and either an INSTI, the NNRTI, rilpivirine, or the boosted PI, DRV {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. Virologically suppressed, HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification.

A considerable challenge in achieving long-term virologic suppression is the avoidance of development of drug resistance. Incomplete or partial adherence to treatment regimens is a critical factor contributing to the development of resistance. All patient populations may benefit from once-daily FDC regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {Aldir 2014, Sterrantino 2012}. In addition, B/F/TAF tablets (approximately 15 mm in length and 8 mm in width) are smaller than ABC/DTG/3TC tablets (approximately 22 mm in length and 11 mm in width) or GEN tablets (approximately 19 mm in length and 8.5 mm in width), which can also assist with adherence, as larger tablets are more difficult to swallow and may lead to intentional nonadherence {Liu 2014}.

Compared with other ARV drug classes, INSTIs induce rapid virologic suppression and have high barriers to resistance. Three INSTIs are currently available: raltegravir (RAL), elvitegravir (EVG), and DTG. Raltegravir has the benefit of relatively few DDIs with non-ARV medications {European AIDS Clinical Society (EACS) 2017}; however, it has not been coformulated as part of an FDC that is a complete regimen. Further, up to 50% of patients who switch to RAL after virologic failure develop resistance to RAL, usually in combination with some degree of NRTI resistance, most commonly the M184V mutation that confers resistance to both 3TC and FTC, limiting future treatment options. Viral isolates resistant to RAL are typically also resistant to EVG. Elvitegravir is available within the context of the Stribild® (STB) and GEN FDCs, which are complete regimens for the treatment of HIV-1 infection. Both FDCs include the PK enhancer, COBI, which is required to obtain therapeutic exposures of EVG, but which results in a number of DDIs with non-ARV medications {European AIDS Clinical Society (EACS) 2017}. In addition, both FDCs must be taken with food, and initiation of STB is not recommended in patients with $eGFR_{CG}$ < 70 mL/min. Dolutegravir is dosed once daily in most circumstances and is available as an FDC with ABC and 3TC, forming a complete regimen for the treatment of HIV-1, with a similar DDI profile to RAL; however, DTG must be dosed twice daily in combination with certain UGT1A or CYP3A inducers {European AIDS Clinical Society (EACS) 2017}. In addition, 3TC requires dose adjustment in patients with $eGFR_{CG}$ < 50 mL/min, ABC has been linked to cardiovascular toxicity in multiple epidemiological studies {Ding 2012, Friis-Møller 2010, Sabin 2008, Worm 2010}, and hypersensitivity reactions have occurred with ABC. To decrease the risk of severe, life-threatening ABC hypersensitivity reactions, ABC is only recommended for patients who are human leukocyte antigen (HLA)-B*5701 negative. Few cases of DTG resistance have been reported, suggesting a higher barrier to resistance for DTG than for RAL or EVG, and DTG retains activity against many (but not all) RAL- and EVG-resistant isolates.

6.2. Benefits

Gilead has coformulated the INSTI BIC with the NRTI FTC and the NtRTI TAF into an FDC tablet that is suitable for once-daily use. B/F/TAF is a once-daily regimen containing a novel, potent INSTI that provides a high barrier to resistance, does not require pharmacokinetic enhancement (ie, coadministration with COBI or RTV), has low potential for drug-drug interaction, and may be taken with or without food. B/F/TAF offers a simple, effective, and safer alternative to current guideline-recommended regimens, without the need for HLA testing. B/F/TAF is an FDC with improved bone and renal safety profiles, that avoids the risk of hypersensitivity reactions, does not contribute to an increased risk of cardiovascular events, can be used in patients with chronic hepatitis B or C infection or renal impairment, and that can be continued as patients age and confront non-HIV-related comorbidities. The small tablet size of the FDC is expected to provide an additional benefit, especially in patients for whom pill swallowing can be a barrier to treatment compliance (eg, the elderly).

Bictegravir is a potent inhibitor of HIV-1 integrase that is active against a broad panel of HIV-1 viral lab strains and clinical isolates. Bictegravir is fully active against a panel of mutant viruses with resistance to NRTIs, NNRTIs, and protease inhibitors (PIs). Compared with DTG, RAL, and EVG, BIC has an improved resistance profile and a longer dissociation half-life from HIV-1 integrase-DNA complexes. No subject treated with B/F/TAF in the Phase 2 or Phase 3 studies developed treatment-emergent resistance to any component of B/F/TAF.

B/F/TAF has many benefits for patients living with HIV infection including the following:

- **B/F/TAF is Highly Efficacious in ART-Naive and Virologically Suppressed Adults**

B/F/TAF has demonstrated potent and durable efficacy in 4 Phase 3 studies (GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878) and 1 Phase 2 study (GS-US-141-1475). Using the US FDA-defined snapshot algorithm at Week 48, B/F/TAF was noninferior to comparator regimens. Results were consistent across multiple treatment populations and were supported by several sensitivity analyses. Immunologic benefits of treatment were demonstrated by increases in CD4 cell counts in ART-naive subjects and maintenance of CD4 cell counts in virologically suppressed subjects.

The percentages of ART-naive subjects with HIV-1 RNA < 50 copies/mL at Week 48 were high for both the Pooled B/F/TAF group and the comparator groups, demonstrating the potent antiviral efficacy of B/F/TAF against approved and guideline-recommended first-line and preferred regimens.

Subgroup analyses revealed no meaningful differences in the efficacy of B/F/TAF, supporting B/F/TAF as an effective treatment for the treatment of HIV-1 infection regardless of demographics or disease baseline characteristics.

- **B/F/TAF is an FDC with a Low Potential for Resistance Development**

The development of resistance and loss of regimen efficacy is a risk of ART. Generally, the risk of resistance development is dependent on the efficacy, tolerability, and adherence to an ART regimen. Once-daily FDC regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {Aldir 2014, Sterrantino 2012}.

Bictegravir has an improved resistance profile compared with EVG, RAL, and DTG in patient isolates, particularly for isolates with high-level INSTI resistance containing combinations of mutations such as E92Q + N155H or G140C/S + Q148R/H/K ± additional INSTI mutations, and may have unmet clinical utility in these patients.

No subject treated with B/F/TAF in the Phase 2 or Phase 3 studies developed treatment-emergent resistance to any component of B/F/TAF.

- **B/F/TAF is Well Tolerated in ART-Naive and Virologically Suppressed Adults**

Treatment with B/F/TAF was well tolerated in ART-naive and virologically suppressed subjects, as demonstrated by the low frequency of related SAEs and AEs leading to discontinuation. The most commonly reported AEs for B/F/TAF were diarrhea, headache, and nausea for ART-naive subjects, upper respiratory tract infection, diarrhea, and nasopharyngitis for virologically suppressed subjects switching to B/F/TAF from ABC/DTG/3TC, and headache, diarrhea, nasopharyngitis, and upper respiratory tract infection in virologically suppressed subjects switching to B/F/TAF from a regimen consisting of boosted ATV or DRV plus FTC/TDF or ABC/3TC. These events were generally consistent with AEs from prior studies of GEN and other F/TAF-based regimens in HIV-1 infected subjects.

- **B/F/TAF Has Bone and Renal Safety Profiles Comparable With ABC/DTG/3TC, a Regimen That is Not Associated With Bone or Renal Toxicity**

B/F/TAF or ABC/DTG/3TC treatment resulted in comparable changes from baseline in hip and spine BMD for ART-naive subjects and minimal changes from baseline in virologically suppressed subjects who switched to B/F/TAF from a DTG+ABC/3TC regimen.

B/F/TAF or ABC/DTG/3TC treatment resulted in comparable changes from baseline in markers of albuminuria or renal tubular proteinuria for ART-naive subjects and for virologically suppressed subjects who switched to B/F/TAF from a DTG+ABC/3TC regimen. In virologically suppressed subjects who switched to B/F/TAF from a regimen consisting of boosted ATV or DRV plus FTC/TDF or ABC/3TC, decreases in tubular proteinuria were observed primarily by subjects who switched to B/F/TAF from FTC/TDF-containing regimens. Subjects who switched to B/F/TAF from ABC/3TC-containing regimens also showed an improved tubular proteinuria profile relative to subjects who remained on their baseline regimen.

No subject treated with B/F/TAF in Phase 2 or Phase 3 studies had proximal tubulopathy (including Fanconi Syndrome) or discontinued study drugs due to a renal and urinary disorder or associated investigation AE.

Changes in serum creatinine and $eGFR_{CG}$ following treatment with B/F/TAF are consistent with the inhibitory effect of BIC on renal secretion of creatinine via OCT2 and/or MATE1. These changes were not clinically relevant and are not reflective of changes in actual glomerular filtration rate.

- **B/F/TAF Can Be Administered to Patients With $eGFR_{CG} \geq 30$ mL/min Without Dose Adjustment**

Bictegravir is not renally eliminated, and no clinically meaningful changes in BIC PK were observed in subjects with $eGFR_{CG}$ between 15 and 29 mL/min (inclusive). The F/TAF FDC is approved for treatment of HIV-1 infection in patients with $eGFR_{CG} \geq 30$ mL/min. Therefore, B/F/TAF can be administered to patients with an eGFR ≥ 30 mL/min without dose adjustment.

- **B/F/TAF May Be Used Without Dose Adjustment in Patients With Mild or Moderate Hepatic Impairment**

Moderate hepatic impairment did not result in clinically relevant changes in BIC exposure. The F/TAF FDC is approved for use in patients with mild and moderate hepatic impairment. Therefore, B/F/TAF may be administered without dose adjustment in subjects with mild to moderate hepatic impairment.

- **Hypersensitivity Reactions are not Associated With B/F/TAF**

Serious and fatal hypersensitivity reactions have occurred with ABC. Patients who carry the HLA-B*5701 allele are at higher risk of developing ABC hypersensitivity reactions. F/TAF-containing products are not associated with hypersensitivity, and no hypersensitivity reactions related to B/F/TAF were observed in Phase 2 or Phase 3 studies of B/F/TAF. Therefore, screening for the HLA-B*5701 allele is not required prior to initiation of B/F/TAF.

- **B/F/TAF is Safe for Administration to Patients Coinfected with HIV-1 and HBV or HCV**

Lamivudine use in chronic hepatitis B is frequently associated with development of 3TC-resistant HBV, often within the first 48 weeks of treatment. Treatment guidelines recommend the use of TAF-containing regimens in HIV/HBV-coinfected patients. The safety profile of B/F/TAF in HIV/HBV coinfected subjects in the Phase 3 studies was comparable with that observed in HIV-monoinfected patients, and no loss of HBV virologic control was observed through 48 weeks of treatment.

In HIV/HCV-coinfected subjects, the safety profile of B/F/TAF was similar to that in subjects with HIV monoinfection. The hepatic AE profile in these subjects was consistent with underlying HCV infection. As expected in this subject population, elevations in AST and ALT occurred more frequently than in the subjects without HCV infection.

- **B/F/TAF has a Low Potential for Drug-Drug Interaction and May Be Taken With or Without Food**

Because no PK enhancer, such as COBI or RTV, is required to maintain BIC plasma concentrations above the protein-adjusted 95% effective concentration ($paEC_{95}$), the DDI potential of B/F/TAF is lower than that of STB, GEN, and other COBI- or RTV-boosted regimens. This simplifies the management of comorbid conditions in HIV-infected patients.

Administration of B/F/TAF with or without food does not result in clinically meaningful changes in the PK of its components. The cumulative safety, efficacy, PK, and PK/PD data support administration of B/F/TAF without regard to food, simplifying adherence to recommended B/F/TAF dosing.

- **B/F/TAF is the Smallest of the INSTI-Containing FDC Tablets**

The small tablet size of the B/F/TAF FDC is expected to provide an additional benefit, especially in patients for whom pill swallowing can be a barrier to treatment compliance (eg, the elderly). B/F/TAF tablets are approximately 15 mm in length and 8 mm in width, whereas ABC/DTG/3TC tablets are approximately 22 mm in length and 11 mm in width and GEN tablets are approximately 19 mm in length and 8.5 mm in width.

6.3. Risks

The clinical safety database is robust and includes data originating from the individual components of B/F/TAF as well as an in-depth and comprehensive B/F/TAF clinical development program conducted in HIV-1 infected, ART-naive and virologically suppressed subjects. Treatment with the B/F/TAF FDC was well tolerated across all patient populations evaluated (Section 6.2).

B/F/TAF is proposed for the treatment of adults infected with HIV-1 without any known mutations associated with resistance to the individual components. B/F/TAF should not be administered with other medicinal products containing its components or with 3TC, TDF, or adefovir dipivoxil.

Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness is considered an important potential risk in the B/F/TAF risk management plan (RMP). Across the B/F/TAF study program, the incidence of suicide-related AEs was low, and comparable to that observed previously with other non-INSTI ART regimens that have not been associated with suicide events. Most subjects who experienced a suicide-related AE when receiving B/F/TAF in clinical studies had a pre-existing history of depression or mental illness.

The B/F/TAF clinical development program provides the first large-scale data set comparing a TAF-containing regimen to a non-TDF-containing regimen: in 3 of 4 Phase 3 studies, B/F/TAF was compared with ARV regimens containing either ABC/3TC or F/TAF as the N(t)RTI backbone. The data do not support renal, bone, or ocular effects being risks for B/F/TAF:

- Bone and renal safety profiles of B/F/TAF were comparable with those of ABC/DTG/3TC, a regimen that is not associated with bone or renal toxicity {TRIUMEQ 2017a, Triumeq 2017b}.

- No subject treated with B/F/TAF had proximal tubulopathy (including Fanconi Syndrome) or discontinued study drugs due to a renal or urinary disorder or associated investigation AE.

- There were no reports of posterior uveitis.

Discontinuation of therapy with B/F/TAF in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC and TAF components of B/F/TAF. Therefore, precautionary language is included in the proposed prescribing information. Given that guidance is also included in the European AIDS Clinical Society (EACS) guidelines {European AIDS Clinical Society (EACS) 2017}, and that no additional pharmacovigilance activities are required for this risk, post-treatment hepatic flare in HIV/HBV coinfected patients is included in the B/F/TAF RMP as an important risk that is not considered important.

Due to the limited data in pregnant women, the proposed prescribing information provides the guidance that B/F/TAF should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Because of the potential for HIV transmission, and insufficient information on the effects of the components of B/F/TAF in newborns/infants, the proposed prescribing information provides the guidance that mothers should be instructed not to breastfeed if they are receiving B/F/TAF.

Precautionary language has also been included in the proposed prescribing information for class effects of ARVs: liver disease, weight and metabolic parameters, mitochondrial dysfunction following exposure in utero, immune reconstitution syndrome (including autoimmune disorders), opportunistic infections, and osteonecrosis. The B/F/TAF data do not support these being specific risks for B/F/TAF.

6.4. Benefit-Risk Assessment

B/F/TAF shows potent antiviral efficacy and a safety profile that provides important improvements over currently available treatments, with a high barrier to resistance, no evidence of bone or renal toxicity, no risk of hypersensitivity reactions, an acceptable safety profile in patients coinfected with HBV or HCV and HIV-1, a low potential for drug-drug interactions, flexibility to dose without regard to food, and a smaller tablet size.

B/F/TAF has demonstrated both potent antiviral efficacy and a safety and tolerability profile that offer advantages over existing recommended ARV regimens, meeting important unmet medical needs. B/F/TAF represents a favorable new therapeutic once-daily option for the treatment of adults infected with HIV-1 without any known mutations associated with resistance to the individual components.

7. REFERENCES

Aldir I, Horta A, Serrado M. Single-tablet regimens in HIV: does it really make a difference? Curr Med Res Opin 2014;30 (1):89-97.

Antiretroviral Therapy Cohort Collaboration. Survival of HIV-Positive Patients Starting Antiretroviral Therapy Between 1996 and 2013: A Collaborative Analysis of Cohort Studies. The Lancet HIV 2017:1-9.

Costagliola D. Demographics of HIV and aging. Curr Opin HIV AIDS 2014;9 (4):294-301.

Descovy, Gilead Sciences Ireland UC. Descovy 200 mg/10 mg film-coated tablets. Summary of Product Characteristics (SmPC). County Cork, Ireland. Revised 31 March. 2017:

DESCOVY®, Gilead Sciences Inc. DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use. U. S. Prescribing Information. Foster City, CA. Revised April. 2017:

Ding X, Andraca-Carrera E, Cooper C, Miele P, Kornegay C, Soukup M, et al. No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. J Acquir Immune Defic Syndr 2012;61 (4):441-7.

European AIDS Clinical Society (EACS). European AIDS Clinical Society (EACS) Guidelines Version 8.2 January, 2017.

European Medicines Agency (EMEA). Committee for Medicinal Products for Human Use (CHMP), Guideline on the clinical development of medicinal products for the treatment of HIV infection. April 2016, 2016.

Friis-Møller N, Thiebaut R, Reiss P, Weber R, Monforte AdA, Wit SD, et al. Predicting The Risk of Cardiovascular Disease in HIV-Infected Patients: The Data Collection on Adverse Effects of Anti-HIV Drugs Study. European Journal of Cardiovascular Prevention and Rehabilitation 2010;00:1-11.

Gallant J, Thompson M, DeJesus E, Voskuhl G, Wei X, Zack J, et al. Novel Integrase Strand Transfer Inhibitor Bictegravir 10 Day Monotherapy in HIV-1–Infected Patients [Poster PW-030]. ASM Microbe; 2016 16-20 June; Boston, MA.

Genvoya, Gilead Sciences International Limited. Genvoya 150mg/150mg/200mg/10mg film coated tablets. Summary of Product Characteristics (SmPC). Cambridge, UK. Revised 26 May. 2017:

GENVOYA®, Gilead Sciences Inc. GENVOYA® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use. U.S. Prescribing Information. Foster City, CA. Revised April. 2017:

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

Joint United Nations Programme on HIV/AIDS (UNAIDS). Fact Sheet 2016. Available at: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf . 2016.

Koteff J, Borland J, Chen S, Song I, Peppercorn A, Koshiba T, et al. A phase 1 study to evaluate the effect of dolutegravir on renal function via measurement of iohexol and para-aminohippurate clearance in healthy subjects. Br J Clin Pharmacol 2013;75 (4):990-6.

Liu F, Ranmal S, Batchelor HK, Orlu-Gul M, Ernest TB, Thomas IW, et al. Patient-Centred Pharmaceutical Design to Improve Acceptability of Medicines: Similarities and Differences in Paediatric and Geriatric Populations. Drugs 2014;74 (16):1871-89.

McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. J Infect Dis 2011;203 (12):1791-801.

Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet 1998;352 (9142):1725-30.

Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining Morbidity and Mortality Among Patients With Advanced Human Immunodeficiency Virus Infection. N Eng J Med 1998;338 (13):853-60.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC) Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Last Updated 14 July. 2016.

Reyataz, Bristol Myers Squibb. Reyataz (atazanavir) highlights of prescribing information. Updated September 2016. 2016:

Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet 2008;371 (9622):1417-26.

Sax PE, DeJesus E, Crofoot G, Ward D, Benson P, Dretler R, et al. Bictegravir versus dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, phase 2 trial. The lancet. HIV 2017.

Sterne J, Hernán M, Ledergerber B, Tilling K, Weber R, Sendi P, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. Lancet 2005;366 (9483):378-84.

Sterrantino G, Santoro L, Bartolozzi D, Trotta M, Zaccarelli M. Self-reported adherence supports patient preference for the single tablet regimen (STR) in the current cART era. Patient preference and adherence 2012;6:427-33.

TRIUMEQ, GlaxoSmithKline. TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets, for oral use. US Prescribing Information. Research Triangle Park, NC. Revised March. 2017a:

Triumeq, GlaxoSmithKline Pharmaceuticals S.A. Triumeq 50 mg/600 mg/300 mg film-coated tablets. Summary of Product Characteristics (SmPC). Poznan, Poland. Revised 22 February. 2017b:

U. S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. Guidance for Industry. Silver Spring, MD. November, 2015.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER). Guidance for Industry. Antiretroviral Drugs Using Plasma HIV RNA Measurements — Clinical Considerations for Accelerated and Traditional Approval Oct, 2002.

Vemlidy, Gilead Sciences International Ltd. Vemlidy 25 mg film-coated tablets. Summary of Product Characteristics (SmPC). January. 2017:

VEMLIDY®, Gilead Sciences Inc. VEMLIDY® (tenofovir alafenamide) tablets, for oral use. U.S. Prescribing Information. Foster City, CA. Revised November. 2016:

Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis 2010;201 (3):318-30.

Justification for Absent Clinical Data in Module 5

Section		Comment
5.3.1.1	Bioavailability Study Reports	*Bictegravir, Tenofovir alafenamide & Bictegravir/Emtricitabine/Tenofovir alafenamide* Absolute bioavailability studies have not been conducted.
5.3.1.2	Comparative BA and Bioequivalence (BE) Study Reports	*Bictegravir, Emtricitabine & Tenofovir alafenamide* Comparative BA and BE studies have not been conducted with the individual components, however a study is provided in m5.3.1.2 using the fixed-dose combination (FDC) B/F/TAF.
5.3.1.3	*In vitro-In vivo* Correlation Study Reports	*Bictegravir, Emtricitabine, Tenofovir alafenamide & Bictegravir/Emtricitabine/Tenofovir alafenamide* *In vitro* dissolution profiles are discussed in m2.7.1 Section 1.2. Reports of *in vitro* dissolution tests can be found in the Quality section of the eCTD, see m3.2.P.5.4.
5.3.2.1	Plasma Protein Binding Reports	*Bictegravir/Emtricitabine/Tenofovir alafenamide* The plasma protein binding studies conducted with the individual components are located in m5.3.2.1. Studies have not been conducted on the FDC.
5.3.2.2	Reports of Hepatic Metabolism and Drug Interaction Studies	*Bictegravir/Emtricitabine/Tenofovir alafenamide* The hepatic metabolism and drug interaction studies conducted with the individual components are located in m5.3.2.2. Studies have not been conducted on the FDC.
5.3.2.3	Reports of Studies Using Other Human Biomaterials	*Bictegravir, Emtricitabine, Tenofovir alafenamide & Bictegravir/Emtricitabine/Tenofovir alafenamide* There are no additional studies conducted using other human biomaterials.
5.3.3.2	Patient PK and Initial Tolerability Study Reports	*Bictegravir* The reports are provided in m5.3.4.2. *Tenofovir alafenamide* The report is provided in m5.3.4.2. *Bictegravir/Emtricitabine/Tenofovir alafenamide* There are no reports for the FDC as the relevant data are extrapolated from the components. A study of BIC+F/TAF (provided in m5.3.3.1) demonstrated that no relevant differences in the PK of BIC, FTC, TAF or TFV (major metabolite of TAF) were observed upon co-administration of BIC with F/TAF.

Section		Comment
5.3.4.1	Healthy Subject PD and PK/PD Study Reports	*Emtricitabine* The report is provided in m5.3.3.5 as a combined analysis conducted in healthy volunteers and patients. *Bictegravir/Emtricitabine/Tenofovir alafenamide* There are no reports for the FDC as the relevant data are extrapolated from the components. A study of BIC+F/TAF (provided in m5.3.3.1) demonstrated that no relevant differences in the PK of BIC, FTC, TAF or TFV (major metabolite of TAF) were observed upon co-administration of BIC with F/TAF.
5.3.4.2	Patient PD and PK-PD Study Reports	*Emtricitabine* The report is provided in m5.3.3.5 as a combined analysis conducted in healthy volunteers and patients.
5.3.5.2	Study Reports of Uncontrolled Clinical Studies	*Bictegravir, Emtricitabine, Tenofovir alafenamide & Bictegravir/Emtricitabine/Tenofovir alafenamide* No uncontrolled clinical studies have been conducted.
5.3.5.3	Reports of Analyses of Data from More than One Study	*Bictegravir, Emtricitabine & Tenofovir alafenamide* Integrated analyses have only been conducted on the FDC.
5.3.5.4	Reports of Analyses of Data from More than One Study	*Bictegravir, Emtricitabine & Tenofovir alafenamide* Integrated analyses have only been conducted on the FDC.
5.3.6	Reports of Post-Marketing Experience	*Bictegravir, Emtricitabine, Tenofovir alafenamide & Bictegravir/Emtricitabine/Tenofovir alafenamide* The proposed product has not been marketed in any country at the time of this MAA.
5.3.7	Case Report Forms and Individual Patient Listings	*Bictegravir, Emtricitabine, Tenofovir alafenamide & Bictegravir/Emtricitabine/Tenofovir alafenamide* Not applicable.