1. INTRODUCTION

Gilead Sciences (Gilead) is submitting this dossier in support of a new marketing application for bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) fixed-dose combination (FDC) tablets (B/F/TAF 50/200/25 mg) for the treatment of HIV-1 infection. B/F/TAF (50/200/25 mg) tablets are administered orally, once daily, without regard to food.

Bictegravir (BIC; B [previously referred to as GS-9883]) is a potent integrase strand-transfer inhibitor (INSTI) that is being evaluated for the treatment of HIV-1 infection and has demonstrated a terminal half-life suitable for once-daily administration without a boosting agent. Gilead Sciences, Inc. (Gilead) has coformulated BIC with the guideline-recommended nucleos(t)ide reverse transcriptase inhibitor (N[t]RTI) backbone, FTC and TAF, into a FDC tablet. Pending regulatory approval, B/F/TAF could offer a potent, convenient, tolerable, and practical regimen for the long-term treatment of patients with HIV infection.

Primary studies that support the safety and efficacy of B/F/TAF are two Phase 3 studies of B/F/TAF in HIV-infected, ART naive adult subjects (Studies GS-US-380-1489 and GS-US-380-1490), and two Phase 3 studies of B/F/TAF in HIV-infected, virologically suppressed adult subjects (Studies GS-US-380-1844 and GS-US-380-1878). These data are supported by a Phase 2 study of BIC+ F/TAF in HIV-infected, ART naive adult subjects (Study GS-US-141-1475). Information on study design and populations for these studies is presented in Table 1.

Table 1. Primary Studies to Support Safety and Efficacy of B/F/TAF

Study	Study Design	Data Presented
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	Week 48 efficacy, PK, and safety
GS-US-380-1490	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs DTG+F/TAF	Week 48 efficacy, PK, and safety
GS-US-141-1475	Phase 2, randomized, double-blinded study to evaluate the safety and efficacy of BIC+F/TAF vs DTG+F/TAF[a] Open-label extension phase allowed crossover from DTG+F/TAF to B/F/TAF or continuation of BIC+F/TAF as the B/F/TAF FDC	Double-blinded phase: Week 48 efficacy, PK, and safety Open-label extension phase: Week 72 efficacy and safety
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	Week 48 efficacy, PK, and safety
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	Week 48 efficacy, PK, and safety

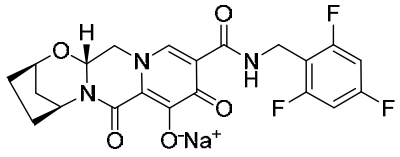
a The double blind phase of Study GS-US-141-1475 evaluated BIC (75 mg) compared with DTG (50 mg), each administered with F/TAF (200/25 mg). During open-label treatment, subjects received B/F/TAF (50/200/25 mg) FDC tablet.

This marketing application contains full administrative, quality, nonclinical, and clinical data supporting of B/F/TAF (50/200/25 mg) tablets for the proposed indication of treatment of HIV-1 infection.

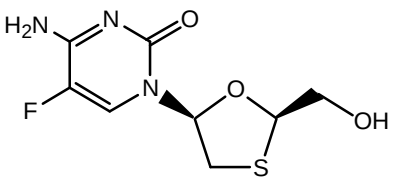
1.1. Chemical Names and Structures

The active ingredients in B/F/TAF are bictegravir sodium, emtricitabine, and tenofovir alafenamide fumarate.

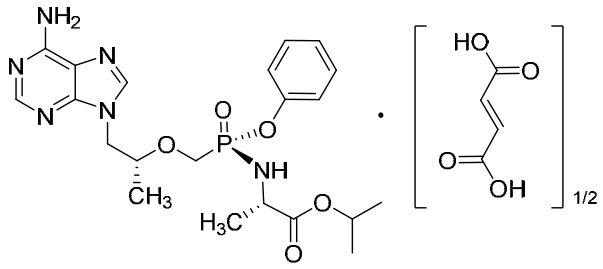
Bictegravir

USAN Name	Bictegravir sodium
Gilead Product No:	GS-9883-01
CAS Name:	2,5-Methanopyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazepine-10-carboxamide, 2,3,4,5,7,9,13,13a-octahydro-8-hydroxy-7,9-dioxo-*N*-[(2,4,6-trifluorophenyl)methyl]-, sodium salt (1:1), (2*R*,5*S*,13a*R*)-
IUPAC Name:	Sodium (2*R*,5*S*,13*aR*)-7,9-dioxo-10-[(2,4,6-trifluorobenzyl)carbamoyl]-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate
Molecular Formula:	$C_{21}H_{17}F_3N_3NaO_5$
Molecular Weight:	471.4
Chemical Structure:	

Emtricitabine

USAN Name:	Emtricitabine
Gilead Product No:	GS-9019
CAS Name:	4-Amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1*H*)-pyrimidin-2-one
IUPAC Name:	5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-cytosine
Molecular Formula:	$C_8H_{10}FN_3O_3S$
Molecular Weight:	247.2
Chemical Structure:	

Tenofovir Alafenamide

USAN Name:	Tenofovir alafenamide fumarate
Gilead Product No:	GS-7340-03
CAS Name:	L-Alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1)
IUPAC Name	Propan-2-yl *N*-[(*S*)-({[(2*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-L-alaninate, (2*E*)-but-2-enedioate (2:1)
Molecular Formula:	$C_{23}H_{31}O_7N_6P$
Molecular Weight:	534.5
Chemical Structure:	

1.2. Pharmacologic Class

Bictegravir

Bictegravir is an HIV integrase strand transfer inhibitor (INSTI) that binds to the integrase active site and blocks the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Bictegravir sodium is the drug substance.

Emtricitabine

Emtricitabine, a synthetic nucleoside analog of 2’deoxycytidine, is a nucleos(t)ide reverse transcriptase inhibitor [N(t)RTI]. Intracellular emtricitabine is phosphorylated to form emtricitabine 5'-triphosphate, which inhibits HIV replication by competing with the natural substrate deoxycytidine 5'-triphosphate for incorporation into viral DNA by HIV reverse transcriptase, resulting in chain termination.

Tenofovir Alafenamide

Tenofovir alafenamide is an oral prodrug of the NtRTI tenofovir, a 2’-deoxyadenosine monophosphate analogue. Intracellular tenofovir is phosphorylated to form tenofovir diphosphate, which inhibits HIV replication by competing with the natural substrate deoxyadenosine 5’-triphosphate for incorporation into viral DNA by HIV reverse transcriptase, resulting in chain termination. Tenofovir alafenamide fumarate is the drug substance.