EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2018
EMA/293559/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Biktarvy

International non-proprietary name: bictegravir / emtricitabine / tenofovir alafenamide

Procedure No. EMEA/H/C/004449/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Biktarvy
Applicant:	Gilead Sciences International Limited Flowers Building Granta Park Abington Cambridge CB21 6GT UNITED KINGDOM
Active substance:	Bictegravir / Emtricitabine / Tenofovir Alafenamide
International Non-proprietary Name/Common Name:	Bictegravir / Emtricitabine / Tenofovir Alafenamide
Pharmaco-therapeutic group (ATC Code):	Direct acting antivirals, antivirals for treatment of HIV infections, combinations (J05AR)
Therapeutic indication(s):	Biktarvy is indicated for the treatment of adults infected with human immunodeficiency virus 1 (HIV 1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir (see section 5.1).
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	50 mg / 200 mg / 25 mg
Route(s) of administration:	Oral use
Packaging:	bottle (HDPE)
Package size(s):	30 tablets and 90 (3 x 30) tablets

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List of abbreviations

%CV percentage coefficient of variation

3TC lamivudine

ABC abacavir

AE adverse event

AIDS acquired immunodeficiency syndrome

ALT alanine aminotransferase

ANOVA analysis of variance

anti-HBe antibody against hepatitis B e antigen

anti-HBs antibody against hepatitis B surface antigen

ART antiretroviral therapy

ARV antiretroviral

ATV atazanavir

AUC area under the concentration versus time curve

AUClast area under the concentration versus time curve from time zero to the last quantifiable concentration

AUCtau area under the concentration versus time curve over the dosing interval

B/F/TAF bictegravir/emtricitabine/tenofovir alafenamide (coformulated)

BCS Biopharmaceutics Classification System

BIC bictegravir

BIC Bictegravir sodium

BLQ below the limit of quantitation

BMD bone mineral density

BMI body mass index

CHB chronic hepatitis B

CI confidence interval

Clast last observed quantifiable concentration of the drug

Cmax maximum observed concentration of drug

CMH Cochran-Mantel-Haenszel

COBI cobicistat (Tybost)

CPK creatine phosphokinase

CQA Critical Quality Attribute

CRF case report form

CSR clinical study report

Ctau observed drug concentration at the end of the dosing interval

CV coefficient of variation

DAVG11 time-weighted average change from baseline to study Day 11

DNA deoxyribonucleic acid

DRV darunavir

DSC Differential Scanning Calorimetry

DTG dolutegravir

EC European Commission

EC50 estimated concentration of drug for a half maximal response

ECG electrocardiogram

eCRF electronic case report form

eGFRCG estimated glomerular filtration rate calculated using the Cockcroft-Gault equation

EU European Union

EVG elvitegravir (Vitekta)

F/TAF emtricitabine/tenofovir alafenamide (coformulated; Descovy®)

FAS Full Analysis Set

FDA Food and Drug Administration

FDC fixed-dose combination

FSH follicle-stimulating hormone

FTC emtricitabine (Emtriva)

FTC Emtricitabine

FTC/TDF emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)

GC Gas Chromatography

GCP Good Clinical Practice

GEN elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)

GI gastrointestinal

GLSM geometric least-squares mean

GS-9883 bictegravir

HBeAb hepatitis B e antibody

HBeAg hepatitis B e antigen

HBsAb hepatitis B surface antibody

HBsAg hepatitis B surface antigen

HBV hepatitis B virus

HCV hepatitis C virus

HDPE High Density Polyethylene

HIV human immunodeficiency virus

HIV-1 human immunodeficiency virus type 1

HLA human leukocyte antigen

HPLC High performance liquid chromatography

HPLC-CAD High performance liquid chromatography – charged aerosol detection

HPLC-MS High performance liquid chromatography – mass spectrometry

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICP-MS Inductively coupled plasma mass spectrometry

IDMC independent data monitoring committee

IN integrase

INSTI integrase strand-transfer inhibitor

INSTI-R integrase strand-transfer inhibitor resistant

IPC In-process control

IQ inhibitory quotient

IQ95 inhibitory quotient of 95%

IR Infrared

ISE Integrated Summary of Efficacy

ISS Integrated Summary of Safety

IV intravenous

KF Karl Fischer titration

LC-MS/MS liquid chromatography/tandem mass spectrometry

LDH lactate dehydrogenase

LDL low-density lipoprotein

LLOQ lower limit of quantitation

LOCF last observation carried forward

LSM least-squares mean

M = E missing = excluded

M = F missing = failure

MedDRA Medical Dictionary for Regulatory Activities

MH Mantel-Haenszel

N number of subjects in a population (N)

NLT Not less than

NMR Nuclear Magnetic Resonance

NMT Not more than

NNRTI nonnucleoside reverse transcriptase inhibitor

NRTI nucleoside reverse transcriptase inhibitor

OL open label

paEC95 protein-adjusted 95% effective concentration

paIC95 protein-adjusted concentration that results in 95% inhibition

paIQ95 protein-adjusted inhibitory quotient of 95%

PAR Proven Acceptable Range

PD pharmacodynamic(s)

PDE Permitted Daily Exposure

PE Polyethylene

Ph. Eur. European Pharmacopoeia

PI protease inhibitor

PK pharmacokinetic(s)

PP per protocol

PR protease

PrEP pre-exposure prophylaxis

Q1 first quartile

Q3 third quartile

QD once daily

RAL raltegravir

RAM resistance-associated mutation

RAP resistance analysis population

RBC red blood cell

RE relative error

RH Relative Humidity

RNA ribonucleic acid

ROW rest of world

RT reverse transcriptase

RTV ritonavir

SAE serious adverse event

SAP statistical analysis plan

SBR stay on baseline regimen

SD standard deviation

SDS Sodium dodecyl sulfate

SmPC Summary of Product Characteristics

t1/2 estimate of the terminal elimination half-life of the drug

TAF tenofovir alafenamide (Vemlidy)

TAF Tenofovir alafenamide

TDF tenofovir disoproxil fumarate (Viread)

TFV tenofovir

Tmax time (observed time point) of Cmax

TSH thyroid-stimulating hormone

UGT1A1 uridine diphosphate glucuronosyltransferase 1A1

ULN upper limit of normal

UPLC Ultra performance liquid chromatography

USP United States Pharmacopoeia

USP United States Pharmacopoeia

UV Ultraviolet

XRPD X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences International Limited submitted on 21 June 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Biktarvy through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 April 2016.

The applicant applied for the following indication: *The treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the individual components (see section 5.1).*

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0339/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0339/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active substance status

The applicant requested the active substance bictegravir contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received scientific advices from the CHMP:

Scientific advice	date	Area
EMA/CHMP/SAWP/629722/2012	18 October 2012	Non-clinical
EMA/CHMP/SAWP/214541/2013	25 April 2013	Quality, non-clinical and clinical

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Joseph Emmerich Co-Rapporteur: Bruno Sepodes

The application was received by the EMA on	21 June 2017
The procedure started on	13 July 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	29 September 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	27 September 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	12 October 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	9 November 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 December 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	31 January 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 February 2018
The Rapporteurs circulated Updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	16 February 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	22 February 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 March 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 April 2018
The Rapporteurs circulated Updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	20 April 2018

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Biktarvy	26 April 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

HIV-1 infection is a blood-born infection. HIV is a retrovirus that infects and replicates primarily in human CD4+ T cells and macrophages. HIV can be transmitted via blood, blood products, sexual fluids, other fluids containing blood, and breast milk. Most individuals are infected with HIV through sexual contact, before birth or during delivery, during breast-feeding, or when sharing contaminated needles and syringes (intravenous drug users). Sexual intercourse is the most common, albeit inefficient, mode of HIV transmission. The risk of transmission per exposure is low; estimates are on the order of 0.1% per contact for heterosexual transmission, but this varies considerably and increases with concurrent ulcerative STDs, high HIV viral load in the subject, and lack of antiretroviral therapy.

2.1.2. Epidemiology

There are approximately 37 million people worldwide living with HIV-1. HIV-1 infection remains a life-threatening disease in infected persons who do not receive adequate treatment sufficiently early in the course of the infection and/or are infected with virus that is resistant to anti-retroviral agents of several classes such that an adequate treatment regimen cannot be constructed from approved agents.

2.1.3. Clinical presentation, diagnosis and prognosis

Acute HIV-1 infection is often missed, as it usually presents with nonspecific signs and symptoms (including fever, rash, or diarrhoea), or goes without clinical symptoms. If symptoms are present, these generally emerge approximately 2 weeks following HIV infection. Among those presenting with symptoms, the number of symptoms correlates with higher pre-seroconversion peak plasma viral load.

Diagnosis most often occurs during chronic infection. Recent estimates suggest that even in high income settings; about 25-35% of people living with HIV starting ART have a CD4 cell count of less than 200 cells/mm3. In some settings, up to half of people present to care with advanced HIV disease – defined by WHO as having a CD4 cell count <200 cells/mm3 or a WHO clinical stage 3 or 4 disease.

Most HIV-infected individuals will eventually develop progressive immunodeficiency marked by CD4 T lymphocyte (CD4) cell depletion and leading to AIDS-defining illnesses and premature death, if remain untreated. Leading causes of mortality among adults with advanced HIV disease globally include tuberculosis (TB), severe bacterial infections, cryptococcal meningitis, toxoplasmosis and *Pneumocystis jirovecii* pneumonia.

Diagnostic tests for HIV-1 infection include assays for HIV-1 RNA, p24 antigen, and HIV-1 and HIV-2 antibodies.

2.1.4. Management

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 consists of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either an integrase strand transfer inhibitor (INSTI), the non-nucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine, or the boosted protease inhibitor (PI), darunavir (DRV). 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.

Integrase strand-transfer inhibitors (INSTI), such as raltegravir (RAL) and elvitegravir (EVG), exhibit strong antiviral activity, good clinical tolerability and have become attractive options as third agents in combination therapy for HIV-1 infected patients. Both RAL and EVG have relatively short human half-lives and must be administered twice daily (BID) (for RAL) or in combination with a boosting agent (for EVG) for once daily (QD) administration. The most recently approved INSTI, dolutegravir (DTG), has a PK profile that allows administration once a day (QD) without a boosting agent; however, BID dosing is recommended when DTG is co-administered with CYP and/or UGT inducers (e.g., EFV, fos-AMP/r, TPV/r, or rifampin) and in patients with INSTI associated resistance substitutions or clinically suspected INSTI resistance. Dolutegravir is available as a fixed dose combination with abacavir and lamivudine and is currently used as first line therapy. The new fixed dose combination with Bictegravir as INSTI contains tenofovir alafenamide (TAF) and emtricitabine as a backbone.

About the product

Bictegravir is a potent INSTI that is being evaluated for the treatment of HIV-1 infection and that has demonstrated a terminal half-life suitable for once-daily administration without a boosting agent.

Emtricitabine and TAF form a guideline-recommended N(t)RTI backbone for ART-naïve HIV-infected patients. Tenofovir alafenamide is also approved as a single agent for the treatment of chronic hepatitis B infection, and F/TAF is a guideline-recommended backbone for patients co-infected with HIV and hepatitis B virus (HBV).

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). Based on the clinical studies performed within this application, the Applicant claims that:

- 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)

The Applicant's proposed indication was:

TRADENAME is indicated for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the individual components

The Applicant's proposed posology was:

One tablet to be taken once daily in adults.

2.2. Quality aspects

2.2.1. Introduction

Biktarvy is a fixed dose combination product presented as film-coated tablets containing bictegravir sodium equivalent to 50 mg bictegravir free acid, 200 mg of emtricitabine and tenofovir alafenamide fumarate equivalent to 25 mg tenofovir alafenamide as active substances.

Other ingredients are:

Tablet core: microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

Film-coating: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, iron oxide red (E172) and iron oxide black (E172).

The product is available in white, high density polyethylene (HDPE) bottles with polypropylene continuous-thread child-resistant caps, lined with induction activated aluminium foil liners. Each bottle contains silica gel desiccant and a polyester coil.

2.2.2. Active Substance

Emtricitabine (FTC)

The information on chemistry, manufacturing and control of emtricitabine active substance has been assessed previously *via* the centralised procedure and approved in the EU as part of the marketing authorisations for Emtriva, Truvada, Atripla, Eviplera, Stribild, Descovy, Genvoya and Odefsey.

The Module 3.2.S sections of the dossier for emtricitabine provided by the applicant are identical to the 3.2.S sections submitted and approved with the aforementioned marketing authorisations.

General information

The chemical name of emtricitabine is 4-amino-5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one corresponding to the molecular formula $C_8H_{10}FN_3O_3S$. It has a relative molecular mass of 247.24 g/mol and the following structure (figure 1).

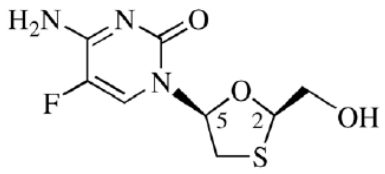


Figure 1: emtricitabine structure

The structure of emtricitabine was elucidated by a combination of ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, IR spectroscopy, UV spectroscopy, mass spectrometry and single crystal x-ray determination.

Emtricitabine appears as a white to off-white non-hygroscopic crystalline powder, freely soluble in methanol and water. Its pKa is 2.65 and the partition coefficient Log P is -0.43. It has 2 chiral centres at carbons 2 and 5 of the oxathiolane ring. Two enantiomeric pairs of diastereomers can exist: *cis*-(-)-FTC and *cis*-(+)-FTC, *trans*-(-)-FTC and *trans*-(+)-FTC. The synthetic route has been chosen to be stereoselective for the formation of the desired *cis*-(-) enantiomer, emtricitabine. Three polymorphs of emtricitabine have been observed. However, the most stable thermodynamically form at room temperature, is consistently produced.

Manufacture, characterisation and process controls

Emtricitabine is manufactured by two possible synthetic routes sharing a common first step and followed by two options comprising either one or two extra steps. The synthesis was described in sufficient detail.

The synthetic process results in the stereoselective formation of an intermediate and thus the formation of the desired emtricitabine enantiomer. Five manufacturing sites are involved. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The process has been shown to consistently produce emtricitabine that meets the required quality standards.

The active substance is packaged in double polyethylene (PE) bags inside HDPE drums which comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

Emtricitabine specification includes tests and limits for appearance (visual), identification (IR, HPLC), clarity of solution (visual), water content (Ph. Eur.), enantiomeric purity (chiral HPLC), assay (HPLC), impurities (HPLC), heavy metals (Ph. Eur.), residue on ignition (Ph. Eur.), residual solvents (GC), and particle size (Laser Light Scattering). Analytical methods have been validated in accordance with ICH guidelines. The testing and the proposed limits applied, conform to current ICH guidelines and are acceptable from a toxicological and clinical perspective.

Extended testing during development has demonstrated that only a single polymorphic form results from the synthetic process of emtricitabine. Therefore as per ICH Q6A, testing for polymorphic form at release is not necessary. Development data demonstrate the absence of indicator organisms and therefore, as per ICH Q6, microbial testing of the active substance is not required. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis data on 22 commercial scale batches of emtricitabine from all proposed manufacturers were provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process.

Stability

Stability data from 3 production scale batches of finished product covering both manufacturers and processes stored for up to 24 months under long term conditions (30 ºC / 65% RH) according to the ICH guidelines were provided. The batches were packaged in the primary packaging proposed for marketing. Samples were tested for appearance, assay, impurity content and water content. No changes were observed to any of the measured parameters over time, and no trends were visible. Emtricitabine is known not to be photosensitive.

Based on the long-term stability data, the proposed re-test period and storage conditions when emtricitabine is packed in the proposed packaging materials is considered acceptable.

Tenofovir Alafenamide Fumarate (TAF Fumarate)

The information on chemistry, manufacturing and control of tenofovir alafenamide fumarate has been assessed previously *via* the centralised procedure and approved in the EU as part of the marketing authorisations Descovy, Genvoya, Odefsey, Vemlidy and Symtuza.

The Module 3.2.S sections of the dossier for tenofovir alafenamide fumarate provided by the applicant are identical to the 3.2.S sections submitted and approved within the aforementioned marketing authorisations.

General information

The chemical name of tenofovir alafenamide fumarate is 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) corresponding to the molecular formula $C_{23}H_{31}N_6O_7P$. It has a relative molecular mass of 534.5 g/mol and the following structure (Figure 2):

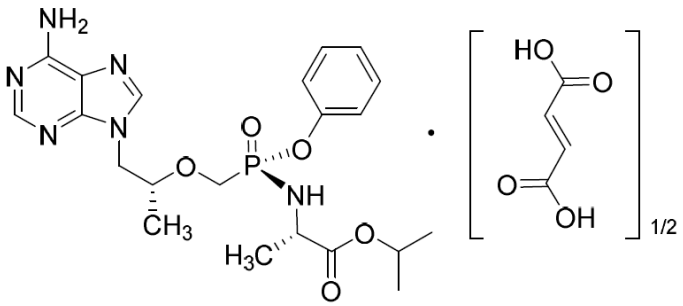


Figure 2: tenofovir alafenamide fumarate structure

The chemical structure of tenofovir alafenamide fumarate has been adequately demonstrated by infrared spectroscopy, NMR spectroscopy (^{1}H, ^{13}C, and ^{31}P), mass spectrometry, elemental analysis, ultraviolet absorption spectroscopy, and X-ray crystallography.

The active substance is a white to off-white or tan, slightly hygroscopic powder. Tenofovir alafenamide fumarate is a BCS Class III compound, with pH-dependent aqueous. solubility decreasing with

increasing basicity. It is soluble at low pH (pH 2.0), sparingly soluble at pH 3.8, and slightly soluble at pH values up to 8.0. Tenofovir alafenamide fumarate is freely soluble in methanol, soluble in ethanol, sparingly soluble in isopropanol and slightly soluble in acetone.

Tenofovir alafenamide exhibits stereoisomerism due to the presence of three chiral centres. The chiral centre at the propyloxy- side chain is in the *R*-configuration. The absolute stereoconfiguration of the carbonylethylamino- substituent is derived from the amino acid *L*-alanine, which has the *S*-configuration at the alpha-carbon. The remaining stereocentre is located at the phosphorus atom and is in the *S*- configuration. Enantiomeric purity is controlled routinely by chiral HPLC at the point of the introduction of the chiral starting material and in a manufacturing process intermediate.

Polymorphism has been observed for tenofovir alafenamide fumarate. A single polymorphic form is consistently generated through the manufacturing process and this form has been adequately characterised.

Manufacture, characterisation and process controls

Tenofovir alafenamide fumarate is obtained from two manufacturers using the same synthetic route.

The active substance is synthesized in multiple steps using well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Potential and actual impurities were well discussed with regards to their origin and characterised.

Critical process parameters and material attributes were identified using a risk assessment approach.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in double-lined polyethylene bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. The bags are held in high-density polyethylene drums (or other suitable secondary container) with lids of appropriate size and fitted with a security seal.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances.

Specification

The specification for tenofovir alafenamide fumarate includes tests for appearance (visual examination), identity (IR, HPLC), identity of fumaric acid (HPLC), clarity of solution (visual examination), water content (Ph. Eur.), assay (HPLC), impurities (HPLC, HPLC-MS, GC), residual solvents (GC), elemental impurities (ICP MS), and melting point (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standard used for assay testing has been presented.

Batch analysis data from 16 batches of tenofovir alafenamide fumarate, (13 of which were commercial scale and 3 pilot scale), manufactured at both proposed manufacturing sites were provided. Additional batch analysis data for development batches used in pre-clinical pharmacokinetics and toxicological studies were also provided. The results were within the specifications and consistent from batch to batch.

The tenofovir alafenamide fumarate specifications are based on the active substance critical quality attributes (CQA).

Stability

Stability data on 6 commercial scale batches of tenofovir alafenamide fumarate from the both proposed manufacturers stored in the intended commercial package for up to 36 months under long term conditions at 5 ºC and for up to 24 months under accelerated conditions at 25 ºC / 60% RH according to the ICH guidelines were provided. Results under stressed conditions for up to 6 months at 40 ºC / 75% RH on 5 batches were provided. Additionally, results for 4 days at 60 ºC / ambient RH, for 4 days at 50 ºC / ambient RH and for 4 days at -20 ºC were also provided on one batch.

Samples were tested for appearance, impurities, assay, water content, and solid state characteristics (XRD and melting point). The analytical methods used were the same as for release and were stability indicating.

Photostability testing following the ICH guideline Q1B was performed on one batch, indicating that the active substance is not photosensitive.

The stability results indicate that tenofovir alafenamide fumarate manufactured by the both proposed suppliers is sufficiently stable. The stability results justify the proposed re-test period at the recommended long-term storage condition in the proposed container.

Bictegravir sodium (BIC)

Bictegravir sodium is a new active substance. Information is provided by the applicant in a full module 3.2.S.

General information

The chemical name of bictegravir sodium is sodium (2*R*,5*S*,13a*R*)-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 corresponding to the molecular formula $C_{21}H_{17}F_3N_3NaO_5$. It has a relative molecular mass of 471.4 g/mol and the following structure (figure 3):

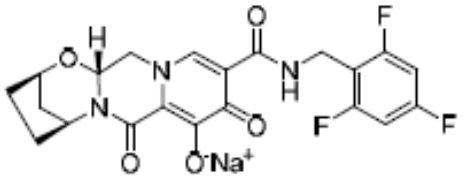


Figure 3: bictegravir sodium structure

The chemical structure of bictegravir sodium was elucidated by a combination of ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, mass spectrometry, UV and IR spectroscopy, elemental analysis and x-ray crystallography.

Bictegravir sodium contains 3 chiral centres. Overall stereochemistry is tested in the active substance by chiral HPLC before release.

The solid state properties of bictegravir sodium were established by x-ray powder diffraction, differential scanning calorimetry and dynamic vapour sorption. The active substance is an off-white to yellow slightly hygroscopic crystalline solid. Only 1 polymorphic form was identified during development. It is practically insoluble in aqueous media across the physiological pH range, including simulated fed and fasted state intestinal fluids, and very slightly soluble at pH 8.8. Particle size is limited in the active substance specification.

Manufacture, characterisation and process controls

Bictegravir sodium is synthesized in multiple steps using well-defined starting materials with acceptable specifications. The starting materials were justified in line with the expectations in ICH Q11 and its Q&A and are deemed acceptable.

Adequate in-process controls are applied during the synthesis. The process was optimised through a series of univariate and multivariate experiments, informed by risk assessment as to which steps were likely to be most critical. Operational ranges and set-points are defined for each step of the manufacturing process and are justified by the data provided. No design spaces are claimed.

Detailed information on the origin, fate and purge of impurities was provided in order to justify limits for impurities in the starting materials, intermediates, and the active substance. A risk assessment for mutagenic impurities was carried out in line with ICH M7. One impurity with a structural alert was shown to be negative in an Ames test. Another known mutagenic impurity was consistently found in an intermediate at levels well below 30% of the TTC and is thus controlled according to ICH M7 option 4. The specifications and control methods for intermediates, starting materials and reagents have been presented and are deemed acceptable.

The active substance is packaged in double PE bags, inside an HDPE drum, which comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), clarity of solution (visual inspection), water content (KF), sodium content (HPLC-CAD), assay (HPLC), impurities (HPLC), residual solvents and organic volatile impurities (GC), enantiomeric purity (chiral HPLC) and particle size (laser light scattering).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. A risk assessment and batch analysis carried out for the finished product in line with ICH Q3D demonstrated that no test for elemental impurities, other than the sodium content, is needed. The active substance has low water activity and no significant bioburden was noted during release testing and stability studies so no test for microbiological quality is included. Only 1 polymorphic form has been identified, which is stable and routinely produced by the manufacturing process as determined by XRPD, so no test is needed.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 22 lab, pilot and production scale batches of bictegravir sodium covering both manufacturers and an additional manufacturer used in early development, were provided. These included the 3 productions scale validation batches from each manufacturer. The results were within the specifications and consistent from batch to batch.

Stability

Stability data from 8 pilot scale batches of active substance covering both proposed manufacturers, and an additional manufacturer used in early development, stored in the intended commercial package for up to 24 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Samples were tested for appearance, assay, related substances, water content, enantiomeric purity, polymorphic form and microbial purity. No significant changes were noted over time and all parameters remained within specification throughout the study period. In addition, studies have begun using the 3 process validation batches from each proposed commercial manufacturer which will be tested according to the accepted protocol.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. Bictegravir sodium is not photosensitive.

Samples were also stored at either -20 or 60 ^{o}C for up to 2 weeks. No changes to any of the measured parameters were observed.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period when stored at the recommended long term storage condition in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Biktarvy is a fixed dose combination, immediate release, film-coated tablet containing bictegravir sodium, emtricitabine and tenofovir alafenamide fumarate as active substances. The tablets are purplish-brown capsule-shaped, and debossed with GSI on one face and “9883” on the other.

Bictegravir sodium is a crystalline, stable, BCS class II compound exhibiting low solubility but high permeability. Emtricitabine is a crystalline BCS class I compound with high solubility and permeability which degrades by hydrolysis in aqueous solution and to a much smaller degree, in the solid phase. TAF fumarate is a BCS class III molecule, highly soluble but poorly permeable, which undergoes pH-dependent hydrolysis in aqueous solution.

The formulation evolved throughout development. The commercial formulation is the same as that used in phase III clinical trials, which was shown to be equivalent to earlier clinical formulations by suitable bridging studies.

The choice of manufacturing process and excipients was based on the properties of the active substances. Process parameters for the film-coating process are considered suitable.

The development of the dissolution method took into account the differing solubilities and stabilities of the 3 active substances. Emtricitabine and TAF fumarate are soluble in aqueous media, whereas bictegravir is poorly soluble in aqueous media across the physiological pH range. However, TAF fumarate is unstable below pH 5 and above pH 6, so a medium with pH 5.5 was selected.

Various manufacturing parameters with potential to impact the dissolution rate were examined during development and have been set at levels guaranteed to produce Biktarvy tablets of the required quality. The dissolution method was developed in order to identify tablets manufactured outside of the defined process and its discriminatory power is considered adequate.

The manufacturing development has been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development and process design. The critical process parameters have been adequately identified. No design space is claimed.

All excipients other than the Opadry film coat are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. Opadry is commercially available and the constituent ingredients are of compendial grade. The colourants comply with directive 2009/35/EC. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The primary packaging is a white HDPE bottle with polypropylene continuous-thread, child-resistant cap, lined with an induction activated aluminium foil liner. Each bottle contains silica gel desiccant and a polyester coil. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process is carried out at 2 different sites and consists of production of final blends by granulation, milling and lubrication followed by tabletting. The process is considered to be a standard manufacturing process.

It has been demonstrated that the manufacturing process is capable of producing finished product of intended quality in a reproducible manner. A process validation protocol has been provided, explaining how validation will be carried out at both manufacturing sites on full production scale prior to commercialization. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form, and suitable limits have been set for the individual tests.

Product specification

The finished product release specifications comprise appropriate tests for this kind of dosage form including appearance, identity (UV, UPLC), water content (KF), assay (UPLC), degradation products (UPLC), uniformity of dosage units (Ph. Eur.), dissolution (UPLC) and microbiological quality (Ph. Eur.).

The limits for impurities have been justified 7 batches of finished product were analysed for all class 1, class 2A and selected class 3 elemental impurities as defined in ICH Q3D. The amount of each tested element was well below 30% of the PDE and this justifies their omission from the finished product specification.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 14 pilot to production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 pilot scale batches of finished product from each manufacturer stored for up to 12 months under long term conditions (25 ºC / 60% RH), up to 12 months under intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, water content, assay, degradation products, dissolution and microbiological quality. The analytical procedures used are stability indicating. No significant changes to any of the measured parameters were observed.

In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results indicate that the product is photostable.

Stressed studies were carried out on another batch, stored at either -20 ^{o}C or 50 ^{o}C for 1 week at ambient humidity. No significant changes were observed.

An in-use stability study was carried out on 1 batch of product. Bottles were stored at 30 ^{o}C / 75% RH with the induction seals removed. One tablet was removed each day for 30 days to simulate the recommended dosing regimen. No significant changes to any of the measured parameters were observed.

Based on available stability data the proposed shelf-life of 24 months stored in the original container with the lid tightly closed in order to protect from moisture as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. The magnesium stearate is of vegetal origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The control strategy, combining a mixture of process parameters and release tests, is considered sufficient to ensure the quality of the product. No design spaces are claimed.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The definitive safety pharmacology, toxicology, and toxicokinetic studies provided for BIC, FTC, and TAF were conducted in accordance with guidelines issued by the International Council for Harmonisation (ICH) and with Good Laboratory Practice (GLP) or other applicable regulations promulgated by international health authorities. Pilot, exploratory, and mechanistic studies were either conducted in full compliance with GLP procedures or were conducted using appropriate protocols and documentation to assure data integrity.

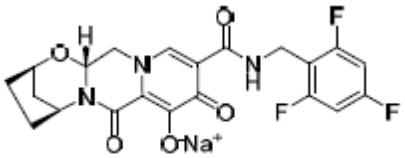
2.3.2. Pharmacology

Brief summary

BIC

Bictegravir is a potent investigational integrase strand-transfer inhibitor (INSTI) with in vitro activity against wild-type HIV-1 and HIV-1 with INSTI-resistance associated mutations. Bictegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle, demonstrating high potency and selectivity in antiviral assays. Bictegravir displays a high resistance barrier and has an improved phenotypic resistance profile compared to dolutegravir (DTG), raltegravir (RAL) and elvitegravir (EVG; E). Bictegravir has a longer dissociation half-life from both wild-type and mutant HIV-1 integrase/DNA complexes compared with DTG, RAL, and EVG.

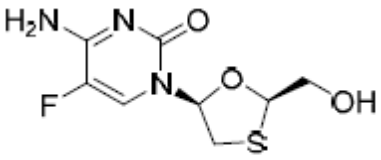
Figure 4. BIC chemical structure



FTC

Emtricitabine (FTC) is a NRTI and a (-) enantiomer of a thio analogue of cytidine, which differs from other cytidine analogues in that it has a fluorine in the 5-position. Intracellularly, FTC is phosphorylated by enzymes to form emtricitabine triphosphate (FTC-TP), the active metabolite. Emtricitabine is an NRTI that has activity against HIV and hepatitis B virus (HBV). Following absorption, FTC is phosphorylated by cellular enzymes to emtricitabine triphosphate (FTC-TP), the active metabolite, an analog of 2'-deoxycytidine triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of HIV-1 reverse transcriptase through high-affinity binding, competing with the natural substrate 2'-deoxycytidine 5'-triphosphate. Emtricitabine 5'-triphosphate is efficiently incorporated into the nascent viral DNA chain by HIV-1 reverse transcriptase resulting in termination of DNA synthesis due to the lack of a hydroxyl group at the 3'- position of the sugar moiety of FTC, which in turn inhibits viral replication. In a clinical study, the intracellular half-life of FTC-TP in peripheral blood mononuclear cells (PBMCs) was 39 hours. Intracellular triphosphate levels increased with dose but reached a plateau at doses of 200 mg or greater. Emtricitabine has activity against retroviruses and hepadnaviruses.

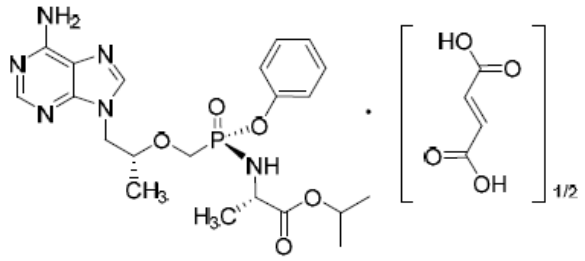
Figure 5. Chemical structure of FTC



TAF

Tenofovir alafenamide is a prodrug of tenofovir (TFV), a nucleotide reverse transcriptase inhibitor (NtRTI). After absorption, TAF is converted to TFV intracellularly, which is phosphorylated to the active metabolite, tenofovir diphosphate (TFV-DP) (Robbins 1998). Tenofovir diphosphate is a very weak inhibitor of mammalian DNA polymerases α, β, δ, and ε and mitochondrial DNA (mtDNA) polymerase γ. Cells are permeable to TAF and, due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, TAF is more efficient than TDF in loading tenofovir into PBMCs (including lymphocytes and other HIV target cells) and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite, tenofovir diphosphate. Tenofovir diphosphate inhibits HIV and HBV replication through incorporation into viral DNA by the HIV-1 or HBV reverse transcriptase, which results in DNA chain-termination.

Figure 6. Chemical structure of TAF hemi-fumarate



B/F/TAF

The proposed FDC is based on the complimentary pharmacology of BIC, FTC and TAF and the body of clinical experience with INSTI or N[t]RTIs in HIV-infected patients. Combinations of these agents in cell-based *in vitro* assays show favourable anti-HIV activity and no evidence for antagonism. The anti-HIV-1 activity of 3-drug combination of BIC, FTC, and TAF was found to be highly synergistic with no evidence of antagonism in vitro, supporting the use of these agents in combination in HIV-1 infected patients. The resistance profiles of the individual agents BIC, FTC, and TAF are distinct and non-overlapping.

Primary pharmacodynamic studies

BIC

Bictegravir is a novel strand transfer inhibitor of HIV-1 integrase with high potency and selectivity in antiviral assays and does not require metabolic modification to exert ARV activity. Using lymphoblastoid T-cell lines and primary human T-lymphocytes in HIV-1 antiviral assays, the estimated concentration of drug for a half-maximal response (EC50) of BIC ranged from 1.5 to 2.4 nM and the selectivity indices ranged from 1500 to 8800. When tested in primary human PBMCs against clinical isolates of all HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G, BIC displayed similar antiviral activity across all clinical isolates with mean and median EC50 values of 0.60 and 0.55 nM, respectively, based on a range of EC50 values between < 0.05 and 1.71 nM. HIV-2 was similarly susceptible to BIC with an EC50 value of 1.1 nM. Bictegravir is a specific inhibitor of HIV with no measurable antiviral activity against non-HIV viruses, including HBV, hepatitis C virus (HCV), influenzas A and B, human rhinovirus, and respiratory syncytial virus (RSV).

Bictegravir maintained potent antiviral activity against HIV-1 variants resistant to currently approved ARVs from the NRTI, NNRTI, and protease inhibitor (PI) classes. Bictegravir displays a resistance profile similar to that of dolutegravir (DTG) and markedly improved compared with that of raltegravir (RAL) and elvitegravir (EVG; E). Bictegravir maintained full activity against clonal isolates from virologic failures treated with Stribild. Bictegravir had an improved resistance profile compared to 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. Bictegravir had a longer dissociation half-life from HIV-1 integrase-DNA complexes compared with DTG, RAL, and EVG.

HIV-1 isolates with reduced susceptibility to BIC have been selected in cell culture. These selections showed that BIC displayed a comparable barrier to resistance emergence as DTG, and a higher barrier than EVG. Bictegravir selected the M50I + R263K combination and S153F with a transient T66I substitution in HIV-1 integrase. The R263K single mutant and M50I + R263K double mutant viruses had low-level reduced susceptibility to BIC, but the single M50I mutant was fully sensitive to BIC. The M50I + R263K selected variants exhibited low-level cross-resistance to RAL and DTG and intermediate cross-resistance to EVG but remained susceptible to other classes of ARVs. The effect of the T66I and S153F/Y single mutants and the T66I + S153F double mutant in integrase on BIC susceptibility was minimal.

Similar to a number of other ARV agents, the in vitro activity of BIC was reduced in the presence of human serum due to significant protein binding. Bictegravir exhibited approximately 70-fold increase in the EC50 value in the presence of 100% serum relative to its activity in cell culture medium. The 95% effective concentration (EC95) calculated from the high density antiviral dose response was used in

conjunction with the human serum shift determined by equilibrium dialysis to calculate the protein-adjusted EC95 (PAEC95) of 361 nM.

FTC

Emtricitabine, an NRTI, is a synthetic analogue of the naturally occurring pyrimidine nucleoside, 2′ -deoxycytidine. Intracellularly, FTC is converted through 3 phosphorylation reactions to its active tri-phosphorylated anabolite emtricitabine 5′ -triphosphate (FTC-TP) [Furman 1992, Paff 1994]. Emtricitabine 5'-triphosphate inhibits the activity of viral polymerases, including HIV-1 RT by direct binding competition with the natural deoxyribonucleotide substrate (deoxycytidine triphosphate) and by being incorporated into nascent viral DNA, which results in chain termination {Wilson 1993}. FTC has activity that is specific to HIV (HIV-1 and HIV-2) and HBV. The EC50 of FTC against laboratory adapted strains of HIV-1 ranged from 0.001 to 0.62 µM depending on cell type and virus strain used in the assay [Jeong 1993, Painter 1995, Schinazi 1992]. With clinical isolates of HIV-1, EC50 values ranged from 0.002 to 0.028 µM [Schinazi 1992]. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and ε and mtDNA polymerase γ [Painter 1995]. There was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and PBMCs. The EC50 values for FTC were in the range of 0.001 to 0.62 µM. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC50 values ranged from 0.007 to 0.140 µM) and showed activity against HIV-2 (EC50 values ranged from 0.007 to 1.5 µM).

HIV-1 isolates with reduced susceptibility to FTC have been selected in cell culture. Reduced susceptibility to FTC was associated with M184V/I mutations in HIV-1 RT.

TAF

TAF is a phosphonamidate prodrug of TFV (2'-deoxyadenosine monophosphate analogue). Cells are permeable to TAF, and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, TAF is more efficient than TDF in loading TFV into PBMCs, including T cells and macrophages [Birkus 2008, Birkus 2007]. Intracellular TFV is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate (TFV-DP) [Robbins 1998]. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination [Cherrington 1995, Yokota 1994]. Tenofovir has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and HBV [Delaney 2006, Kalayjian 2003, Lee 2005]. In vitro studies have shown that both FTC and TFV can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mtDNA polymerase γ [Cherrington 1994, Kramata 1998], and there is no evidence of mitochondrial toxicity in vitro based on several assays including mtDNA analyses [Birkus 2002, Stray 2017].

The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4-T lymphocytes. The EC50 values for TAF were in the range of 2.0 to 14.7 nM. TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G (EC50 values ranged from 0.10 to 12.0 nM) and activity against HIV-2 (EC50 values ranged from 0.91 to 2.63 nM) (m2.6.3, Section 1.3, PC-120-2004). The antiviral activity of two TAF metabolites, M18 (GS-645552; isopropylalaninyl TFV) and M28 (GS-652829; alaninyl TFV), were evaluated in two T-lymphoblastoid cell lines (MT-2 and MT-4) following 5 days of compound exposure. GS-645552 is also a drug product

degradant. Both metabolites showed weak inhibition of HIV-1 replication with 1723 to 2630-fold lower inhibitory potency relative to TAF (EC50 values of 7.41 to 21.0 µM) for metabolite M28 and 121 to 130-fold lower inhibitor potency relative to TAF (EC50 values of 0.56 to 0.97 µM) for metabolite M18.

HIV-1 isolates with reduced susceptibility to TAF have been selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed [Margot 2006]. HIV-1 isolates with the K65R mutation have low-level reduced susceptibility to abacavir, FTC, TFV, and lamivudine (LAM) [Kagan 2007, Margot 2006]. In vitro drug resistance selection studies with TAF have shown no development of high-level resistance after extended time in culture.

Tenofovir has activity that is specific to HBV in addition to HIV-1 and HIV-2. The antiviral activity of TAF against a panel of HBV clinical isolates representing genotypes A-H was assessed in HepG2 cells. The EC50 values for TAF ranged from 34.7 to 134.4 nM, with an overall mean EC50 of 86.6 nM. The concentration that resulted in 50% cytotoxicity (CC50) in HepG2 cells was >44,400 nM. The combination of TFV and FTC was studied for cytotoxicity in MT-2 cells. No cytotoxicity was observed at the highest concentrations tested, up to 50 µM TFV and 5 µM FTC. Cytotoxicity studies were also conducted on the combination of TFV and FTC in HepG2 cells and no cytotoxicity was observed.

The antiviral activity of TAF was evaluated against a panel of HBV isolates containing nucleos(t)ide RT inhibitor mutations in HepG2 cells. HBV isolates expressing the rtV173L, rtL180M, and rtM204V/I substitutions associated with resistance to LAM remained susceptible to TAF (< 2-fold change in EC50). HBV isolates expressing the rtL180M, rtM204V plus rtT184G, rtS202G, or rtM250V substitutions associated with resistance to entecavir remained susceptible to TAF. HBV isolates expressing the rtA181T, rtA181V, or rtN236T single substitutions associated with resistance to adefovir remained susceptible to TAF; however, the HBV isolate expressing rtA181V plus rtN236T exhibited reduced susceptibility to TAF (3.7-fold change in EC50). The clinical relevance of these substitutions is not known.

B/F/TAF

Bictegravir, FTC, and TAF are potent and selective inhibitors of HIV-1. All 3 drugs show potent ARV activity against diverse subtypes of HIV-1 in vitro. Emtricitabine and TFV are phosphorylated intracellularly through non-overlapping pathways, and in combination show no antagonism for the formation of their active metabolites. Bictegravir does not require metabolic modification for activity. The anti-HIV-1 activity of the 3-drug combination of BIC, FTC, and TAF was found to be highly synergistic with no evidence of antagonism in vitro, supporting the use of these agents in combination in HIV-1 infected patients. In addition, in vitro combination studies have shown that in 2-drug combination studies BIC, FTC, and TFV have additive to synergistic anti-HIV-1 activity with other approved NRTIs, NNRTIs, and PIs [Hill 1997, Miller 1999, Rimsky 2001]. The resistance profiles of the individual agents BIC, TFV, and FTC are distinct and non-overlapping.

Secondary pharmacodynamic studies

Cytotoxicity

BIC

For BIC, the concentration that resulted in 50% cytotoxicity (CC50) in primary CD4+ T-lymphocytes, MT-4, MT-2, resting and activated PBMCs, and monocyte-derived macrophages cells ranged from of 3700 to 29800 nM.

FTC

The cytotoxicity of FTC has been evaluated extensively in vitro. In all the cell lines examined, cell growth was not affected at concentrations of FTC≥ 100 µM (Schinazi 1994, Van Draanen 1994, Furman 1992).

TAF

Both TAF and its metabolites M18 and M28 had no cytotoxicity up to the highest tested concentration (57 µM).

Safety pharmacology programme

BIC

Bictegravir was evaluated in safety pharmacology studies of the central nervous system (CNS), respiratory, and cardiovascular systems. At the highest doses tested, BIC had no effects on the central nervous and respiratory systems of rats (300 mg/kg), no effects on the cardiovascular system of monkeys (1000 mg/kg), and no notable inhibition of the human ether-a-go-go-related gene (hERG) potassium channel current at a concentration > 7.1 µM. Plasma exposures (free [unbound] Cmax) in the in vivo studies were at least 0.92-fold (rats) and 22-fold (monkeys) of the free BIC Cmax concentration following clinical administration of the B/F/TAF fixed-dose combination (FDC). In the hERG study, exposures were at least 200-fold above free BIC Cmax concentration following clinical administration of the B/F/TAF FDC.

FTC

A comprehensive range of safety pharmacology studies revealed no treatment-related adverse effects on any organ system at systemic exposure levels much higher than those anticipated in patients at the recommended clinical dose (10- to more than 50-fold).

No effects on the CV system were reported in anesthetized dogs administered a cumulative dose of 38.5 mg/kg of FTC intravenously over a 1-hour period. In addition, there were no abnormalities reported on the electrocardiogram (ECG) data obtained from the repeated-dose toxicity studies in monkeys, where plasma AUC exposures were up to 26-fold higher than in humans administered the 200-mg dose.

TAF

Tenofovir alafenamide was evaluated in safety pharmacology studies of the rat central nervous, renal, gastrointestinal (GI), and CV systems. In vivo safety pharmacology experiments were conducted using TAF as the monofumarate form in 50 mM citric acid. The 50% inhibitory concentration (IC50) for the inhibitory effect of TAF on hERG potassium current was estimated to be > 10 µM, far above human plasma exposure. There were no adverse effects detected in the CNS in rats dosed at 1000 mg/kg or in the renal system in rats administered 1000 mg/kg. In the chronic repeat dose dog study, a dose-related prolongation of PR interval was noted at Week 39; however, in the single dose CV safety pharmacology study in dogs dosed t 100 mg/kg (80 mg free base equivalents/kg), there were no findings. There was reduced gastric emptying in rats dosed at 1000 mg/kg but not at 100 mg/kg.

B/F/TAF

A comprehensive safety pharmacology program has been conducted for the 3 individual components of the B/F/TAF regimen. While the designs for these safety studies varied between the agents, the major organ systems were evaluated. Bictegravir had no effect on vital organ systems in safety pharmacology studies. Neither FTC nor TAF had clinically relevant effects on vital organ systems in safety pharmacology studies. Although TAF showed some potential to prolong the PR interval in the 39-week dog study (TOX-120-002), no PR prolongation or any change in ECG results occurred in the CV safety pharmacology study r in the thorough QT study (GS-US-120-0107). Neither BIC nor FTC had an effect on PR interval in safety pharmacology studies; therefore, there is no potential for overlapping toxicity. Overall, the pharmacological assessment of BIC, FTC, and TAF supports the effective use of these 3 agents together in combination therapy for HIV-1 infection.

Pharmacodynamic drug interactions

The anti-HIV-1 activity of 2-drug and 3-drug combinations of BIC, FTC, and TAF were found to be additive to highly synergistic with no evidence of antagonism in multiple in vitro assay systems, supporting the use of these agents in combination in HIV-infected patients.

In vitro two-drug combination studies have shown that BIC has additive to synergistic anti- HIV-1 activity with other approved NRTIs, NNRTIs, and PIs, including synergistic activity with TAF, FTC, and darunavir (DRV). No antagonistic antiviral interaction was found between BIC and the tested clinically relevant classes of antiretrovirals.

In two-drug combination studies of FTC with NRTIs, NNRTIs, PIs, and INSTIs, additive to synergistic effects were observed. No antagonism was observed for these combinations (Hill 1997, Rimsky 2001).

Pharmacokinetics

A comprehensive nonclinical program defining the absorption, distribution, metabolism, excretion and drug interaction potential of BIC, FTC and TAF/TFV has been completed. The nonclinical pharmacokinetic and disposition studies discussed in this section provide an adequate basis for comparing and interpreting results from toxicology and clinical studies.

Methods of analysis

The plasma BIC concentrations in nonclinical PK studies in mouse, rat, rabbit, dog, and monkey were quantified by high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) or by liquid chromatography (LC) coupled to ultraviolet (UV) detection (LC-UV) methods.

FTC: Analytical methods used to quantify FTC in mouse, rat, and monkey plasma from the early preclinical absorption, distribution, metabolism, and excretion studies employed reverse-phase high performance liquid chromatography (HPLC), and HPLC-MS (plasma and urine). LC-radio-profiling has been utilised to detect [3H]FTC in mice and monkeys, and to detect [14C]FTC in rats and monkeys.

TAF: Levels of TAF and TFV in rats and dog plasma and PBMCs were determined using fluorescence derivitization/HPLC. Additional methods to detect levels of TAF and TFV in mouse, rat, rabbit and dog plasma/PMBCs included validated LC/MS/MS methods, and HPLC detection methods. The absorption, distribution, metabolism, and excretion of TAF were assessed in various species following a single oral administration of [14C]TAF, and levels of TAF and its metabolites were measured using LSC, HPLC or LC/MS/MS coupled with flow-through detector (RFD). *In vitro* determination of TAF levels were in the main determined by LC/MS/MS, with some LC-radio-profiling. Induction potential of TAF on CYP activity measured mRNA levels using qRT PCR methods.
The bioanalytical methods are considered adequate.

Absorption

Bictegravir was absorbed quickly following oral solution administration, reaching maximal plasma concentrations (C_{max}) within 4 hours post-dose. The oral bioavailability of BIC solution formulation was moderate to high (42% to 74%).

Bictegravir was highly permeable and showed efflux transport in Caco-2 cell monolayers. Bictegravir was a substrate of P-glycoprotein (P-gp). The PK of BIC was determined in male rats, dogs, and monkeys following administration of oral solutions. Bictegravir systemic plasma clearance was low in nonclinical species (0.1% to 1.3% of hepatic blood flow). Bictegravir volume of distribution (Vss; 0.09 to 0.22 L/kg) in animals was lower than total body water. Bictegravir showed moderate to high oral bioavailability (42% to 74%) in nonclinical species. Bictegravir plasma exposure increased following repeat oral administration of BIC; the increases in C_{max} and AUC were less than dose proportional. In rats, females had higher BIC Cmax and AUC0-24 values than males, with gender-based differences of 2-to 3-fold on study days 90 and 181 for animals administered the high dose (300 mg/kg/day). In female rats administered the low dose (5 mg/kg/day), an accumulation (~ 3-fold) was observed. In monkeys, gender-based differences in BIC Cmax and AUC values were less than 2-fold and no accumulation (< 2-fold) of BIC was observed after repeat dosing.

FTC: No *in vitro* permeability studies have been carried out with FTC, as FTC shows high, dose-independent bioavailability *in vivo* in mice and monkeys. Single-dose pharmacokinetics of FTC have been studied in mice, rats and cynomolgus monkeys. FTC was rapidly and well absorbed with oral bioavailability ranging from 58% to 97% over the dose range of 10 to 600 mg/kg.

The multiple-dose pharmacokinetic parameters for FTC were derived as part of the repeat-dose toxicity studies in mice (80 to 3000 mg/kg/day; Study Nos. TOX109; IUW00701; TOX599; TOX628), in rats (60 to 3000 mg/kg/day; Study Nos. TOX108; TOX097), and monkeys (40 to 2000 mg/kg/day; Study Nos. TOX600; TOX627; TOX032) dosed for periods of 3 days to 104 weeks. There were no significant differences in pharmacokinetics following single and multiple dosing. Exposure to FTC (Cmax and AUC) increased approximately proportionally with dose and was similar between males and females.

TAF: Permeability of TAF was examined using Caco-2 cells (Study No. AD-120-2037). TAF was applied to monolayers of these cells at 10, 100, and 1000 µM, and TAF showed a dose dependent increase in forward permeability and a decrease in efflux ratio indicating saturable efflux transport. Addition of the efflux transport inhibitor, cyclosporine A (CsA) diminished the efflux ratio and increased the permeability.

In rats, no consistent differences in plasma pharmacokinetic parameters were found between male and female rats. Mean tenofovir Cmax and AUC values increased dose proportionally over the dose range of 5 to 100 mg/kg/day. Mean TFV AUC obtained on Day 1 was slightly lower than that measured during Weeks 13 and 26, which suggested that there was a slight accumulation of tenofovir with repeat dosing. In dogs, there was some accumulation of tenofovir following repeat dosing (~3-fold).

Distribution

BIC was highly protein bound in plasma from all species tested (> 98% bound) and was 99.75% bound in humans. BIC is widely distributed with a rapid distribution but a very slow elimination (radioactivity was not eliminated from most tissues by 168h). BIC poorly crosses the blood:brain, blood:eye and blood:testis barriers and there is no preferential association with melanin. Pups were exposed to BIC according prenatal and postnatal development study in rats.

FTC: The protein binding of FTC was very low (< 5%) in mouse, rabbit, monkey, and human plasma (Study No. TBZZ/93/0025). The tissue distribution of [14C]FTC was characterized in rats and cynomolgus monkeys after a single oral dose of 200 mg/kg (Study Nos. TOX092 and TOX063, respectively). Distribution was extensive and rapid; levels were detected within 1 h post oral administration. There was no sign of FTC accumulation and elimination was rapid, no radioactivity was observed after 72 hours post-dose.

Pharmacokinetic parameters for FTC in pregnant animals appeared to be generally similar to those reported for non-pregnant animals. Emtricitabine was readily transferred across the placenta. Excretion into milk has not been evaluated for FTC.

TAF: The protein binding of TFV has been determined in human plasma and serum using centrifugal ultrafiltration (Study No. P0504-00039.1). Percent of unbound TFV was 99.3 ± 3.3% in human plasma, and 92.8 ± 3.6% in human serum. Tenofovir therefore showed very low protein binding in either human plasma or serum. There was rapid distribution to most tissues, both to mice, pigmented and non-pigmented rats. The tissues showing the highest maximum concentrations of radioactivity included kidney cortex, kidney(s), kidney medulla, and liver in mice and rats. In animal studies it has been shown that tenofovir was transferred across the placenta and was excreted in milk.

Metabolism

Unchanged BIC was the principal radiolabel component in all species (≥ 67 % in plasma). Bictegravir is metabolized by CYP3A oxidation and UGT conjugation and, hence, BIC plasma exposure may be altered by inducers or inhibitors of these enzymes. Despite the fact that the sulfate conjugate of hydroxylated BIC (M20) was present at higher concentrations in human than other species (20.1% in human versus 11.3% in rat and 0.77% in monkey), exposure of M20 in rats is estimated to be approximately 9-fold higher than observed human exposure at the clinical dose of 50 mg, and therefore further nonclinical characterization according to ICH M3 (R2) is not warranted.

There are no metabolism data in rabbit and therefore it cannot be concluded if findings in the EFD study in rabbit are caused by rabbit specific metabolites. However, rabbit have been exposed to BIC and rats have been well exposed to the major human metabolite M20.

FTC: FTC is not subject to significant metabolism by CYP enzymes. Generation of a minor (~1%) sulfoxide metabolite (M1 and/or M2) was catalysed by CYP3A4, and inhibitor studies suggested that at least one other enzyme, possibly flavin-containing monooxygenase, may play a role (Study No. 15396 v1). A minor direct glucuronide metabolite, M3, was also detected.

FTC was not extensively metabolised and is eliminated primarily as unchanged drug by renal excretion in mice, rats, and cynomolgus monkeys. Over 90% of the radioactivity in mouse and rat urine and 64% of the radioactivity in monkey urine was unchanged drug. Only trace levels of metabolites were found in faeces (Study Nos. TEIN/93/0015, TEIN/93/0016, TOX063). In all 3 species, metabolism accounted for only a minor percentage of FTC elimination. FTC is subject to Phase I metabolism (oxidation to a diastereomeric sulfoxide) and to some direct conjugation (glucuronidation of hydroxymethyl group) as minor metabolic routes.

TAF: Tenofovir alafenamide is subject to intracellular metabolism to TFV, which is further phosphorylated to the anabolites, TFV-MP and TFV-DP with TFV-DP being the pharmacologically active form.

The Applicant has proposed a possible metabolism pathway based upon the findings from mice, rats, dogs and humans. TAF is also subject to intracellular metabolism to TFV, which is further phosphorylated to the anabolites, tenofovir-monophosphate and TFV-DP with TFV-DP being the pharmacologically active form.

Excretion

BIC was mainly eliminated through metabolism by the liver (34-40%) followed by excretion into feces (20-40%) and urine (7-15%).

FTC: The primary route of elimination of [3H]FTC and [14C]FTC was via renal excretion of parent drug after oral and IV administration in mice, rats, and cynomolgus monkeys. The majority of the FTC recovered in the faeces after oral administration most likely represents unabsorbed drug, rather than biliary excretion. Although FTC is metabolized to only a minor extent, its metabolites are also excreted via the kidneys. Excretion into milk has not been evaluated for FTC.

TAF: Recovery of radioactivity was 41.3 and 27.7% in faeces and urine, respectively, by 168 hours post-dose in mice. [14C]TAF was rapidly excreted within 24 hours after oral dosing in bile duct-intact and BDC male SD rats. The mean values of 71.9 and 22.2% of the administered radioactivity were excreted in faeces and urine, respectively, by 168 hours post-dose. In dogs the excretion of [14C]TAF was determined after administration of a single 15-mg/kg oral dose of 14C-TAF to bile duct-intact and BDC male dogs. [14C]TAF was readily excreted mostly within 48 hours after oral dosing. The mean values of 37.4% and 35.9% of the administered radioactivity were excreted in faeces and urine, respectively, by 168 hours post-dose. Mean values of 2.11% and 14.0% of the administered radioactivity were excreted in bile in rat and dog, respectively, through 168 hours post-dose.

Excretion to milk: The extent of TFV excretion in lactating monkeys was evaluated. Milk was obtained from 2 lactating adult female rhesus monkeys following a single 30 mg/kg subcutaneous dose of TFV (Study No. P2000116). TFV was detected in the milk, the AUC in milk was between 18.6-21.5% of that seen in plasma.

2.3.3. Toxicology

The toxicological profiles of BIC, FTC and TAF have been evaluated in a comprehensive set of non-clinical studies where the compounds have been evaluated separately. The performed studies include repeat-dose toxicity studies up to 6 months in rodents and 9 months in a non-rodent species, in vitro and in vivo genotoxicity, carcinogenicity, male and female fertility and early embryonic development in rodent, embryo-foetal development toxicity, peri- and post-natal development studies in rodents, phototoxicity studies.

Single dose toxicity

No new single dose toxicity studies have been conducted, namely, no studies using bictegravir or the bictegravir/emtricitabine/tenofovir alafenamide combination. Studies conducted with emtricitabine, tenofovir disoproxil and tenofovir alafenamide, administered separately, revealed no risks of acute toxicity. The lack of dedicated single dose toxicity studies with bictegravir was considered acceptable. Other toxicological studies using this active substance indicate no risk of acute toxicity.

Repeat dose toxicity

Bictegravir

The oral toxicity of BIC has been studied in rats, and monkeys for treatment periods up to 39 weeks. Preliminary carcinogenicity study in transgenic mouse was also conducted for up to 4 weeks.
In rats, no major effect have been observed at up to 300 mg/kg/d for 26-weeks (20 fold the exposure following clinical administration of the B/F/TAF FDC).
However, BIC induced a high liver toxicity (bile duct hyperplasia, hepatocyte hypertrophy, regenerative hyperplasia, neutrophil infiltrate) with increased ALT activities in monkeys that persisted through the recovery phase at high dose of 1000 mg/kg/day (16 fold the exposure following clinical administration of the B/F/TAF FDC) in a 39-week toxicology study at the exception of increased ALT activities. The Applicant's conclusion on that the hepatobiliary effects observed in monkeys are not of relevance for humans is essentially solely based on the results of 4 Phase 3 clinical studies. It is not to be excluded the possibility that, depending on systemic exposure levels, the hepatobiliary effects observed in monkeys may represent a potential risk to humans, for which there is not a high safety margin. This information is considered of potential relevance to the prescriber and is included in section 5.3 of the SmPC.

FTC

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies repeated dose toxicity. Treatment-related effects were confined to high-dose groups only and included changes in red blood cell (RBC) parameters, interpreted as a mild, reversible anaemia (mice 1 month, 6 months; rat 3 months; monkey 1 year); changes in various organ weights without any associated adverse histopathological effects in rodents (mouse 1 month, 6 months; rat 3 months), increased urine output (mice 6 months), and soft faeces (monkeys 1 month, 3 months). No observed effect levels (NOELs) could be established for all treatment-related effects, and in several cases the minor effects observed were reversible after a recovery period.

TAF

Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced BMD in rats and dogs at tenofovir exposures at least four times greater than those expected after administration of Descovy. A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 4 and 17 times greater, respectively, than those expected after administration of Descovy.

Bictegravir / FTC / TAF

No repeated dose toxicity studies have been conducted with the bictegravir/emtricitabine/tenofovir alafenamide triple combination. This is accepted, taking into account the lack of overlapping toxicities and the already available clinical experience with the combination. The Applicant considers that the increased phosphorous levels observed in rat repeat dose toxicity studies with bictegravir is not biologically significant and not relevant for consideration of the safety profile of the combination. This is based mostly on the lack of bone or renal microscopic findings in the rat 26 week repeated dose toxicity and carcinogenicity studies conducted with bictegravir and on an, as claimed, acceptable renal and bone clinical safety data for B/F/TAF.

Genotoxicity

Bictegravir

Despite precipitate and toxicity, no increase in the numbers of revertant colonies was observed in Ames test. In chromosome aberration test, an increase in the number of polyploid cells has been observed and the reason of this event is not fully understood. However, no increase in the number of cells with chromosomal aberrations or endoreduplication. No effect have been observed *in vivo* in micronucleus assessment at doses up to 29 fold the exposure following clinical administration of the B/F/TAF FDC, and therefore could be considered as non-genotoxic.

FTC / TAF

FTC and tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxicity assays.

Carcinogenicity

Bictegravir

The transgenic Tg-rasH2 model is acceptable for regulatory authorities as an alternative to the standard mouse long-term study (CHMP SWP Conclusions and recommendations on the use of genetically modified animal models for carcinogenicity assessment, CPMP/SWP/2592/02 Rev, June 2004). BIC did not induce a significant carcinogenic response in this animal model at exposures 15-fold above clinical exposure levels. It could be noted that disturbing data have been observed in the rat carcinogenicity study (tumours with statistically significant increase in treated rats) in addition to carcinoma observed in the 26-weeks study in rats, hyperplasia not reversed in the 39-weeks in monkeys, the lack of the major human metabolite M20 in TG mice in carcinogenicity study and the increase of combined spleen/urinary bladder/uterus/vagina b-hemangioma/m-hemangiosarcoma tumors at the mid-dose in the TG mice carcinoma study. However tumours observed in the rat carcinogenicity study were comparable to historical control data.

Reproductive and developmental toxicity

Bictegravir

In rats, BIC did not affect fertility or early embryonal development in rats at exposure margins of up to 22 times the 50 mg human clinical exposure based on AUC.

Concerning embryo-foetal development in rats, BIC did not affect implantations, percent preimplantation loss, litter sizes, live foetuses, early resorptions or percent post-implantation loss.

BIC was shown to be devoid of embryo-foetotoxic or teratogenic potential in rabbits at exposure margins at the NOAEL of 0.59 times the 50 mg human clinical exposure based on AUC. The high dose level induced some maternal toxicity, as shown notably by significant decreases in body weight with abortion in 2 does.

Concerning prenatal and postnatal development study in rats, the Applicant states that no test article-related effects were noted at any dosage level during the study and the NOEL for F0 maternal systemic toxicity, and F1 neonatal/developmental toxicity, parental systemic toxicity, and reproductive toxicity, and F2 neonatal/early postnatal toxicity was 300 mg/kg/day.

FTC / TAF

No special hazard for humans was revealed in conventional studies of toxicity to reproduction and development with FTC.

Because there is a lower tenofovir exposure in rats and mice after the administration of tenofovir alafenamide compared to tenofovir disoproxil fumarate, a rat peripostnatal study was conducted only with tenofovir disoproxil fumarate. No special hazard for humans was revealed in conventional studies of toxicity to reproduction and development. Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil fumarate reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses.

Juvenile toxicity

Bictegravir / FTC / TAF

No juvenile toxicity studies have been conducted with BIC, F or TAF. This is acceptable, since the presently sought indication of BIC/F/TAF is confined to the adult population.

Local Tolerance

Bictegravir

BIC could be considered to be non-corrosive, non-irritant in the in vitro skin model EpiDerm.

FTC / TAF

No specific local tolerance studies have been conducted with FTC and no particular alert in repeat dose toxicity studies has been observed.

In a bovine corneal opacity and permeability assay (BCOP) TAF elicited an in vitro irritancy score of 21.0 ± 8.7 with a 4-hour incubation and was predicted to be a noncorrosive/non-severe eye irritant.

In a dermal irritation study in rabbits animals were given a single 4 hour, semi-occlusive, dermal administration of approximately 0.5 g of TAF and were observed for 4 days (Study number: TX-120-2011). No local dermal reaction was observed in any animal throughout the duration of the study. The Primary Irritation Index was calculated to be 0.0; TAF was classified as a 'non-irritant'.

The potential for additive effects among the three agents in the B/F/TAF FDC is minimal.

Immunotoxicity

Bictegravir / FTC / TAF

No specific immunotoxicity studies have been conducted with BIC and TAF and no particular alert in repeat dose toxicity studies has been observed.

An immunotoxicity study was conducted with FTC and there was no effect on the immune system as evaluated by IgM antibody response in the rat to sheep red blood cells with doses up to 1000 mg/kg/day.

Antigenicity

Bictegravir

BIC is not a potential skin sensitizer.

FTC / TAF

No specific antigenicity studies have been conducted with FTC and no particular alert in repeat dose toxicity studies has been observed.

Female mice were given TAF (GS-7340-03) at of 10, 25 or 50% w/v. The animals were administered TAF by daily application of 25 µL of the appropriate concentration or control (vehicle or positive), to the dorsal surface of both ears for 3 consecutive days. The proliferative response of the lymph node cells (LNCs) from the draining auricular lymph nodes was assessed 5 days following the initial application, by measurement of the incorporation of 3H-methyl thymidine (3HTdR) by β-scintillation counting of LNC suspensions.

The response was expressed as radioactive disintegrations per minute per lymph node (dpm/node) and as the ratio of 3HTdR incorporation into LNC of test nodes relative to that recorded for control nodes (test/control ratio), termed as SI. The test substance is regarded as a sensitizer if at least one concentration of the chemical has a SI of 3 or more. The SI obtained for 10%, 25%, and 50% w/v were 0.9, 1.0, and 1.0, respectively, which indicates that TAF did not show the potential to induce skin sensitisation. The EC3 value (the "estimated concentration of 3" is the concentration of test substance

which would result in a SI of 3 in the LLNA) was determined to be higher than 50% w/v. The SI for the positive control substance hexyl cinnamic aldehyde was 6.3, which demonstrates the validity of this study.

Impurities

Bictegravir / FTC / TAF

The impurities and degradation products in the BIC, FTC or TAF drug substance have been identified and qualified in toxicology studies.

Phototoxicity

Bictegravir

The irradiation sources used in the positive in vitro study and negative in vivo study differ. The emission spectra of the light source used for the in vitro study starts at 300-310 nm while the spectra of the light source used for the in vivo study starts at 310-320 nM. It remains that the absorbance of BIC is substantially equivalent between 290 and 320 nm, and the animals have been well exposed to BIC in the in vivo study.

FTC / TAF

FTC and TAF fumarate does not absorb light within the range of natural sunlight; therefore no phototoxicity studies are not considered necessary for FTC or TAF.

Other toxicity studies

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TAF - Bone metabolism

Three relevant non-GLP rat studies and one GLP dog study were conducted to evaluate the potential for TAF to alter bone metabolism.

Male rats were given 400 mg/kg TAF by oral gavage daily for 6 days. One animal was due to non-drug related injury (study number: R990177). The results of this study demonstrated that TAF had effects on selected urinary and serum parameters. The Applicant states that due to the lack of strong statistical comparison to controls and lack of correlation between data, interpretation on overall toxicity was not possible.

In the second study, an additional dose was evaluated. This study examined changes in markers of calcium homeostasis in male Sprague-Dawley rats after once daily oral administration of TAF. Animals were given 100 or 400 mg/kg TAF by oral gavage on Days 0, 1, 2, 3, 4, and 5. The results indicated that daily administration of TAF to rats for 6 days altered plasma vitamin D, calcium and phosphate levels as well as urinary excretion of calcium. It is stated that the mechanistic basis of these changes and their biological relationships in terms of cause and effect are unknown.

Dogs were given oral doses of 37.5 or 75 mg/kg/day of TAF for 5 days (1/dose). The Applicant states that there were no biologically important changes observed in mean values for ionized calcium or N telopeptide. The Applicant states that the lack of the expected age-related reduction in mean serum bone ALP (B-ALP) suggested increased bone remodelling. The mean serum calcitriol (1, 25 dihydroxycholecalciferol) concentration was reduced by approximate 68% at both doses. The mean serum 25-hydroxyvitamin D (25 hydroxycholecalciferol) concentration was reduced approximately 35% and 33% at 37.5 and 75 mg/kg/day. Gastrointestinal lesions characterised by epithelial cell necrosis, regenerative hyperplasia, and cyst formation were most prevalent in animals at 75 mg/kg/day. Lymphoid cell depletion was noted in the lymph nodes, thymus and tonsil at 75 mg/kg/day animals. Bile duct hyperplasia and peri-portal inflammation was observed at both doses.

TAF - Renal Function

An investigative study was conducted in SD rats to evaluate renal parameters. Animals were given a single oral dose of 100 or 1000 mg/kg/day TAF. Urinary output of calcium was increased at 1000 mg/kg/day which correlated with an increase in serum calcium concentration and indicated that the kidneys were functioning in order to reduce the serum calcium load.

2.3.4. Ecotoxicity / environmental risk assessment

Bictegravir

This environmental risk assessment is in accordance with guidelines, and based on the data generated for the Phase II A assessment, the proposed use of BIC poses no unacceptable risk to the environment. The Phase II B assessment is ongoing and the final results from the required studies are pending. The Applicant committed to submit the completed study reports post-authorisation (December 2018) along with an updated risk assessment. The results of the environment risk assessment of BIC are summarised below.

Summary of main study results

Substance (INN / Invented Name): BIC			
CAS-number (if available): 1807988-02-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log Dow = 2.2 at pH 7	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.2	
	BCF		not B
Persistence	DT50 or ready biodegradability	96.5 - 911 d (Sediment)	vP
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.3 (F*pen* 0.012)	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	KF^{ads} soil 1089 – 4123 L/kg $KFoc^{ads}$ soil 67640-248373	

		L/kg KF^{ads} sewage sludge 5605 - 5683 L/kg $KFoc^{ads}$ sewage sludge 12829-14634 L/kg			
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 0.4-1.1 d $DT_{50, sediment}$ = 45.2-437 d $DT_{50, whole\ system}$ =2.6-439 d *(At 12°C: $DT_{50, sediment}$ = 911 $DT_{50, whole\ system}$ = 369 d (calculation with Cake3.3 according assessor's assessment))* % shifting to sediment >10% AR in sediment at or after 14 d			Very persistent BIC distributes to the sediment with more than 10% of the applied dose associated with sediment after Day 14
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *species*	OECD 201	NOEC	0.066	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.17	mg/L	
Fish, Early Life Stage Toxicity Test/ *species*	OECD 210	NOEC	1.2	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	26	mg/L	*Sewage microorganisms*
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	Not required
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			***In progress****
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	***In progress****
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	***In progress****
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	***In progress****
Collembola, Reproduction Test	OECD 232	NOEC		mg/kg	***In progress****
Sediment dwelling organism *Chironomus*.sp	OECD 218	NOEC		mg/kg	***In progress****

* ERA report will be updated by December 2018

FTC / TAF

The environmental risk assessment of Descovy has shown that FTC does not bioaccumulate and is of low risk to the aquatic or terrestrial environments. TAF is a next generation pro-drug of tenofovir (TFV) and TFV has been identified as persistent in the environment, but it is considered to be of low risk to aquatic organisms, it is not bioaccumulative and does not pose significant risk to the environment.

Substance (INN/Invented Name): Emtricitabine			
CAS-number (if available): 143491-57-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log *K*ow	OECD107	-0.693 – -0.670	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log *K*ow	-0.693 – -0.670	not B
	BCF	Not required	not B
Persistence	DT50 or ready biodegradability	$DT_{50, water}$ = 81-209 d $DT_{50, whole\ system}$ = 92.2-286 d No significant metabolites formed	vP
Toxicity	NOEC or CMR		not T

PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC surfacewater, refined	1.2 (F*pen* 0.012)	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	*Kd* sludge =12.9 L.kg-1			
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 38-98 d $DT_{50,\ sediment}$ = χ^2 always > 15 % $DT_{50,\ whole\ system}$ = 43.2-134 d *(At 12°C: $DT_{50,\ water}$ = 81-209 d* *$DT_{50,\ whole\ system}$ = 92.2-286 d* *(calculation with KinGUII 2.1 according assessor's assessment))* % shifting to sediment >10% AR in sediment at or after 14 d			Very persistent in water/whole system. Sediment toxicity assessment is triggered.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	≥ 110	mg.L-1	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥ 110	mg.L-1	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	6.10	mg.L-1	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	≥ 1000	mg.L-1	Sewage microorgnisms
Phase IIb studies					
Sediment dwelling organism	OECD 218	NOEC	≥38 ≥ 200 (normalised)	mg/kgd wt	*Chironomus riparius* normalised for 10% OC 200 mg.kgdwt -1)

Substance (INN/Invented Name): Tenofovir alafenamide (as environmentally relevant TFV)			
CAS-number (if available): 1392275-56-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log *K*ow	OECD107	-3.8 – -4.3	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log *K*ow	-3.8 – -4.3	not B
	BCF	Not required	not B
Persistence	DT50 or ready biodegradability	$DT_{50,\ water\ =}$ 8.3-22 d $DT_{50,\ sediment}$ = 142-303 d $DT_{50,\ whole\ system}$ = 12.8-60 d Formation of three significant transformation products, two of which are persistent.	vP
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater, refined	0.07 µg/L (F*pen* 0.012)	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Koc ads soil 351 - 1091 L.kg-1 Koc des soil 968 - 2791 L.kg-1 KF ads sludge 6.0 - 21 L.kg-1 KF des sludge 16 - 62 L.kg-1	
Ready Biodegradability Test	OECD 301	Not readily biodegradable	

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 3.9-10.3 d $DT_{50, sediment}$ = 66.5-142 d $DT_{50, whole system}$ = 6.0-28 d *(At 12°C: $DT_{50, water}$ = 8.3-22 d* *$DT_{50, sediment}$ = 142-303 d* *$DT_{50, whole system}$ = 12.8-60 d* *(calculation with KinGUII 2.1 according assessor's assessment))* % shifting to sediment >10% AR in sediment at or after 14 d Formation of three significant transformation products, two of which are persistent.			Very persistent in sediment. Formation of three significant transformation products, two of which are persistent. Sediment toxicity assessment is triggered.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	32	mg.L-1	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥ 100	mg.L-1	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	≥10	mg.L-1	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	mg.L-1	Sewage microorganisms
Phase II b studies					
Sediment dwelling organism	OECD 219	NOEC	≥ 290 ≥ 1261 (normalised)	mg/kg dwt	*Chironomous riparius* normalised for 10% OC 17.06 mg.kgdwt-1

2.3.5. Discussion on non-clinical aspects

Pharmacology

No novel non-clinical pharmacology studies with F and TAF have been submitted with this application. The studies supporting the use of these substances are well known. There are no findings in the secondary pharmacology or safety pharmacology studies with BIC to be considered in the safety evaluation, and therefore no findings in studies on secondary pharmacology or safety pharmacology to be considered specifically in the safety evaluation of the triple combination.

Pharmacokinetics

The single dose PK of BIC has been determined in rats, dogs and monkeys. In rats, females had higher BIC Cmax and AUC0-24 values than males, with gender-based differences of 2-to 3-fold on study days 90 and 181 for animals administered the high dose (300 mg/kg/day). In female rats administered the low dose (5 mg/kg/day), an accumulation (~ 3-fold) was observed.

Bictegravir was absorbed quickly following oral solution administration, reaching maximal plasma concentrations (C_{max}) within 4 hours post-dose, and is widely distributed with a rapid distribution but a very slow elimination. The oral bioavailability of BIC solution formulation was moderate to high (42% to 74%). Despite the fact that the sulfate conjugate of hydroxylated BIC (M20) was present at higher concentrations in human than other species (20.1% in human versus 11.3% in rat and 0.77% in monkey), exposure of M20 in rats is estimated to be approximately 9-fold higher than observed human exposure at the clinical dose of 50 mg, and therefore further nonclinical characterization according to ICH M3 (R2) is not warranted. There are no metabolism data in rabbit.

No novel nonclinical pharmacokinetics studies with FTC or TAF have been submitted with this application. There were no findings in these studies on pharmacokinetics to be considered specifically in the safety evaluation of the triple combination.

Toxicology

The oral toxicity of BIC has been studied in rats and monkeys for treatment periods up to 39 weeks. Preliminary carcinogenicity study in transgenic mouse was also conducted for up to 4 weeks.
In rats, no major effect has been observed at up to 300 mg/kg/d for 26-weeks. BIC induced a high liver toxicity (bile duct hyperplasia, hepatocyte hypertrophy, regenerative hyperplasia, neutrophil infiltrate) with increased ALT activities in monkeys that persisted through the recovery phase at high dose of 1000 mg/kg/day. The Applicant considered that there is no evidence for that the hepatobiliary effects observed in the chronic toxicity study with administration of bictegravir to cynomolgus monkeys is significant or relevant for humans. Information on the hepatobiliary effects is included in section 5.3 of the SmPC.

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies repeated dose toxicity. Treatment-related effects were confined to high-dose groups only and included changes in red blood cell (RBC) parameters. Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidney as the primary target organs of toxicity.

BIC, FTC and tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxicity assays. No special hazard for humans was revealed in conventional studies of carcinogenic potential for F or TDF. BIC did not induce a significant carcinogenic response in this transgenic mouse or in rats at exposures 15-fold and 21-fold above clinical exposure levels respectively.
Studies in animals with bictegravir have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with bictegravir during pregnancy, there were no toxicologically significant effects on developmental endpoints.

There were no other findings in all non-clinical studies to be considered specifically in the safety evaluation of the triple combination.

Environmental risk assessment
Studies for BIC are ongoing and will be submitted post-authorization.

2.3.6. Conclusion on the non-clinical aspects

There are no objections to an approval of BIC/F/TAF from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

An overview of clinical studies in support of this application is provided in Table 6 and 7.

Table 6. Clinical Pharmacology studies

Study Number, Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
GS-US-141-1218,	Phase 1 placebo-controlled study to evaluate the safety, tolerability, and PK of single- and multiple-ascending doses of BIC and the DDI potential between BIC and F/TAF in healthy subjects	**BIC** 5-mg tablet (EC1401B1), 25-mg tablet (EC1402C1), 50 mg (2 × 25-mg tablets), 100-mg tablet (EC1402D1), 300 mg (3 × 100-mg tablets), 600 mg (6 × 100-mg tablets) **F/TAF** 200/25-mg tablet (CR1305B2)	130	**Placebo-to-match BIC**
GS-US-141-1219,	Phase 1b placebo-controlled study to evaluate the safety, PK, and short-term antiviral activity of BIC compared with placebo-to-match in HIV-infected subjects	**BIC** 5-mg tablet (EC1401B1), 25-mg tablet (EC1402C1), 50 mg (2 × 25-mg tablets), 100-mg tablet (EC1402D1)	20	**Placebo-to-match BIC**
GS-US-141-1475,	Phase 2, randomized, double-blinded study to evaluate the safety and efficacy of BIC+F/TAF vs DTG+F/TAF	**BIC** 75-mg tablet (EC1504B1, EC1504B2, EC1506B1) + **F/TAF** 200/25-mg tablet (CR1408B1, CR1412B1) **B/F/TAF** 50/200/25-mg tablet (EN1504B1, EN1602B2)	98	**DTG** 50-mg tablet + **F/TAF** 200/25-mg tablet **Placebo-to-match BIC**
GS-US-141-1478,	Phase 1 study to evaluate the PK of single-dose BIC in subjects with normal or impaired hepatic function	**BIC** 75-mg tablet (EC1504B2)	20	Not applicable
GS-US-141-1479,	Phase 1 study to evaluate the PK of single-dose BIC in subjects with normal or impaired renal function	**BIC** 75-mg tablet (EC1504B1)	18	Not applicable
GS-US-141-1480,	Phase 1 placebo- and positive-controlled study to evaluate the effects of BIC (at therapeutic and supratherapeutic doses) on ΔΔQTcF in healthy subjects	**BIC** 75-tablet (EC1504B1) and 300 mg (4 × 75-mg tablets)	48	**Placebo-to-match BIC** **Moxifloxacin** 400-mg tablet
GS-US-141-1481,	Phase 1 mass balance study to evaluate the PK, metabolism, and excretion of a single oral dose of radiolabeled [^{14}C]BIC in healthy male subjects	**BIC** 100 mg (99 mg of nonradiolabeled BIC [as GS-9883-01] plus approximately 100 µCi [1 mg] radiolabeled [^{14}C]GS-9883 administered orally as an approximately 40-mL ethanolic solution) (EC1505Aand GS017-023-0583-B-20150324CLI, GS017-023-0583-C-20150324CLI, GS017-023-0583-D-20150324CLI, and GS017-023-0583-E-20150324CLI)	8	Not applicable

Study Number, Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
GS-US-141-1485,	Phase 1 study to evaluate the effects of the probe drugs, ATV +COBI (a mixed inhibitor of UGT1A1/CYP3A4/P-gp), RIF (a CYP3A4/P-gp/UGT1A1 inducer), ATV (a UGT1A1/CYP3A4 inhibitor), VORI (a CYP3A4 inhibitor), RBT (a CYP3A4/P-gp inducer), and DRV/co (a CYP3A4 inhibitor) on the PK and safety of BIC in healthy subjects	**BIC** 75 mg (3 × 25-mg tablets) (EC1402C1) + **ATV** 300-mg capsule + **COBI** 150-mg tablet **BIC** 75 mg (3 × 25-mg tablets) (EC1402C1) + **RIF** 600 mg (2 × 300-mg capsules) **BIC** 75 mg (3 × 25-mg tablets) (EC1402C1) + **ATV** 400 mg (2 × 200-mg capsules) **BIC** 75 mg (3 × 25-mg tablets) (EC1402C1) + **VORI** 300 mg (2 × 50-mg tablets + 1 × 200-mg tablet) **BIC** 75-mg tablet (EC1504B1) or 3 × 25-mg tablets (EC1402C1) + **RBT** 300 mg (2 × 150-mg capsules) **BIC** 75-mg tablet (EC1504B1) or 3 × 25-mg tablets (EC1402C1) + **DRV/co** 800/150-mg tablet	90	**BIC** 75-mg tablet or 3 × 25-mg tablets
GS-US-141-1487,	Phase 1 placebo-controlled study to evaluate the effect of BIC on renal function as assessed by markers of GFR in healthy subjects	**BIC** 75-mg tablet (EC1504B1)	40	**Placebo-to-match BIC**
GS-US-311-1790 (Cohort 2)[c],	Phase 1 study to evaluate the effect of BIC on the PK of a representative hormonal contraceptive medication, NGM/EE (Ortho Tri-Cyclen® Lo), in healthy women of childbearing age	**BIC** 75-mg tablet (EC1504B1) + **Ortho Tri-Cyclen Lo** NGM 0.180 mg/0.215 mg/ 0.250 mg/EE 0.025 mg	16	**Ortho Tri-Cyclen Lo** NGM 0.180 mg/0.215 mg/ 0.250 mg/EE 0.025 mg
GS-US-141-1233,	Phase 1 study to evaluate the relative bioavailability of 2 B/F/TAF FDC tablets (75/200/25 mg and 50/200/25 mg) compared with BIC 75-mg + F/TAF 200/25 mg administered simultaneously under fasted conditions and of the effect of food on the PK of BIC, FTC, and TAF when administered as the B/F/TAF FDC in healthy subjects	**B/F/TAF** 75/200/25-mg tablet (EN1501B1) **B/F/TAF** 50/200/25-mg tablet (EN1503B1)	56	**F/TAF** 200/25-mg tablet **BIC** 75-mg tablet
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** 50/200/25-mg tablet (EN1503B2, EN1504B1, EN1601B2, EN1604B2, EN1606B2, EN1608B1, EN1609B1) **Placebo-to-match ABC/DTG/3TG** (EJ1502B1, EJ1501B1R, EJ1601B1, EJ1602B1)	308	**ABC/DTG/3TG** 600/50/300-mg tablet **Placebo-to-match B/F/TAF**

Study Number, Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
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** 50/200/25-mg tablet (EN1503B2, EN1504B1, EN1601B2, EN1604B2, EN1606B2, EN1608B1, EN1609B1) **Placebo-to-match DTG** (EK1501B1, EK1502B1, EK1503B1) **Placebo-to-match F/TAF** (CR1311B1, CR1507B1, CR1507B2, CR1602B1)	98	**DTG** 50-mg tablet + **F/TAF** 200/25-mg tablet **Placebo-to-match B/F/TAF**
GS-US-380-1844,	Phase 3, randomized, double-blinded 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 FDC ABC/DTG/3TC	**B/F/TAF** 50/200/25-mg tablet (EN1503B2, EN1504B1, EN1601B2, EN1602B2, EN1604B2, EN1608B1) **Placebo-to-match ABC/DTG/3TG** (EJ1502B1, EJ1501B1R, EJ1601B1)	563	**ABC/DTG/3TG** 600/50/300-mg tablet **Placebo-to-match B/F/TAF**
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	**B/F/TAF** 50/200/25-mg tablet (EN1503B2, EN1504B1, EN1601B2, EN1602B2, EN1604B2, EN1606B2, EN1608B1, EN1609B1)	577	Current ARV drug regimen consisting of RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC administered orally once daily with food. Investigators provided a prescription for the ARV treatment, and subjects were responsible for obtaining the medication
GS-US-380-1991,	Phase 1 study to investigate the steady-state PK of B/F/TAF in healthy Japanese and Caucasian subjects	**B/F/TAF** 50/200/25-mg tablet (EN1503B2)	50	Not applicable
GS-US-380-1761,	Phase 1 study to evaluate the steady-state PK of BIC, FTC, TAF, its metabolite TFV, and to evaluate the steady-state PK of SOF, its metabolites GS-566500 and GS-331007, and LDV after administration of LDV/SOF+B/F/TAF in healthy subjects	**LDV/SOF** 90/400-mg tablet + **BIC/F/TAF** 75/200/25-mg tablet (EN1501B1)	30	**LDV/SOF** 90/400-mg tablet **B/F/TAF** 75/200/25-mg tablet

Study Number, Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
GS-US-380-1999,	Phase 1 study to evaluate the DDI potential between B/F/TAF and SOF/VEL/VOX in healthy subjects	**B/F/TAF** 50/200/25-mg tablet (EN1503B1) + **SOF/VEL/VOX** 400/100/100-mg tablet + **VOX** 100-mg tablet	30	**B/F/TAF** 50/200/25-mg tablet **SOF/VEL/VOX** 400/100/100-mg tablet + **VOX** 100-mg tablet
GS-US-380-3908,	Phase 1 placebo-controlled study to assess the effect of B/F/TAF on metformin PK and PD in healthy subjects	**B/F/TAF** 50/200/25-mg tablet (EN1503B2) **Metformin** 500-mg tablet and 850-mg tablet	32	**B/F/TAF placebo-to-match** **Metformin** 500-mg tablet and 850-mg tablet
GS-US-380-3909,	Phase 1 study to evaluate the effect on BIC PK of simultaneous administration of antacid, calcium, or iron supplements with B/F/TAF compared with administration of B/F/TAF alone under fasted and fed conditions and evaluate the effect on BIC PK of staggered administration of B/F/TAF and antacid, calcium, or iron supplements compared with administration of B/F/TAF alone in healthy subjects	**B/F/TAF** 50/200/25-mg tablet (EN1503B2) + **Maximum strength antacid** 20 mL oral suspension **B/F/TAF** 50/200/25-mg tablet (EN1503B2) **+ Calcium carbonate** 2 × 600-mg tablets **B/F/TAF** 50/200/25-mg tablet (EN1503B2) + **Ferrous fumarate** 324-mg tablet	42	**B/F/TAF** 50/200/25-mg tablet
GS-US-380-4270,	Phase 1 study to evaluate the effect of BIC when administered as the B/F/TAF on the PK of the CYP3A probe MDZ in healthy subjects	**B/F/TAF** 50/200/25-mg tablet (EN1503B2) **MDZ** 2-mg oral syrup	14	**MDZ** 2-mg oral syrup

a Lot number provided only for BIC, FTC, or TAF-containing products.

b Number of subjects who were administered any test treatment.

c The study information for Study GS-US-311-1790 (Cohort 2) is provided in this table.

Clinical Efficacy studies:

Table 7. Primary Studies Supporting Efficacy of B/F/TAF

Study	Study Design	Number of Subjects[a] by Treatment Regimen	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	B/F/TAF (N = 314) ABC/DTG/3TC (N = 315)	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	B/F/TAF (N = 320) DTG+F/TAF (N = 325)	Week 48 efficacy, PK, and safety
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 from DTG+F/TAF to B/F/TAF or continuation of BIC+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 the B/F/TAF FDC from DTG+F/TAF (N = 30)	Double-blind 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	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
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 (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

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

2.4.2. Pharmacokinetics

Absorption

Bioavailability

The absolute bioavailability of BIC has not been evaluated in humans. The absorption of BIC in humans is expected to be > 61% based on the results of the human ADME study in healthy subjects Study GS-US-141-1481.

Bioequivalence

An FDC formulation containing BIC 75 mg, FTC 200 mg, and TAF 25 mg was initially developed and evaluated for relative bioavailability compared with BIC 75 mg + F/TAF (200/25 mg), each administered under fasted conditions (Study GS-US-141-1233).

Study GS-US-141-1233 – Study Title: *A Phase 1, Open-label, Two-Cohort, Multiple-Period, Fixed-Sequence, Crossover Study to Evaluate 1) the Relative Bioavailability of Two GS-9883/Emtricitabine/Tenofovir Alafenamide (75/200/25 mg and 50/200/25 mg) Fixed-Dose Combination Tablets Versus a GS-9883 (75 mg) Tablet and a Emtricitabine/Tenofovir Alafenamide (200/25 mg) Fixed-Dose Combination Tablet Administered Simultaneously and 2) the Effect of Food on the Pharmacokinetics of GS-9883, Emtricitabine and Tenofovir Alafenamide When Administered as GS-9883/Emtricitabine/Tenofovir Alafenamide (75/200/25 mg and 50/200/25 mg) Fixed-Dose Combination Tablets*

Bictegravir AUC_{inf} and C_{max} for single-dose administration of the B/F/TAF (75/200/25 mg) FDC were approximately 27% and 31% higher, respectively, relative to BIC 75 mg + F/TAF (200/25 mg). Therefore, another FDC formulation was developed that contained BIC 50 mg, FTC 200 mg, and TAF 25 mg. 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 (also in Study GS-US-141-1233), the geometric least-squares mean ratios and their 90% CIs for the BIC primary PK parameters of AUC_{last}, AUC_{inf}, and Cmax were 78.46% (73.38, 83.89), 78.56% (73.44, 84.04), and 78.07% (73.41, 83.01), respectively, and were considered by the Applicant as 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.

Table 8. BIC, FTC, and TAF PK parameters and statistical comparisons for relative bioavailability between the 75-mg or 50-mg B/F/TAF FDC and BIC 75 mg + F/TAF

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	Test	Reference	
B/F/TAF (75/200/25 mg), fasted (Test) (N = 28) vs BIC 75 mg + F/TAF (200/25 mg), fasted (Reference) (N = 28)			
BIC PK Parameter			
AUC_{last} (hr•ng/mL)	151,844.0 (26.9)	119,619.4 (26.6)	126.76 (117.82,136.37)
AUC_{inf} (hr•ng/mL)	156,637.5 (27.5)	123,174.0 (26.6)	126.82 (117.87,136.45)
C_{max} (ng/mL)	7123.9 (21.6)	5593.9 (31.0)	130.72 (119.95,142.45)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	11,412.3 (13.5)	11,199.3 (13.7)	101.89 (99.50, 104.33)
AUC_{inf} (hr•ng/mL)	11,642.8 (13.2)	11,436.4 (13.2)	101.78 (99.45, 104.16)
C_{max} (ng/mL)	2264.3 (22.7)	2153.6 (21.5)	104.86 (97.73, 112.50)
TAF PK Parameter			
AUC_{last} (hr•ng/mL)	205.5 (45.5)	223.6 (45.2)	91.62 (82.13, 102.21)
AUC_{inf} (hr•ng/mL)	206.8 (45.2)	225.1 (45.0)	91.56 (82.27, 101.91)
C_{max} (ng/mL)	253.3 (44.2)	276.7 (51.7)	95.47 (79.88, 114.10)
B/F/TAF (50/200/25 mg), fasted (Test) (N = 27) vs BIC 75 mg + F/TAF (200/25 mg), fasted (Reference) (N = 28)			
BIC PK Parameter			
AUC_{last} (hr•ng/mL)	109,061.4 (21.0)	142,396.6 (30.5)	78.46 (73.38, 83.89)
AUC_{inf} (hr•ng/mL)	112,619.6 (21.9)	146,931.6 (31.1)	78.56 (73.44, 84.04)
C_{max} (ng/mL)	5228.1 (16.9)	6791.1 (26.4)	78.07 (73.41, 83.01)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,652.9 (13.6)	11,035.5 (14.4)	96.52 (93.95, 99.15)
AUC_{inf} (hr•ng/mL)	10,873.9 (13.6)	11,234.6 (14.2)	96.76 (94.22, 99.37)
C_{max} (ng/mL)	2220.4 (30.1)	2166.4 (27.0)	102.36 (93.85, 111.64)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	207.1 (46.5)	236.7 (45.3)	85.37 (75.24, 96.85)
AUC_{inf} (hr•ng/mL)	208.8 (46.3)	238.3 (45.0)	85.48 (75.33, 97.00)
C_{max} (ng/mL)	249.2 (51.6)	291.9 (55.4)	84.17 (67.59, 104.81)

a N = 28 for both the Test and Reference groups

Food effect

GS-US-141-1233 showed that after a high-fat meal, BIC AUC and Cmax were increased by 1.24 and 1.13 fold, and after a moderate-fat meal, BIC AUC and C_{max} were increased by 1.24 and 1.20 fold. This food effect was larger with the 75 mg FDC (1.45 fold increase in AUC and 1.27 fold increase in Cmax).

Table 9. BIC, FTC, and TAF PK parameters and statistical comparisons for food effect for the 75-mg or 50-mg B/F/TAF FDC

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	Test	Reference	
B/F/TAF (75/200/25 mg), high fat (Test) (N = 28) vs B/F/TAF (75/200/25 mg), fasted (Reference) (N = 28)			
BIC PK Parameter			
AUC_{last} (hr•ng/mL)	216,733.1 (23.4)	151,844.0 (26.9)	144.45 (134.26, 155.40)
AUC_{inf} (hr•ng/mL)	226,142.1 (24.9)	156,637.5 (27.5)	145.88 (135.58, 156.95)
C_{max} (ng/mL)	8941.1 (16.9)	7123.9 (21.6)	126.74 (116.30, 138.12)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	11,483.0 (15.7)	11,412.3 (13.5)	100.34 (97.99, 102.75)
AUC_{inf} (hr•ng/mL)	11,706.5 (15.6)	11,642.8 (13.2)	100.24 (97.95, 102.59)
C_{max} (ng/mL)	1872.5 (20.1)	2264.3 (22.7)	83.18 (77.53, 89.25)
TAF PK Parameter			
AUC_{last} (hr•ng/mL)	315.3 (44.0)	205.5 (45.5)	156.81 (140.57, 174.94)
AUC_{inf} (hr•ng/mL)	319.7 (43.1)	206.8 (45.2)	158.20 (142.14, 176.08)
C_{max} (ng/mL)	212.2 (49.4)	253.3 (44.2)	83.22 (69.63, 99.46)
B/F/TAF (50/200/25 mg), high fat (Test) (N = 27) vs B/F/TAF (50/200/25 mg), fasted (Reference) (N = 27)			
BIC PK Parameter			
AUC_{last} (hr•ng/mL)	135,117.3 (21.1)	109,061.4 (21.0)	123.96 (115.91, 132.57)
AUC_{inf} (hr•ng/mL)	140,032.4 (21.8)	112,619.6 (21.9)	124.41 (116.27, 133.11)
C_{max} (ng/mL)	5936.3 (18.3)	5228.1 (16.9)	113.23 (106.45, 120.43)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,213.0 (12.0)	10,652.9 (13.6)	96.02 (93.47, 98.65)
AUC_{inf} (hr•ng/mL)	10,467.0 (11.9)	10,873.9 (13.6)	96.41 (93.88, 99.02)
C_{max} (ng/mL)	1881.1 (24.2)	2220.4 (30.1)	85.52 (78.37, 93.31)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	310.3 (34.9)	207.1 (46.5)	162.62 (143.10, 184.80)
AUC_{inf} (hr•ng/mL)	318.4 (32.8)	208.8 (46.3)	166.55 (146.54, 189.29)
C_{max} (ng/mL)	236.6 (65.1)	249.2 (51.6)	91.71 (73.46, 114.49)

a N = 28 for both the Test and Reference groups

Study GS-US-141-1218 – Study Title: *A Phase 1, Double Blind, Randomized, Placebo-Controlled, First-in-Human, Single- and Multiple-Ascending Dose Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Oral GS-9883 in Healthy Subjects and a Randomized, Open-Label, 2-Cohort, 3-Period, Crossover, Pharmacokinetic Study Evaluating the Drug Interaction Potential between Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination Tablet and GS-9883 in Healthy Subjects*

Study GS-US-141-1218 also provided results on food effect of BIC alone, with the largest food effect: Cmax increased 2 fold and AUCs 1.8 fold after a high-fat meal.

Table 10. GS-US-141-1218: GS-9883 Plasma Pharmacokinetic Parameters Following Single-Dose Administration of GS-9883 in the Fasted and Fed States (Analysis Set: GS-9883 PK Part C: Food Effect)

GS-9883 PK Parameter[a] Mean (%CV)	GS-9883 100 mg Fasted (n=8)	GS-9883 100 mg Fed (n=8)
AUC_{inf} (hr*ng/mL)	117,777.1 (23.3)	214,146.3 (15.9)
C_{max} (ng/mL)	5885.0 (34.9)	11,268.8 (15.1)
$t_{½}$ (hr)	16.04 (15.32, 17.12)	16.87 (16.30, 17.93)
T_{max} (hr)	1.75 (1.25, 3.50)	3.00 (1.75, 3.00)
V_z/F (mL)	21,685.2 (40.3)	11,699.4 (13.3)
CL/F (mL/hr)	891.6 (24.1)	479.4 (18.6)

a Data are presented as mean (%CV), except for Tmax, and t½, which are presented as median (Q1, Q3)

Summary of main PK parameters

Table 11. PK parameters of BIC, FTC and TAF after multiple doses of the FDC with and 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

Distribution

Vz/F was observed between 9.919 and 34.770 L (CV 10.7% to 58.85%). Population PK modelling: 12,500 mL (11.1% variability), with extreme weights (5th and 95th percentiles) ranged from 9,800 to 16,200 mL.

Bictegravir is > 99% bound to human plasma proteins.

In subjects with severe renal impairment, the percent bound remained > 99%, but the percent unbound was higher (0.75%) compared with healthy matched control subjects (0.49%) (Study GS-US-141-1479). Similarly, percent unbound was also higher in subjects with severe hepatic impairment (0.81%) compared with healthy matched control subjects (0.61%) (Study GS-US-141-1478).

Following a single oral dose of [14C]BIC in healthy subjects, the blood-to-plasma ratio of [14C]-radioactivity ranged between 0.50 and 0.55 through 120 hours post-dose, indicating that BIC was

predominantly distributed to plasma rather than the cellular components of blood (Study GS-US-141-1481).

Elimination and metabolism

Average T1/2 in studies was observed between 15.6 h and 20.88 h (ranging between 12.14 h and 14.47h in first and 4th quartiles). In population PK modelling, terminal half-life was estimated at 17.2hr.

Average CL/F in studies was observed between 349.4 and 900 mL/h (CV between 15.3% and 74.2%). In population PK modelling, CL/F was estimated at 504 mL/h, with variability 27.4%, and at extreme weights (5th and 95th percentiles) it ranged from 428 to 601 ml/h.

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 100-mg [14C]BIC in healthy male subjects, 95.3% of the [14C]BIC dose was recovered with 60.3% of the dose from faeces and 35.0% of the dose from urine (Study GS-US-141-1481). M20 (hydroxy-BIC-sulphate, 20.1%) and M15 (BIC-glucuronide, 8.6%) were the major metabolites identified in plasma.

Unchanged drug accounted for 31% to 34% of the radioactive dose in the faeces that likely represents a combination of both unabsorbed drug and deconjugated BIC glucuronide. Desfluoro-hydroxy- BIC-cysteine-conjugate (10%−13% of dose) and other minor oxidative metabolites were identified in faeces. Radioactivity in urine consisted primarily of M15/M58 (BIC-glucuronide; 21% of dose) and other minor oxidative metabolites and their conjugates. Renal clearance of the unchanged parent was minimal (1.3% of dose).

Figure 7. Bictegravir metabolism pathway

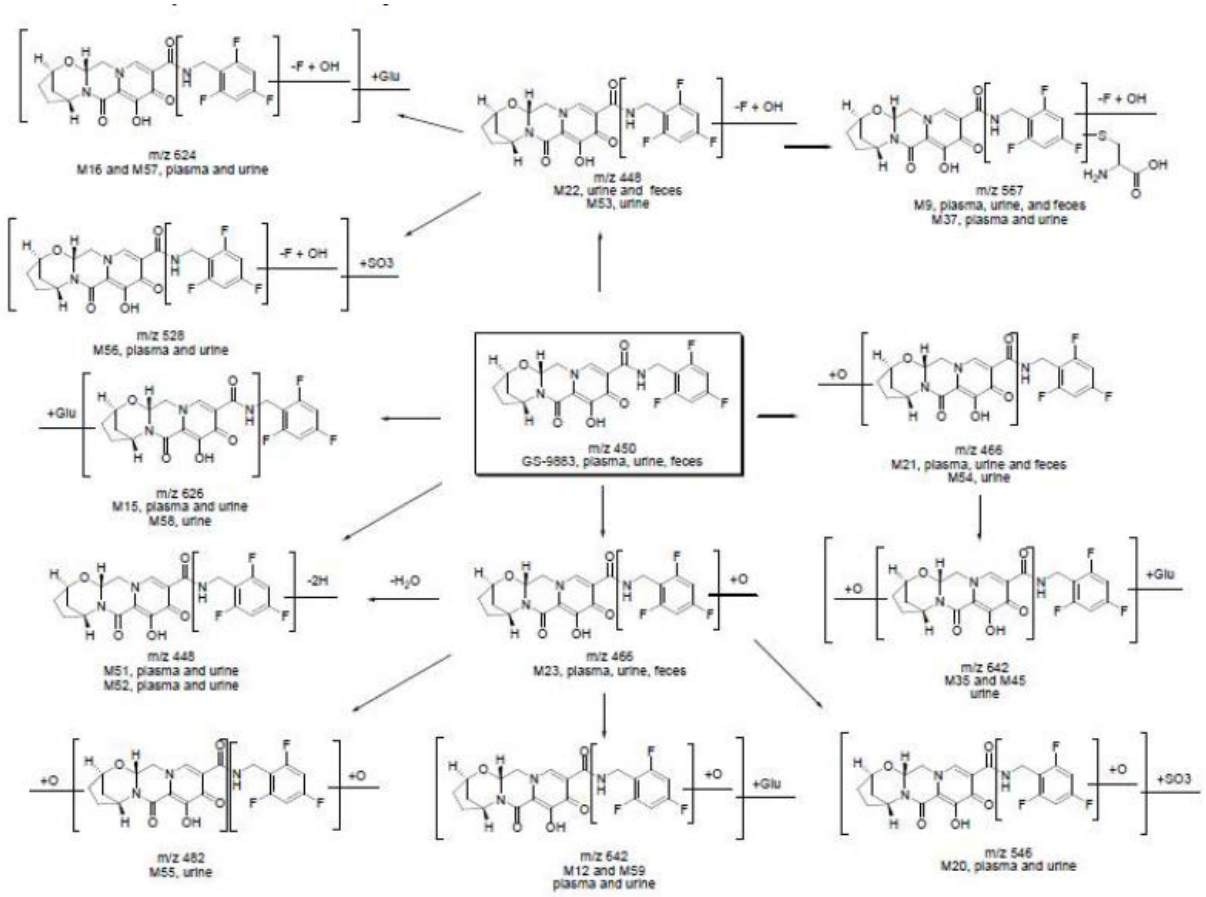

Table 12. M20 (hydroxy-BIC-sulphate) and M15 (BIC-glucuronide) were the major metabolites identified in plasma:

PK Parameter	BIC	M15	M20
AUC_{0-144} (µg•h/mL)	166	21.1	49.3
C_{max} (µg/mL)	8.22	0.669	1.42
T_{max} (h)	4	24	8
T_{last} (h)	72	72	72

Dose proportionality and time dependency

Dose proportionality is mainly explored in study GS-US-141-1218. Bictegravir exposure is dose-proportional over the dose range of 25 to 100 mg; Less than dose-proportional increases in BIC exposure were observed at doses greater than 100 mg, presumably limited by solubility. In study GS-US-141-1219, mean BIC AUC0-24 and Cmax were approximately dose proportional following single-dose administration of 5 to 50 mg dose administration, with decreasing dose proportionality at the 100

mg dose. Following multiple-dose administration, dose proportionality was observed in AUC_{tau}, C_{max}, and C_{tau} over the dose range of 5 to 100 mg using the 50-mg dose as a reference.

Steady state levels of BIC were achieved between Study Days 4 to 6 of dosing and maintained through Day 14. Accumulation rate was around 1.6 fold.

Inter and intra-individual variability

Interindividual variability in the population study was 27.4 for CL/F and 1.1 for Vc/F. Intra individual variability may be estimated by the remaining residual variability (as CV) at 29.2%

PK in target populations

In the population PK analysis, healthy subjects exhibited 7.3% lower Vc/F compared to HIV-infected subjects. This seemed to be the only variation, and is not considered clinically relevant.

Special populations

Impaired renal function

Study GS-US-141-1479: Study Title: *A Phase 1, Open-Label, Parallel-Group, Adaptive Single-dose Study to Evaluate the Pharmacokinetics of GS-9883 in Subjects with Normal and Impaired Renal Function*

Impaired renal function was studied in GS-US-141-1479. Severe renal impairment decreased BIC AUCs and C_{max} by 0.73 and 0.80 fold respectively; this was considered not clinically significant.

Table 13. Plasma PK parameters for GS-9883 and statistical comparisons

GS-9883 PK Parameter	Mean (%CV)		GLSM Ratio % (90% CI)
	Severe Renal Impairment (Test) (N = 10)	Normal Renal Function (Reference) (N = 8)	
Total AUC_{inf} (h•ng/mL)	138,169.7 (44.4)	170,105.6 (24.8)	72.63 (48.80, 108.10)
Total AUC_{last} (h•ng/mL)	136,956.4 (44.2)	168,876.8 (24.7)	72.43 (48.54, 108.07)
Total C_{max} (ng/mL)	5977.0 (34.8)	7227.5 (29.5)	80.32 (59.56, 108.30)
Free AUC_{inf} (h•ng/mL)[a]	830.6 (32.1)	824.5 (24.7)	99.29 (79.49, 124.04)
Free AUC_{last} (h•ng/mL)[a]	822.5 (32.0)	818.6 (24.6)	99.02 (79.24, 123.74)
Free C_{max} (ng/mL)[a]	37.7 (21.6)	35.0 (28.4)	109.80 (87.46, 137.85)

a Free AUClast, free AUCinf, and free Cmax were calculated based on unbound plasma GS-9883 (PK parameter × percentage unbound GS-9883 ÷ 100 for each subject).

Impaired hepatic function

Study GS-US-141-1478 – Study Title: *A Phase 1, Open Label, Parallel Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics of GS-9883 in Subjects with Normal and Impaired Hepatic Function*

Impaired hepatic function was studied in GS-US-14-1478. Moderate hepatic impairment decreased bic AUCs and Cmax by 0.58 and 0.63 fold respectively; percent of unbound fraction of BIC increases to 0.8% instead of 0.6%.

Table 14. Plasma PK parameters for BIC and statistical comparisons

	Mean (%CV)		
BIC PK Parameter	Moderate Hepatic Impairment (Test) (N = 10)	Healthy Control (Reference) (N = 10)	%GLSM Ratio (90% CI)
AUC_{inf} (h•ng/mL)	113,086.2 (50.7)	172,883.6 (23.4)	58.71 (41.28,83.50)
C_{max} (ng/mL)	5013.0 (29.1)	7849.0 (27.8)	63.50 (49.80,80.96)
C_{24} (ng/mL)	1643.6 (47.5)	2666.0 (24.9)	51.56 (30.96,85.87)
Free AUC_{inf} (h•ng/mL)	880.9 (55.7)	1054.2 (22.7)	76.54 (56.48,103.71)
Free C_{max} (ng/mL)	39.6 (27.7)	48.1 (28.2)	82.78 (64.98,105.45)

GLSM = geometric least-squares mean

Free PK parameter is calculated as: Mean unbound fraction (%) * PK Parameter /100 for a single subject.

Other

No clinically relevant PK differences due to gender and race were identified.

Weight was a significant factor in the population PK study, impacting CL/F and Vd/F. Subjects corresponding to the 5th and 95th percentile of body weight (58 kg and 113 kg, respectively) demonstrated a -15.1 % and 19.2 % difference in CL/F, respectively, and a - 21.5 % and 29.7 % difference in Vc/F, respectively, as compared to the typical 80 kg subject. This was considered clinically not significant.

Age was tested as a potential covariate in both the BIC and TAF population PK analyses for B/F/TAF, but was determined to be not significant for both analytes. As such, age is not expected to substantially affect exposure of BIC or TAF.

No data are available in children.

Pharmacokinetic interaction studies

In vitro

BIC is a substrate of UGT1A1 and CYP3A4. Clinically relevant interaction with inhibitors and inducers of these enzymes has been carried out with darunavir/cobicistat (DRV/RTV) or with atazanavir/ritonavir (ATV/RTV) for CYP and UGT inhibition, and with rifampicin (RIF) for induction.

BIC is not a direct or TDI of all tested CYPs up to 100µM. However, even though with CYP3A4, TDI by bictegravir is observed but with a KI>100 µM, the Applicant performed a DDI study with midazolam that allow to consider BIC as a weak CYP3A inhibitor.

BIC inducing effect has been demonstrated in vitro on CYP3A4, 2B6, P-gp and UGT1A1 but no clinical consequences are expected.

With an IC50=176 µM, BIC is not expected to affect exposure of drugs the metabolism of which is UGT1A1-dependant.

BIC is both a P-gp and BCRP substrate. Bictegravir (1 µM) is not a substrate of OATP1B1 or OATP1B3.

Up to 100µM, BIC does not exhibit in vitro inhibition of P-gp, BCRP, BSEP, OATP1B1, 1B3, OCT1, OAT1. Therefore, clinically relevant interactions related to this transporter inhibition are not expected at the expected systemic and intestinal concentrations.

With OAT3, BIC IC50=55 µM that is higher the worst concentration expected at the systemic level (5 µM), then, clinically relevant interaction related to the inhibition of this transporter can be ruled out.

With OCT2 and MATE1 IC50=0.42 µM and 8 µM respectively. Risk of DDI is, then, not excluded with OCT2 and borderline with MATE1.

FTC and TAF

FTC is predominantly eliminated by the kidney. TAF is primarily hydrolyzed by carboxylesterase 1 (CES) and Cat A (cathepsin A) and not recommended in combination with inhibitor of this enzyme such as boceprevir. Tenofovir alafenamide was slowly metabolized by CYP3A4.

Clinically relevant interactions related to any inhibition or induction of CYPs by emtricitabine are not expected. Likewise, in vitro, TAF did not show any inducing or inhibition potential towards main CYP450 enzymes, excepted with CYP3A4. Nonetheless, a DDI study with midazolam (study GS-US-1538) and rilpivirine (GS-US-120-0117), both CYP3A4 substrates, discard any significant induction or inhibition of CYP3A4 by TAF in vivo.

No UGT1A1 inhibition is expected by FTC and TAF. Likewise, no induction of UGTs is expected by FTC or TAF.

FTC is not expected to be a substrate and inhibitor of uptake and efflux transporters according to its extensive and high absorption.

TAF is a substrate of the efflux transporters P-gp and BCRP and, also, of the uptake transporters OATP1B1 and 1B3. Therefore, inhibition of these transporters may alter TAF exposure and then of TFV. TAF is neither a substrate of the hepatic uptake transporter OCT1 nor of the renal uptake transporters OAT1 and OAT3.

As regards inhibition of P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, BSEP, OCT1, and MATE1 by TAF, IC50 values are > 100 µM far higher the estimated cut-off values at the intestinal, hepatocyte and systemic level (21 µM, 18.5 µM and 4.5 µM respectively). Therefore, clinically relevant interactions related to any inhibition of these transporters by TAF are unlikely.

In vivo

B/F/TAF

Interactions between the components BIC and FTC/TAF was explored in study GS-US-141-1218. TAF and FTC do not alter BIC absorption. BIC does not alter FTC absorption. Only TAF exposure is changed by coadministration of BIC and F/TAF, but TFV is by far more relevant and shows no DDI impact.

	GLSM		GLSM Ratio (90% CI), %
	Test	Reference	
GS-9883 PK Parameter: GS-9883+F/TAF (Test) (N = 34) vs. GS-9883 (Reference) (N = 34)			
AUC_{tau} (hr*ng/mL)	212,852.8	210,816.0	100.97(98.22,103.79
C_{max} (ng/mL)	14,693.24	14,761.70	99.54 (96.41,102.76)
C_{tau} (ng/mL)	5681.53	5553.18	102.31(98.48,106.29)
FTC PK Parameter: GS-9883+F/TAF (Test) (N = 34) vs. F/TAF (Reference) (N = 33)			
AUC_{tau} (hr*ng/mL)	9545.74	9363.40	101.95 (100.13,103.80)
C_{max} (ng/mL)	1759.80	1773.33	99.24 (94.19,104.55)
C_{tau} (ng/mL)	67.04	63.33	105.86 (101.26,110.67)
TAF PK Parameter: GS-9883+F/TAF (Test) (N = 34) vs. F/TAF (Reference) (N = 33)			
AUC_{last}(hr*ng/mL)	352.61	272.28	129.50 (123.67,135.61)
C_{max} (ng/mL)	277.95	203.10	136.86 (116.99,160.09)
TFV PK Parameter: GS-9883+F/TAF (Test) (N = 34) vs. F/TAF (Reference) (N = 33)			
AUC_{tau} (hr*ng/mL)	299.66	263.52	113.72 (110.07,117.49)
C_{max} (ng/mL)	17.66	16.01	110.30 (105.27,115.56)
C_{tau} (ng/mL)	10.46	9.09	115.04 (110.79,119.46)

FTC = emtricitabine; F/TAF = emtricitabine/tenofovir alafenamide (coformulated); GLSM = geometric least-squares mean; TFV = tenofovir

Studies GS-US-380-1761 and GS-US-380-1999 with the FDC **ledipasvir/sofosbuvir (LDV/SOF)** and **sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX)** did not highlight significant PK interaction between studied drugs.

In study GS-US-380-3908, B/F/TAF significantly increases **metformin** AUC_{τ} about 39% with an 90%CI [131%-148]. However, the lack of significant changes on PD parameters (plasma glucose, active glucagon-like peptide 1 (GLP-1) and lactate levels) brings a reassuring information and could allow to conclude that no dose adjustment of metformin is needed when it is combined with B/F/TAF.

Interaction between B/F/TAF and **antacids, calcium carbonate and ferrous fumarate** was explored in study GS-US-380-3909:

BIC PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	B/F/TAF Under Test Conditions (N = 14)	B/F/TAF Alone (Fasted) (Reference) (N = 14)	
B/F/TAF (fasted) with 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng•h/mL)	27,960.7 (52.5)	121,887.9 (24.4)	21.23 (17.57, 25.65)
C_{24} (ng/mL)	427.0 (57.4)	1795.7 (26.3)	21.94 (17.80, 27.04)
C_{max} (ng/mL)	1199.8 (52.0)	5635.0 (18.8)	19.89 (16.46, 24.02)
B/F/TAF (fasted) with calcium carbonate (Test)			
AUC_{inf} (ng•h/mL)	85,037.3 (43.1)	121,887.9 (24.4)	66.67 (56.67, 78.42)
C_{24} (ng/mL)	1222.9 (43.9)	1795.7 (26.3)	64.89 (54.47, 77.31)
C_{max} (ng/mL)	3442.1 (36.9)	5635.0 (18.8)	58.31 (50.72, 67.04)
B/F/TAF (fasted) with ferrous fumarate (Test)			
AUC_{inf} (ng•h/mL)	46,148.7 (32.9)	121,887.9 (24.4)	37.11 (32.95, 41.80)
C_{24} (ng/mL)	674.8 (32.8)	1795.7 (26.3)	36.92 (32.59, 41.83)
C_{max} (ng/mL)	1667.1 (27.1)	5635.0 (18.8)	29.10 (25.87, 32.72)
B/F/TAF (fasted) 2 hours before 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng•h/mL)	115,908.1 (30.3)a	132,814.0 (27.0)	86.70 (81.01, 92.78)
C_{24} (ng/mL)	1699.2 (27.9)[a]	2009.3 (28.3)	85.46 (79.92, 91.38)
C_{max} (ng/mL)	5616.2 (22.7)[a]	5920.0 (16.5)	93.40 (87.53, 99.66)
B/F/TAF (fasted) 2 hours after 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng•h/mL)	67,704.6 (47.0)[a]	132,814.0 (27.0)	47.66 (38.26, 59.35)
AUC_{last} (ng•h/mL)	63,447.0 (45.8)[a]	124,721.4 (28.0)	47.34 (37.91, 59.12)
C_{max} (ng/mL)	2735.0 (48.3)[a]	5920.0 (16.5)	41.51 (33.25, 51.83)
B/F/TAF (fed) with 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng•h/mL)	50,813.5 (34.8)	93,658.3 (27.2)	53.25 (44.21, 64.14)
C_{24} (ng/mL)	803.6 (36.4)	1410.1 (29.7)	56.01 (46.21, 67.88)
C_{max} (ng/mL)	2446.4 (31.4)	4700.7 (23.6)	51.46 (42.69, 62.03)
B/F/TAF (fed) with calcium carbonate (Test)			
AUC_{inf} (ng•h/mL)	94,832.8 (21.2)	93,658.3 (27.2)	103.29 (88.96, 119.93)
AUC_{last} (ng•h/mL)	91,454.0 (20.1)	91,204.9 (26.5)	102.36 (88.07, 118.98)
C_{max} (ng/mL)	4105.0 (13.7)	4700.7 (23.6)	89.58 (77.83, 103.10)
B/F/TAF (fed) with ferrous fumarate (Test)			
AUC_{inf} (ng•h/mL)	77,307.8 (24.8)	93,658.3 (27.2)	83.84 (74.07, 94.89)
C_{24} (ng/mL)	1228.7 (25.0)	1410.1 (29.7)	88.93 (78.12, 101.24)
C_{max} (ng/mL)	3485.0 (23.2)	4700.7 (23.6)	75.12 (64.82, 87.05)

a N = 13 for Test treatment

With antacids containing magnesium or aluminium, under fasted conditions, and given simultaneously, BIC AUC and C_{24h} substantially decrease, more than with RIF, about 79%. This interaction can be compensated by staggered the administration of BIC 2 hours before antacids (based on results from cohort 2) or alternatively, B/F/TAF can be taken with food 2 hours after antacids containing magnesium or aluminium.

With calcium carbonate and ferrous fumarate, under fasted conditions and given simultaneously, BIC AUC and C_{min} decrease about 33% and 42%, respectively, with calcium carbonate, and about 63% with ferrous fumarate. Even though the effect of calcium carbonate or ferrous fumarate has not been studied with staggered doses of the FDC, one can take B/F/TAF at least 2 hours before ferrous fumarate and can take B/F/TAF together with calcium-containing supplements without regard to food.

- Results from study GS-US-380-4270 show that B/F/TAF significantly, but weakly, increases **midazolam** exposure about 15% with a 90%CI [99.7-131]. This effect is likely driven by BIC the in vitro data of which demonstrate the ability of BIC to be a time-dependant inhibitor at high concentrations. The mild increase observed with midazolam is not expected to be clinically meaningful.

BIC alone

In study GS-US-311-1790, no significant effect of BIC and FTC/TAF on **ethinylestradiol, norgetromine and norgestrel** PK was observed. Therefore no dose adjustment of combined oral contraception is needed when co-administered with B/F/TAF.

Study GS-US-141-1485: A Phase 1 Adaptive Study to Evaluate Transporter, Cytochrome (CYP) 450-Mediated and UGT1A1 Drug-Drug Interactions Between GS-9883 and Probe Drugs. This study assessed the interaction of BIC with **ATV/COBI, rifampicin, ATV alone, voriconazole, rifabutin and DRV/COBI.**

GS-9883 PK Parameter	Test[a]	Reference[a]	%GLSM Ratio (90% CI) (Test/Reference)
Cohort 1: GS-9883 75 mg SD + ATV 300 mg QD + COBI 150 mg QD (Test; N = 15) vs GS-9883 75 mg SD (Reference; N = 15); fed			
AUC_{inf} (h*ng/mL)	628,290.3 (17.4)	154,433.7 (16.0)	405.62 (376.07, 437.49)
C_{max} (ng/mL)	9033.3 (12.2)	6890.0 (12.3)	131.11 (122.71, 140.08)
$t_{1/2}$ (h)	59.99 (52.94, 63.10)	18.62 (15.87, 20.96)	
Cohort 2: GS-9883 75 mg SD + RIF 600 mg QD (Test; N = 15) vs GS-9883 75 mg SD (Reference; N = 15); fed			
AUC_{inf} (h*ng/mL)	36,398.0 (21.5)	155,986.3 (41.8)	24.52 (22.00, 27.33)
C_{max} (ng/mL)	5131.3 (15.7)	7118.7 (17.0)	72.21 (67.06, 77.75)
$t_{1/2}$ (h)	5.65 (5.30, 6.18)	18.09 (14.47, 20.75)	
Cohort 3: GS-9883 75 mg SD + ATV 400 mg QD (Test; N = 15) vs GS-9883 75 mg SD (Reference; N = 15); fed			
AUC_{inf} (h*ng/mL)	638,857.0 (20.5)	154,253.8 (21.8)	414.51 (381.02, 450.94)
C_{max} (ng/mL)	9110.7 (16.6)	7078.7 (13.3)	128.10 (122.95, 133.47)
$t_{1/2}$ (h)	56.86 (50.70, 66.90)	17.47 (15.26, 19.81)	
Cohort 4: GS-9883 75 mg SD + VORI 300 mg BID (Test; N = 15) vs GS-9883 75 mg SD (Reference; N = 15); fasted			
AUC_{inf} (h*ng/mL)	160,519.3 (26.9)	101,659.4 (37.2)	161.14 (141.07, 184.06)
C_{max} (ng/mL)	5442.7 (33.6)	4844.0 (21.5)	108.94 (96.14, 123.43)
$t_{1/2}$ (h)	25.45 (18.65, 28.08)	15.92 (15.12, 19.76)	
Cohort 5: GS-9883 75 mg QD + RBT 300 mg QD (Test; N = 13) vs GS-9883 75 mg QD (Reference; N = 15); fasted			
AUC_{tau} (h*ng/mL)	66,164.3 (37.4)	106,486.2 (37.2)	62.01 (53.06, 72.47)
C_{max} (ng/mL)	6140.0 (36.0)	7624.7 (35.5)	80.37 (66.93, 96.50)
C_{tau} (ng/mL)	1212.2 (43.0)	2732.9 (40.7)	43.98 (37.14, 52.07)
Cohort 6: GS-9883 75 mg QD + DRV/COBI 800/150 mg QD (Test; N = 13) vs GS-9883 75 mg QD (Reference; N = 15); fed			
AUC_{tau} (h*ng/mL)	265,249.0 (19.3)	152,356.1 (16.2)	173.60 (161.55, 186.54)
C_{max} (ng/mL)	17,300.0 (15.0)	11,402.0 (15.2)	151.56 (140.15, 163.90)
C_{tau} (ng/mL)	8486.9 (24.9)	4017.3 (21.6)	211.43 (195.18, 229.03)

BID = twice daily; QD = once daily; SD = single dose

a Mean (%CV) for AUClast, AUCinf, AUCtau, Cmax, and Ctau; median (Q1, Q3) for t1/2

There was a substantial increase of BIC exposure, about 4-fold, with ATV/COBI (cohort 1) similar to the increase exposure of BIC with ATV alone (cohort 3) and suggesting that this effect is mainly driven by UGT1A1 inhibition by ATV. This assumption is corroborated by results obtained with two strong CYP3A4 inhibitors, VORI and DRV/COBI, with which BIC exposure increases about 61% and 74%, respectively. This highlights the moderate involvement of CYP3A4 in the overall hepatic clearance of BIC. Rifampicin substantially decreases BIC exposure about 75% whereas with rifabutin AUC decrease about 38% and C_{min} about 56%.

The following is reflected in the SmPC:

- no dose adjustment is recommended with VORI
- with rifabutin, BIC is not recommended
- with rifampicin, BIC is contra-indicated

2.4.3. Pharmacodynamics

Mechanism of action

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 non-overlapping 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.

Primary pharmacodynamics

BIC is a novel strand transfer inhibitor of HIV-1 integrase (INSTI) with high potency and selectivity in antiviral assays and does not require metabolic modification to exert ARV activity. BIC inhibited the strand transfer activity with an IC50 value of 7.5 nM, an activity comparable to those of EVG and DTG.

Table 15. Inhibitory Activity in HIV-1 Integrase Strand Transfer and 3'-Processing Assays

	Inhibition of Strand Transfer[a]		Inhibition of 3'-Processing[b]	
Compound	IC50 (nM)	Maximum Inhibition (%)[c]	IC50 (nM)	Maximum Inhibition (%)[c]
GS-9883	7.5 ± 0.3	99.4 ± 0.7	241 ± 51	106 ± 4
DTG	7.4 ± 0.6	100.3 ± 0.6	232 ± 33	115 ± 3
EVG	8.4 ± 0.7	99.9 ± 0.3	556 ± 40	93 ± 2

a The data represent the mean ± SD of 3 independent experiments done in triplicates.
b The data represent the mean ± SD of 5 independent experiments done in triplicates.
c Maximum inhibition was determined by curve fitting.

Thus, the integration of HIV in cell was inhibited. This inhibition of HIV-1 DNA integration was evaluated by assessing the quantity of aborted circular HIV DNA species containing 1 or 2 long terminal repeats (2-LTR circles), as well as the quantity of authentic HIV-1 integration products in infected MT-2 cells. BIC enhanced the accumulation of 2-LTR circles, a product of integration failure. BIC profoundly decreased integration junctions but did not affect viral DNA synthesis as measured by

the late reverse transcription products, demonstrating an authentic inhibition of HIV-1 integration. As expected, DTG exhibited a similar effect on the integration junctions.

The dissociation kinetics of ^{3}H-labelled INSTIs BIC, DTG, RAL, and EVG were measured using wild-type HIV integrase/DNA complexes and a scintillation proximity assay. By both data analysis methods, BIC had a longer dissociation half-life from HIV-1 integrase/DNA complexes compared to DTG, RAL, and EVG; the long dissociation half-life has been proposed to contribute to a high barrier to resistance.

Against HIV

Using lymphoblastoid T-cell lines and primary human T-lymphocytes in HIV-1 antiviral assays, the estimated concentration of drug for half-maximal effective concentration (EC50) of BIC ranged from 1.5 to 2.4 nM and the selectivity indices ranged from 1500 to 8800.

Table 1. Antiviral Activity of BIC in T-Cell Lines

	EC_{50} (nM)	
Compound	**MT-2 Cells[a]**	**MT-4 Cells[a]**
BIC	1.5 ± 0.2	2.4 ± 0.4
DTG	1.5 ± 0.2	1.5 ± 0.3

a EC_{50} values represent the mean ± SD of at least 4 independent measurements performed in triplicate.
Source: PC-141-2032.

Table 2. Antiviral Activity of BIC in Primary Cells

	EC_{50} (nM)	
Compound	**$CD4^{+}$ T Lymphocytes[a]**	**Monocyte-derived Macrophages[a]**
BIC	1.5 ± 0.3	6.6 ± 4.1
DTG	1.0 ± 0.3	3.1 ± 2.5

a EC_{50} values represent the mean ± SD of 4 independent donor determined in triplicate.
Source: PC-141-2034.

When tested in primary human PBMCs against clinical isolates of all HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G, BIC displayed similar antiviral activity across all clinical isolates with mean and median EC50 values of 0.60 and 0.55 nM, respectively, based on a range of EC50 values between < 0.05 and 1.71 nM. DTG tested in parallel exhibited a similar potency with mean and median EC50 values of 0.61 nM and 0.68 nM, respectively, and a range of EC_{50} values from 0.09 to 1.13 nM against the same tested isolates. HIV-2 was similarly susceptible to both BIC and DTG with EC50 values of 1.1 nM and 2.1 nM, respectively.

Against other viruses

BIC and DTG were tested against hepatitis B and C viruses, influenza A virus, human rhinovirus (HRV), and RSV in cell-based assays. For both drugs, no antiviral activity against these viruses was observed.

Effect of serum proteins on BIC

The antiviral EC50 of BIC was determined in MT-2 cells in the presence of two key human serum components, human serum albumin (HSA) and α1-acid glycoprotein (α1-AGP) or in the presence of complete human serum.

The presence of the two serum components reduced the antiviral activity of BIC by 20-fold, compared to 11-fold reduction of the potency of DTG. These data indicate that the two tested components of human serum are capable of binding BIC as well as DTG.

In the presence of human serum, the shift in EC50 for both BIC and DTG exhibited similar trends as observed with the serum protein components: the BIC EC50 value, extrapolated to 100% human serum, shifted 74-fold and was comparable to the 39-fold shift extrapolated for DTG.

Viral resistance to BIC in clinical studies

Analyses were performed for HIV-infected subjects with clinical virology data from 4 B/F/TAF Phase 3 studies (GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878). An integrated virology analysis was performed for HIV-infected subjects with clinical virology data from Studies GS-US-380-1489 and GS-US-380-1490. All of the previously identified drug resistance mutations by antiretroviral drug class is shown in Table 16.

Table 16. Resistance Substitutions by Antiretroviral Class for the B/F/TAF Program

Resistance Associated Substitutions[a]	
Mutation Groups	**Codon Mutations**
Primary Integrase Strand Transfer Inhibitor (INSTI) Resistance (-R) substitutions	T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K
Secondary INSTI-R substitutions	M50I, H51Y, L68V/I, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C, A128T, E138K/A, G140A/C/S, P145S, Q146R/I/K/L/P, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A
Primary Nucleoside and Nucleotide Reverse Transcriptase Inhibitor (N(t)RTI)-R substitutions	M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F, K219E/Q/N/R
Thymidine Analogue Mutations (TAMs)	M41L, D67N, K70R, L210W, T215Y/F, K219Q/N/E/R
Tenofovir (TFV) resistance associated substitutions	K65R/E/N, K70E
Emtricitabine (FTC) and lamivudine (3TC) resistance associated substitutions	M184V/I
Abacavir (ABC) resistance associated substitutions	K65R/E/N, K70E, L74V, Y115F, M184V/I
Secondary NRTI-R substitutions	E44D, A62V, T69D/N, V75I, F77L, F116Y, V118I, T215A/C/D/E/G/H/I/L/N/S/V[b]
Primary Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)-R substitutions	L100I, K101E/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230L/I
Secondary NNRTI-R substitutions	V90I, A98G, K101H, V106I, V179D/F/T
Primary Protease Inhibitor (PI)-R substitutions	D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M
Atazanavir (ATV) or Darunavir (DRV) resistance associated substitutions	I47V, I50L/V, I54M/L, L76V, I84V, N88S

a Adapted from the current IAS-USA list with some modifications [Wensing 2017]

b Reversion mutations at RT codon T215 including T215A/C/D/E/G/H/I/L/N/S/V have not been definitively shown to be associated with reduced response to either emtricitabine or tenofovir DF.

Studies GS-US-380-1489 and GS-US-380-1490:

Both studies were performed in ART-naïve patients: Study GS-US-380-1489 compares B/F/TAF vs ABC/DTG/3TC and study GS-US-380-1490 compares B/F/TAF vs DTG+F/TAF. At baseline, the INSTI-RAM detected are as follows:

Mutation Class[a]	Number of Subjects, n (%)			
	B/F/TAF 380-1489,1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)	All (N = 1274)
Primary INSTI-R	6 (1.0)	4 (1.3)	6 (1.9)	16 (1.3)
Average Number of Primary INSTI-R Mutations	1.0	1.0	1.0	1.0
T97A	5 (0.8)	4 (1.3)	6 (1.9)	15 (1.2)
Q148H	1 (0.2)	0	0	1 (0.1)
Secondary INSTI-R	325 (51.5)	152 (48.4)	158 (49.1)	635 (50.1)
Average Number of Secondary INSTI-R Mutations	1.2	1.2	1.2	1.2
M50I	124 (19.7)	47 (15.0)	60 (18.6)	231 (18.2)
H51Y	0	1 (0.3)	1 (0.3)	2 (0.2)
L68I/V	4 (0.6)	2 (0.6)	2 (0.6)	8 (0.6)
V72T	3 (0.5)[c]	1 (0.3)	3 (0.9)	7 (0.6)[c]
L74M	1 (0.2)	5 (1.6)	2 (0.6)	8 (0.6)
Q95K	1 (0.2)	0	0	1 (0.1)
S119P/R/T	197 (31.2)	103 (32.8)	99 (30.7)	399 (31.5)
A128T	3 (0.5)	0	0	3 (0.2)
E138A/K	1 (0.2)	2 (0.6)	2 (0.6)	5 (0.4)
G140S	1 (0.2)	0	0	1 (0.1)
Q146R	1 (0.2)	0	0	1 (0.1)
S153A	3 (0.5)	1 (0.3)	2 (0.6)	6 (0.5)
E157K/Q	35 (5.5)	12 (3.8)	12 (3.7)	59 (4.7)
G163K/R	6 (1.0)	5 (1.6)	6 (1.9)	17 (1.3)

There is no impact of pre-treatment RAMs or subtype to reach HIV-1 RNA < 50 copies/mL at Week 48 or virologic failure (HIV-1 RNA ≥ 50 copies/mL) for all treatment groups ($p > 0.05$ for all comparisons). In the B/F/TAF group, all 5 subjects with T97A and the one subject with Q148H + G140S in IN at baseline achieved HIV-1 RNA < 50 copies/mL at Week 4 and maintained HIV-1 RNA < 50 copies/mL through Week 48.

Of the 1274 FAS subjects in Studies GS-US-380-1489 and GS-US-380-1490, 17 subjects experienced virologic failure during the first 48 weeks and comprised the resistance analysis population (RAP). The final RAP (which did not include subjects who re-suppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs) was comprised of 8 subjects in the B/F/TAF group, 2 subjects in the ABC/DTG/3TC group and 3 subjects in the DTG + F/TAF group:

Table 17. Integrated Summary: HIV-1 Genotypic Resistance through Week 48 for Studies GS-US-380-1489 and GS-US-380-1490

Resistance Category[a]	Number of Subjects, n (%)			
	B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)	P-Value[b]
RAP (% of FAS)	8 (1.3)	4 (1.3)	5 (1.5)	1.00; 0.77
Subjects with Data (Any Gene)	8 (100)	3 (75)	5 (100)	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	0	2 (50)	2 (40)	
Final RAP[c] (% of FAS)	8 (1.3)	2 (0.6)	3 (0.9)	0.51; 0.76
Subjects with Data (Any Gene)	8 (100)	1 (50)	3 (100)	
Developed Resistance Mutations to Study Drugs (% of FAS)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Developed Resistance Mutations to Study Drugs (% of Final RAP)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Developed Any INSTI-R	0	0	0	
Developed Primary NRTI-R	0	0	0	
Developed Primary NNRTI-R	0	0	0	
Developed Primary PI-R	0	0	0	

3TC = lamivudine; ABC = abacavir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG = dolutegravir; FAS = full analysis set; INSTI = integrase strand transfer inhibitor; INSTI = integrase strand transfer inhibitor; NA = not applicable; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistance

a Drug resistance mutations are defined in Table 2.

b P-value determined using Fisher's exact test; (B/F/TAF vs ABC/DTG/3TC; B/F/TAF vs DTG + F/TAF)

c Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs.

None of the subjects had resistance mutations emerge. Other substitutions in IN and/or RT that developed were at polymorphic sites; none of these changes were associated with a phenotypic change to BIC, FTC, or TFV.

Secondary pharmacology

Effect of BIC on cardiac conduction

Study GS-US-141-1480 was a partially-blinded, randomized, placebo- and positive-controlled, 4-period, single-dose, crossover study evaluating the effects of BIC (at therapeutic and supra-therapeutic doses) on ΔΔQTcF in healthy subjects. Forty-eight subjects completed 4 dosing periods; each period consisted of 1 day of dosing with 75 mg BIC, 300 mg BIC, placebo-to-match BIC, or moxifloxacin (400 mg) according to randomized sequence. Dosing in the first 3 periods was followed by a washout period of 7 days. Moxifloxacin was administered open label.

BIC was concluded to have no QTcF prolongation effect as the upper bounds of the 2-sided 90% CIs for the mean difference between therapeutic or supra-therapeutic doses of BIC and placebo were below 10 msec at all time points after dosing. No subject had a QTcF interval change from predose baseline > 30 or > 60 msec at any time point during any treatment (BIC 75 and 300 mg, placebo, and

moxifloxacin). Treatment-emergent absolute QTcF intervals > 450, > 480, or > 500 msec were not observed for any subject following BIC 75 and 300 mg, or moxifloxacin. One subject had treatment-emergent absolute QTcF interval > 450 msec following placebo administration.

2.4.4. Discussion on clinical pharmacology

The PK/PD properties of FTC and TAF have been evaluated throughout their respective development programs. Therefore, we will focus on discussing the BIC PK/PD properties as part of the B/F/TAF application.

Analytical methods:

Analytical methods are well described and acceptable. In particular, analytical method validation for BIC in plasma for the main studies was provided. PK parameters calculation was classical and well explained.

Bioavailability:

The absorption of BIC in humans is expected to be > 61% based on the results of the human ADME study in healthy subjects. This is not enough to classify BCS as a molecule with sufficient permeability (>85% of absorption), therefore we disagree with the Applicant's suggestion that BIC be a BCS Class II compound, and we consider a BCS Class IV classification.

Bioequivalence and food effect:

Relative bioavailability study GS-US-141-1233 showed higher than expected BIC exposures when BIC was administered as the B/F/TAF 75/200/25 mg FDC (BIC AUC and Cmax increased by 1.27 and 1.31 fold, out of the 80-125 acceptance range for the confidence interval). The dose of BIC was therefore reduced from 75 mg to 50 mg and a new B/F/TAF 50/200/25 mg FDC tablet was developed, showing lower BIC exposures (BIC AUC and Cmax decreased by 0.78 fold as compared to the 75 mg BIC + FTC/TAF) but within the confidence interval that was enlarged (70-143%) to take into account the different BIC doses. An enlarged CI could be accepted given the lack of lower boundary of BIC therapeutic window and the clinical efficacy results.

GS-US-141-1233 showed that after a high-fat meal, BIC AUC and Cmax were increased by 1.24 and 1.13 fold, and after a moderate-fat meal, BIC AUC and Cmax were increased by 1.24 and 1.20 fold. This food effect was larger with the 75 mg FDC (1.45 fold increase in AUC and 1.27 fold increase in Cmax). GS-US-141-1218 also provided results on food effect of BIC alone, with the largest food effect: Cmax increased 2 fold and AUCs 1.8 fold after a high-fat meal. However, given the efficacy and PK values (and notably IQ values) of B/F/TAF administered with or without food in the Phase 3 studies, there is no evidence of loss of efficacy when B/F/TAF is administered without food.

Metabolism:

BIC has three stereo-centres and is produced as a single stereoisomer, but stability data and routine manufacturing data did not show a risk of epimerization. Therefore, there is no risk of inter-conversion.

M20 (hydroxy-BIC-sulphate) and M15 (BIC-glucuronide) were the major metabolites identified in plasma. Considering the high proportion of M20 (>20%), further in-vitro interaction studies are needed

notably on the effect of M20 on CYP1A2, 2C9, 2C19, 2C8, 2B6, 2D6 and transporters, such as P-gp and BCRP.

PK in subjects with impaired renal function:

In subjects with severe renal impairment, BIC AUC and Cmax were decreased by 0.73 and 0.80 fold respectively. This decrease of exposure seems paradoxical in case of renal impairment, and was unexpected given the PK profile of BIC (renal excretion of intact bictegravir is a minor pathway, ~1% of dose). However, unbound BIC exposure was similar between the 2 groups. As explained by the Applicant, the fractions of BIC plasma protein binding in individual subjects overlapped between the 2 groups, with the percentages of unbound plasma BIC ranging from 0.43% to 0.63%, except in 1 subject with severe renal impairment. This subject showed an unexpectedly higher percentage of unbound plasma BIC (2.28%), which may have led to lower BIC exposure and shorter BIC half-life compared with the other subjects in the study, despite no medical history or concomitant medications explaining this anomaly. When data from this subject were excluded, GLSM ratios for AUClast, AUCinf, and Cmax were 87.44%, 87.51%, and 90.12%, respectively, when subjects with severe renal impairment were compared with subjects with normal renal function. The lack of clinical relevance of such BIC decrease of exposure is endorsed.

PK in subjects with impaired hepatic function:

In subjects with moderate hepatic impairment, BIC AUC and C_{max} were decreased by 0.58 and 0.63 fold respectively. This decrease of exposure seems paradoxical in case of hepatic impairment, notably given that BIC is primarily eliminated by hepatic metabolism.

The higher percentage of unbound fraction of BIC in subjects with hepatic impairment may be due to the decreased production of albumin in these subjects, resulting in lower plasma protein binding of BIC, which is highly protein bound.

Based on the mean (%CV) BIC C_{tau} value of 2610 (35.2) ng/mL following administration of B/F/TAF to HIV-infected subjects (N = 1193) in the Phase 3 clinical studies (representing an IQ of 16.1), a potential decrease of approximately 23% in subjects with moderate hepatic impairment would represent a C_{tau} value 12.4-fold above the paEC95 (162 ng/mL) against wild type HIV-1 virus. Additionally, the lack of an exposure-efficacy relationship for BIC over an IQ range of 4.7 to 40.1 following administration of B/F/TAF in the Phase 3 clinical studies confirms that this small decrease in BIC exposure in subjects with moderate hepatic impairment is not deemed significant. In accordance to the Applicant, the small difference in free BIC exposure is not clinically relevant, and subjects with moderate hepatic impairment may take B/F/TAF with or without food.

Interactions

In vitro, BIC is a substrate of UGT1A1, CYP3A4, P-gp and BCRP. BIC is not a substrate of OATP1B1, OATP1B3. BIC is a weak CYP3A4, OCT2 and MATE1 inhibitor, and has demonstrated in vitro inducing effect on CYP3A4, 2B6, P-gp and UGT1A1, without relevant clinical consequences in vivo. BIC is not expected to affect exposure of drugs the metabolism of which is UGT1A1-dependant. In vitro, BIC is not an inhibitor of P-gp, BCRP, BSEP, OATP1B1, 1B3, OCT1, OAT1.

In study GS-US-380-3908 (ddi metformin), B/F/TAF significantly increases metformin AUC_{τ} about 39% with an 90%CI [131%-148]. Beyond the PD effect of metformin regardless the HIV patient status, the safety profile of the biguanide could be impacted due to renal impaired function that frequently occurs

in HIV- and diabetic patients. In this clinical situation, metformin exposure could be more pronounced increasing the risk of metformin related adverse events. Caution, and eventually a dose adjustment is, then, advised in patients having a moderate renal function.

When B/F/TAF is given simultaneously with antacids under fasted conditions, BIC AUC and C24h substantially decrease, more than with rifampicin, about 79%. This interaction can be compensated by staggering the administration of BIC 2 hours before antacids. When administered 2 hours after, about a half of BIC exposure decreases, in a same magnitude as rifabutin combination. Consequently, B/F/TAF should not begiven simultaneously and in fasted conditions with magnesium or aluminium-containing antacids; B/F/TAF is recommended 2 hours before, or with food 2 hours after magnesium or aluminium-containing antacids.

No DDI study has been performed on the effect of H2-antagonists (e.g. ranitidine) or proton-pump inhibitors (e.g. omeprazole) on BIC pharmacokinetics, because BIC absorption, unlike that of other INSTIs, is not pH dependent under physiologically relevant conditions. This is confirmed by population PK analyses indicating that the extent of BIC absorption was unaffected by PPIs:

	Mean (%CV)		
BIC PK Parameter	B/F/TAF With PPI Usage (Test) (N = 109)	B/F/TAF Without PPI Usage (Reference) (N = 1084)	GLSM Ratio (%) (90% CI)
AUC_{tau} (ng•h/mL)	97,971.9 (29.3)	102,406.2 (26.7)	95.2 (90.8, 99.8)
C_{max} (ng/mL)	5643.8 (25.4)	6196.3 (22.5)	90.6 (87.0, 94.4)
C_{tau} (ng/mL)	2581.0 (38.0)	2612.8 (34.9)	98.0 (92.0, 104.4)

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Pharmacodynamics/antiviral activity:

The antiviral properties of BIC and DTG were compared.

In vitro data suggest that BIC is better than RAL and EVG and at least equivalent to DTG in terms of antiviral activity and resistance profile. In addition, some particularities might contribute to improve its properties against HIV strains with INSTI-RAM:

BIC has a longer dissociation T1/2 from HIV-1 integrase/DNA complexes than DTG, which may be associated to a higher barrier to resistance.

The antiviral activity of BIC against several HIV strains with INSTI-RAM is at least similar to DTG but also less impacted than DTG by some primary mutations (notably for the mutations G140S + Q148R ± additional INSTI mutation).

On the other hand, a study has shown a higher level of resistance to BIC (susceptibility decreased by 44-fold) than DTG (susceptibility decreased by 26-fold) with the mutations T66I + E138K + Q148K.

Finally, because BIC and F/TAF have a high genetic barrier to the development of resistance, the emergence of resistance with the combination B/F/TAF is expected to be low in clinical practice.

Overall, despite pharmacodynamics properties, the clinical development of BIC has been confined to patients with viral strains not harbouring INSTI-R. As for DTG, if BIC were to be developed in patients with INSTI-R testing a higher dose would have to be considered.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of BIC/F/TAF has been sufficiently characterized.

2.5. Clinical efficacy

Primary studies that support the efficacy of the B/F/TAF (50/200/25 mg) FDC are two Phase 3 studies in HIV-infected, ART-naive adults (Studies GS-US-380-1489 and GS-US-380-1490) and two Phase 3 studies in HIV-infected, virologically suppressed adults (Studies GS-US-380-1844 and GS-US-380-1878). 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).

2.5.1. Dose response study

Dose selection

The 50-mg dose of BIC was selected for the B/F/TAF FDC based on the following studies:

Study GS-US-141-1218 was a single-ascending doses (5, 25, 50, 100, 300, or 600 mg) and multiple-ascending doses (5, 25, 50, 100, or 300 mg once daily for 7 days) of single-agent BIC were well tolerated in healthy subjects, and a lack of drug-drug interaction was confirmed between BIC and F/TAF.

- the dose-ranging proof-of-concept study GS-US-141-1219. Once-daily doses of single-agent BIC (5, 25, 50, or 100 mg) administered for 10 days were also well tolerated, and led to dose-dependent decreases in HIV-1 viral load:

Table 18. GS-US-141-1219: Time Weighted Average Change from Baseline up to Day 11 (DAVG11) in Plasma HIV-1 RNA (log10 copies/mL) (PP Analysis Set)

	GS-9883 5 mg (N=3)	GS-9883 25 mg (N=4)	GS-9883 50 mg (N=4)	GS-9883 100 mg (N=4)	Placebo (N=4)
$DAVG_{11}$[a]					
N	3	4	4	4	4
Mean (SD)	-0.92 (0.104)	-1.33 (0.174)	-1.37 (0.310)	-1.61 (0.256)	-0.01 (0.144)
95% CI	(-1.18 , -0.66)	(-1.61 , -1.06)	(-1.87 , -0.88)	(-2.01 , -1.20)	(-0.24 , 0.22)
Median	-0.87	-1.33	-1.45	-1.57	0.02
Q1, Q3	-1.04, -0.85	-1.46, -1.20	-1.61, -1.13	-1.77, -1.44	-0.11, 0.10
Min, Max	-1.04, -0.85	-1.54, -1.13	-1.63, -0.96	-1.95, -1.34	-0.21, 0.12
Pairwise p-values[b]					
vs. Placebo	<.001	<.001	<.001	<.001	
vs. GS-9883 100 mg	<.001	0.097	0.15		
vs. GS-9883 50 mg	0.016	0.81			
vs. GS-9883 25 mg	0.026				

a One subject in 5 mg group was excluded from the Per-Protocol (PP) Analysis Set as this subject's baseline HIV-1 RNA value was 173 copies/mL.
b P-value was calculated from two-sided t test.

The plasma exposure-response relationship was well characterized by an E_{max} model. Inhibitory quotient (IQ) was estimated by dividing pre-dose concentration on Day 11 (C_{tau}) by the in vitro protein-adjusted concentration that results in 95% inhibition (paIC95, 162 ng/mL - from study PC-141-2032). BIC doses of 25, 50, and 100 mg once daily yielded median protein-adjusted IQ of 95% (paIQ95) values of 4.9, 13.4, and 25.9, respectively. Based on PK/PD analyses, exposure associated with a 75 mg dose of single agent BIC is expected to provide near-maximal virologic response, with a predicted paIQ95 of approximately 20, providing considerable coverage above the target concentration of 162 ng/mL (paIC95).

The Phase 2 safety and efficacy study GS-US-141-1475 was a randomized, double-blinded study of the safety and efficacy of BIC 75 mg + F/TAF versus DTG 50 mg + F/TAF in HIV-1 infected antiretroviral treatment-naive adults. Treatments were administered without regard to food.

Baseline demographic and disease characteristics were similar between the 2 treatment groups. Efficacy outcomes are as follows:

Table 19. GS-US-141-1475: Overall Summary of Virologic Outcomes at Week 12, 24 and 48 Using the US FDA-Defined Snapshot Algorithms

			BIC+F/TAF vs DTG+F/TAF	
	BIC+F/TAF	DTG+F/TAF	p-value[a]	Difference in Percentages (95% CI)[b]
Full Analysis Set	**N = 65**	**N = 33**		
HIV-1 RNA < 50 copies/mL Week 12	61 (93.8%)	31 (93.9%)	0.79	−1.3% (−12.9% to 10.2%)
HIV-1 RNA < 50 copies/mL Week 24	63 (96.9%)	31 (93.9%)	0.50	2.9% (−8.5% to 14.2%)
HIV-1 RNA < 50 copies/mL Week 48	63 (96.9%)	30 (90.9%)	0.17	6.4% (−6.0% to 18.8%)
Per Protocol Analysis Set	**N = 63**	**N = 30**		
HIV-1 RNA < 50 copies/mL Week 24	62 (98.4%)	30 (100.0%)	0.40	−2.0% (−10.0% to 5.9%)
HIV-1 RNA < 50 copies/mL Week 48[a]	61[a] (100.0%)	29 (96.7%)	0.14	3.5% (−6.2% to 13.1%)

a N = 61 at Week 48.

b Difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on the baseline HIV-1 RNA stratum-adjusted MH proportion.

For each of the subgroups analysed (age, race, baseline HIV-1 RNA, baseline CD4 cell count, and study drug adherence), there was no difference between the 2 treatment groups in the percentage of subjects with HIV-1 RNA < 50 copies/mL.

At Week 48, mean changes from baseline in HIV-1 RNA and CD4 cell count were similar in both groups.

Based on this study, a BIC dose at 75 mg was selected.

The relative bioavailability study GS-US-141-1233 evaluated two FDC tablet formulations (B/F/TAF [50/200/25 mg] FDC and B/F/TAF [75/200/25 mg] FDC) compared with BIC 75 mg + F/TAF (200/25 mg). According to these results, the FDC containing BIC 50 mg instead of BIC 75 mg was selected for further evaluation in Phase 3 studies, in order to achieve equivalent BIC exposure than with BIC 75 mg single component.

2.5.2. Main studies

Studies in ART-naïve patients

Study GS-US-380-1489: *A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Abacavir/Dolutegravir/Lamivudine in HIV-1 Infected, Antiretroviral Treatment-Naive Adults.*

Patients were generally treated in ambulatory environment and were enrolled and treated at a total of 122 study centers: 2 in Belgium, 8 in Canada, 1 in the Dominican Republic, 6 in France, 3 in Germany, 3 in Italy, 10 in Spain, 8 in the United Kingdom (UK), and 81 in the United States (US).

Study GS-US-380-1490: *A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults.*

Subjects were ambulatory patients that were enrolled and treated at a total of 126 study centers: 6 in Australia, 2 in Belgium, 6 in Canada, 1 in the Dominican Republic, 4 in France, 8 in Germany, 3 in Italy, 8 in Spain, 11 in the United Kingdom (UK), and 77 in the United States (US).

Main inclusion criteria

Eligible subjects for studies 1489 and 1490 were ART-naive (≤ 10 days of prior therapy with any antiretroviral agent except the use for pre-exposure prophylaxis [PrEP] or postexposure prophylaxis [PEP], up to 1 month prior to screening); HLA-B*5701-negative, HIV- infected adults with plasma HIV-1 RNA levels ≥ 500 copies/mL; a screening genotype showing sensitivity to FTC, tenofovir (TFV), 3TC, and ABC; an estimated glomerular filtration rate (eGFR) ≥50 mL/min (≥ 0.83 mL/sec) according to the Cockcroft-Gault formula (eGFRCG); and the absence of chronic hepatitis B virus (HBV) infection.

Objectives

The primary objective for studies 1489 and 1490 is as follows:

- To evaluate the efficacy of B/F/TAF versus ABC/DTG/3TC or DTG + F/TAF in HIV-1 infected, ART-naïve adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48

The secondary objective of studies 1489 and 1490 is:

- To evaluate the efficacy, safety, and tolerability of the 2 treatment groups through Weeks 48, 96, and 144.

Study 1489 has the additional secondary objective

- To evaluate the bone safety of the 2 treatment groups as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) through Weeks 48, 96, and 144.

Results

There were 4 Phase 3 studies. The following tables summarise the efficacy results from these main studies supporting the present application:

Table 20. Summary of efficacy for trial GS-US-380-1489

Title: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Abacavir/Dolutegravir/Lamivudine in HIV-1 Infected, Antiretroviral Treatment-Naive Adults		
Study identifier	GS-US-380-1489	
Design	Randomized, double-blinded, multicenter, active-controlled study	
	Duration of main phase:	144 weeks
Hypothesis	Non-inferiority	
Treatments groups	B/F/TAF	B/F/TAF 50/200/25 mg QD N = 314

	ABC/DTG/3TC		ABC/DTG/3TC (ABC/DTG/3TC) 600/50/300 mg QD N = 315
Endpoints and definitions	Primary endpoint	% subjects with HIV-1 RNA <50 c/mL	At Week 48, using FDA Snapshot algorithm
	Secondary efficacy endpoints	% subjects with HIV-1 RNA <50 c/mL	At Week 96
		% subjects with HIV-1 RNA <20 c/mL	At Week 48 and 96
		Change from baseline in plasma HIV-1 RNA	
		Change from baseline in CD4 cell count	
Database lock	09 May 2017		

Results and Analysis

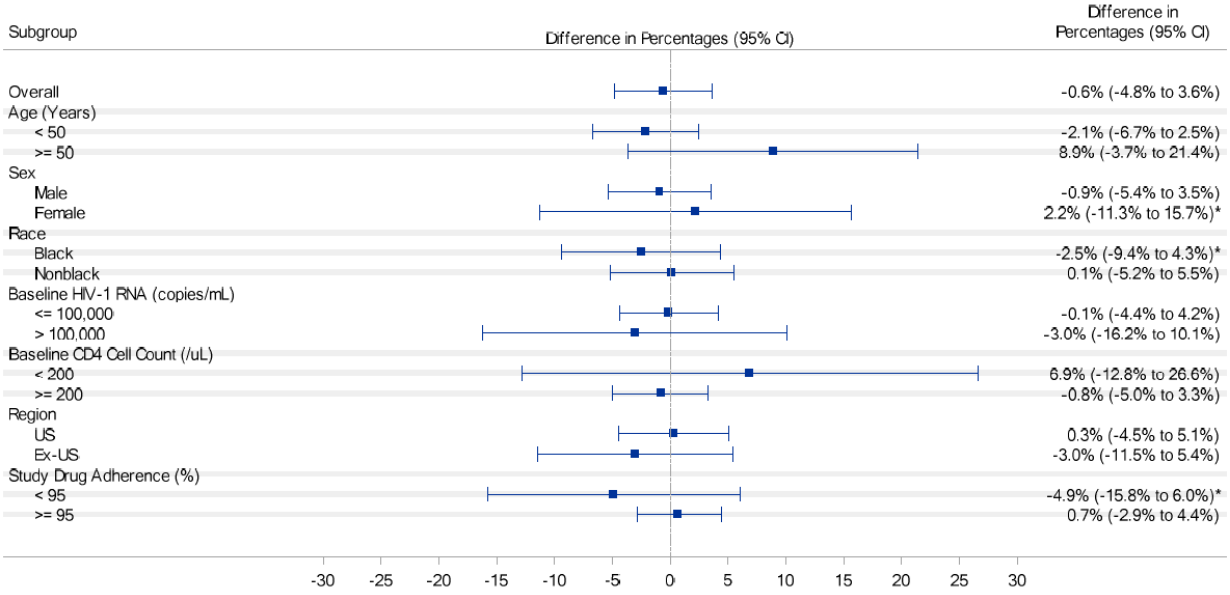
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Time point: Week 48		
Descriptive statistics and estimate variability	Treatment group	B/F/TAF	ABC/DTG/3TC
	Number of subject	314	315
	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	290 (92.4%)	293 (93.0%)
	Subjects with HIV-1 RNA <20 c/mL at W48 (%)	275 (87.6%)	275 (87.3%)
	Mean change from Baseline in HIV-1 RNA (log10 c/ml at Week 48)	-3.11	-3.08
	SD	0.660	0.719
	Mean change from Baseline in CD4+ cell counts (cells/mm3 at Week 48)	233	229
	SD	185.2	188.8
Effect estimate per comparison	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	Adjusted difference in proportion	-0.6%
		95% CI	-4.8% to 3.6%

This primary endpoint was supported by the PP analysis, with virologic success rates of B/F/TAF and ABC/DTG/3TC groups at respectively 99.3% and 98.6% (difference in percentages: 0.7%, 95.002% CI: −1.4% to 2.8%). No subject developed treatment-emergent resistance to any study drug.

Subgroups analyses of study GS-US-380-1489:

The percentage of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm based on the FAS was similar between the 2 treatment groups for all of the subgroups analyzed (age, sex, race, baseline HIV-1 RNA, baseline CD4 cell count, region, and study drug adherence):

Figure 8. GS-US-380-1489: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm (FAS)



The Week 48 window was between Day 295 and 378 (inclusive).

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 MH proportions adjusted by baseline HIV-1 RNA stratum (≤ 100,000 or > 100,000 copies/mL), and region stratum (US or ex-US) (if not the subgroup factor)

Study drug adherence subgroup analyses were based on the adherence up to the Week 48 visit for active study drugs.

Relative to the vertical line at 0, differences on the right favor the B/F/TAF group and differences on the left favor the ABC/DTG/3TC group.

* Proportion difference and 95% CI from normal approximation without stratification as they were not calculable by stratum adjusted MH method.

Table 21. Summary of efficacy for trial GS-US-380-1490

Title: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults			
Study identifier	GS-US-380-1490		
Design	Randomized, double-blinded, multicenter, active-controlled study		
	Duration of main phase:		144 weeks
Hypothesis	Non-inferiority		
Treatments groups	B/F/TAF		B/F/TAF 50/200/25 mg QD N = 320
	DTG+F/TAF		DTG 50 mg + FTC/TAF 200 mg/25 mg QD N = 325
Endpoints and definitions	Primary endpoint	% subjects with HIV-1 RNA <50 c/mL	At Week 48, using FDA Snapshot algorithm
	Secondary efficacy endpoints	% subjects with HIV-1 RNA <50 c/mL	At Week 96
		% subjects with HIV-1 RNA <20 c/mL	At Week 48 and 96
		Change from baseline in plasma HIV-1 RNA	
		Change from baseline in CD4 cell count	
Database lock	12 May 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		

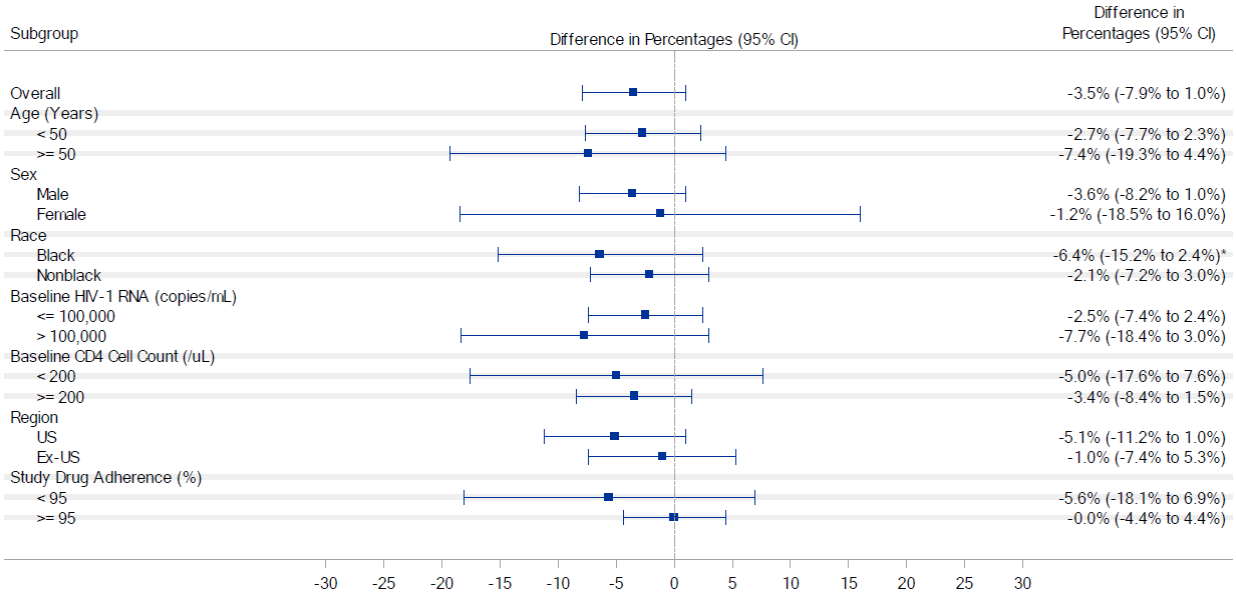
Analysis population and time point description	Intent to treat Time point: Week 48		
Descriptive statistics and estimate variability	Treatment group	B/F/TAF	DTG+F/TAF
	Number of subject	320	325
	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	286 (89.4%)	302 (92.9%)
	Subjects with HIV-1 RNA <20 c/mL at W48 (%)	263 (82.2%)	283 (87.1%)
	Mean change from Baseline in HIV-1 RNA (log10 c/ml at Week 48)	-3.08	-3.12
	SD	0.716	0.671
	Mean change from Baseline in CD4+ cell counts (cells/mm3 at Week 48)	180	201
	SD	166.6	166.4
Effect estimate per comparison	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	Adjusted difference in proportion	-3.5%
		95% CI	-7.9% to 1.0%

This primary endpoint was supported by the PP analysis, with virologic success rates of B/F/TAF and DTG+F/TAF groups at respectively 98.9% and 99.7% (difference in percentages: −0.7%, 95.002% CI: −2.6% to 1.2%). No subject developed treatment-emergent resistance to any study drug.

Subgroups analyses of study GS-US-380-1490:

The percentage of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm based on the FAS was similar between the 2 treatment groups for all of the subgroups analyzed (age, sex, race, baseline HIV-1 RNA, baseline CD4 cell count, region, and study drug adherence):

Figure 9. GS-US-380-1490: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm (FAS)



The Week 48 window is between Days 295 and 378 (inclusive).

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 MH proportions adjusted by baseline HIV-1 RNA (≤ 100,000 or > 100,000 copies/mL) and region stratum (US or ex-US) (if not the subgroup factor).

Study drug adherence subgroup analyses are based on the adherence up to Week 48 visit for active study drug.

Relative to the vertical line at 0, differences on the right favor the B/F/TAF group and differences on the left favor the DTG+F/TAF group.

* Proportion difference and 95% CI from normal approximation without stratification as they were not calculable by stratum adjusted MH method.

Studies in virologically suppressed patients

Study GS-US-380-1844: *A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed Dose Combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed.*

Outpatient subjects were enrolled and treated at a total of 96 study centers: 3 in Australia, 1 in Belgium, 5 in Canada, 4 in France, 8 in Germany, 1 in Italy, 7 in Spain, 3 in the United Kingdom (UK), and 64 in the United States (US; including Puerto Rico).

Main inclusion criteria

Eligible subjects were HIV-1 infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen with the comparator ARV combination for ≥ 3 consecutive months prior to screening, with no documented resistance to any of the study agents at any time in the past; an estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault formula (eGFRCG); and the absence of chronic hepatitis B virus (HBV) infection.

Objectives

The primary objective of this study was as follows:

- To evaluate the efficacy of switching from a regimen of dolutegravir (DTG) and abacavir/lamivudine (ABC/3TC) or an FDC of ABC/DTG/3TC to an FDC of bictegravir (BIC, B; previously referred to as GS 9883)/emtricitabine (FTC)/tenofovir alafenamide (TAF) (B/F/TAF) versus continuing DTG and ABC/3TC as the FDC ABC/DTG/3TC in virologically suppressed HIV-1 infected subjects as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of the 2 treatment groups through Week 48
- To evaluate the bone safety of the 2 treatment groups as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) through Week 48

Study GS-US-380-1878: *A Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Boosted Atazanavir or Darunavir plus either Emtricitabine/Tenofovir or Abacavir/Lamivudine to GS-9883/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed HIV-1 Infected Adults.*

Outpatient subjects were enrolled and treated at 121 study centers in the United States (68), United Kingdom (UK) (14), Germany (12), Australia (7), Canada (6), France (6), Spain (3), Belgium (2), Italy (2), and the Dominican Republic (1).

Main inclusion criteria

Eligible subjects were medically stable HIV-1 infected adults who met the following criteria: on a stable once daily ARV regimen consisting of RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC with documented HIV-1 RNA < 50 copies/mL for ≥6 months preceding and at the screening visit; estimated glomerular filtration rate (eGRF) ≥ 50 mL/min according to the Cockcroft-Gault formula for creatinine clearance (eGRFCG); no previous use of any approved or experimental integrase strand transfer inhibitor (INSTI); and no documented or suspected resistance to FTC, tenofovir (TFV), ABC, or 3TC, including but not limited to the reverse transcriptase resistance mutations K65R and M184V/I. Subjects with chronic hepatitis B infection (unless receiving a non-TDF-containing regimen) or chronic hepatitis C infection were permitted to enter the study.

Objectives

The primary objective of this study was as follows:

To evaluate the efficacy of switching to a fixed-dose combination (FDC) of bictegravir (BIC, B; previously referred to as GS-9883)/emtricitabine (FTC)/tenofovir alafenamide (TAF) (B/F/TAF) versus continuing on a regimen consisting of boosted atazanavir (ATV) or darunavir (DRV) plus either emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or abacavir/lamivudine (ABC/3TC) in HIV-1 infected adult subjects who were virologically suppressed, as determined by the proportion of subjects with HIV-1 RNA ≥50 copies/mL at Week 48

The secondary objective of this study was as follows:

To evaluate the safety and tolerability of the 2 treatment groups through Week 48

Results

Table 22. Summary of efficacy for trial GS-US-380-1844

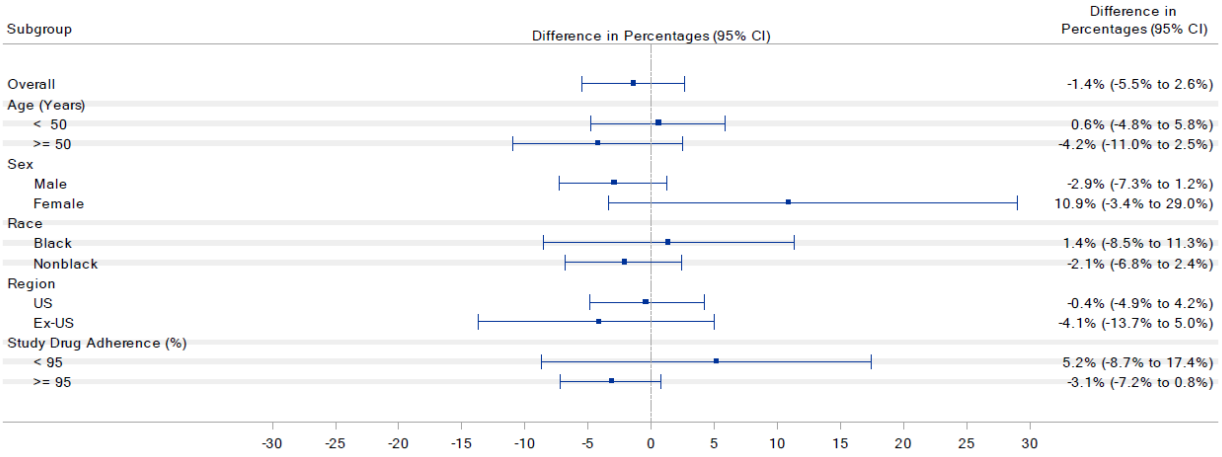
Title: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed Dose Combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed				
Study identifier	GS-US-380-1844			
Design	Randomized, double-blinded, multicenter, active-controlled study			
	Duration of main phase:		48 weeks	
Hypothesis	Non-inferiority			
Treatments groups	B/F/TAF		B/F/TAF 50/200/25 mg QD N = 282	
	ABC/DTG/3TC		ABC/DTG/3TC 600/50/300 mg QD N = 281	
Endpoints and definitions	Primary endpoint	% subjects with HIV-1 RNA ≥50 c/mL	At Week 48, using FDA Snapshot algorithm	
	Secondary efficacy endpoints	% subjects with HIV-1 RNA <50 c/mL	At Week 48	
		% subjects with HIV-1 RNA <20 c/mL	At Week 48	
		Change from baseline in CD4 cell count		
Database lock	26 April 2017			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat Time point: Week 48			
Descriptive statistics and estimate variability	Treatment group		B/F/TAF	ABC/DTG/3TC
	Number of subject		282	281
	Subjects with HIV-1 RNA ≥50 c/mL at W48 (%)		3 (1.1%)	1 (0.4%)
	Subjects with HIV-1 RNA <50 c/mL at W48 (%)		264 (93.6%)	267 (95.0%)
	Subjects with HIV-1 RNA <20 c/mL at W48 (%)		254 (90.1%)	257 (91.5%)
	Mean change from Baseline in CD4+ cell counts (cells/mm3 at Week 48)		-31	4
	SD		181.3	191.0
Effect estimate per comparison	Subjects with HIV-1 RNA ≥50 c/mL at W48 (%)		Adjusted difference in proportion	0.7%
			95% CI	-1.0% to 2.8%

This primary endpoint was supported by the PP analysis, with virologic failure rates of B/F/TAF and DTG+F/TAF groups at respectively 0.4% and 0.0% (difference in percentages: 0.4%, 95.002% CI: −1.1% to 2.2%). No subject developed treatment-emergent resistance to any study drug.

Subgroups analyses of study GS-US-380-1844:

The percentage of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm based on the FAS was similar between the 2 treatment groups for all of the subgroups analyzed (age, sex, race, region, and study drug adherence):

Figure 10. GS-US-380-1844: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm (FAS)



The Week 48 window is between Days 295 and 378 (inclusive).

The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on an unconditional exact method using 2 inverted 1-sided tests.

Study drug adherence subgroup analyses are based on the adherence up to Week 48 visit for active study drug.

Relative to the vertical line at 0, differences on the right favor the B/F/TAF group and differences on the left favor the ABC/DTG/3TC group

Table 23. Summary of efficacy for trial GS-US-380-1878

Title: A Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Boosted Atazanavir or Darunavir plus either Emtricitabine/Tenofovir or Abacavir/Lamivudine to GS-9883/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed HIV-1 Infected Adults			
Study identifier	GS-US-380-1878		
Design	Randomized, open-labelles, multicenter, active-controlled study		
	Duration of main phase:		48 weeks
Hypothesis	Non-inferiority		
Treatments groups	B/F/TAF		B/F/TAF 50/200/25 mg QD N = 290
	SBR (stay on baseline regimen)		Boosted ATV or DRV + FTC/TDF or ABC/3TC N = 287
Endpoints and definitions	Primary endpoint	% subjects with HIV-1 RNA ≥50 c/mL	At Week 48, using FDA Snapshot algorithm
	Secondary efficacy endpoints	% subjects with HIV-1 RNA <50 c/mL	At Week 48

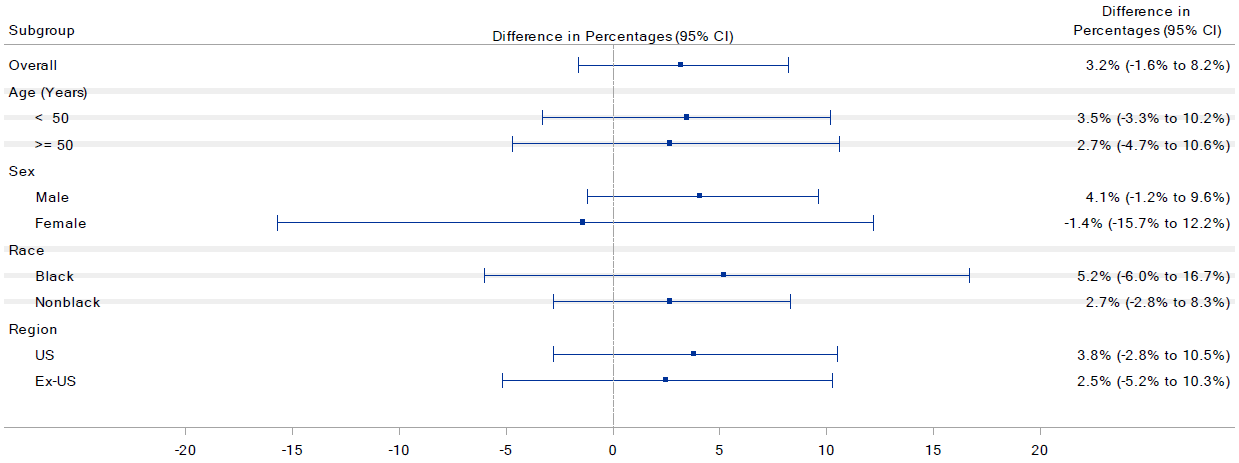
		% subjects with HIV-1 RNA <20 c/mL	At Week 48
		Change from baseline in CD4 cell count	
Database lock	15 May 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Time point: Week 48		
Descriptive statistics and estimate variability	Treatment group	B/F/TAF	SBR
	Number of subject	290	287
	Subjects with HIV-1 RNA ≥50 c/mL at W48 (%)	5 (1.7%)	5 (1.7%)
	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	267 (92.1%)	255 (88.9%)
	Subjects with HIV-1 RNA <20 c/mL at W48 (%)	249 (85.9%)	243 (84.7%)
	Mean change from Baseline in CD4+ cell counts (cells/mm3 at Week 48)	25	0
	SD	151.2	159.4
Effect estimate per comparison	Subjects with HIV-1 RNA ≥50 c/mL at W48 (%)	Adjusted difference in proportion	-0.0%
		95% CI	-2.5% to 2.5%

This primary endpoint was supported by the PP analysis, with virologic failure rates of B/F/TAF and DTG+F/TAF groups at respectively 1.1% and 0.8% (difference in percentages: 0.3%, 95.002% CI: −1.9% to 2.5%). No subject developed treatment-emergent resistance in the B/F/TAF group. One subject in the SBR group (on a regimen of RTV-boosted DRV plus ABC/3TC) developed L74V in reverse transcriptase.

Subgroups analyses of study GS-US-380-1878:

The percentage of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm based on the FAS was similar between the 2 treatment groups for all of the subgroups analysed (age, sex, race and region):

Figure 11. GS-US-380-1878: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm (FAS)



Week 48 window was between Day 295 and 378 (inclusive).

The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on an unconditional exact method using 2 inverted 1-isded tests.

Regardless of prior treatment regimen (FTC/TDF vs ABC/3TC), the response rates in Study GS US-380-1878 were high and similar between both treatment groups:

- Baseline FTC/TDF-containing regimen: B/F/TAF 92.2%; SBR 89.3%

- Baseline ABC/3TC-containing regimen: B/F/TAF 91.1%; SBR 86.4%

Clinical studies in special populations

There was no clinical study performed in special populations (notably paediatric subjects, HIV/HBV-co-infected subjects or renal impaired HIV-infected subjects).

The number of elderly subjects in the B/F/TAF clinical development program was limited. Age was tested as a potential covariate in both the BIC and TAF population PK analyses for B/F/TAF, but was determined to be not significant for both analytes. As such, age is not expected to substantially affect exposure of BIC or TAF.

Supportive studies

The week 48 results of study GS-US-380-1961 became available during the evaluation.

Study GS-US-380-1961 is an ongoing, Phase 3, randomized, open-label study to evaluate the safety and efficacy of switching to B/F/TAF in HIV-infected, virologically suppressed women on a regimen consisting of GEN, STB, or ATV+RTV+FTC/TDF for ≥ 12 weeks prior to screening.

Subjects were enrolled and treated at a total of 58 study centers in 5 countries: Uganda (27.0%, 127 subjects), Russia (23.8%, 112 subjects), Thailand (21.5%, 101 subjects), US (15.3%, 72 subjects), and the Dominican Republic (12.3%, 58 subjects). Overall, 470 subjects (B/F/TAF 234, SBR 236) who were randomized and received at least 1 dose of study drug were included in both the Safety Analysis Set and FAS.

As of the Week 48 data cut date, 98.1% of randomized and treated subjects (461 subjects; B/F/TAF 98.7%, 231 subjects; SBR 97.5%, 230 subjects) had completed study drug in the randomized phase

and 0.2% of subjects (1 subject in the SBR group) were continuing study drug in the randomized phase. Overall, 1.7% of subjects (8 subjects; B/F/TAF 1.3%, 3 subjects; SBR 2.1%, 5 subjects) prematurely discontinued study drug in the randomized phase prior to the Week 48 data cut date. Reasons for premature discontinuation of study drug were generally comparable between treatment groups.

Demographic and baseline characteristics were similar between the 2 treatment groups. Most of the women were not Hispanic/Latino (84.3%), and most were black (37.0%), white (28.3%), or Asian (21.7%). Median age was 39 years (range: 20 to 63 years). Median (Q1, Q3) body mass index was 25.6 (22.1, 30.5) kg/m2. Baseline disease characteristics were generally similar between the 2 treatment groups: the median (Q1, Q3) baseline CD4 cell count was 686 (541, 867) cells/µL, with 83.2% of subjects having a baseline CD4 count ≥ 500 cells/µL. The median (Q1, Q3) baseline CD4% was 36.7% (31.1%, 42.6%). Most subjects were receiving GEN (53.0%, 249 subjects) or STB (41.9%, 197 subjects) at baseline. The most common HIV risk factor was heterosexual sex (98.3% of subjects). Most subjects had asymptomatic HIV-1 infection (90.4%); 7.0% had symptomatic HIV-1 infection, and 2.6% were diagnosed with AIDS. The median (Q1, Q3) eGFRCG at baseline was 100.8 (84.0, 119.8) mL/min.

The percentages of subjects in the FAS with HIV-1 RNA ≥ 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm (primary endpoint) were similar between the 2 treatment groups (B/F/TAF 1.7%; SBR 1.7%; difference in percentages: 0.0%, 95.001% CI: −2.9% to 2.9%). Because the upper bound of the 2-sided 95.001% CI of the difference between treatment groups (B/F/TAF − SBR) was less than the pre-specified 4% margin, switching to B/F/TAF was determined to be non-inferior to maintaining baseline regimen. Similarly, the percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL and < 20 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were similar between the 2 treatment groups.

Table 24. GS-US-380-1961: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 copies/mL (Full Analysis Set)

	B/F/TAF (N = 234)	SBR (N = 236)	B/F/TAF vs. SBR	
			p-value	Difference in Percentages (95.001% CI)
HIV-1 RNA < 50 copies/mL	224 (95.7%)	225 (95.3%)	1.00	0.4% (−3.7% to 4.5%)
HIV-1 RNA >= 50 copies/mL	4 (1.7%)	4 (1.7%)	1.00	0.0% (−2.9% to 2.9%)
HIV-1 RNA >= 50 copies/mL in Week 48 Window	4 (1.7%)	4 (1.7%)		
Discontinued Study Drug Due to Lack of Efficacy	0	0		
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA >= 50 copies/mL	0	0		
Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA >= 50 copies/mL	0	0		
No Virologic Data in Week 48 Window	6 (2.6%)	7 (3.0%)		
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA < 50 copies/mL	0	1 (0.4%)		
Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA < 50 copies/mL	3 (1.3%)	4 (1.7%)		
Missing Data During Window but on Study Drug	3 (1.3%)	2 (0.8%)		

CD4 cell counts were maintained in both groups. Mean (SD) changes from baseline at Week 48 for the FAS were as follows: B/F/TAF 29 (159.4) cells/μL; SBR 26 (170.3) cells/μL; difference in least-squares mean: 3 cells/μL, 95% CI: −27 to 34 cells/μL.

Analysis performed across trials (pooled analyses and meta-analysis)

The pooled-results of the studies GS-US-380-1489 and GS-US-380-1490 in ART-naïve subjects are as follows:

Table 25. 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 Cut-off at 50 copies/mL – Pooled Data (Full Analysis Set)

	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%)
B/F/TAF vs. ABC/DTG/3TC			
Difference in Percentages (95% CI)	-2.1% (−5.9% to 1.6%)		
p-value	0.26		
B/F/TAF vs. DTG + F/TAF			
Difference in Percentages (95% CI)	-1.9% (-5.6% to 1.8%)		
p-value	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 CMH 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 was calculated based on the MH proportion adjusted by baseline HIV-1 RNA stratum (<= 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. ex-US).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

There are 4 Phase 3 pivotal studies assessing B/F/TAF 50/200/25 mg: 2 in ART-naïve subjects, and 2 in virologically supressed subjects. The design, statistical method, outcomes and inclusion/exclusion criteria are acceptable. The choice of the comparators (DTG-based regimen in the 2 studies in ART-naïve subjects and in one switch study, PI-based regimen in the other switch study) is endorsed given DTG is the more effective and used INSTI, in comparison to raltegravir and elvitegravir. While this comparator has been used in both pivotal studies in TN patients, the backbone with DTG was different in both studies, ABC/3TC or F/TDF. The comparison of B/F/TAF to a PI-based regimen in a switch study provides additional data to reinforce the place of such INSTI with significant barrier of resistance into the HIV therapeutic strategy.

Of note, the comparison with DTG is done in TN and in virologically suppressed patients.

Although a more stringent 10% non-inferiority margin would have been regarded as more appropriate than the 12% selected margin for the studies performed in ART-naïve subjects, ultimately results are overall compatible with a more stringent non inferiority margin.

In these pivotal studies, enrolled subjects are predominantly white homosexual men with unaltered immune function and asymptomatic HIV infection, as for main of the Phase 3 studies in HIV clinical studies. The proportion of women and ART-naïve subjects with VL >100,000 c/mL is low (10-15%) but an additional switch study only performed in women confirms this non-inferiority.

Efficacy data and additional analyses

The short-term monotherapy study suggested that 100 mg bictegravir might be slightly better than 50 mg. The Applicant initially chose 75 mg primarily based on the Emax model. The choice of this dose might be endorsed considering that the clinical development of BIC does not encompass patients with viral strains harbouring INSTI-RAM, where higher dose might have been required as for dolutegravir. Then, the dose of bictegravir was subsequently lowered to 50 mg when bictegravir was incorporated into the FDC with FTC and TAF based on PK data.

While it is clear that the BIC dose was to be different as part of the FDC vs outside the FDC, there might still be some room for maximizing the dose. Nevertheless, it can ultimately be acknowledged that the dose as selected has enabled to achieve non-inferiority of B/F/TAF vs DTG+2 NRTIs. However, it is expected that higher BIC dose would be required in the context of INI-RAM emergence.

Overall, the efficacy endpoints support the non-inferiority of B/F/TAF compared to DTG-based regimen (FTC/TAF or ABC/3TC) in ART-naïve subjects and when switching from such regimen in virologically suppressed subjects. These results are supported by the Per Protocol analyses and other secondary endpoints, especially the changes from baseline in plasma HIV-1 RNA and CD4 cell count. In addition, the switch to B/F/TAF is non-inferior to the continuation of a DRV- or ATV-based regimen. This is consistent with the known efficacy of DTG in comparison to PI. The rates of virological success or lack of efficacy with B/F/TAF are consistent with the historical data from F/TAF-studies.

In the Phase 3 studies comparing B/F/TAF vs DTG+F/TAF or ABC/DTG/3TC in ART-naïve subjects, there is a trend for lower response rate in the subgroup of patients with high viral load (>100,000 c/ml) treated with B/F/TAF. It is noteworthy that given that ABC/3TC is somewhat regarded as not maximizing efficacy in patients with high viral load, the trend for higher efficacy of DTG was more pronounced when DTG was combined with the same backbone as for BIC (i.e. FTAF) than when DTG was combined with ABC-3TC. Given that the subgroup of patients with high viral load is regarded as discriminatory, the results in patients with high viral load might translate a somewhat lower performance of BIC as compared to DTG which might be related to a non-maximized dose of BIC. While it can be acknowledged that in the subgroup of patients with adherence <95% the trend favouring dolutegravir might be driven by the missing data rather than virologic failure (which would otherwise have argued that limited adherence might be more pejorative for bictegravir than dolutegravir), this is not the case for the overall analysis in patients with high viral load. Overall, the trend in favour of dolutegravir in patients with high viral load as reflected in section 5.1 of the SmPC.

In studies GS-US-380-1490 (B/F/TAF vs DTG+F/TAF in ART-naïve subjects) and GS-US-380-1844 (B/F/TAF vs ABC/DTG/3TC in virologically suppressed subjects), there is a slightly higher rate of subjects who discontinued from B/F/TAF treatment due to adverse events, although not statistically significant.

Across all these studies, no INSTI-RAM had emerged in the B/F/TAF groups, as in the DTG groups. This is consistent with the favourable resistance profile of BIC, with a barrier to resistance development expected to be similar to DTG. However, as already stated the efficacy of B/F/TAF in subjects with history of virological failure under INSTI therapy was not evaluated.

2.5.4. Conclusions on the clinical efficacy

B/F/TAF 50/200/25 mg has been demonstrated to be overall non inferior to DTG + FTC/TAF or ABC/3TC in ART-naïve or virologically suppressed subjects without history of INSTI resistance. High percentage of patients have achieved HIV RNA level <50 copies/ml at week 48 (≥90% at Week 48) and this demonstration is derived from three well-designed studies (double blind, large sample and primary endpoint in line with EU guidelines) with comparable populations enrolled. In addition, an additional switch study demonstrated the non-inferiority of B/F/TAF vs DRV- or ATV-based regimen, which is consistent with DTG. The clinical demonstration can support the use of BFTAF for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated *with resistance to the integrase inhibitor class*, emtricitabine or tenofovir.

2.6. Clinical safety

Patient exposure

A total of **1511 subjects** have received at least 1 dose of B/F/TAF in the Phase 2 and 3 studies, including 1206 subjects from the randomized phases of the Phase 3 studies. This population exposure to B/F/TAF exceeds the requirements of the ICH E1 guideline for the safety evaluation of drugs, but the number of subjects with high duration of treatment (≥72 weeks) is very limited. The duration of exposure was similar between groups within each study.

Table 26. GS-US-380-1489, GS-US-380-1490, GS-US-141-1475, GS-US-380-1844, GS-US-380-1878: Duration of Exposure to Randomized Study Drug (Safety Analysis Set)

	ART-Naive Adult Subjects					Virologically Suppressed Adult Subjects			
	GS-US-380-1489/GS-US-380-1490			GS-US-141-1475[a]		GS-US-380-1844		GS-US-380-1878[b]	
	Pooled	380-1489	380-1490						
	B/F/TAF (N = 634)	ABC/DTG/ 3TC (N = 315)	DTG + F/TAF (N = 325)	BIC + F/TAF (N = 65)	DTG + F/TAF (N = 33)	B/F/TAF (N = 282)	ABC/DTG/ 3TC (N = 281)	B/F/TAF (N = 290)	SBR (N = 287)
Exposure Duration									
Mean (SD)	49.8 (11.97)	51.6 (10.60)	49.7 (10.88)	58.0 (8.69)	57.4 (10.43)	50.7 (10.59)	50.9 (10.20)	44.9 (7.09)	44.3 (8.92)
Median	49.2	51.3	48.6	59.9	60.0	49.9	50.3	46.7	46.7
Q1, Q3	45.6, 56.1	46.3, 57.6	45.6, 55.1	59.1, 60.0	59.7, 60.1	45.1, 56.3	45.1, 56.3	44.0, 48.0	44.0, 48.0
Min, Max	0.1, 74.3	0.6, 72.6	1.4, 74.4	0.1, 63.0	2.3, 61.1	0.1, 72.9	7.6, 72.4	1.3, 56.6	0.1, 56.7
Exposure Cutoffs									
≥ 4 Weeks (28 days)	631 (99.5%)	314 (99.7%)	324 (99.7%)	64 (98.5%)	32 (97.0%)	281 (99.6%)	281 (100.0%)	289 (99.7%)	285 (99.3%)
≥ 8 Weeks (56 days)	622 (98.1%)	312 (99.0%)	321 (98.8%)	64 (98.5%)	32 (97.0%)	279 (98.9%)	280 (99.6%)	287 (99.0%)	282 (98.3%)
≥ 12 Weeks (84 days)	615 (97.0%)	312 (99.0%)	317 (97.5%)	64 (98.5%)	32 (97.0%)	278 (98.6%)	280 (99.6%)	284 (97.9%)	277 (96.5%)
≥ 24 Weeks (168 days)	605 (95.4%)	307 (97.5%)	314 (96.6%)	63 (96.9%)	32 (97.0%)	273 (96.8%)	273 (97.2%)	281 (96.9%)	273 (95.1%)
≥ 36 Weeks (252 days)	595 (93.8%)	301 (95.6%)	310 (95.4%)	63 (96.9%)	32 (97.0%)	271 (96.1%)	269 (95.7%)	276 (95.2%)	265 (92.3%)
≥ 48 Weeks (336 days)	370 (58.4%)	204 (64.8%)	180 (55.4%)	63 (96.9%)	31 (93.9%)	169 (59.9%)	172 (61.2%)	98 (33.8%)	102 (35.5%)
≥ 60 Weeks (420 days)	102 (16.1)	63 (20.0%)	49 (15.1%)	29 (44.6%)	20 (60.6%)	46 (16.3%)	47 (16.7%)	—	—
≥ 72 Weeks (504 days)	5 (0.8%)	3 (1.0%)	3 (0.9%)	—	—	5 (1.8%)	5 (1.8%)	—	—

Duration of exposure to study drug was the number of weeks between the first dose and the last dose of randomized study drug.

For subjects who had prematurely discontinued randomized study drug, if the last dose date of randomized study drug was completely missing or only year was known, the latest of randomized study drug start and end dates or randomized clinic and laboratory visit dates (excluding the 30-day follow-up visit date) was used to impute the last dose date.

For subjects who had not prematurely discontinued randomized study drug, the data cut date was used to impute the last dose date.

a Includes only double-blinded, randomized treatment

b Includes only randomized treatment

Adverse events

The adverse event (AE) profile was generally similar in ART-naive and virologically suppressed adults, with similar rates of any AEs, Grade 3 or 4 AEs, SAEs, SAEs considered related to study drugs, and AEs leading to study drug discontinuation across the different treatment groups.

Table 27. 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.

Table 28. GS-US-380-1489 and GS-US-380-1490: Study Drug–Related Adverse Events by Preferred Term Reported for at Least 1% of Subjects in Any Treatment Group (Safety Analysis Set)

	B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)
Number of Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	139 (21.9%)	127 (40.3%)	83 (25.5%)
Nausea	26 (4.1%)	55 (17.5%)	17 (5.2%)
Headache	29 (4.6%)	15 (4.8%)	10 (3.1%)
Diarrhoea	29 (4.6%)	13 (4.1%)	11 (3.4%)
Fatigue	16 (2.5%)	10 (3.2%)	7 (2.2%)
Dizziness	13 (2.1%)	9 (2.9%)	2 (0.6%)
Insomnia	11 (1.7%)	9 (2.9%)	1 (0.3%)
Abnormal dreams	9 (1.4%)	8 (2.5%)	2 (0.6%)
Abdominal distension	7 (1.1%)	5 (1.6%)	4 (1.2%)
Flatulence	6 (0.9%)	2 (0.6%)	7 (2.2%)
Vomiting	6 (0.9%)	5 (1.6%)	2 (0.6%)
Constipation	7 (1.1%)	2 (0.6%)	3 (0.9%)
Abdominal discomfort	4 (0.6%)	4 (1.3%)	3 (0.9%)
Abdominal pain	3 (0.5%)	6 (1.9%)	2 (0.6%)
Dyspepsia	4 (0.6%)	4 (1.3%)	3 (0.9%)
Somnolence	4 (0.6%)	3 (1.0%)	2 (0.6%)
Decreased appetite	3 (0.5%)	3 (1.0%)	2 (0.6%)
Sleep disorder	3 (0.5%)	5 (1.6%)	0
Anxiety	1 (0.2%)	3 (1.0%)	1 (0.3%)

Adverse events were coded using MedDRA 19.1.

Preferred terms are presented by descending order of the total frequencies.

Multiple AEs were counted only once per subject per preferred term.

Relatedness to study drug is assessed by the investigator.

Serious adverse event / deaths

Across the Phase 2-3 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 by the Applicant. No treatment-emergent deaths were reported in Phase 1 studies with single-agent BIC or regimens containing BIC and F/TAF.

The incidence of SAEs in Phase 2-3 studies was comparable between treatment groups within each study.

Adverse events of special interest

Hepatic safety

The hepatic safety results can be summarised as follows:

	B/F/TAF Group	Control Group	Studies
Hepatic AEs	1.4%	1.9% - 3.1 %	Pooled studies GS-US-380-1489-1490
	4.6%	0%	Phase 2 study GS-US-141-1475
	1.8%	0.4%	Switch study GS-US-380-1844

	B/F/TAF Group	Control Group	Studies
	1.4%	3.5%	Switch study open label GS-US-380-1878
ALT increase	11.3%	12% -14%	Pooled studies GS-US-380-1489-1490
	25%	**9.4%**	Phase 2 study GS-US-141-1475
	18.4%	**9.6%**	Switch study GS-US-380-1844
	23.4%	**10.5%**	Switch study open label GS-US-380-1878
AST increase	13.1%	11.1%-15.2%	Pooled studies GS-US-380-1489-1490
	23.4%	**9.4%**	Phase 2 study GS-US-141-1475
	16.3%	**9.6%**	Switch study GS-US-380-1844
	14.8%	**10.2%**	Switch study open label GS-US-380-1878
Hyperbilirubinemia	**11.6%**	**4.1% - 5.8%**	Pooled studies GS-US-380-1489-1490
	14.1%	12.5%	Phase 2 study GS-US-141-1475
	7.4%	**3.6%**	Switch study GS-US-380-1844
	5.5%	33.7%	Switch study open label GS-US-380-1878
ALP increase	2.2%	2.2% -3.2%	Pooled studies GS-US-380-1489-1490
	0%	3.1%	Phase 2 study GS-US-141-1475
	2.5%	0.7%	Switch study GS-US-380-1844
	0.3%	3.5%	Switch study open label GS-US-380-1878

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.

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.

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. Transaminase elevations were reported in a higher proportion in virologically suppressed subjects who switched treatment to B/F/TAF than in subjects in the comparator groups. However, these transaminase elevations were mainly Grade 1 or 2, resolved without B/F/TAF discontinuation and were not associated with AEs.

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, due to ATV treatment in some subjects in the SBR group).

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. In both ART-naive (study GS-US-380-1489) and virologically suppressed subjects (GS-US-380-1844), mean (SD) percentage changes from baseline in hip and spine BMD were comparable between the B/F/TAF and ABC/DTG/3TC treatment groups.

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.

No subject 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. Changes in serum creatinine and $eGFR_{CG}$ were observed by Week 4 and remained stable thereafter through Week 48:

Median (Q1, Q3) change from baseline to Week 48	**Serum creatinine**	**$eGFR_{CG}$**
Pooled studies GS-US-380-1489 and GS-US-380-1490	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	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
Switch study GS-US-380-1844	B/F/TAF: 0.00 (−0.07, 0.06) mg/dL ABC/DTG/3TC: 0.02 (−0.05, 0.09) mg/dL	B/F/TAF: 1.0 (−5.2, 9.4) mL/min ABC/DTG/3TC: −1.8 (−9.0, 4.8) mL/min
Switch study GS-US-380-1878	B/F/TAF: 0.06 (−0.03, 0.13) mg/dL SBR: 0.00 (−0.07, 0.07) mg/dL	B/F/TAF: −4.3 (−12.6, 4.8) mL/min SBR: 0.2 (−6.6, 7.6) mL/min

Ocular safety

Overall, the incidence of AEs in the eye disorders SOC and the incidence of AEs potentially related to uveitis were low and comparable between treatment groups in the 4 Phase 3 B/F/TAF studies. Clinically, none of the AEs potentially related to uveitis were considered representative of an actual case of posterior uveitis.

Table 29. GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878: Adverse Events in the Eye Disorders System Organ Class and Potential Uveitis 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)
Eye Disorders SOC	19 (3.0%)	10 (3.2%)	18 (5.5%)	9 (3.2%)	9 (3.2%)	7 (2.4%)	5 (1.7%)
Potential Uveitis AEs[a]	4 (0.6%)	1 (0.3%)	8 (2.5%)	3 (1.1%)	3 (1.1%)	1 (0.3%)	1 (0.3%)

a Based on the list of terms used for the GEN development program, which was reviewed and edited by an external ophthalmologist for comprehensiveness.

Psychiatric disorders

Adverse events based on the suicide/self-injury Standard MedDRA Query were infrequent in the 4 Phase 3 B/F/TAF studies through 48 weeks of treatment. Most subjects who experienced a suicide-related AE when receiving B/F/TAF had a pre-existing history of depression or mental illness.

Table 30. GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878: Suicide Events by Suicide/Self-Injury SMQ (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)
Suicide Events	7 (1.1%)	3 (1.0%)	2 (0.6%)	3 (1.1%)	1 (0.4%)	0	1 (0.3%)
Depression suicidal	1 (0.2%)	0	0	1 (0.4%)	0	0	0
Intentional overdose	0	0	0	1 (0.4%)	0	0	0
Suicidal ideation	3 (0.5%)	3 (1.0%)	1 (0.3%)	2 (0.7%)	1 (0.4%)	0	0
Suicide attempt	3 (0.5%)	0	1 (0.3%)	1 (0.4%)	0	0	1 (0.3%)

Laboratory findings

B/F/TAF demonstrated a clinical laboratory safety profile similar to that of comparator regimens. 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. Of note, higher rates of minor transaminase increases were observed in the B/F/TAF groups than in the DTG-containing groups, but were not considered clinically significant.

Safety in special populations

The AE profile for subjects receiving B/F/TAF was not affected by sex, age and race.

Renal impairment

In study GS-US-141-1479, BIC 75 mg was administered in subjects with severe impaired renal function (n=10) compared with control subjects with normal renal function (n=8). One AE in each renal function group was considered related to study drug by the investigator (nausea in a subject with severe renal impairment and headache in a subject with normal renal function). The safety profile of BIC was similar between the 2 renal function groups.

Hepatic impairment

In study GS-US-141-1478, BIC 75 mg was administered in subjects with normal (n=10) or moderate (n=10) hepatic impairment. The AEs considered related to study drug by the investigator were reported in 3 subjects (30%) with moderate hepatic impairment and in none of the normal matched control subjects. These events were headache (2 subjects) and somnolence (1 subject).

HBV / HCV-coinfection

In HIV/HBV-co-infected subjects (14 subjects in study GS-US-380-1490 and 14 subjects in study GS-US-380-1878), the safety profile of B/F/TAF was similar to that in patients with HIV mono-infection. In study GS-US-380-1490, 1 subject in the B/F/TAF group had a confirmed on-treatment ALT flare (defined as ALT > 10 x ULN and ALT > 2 x baseline on 2 consecutive occasions) at Week 12. The ALT flare was reported as a Grade 2 AE of immune reconstitution inflammatory syndrome that was not considered related to study drug. No hepatic AEs were reported for this subject. Another HIV/HBV co-infected subject in the B/F/TAF group, with normal ALT (30 U/L) and AST (24 U/L) at baseline, experienced Grade 3 ALT (316 U/L) and Grade 2 AST (136 U/L) at Week 8, both of which resolved to within the normal range by Week 24. One additional subject (DTG+F/TAF group) experienced Grade 1 ALT and AST elevations. In study GS-US-380-1878, 3 subjects in the B/F/TAF group experienced treatment-emergent Grade 1 ALT elevation, one of whom also experienced Grade 1 AST elevation. One subject in the SBR group experienced Grade 2 total bilirubin abnormality.

In HIV/HCV-co-infected subjects (n=25), elevations in AST and ALT occurred more frequently than in the subjects without viral hepatitis infection. The incidence of graded AST and ALT elevations for HIV/HCV baseline-co-infected subjects was similar between the 2 treatment groups.

Pregnancy

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 (11 pregnancies reported in the Phase 3 studies, including 5 subjects treated with B/F/TAF) or from Antiretroviral Pregnancy Registry (APR) data for FTC and from the limited data for TAF.

Discontinuation due to adverse events

The rate of discontinuation due to AE with B/F/TAF is low (≤2%), similarly to the comparators groups. These AEs are generally gastro-intestinal, neuropsychiatric or allergic disorders.

2.6.1. Discussion on clinical safety

As expected, the safety profile of B/F/TAF is similar to DTG+FTC/TAF. The more frequent AEs are gastrointestinal disorders (diarrhoea, nausea, vomiting), headache, fatigue and insomnia (<5% of subjects). It has to be underlined that only 48 weeks data from the ongoing longer term pivotal phase 3 studies have been made available.

The relevant aspects of the safety profile of B/F/TAF are:

Hepatotoxicity: Although no liver hypersensitivity reaction or severe drug-induced liver occurred in subjects treated with B/F/TAF, higher rates of transaminases elevations and hyperbilirubinemia were observed compared to DTG-based regimen. These elevations were mild and transient. Considering the available data in monkeys which showed bile duct hyperplasia a at the higher doses of B tested (1000 mg/kg/day) not always reversible and the cases of increased ALT activities also reported at the highest doses and the potential competition of B for the UGT1A1 enzyme with unconjugated bilirubin, the risk of hepatobiliary disorders is a potential concern for bictegravir-containing regimen. Of note, an

amendment to the study protocols GS-US-380-1489 and GS-US-380-1844 was made to include recommendations for the management of potential hepatobiliary toxicity. The recommendation was to highlight the potential hepatobiliary toxicity of bictegravir based on data available in monkeys at the highest dose tested (biliary hyperplasia and hepatocyte hypertrophy) and that further investigations might be necessary in case of signs/ laboratory abnormalities suggestive of hepatobiliary disorders. Hepatotoxicity will be actively monitored through PSURs.

Renal disorders: as DTG, BIC also increases serum creatinine level within the first weeks of treatment and remained stable thereafter, due to the inhibition of the transporters OCT2 and MATE-1. This is not considered to be clinically relevant since do not reflect a change in glomerular filtration rate, but should be considered for the biological monitoring of renal impaired subjects treated with B/F/TAF.

Psychiatric disorders: depression, suicidal ideation and suicidal behaviour (particularly in patients with pre-existing history of psychiatric illness) are a class-effect of integrase inhibitors and listed in the SmPC of dolutegravir, raltegravir and elvitegravir. The rate of suicide events is ~1% across the different study groups, and seems not increased with B/F/TAF compared to the other INSTI. However, considering the limited number of patients included in all the studies, it is difficult to draw any conclusion. At least, the level of risk might be similar with BIC than with DTG. Outside the suicide events, a number of other psychiatric AEs have been reported with B/F/TAF. Based on the data provided on psychiatric disorders, 1/3 of patients included in the pivotal studies had “medical history of psychiatric disorders”. Overall, similar patterns of psychiatric disorders (qualitative and quantitative aspects) were observed in comparative studies versus DTG. The CHMP requested the inclusion of psychiatric disorders in section 4.8 of the SmPC in line with other integrase inhibitors.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Based on safety data provided it can be concluded that no new risks or safety issues have been identified for the FDC of BIC/F/TAF.

2.7. Risk Management Plan

Safety concerns

Important Identified Risks	None
Important Potential Risks	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness
Missing Information	Long term safety information

	Safety in pregnancy and lactation

Pharmacovigilance plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
GS-US-380-1489 – Long term safety and efficacy study comparing B/F/TAF to ABC/DTG/3TC Ongoing	To evaluate the efficacy, safety, and tolerability of B/F/TAF and ABC/DTG/3TC through 144 weeks in HIV-infected, ART-naive adults.	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness (important potential risk) Long-term safety (missing information)	Submission of final study report	Q2 2020
GS-US-380-1490 – Long term safety and efficacy study comparing B/F/TAF to DTG+F/TAF Ongoing	To evaluate the efficacy, safety, and tolerability of B/F/TAF and DTG+F/TAF through 144 weeks in HIV-infected, ART-naive adults.	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness (important potential risk) Long-term safety (missing information)	Submission of final study report	Q2 2020
Antiretroviral Pregnancy Registry (APR) Ongoing	To collect information on the risk of birth defects with antiretroviral drugs, including B/F/TAF, to which pregnant women are exposed.	Safety in pregnancy (missing information)	Submission of interim reports	In the B/F/TAF PSUR (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs).

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
None	N/A	N/A
Important potential risk(s)		
Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness.	Routine risk communication: SmPC section 4.8 PL section 4	*Additional pharmacovigilance activities:* GS-US-380-1489 – Long term safety and efficacy study comparing B/F/TAF to ABC/DTG/3TC GS-US-380-1490 – Long term safety and efficacy study comparing B/F/TAF to DTG+F/TAF
Missing information		
Long term safety information	No risk minimization measures are considered necessary for this missing information.	*Additional pharmacovigilance activities:* GS-US-380-1489 – Long term safety and efficacy study comparing B/F/TAF to ABC/DTG/3TC GS-US-380-1490 – Long term safety and efficacy study comparing B/F/TAF to DTG+F/TAF
Safety in pregnancy and lactation	Routine risk communication: SmPC section 4.6 PL section 2	*Additional pharmacovigilance activities:* Antiretroviral Pregnancy Registry

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR

cycle with the international birth date (IBD). The IBD is 7 February 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of bictegravir with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers bictegravir to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Descovy (emtricitabine/ tenofovir alafenamide). The bridging report submitted by the applicant has been found acceptable.

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Biktarvy (bictegravir / emtricitabine / tenofovir alafenamide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

While untreated HIV-1 infection remains a life threatening disease, for years it has become a chronic disease with combined antiretroviral therapy being early introduced to prevent pejorative impact of immune deficiency (notably including opportunistic infections in patients with CD4<200/mm3).

The goal of ARV therapy for HIV-1 infection is to delay disease progression and prolong survival by achieving maximal and durable suppression of HIV-1 replication. Thanks to combined antiretroviral therapies nowadays available high level of viral suppression (>85% of patients with HIV RNA <50 copies/ml) can be achieved in HIV infected patients.

B/F/TAF is indicated for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the individual components. B/F/TAF is a FDC combining a novel INSTI, bictegravir (BIC), with the backbone emtricitabine (F)/tenofovir

alafenamide (TAF), already available as Descovy. Therefore, no other ARV are expected to be coadministered with B/F/TAF, considered as a single-tablet regimen (STR) for the treatment of HIV-1 infection. B/F/TAF is intended to be administered in subjects infected with HIV-1 without any known mutations associated with resistance to the individual components (i.e. including patients in first line treatment and virologically supressed patients).

3.1.2. Available therapies and unmet medical need

Multiple therapeutic options have become available over time notably in first line therapy. Other STR are already available on the market for first line therapy, combining 2 NRTI s + 1 NNRTI, 1 INSTI or 1 boosted-PI.

Overall, B/F/TAF is not aimed at responding to an unmet medical need, but rather as an alternative options to other first line antiretroviral regimens.

3.1.3. Main clinical studies

The clinical development of B/F/TAF is supported by 4 Phase 3 studies performed in ART-naïve subjects (GS-US-380-1489 and GS-US-380-1490) or virologically-suppressed subjects (GS-US-380-1844 and GS-US-380-1878) and a small underpowered phase 2 study GS-US-1475 in treatment naïve. In studies GS-US-380-1489, GS-US-380-1490 and GS-US-380-1844 the comparator was a dolutegravir-based regimen which is relevant given its potency and its wide use in clinical practice (through ABC/DTG/3TC). Study GS-US-380-1878 is aimed at substantiating the switch to Protease inhibitor (PI) based regimen. The design and methodology of these studies are endorsed (non-inferiority with standard primary endpoints).

In addition, the bioequivalence study GS-US-141-1233 is pivotal for the selection of a bictegravir dose as part of the FDC. Indeed, it was shown that a higher exposure of BIC was observed when BIC 75 mg was contained within the FDC as compared to BIC 75 mg+FTAF leading to select 50 mg of BIC for the FDC. The selected regimen of the FDC (BIC 50mg) FTAF is a once daily regimen with or without food as tested in the phase III studies.

It is important to underline that the clinical development of BIC encompassed patients without viral strains harbouring INSTI-RAM, despite its similarly enhanced pharmacodynamics properties as compared to other INSTI. A higher BIC dose (75 mg) might have to be considered in such situation. BIC-FTAF targets first line and virologically suppressed patients without viral strains harbouring mutations of resistance to any components of the FDC and to the INI class.

3.2. Favourable effects

Overall, the efficacy endpoints support the non-inferiority of B/F/TAF compared to DTG-based regimen (FTC/TAF or ABC/3TC) in ART-naïve subjects and when switching from such regimen in virologically suppressed subjects. These results are supported by the Per Protocol analyses and other secondary endpoints, especially the changes from baseline in plasma HIV-1 RNA and CD4 cell count. In addition, the switch to B/F/TAF is non-inferior to the continuation of a DRV- or ATV-based regimen. This is consistent with the known efficacy of DTG in comparison to PI. High level of virologic suppression is achieved and in the B/F/TAF groups and the DTG-based regimen groups, no subject developed treatment-emergent resistance to any study drug.

In ART-naïve subjects, B/F/TAF is non-inferior to DTG-based regimen (primary endpoint: percentage of subjects with HIV-1 RNA <50 c/mL at Week 48 non inferiority margin of 12%; difference in

percentages: -0.6% [-4.8% to 3.6%] vs ABC/DTG/3TC; -3.5% [-7.9% to 1.0%] vs DTG+F/TAF). While disputable 12% large non inferiority margin was selected, results are compatible with more stringent margin.

In virologically-suppressed subjects (primary endpoint: percentage of subjects with HIV-1 RNA ≥ 50 c/mL at Week 48, non-inferiority margin of 4%), B/F/TAF is non-inferior to ABC/DTG/3TC (difference in percentages: 0.7% [-1.0% to 2.8%]) and PI-based regimen (difference in percentages: 0.0% [-2.5% to 2.5%]).

The efficacy results were similar between the treatment groups for all of the subgroups analysed (by age, sex, race, baseline CD4 cell count, region and study drug adherence).

Adherence is required to prevent loss of virologic suppression and potential development of drug resistance. The adherence to ARV regimen is expected to be improved by reducing the pill burden and dosing frequency. Thus, the use of this once-daily single-tablet regimen such as B/F/TAF is expected to favour adherence and consequently optimise virologic outcomes.

3.3. Uncertainties and limitations about favourable effects

In the Phase 3 studies comparing B/F/TAF vs DTG+F/TAF or ABC/DTG/3TC in ART-naïve subjects, there is a trend for lower response rate in the subgroup of patients with high viral load (>100,000 c/ml) treated with B/F/TAF. It is noteworthy that given that ABC/3TC is somewhat regarded as not maximizing efficacy in patients with high viral load, the trend for higher efficacy of DTG was more pronounced when DTG was combined with the same backbone as for BIC (i.e. FTAF) than when DTG was combined with ABC-3TC. Given that the subgroup of patients with high viral load is regarded as discriminatory, the results in patients with high viral load might translate a somewhat lower performance of BIC as compared to DTG which might be related to a non-maximized dose of BIC. The results of the subgroup analyses in patients with high viral load at baseline are reflected in section 5.1.

Due to the high level of virologic suppression achieved the resistance pattern of BIC remains to be established. Possibility of rescue therapy with dolutegravir (with higher dose for INSTI-R strain) is unlikely given the overlap of resistance profile, but there are several options for rescue therapy with other cARTs.

3.4. Unfavourable effects

The safety profile of B/F/TAF appears similar to that DTG+F/TAF. The more frequent AEs are gastrointestinal disorders (diarrhea, nausea, vomiting), headache, fatigue and insomnia (<5% of subjects). The rates of Grade 3 or 4 related AE and AE leading to discontinuation are low (≤ 2%).

No liver hypersensitivity reaction or severe drug-induced liver were observed, but the rates of transaminases elevations and hyperbilirubinemia were higher with B/F/TAF compared to DTG-based regimen. These elevations were mainly minor and transient.

Similarly to DTG, increases of creatinine level were observed within the first weeks of treatment by B/F/TAF. These increases remained stable thereafter and are due to the inhibition of the transporters OCT2 and MATE-1. There was no relevant renal AE, including tubulopathy.

Psychiatric disorders are a class-effect of integrase inhibitors and therefore were scrutinized within B/F/TAF application. The rate of suicide events is ≈ 1% across the different studies and is not different between B/F/TAF and DTG groups. Most subjects with a suicide-related AE while receiving B/F/TAF had a history of depression or mental illness.

3.5. Uncertainties and limitations about unfavourable effects

Only 48 weeks data from the ongoing longer term pivotal phase 3 studies have been made available which carries some level of uncertainties on the long term safety of bictegravir

Given the non-clinical findings in favour of hepatobiliary impact [based on data available in monkeys at the highest dose tested (biliary hyperplasia and hepatocyte hypertrophy]), and the particular awareness of physicians through a dedicated amendment across the clinical studies to recommend further investigations in case of signs/ laboratory abnormalities suggestive of hepatobiliary disorders (notably appropriate imaging consultation with a specialist), such a safety issue should be kept under scrutiny for the future use of the drug in the real life setting.

Moreover, as for other TAF containing regimen, attention of physicians should be warranted on the potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir.

3.6. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Virologic success in ART-naive subjects, Week 48 (FAS)	HIV-1 RNA <50 copies/mL	n/N (%)	576/634 (90.9%)	ABC/3TC: 293/315 (93%) DTG+F/TAF: 302/325 (92.9%)	Difference in percentages (95% CI): Vs ABC/3TC: -2.1% (-5.9% to 1.6%) Vs DTG+F/TAF: -1.9% (-5.6% to 1.8%) Trend to lower rate of virologic success in subjects with baseline VL >100,000 c/ml	Pooled studies GS-US-380-1489 and -1490
Virologic failure in virologically-suppressed subjects, Week 48 (FAS)	HIV-1 RNA ≥50 copies/mL	n/N (%)	3/282 (1.1%)	1/281 (0.4%)	Difference in percentages (95% CI): 0.7% (-1.0% to 2.8%)	GS-US-380-1844
			5/290 (1.7%)	5/287 (1.7%)	Difference in percentages (95% CI): 0.0% (-2.5% to 2.5%) Open-label study	GS-US-380-1878
Unfavourable Effects						
AEs related to study drug	According to investigator	%	Diarrhoea (4.6%) Headache (4.6%) Nausea (4.1%)	DTG+F/TAF: Nausea (5.2%) Diarrhoea (3.4%) Headache (3.1%)	Duration of treatment no longer than 72 weeks, no information in elderly subjects, low number of subjects with HBV or HCV-coinfection, lack of HIV-infected subjects with renal or hepatic impairment	Pooled studies GS-US-380-1489 and -1490
			Headache (2.5%) diarrhoea (0.7%)	Headache (2.8%) abnormal dreams, flatulence, and nausea (each 1.8%)	As above.	GS-US-380-1844
			Headache (4.8%) flatulence and nausea (each 2.4%)	Proteinuria (0.7%)	As above. Open-label study.	GS-US-380-1878

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Hepatic AEs	Graded hyperbilirubinemia	%	11.6%	DTG+F/TAF: 5.8% ABC/DTG/3TC: 4.1%	Mainly Grade 1 or 2. No difference in the rates of Grade 3 or 4. Similar rates of graded ALT/AST increases. No Hy's law criteria.	Pooled studies GS-US-380-1489 and -1490
Psychiatric AEs	Suicide events	n/N (%)	7/634 (1.1%)	DTG+F/TAF: 2/325 (0.6%) ABC/DTG/3TC: 3/315 (1.0%)	Class effect of INSTI. One suicide attempt in the B/F/TAF group considered related to study drug.	Pooled studies GS-US-380-1489 and -1490
			3/282 (1.1%)	1/281 (0.4%)	Class effect of INSTI.	GS-US-380-1844
			0/290	1/287 (0.3%)	As above. In addition, 1 case of schizophrenia considered related to study drug in the B/F/TAF group.	GS-US-380-1878

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Bictegravir is a potent new integrase inhibitor close to dolutegravir as regards its enhanced pharmacodynamics properties as compared to raltegravir and elvitegravir. A high level of virologic suppression has been achieved in the two phase 3 studies versus dolutegravir, although a trend for somewhat lower performance of BIC as compared to DTG in the discriminatory high viral load strata (>100 000 copies/ml) is observed and is shown in section 5.1. No emergence of resistance has been observed across the development programme.

BIC safety profile is similar to that of other components of the INSTI class, with mainly potential psychiatric disorders.

3.7.2. Balance of benefits and risks

BFTAF represents a new potent once daily single tablet (STR) regimen. This STR do not address a high medical need, but provides a new option to the HIV therapeutic armamentarium with a different backbone to ABC/DTG/3TC (acknowledging the need for HLA testing for minimizing the risk of hypersensitivity reactions with abacavir contained in ABC/DTG/3TC).

The clinical demonstration can support the use of BFTAF for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir.

3.8. Conclusions

The overall B/R of Biktarvy is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Biktarvy is favourable in the following indication:

Biktarvy is indicated for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that bictegravir is a new active

substance as it is not a constituent of a medicinal product previously authorised within the European Union.